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(54) Benevnelse **EMULSIONS FOR THE TREATMENT OF VAGINAL INFECTIONS**

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EMULSIONS FOR THE TREATMENT OF VAGINAL INFECTIONS

Description

The invention relates to emulsions for the treatment of mucous membrane infections, in particular inflammatory vaginal infections.

The WO 2007/131253 A2 relates to the use of an antifungal active ingredient and an epithelial cell or endothelial cell adhesion inhibitor for the production of a combination drug for the topical treatment of candidiasis selected from vulvovaginal candidiasis, oropharyngeal candidiasis (oral thrush), diaper rash (diaper thrush) and intertriginous eczema.

WO 02/0768648 A2 relates to pharmaceutical compositions for topical use containing an antimycotic, e.g.

B. terbinafine, and a second active ingredient, e.g.

B. Diclofenac or indomethacin. The compositions can be used to prevent or treat fungal infections, particularly those caused by dermatophytes.

US 5,686,089 A relates to pharmaceutical compositions for topical use which contain an antimicrobial active ingredient and a moisturizing component.

The compositions can e.g. B. are used for vaginal fungal infections.

Mendling et al. (

Mendling, Werner, et al. " Use of locally delivered dequalinium chloride in the treatment of vaginal infections: a review. "Archives of gynecology and obstetrics 293.3 (2016): 469-484) describes treatment options for vaginal infections with dequalinium chloride.

The present invention aims to provide improved NSAID preparations that are particularly suitable for the treatment of mucous membrane infections and inflammations.

In particular, it is an object of the invention to provide combination preparations of an antimycotic and an NSAID that are particularly suitable for the topical treatment

of vaginal and dermal fungal infections. Such emulsions should also be effective for stubborn fungal infections, which occur particularly in the vaginal area, and should be microbiologically and chemically stable.

Accordingly, the present invention relates to an emulsion, preferably in the form of an ointment or a cream, which comprises an aqueous phase and an oil phase (fatty phase), containing an antimycotic and an NSAID, characterized in that (a) the NSAID 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 percent by weight, ibuprofen in a concentration of 0.5 to 2.5 percent by weight, dexibuprofen in one concentration of 0.25 to 1.25 percent by weight, ketoprofen in a concentration of 0.25 to 1.25 percent by weight, mefenamic acid in a concentration of 0.5 to 4 percent by weight, or lornixocam in a concentration of 0.02 to 0.04 % by weight, the NSAID being in salt form; that (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 included in either the water or the oil phase and that (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 8.0, preferably for the treatment of dermal and vaginal fungal infections.

The invention also relates to said emulsion for use in the treatment of vaginal fungal infections, in particular chronic vaginal fungal infections, preferably where the treatment is a topical treatment.

The present invention further relates to methods for producing said emulsion according to independent claims 12-15.

The present invention provides improved preparations of the type described above.

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.

The preparations according to the invention enable the NSAIDs to be sufficiently effective when used in low concentrations - and therefore with few side effects. In the case of the combination preparations according to the invention, this not only enables a particularly good effectiveness of the antimycotic, 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.). In practice, this means that combinations of antimycotics 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.

The NSAIDs used according to the invention are selected from the group consisting of diclofenac, ibuprofen, dexibuprofen, ketoprofen, lornoxicam, mefenamic acid, naproxen and indomethacin.

The usual concentration in which diclofenac is used in medications approved for topical therapy is in the range of 1 to 2 % (10 mg/or 20 mg/g). According to the invention, diclofenac is used in a concentration of 0.1 % to 0.5 % (1 - 5 mg per g cream), preferably 0.2 % to 0.35 %. The usual concentration in which ibuprofen is used in medications approved for topical therapy is 5 % (50 mg/g cream/gel). According to 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 according to the invention”) in relation to the 'usual' doses can be seen in Table A.

Table A

Active substance	Individual dose	Daily maximum dose	Example	Individual dose	Daily maximum dose	Example	Concentration according to the invention
	oral/i.v.			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 2 %, 20 mg/g	0.2 - 0.5 wt. %
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 FT 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/100 g	0.5 - 2.5
							wt. %

The following NSAIDs are provided 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
Mefenanic acid	0.5-4	10 - 40 mg
Lornoxicam	0.02-0.04	0.4 to 8 mg

According to the invention, it has been shown that the treatment of fungal diseases, in particular candida mycoses, can be carried out particularly effectively with the help of a combination preparation of an antimycotic with a drug, which at the same time influences the adhesion of the microorganisms.

The drugs are advantageously applied topically because the site of action is reached immediately and at the same time there is minimal systemic exposure.

Such combinations of active ingredients are protected in the patents derived from WO 2007/131253 A2.

The subject of the invention are drug combinations that are particularly suitable for vaginal application, as well as their production and use.

By taking into account the special physiological and pathophysiological conditions in the vagina, both a special composition and a special manufacturing process prove to be particularly advantageous.

Observing specific parameters means that a particularly good therapeutic effect is achieved in the treatment of vaginal infections.

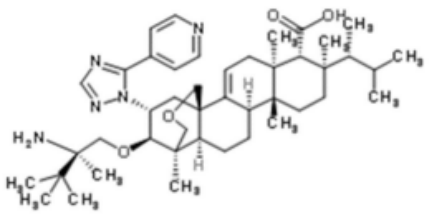
With regard to the anti-adhesion component, the present compound only concerns the group of NSAIDs (non-steroidal anti-inflammatory drugs), because drugs in this group, in addition to the anti-adhesive effect, which prevent adhesion, also have a pain-relieving and anti-inflammatory effect.

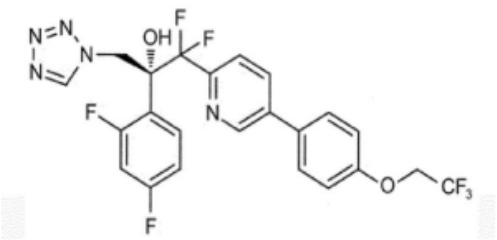
Both effects, especially the anti-inflammatory effect, are particularly welcome in recurrent forms of candida mycoses because they are associated with chronic inflammation and severe pain.

Intended NSAIDs are diclofenac, ibuprofen, dexibuprofen ketoprofen, mefenamic acid, naproxen, lornoxicam and indomethacin.

Preferred antimycotics are nystatin, ciclopirox or ciclopiroxolamine, or antimycotics 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), from Ibrexafungerp (SCY-078)..

Structural formula of Ibrexafungerp (SCY-078): Structural formula of Oteseconazole (VT-1161):





Surprisingly, it has been shown during use that the ratio of the proportions of the antimycotic and the NSAID is of particular importance in order to achieve an optimal effect.

In the combinations of an antifungal with an NSAID, the antifungal can be used in usual ways

Dosages are used (clotrimazole 1-10 %, ketoconazole 1-5 %, preferably 2 %, nystatin 100,000 IU/ml or g).

Since the NSAID exerts its effect in the same way on the pathogen in the vagina and on the vaginal epithelium, on the one hand, the topical application of the drug, in which it is applied directly to the site of action, is clearly superior to systemic use; on the other hand, the NSAID should therefore be used in Much lower doses are used than in usual systemic applications as painkillers.

When used vaginally, a therapeutic effect is achieved from just one tenth, preferably one fifth, of the active ingredient concentration that is used in common dermal NSAID formulations (in the case of diclofenac 200 to 500 mg/100g ointment).

The low active ingredient concentration is also particularly advantageous because the systemic absorption of the NSAID is negligible and there is no risk of systemic side effects.

At the same time, it must be noted that an overdose of the NSAID can easily occur when applied topically to mucous membranes (e.g.

B. is a cream with diclofenac: from 0.5 % it is painful and the rapid pain relief effect no longer occurs).

The respective instructions for use warn against using NSAID-containing creams (1-2 % diclofenac, 5 % ibuprofen) on the mucous membranes (e.g.

B. Instructions for use Voltaren Emulgel, Ibutop-Gel) because it leads to irritation of the mucous membranes, which counteracts the anti-inflammatory effect.

According to the invention, the NSAID should therefore not be used in an amount greater than 50 % of the usual lowest formulation for dermal applications.

Irritation can occur at this concentration.

The active ingredient concentration of the NSAID to be used is therefore preferably within a relatively small therapeutic window of 10 - 60, preferably 20 - 40 % of the value usual for topical formulations.

Accordingly, a particularly preferred emulsion according to the present invention contains diclofenac as an NSAID, with diclofenac being contained in a concentration range of 0.2 - 0.4 percent by weight of the emulsion.

It is even more preferred if diclofenac is present in a concentration range of 0.2 - 0.35 percent by weight of the emulsion.

A concentration range of 0.25 - 0.35 percent by weight is most preferred.

Higher proportions of lower alcohols, such as ethanol or isopropanol, (>10 %) increase the irritating effect and therefore counteract the pain-relieving and inflammatory effects.

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 dosage difficult and prevents a sufficient duration of action.

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.

Solutions, emulsions or gels with a high water and/or alcohol content are to be excluded as dosage forms according to the present invention because uncontrolled loss through leakage from the vagina is to be expected.

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 biofilms.

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.

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 fungus 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.

)

It has surprisingly been shown that chronic fungal infections of the vagina are often not caused by greater resistance of the pathogens, but rather by a simultaneous chronic inflammation of the vaginal epithelium initially caused by the infection.

In such chronic cases, a cure can only be achieved if the NSAID remains in the vagina.

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 2.55, 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 is present in the aqueous phase of the emulsion, 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.

The emulsion according to the invention is preferably suitable for vaginal application.

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 not more than 10 % by weight, in particular not more than 5 % by weight.

%, contains ethanol.

It is also preferred that the emulsion according to the invention contains not more than 15 % by weight, in particular not more than 7.5 % by weight.

%, contains isopropanol.

The combination of a lipophilic antimycotic, of the structural type of clotrimazole, with the weak acids of NSAIDs also means that the combination is only stable in a relatively narrow pH window.

Clotrimazole becomes unstable below a pH of 6, while NSAIDs can experience a decrease in chemical stability in an alkaline environment (in the case of diclofenac from pH 8.00 - 8.5).

The chemical stability is also influenced by the water:oil ratio and the proportion of alcoholic substances.

In combination medications made from azoles and the acidic NSAIDs, unfavorable stability requirements arise from the direct reactivity of the active ingredients.

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.

Since the introduction of the NSAID salt into an antifungal medication makes the pH more alkaline, the preservatives commonly used in comparable emulsions that only contain clotrimazole are not always sufficiently effective.

The semi-solid antifungal medicaments according to the present invention are therefore preferably protected against microbial attack with preservatives and antiseptics which are effective in the pH range of the emulsion.

In medications according to the invention which are used to treat a pure fungal infection, the antiseptic content is expediently kept low so as not to impair the normal vaginal flora.

The biofilms that form through the growth of fungi often contain not only fungi, but also other pathogenic microorganisms.

Such mixed infections can also be treated therapeutically simply by increasing the concentration of the antiseptic.

Therefore, the addition of a higher amount of an antiseptic to the claimed medication, sufficient for an acute antimicrobial effect, is a further subject of the invention.

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.

Among the bacterial microorganisms found in the vaginal biofilms are typical intestinal germs such as Enterobacter, E. coli and/or Klebsiella pneumoniae as well as anaerobes such as Gardnerella vaginalis and Prevotella spp. a special role.

These are probably also covered by the antiseptics claimed, but in proven cases of such an infection, it is advisable to use an antibiotic that is active against anaerobes instead of the antiseptic or in addition to it.

Therefore, the addition of an antibiotic that acts against anaerobic germs is a further subject of the invention.

Preferred antibiotics are phosphomycin, clindamycin, metronidazole, nitrofurantoin, nitrofurazone, nitrofurantoin, nifuratel, nifuroxacin, nitroxoline, trimethoprim, sulfadiazine and cotrimoxazole.

The decisive factor for breaking up the biofilm is the presence of an NSAID in the concentrations and conditions described in an emulsion in the composition and proportions described.

Mucosal surfaces offer ideal conditions for the formation of biofilms, which are particularly resistant to therapy.

By influencing the moist, physiologically acidic environment of the vagina, the vaginal microbiome makes a decisive contribution to the effectiveness of topically applied forms of medication, since the availability of the medication is pH-dependent.

These conditions are one of the reasons why the currently marketed topical antimycotics have only very limited success in the treatment of chronic vulvovaginitis, especially in the presence of mixed bacterial infections.

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.

Since biofilms also form in many dermal fungal infections, emulsions according to this invention are also very suitable for the treatment of mycoses, in particular Candida mycoses, but also infections with Malassezia.

Accordingly, the emulsions according to the invention are preferably used in the treatment of dermal and vaginal fungal infections, in particular for use in the topical treatment of vaginal fungal infections.

In general, the emulsions according to the invention can be used in the treatment of infectious diseases, in particular vaginal infections caused by Candida albicans or mixed vaginal infections caused by Candida albicans and bacteria such as Enterobacter, E. coli, Klebsiella pneumoniae, Gardnerella vaginalis, Prevotella spp.

A special embodiment of the present invention is used in the treatment of bacterial vaginoses.

A further special embodiment of the present invention is used in the treatment of dermal and mucosal fungal and mixed infections, preferably candida mycoses, in particular vulvovaginal candidiasis, oropharyngeal candidiasis (oral thrush), diaper rash (diaper thrush), anal eczema, intertriginous eczema, and malassezia mycoses (pityriasis versicolor).

Since inflammation of the epithelium can continue in the case of chronic infections, the present invention also includes emulsions that do not contain any antifungal or antimicrobial active ingredient.

Because of their reliable release of the NSAID, which results from the special composition, they are very suitable for use in the follow-up treatment of mucous membrane infections, especially vaginal inflammation.

Such semi-solid emulsions are also very suitable for treating chronic inflammations of other causes, especially inflammations of mucous membranes and the immediately adjacent tissues.

Examples of this arise in the follow-up treatment of chronic bladder infections, atrophic vaginitis or inflammation of the anal mucosa.

The emulsions according to the invention are therefore used in particular for the treatment of inflammation of the mucous membranes and mucous membranes, in particular vaginal infections and vaginal inflammations, especially chronic inflammations and infections.

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

Characters:

Figure 1: Clinical Phase II study.

Pain diaries of patients with recurrent vulvovaginal candidiasis (RVVC) who were treated with emulsions according to the invention containing different diclofenac-Na concentrations (CP1: 0.2 % by weight, CP2: 0.3 % by weight, CP3: 0.4 % by weight) or with a control composition were treated without Diclofenac-Na (“Comparator”).

The pain intensity was recorded by the patients at the time of recording on a pain scale of 0 to 10.

The diagram shows the mean values of the treatment groups over the course of treatment.

At CP 1 there is a rapid decrease in pain intensity. However, the healing curve flattens as soon as the daily dose is halved (from day 4).

CP 2 shows an optimal healing process.

Already on the 2nd

By day the pain level had fallen to 50 % of the initial value.

Examples:

Preliminary remark

Changes in the manufacturing process and in the percentage composition of an oil-water mixture according to basic formulation A showed surprising changes in clinical effectiveness beyond usual dose-response relationships.

The significantly improved or possibly reduced effectiveness can be derived from a particularly rapid onset of action (local pain relief) or a delay in the onset of action or the increase in pre-existing pain.

Example 1 - Basic recipe

Composition of the emulsion	
Clotrimazole	1.00
Diclofenac Na	0 .20
Sorbitan monostearate	2.00
Polysorbate 60	1.50
Cetylpalmitate	3.00
2-octyldodecanol	13.50
Cetostearyl alcohol	10.00
Benzyl alcohol	1.00
Purified water Ph.Eu.	67.80
Total	100.00
Ph	7.8

Table 1: Basic formulation A

If the concentration of the NSAID changes, it is replaced with purified water; the content of the lipid components remains the same, unless otherwise stated.

The clinical effectiveness in the following preparations is related to a clinically effective basic formulation A.

Example 2: Variations in the pH range and clinical effectiveness

Changes in preservatives are associated with changes in pH.

The examples mentioned are produced according to general working instructions 1.

The pH value is adjusted to achieve the optimum effectiveness of the respective preservative water.

The pH value has a significant influence on the locally bioavailable amount of active ingredient through the shift in the free active ingredient proportion compared to the portion present as a salt.

Depending on the pKa values of the non-steroidal anti-inflammatory drugs used, this results in a pH optimum of the combination preparations according to the invention according to the present invention.

The composition with a pH of 5.6 is a reference example.

Composition	Cone. wt. %	Cone. wt. %
Clotrimazole	1	1
Diclofenac Na	0.25	0.25
Sorbitan monostearate	2	2
Polysorbate 60	1.5	1.5
CetylpaImitate	3	3
2-octyldodecanol	13.5	13.5
Cetylstearyl alcohol	10	10
Phenoxyethanol	1	0
Bronopol	0.1	0
Sorbic acid	0	0.2
Buffer solution	0.2201	0.0874
Purified water Ph.Eur.	67.4299	68.4626
Total	100	100

Ph	7.5	5.6
Clin, efficacy	conforms	reduced
Microbiol. stability	conforms	conforms

Table 2: pH dependence of clinical efficacy

Example 3: Influence of the weight ratio of aqueous phase/oil

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

phase

Phase	Fat component / viscosity reduced		Basic formulations		Fat component / viscosity increased	
Clotrimazole (oil)	1	1.0	1.0	1.0	1.0	1.0
Diclofenac Na (water)	0.3	0.3	0.3	0.3	0.3	0.3
Sorbitan	2.0	2.0	2.0	2.0	2.0	2.0
monostearate (-)						
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 (oil)	1.0	1.0	1.0		1.0	1.0
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 phase / fat	2.7	3.1	2.4	2.4	2.0	1.7

Formulations with a ratio of aqueous to oil 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 scope of the invention and would therefore not be suitable in the context of 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.

Example 4: Variation of the non-steroidal anti-inflammatory drug

Instead of diclofenac, various other non-steroidal anti-inflammatory drugs were added to basic formulation A and their clinical effectiveness was examined.

Formulation no.	Non-steroidal antiphlogistic	Preparation	Preparation variant	Efficacy
1.1	Mefenamic acid	1 g/100 g	Basic formulation A + mefenamic acid micronised	conforms
1.2	Indometacin	0.15 g/100 g	Basic formulation A + indometacin	conforms
			miscronised	
1.3	Ibuprofen	1 g/100 g	Basic formulation A + ibuprofen hydrogel	conforms

1.4	Ibuprofen	0.5 g/100 g	Basic formulation A + ibuprofen hydrogel	conforms
1.5	Naproxen	1 g/100 g	Basic formulation A + naproxen micronised	conforms

Table 4: Variations of non-steroidal antiphlogistics

Example 5: Optimum concentration

Emulsions with different concentrations of diclofenac Na were prepared according to basic formulation A and tested for their clinical effectiveness.

	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

Table 5: Dependence of clinical efficacy on the concentration of NSAIDs

Example 6: Variation of preservatives and microbiological stability

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

Composition	wt. %	wt. %	wt. %	wt. %	wt. %
Clotrimazole	1	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	1.5
Cetylpalmitate	3	3	3	3	3
2-octyldodecanol	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 Ph.Eur.	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	conforms	conforms	conforms	conforms	reduced
Microbiol. stability	conforms	conforms	conforms	conforms	conforms

Table 6: Variants with different preservatives

Example 7:

Production of basic recipe A,

General manufacturing instructions 1:

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

Clotrimazole and then benzyl alcohol 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.

Components of the emulsion		
Clotrimazole	1.00	1.00
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
Cetylstearyl alcohol	10.00	10.00
Benzyl alcohol	1.00	1.00
Purified water Ph.Eur.	67.80	67.70
	100.00	100.00

Table 8: Formulations based on Formulation A, preparation instructions 1

The clinical effectiveness of the formulations in Table 8 is identical.

General manufacturing instructions 2

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

Clotrimazole is added to the clear melt while stirring at a temperature of 60 °C - 70 °C and melted.

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

After adding phenoxyethanol and, if necessary, propylene glycol, the aqueous solution is added to the oil phase at a temperature of 60 ° C - 70 ° C with stirring and homogenized.

With slow cooling and further homogenization of the initially formed w/o emulsion, a phase reversal to an o/w emulsion takes place, in which a hydrophilic, homogeneous cream is formed.

(Clin.

Results see Table 6)

Instead of dissolving in water, the NSAID can also be incorporated by stirring in an NSAID dissolved in a hydrogel or by stirring in the (micronized) NSAID as a solid during emulsion preparation.

Example 9: Production of basic formulation A by incorporating the NSAID into the oil phase

Creams with different concentrations of diclofenac Na were prepared according to basic recipe A according to general manufacturing instructions 2 and tested for their clinical effectiveness.

Purified water was exchanged for diclofenac Na; the content of the lipid components, the O/W emulsifier polysorbate 60 and the preservative benzyl alcohol was identical in the recipes.

General manufacturing instructions 3

The components sorbitan monostearate, polysorbate 60, cetyl palmitate, 2-octyldodecanol and cetostearyl alcohol are melted.

Benzyl alcohol is added to the clear melt while stirring (lipid phase).

Purified water is heated to boiling and 70 % of the required mass is added to the lipid phase while stirring according to the recipe (phase reversal and formation of an O/W preemulsion).

About 30 % of the preemulsion is removed from the kettle and clotrimazole and diclofenac sodium are dispersed in it.

The active ingredient-containing pre-emulsion is added to the kettle for the active-ingredient- free pre-emulsion and topped up to the final mass with purified water (remaining 30 %).

The cream is stirred until it reaches room temperature and then passed twice over the three-roll mill for homogenization (pH 6.99).

Composition		
Clotrimazole	2.00	2.00
Diclofenac Na	0.10	0.20
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
Benzyl alcohol	1.00	1.00
Purified water Ph.Eur.	66.90	66.80
	100.00	100.00
Clin. efficacy	reduced	reduced

Table 9: Formulations based on formulation A, preparation instructions 3.

From the examples according to manufacturing instructions 3, there is a significant influence of the manufacturing process, which must be designed in such a way that the non-steroidal anti-inflammatory agent is incorporated via the aqueous phase and is predominantly present in the aqueous phase.

Example 10: Production of basic recipe A

Production of basic formulation A with incorporation of a non-steroidal anti-inflammatory drug (Diclofenac Na) according to general manufacturing instructions 4: The components sorbitan monostearate, polysorbate 60, cetyl palmitate, 2-octyldodecanol and cetostearyl alcohol are melted.

Benzyl alcohol is added to the clear melt while stirring (lipid phase).

Purified water is heated to boiling and 70 % of the required mass is added to the lipid phase while stirring according to the recipe (phase reversal and formation of an O/W preemulsion).

About 30 % of the preemulsion is taken out of the kettle and clotrimazole is dispersed in it.

The active ingredient-containing pre-emulsion is added to the kettle for the active-ingredient- free pre-emulsion and topped up to the final mass with purified water (remaining 30 %).

The cream is stirred in several portions with the addition of micronized diclofenac sodium until it reaches room temperature and then passed twice over the three-roll mill for homogenization.

Example 11: Clinical Phase II study

The clinical effectiveness of emulsions according to the invention for the treatment of chronic vaginal infections was examined in a clinical phase II study.

According to General Manufacturing Instructions 1, three emulsions according to the invention were prepared with different concentrations of diclofenac Na.

An emulsion without NSAID was used as a control:

- Emulsion CP1: 0.2 wt. diclofenac Na
- Emulsion CP2: 0.3 wt. % diclofenac Na
- Emulsion CP3: 0.4 wt. diclofenac Na
- Emulsion Comparator: 0 wt. % diclofenac Na

31 patients with chronic recurrent vaginal infections (chronic recurrent vulvovaginal candidiasis, RVVC) were treated.

If there were corresponding clinical symptoms with at least moderate symptoms, the patients were included in the study after positive fungal detection.

In the first 3 days, 2.5 ml of cream was administered intravaginally twice daily using an applicator; in the following 3 days, 2.5 ml of cream was applied once daily.

A check-up was carried out after 7 - 10 days.

Each of the three emulsions according to the invention led to better healing success than the control that did not contain any NSAID.

Emulsion 2, containing 0.3 % by weight of diclofenac-Na, proved to be particularly advantageous. Complete clinical healing (complete freedom from symptoms upon check-up by the treating physician) was achieved in all patients in this group.

In the control group, healing was only achieved in 40 % of the patients.

The development of pain in the chronic patients (pain diary) was used as a further clinical parameter - in addition to the healing effect.

The pain intensity was recorded by the patients at the time of recording on a pain scale of 0 to 10.

The mean values of the treatment groups over the course of treatment are shown in Figure 1.

With the concentration of the antimycotic remaining the same, it was found that in the highest concentration of the NSAID (emulsion 3) the healing process was better compared to the control, but the reduction in pain intensity showed no significant difference to the control group.

The optimal concentration (emulsion 2), at which all patients were cured, quickly led to a complete reduction in pain.

The clear dose dependence was also evident in the patients with the lowest concentration (emulsion 1), in whom the pain decreased significantly until the twice-day dosage was changed to a once-day dosage, whereupon the healing process slowed down accordingly (see Figure 1).

Microbiological tests carried out in parallel showed that none of the patients were infected with resistant Candida strains, but the majority of RVVC patients did not respond to antifungal therapy.

PATENTKRAV

1. Emulsjon som har en vandig fase og en oljefase som inneholder et soppdrepende middel og et NSAID, **karakterisert ved at** (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; **ved at** (b) vektforholdet mellom vannfasen og oljefasen i emulsjonen er mellom verdiene 2,0 og 2,7, hvori vektforholdet beregnes som inkluderer tekstilene oppløst i fasene, hvori emulgatorene ikke inkluderes i noen av vannfasen eller oljefasen, og **ved at** (c) pH-en i emulsjonen ikke er mindre enn verdien 6,5 og ikke mer enn 8,5, fortrinnsvis i området 7,0 til 8,0.

2. Emulsjon ifølge krav 1, **karakterisert ved at** den er i form av en salve eller en krem.

3. Emulsjon ifølge krav 1 eller 2, **karakterisert ved at** emulsjonen er halvfast.

4. Emulsjon ifølge et hvilket som helst av kravene 1 til 3, **karakterisert ved at** det soppdrepende midlet er nystatin, ciklopiroks eller ciklopiroksolamin, eller et soppdrepende middel valgt fra gruppen av azoler, fortrinnsvis klotrimazol, flukonazol, mikonazol, itrakonazol, tiokonazol, vorikonazol, bifonazol, ekonazol, isokonazol, fentikonazol, sertakonazol, ketokonazol, posakonazol, quilsekonazol, otesekonazol (VT-1161) eller ibrexafungerp (SCY-078), spesielt klotrimazol.

5. Emulsjon ifølge et hvilket som helst av kravene 1 til 4, **karakterisert ved at** NSAID er diklofenak og dette er inneholdt i et konsentrasjonsområde på 0,2–0,4 vektprosent av emulsjonen.

6. Emulsjon ifølge et hvilket som helst av kravene 1 til 5, hvori et konserveringsmiddel aktivt i pH-området til emulsjonen er inneholdt, fortrinnsvis hvori konserveringsmidlet er fenoksyetanol eller propylenglykol eller en kombinasjon derav, eller dekvaliniumklorid.

7. Emulsjon ifølge et hvilket som helst av kravene 1 til 6, **karakterisert ved at** ytterligere et antibiotikum aktivt mot bakterielle bakterier er inneholdt, hvori antibiotikumet fortrinnsvis er fosfomycin, klindamycin, metronidazol, nitrofurantoin, nitrofurazon, nitrofurantoin, nifuratel, nifuroksacin, nitroksolin, trimetoprim, sulfadiazin eller kotrimoksazol.

8. Emulsjon ifølge et hvilket som helst av kravene 1 til 7, **karakterisert ved at** et antiseptisk middel videre er inneholdt, fortrinnsvis i en mengde tilstrekkelig for akutt antimikrobiell aktivitet, hvori det antiseptiske midlet fortrinnsvis er et kvaternært ammoniumsalt, 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.

9. Emulsjonen ifølge et hvilket som helst av kravene 1 til 8 for anvendelse i behandling av vaginale soppinfeksjoner, spesielt kroniske vaginale soppinfeksjoner, fortrinnsvis hvori behandlingen er en topisk behandling.

10. Emulsjonen for anvendelse ifølge krav 9, **karakterisert ved at** den vaginale soppinfeksjonen er en blandet vaginal infeksjon av Candida albicans og bakterier slik som Enterobacter, E.coli, Klebsiella pneumoniae, Gardnerella vaginalis, Prevotella spp.

11. Emulsjonen for anvendelse ifølge krav 9 eller 10, **karakterisert ved at** den vaginale soppinfeksjonen er en candidamykose, spesielt vulvovaginal candidiasis.

12. Fremgangsmåte for fremstillingen av en emulsjon ifølge et hvilket som helst av kravene 1 til 8, **karakterisert ved at** i fremstillingen av emulsjonen innføres NSAID via den vandige fasen.

13. Fremgangsmåte for fremstillingen av en emulsjon ifølge et hvilket som helst av kravene 1 til 8, **karakterisert ved at** NSAID inkorporeres som et fint krystallinsk eller mikronisert salt i emulsjonen som inneholder det soppdrepende midlet.

14. Fremgangsmåte for fremstillingen av en emulsjon ifølge et hvilket som helst av kravene 1 til 8, **karakterisert ved at** NSAID innføres i emulsjonen som inneholder det soppdrepende midlet via en hydrogel.

15. Fremgangsmåte for fremstillingen av en emulsjon ifølge krav 7 eller 8, hvori tilsetningen av tekstilene er slik at de tilveiebringer en terapeutisk effektiv antibakteriell effekt.

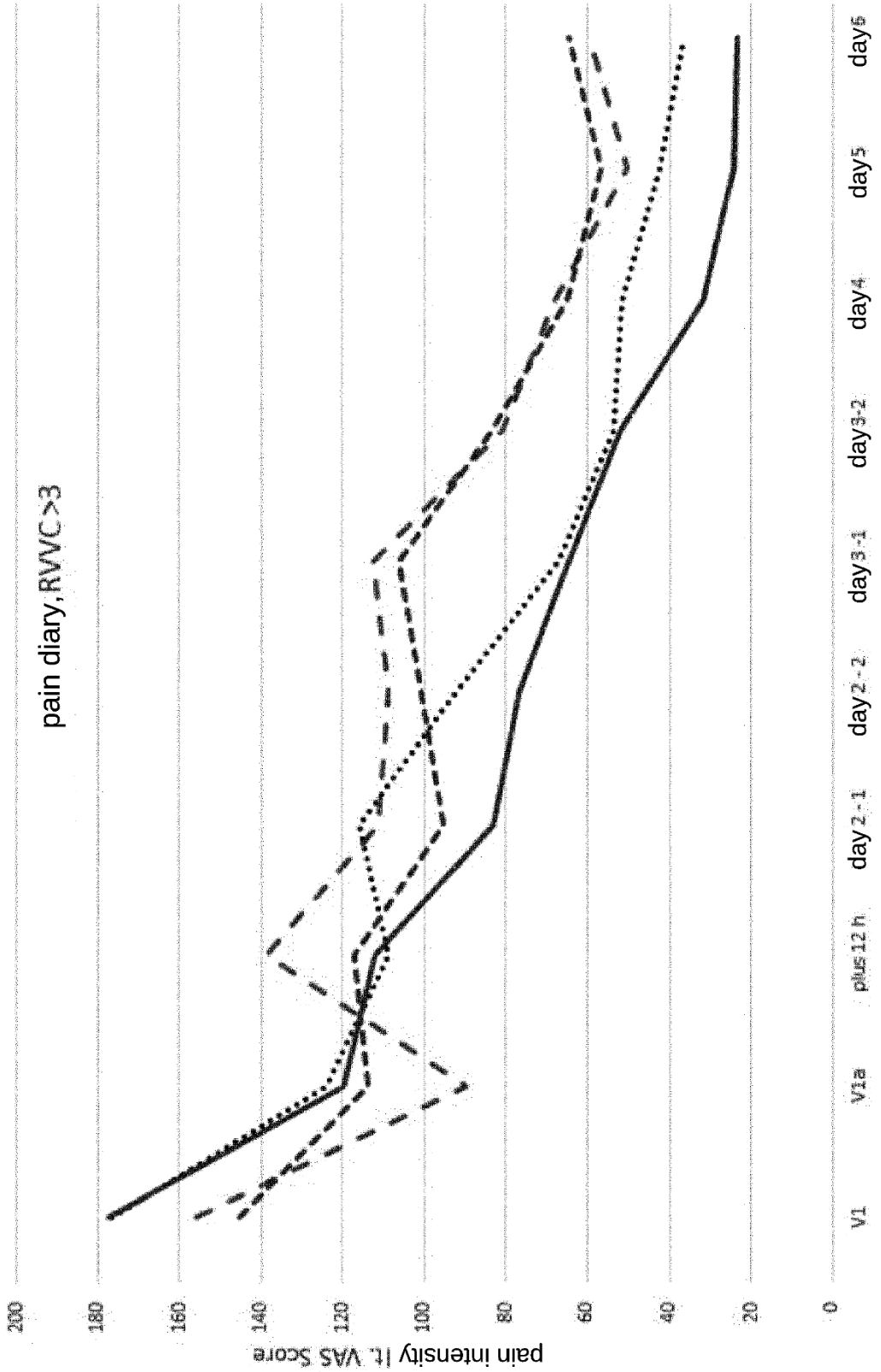

pain diary, RVVC>3
pain intensity lt. VAS Score
200
180
160
140
120
100
80
60
40
20
0
V1
V1a
plus 12 h
day 2 - 1
day 2 - 2
day 3 -1
day 3 -2
day 4
day 5
day 6
treatment days : V1: inclusion, V1a: 60 min after first dose
Comparator
CP 0.2
CP 0.3
CP 0.4

Fig. 1