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(54) Benevnelse **EMULSIONS FOR THE TOPICAL TREATMENT OF DERMAL AND MUCOSAL INFECTIONS**

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US-A- 5 686 089
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EMULSIONS FOR THE TOPICAL TREATMENT OF DERMAL AND MUCOSAL INFECTIONS

Description

The invention relates to emulsions for the topical treatment of dermal infections and mucous membrane infections, in particular urogenital infections.

Humans live in symbiosis with a gigantic number of microorganisms, which primarily colonize their intestines and skin surface as commensals.

The entirety of these microorganisms is called the human microbiome. The microbiome of the woman's vagina has a very special composition, in which lactic acid bacteria predominate. Under normal physiological conditions, these create a weakly acidic environment in the vagina that has a protective effect against bacterial infections. However, vaginal infections often occur for various reasons, on the one hand caused by the almost ubiquitous fungi of the Candida species, which easily transform from commensals to pathogens, and on the other hand by bacteria such as Gardnerella vaginalis, Mobiluncus or Prevotella spp., as well as by streptococci or staphylococci For example, through typical intestinal germs such as Enterobacter, E. coli and/or Klebsiella pneumoniae, which can easily enter the vagina through smear infection simply because of the spatial proximity of the body openings. Initially, asymptomatic incorrect colonizations are the result.

When certain threshold levels of foreign germs are exceeded and infection-supporting factors come into play, a virulent infectious event ultimately breaks out. If this is not treated in a timely manner, the infection can become chronic, usually with biofilm formation. Even asymptomatic colonizations are increasingly being recognized as risk factors for infertility, miscarriage and prematurity, as well as bladder infections and certain forms of incontinence.

US 2007/292355 A1 relates to anti-infectious foamable compositions containing an anti-infective and a keratolytic agent.

The compositions are used in the treatment of fungal, bacterial or viral infections.

AT 11 910 U1 relates to composition comprising chlorhexidine, bisphosphonate, a non-steroidal anti-inflammatory drug (NSAID) and an immunomodulator (tetracycline), among other things, for the treatment or prevention of oral, mucosal or dermal infections or inflammations.

DE 10 2008 034944 A1 relates to honey-based microemulsions, which can be introduced into the body together with other active ingredients, including NSAIDs, by topical application into the skin or orally, nasally or percutaneously into the body.

WO 2011/060083 A1 relates to methods for preventing or treating external ear infections with compositions containing antibiotics, antimycotics, antiparasitics, antiviral agents, NSAIDs, analgesics, anesthetics and/or steroids.

WO 02/078648 A2 relates to topical pharmaceutical compositions containing an antimycotic, e.g.

B. terbinafine, and another drug, e.g.

B. Diclofenac or indomethacin.

The present invention relates to drugs for the topical treatment of bacterial dysbiosis and manifest infectious diseases, including mixed infections with fungi and other microorganisms.

Accordingly, the present invention relates to an emulsion for the topical treatment of dermal infections and mucous membrane infections, in particular of urogenital infectious diseases, in particular for use in the topical treatment of urogenital bacterial infections, which is characterized in that an antimicrobial active ingredient selected from an antibiotic and an antiseptic, and an NSAID are used in combination, where (a) the NSAID is diclofenac in a concentration of 0.1 to 0.5 percent by weight, indomethacin in a concentration of 0.1 to 0.4 percent by weight, naproxen in a concentration of 1 to 5 Percentage by weight, ibuprofen at a concentration of 0.5 to 2.5 percent by weight, dexibuprofen at a concentration of 0.25 to 1.25 percent by weight, ketoprofen at a concentration of 0.25 to 1.25 percent by weight, mefenamic acid at a concentration of 0 .5 to 4 percent by weight, or lornixocam at a concentration of 0.02 to 0.04 percent by weight, the

NSAID being in salt form; (b) the weight ratio of the water to the oil phase in this emulsion is between the values 2.0 and 2.7, the weight ratio being calculated taking into account the substances dissolved in the phases, with emulsifiers not being attributed to either the water or the oil phase, and (c) the pH of the emulsion is not less than 6.5 and not more than 8.5, preferably in the range 7.0 to 8.

The invention further relates to said emulsion for use in medical procedures according to independent claims 6 and 11-13, and to processes for producing said emulsion according to independent claims 14 and 15.

Bacterial colonization of the vagina and even symptomatic vaginal infections are common.

The transition from asymptomatic, non-inflammatory colonization to symptomatic disease is defined in more detail by the terms vaginosis and vaginitis.

The terms aerobic vaginosis/vaginitis and anaerobic vaginosis/vaginitis (syn: bacterial vaginosis) represent a more precise definition of the causative pathogen.

A problem that is common to all vaginal infections, regardless of the pathogen organism, is the formation of so-called biofilms.

The mucosal surfaces of the affected organs (vagina, urethra, bladder, penis) are covered by these biofilms. In these, the microorganisms are surrounded by a layer of mucous substances. The individual microbial components of the biofilm take on different tasks in the cell network and also exchange resistance mechanisms. The germs most commonly found in bacterial dysvaginosis are above-average biofilm formers. This makes the therapeutic approach to a manifest infection massively more difficult and chronification or frequent relapses in the infection process are the result. Recent studies confirm that reinfection often occurs through the partner. Partner treatment is therefore always indicated. In men, the germ reservoirs are usually found in the fold of the foreskin and/or in the first third of the urethra.

Bacterial dysbiosis and infections can be treated efficiently using a drug combination consisting of an antimicrobial drug with an anti-adhesive active ingredient.

By inhibiting adhesion, the biofilm is broken up and detached from the host's epithelium. At the same time, all the germs contained therein are released and made accessible to direct antimicrobial treatment again. A particularly popular class of drugs among the anti-adhesive agents are the non-steroidal anti-inflammatory drugs (NSAIDs). In addition to the anti-adhesive effect, these have an anti-inflammatory effect and immediate pain inhibition, which is a further special advantage in view of the vaginal infections that are often associated with pain . Since chronic infections are accompanied by chronic inflammation, the anti-inflammatory effect is particularly important in chronic infections. The decisive factor for breaking up the biofilm is the presence of the NSAID in the concentrations and conditions described in an emulsion in the composition and proportions described.

NSAIDs intended for the purposes of the invention are diclofenac, ibuprofen, dexibuprofen, ketoprofen, lornoxicam, mefenamic acid, indomethacin or naproxen.

The usual concentration in which diclofenac is used topically is in the range of 1 to 2 % (10 mg/or 20 mg/g).

In the context of the present invention, it is preferred that diclofenac is used in an amount of 0.1 % to 0.5 % (1 - 5 mg per g of cream), preferably 0.2. %. up to 0.4 %. The usual concentration at which ibuprofen is used topically is 5 % (50 mg/g cream/gel). In the context of the invention, ibuprofen is used in a preferred amount of 0.5 to 2.5 % (5 - 25 mg per g of cream), preferably 1 to 2 %. Further examples of preferred NSAIDs and their preferred amounts (“Concentration of the Invention”) can be seen in Table A.

Tab: A - Examples of common and preferred concentrations according to the invention

Active substance	Individual does	Daily maximum dose	Example	Individual dose	Daily maximum dose	Example	Concentration according to the invention
	oral/i.y.			topical			
Diclofenac sodium	50-75 mg	150-225 mg	Voltaren 50 mg tablets 75 mg amp.	40-80 mg	240 mg	Voltadol pain relief gel 1 %, 10 mg/g	0.2-0.5 wt.%

						2 %, 20 mg/g	
Indometacin	25-75 mg	50-150 mg	Indocid 25 mg 75 mg ret.	20-40 mg	40-80 mg	IndometGel 1 %, 10 mg/g	0.1-0.4 wt.%
Naproxen	250-500 mg	1000 mg	Naproxen PT 250/500 mg Naproxen Susp. 50 mg/ml				0.5-2.5 wt. %
Ibuprofen	200-800 mg	2400 mg	Ibuprofen FT 200/400/800 mg	100-250 mg	1000 mg	Ibutrop cream/gel 5 %, 5 g/100g	0.5-2.5 wt.%

The following NSAIDs are particularly preferred within the scope of the invention:

NSAID	**Preferred concentration (wt.%)**	**Preferred individual dose (mg)**
Diclofenac	0.1-0.5 (preferably 0.2-0.4)	4 to 8 mg
Indometacin	0.1-0.4	2-8 mg
Naproxen	1-5	20 to 100 mg
Ibuprofen	0.5-2.5	10 to 50 mg
Dexibuprofen	0.25-1.25	5 to 25 mg
Ketoprofen	0.25-1.25	5 to 25 mg
Mefenamic acid	0.5-4	10-40 mg
Lornoxicam	0.02-0.04	0.4 to 0.8 mg

The concentration restrictions in the table apply to use on open wounds (possible in the case of dermal fungal infections) and on mucous membranes.

For use on less severely inflamed skin, an NSAID concentration up to a maximum of the usual topical amount is possible.

In a preferred embodiment, the emulsion is in the form of an ointment or a cream.

The emulsion is preferably for the treatment of urogenital infectious diseases, in particular for use in the topical treatment of vaginal infections and bladder infections in women as well as for local partner treatment (glans penis, initial third of the urethra).

In particular, the preparations according to the invention show, in addition to the optimized pharmacokinetics due to the attack directly at the site of infection, also optimal pharmacodynamics.

This not only enables a particularly good effectiveness of the antimicrobial drug, but also significantly improves the interaction with the NSAID, in that a low concentration of NSAID still ensures sufficient effectiveness without the side effects that occur (irritation, burning, etc.). having to accept.

In practice, this means that combinations of antimicrobial drugs and NSAIDs that were previously unusable due to these side effects can be made available to patients with the teaching of the present invention and these patients can now be treated successfully.

However, according to the invention it has been shown that the concentration of the NSAID in the aqueous phase is of crucial importance for an optimal pharmacodynamic effect.

The availability of the introduced NSAID is achieved through the interaction of the manufacturing process, the water/oil ratio and the pH value, which ensures that the NSAID is predominantly present in its salt form.

Semi-solid emulsions (oil in water or water in oil), preferably in the form of a cream, are particularly suitable for delivering the active ingredients efficiently and in a concentrated manner to surfaces affected by biofilm.

The viscosity of the emulsions is largely determined by the water to oil ratio.

Surprisingly, it turned out that the water: oil ratio is particularly important when formulating the emulsion.

If the proportion of fat components is higher, the development of effectiveness is hindered.

On the other hand, a lower fat content has a stronger irritant effect.

It is known that finding a dosage form for topical application in the vagina is complicated by the fact that the drug can easily leak during use, which makes reliable dosing difficult.

In view of the relatively narrow therapeutic window, medications according to the present invention require the safe retention of the active ingredient, especially the NSAID component, at the site of action in order to achieve the desired therapeutic effect.

Therefore, the ratio of the oil phase, which contains the antimycotic, to the water phase, in which the NSAID is located, is within a relatively narrow range.

If the viscosity is further reduced to a greater extent by increasing the proportion of the aqueous phase, uncontrolled loss through vaginal leakage is to be expected.

Liquid emulsions or gels with a high water content or with a low viscosity should be excluded as dosage forms for vaginal use according to the present invention.

Since chronic infections of the vagina are also associated with chronic inflammation of the vaginal epithelium, in such cases a cure can only be achieved if the NSAID remains in the vagina.

To achieve an optimal therapeutic effect, the water: oil ratio should not exceed 2.7.

Above this area, the active ingredient is washed out too quickly with the vaginal secretion, which means there is not enough time to develop the effect that contributes to preventing adhesion on the outer layer of the vaginal epithelium to which the pathogen adheres.

The active ingredient, which is washed out very quickly if the water: oil ratio is too high, can also cause an irritating effect as a side effect.

In the same way that too high a water content in the emulsion has a negative effect, too high a fat content should also be avoided.

Given the low concentration in which the NSAID is used, in order to achieve the therapeutic effect it is particularly important that the release of the active ingredient at the site of action occurs quickly and not in a protracted manner.

With a slow release, as occurs from the oily phase, there is no guarantee that the required therapeutic concentration will be achieved at the site of action.

For this reason, the water: oil weight ratio in the emulsion should not be less than 2.0.

This also results in a window between 2.0 and 2.7, preferably between 2.1 and 2.6, even more preferably between 2.2 and 2.5 for the value of the water-oil weight ratio of the emulsions according to the invention.

It is essential that the NSAIDs according to the invention are in salt form (or ionic form) both during incorporation and during use.

Therefore, their inclusion in the formulation is important.

If the NSAID is incorporated in its free form or as a salt in the oily phase, the therapeutic effect is massively impaired.

While the antimycotic is preferably incorporated into the oily phase and is present in it, according to the method according to the invention, the NSAID is usually introduced into the aqueous phase before the emulsion is produced.

Alternatively, the solid salt of the NSAID can be incorporated into the (largely) finished emulsion in finely crystalline or micronized form, or as a hydrogel.

Rapid release is guaranteed if the active ingredient in the emulsion is present in the aqueous phase, which requires that the NSAID is present as a salt.

Most NSAIDs are weak acids with a pKa value of 4 - 5 (diclofenac 4.15, ibuprofen 4.91, mefenamic acid 4.2, indomethacin 4.5, naproxen 4.2).

Accordingly, some of them are already present in free form in the weakly acidic environment and are thus extracted into the oil phase, which can lead to a reduced effect or loss of effectiveness.

Since the active ingredient content of the NSAID present as a free acid in the oil phase increases as the pH value decreases, a pH value of at least pH = 6 is

advisable in order to have a therapeutic effect with the drugs in the active ingredient concentrations according to the invention.

However, with NSAIDs there can be a decrease in chemical stability in an alkaline environment (in the case of diclofenac from pH 8.00 - 8.5).

It must also be noted that the pH value of an emulsion influences the basic physiological compatibility.

There are therefore relatively narrow limits with regard to the pH value of the formulation.

According to the invention, the (aqueous phase of the emulsion) has a pH in the range from 6.5 to 8.5, preferably from 7 - 8.

In the context of the invention, antibiotics or antiseptics are used as antimicrobial active ingredients.

Among the bacterial microorganisms found in the vaginal biofilms, typical mostly facultative anaerobic intestinal germs, such as Enterobacter, E. coli, Klebsiella pneumoniae and enterococci, but also ureaplasma and mycoplasma, as well as Gardnerella vaginalis, Prevotella spp. and Mobiluncus play a special role.

Preferred antibiotics in the context of the present invention, which are also particularly suitable for treating these germs, are phosphomycin, clindamycin, metronidazole, nitrofurantoin, nitrofurazone, nitrofurantoin, nifuratel, nifuroxacin, nitroxoline, trimethoprim, sulfadiazine, cotrimoxazole.

Antiseptics can act on both non-bacterial microorganisms such as trichomonas and bacteria.

At higher concentrations, antiseptics have an antibacterial effect and are suitable alone or together with an antibiotic for combination with an anti-adhesive active ingredient according to the invention.

The antimicrobial effect of antiseptics is primarily based on disrupting the integrity of the plasma membrane.

Because the membrane of the endothelial cells has essentially the same structure, these active ingredients have an inherent potential to stimulate inflammation.

Since this potential is prevented by NSAIDs, the combination preparations of antiseptics according to the invention offer a very special therapeutic advantage.

Preferred antiseptics are quaternary ammonium salts such as benzalkonium chloride and dequalinium chloride, as well as phenoxyethanol.

Preferred concentrations are at least 0.2 percent by weight for benzalkonium chloride, at least 0.2 percent by weight for dequalinium chloride, and at least 2 percent by weight for phenoxyethanol.

In connection with the present invention, the terms “antimicrobial agent”, “antibacterial agent”, “antibiotics”, “antiseptics”, etc.

Substances are understood to be understood as such active ingredients in normal pharmaceutical use.

Which substances are considered such active ingredients can be found, for example, in the Red List drug directory (Rote Liste Service GmbH (publisher and publisher), Red List 2014 - Drug directory for Germany (including EU approvals and certain medical devices), 2047 pages, ISBN 978-3 -939192-80-0).

Benzyl alcohol, ethanol or propanol are not antibacterial active ingredients within the meaning of the invention.

The composition of the drug combinations according to the invention is particularly suitable in the combinations described for the treatment of even complex chronic vaginal infections.

In special applications it is useful to add an odorant to the emulsion.

The addition of a terpene to the emulsion, preferably farnesol, which also has a biofilm-inhibiting effect, is therefore a preferred subject of the invention.

The emulsions according to the invention are suitable for use on mucous membranes, particularly urogenital infections.

For example, compositions that have a high content of substances that are harmful to the mucous membrane, such as ethanol or isopropanol, are unsuitable for vaginal application.

It is therefore preferred that the emulsion according to the invention contains no more than 10 % ethanol.

It is also preferred that the emulsion according to the invention contains no more than 20 % isopropanol.

Since keratinized layers of mucous membranes, e.g.

B. in the urogenital area, a keratoytic effect is not desired.

For this reason, the strongly acidic, keratinolytic salicylic acid is not an NSAID according to the invention.

Emulsions according to the present invention are also suitable for the treatment of urogenital mucous membrane diseases in men on the glans penis and in the urethra.

Bladder infections are common.

They are mostly caused by bacterial infection.

The bladder is difficult to access for topical treatment.

However, since the woman's urethra is located in the front entrance to the vagina, the most common route of infection runs from the vagina into the urethra.

In addition, in urological and gynecological practice, symptoms are often seen that can be traced back to an isolated inflammation of the urethra.

The vagina therefore becomes the primary reservoir of germs for urethral and bladder infections.

Even if the antibiotic treatment of acute bladder infections can be supported by the oral administration of adhesion-inhibiting plant extracts, which adhere to the

bladder wall, the sanitation of the vaginal flora, which is usually also affected by the infection, is still the basic prerequisite for sustainable healing.

This can be achieved with the drugs according to the invention.

For this reason, drugs according to the present invention are efficient therapeutic agents against cystitis, both alone and in combination with drugs acting only in the bladder.

Apart from purely bacterial infections, mixed infections with fungi (mainly yeasts of the genus Candida) also often occur.

WO 2007/131253 A2 claims drug combinations for the topical treatment of fungal infections, the special effect of which is based on the fact that, in addition to the antifungal active ingredient, another active ingredient is added, which prevents the adhesion of the fungus to the epithelium.

Some of the mixed infections mentioned can be treated using the combinations claimed in WO 2007/131253 A2.

In severe cases of mixed infections, however, it is advisable or necessary not to limit yourself to treating the fungal infection, but to supplement the medication with an antibacterial agent in a triple combination.

The antifungal active ingredient is preferably a drug from the group of nystatin, ciclopirox or ciclopiroxolamine, or one from the group of azoles (imidazoles, triazoles, tetraazoles) such as clotrimazole, fluconazole, miconazole, itraconazole, tioconazole, voriconazole, bifonazole, econazole, isoconazole, fenticonazole, Sertaconazole, Ketoconazole, Posaconazole, Quilseconazole, Oteseconazole (VT-1161), Ibrexafungerp (SCY-078).

Medicaments according to the present invention were developed primarily for the treatment of vaginoses and bladder infections.

The invention therefore relates to the use of the emulsions according to the invention in the topical treatment of infectious diseases, in particular for use in the topical treatment of urogenital infections.

Preferably, the infectious disease is a microbial (in particular a bacterial) urogenital infection, in particular a microbial (in particular a bacterial) urogenital infection in women.

In a particularly preferred embodiment, the infectious disease is a mixed vaginal infection caused by Candida albicans and bacteria such as Enterobacter, E. coli, Klebsiella pneumoniae, Gardnerella vaginalis, Prevotella spp.

In a further preferred embodiment, the infectious disease is an asymptomatic or symptomatic bacterial vaginosis or an asymptomatic or symptomatic dysbiosis of the glans penis and/or the male urethra.

Both acne and genetic hair loss are associated with the male sex hormone testosterone.

In fact, the contribution of this hormone to the pathogenetic process consists primarily in the activation of sebaceous glands in the skin and in the hair follicles.

The accumulated sebum is subsequently an ideal substrate for both a bacterial infection, especially with propionibacteria or with the fungi Candida and Malassezia.

While Malassezia is primarily associated with pityriasis versicolor, Propionibacterium acnis is the main cause of acne.

Both are involved in hair loss.

The large amount of sebum that accumulates in the hair follicles is an ideal substrate for the formation of a biofilm.

Basically, the same criteria apply to this biofilm as to biofilms that form in the vagina.

In this case, too, the biofilm must first be broken up and its attachment to the epithelium dissolved so that the anti-infective agent can then exert its effect.

Accordingly, the emulsions according to the present invention are also very suitable for the treatment of skin diseases, especially pityriasis versicolor, acne and hair loss.

Since dermal applications can affect a much larger and much less well-defined area than vaginal infections, special emulsions can be preferred in these cases.

In particular, shampoos are suitable for treating hair loss and acne creams, acne sticks or acne solutions are suitable for treating acne.

The invention is explained in more detail using the following examples, to which, however, it is not limited.

Examples:

Production of basic recipe A, general production instructions 1:

The components sorbitan monostearate, polysorbate 60, cetyl palmitate, 2-octyldodecanol and cetostearyl alcohol are melted at a temperature of 70-75 °C.

Clindamycin (and optionally clotrimazole) and then phenoxyethanol are added to the clear melt while stirring at a temperature of 60 °C - 70 °C.

At the same time, diclofenac sodium is dissolved in purified water with heating.

The aqueous solution is added to the oil phase while stirring and homogenized.

With slow cooling and further homogenization of the resulting w/o emulsion, a phase reversal occurs, resulting in a hydrophilic, homogeneous cream.

Constituents of the emulsion		
Clindamycin	2.00	2.00
Diclofenac Na	0.20	0.30
Sorbitan monostearate	2.00	2.00
Polysorbate 60	1.50	1.50
Cetylpalmitate	3.00	3.00
2-octyldodecanol	13.50	13.50
Cetostearyl alcohol	10.00	10.00

Phenoxyethanol	1.00	1.00
Purified water Ph.Eur.	66.80	66.70
	100.00	100.00

Emulsions containing phenoxyethanol as an antibacterial agent

Tab.: F1 - Phenoxyethanol as an antibacterial agent

Composition of the emulsion	wt. %
Clotrimazole	1
Diclofenac Na	0.4
Sorbitan monostearate	2
Polysorbate 60	1.5
Cetylpalmitate	3
2-octyldodecanol	13.5
Cetylstearyl alcohol	10
Phenoxyethanol	4
Purified water Ph.Eur.	64.6
Total	100

Case study: 24-year-old patient (EH), almost constant complaints from fungal infections for 3 years, hardly possible in the GV for years.

Extreme symptoms for 1 week.

Burning and itching in the introitus.

Gynecological examination (gyn.

U.): Vulva and vaginal mucosa massively reddened, massive creamy-greenish vaginal contents, native secretion smear: masses of leukocytes adhering to the epithelial cells and masses of fungal hyphae, mixed flora, few lactobacilli, dirty background - lytic cells, intermediate flora.

Therapy: F1 over 2 weeks, 0-0-1 Hb applied vaginally, then F1 if necessary.

Ko. after 3 years: free of symptoms since last therapy;

Gyn.

U.: Mucous membrane bland, normal vaginal flora, lactobacillus flora.

Example: Emulsions containing dequalinium chloride

Tab: F2 - Dequalinium chloride as an antibacterial agent

Composition of the emulsion	wt. %
Clotrimazole	1
Diclofenac Na	0.3
Sorbitan monostearate	2
Polysorbate 60	1.5
Cetylpalmitate	3
2-octyldodecanol	13.5
Cetostearyl alcohol	10
Phenoxyethanol	1
Dequalinium chloride	0.4
Purified water Ph.Eur,	67.3
Total	100

Case study: 40-year-old patient (AKS), who has been suffering from fungal infections almost every month for years, each lasting approx.

1 Week to 10 days, sexual intercourse has hardly been possible for years. For 1 week, vaginal secretions have also been thin and smelly.

Burning and itching in the introitus.

Gynecological examination: mucous membrane very red, secretion thin, slightly greenish.

Native secretion smear: abundant biofilm plaques on thick fungal hyphae, leukocytes +++, hardly any lactobacilli, intermediate flora.

Therapy: F2 over 1 week, 0-0-1 Hb applied vaginally.

Ko. after 2 years: symptom-free for 2 years, only occasionally very slight fungal infections, with residual.

F2 treated;

Gyn.

U.: mucous membrane bland, lactobacillus flora

Tab.: F3 - Dequalinium chloride as an antibacterial agent

Composition of the emulsion	wt. %
Clotrimazole	1.00
Diclofenac Na	0.20
Sorbitali monostearate	2.00
Polysorbate 60	1.50
Cetylpalmitate	3.00
2-octyldodecanol	13.50
Cetostearyl alcohol	10.00
propylene glycol	7.00
Dequalinium chloride	0.40
Purified water Ph.Eur.	61.40
Total	100.00

Case study: 31-year-old patient (FJ), for approx.

3 Premenstrual symptoms almost monthly for years, each lasting approx.
1 Week to 10 days, due to recurrent fungal infections.
For 1 week, vaginal secretions have also been thin and smelly.

Burning and itching in the introitus.

Gyn.

U: Mucous membrane slightly red, secretion thin, odor.

Native secretion smear: bacterial vaginosis (RG III), additional fungal hyphae, abundant leukocytes.

Therapy: F3 over 1 week, 0-0-1 Hb applied vaginally.

Check-up after 4 months: subjectively no more complaints since therapy.

Gyn.

U: mucous membrane bland, secretion smear native: normal vaginal flora (RG I)

Example: Emulsions containing clindamycin

Tab: F4

Composition Of the emulsion	wt. %
Clindamycin	**2**
Diclofenac Na	**0.3**
Sorbitan monostearate	2
Polysorbate 60	1.5
Cetylpalmitate	3
2-octyldodecanol	13.5
Cetostearyl alcohol	10
Propylene glycol	7
Phenoxyethanol	1
Purified water Ph.Eur.	59 .70
Total	100

Case study: 31-year-old patient (EK), therapy-resistant for months. Bacterial vaginosis, foul-smelling discharge, especially postmenstrual.

The microbial smear results showed abundant Gardnerella and Prevotella.

Gyn.

U: Mucous membrane very red, vaginal secretion thin and foul-smelling.

Native secretion swab: plentiful.

Clue cells, leukocytes +++, bacterial vaginosis (RG III) Therapy: F4 over 1 week, 0-0-1 applied vaginally, then Hylaktiv Vagilact.

Check after 2 years: since the above

Therapy symptom-free, once very mild fungal infection; Gyn.

U.: mucous membrane bland, normal lactobacillus flora (RG I)

Example: Emulsions containing phosphomycin trometamol

Tab: F5

Composition of the emulsion	wt. %
Phosphomycin trometamol	2
Diclofenac Na	0.4
Sorbitan monostearate	2
Polysorbate 60	1.5
Cetylpalmitate	3
2 -octyld.odecanol	13.5
Cetylstearyl alcohol	10
Phenoxyethanol	1
Purified water Ph.Eur.	66.6
Total	100

Case example: 69-year-old patient (ET), for approx.

2 Recurrent urinary tract infections for years, repeatedly treated with Ciproxin. Increased urge to urinate and burning in the introitus again for 2 weeks.

Gyn.

U: tenderness over bladder; Mucous membrane atrophic, bleeds on contact, cervix atrophic, soldered, opened with cervical brush, secretion: atrophy, mixed aerobic flora (RGIII), abundant leukocytes.

Therapy: F5 over 1 week, 0-0-1 Hb applied vaginally, additionally Ovestin.

Check-up after 2 weeks: subj. No more symptoms since therapy.

Gyn.

U: mucous membrane bland, no DS over bladder and urethra; Native secretion smear: starting with normal vaginal flora (RG I), no leukocytes.

Tab.: F6

Composition of the emulsion	wt. %
Phosphomycin trometamol	2
Clotrimazole	1
Diclofenac Na	0.3
Sorbitan monostearate	2
Polysorbate 60	1.5
Cetylpalmitate	3
2-octyldodecanol	13.5
Cetostearyl alcohol	10
Propylene glycol	7
Phenoxyethanol	1
Purified water Ph.Eur.	58.7
Total	100

Case study: 36-year-old patient (CS), 2 years ago for the first time UTI after a vacation in Thailand with gross hematuria and long-lasting burning, for 2 months now UB pain and UTI (again after a vacation in Thailand), recurring burning especially after urinating, more severe again for 2 weeks Urge to urinate, after AB treatment (1 week) no improvement in bladder problems but now additional itching and burning in the introitus.

Gynecological examination: tenderness over bladder; Vaginal mucosa is rather inconspicuous in appearance, pronounced cervicitis with bloody erosion measuring approx. 1 cm around the cervix, secretion/native preparation: bacterial vaginosis, masses of leukocytes, these covered with bacteria, a few lactobacilli, hyphae ++.

Microbiol smear - secretion culture: masses of E. coli.

Therapy: F6 over 10 days, 0-0-1 applied vaginally, additionally 2 bags of Monuril at intervals of 3 days.

Check-up after 4 weeks: subj. No more symptoms since therapy.

Gyn.

U: mucous membrane bland, no tenderness over bladder and urethra; Native secretion smear: normal vaginal flora (RG I), no leukocytes.

Tab: F7

Composition of the emulsion	wt. %
Phosphomycin trometamol	**2**
Diclofenac Na	**0.3**
Sorbitan monostearate	2
Polysorbate 60	1.5
Cetylpalmitate	3
2-octyldodecanol	13.5
Cetostearyl alcohol	10
Propylene glycol	7
Phenoxyethanol	1
Purified water Ph.Eur.	59.7
Total	100

Example: Influence of the aqueous phase/oil weight ratio on the clinical effectiveness of the NSAID

Surprisingly, changes in viscosity show clear influences on clinical effectiveness even with small variations.

The examples mentioned are produced according to general working procedure 1 by varying the content of the fatty components and the water content.

An increase in the water content and thus a reduction in viscosity leads to local irritation and reduced clinical effectiveness via increased release and increased wetting of the mucous membranes.

Tab.: Influence of the weight ratio of aqueous phase/oil on the clinical phase

Phase	Fat component / viscosity reduced		Basic formulations		Fat component / viscosity increased	
Clotrimazole (oil)	1	1.0	1.0	L C	1.0	1 . Cl
Diclofenac Na (water)	0,1	0,3	0.3	0.3	• !	0.3
Sorbitan monostearate (-)	2.0	2.0	2.0	2.0	2.0	J . 0
Polysorbate 60 (-)	1.5	1.5	1.5	1.5	1.5	1.5
Cetylpalmitate (oil)	3.0	3.0	3.0	3.0	3.0	3.0
2-octyldodecanol (oil)	13.5	13.5	13.5	13.5	13.5	14.5
Cetylstearyl alcohol (oil)	7,5	5	10	10	14	16
Benzyl alcohol	1. o	1.0	1.0		1.0	1.0
(oil)						
Phenoxyethanol (oil)				1.0		
Propylene glycol (water)				7		
Water (water)	70.2	72 .7	67.75	60.7	63.7	60.7
Total	100	100	100	100	100	100
Clinical efficacy	**irritating**	**irritating**	**conforms**	**conforms**	**reduced**	**reduced**
Water phase total	70.5	73.0	68.0	68.0	64.0	61.0
Fat phase total	26	23.5	28.5	28.5	32.5	35.5
Aqueous / fat	2.7	3.1	2.4	2.4	2.0	1.7

Formulations with a ratio of aqueous phase to fat phase outside 2.0 to 2.7 are reference formulations.

To calculate the weight ratio of the water to oil phase, the individual proportions of the water and oil phases are added up as shown in the table.

Since emulsifiers, e.g.

B. sorbitan monostearate and polysorbate 60, lie on the interfaces between the two phases, they are neither the water nor the oil phase.

If you calculate the ratio of the aqueous phase to the oil phase of the concentrated emulsion (i.e. the intermediate product from components A, B, J, C, E, G, H and half of K) from Example 2 of WO 02/0768648 A2, you get a Ratio of 3.1 (oil phase: terbinafine, butylhydroxytoluene, benzyl alcohol, isopropyl myristate, total 11.52 g / 100 g; water phase: diclofenac sodium and water, total 35.94 g / 100 g; ratio 3.1).

Such an emulsion therefore has a water:oil ratio outside the range preferred according to the invention and would therefore not be according to the invention in connection with the present invention.

Alternatively, the weight ratio of the water to oil phase could be calculated without taking into account the substances dissolved in the phases (clotrimazole, diclofenac-Na, benzyl alcohol, cetostearyl alcohol).

With this calculation method, only water and propylene glycol would be assigned to the water phase in Table 3, and cetyl palmitate, 2-octyldodecanol and cetystearyl alcohol would be assigned to the oil phase.

The water-oil ratios 2.7, 3.1, 2.4, 2.4, 2.0, 1.7 given in Table 3 would correspond to the values 2.9, 3.4, 2.6 according to this calculation method, 2.6, 2.1, 1.8 correspond.

The range of 2.0 to 2.7 according to the invention would correspond to a range of 2.1 to 2.9 in this calculation method.

In the context of the present invention, the calculation of the weight ratio of the water to oil phase should be carried out as shown in Table 3, i.e. taking into account the substances dissolved in the phases.

Further examples of the influence of the aqueous phase/oil weight ratio on clinical effectiveness:

		Fat component / viscosity reduced		**Basic formulations**			**Fat component / viscosity increased**	
Clotrimazole	oil	1.00	1.00	1	1	1	1.00	1.00

Diclofenac Na	water	0.30	0.30	0.25	0.3	0.4	0.30	0.30
Sorbitan monostearate		2.00	2.00	2	2	2	2.00	2.00
Polysorbate 60		1.50	1.50	1.5	1.5	1.5	1.50	1.50
Cetylpalmitate	oil	3.00.	3.00	3	3	3	3.00	3.00
2-octyldodecanol	oil	13.50	13.50	13.5	13.5	13.5	13.50	14.50
Cetylotearyl alcohol	oil	7.50	5.00	10	10	10	14.00	16.00
Benzyl alcohol	oil	1.00	1.00	1			1.00	1.00
Phenoxyethanol	oil				1	4		
Propylene glyool	water				7			
Purifief water Ph. Eur	water	70.20	72.710	67.75	60.7	64.6	63.70	60.70
Total		100.00	100.00	100.00	100.00	100.00	100.00	100.00
Clinical efficacy		**irritating**	**irritating**	**conforms**	**conforms**	**conforms**	**reduced**	**reduced**
Aqueous phase / fat		**2.7**	**3.1**	**2.4**	**2.4**	**2.1**	**2.0**	**1.7**
Water phase		70.50	73.00	68.00	68.00	65.00	64.00	61.00
Fat phase		26.00	23.50	28.50	28.50	31.50	32.50	35.50

Example: Influence of the pH value on the clinical effectiveness of the NSAID

The influence of pH on the clinical effectiveness of the NSAID was examined using emulsions containing clotrimazole and NSAIDs.

Emulsions with different concentrations of diclofenac Na were prepared and tested for their clinical effectiveness.

Tab.: Dependence of clinical effectiveness on the concentration of the NSAID

	Conc. wt.%	**Conc. wt.%**	**Conc, wt.%**	**Conc, wt.%**
Clotrimazole	1	1	1	1
Diclofenac Na	0.1	0.25	0.5	0.75
Sorbitan monostearate	2	2	2	2
Polysorbate 60	1.5	1.5	1.5	1.5
Cetylpalmitate	3	3	3	3
2-octyldodecanol	13.5	13.5	13.5	13.5
Cetylstearyl alcohol	10	10	10	10

Benzyl alcohol	1	1	1	1
Purified water Ph.Eur.	67.9	67.75	67.5	67.25
Total	100	100	100	100
Ph	**7.6**	**7.8**	**8.1**	**8.1**
Clin, efficacy	slightly reduced	conforms	conforms, slightly irritating	irritating to the mucosa

When clotrimazole and NSAIDs are used together, the pH shifts in the emulsion system change both microbiological and chemical stability [Lit.

Pharmacopoeia] compared to a comparable clotrimazole formulation.

Composition	**wt.%**	**wt.%**	**wt.%**	**wt.%**	**wt.%**
Clotrimazole		1	1	1	1
Diclofenac Na	0.4	0.3	0.3	0.25	0.25
Sorbitan monostearate	2	2	2	2	2
Polysorbate 60	. .	1.5	1.5	1.5	1.5
.Cetylpalmitate	3	3	3	3	3
2 -octyidodecanol	13.5	13.5	13.5	13.5	13.5
Cetylstearyl alcohol	10	10	10	10	10
Propylene glycol		7	5		
Phenoxyethanol	4	1	1	1	
Bronopol				0.1	
Sorbic acid					0.2
Buffer solution				0.2201	0.0874
Purified water PhEur.	64.6	60 .7	62.7	67.4299	68.4626
Total	100	100	100	100	100
Ph	7.9	7.6	7.9	7,5	5.6
Clin. efficacy	confarms	conforms	conforms	conforms	reduced
Microbiol, stability	conforms	conforms	conforms	conforms	conforms

Tab: Variants with different preservatives

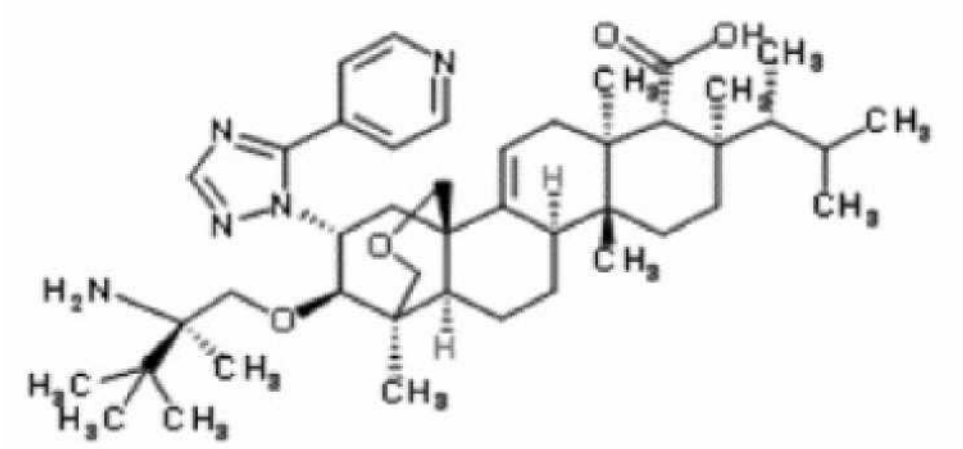
The variant with a pH value of 5.6 is a reference formulation.

Example: Shampoo to treat fungal hair loss:

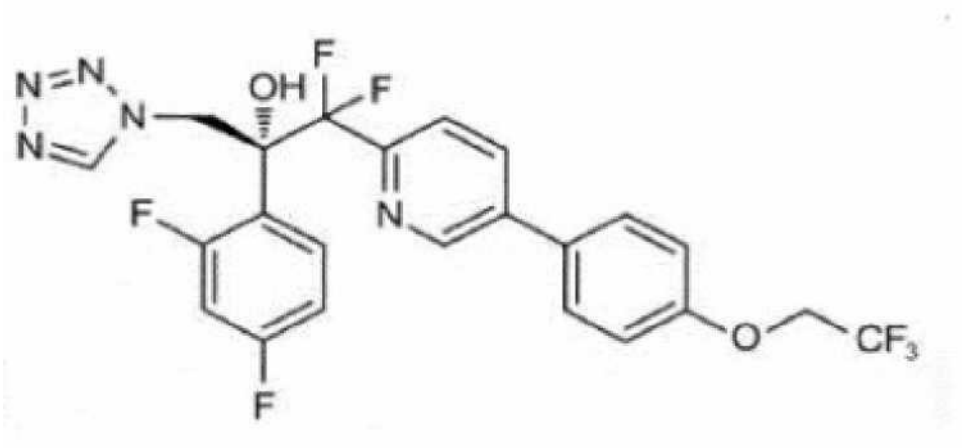
Tab: F8

Composition of the emulsion	wt. %
Ketoconazole	2
Diclofenac Na	0.3
Ammonium lauryl sulfate	15.00
Lauramide	4.00
Sodium chloride	1.00
Farnesol	1
Disodium EDTA	0.2
Methy1paraben	0.08
Propylparaben	0.05
Purified water Ph.Eur.	76.37
	100

Structural formula of Ibrexafungerp (SCY-078).



Structural formula of oteseconazole (VT-1161).


N
N
N
OH
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O
CF3

PATENTKRAV

1. Emulsjon for topisk behandling av dermale infeksjoner og slimhinneinfeksjoner, spesielt urogenitale infeksjonssykdommer, **karakterisert ved at** et antimikrobielt middel valgt fra et antibiotikum og et antiseptisk middel og et NSAID anvendes i kombinasjon, hvori (a) NSAID er diklofenak i en konsentrasjon på 0,1 til 0,5 vektprosent, indometacin i en konsentrasjon på 0,1 til 0,4 vektprosent, naproksen i en konsentrasjon på 1 til 5 vektprosent, ibuprofen i en konsentrasjon på 0,5 til 2,5 vektprosent, deksibuprofen i en konsentrasjon på 0,25 til 1,25 vektprosent, ketoprofen i en konsentrasjon på 0,25 til 1,25 vektprosent, mefenaminsyre i en konsentrasjon på 0,5 til 4 vektprosent, eller lorniksokam i en konsentrasjon på 0,02 til 0,04 vektprosent, hvori NSAID er i saltform; (b) vektforholdet mellom vann- og oljefasen i emulsjonen er mellom verdiene 2,0 og 2,7, hvori vektforholdet beregnes som inkluderer tekstilene oppløst i fasene, hvori emulgatorer ikke inkluderes i verken vann- eller oljefasen, og (c) pH i emulsjonen er ikke mindre enn verdien 6,5 og ikke mer enn 8,5, fortrinnsvis i området 7,0 til 8.

2. Emulsjon ifølge krav 1, som i tillegg inneholder et soppdrepende middel.

3. Emulsjon ifølge krav 1 eller 2, i form av en salve, en krem, en sjampo eller en stift, fortrinnsvis for topisk behandling av dermale infeksjoner, som fortrinnsvis videre inneholder et luktstoff, fortrinnsvis en terpen, spesielt farnesol.

4. Emulsjon ifølge et hvilket som helst av kravene 1 til 3, **karakterisert ved at** det antimikrobielle midlet er et antibiotikum, fortrinnsvis fosfomycin, klindamycin, metronidazol, nitrofurantoin, nitrofurazon, nitrofurantoin, nifuratel, nifuroksacin, nitrokolin, trimetoprim, sulfadiazin eller kotrimoksazol; eller at det antimikrobielle midlet er et antiseptisk middel, fortrinnsvis valgt fra gruppen som består av: benzalkoniumklorid, fortrinnsvis i en konsentrasjon på minst 0,2 vektprosent; dekvaliniumklorid, fortrinnsvis i en konsentrasjon på minst 0,2 vektprosent; og fenoksyetanol, fortrinnsvis i en konsentrasjon på minst 2 vektprosent.

5. Emulsjon ifølge et hvilket som helst av kravene 2 til 4, **karakterisert ved at** det soppdrepende midlet er nystatin, ciklopiroks eller ciklopiroksolamin, eller et soppdrepende middel fra gruppen av azoler, fortrinnsvis klotrimazol, flukonazol, mikonazol, itrakonazol, tiokonazol, vorikonazol, bifonazol,

ekonazol, isokonazol, fentikonazol, sertakonazol, ketokonazol, posakonazol, quilsekonazol, otesekonazol (VT-1161) eller ibreksafungerp (SCY-078).

6. Emulsjon ifølge et hvilket som helst av kravene 1 til 5 for anvendelse i den topiske behandlingen av infeksjonssykdommer, spesielt for anvendelse i den topiske behandlingen av dermale og urogenitale infeksjonssykdommer, fortrinnsvis hvori infeksjonssykdommen er en kronisk infeksjonssykdom.

7. Emulsjonen for anvendelse ifølge krav 6, **karakterisert ved at** infeksjonssykdommen er en slimhinneinfeksjon, spesielt en urogenital infeksjon, fortrinnsvis en mikrobiell urogenital infeksjon, spesielt en kvinnelig mikrobiell urogenital infeksjon, fortrinnsvis hvori den mikrobielle urogenitale infeksjonen er en bakteriell urogenital infeksjon.

8. Emulsjonen for anvendelse ifølge krav 6 eller 7, **karakterisert ved at** infeksjonssykdommen er en blandet vaginal infeksjon av Candida albicans og bakterier slik som Enterobacter, E.coli, Klebsiella pneumoniae, Gardnerella vaginalis, Prevotella spp.

9. Emulsjonen for anvendelse ifølge et hvilket som helst av kravene 6 til 8, **karakterisert ved at** infeksjonssykdommen er en asymptomatisk eller symptomatisk bakteriell vaginose eller en asymptomatisk eller symptomatisk dysbiose av penishodet og/eller det mannlige urinrøret.

10. Emulsjonen for anvendelse ifølge krav 9, **karakterisert ved at** infeksjonssykdommen er en dermal soppinfeksjon, fortrinnsvis valgt fra candidamykoser og malasseziamykoser, eller akne, fortrinnsvis hvori emulsjonen behandles til en aknestift.

11. Emulsjonen ifølge et hvilket som helst av kravene 1 til 5 for anvendelse i den topiske behandlingen av kvinnelig cystitt og for lokal partnerbehandling (penishode, første tredjedel av urinrøret).

12. Emulsjonen, fortrinnsvis sjampo ifølge et hvilket som helst av kravene 1 til 5, for behandling av hårtap.

13. Emulsjonen ifølge et hvilket som helst av kravene 3 til 5, for anvendelse i den topiske behandlingen av atopisk dermatitt.

14. Fremgangsmåte for fremstilling av en emulsjon ifølge et hvilket som helst av kravene 1 til 5, **karakterisert ved at** i fremstillingen av emulsjonen innføres NSAID via den vandige fasen.

15. Fremgangsmåte for fremstillingen av en emulsjon ifølge et hvilket som helst av kravene 2 til 5, **karakterisert ved at** NSAID inkorporeres som et fint krystallinsk eller mikronisert salt i emulsjonen som inneholder det soppdrepende midlet.
