Description

The present invention relates to novel formulations of known antimycotic azole derivatives which have an increased bioavailability of the active compounds and thus make short-term therapy possible.

Formulations of antimycotic azole derivatives in the form of vaginal tablets have already been disclosed for the treatment of fungal infections of the vagina. Using these formulations, a therapy time of 14 to 3 days is required for complete sanitisation of the vagina. This is to be attributed, inter alia, to the fact that the active compounds contained in the customary vaginal tablet formulations are only partly soluble in aqueous media.

In order to shorten the therapy period, an increased bioavailability of the active compounds in an aqueous medium is required, especially to eliminate the germs in the vaginal secretion. The known formulations are suitable for this purpose only to a limited extent because, of the available active compound present, only a small proportion dissolves in the volume of liquid in the vagina. Thus, if a shortening in the period of therapy, for example to one day, with a single administration, is to be achieved by further increasing the concentration of active compound, optimum release of the active compound must be ensured.

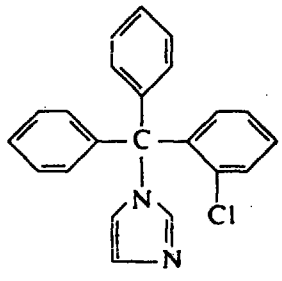
It has now been found that those vaginal tablet formulations of antimycotic azole derivatives which contain the active compound in a very finely ground form, that is to say in particle sizes down to 3-4 µm, the customary tablet auxiliaries and also an acid and/or a buffer system consisting of an organic acid and salts thereof, make it possible for the active compound to be released at a higher rate and thus make a shortened period of therapy of one day possible by achieving fungicidal concentrations of the active compound, for example clotrimazole.

This effect is achieved by reducing the pH value of the known formulations from over 5 - 6 to down to 3 - 4, in aqueous solution. The increase in the release of active compound thereby achieved can be up to one power of ten.

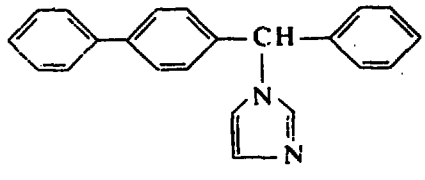
The solubility of the azole derivatives is further increased by ionic bonding by virtue of the ionic strength. The ionic strength here is between 0.1 and 0.8.

Active compounds which can be formulated in this manner are all the azole derivatives, in particular imidazole derivatives, which have an antimycotic action.

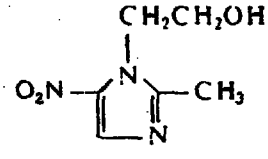
The compounds of the following formulae may be mentioned as examples:



I



II



III

Numerous other azole derivatives having an antimycotic action are known from DE-OS (German Published Specification) 2,430,039. It has been found, in particular, that vaginal tablet formulations of the compound of the formula II, which also contain lactic acid and calcium actate, or of the formula II and III which also contain citric acid or primary sodium citrate, are so much better formulated that a single administration can cure vaginal mycoses, for example those caused by species of Candida and Torulopsis. The tolerance of such formulations is completely satisfactory.

Other buffer systems and/or the acids of the acid salts by themselves also have the favourable effect mentioned on the formulations. Such systems can be: citric acid/primary Na citrate, lactic acid/Na lactate, DL-tartaric acid/K Na tartrate, adipic acid, ascorbic acid/the Na half-salt or Na salt of ethylenediaminetetraacetic acid, fumaric acid, glycine buffer, potassium hydrogen phthalate buffer, tartrate buffer ($KHC_2H_4O_6$) and phosphate buffer.

The compounds below are understood as customary tablet auxiliaries in this context. Starch, for example maize starch, rice starch, potato starch, wheat starch, lactose, glucose, sucrose, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, stearic acid, talc, polyvinylpyrrolidone (linear and crosslinked), sodium chloride, polyethylene glycol, hydroxypropylmethylcellulose, gelatine, Ca phospates, cellulose, mannitol, sodium carboxymethyl-starch, sodium carbonate, sodium bicarbonate, calcium carbonate, sodium carboxymethylcellulose (linear and crosslinked) and magnesium carbonate.

For further tablet auxiliaries see "Die Tablette, Grundlagen und Praxis des Tablettierens, Granulierens und Dragierens" ("Tablets, the Principles and Practice of Tablet-making, Granulating and Coating") by W.A. Ritschel, pages 85 - 144, and "Katalog pharmazeutischer Hilfsstoffe"

("Catalogue of Pharmaceutical Auxiliaries"), compiled by a work group from Messrs. Ciba-Geigy, Hoffmann-La Roche and Sandoz, Basle 1974.

It is known from GB-A-860,877 to ensure rapid disintegration of formulations and maintenance of a physiological pH value in the vaginal medium by the addition of auxiliaries. It is also known from DE-A-2,309,575 to use acids for maintaining the physiological acid protection of the vagina and making the administration form "tissue-friendly".

From FR-A-2,390,162 and US-A-4,032,645, buffer additions to azoles are known, which ensure good and rapid solubility of the active compounds. However, these concern injection solutions, in which the active compound must be fully dissolved in a small volume. By contrast, the formulations according to the invention concern active compounds which are in the solid form and by means of which a further increase in the active compound concentration at the site of the infection is achieved by disintegration of the formulation. In view of the two citations, this effect is surprising. Possibilities of releasing active compounds for higher biopharmaceutical availability are discussed in DAZ, 104 (1964), 950-955, J. Pharm. Pharmacol. 15(T), (1963), 43T-55T, and DAZ 110 (1970), 942-946. In particular, micronisation of the medicaments is also mentioned.

The micronisation of active compounds to increase the bioavailability, as described in this literature, is based on the increase in dissolution rate.

Example 1

500 g of active compound of the formula I are mixed, initially in the dry state, with the following amounts of tablet auxiliaries in a fluidised bed granulator: 190 g of citric acid, 195 g of primary Na citrate, 314 g of lactose, 148 g of maize starch, 230 g of micro-crystalline cellulose and 4 g of polyethylene glycol sorbitane oleate; the mixture is then granulated

by spraying water in and the granules are dried. 34 g of Mg stearate and 85 g of crosslinked polyvinylpyrrolidone are then admixed to the granules and vaginal tablets with a total weight of 1,700 mg are formed from the mixture.

Example 2

500 g of active compound of the formula III are mixed, in the dry state, with 831 g of lactose, 200 g of the Na half-salt of ethylenediaminetetraacetic acid, 126 g of maize starch, 4 g of colloidal silicon dioxide and 4 g of polyethylene glycol sorbitane oleate in a planetary mixer, the mixture is granulated with water in the same apparatus, the granules are dried in a fluidised bed in vacuo or in a circulating air drying cabinet, a further 39 g of Mg stearate are added to the granules obtained and the mixture is then pressed to vaginal tablets weighing 1,700 g.

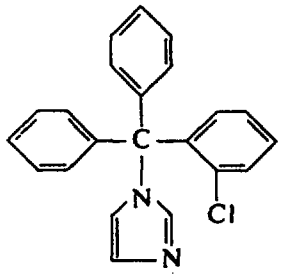
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Patentansprüche

1 Antimykotische Vaginaltabletten mit höherer Bioverfügbarkeit der Wirkstoffe, enthaltend Azolderivate und übliche Tablettenhilfsstoffe, dadurch gekennzeichnet, daß sie einen pH-Wert von 3 bis 4 und eine Ionenstärke von 0.1 bis 0.8 besitzen, den Wirkstoff in Partikeln unter 4 µm und außerdem eine Säure und ein Puffersystem bestehend aus einer organischen Säure und deren Salzen enthalten.

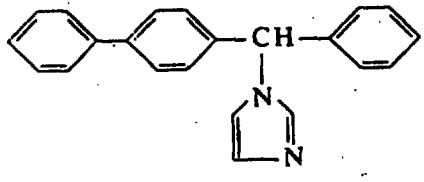
2. Antimykotische Vaginaltabletten nach Anspruch 1, dadurch gekennzeichnet, daß sie als Wirkstoff ein Imidazolderivat enthalten.

3. Antimykotische Vaginaltabletten nach Anspruch 1, dadurch gekennzeichnet, daß sie als Wirkstoff die Verbindung der Formel



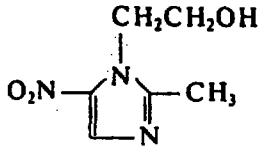
enthalten.

4. Antimykotische Vaginaltabletten nach Anspruch 1, dadurch gekennzeichnet, daß sie als Wirkstoff die Verbindung der Formel



enthalten.

5. Antimykotische Vaginaltabletten nach Anspruch 1, dadurch gekennzeichnet, daß sie als Wirkstoff die Verbindung der Formel



enthalten.

6. Antimykotische Vaginaltabletten nach Anspruch 1, dadurch gekennzeichnet, daß sie den Wirkstoff und außerdem Citronensäure und primäres Natriumcitrat enthalten.

7. Antimykotische Vaginaltabletten nach Anspruch 1, dadurch gekennzeichnet, daß sie den Wirkstoff und außerdem Milchsäure und Calciumactat enthalten.

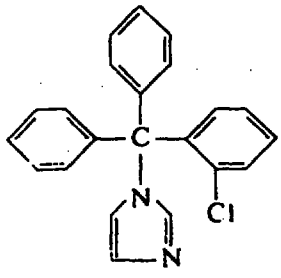
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Claims

1. Antimycotic vaginal tablets with increased bioavailability of the active compounds, containing azole derivatives and customary tablet auxiliaries, characterised in that they have a pH value of 3 to 4 and an ionic strength of 0.1 to 0.8 and contain the active compound in particles of less than 4 µm and in addition an acid and a buffer system consisting of an organic acid and salts thereof.

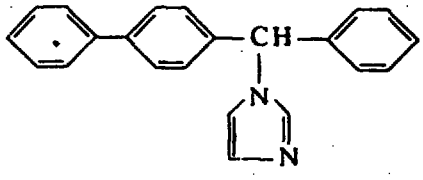
2. Antimycotic vaginal tablets according to Claim 1, characterised in that they contain an imidazole derivative as the active compound.

3. Antimycotic vaginal tablets according to Claim 1, characterised in that they contain the compound of the formula



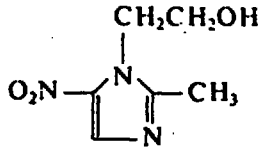
as the active compound.

4. Antimycotic vaginal tablets according to Claim 1, characterised in that they contain the compound of the formula



as the active compound.

5. Antimycotic vaginal tablets according to Claim 1, characterised in that they contain the compound of the formula



as the active compound.

6. Antimycotic vaginal tablets according to Claim 1, characterised in that they contain the active compound and in addition citric acid and primary sodium citrate.

7. Antimycotic vaginal tablets according to Claim 1, characterised in that they contain the active compound and in addition lactic acid and calcium lactate.

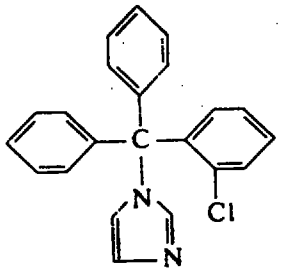
Revendications

1. Comprimés vaginaux antimycotiques ayant une plus haute biodisponibilité des substances actives et contenant des dérivés d'azoles, ainsi que des substances auxiliaires habituelles pour comprimés, caractérisés en ce qu'ils ont un pH de 3 à 4 et une intensité ionique de 0,1 à 0,8, tandis qu'ils contiennent la substance active en particules inférieures à 4 µm et, en outre, un acide et un système tampon constitué d'un acide organique et de ses sels.

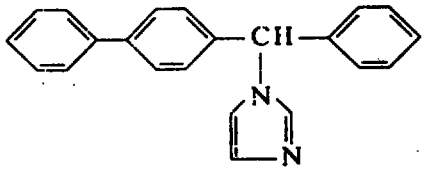
2. Comprimés vaginaux antimycotiques selon la revendication 1, caractérisés en ce que, comme substance active, ils contiennent un dérivé d'imidazole.

3. Comprimés vaginaux antimycotiques selon la revendication 1, caractérisés en ce que, comme substance active, ils contiennent le composé de formule:

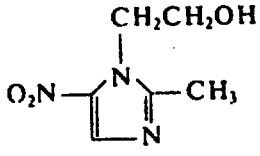
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4. Comprimés vaginaux antimycotiques selon la revendication 1, caractérisés en ce que, comme substance active, ils contiennent le composé de formule:



5. Comprimés vaginaux antimycotiques selon la revendication 1, caractérisés en ce que, comme substance active, ils contiennent le composé de formule:



6. Comprimés vaginaux antimycotiques selon la revendication 1, caractérisés en ce qu'ils contiennent la substance active et, en outre, de l'acide citrique et du citrate de sodium primaire.

7 Comprimés vaginaux antimycotiques selon la revendication 1, caractérisés en ce qu'ils contiennent la substance active et, en outre, de l'acide lactique et du lactate de calcium.

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