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(54) Title: PHARMACEUTICAL CONTAINING 3-(3-DIMETHYLAMINO-1-ETHYL-2-METHYL-PROPYL)PHENOL AND PROVIDING DELAYED RELEASE OF THE ACTIVE INGREDIENT

(54) Bezeichnung: 3-(3-DIMETHYLAMINO-1-ETHYL-2-METHYL-PROPYL)PHENOL ENTHALTENDES ARZNEIMITTEL MIT VERZÖGERTER WIRKSTOFFFREISETZUNG

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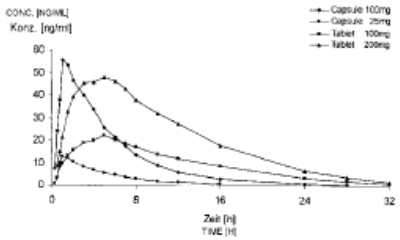

(57) Abstract: The invention relates to a pharmaceutical formulation which is characterised by delayed release of the active ingredient. Said formulation contains 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol or one of its pharmaceutically acceptable salts in a matrix with delayed release of the active ingredient. Said matrix contains between 1 and 80 wt. % of at least one hydrophilic or hydrophobic polymer as a pharmaceutically acceptable matrix forming agent and exhibits, in vitro, the following dissolution speed: between 3 and 35 wt. % (in relation to 100 wt. % of active ingredient) of 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol is released after half an hour, between 5 and 50 wt. % of 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol is released after one hour, between 10 and 75 wt. % of 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol is released after two hours, between 15 and 82 wt. % of 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol is released after three hours, between 30 and 97 wt. % of 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol is released after six hours, more than 50 wt. % of 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol is released after twelve hours, more than 70 wt. % of 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol is released after eighteen hours, and more than 80 wt. % of 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol is released after twenty-four hours.

(57) Zusammenfassung: Die Erfindung betrifft eine pharmazeutische Formulierung mit verzögerter Wirkstofffreisetzung, die 3-(3-Dimethylamino-1-ethyl-2-methyl propyl)phenol oder eines seiner pharmzeutisch akzeptablen Salze in einer Matrix enthält, mit verzögerter Wirkstofffreisetzung enthält, wobei die Matrix 1 bis 80 Gew.-% eines oder mehrerer hydrophiler oder hydrophober Polymere als pharmazeutisch annehmbaren Matrixbildner enthält

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und in vitro die folgende Auflösungsgeschwindigkeit aufweist: 3-35 Gew.-% bezogen auf 100 Gew.-% Wirkstoff) 3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)phenol nach 0,5 Stunden freigesetzt, 5-50 Gew.-% 3-(3Dimethylamino-1-ethyl-2-methyl-propyl)phenol nach 1 Stunde freigesetzt, 10-75 Gew.-% 3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)phenol nach 2 Stunden freigesetzt, 15-82 Gew.-% 3-(3-Dimethylamino-1-ethyl-2-methyl-15 propyl)phenol nach 3 Stunden freigesetzt, 30-97 Gew.-% 3-(3Dimethylamino-1-ethyl-2-methyl-propyl) phenol nach 6 Stunden freigesetzt, mehr als 50 Gew.-% 3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)phenol nach 12 Stunden freigesetzt, mehr als 70 Gew.-% 3-(3-Dimethylamino-1ethyl-2-methyl-propyl)phenol nach 18 Stunden freigesetzt, mehr als 80 20 Gew.-% 3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)phenol nach 24 Stunden freigesetzt.

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(GRA 3066)

Pharmaceutical containing 3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)phenol and providing delayed release of the active ingredient

The invention relates to a pharmaceutical that provides delayed release of the active ingredient and that contains 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol or one of its pharmaceutically acceptable salts in a matrix.

3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)phenol is known from EP 0 693 475 B1 as an analgesic pharmaceutical and may be applied orally. The normal formulations for oral administration of 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol lead to a rapid release of the active ingredient in the gastrointestinal tract so that its analgesic effect begins rapidly. Similarly, its effect wears off rapidly. Thus treating severe chronic pain with 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol in the past has required administration of the pharmaceutical at relatively short intervals, for instance four to six times daily, to ensure an adequate concentration of the active ingredient in the patient's blood. The necessity of frequent dosing, however, easily leads to errors in taking it and to undesired fluctuation in concentrations in the plasma, which detracts from patient compliance and therapeutic benefit, especially when treating chronic pain. A pharmaceutical dosage form having delayed release (delayed release formulation) for oral application of the active ingredient 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol is therefore desirable.

In the prior art, in general delayed release formulations are known for a great number of different active ingredients. Common delayed release forms are inter alia coated forms and matrix forms.

In the case of coated delayed release forms, such as are described in particular in DE 36 25 458 A1, the core of a pharmaceutical composition, which core includes an active ingredient, is provided with a coating that is made of one or a plurality of hydrophilic and/or hydrophobic polymers and that delays the release of the active ingredient.

In matrix delayed release formulations, the active ingredient is contained in a matrix that is formed from one or a plurality of carrier materials and that controls the release of the active ingredient. Thus, for instance, DE 33 09 516 A1 discloses a method for producing matrix formulations having hydroxypropyl methylcellulose (HPMC) as the carrier material and some delayed release of the active ingredient, wherein the carrier material makes up no more than one-third of the weight of the formulation and comprises at least one hydroxypropyl methylcellulose that has a methoxy content of 16-24 wt.%, a hydroxypropyl content of
4-32 wt.%, and a numerical average molecular weight of at least 50,000. The formulations disclosed in DE 33 09 516 A1 include HPMCs having viscosities (in 2 wt.% aqueous solution at 20°C) between 15 and 30,000 cPs (15 to 30,000 mPa·s). DE 33 09 516 A1 does not disclose release behavior independent of the pH of the dissolution medium.

It is therefore an object of the present invention to provide a pharmaceutical formulation containing 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol and providing delayed release of the active ingredient.

This object is attained using a pharmaceutical that provides delayed release and that contains 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol or a pharmaceutically acceptable salt thereof in a matrix having delayed release of the active ingredient, wherein the matrix includes 1 to 80 wt.%, preferably 5 to 80 wt.%, of one or a plurality of hydrophilic or hydrophobic polymers as pharmaceutically acceptable matrix forming agents and has the following release rate *in vitro*, measured using the Ph. Eur. Paddle Method at 75 rpms in a buffer (in accordance with Ph. Eur.) at a pH of 6.8 at 37°C and using UV spectrometry:

3-35 wt.% 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol (relative to 100 wt.% active ingredient) released after 0.5 hours;

5-50 wt.% 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol released after 1 hour;

10-75 wt.% 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol released after 2 hours;

15-82 wt.% 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol released after 3 hours,

30-97 wt.% 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol released after 6 hours;

more than 50 wt.% 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol released after 12 hours;

more than 70 wt.% 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol released after 18 hours;

more than 80 wt.% 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol released after 24 hours.

Surprisingly, it has been demonstrated that the inventive formulation provides delayed release of 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol for oral administration and is thus suitable for administration at intervals of at least 12 hours. The inventive

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