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(54) Titre : COMPOSITIONS PHARMACEUTIQUES CONTENANT DES PRINCIPES ACTIFS ANTI-INFLAMMATOIRES ET UTILISATION DESDITES COMPOSITIONS

(54) Title: PHARMACEUTICAL FORMULATIONS CONTAINING ANTI-INFLAMMATORY ACTIVE INGREDIENTS AND THE USE OF SAID FORMULATIONS

(57) Abrégé/Abstract:
The invention relates to compositions in the form of microemulsion preconcentrates containing: (a) a mixture consisting of a middle-chained triglyceride and an omega 9 fatty acid and/or an omega 6 fatty acid; (b) a surface-active component containing a polyoxyethylene-type surface-active agent; (c) a therapeutic active ingredient which is hardly soluble in water but soluble in component (a) and/or (b) from the category of non-steroidal anti-inflammatory drugs (NSAIDS). Microemulsions are formed when said microemulsions preconcentrates come into contact with water or an aqueous medium, wherein the oil-in-water type microemulsions have an average particle size of less than 150 nm, preferably less than 100 nm. The microemulsion preconcentrates and microemulsions according to the invention are suitable for oral and topical administration of non-steroidal anti-inflammatory drugs.

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(54) Title: PHARMACEUTICAL FORMULATIONS CONTAINING ANTI-INFLAMMATORY ACTIVE INGREDIENTS AND THE USE OF SAID FORMULATIONS

(54) Bezeichnung: PHARMAZEUTISCHE FORMULIERUNGEN ENTHALTEND ENTZÜNDUNGSHEMMENDE WIRKSTOFFE UND DEREN VERWENDUNG

(57) Abstract: The invention relates to compositions in the form of microemulsion preconcentrates containing: (a) a mixture consisting of a middle-chained triglyceride and an omega 9 fatty acid and/or an omega 6 fatty acid; (b) a surface-active component containing a polyoxyethylene-type surface-active agent; (c) a therapeutic active ingredient which is hardly soluble in water but soluble in component (a) and/or (b) from the category of non-steroidal anti-inflammatory drugs (NSAIDS). Microemulsions are formed when said microemulsions preconcentrates come into contact with water or an aqueous medium, wherein the oil-in-water type microemulsions have an average particle size of less than 150 nm, preferably less than 100 nm. The microemulsion preconcentrates and microemulsions according to the invention are suitable for oral and topical administration of non-steroidal anti-inflammatory drugs.

(57) Zusammenfassung: Zusammensetzungen in Form von Mikroemulsion-Prekonzentraten enthaltend (a) eine Mischung bestehend aus einem mittelkettigen Triglycerid und einer Omage-9-Fettsäuren und/oder einer Omega-6-Fettsäure; (b) eine oberflächenaktive Komponente enthaltend ein Tensid vom Polyoxyethylen-Typ; (c) einen in Wasser schwerlöslichen, in Komponente (a) und/oder (b) jedoch löslichen therapeutischen Wirkstoff aus der Klasse der nichtsteroidalen Entzündungshemmer (NSAIDS). Bei Kontakt mit Wasser oder einem wässrigen Medium bilden diese Mikroemulsion-Prekonzentrate Mikroemulsionen, wobei diejenigen vom O/W-Typ eine durchschnittliche Teilgrösse unter 150 nm, vorzugsweise unter 100 nm aufweisen, die vorliegenden Mikroemulsion-Prekonzentrate und Mikroemulsionen ginen sich zu oralen und topischen Verabreichung von nicht steroidalen Entzündungshemmer.

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Pharmaceutical formulations containing antiinflammatory active ingredients and the use thereof

The present invention relates to novel formulations in the form of microemulsion preconcentrates and microemulsions which contain an active ingredient which is slightly soluble in water from the NSAIDs (non-steroidal antiinflammatory drugs) class, and to the use thereof.

Inflammations occur inter alia due to mechanical, thermal and chemical injuries, exposure to radiation, and pathogens (bacteria and viruses), and allergic or autoimmune reactions. The progress and spread of the inflammation are associated with responses by the body's defenses such as antigen-antibody activation and the release of so-called mediators of inflammation, such as, for example, kinins, prostaglandins, leukotrienes, histamine and lymphokines. This is where antiinflammatory drugs act, their activity deriving from intervention in the metabolism of the mediators. The effect of antiinflammatory drugs, which are employed primarily as antiarthritics and antirheumatics, is based for example on inhibition of prostaglandin biosynthesis. Non-steroidal antiinflammatory drugs (NSAIDs) which should be mentioned in particular are pyrazole derivatives, oxicams, and arylacetic and -propionic acids. The latter group includes inter alia indometacin, diclofenac, naproxen and ibuprofen.

Ibuprofen has been employed for more than 30 years in the therapy of rheumatism and pain. Besides the potent analgesic and antiinflammatory activity of ibuprofen, a positive emphasis should be placed in particular on the gastrointestinal tolerability - compared with other NSAIDs.

Ibuprofen is an active ingredient with a chirality

center and exists both in a dextrorotatory R-(-) and a levorotatory S-(+) form. The R form is subject to intensive enantiomeric inversion in the human body to give the analgesically active S-(+)-ibuprofen or dexibuprofen.

The active ingredient ibuprofen, which, as remarked above, is one of the arylpropionic acids, is employed as free acid in conventional dosage forms as coated or uncoated tablet. The weakly acidic ibuprofen with a pK_a of 4.4 is of low solubility in water and in the acidic medium of the gastric juice. Complete dissolution is achieved only in a slightly alkaline medium such as, for example, in the small intestine. The former is, however, the precondition for rapid absorption and thus also for a rapid onset of action. For this reason, conventional ibuprofen acid-containing coated and uncoated tablets show a relatively delayed onset of action. Maximum concentrations of active ingredient are not reached in the blood until 1-2 hours after oral intake.

Absorption can be speeded up by using buffered effervescent granules or tablets which are already dissolved for intake and thus ensure rapid transport from the stomach to the small intestine, which is the site of absorption. However, it is common to "effervescent" pharmaceutical forms that preparation is somewhat troublesome, because the medicament must always be dissolved in water - which is not available in every situation - and/or the taste sensation is negative.

It is an object of the present invention to develop a formulation with analgesic and antiinflammatory effect which combines the necessary rapid onset of action of the active ingredient formulation with a simple, pleasant and neutral-taste intake. It has surprisingly been found that formulations based on a microemulsion preconcentrate or a microemulsion significantly

increase the rate of absorption of ibuprofen after oral dosage compared with coated or uncoated tablets.

The microemulsion preconcentrate of the invention means a system which affords a microemulsion on contact with water or another aqueous medium such as gastrointestinal fluid, e.g. on addition to water. A microemulsion of this type comprises in the conventionally acknowledged sense a non-opaque or virtually non-opaque colloidal dispersion which comprises water and organic components with inclusion of lipophilic (i.e. hydrophobic) components.

Microemulsions in the sense of the invention can be identified by the fact that they have one or more of the following properties:

- They are formed spontaneously when their components are brought into contact with one another; thus, virtually no energy input is necessary for this, and the formation of such microemulsions therefore takes place without heating or use of a high shear force or another substantial mixing.
- They are virtually non-opaque, namely transparent or opalescent, when they are examined under an optical microscope. In their undisturbed state, they are optically isotropic, although an anisotropic structure can be detected on inspection for example using an X-ray technique.
- They contain a disperse or particulate (droplet) phase whose particles have a size of less than 200 nm, this being the origin of their optical transparency. The particles may be spherical or else have other structures; for example, they may be liquid crystals with lamellar, hexagonal or isotropic symmetries. In general, microemulsions comprise droplets or particles with a maximum dimension, for example a diameter, of less than 150 nm, usually about 10-100 nm.

The microemulsion preconcentrates of the invention mentioned at the outset are pharmaceutical systems which comprise an active ingredient from the NSAIDs class which is slightly soluble in water, and are able to form a microemulsion spontaneously or virtually spontaneously, i.e. with a negligible energy input, on being brought into contact with water or gastric and intestinal fluid.

The microemulsion preconcentrates of the invention are characterized in particular in that they comprise

(a) a mixture consisting of a medium chain triglyceride and of an omega-9 fatty acid and/or an omega-6 fatty acid, and
(b) a surface-active component comprising a surfactant of the polyoxyethylene type, and
(c) a therapeutic active ingredient from the NSAIDs class which is slightly soluble in water but soluble in component (a) and/or (b).

The ratio of the ingredients (a):(b):(c), (a):(C) or (b):(c) of the microemulsion preconcentrates of the invention must, of course, be chosen so that the active ingredient (c) is stably solubilized, i.e. precipitates must not occur over several weeks.

In contrast to prior art formulations, the microemulsion preconcentrates of the present invention are essentially free of water-miscible or water-soluble components despite high concentrations of active ingredient. These are, in particular, the components

- C_1-C_5-alkyl or tetrahydrofurfuryl diethers or partial ethers of low molecular weight mono- or polyoxy-C_2-C_{12}-alkanediols;
- 1,2-propylene glycol;
- lower alkanols;
- products of the esterification of polycarboxylic

acids with 2-10, in particular 3-5, carboxyl groups with C_1-C_{10} alcohols; and

- products of the esterification of polyols with 2-10, in particular 3-5, carboxyl groups with C_2-C_{11} carboxylic acids;

in particular essentially free of diethylene glycol monomethyl ether, glycofurol, 1,2-propylene glycol, triethyl citrate, tributy citrate, acetyl tributy citrate, acetyl triethyl citrate, triacetin, ethanol, polyethylene glycol, dimethyl isosorbitol and propylene carbonate.

The microemulsion preconcentrates of the invention can be produced by intimately mixing the individual ingredients with one another, where appropriate with heating. The microemulsion preconcentrates can also be produced by dissolving component (b) with stirring, where appropriate with heating, in component (a), and adding component (c) to the resulting solution with further stirring. It is particularly important in this connection that the component or the active ingredient (c) is soluble either in component (a) or component (b) or else in both components (a) and (b), and that the active ingredient always continues to be in dissolved form during production of the preconcentrate, i.e. the mixture of all three components (a), (b) and (c).

Suitable as component (a) are mixtures of a medium chain fatty acid triglyceride, expediently a fatty acid triglyceride in which the fatty acid residues have 4 to 18, preferably 6 to 18, C atoms, and of an omega-9 and/or an omega-6 fatty acid. These substances are immiscible with water or insoluble or practically insoluble in water and have no or virtually no surface-active function.

Preferred medium chain fatty acid triglycerides are caprylic/capric acid triglycerides as are known and

available commercially for example under the trade name Miglyol (Fiedler, Lexikon der Hilfsstoffe, 3rd edition, pages 808 to 809, 1989). These include, for example, the following products:

Miglyol 810, 812 and 818

This is a fractionated coconut oil which contains triglycerides of caprylic and capric acids and has a molecular weight of about 520 (Miglyol 810 and 812) or 510 (Miglyol 818). It has a fatty acid composition with a maximum of 2 percent (Miglyol 810) and 3 percent (Miglyol 812 and 818) C_6, and with about 65 to 75 percent (Miglyol 810), 50 to 65 percent (Miglyol 812) and 45 to 60 percent (Miglyol 818) C_8. C_{10} represents 25 to 35 percent of Miglyol, about 30 to 45 percent of Miglyol 812 and about 25 to 40 percent of Miglyol 818, and C_{12} a maximum of 2 percent (Miglyol 810), 5 percent (Miglyol 812) and 2 to 5 percent (Miglyol 818). Miglyol 818 additionally has a content of about 4 to 6 percent of $C_{18:2}$.

Also suitable are triglycerides of caprylic acid and capric acid which are known and obtainable under the trade name Myritol (Fiedler, Lexikon der Hilfsstoffe, 3rd edition, page 834, 1989). These include, for example, the product Myritol 813.

Further suitable products of this class are Captex 355, Captex 300, Captex 800, Capmul MCT, Neobee M5 and Mazol 1400.

Suitable omega-9 fatty acids are mainly those having 12-24, in particular 16-24, preferably 18-22, C atoms, for example oleic acid and eicosatrienoic acid. Oleic acid is particularly preferred.

Suitable omega-6 fatty acids are mainly those having 12-24, in particular 16-24, preferably 18-22, C atoms,

for example linoleic acid, gamma-linolenic acid, dihommo-gamma-linolenic acid and arachidonic acid. Linoleic acid is particularly preferred.

In a particularly preferred embodiment, a mixture consisting of a caprylic/capric acid triglyceride, oleic acid and/or linoleic acid is used as component (a).

Component (b), the surface-active component comprising a surfactant of the polyoxyethylene type, may be a hydrophilic surface-active agent or a lipophilic surface-active agent, but mixtures of such agents are also suitable.

Examples of such surfactants are the following:

- Products of the reaction of natural or hydrogenated vegetable oils and ethylene glycol, namely polyoxyethylene glycolated natural or hydrogenated vegetable oils such as polyoxyethylene glycolated natural or hydrogenated castor oils. The various surfactants known and obtainable under the name Cremophor (Fiedler, Lexikon der Hilfsstoffe, 3rd edition, pages 326 to 327, 1989) are particularly suitable, especially the products with the names Cremophor RH 40, Cremophor RH 60 and Cremophor EL. Also suitable as such products are the various surfactants known and obtained under the name Nikkol, for example Nikkol HCO-60.
- Polyoxyethylene sorbitan fatty acid esters, for example the mono- and trilauryl esters, the mono- and tripalmityl esters, the mono- and tristearyl esters and the mono- and trioleyl esters, as are known and obtainable under the name Tween (Fiedler, Lexikon der Hilfsstoffe, 3rd edition, pages 1300 to 1304, 1989), for example the products

Tween 20: polyoxyethylene 20 sorbitan monolaurate,

Tween 40: polyoxyethylene 20 sorbitan monopalmitate,
Tween 60: polyoxyethylene 20 sorbitan monostearate,
Tween 80: polyoxyethylene 20 sorbitan monooleate,
Tween 65: polyoxyethylene 20 sorbitan tristearate,
Tween 85: polyoxyethylene 20 sorbitan trioleate,
Tween 21: polyoxyethylene 4 sorbitan monolaurate,
Tween 61: polyoxyethylene 4 sorbitan monostearate and
Tween 81: polyoxyethylene 4 sorbitan monooleate.

Of this class of compounds, Tween 80 is particularly preferred.

- Polyoxyethylene fatty acid esters, for example the polyoxyethylene stearic esters known and obtainable commercially under the name Myrj (Fiedler, Lexikon der Hilfsstoffe, 3rd edition, page 834, 1989), especially the product Myrj 52, and the polyoxyethylene fatty acid esters known and obtainable under the name Cetiol HE (Fiedler, Lexikon der Hilfsstoffe, 3rd edition, page 284, 1989).
- Copolymers of polyoxyethylene and polyoxypropylene like those known and obtainable for example under the names Pluronic and Emkalyx (Fiedler, Lexikon der Hilfsstoffe, 3rd edition, pages 956 to 958, 1989), especially the product Pluronic F68.
- Block copolymers of polyoxyethylene and polyoxypropylene like those known and obtainable for example under the name Poloxamer (Fiedler, Lexikon der Hilfsstoffe, 3rd edition, page 959, 1989), especially the product Poloxamer 188.
- Polyethoxylated vitamin E derivatives, especially the product Vitamin E TPGS (d-alpha tocoperyl polyethylene glycol 1000 succinate, Eastman).

- Polyethoxylated hydroxy fatty acid esters, especially the product Solutol HS 15 (polyoxyethylene 660 hydroxystearate, BASF).
- Products of the transesterification of natural

vegetable oil glycerides and polyethylene polyols. These include products of the transesterification of various, for example non-hydrogenated, vegetable oils such as corn oil, pumpkinseed oil, almond oil, peanut oil, olive oil and palm oil, and of mixtures thereof with polyethylene glycols, especially with those having an average molecular weight of 200-800. Various transesterification products of this type are known and obtainable under the name Labrafil (Fiedler, Lexikon der Hilfsstoffe, 3rd edition, page 707, 1989); of these, the products Labrafil M 1944 CS and Labrafil M 2130 CS are particularly suitable.

- Ethylene oxide adducts of sterols and derivatives thereof, for example of cholesterol and derivatives thereof, such as products derived from sitosterol, campesterol, or stigmasterol, for example from soybean sterols and derivatives thereof (Fiedler, Lexikon der Hilfsstoffe, 3rd edition, pages 554 and 555, 1989), as are known and obtainable under the names Generol, especially the products Generol 122 E5, 122 E10 and 122 E25.

The microemulsion preconcentrates of the invention include both systems which comprise a single surface-active agent, and systems which comprise a mixture of two or more surface-active agents, e.g. Tween 80 + Cremophor RH 40, Tween 80 + Cremophor RH 40 + Vitamin E TPGS etc.

A surface-active component preferably used according to the invention comprises a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene glycolated natural or hydrogenated vegetable oil or mixtures thereof.

Component ©, the therapeutic active ingredient from the NSAIDs class which is slightly soluble in water but

soluble in component (a) and/or (b), is preferably ibuprofen, dexibuprofen or naproxen; however, it is also possible to use another suitable NSAIDs, where appropriate in combination with antioxidants such as, for example, vitamin E. Examples of other suitable NSAIDs are: anthranilic acid derivatives, acetic acid derivatives, oxicams, propionic acid derivatives, pyrazalone derivatives, salicylic acid derivatives and selective COX-2 inhibitors (cf. Arzneimittel Kompendium der Schweiz 2001, Documed AG, CH-4010 Basle, editors, Jürg Morant and Hans Ruppaner).

The microemulsion preconcentrates of the invention may also comprise further substances such as, for example, antioxidants, thickeners, fragrances and/or flavorings, colors, etc.

The microemulsion preconcentrates of the invention are primarily intended for oral use. Preference is given in this connection to the so-called unit dose form, i.e. the microemulsion preconcentrate is accommodated in a shaped article such as a soft or hard capsule, e.g. made of gelatin or starch. When the active ingredient-containing premicroemulsion is released there is spontaneous formation of a microemulsion in conjunction with gastrointestinal fluid. The compositions of the invention prove to be particularly suitable for oral administration in the form of unit dose forms also because addition of volatile organic solvents, especially of the frequently used ethanol, is unnecessary. When said solvents are employed, evaporation thereof through the outer wall of the shaped article, especially of the soft or hard gelatin capsule, has an adverse effect on storability, and the active ingredient crystallizes out. The occurrence of these adverse effects must be prevented by elaborate measures during packaging and storage.

The novel compositions can also be processed further to

effervescent tablets or as granules.

The microemulsion preconcentrates of the invention expediently comprise from 5 to 45, preferably 20 to 40, percent by weight of a therapeutic active ingredient of the NSAIDs class (component (c)) which is slightly soluble in water but soluble in component (a) and/or (b), from 5 to 60, preferably 15 to 40 percent by weight, of a mixture consisting of a medium chain triglyceride and an omega-9 fatty acid and/or an omega-6 fatty acid (component (a)) and from 20 to 90, preferably from 25 to 65, percent by weight of the surface-active component (b).

The present invention also makes it possible to provide pharmaceutical compositions which comprise a therapeutic active ingredient from the NSAIDs class which is slightly soluble in water but soluble in component (a) and/or (b), and which themselves represent microemulsions; the active ingredient is stably solubilized in these microemulsions, with no precipitates being observed over several weeks. For oral administration it is possible for microemulsions, which are obtained for example by diluting the microemulsion preconcentrates of the invention with water or an aqueous medium, to be used directly as drinkable formulations. If topical or parenteral use is intended, then compositions, in which further excipients may be present, likewise contain water, resulting in an aqueous microemulsion in the form of a spray, gel, lotion, cream, plaster, roll-on, solution for injection, solution for infusion or the like. Such pharmaceutical compositions in the form of microemulsions are likewise novel, and the present invention relates thereto.

The microemulsions of the invention are characterized in particular in that they can be obtained by mixing a microemulsion preconcentrate of the compositions

described above with water or an aqueous medium. When the preconcentrate is mixed with water or gastric and intestinal fluid there is spontaneous or virtually spontaneous, i.e. with negligible energy input, formation of a microemulsion.

Depending on the amount of water present, the microemulsions are W/O microemulsions, bicontinuous microemulsions or O/W microemulsions.

The O/W type (oil-in-water) microemulsions of the invention show stability properties like those described hereinbefore in connection with microemulsions, i.e. in particular that the active ingredient is stably solubilized in these microemulsions, and no precipitate is observable over several weeks. The particle size of these microemulsions is less than 150 nm, preferably less than 100 nm.

The compositions of the invention are explained further by the following examples. Examples 1.1 to 1.5 show the preparation of compositions suitable, for example, for the therapy of pain and rheumatism. Examples 2.1 to 2.4 show the preparation of compositions suitable, for example, for the topical treatment of rheumatism. Example 3.1 shows the preparation of a composition for parenteral use, which is suitable for example for subcutaneous or intramuscular treatment of inflammatory pain. In example 4, the pharmacokinetic parameters (c_{max}, t_{max}, AUC) of a formulation of the invention which was administered orally in soft gelatin capsules are measured and compared with those of coated tablets.

The examples are described with particular reference to ibuprofen and dexibuprofen. However, comparable compositions can be prepared through use of other suitable NSAIDs.

Example 1: Preparation of oral ibuprofen or dexibuprofen dosage forms of the microemulsion preconcentrate type

Example 1.1

Ibuprofen (c1)	20.00%
Miglyol 812 (a1)	20.00%
Oleic acid (a2)	5.00%
Tween 80 (b1)	37.50%
Cremophor RH 40 (b2)	12.50%
Vitamin E acetate (c2)	5.00%

The ibuprofen is dissolved by stirring at room temperature, where appropriate with gentle heating, in components (a1), (a2), (b1), (b2) and (c2). The microemulsion preconcentrate which is formed is used to fill a soft or hard capsule made of gelatin or starch.

An alternative possibility is to use the microemulsion preconcentrate to fill a dispenser. In this case, the patient prepares an oral drinkable solution of the O/W microemulsion type from the microemulsion preconcentrate by appropriate dilution with water or another aqueous liquid.

The following compositions can also be prepared in an analogous manner and be used to fill capsules or dispensers.

Example 1.2

Ibuprofen (c)	20.00%
Miglyol 812 (a1)	25.00%
Oleic acid (a2)	5.00%
Tween 80 (b1)	37.50%
Cremophor RH 40 (b2)	12.50%

Example 1.3

Ibuprofen (c1)	20.00%
Miglyol 812 (a1)	20.00%

Oleic acid (a2)	5.00%
Tween 80 (b1)	37.50%
Cremophor EL (b2)	12.50%
Vitamin E acetate (c2)	5.00%

Example 1.4

Ibuprofen (c)	10.00%
Miglyol 812 (a1)	35.00%
Oleic acid (a2)	5.00%
Tween 80 (b1)	37.50%
Cremophor EL (b2)	12.50%

Example 1.5

Dexibuprofen (c1)	30.00%
Miglyol 812 (a1)	17.50%
Oleic acid (a2)	4.40%
Tween 80 (b1)	32.80%
Cremophor RH 40 (b2)	10.90%
Vitamin E acetate (c2)	4.40%

Dilution, e.g. 1:100, of compositions of the above type with simulated gastric or intestinal fluid results in microemulsions having the following particle sizes in the case of representative examples (cf. table 1):

Table 1

Composition of microemulsion preconcentrate	Particle diameter[1)] of the O/W microemulsion	
	Gastric fluid [nm]	Intestinal fluid [nm]
Example 1.1	17.9 ± 7.2	18.6 ± 6.0
Example 1.2	25.6 ± 10.1	18.8 ± 6.5
Example 1.3	20.4 ± 8.2	19.7 ± 4.7
Example 1.4	25.0 ± 6.7[2)]	-
Example 1.5	56.3 ± 33.2	18.3 ± 6.6

1) The particle diameters and particle size distributions were determined by dynamic laser light scattering measurements (instrument: Nicomp 370 submicron particle sizer, evaluation: volume

weighting).

2) These ibuprofen microemulsions were formed by a 1:10 dilution of the microemulsion preconcentrate with 10 mM phosphate buffer of pH 6 at room temperature.

It is evident from the table below that the microemulsion formation by the microemulsion preconcentrates remains unchanged after being used to fill and being stored in soft gelatin capsules (SGC).

Table 2

Microemulsion preconcentrate of example 1.1 Batch 201111	Particle diameter of the ibuprofen microemulsion[1)]	
	Gastric fluid [nm]	Intestinal fluid [nm]
Before SGC filling	17.9 ± 7.2	18.6 ± 6.0
After SGC filling	19.8 ± 7.0	20.6 ± 5.3
After storage in SGC at 25°C and 60% RH for 1 month	16.9 ± 6.3	20.0 ± 5.4
After storage in SGC at 40°C and 75% RH for 1 month	17.7 ± 6.8	19.8 ± 5.5
After storage in SGC at 25°C and 60% RH for 3 months	13.6 ± 6.9	18.4 ± 5.9

1) The ibuprofen microemulsions were formed by 1:100 dilution of the microemulsion preconcentrates with simulated gastric and intestinal fluids at 37°C. Microemulsion preconcentrates used to fill SGC were removed from the SGC for the microemulsion formation. The particle diameters and particle size distributions of the resulting ibuprofen microemulsions were determined by dynamic laser light scattering measurements (instrument: Nicomp 370 submicron particle sizer, evaluation: volume weighting).

Example 2: Preparation of ibuprofen forms of the microemulsion type which can be used topically

The microemulsion preconcentrates described in example 1.1 to 1.5 are used hereinafter as basis for preparing sprays, gels, creams and other topical dosage forms by combining them with further additives such as water, thickeners and the like.

Example 2.1: Ibuprofen 1.0% microemulsion pump spray

Microemulsion preconcentrate of example 1.4		10.00%
Na_2 EDTA		0.05%
Benzalkonium chloride		0.10%
10 mM phosphate buffer pH 6	ad	100.00%

The microemulsion preconcentrate is added to the phosphate buffer comprising Na_2 EDTA and benzalkonium chloride while stirring at room temperature. The resulting ibuprofen O/W microemulsion is used to fill a pump spray. Compressed gas or aerosol spray are also suitable in place of the pump spray.

Example 2.2: Ibuprofen 1.0% hydrogel

Microemulsion preconcentrate of example 1.4		10.00%
Na_2 EDTA		0.05%
Benzalkonium chloride		0.10%
Sodium carboxymethylcellulose 450 cP		3.50%
10 mM phosphate buffer pH 6	ad	100.00%

The microemulsion preconcentrate is added with stirring to the phosphate buffer containing Na_2 EDTA and benzalkonium chloride. The resulting ibuprofen O/W microemulsion is further processed with the sodium carboxymethylcellulose to give the hydrogel, and packaged, in a conventional way.

Example 2.3: Ibuprofen 1.0% O/W emulsion

Microemulsion preconcentrate of example 1.4	10.000%
Isopropyl palmitate	8.000%

	Glyceryl stearate		7.000%
	Glycerol		5.000%
	Steareth-2 + PEG-8 distearate		4.000%
	Liquid paraffin		4.000%
	Microcrystalline wax		4.000%
	Steareth-21		3.000%
	Dimethicone		1.000%
	Suttocide A		0.250%
	Lanolin alcohol		0.100%
	Sodium hydroxide		0.005%
	Water	ad	100.000%

The microemulsion preconcentrate is added with stirring to the aqueous phase at room temperature. The resulting ibuprofen O/W microemulsion is further processed with the oil phase to give the O/W emulsion, and packaged, in a conventional way.

Example 2.4: Ibuprofen 1.0% microemulsion roll-on

Microemulsion preconcentrate of example 1.4			10.00%
Na_2 EDTA			0.05%
Benzalkonium chloride			0.10%
10 mM phosphate buffer pH 6		ad	100.00%

The microemulsion preconcentrate is added with stirring to the phosphate buffer, containing Na_2 EDTA and benzalkonium chloride, at room temperature. The resulting ibuprofen O/W microemulsion is used to fill a roll-on.

Example 3: Production of microemulsion-type ibuprofen forms which can be used parenterally

The microemulsion preconcentrates described in example 1.1 to 1.5 can serve as basis for producing injection solutions by diluting them appropriately with further additives such as physiological saline or 5% strength glucose solution and the like.

Example 3.1: Ibuprofen 0.1% injection solution

Microemulsion preconcentrate of example 1.4		1.00%
5% strength glucose solution	ad	100.00%

The microemulsion preconcentrate is added with stirring to the glucose solution at room temperature. The resulting ibuprofen O/W microemulsion is sterilized by 0.2 µm filtration and used to fill conventional sterile containers.

Example 4: Pharmacokinetics of the ibuprofen microemulsion preconcentrate of example 1.1 after oral administration in soft capsules made of gelatin and starch

The aim of this study was to establish the pharmacokinetics of a single oral dose of 2 × 200 mg ibuprofen administered in the form of the microemulsion preconcentrate of example 1.1 in soft capsules made of gelatin and starch.

Preparations

A Soft gelatin capsules containing the ibuprofen microemulsion preconcentrate of example 1.1
Active ingredient content: 200 mg of ibuprofen per capsule

B Starch capsules containing the ibuprofen microemulsion preconcentrate of example 1.1
Active ingredient content: 200 mg of ibuprofen per capsule

Dosage: 2 × 200 mg of ibuprofen, orally in 2 capsules

Intake
In the morning, fasting

Subjects: n = 4

Parameter measured: plasma level of ibuprofen [µm/ml plasma]

Results

It is evident from the changes in the plasma levels of test products A and B of the invention that the maximum ibuprofen plasma levels of 45.3 and 49.0 µm/ml are reached after 0.68 and 0.63 hours (cf. figure 1). Test products A and B thus show distinct differences in relation to the rate of rise in level and to the maximum reached in comparison with commercially available 200 mg ibuprofen coated tablets (cf. table 3).

Table 3

Parameter	Test product A	Test product B	200 mg ibuprofen coated tablets[1)]
C_{max} [µg/ml]	45.3	49.0	32.0
T_{max} [h]	0.66	0.63	1.30
AUC_{inf} [µg/ml/h]	123	121	108.0

1) Literature data from a study carried out analogously

Claims

1. A composition in the form of a microemulsion preconcentrate comprising
   (a) a mixture consisting of a triglyceride, in particular a medium chain triglyceride, and of an omega-9 fatty acid and/or an omega-6 fatty acid; and
   (b) a surface-active component comprising a surfactant, in particular of the polyoxyethylene type,
   (c) an active ingredient selected from the class of non-steroidal antiinflammatory drugs, where the active ingredient is soluble in (a) and/or (b).

2. A composition as claimed in claim 1, where the active ingredient is selected from the group consisting of heteroaryl- and arylacetic and -propionic acid and from the group of COX-2 inhibitors, in particular comprising indometacin, diclofenac, naproxen, ibuprofen, dexibuprofen, and celeoxib and rofaecoxib.

3. A composition as claimed in claim 1, characterized in that the active ingredient is ibuprofen.

4. A composition as claimed in claim 1, characterized in that the active ingredient is dexibuprofen.

5. A composition as claimed in claim 1, characterized in that the active ingredient is naproxen.

6. A composition in the form of a microemulsion obtainable by mixing a microemulsion preconcentrate as claimed in any of claims 1 to 5 with water or an aqueous medium.

7. A composition as claimed in any of claims 1 to 6, comprising additional components which do not belong to the following groups of substances:
   - C_1-C_5-alkyl or tetrahydrofurfuryl diethers or partial ethers of low molecular weight mono- or polyoxy-C_2-C_{12}-alkanediols;
   - 1,2-propylene glycol;
   - lower alkanols;
   - products of the esterification of poly-carboxylic acids with 2-10, in particular 3-5, carboxyl groups with C_1-C_{10} alcohols; and
   - products of the esterification of polyols with 2-10, in particular 3-5, carboxyl groups with C_2-C_{11} carboxylic acids.

8. A composition as claimed in any of claims 1 to 7, characterized in that the fatty acid residues of the medium chain triglyceride have 4-18, preferably 6-18, C atoms.

9. A composition as claimed in claim 8, characterized in that the medium chain triglyceride is a caprylic/capric acid triglyceride.

10. A composition as claimed in any of claims 1 to 9, characterized in that the omega-9 fatty acid and/or the omega-6 fatty acid has 12-24, in particular 16-24, preferably 18-22, C atoms.

11. A composition as claimed in any of claims 1 to 10, characterized in that the omega-9 fatty acid is oleic acid.

12. A composition as claimed in either of claims 1 or 10, characterized in that the omega-6 fatty acid is linoleic acid.

13. A composition as claimed in any of claims 1 to 12, characterized in that it comprises as component

(a) a mixture of a caprylic/capric acid triglyceride, oleic acid and/or linoleic acid.

14. A composition as claimed in any of claims 1 to 13, characterized in that the ratio of the amounts of omega-9 fatty acid and/or omega-6 fatty acid to the medium chain triglyceride is from 1:1 to 1:200, preferably from 1:2 to 1:20.

15. A composition as claimed in any of claims 1 to 14, characterized in that the surface-active component (b) comprises a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene glycolated natural or hydrogenated vegetable oil or mixtures thereof.

16. A composition as claimed in any of claims 1 to 5 and 7 to 15, characterized in that component (a) is present in an amount of from 20 to 70 percent by weight based on the total weight of the composition.

17. A composition as claimed in any of claims 1 to 5 and 7 to 16, characterized in that the surface-active component (b) is present in an amount of from 20 to 80 percent by weight based on the total weight of the composition.

18. A composition as claimed in any of claims 6 to 17, characterized in that it is an O/W microemulsion with an average particle size below 150 nm, preferably below 100 nm.

19. A shaped article for oral administration comprising an active ingredient from the class of non-steroidal antiinflammatory drugs in a composition as claimed in any of claims 1 to 18 for administering the active ingredient.

20. A shaped article as claimed in claim 19, charac-

terized in that it comprises a biopolymer, in particular gelatin.

21. A composition comprising an active ingredient from the class of non-steroidal antiinflammatory drugs as claimed in any of claims 1 to 18 for topical, in particular cutaneous, administration.