

Description

The invention relates to pharmaceutical preparations of medicinal substances which are sparingly water-soluble or are instable in water, and to a process for the preparation thereof. The preparations are distinguished by increased solubility in water and improved stability.

Many medicinal substances are not readily water-soluble or are only sparingly water-soluble, so that appropriate medicinal forms are prepared, such as drops or injection solutions using other polar adjuvants, such as propylene glycol, etc.. If the medicinal substance molecule carries basic or acid groups, there is also the possibility of increasing water-solubility by salt formation. As a rule, this is associated with a decrease in activity or a loss in chemical stability. Because of the altered distribution equilibrium, the medicinal substance is able to penetrate only slowly into the lipophilic membrane, depending on the concentration of its undissociated constituent, whereas the ionogenic constituent can undergo rapid hydrolytic decomposition.

Therefore, during the preparation of aqueous solutions of sparingly water-soluble active substances there are used either additional "water-like" solvents, such as low molecular weight polyethylene glycols or 1,2-propylene glycol which, however, cannot be described as pharmacologically inert, or the active substance is solubilised using surfactants by inclusion of medicinal substances in micelles. However, this solubilisation has numerous disadvantages; the surfactant molecules used frequently have a strongly haemolytic action and, after application, the medicinal substance necessarily leaves the micelle by diffusion. This results in a retarding effect (cf. B.W. Müller, "Gelbe Reihe", volume X, pages 132 et seq. (1983)).

Therefore, it can be said that there is no satisfactory and generally applicable solubilising method.

For solid medicinal substances it is also important for the sparingly water-soluble active substance to be used in water-soluble form, because a satisfactory degree of solubility increases the availability of the active substance. It has been already stated that inclusion complexes, e.g. with urea or complexes with polyvinyl pyrrolidone, can improve the solubility of a substance, however, they are no longer stable in aqueous solution. Therefore, inclusion complexes of this type are at best suitable for solid medicinal forms.

The position is different when using alpha, beta and gamma-cyclodextrin, which even in aqueous solution can bind a medicinal substance in complex manner with its ring (W. Sanger, "Angew. Chemie" 92, 343 (1980)). However, it is a disadvantage that the beta-cyclodextrin is itself only sparingly water-soluble (1.8 g per 100 ml), so that the therapeutically required concentrations of medicinal substance are not attained.

If the adjuvant is a cyclodextrin derivative, its solubility and thus also the amount of the medicinal substance brought into solution can be substantially increased. Therefore, DE-A-31 18 218 discloses solubilising with methylated beta-cyclodextrin as a monomethyl derivative with 7 methyl groups and, in particular, as a dimethyl derivative with 14 methyl groups. Using the 2,6-di-O-methyl derivative, for example, it is possible to increase the solubility of indomethacin in water by 20.4 times and that of digitoxin by 81.6 times.

WO-A-820051 discloses inclusion complexes of retinoids with cyclodextrins and cyclodextrin derivatives. The problem with which this publication is concerned is that of lowering the toxic side effects of retinoids by modifying the molecular structure and/or complexing with cyclodextrins. It is intended to decrease the fat solubility of the substances, thereby lowering or obviating their tendency to become concentrated in adipose tissue. In this publication alpha, beta and gamma-cyclodextrins, as well as derivatives thereof, are designated as being equally suitable for complexing, while primarily

methoxy derivatives of alpha, beta and gamma-cyclodextrins are indicated as individual examples of applicable derivatives.

However, the methyl derivatives of beta-cyclodextrin have serious disadvantages for therapeutic application. In view of their highly lipophilic nature, they have a haemolytic effect and also cause irritation to the mucous membranes and eyes. Their acute intravenous toxicity is even higher than the already substantial toxicity of unsubstituted beta-cyclodextrin. A further serious disadvantage in respect of practical application is that the solubility of dimethyl-beta-cyclodextrin and its complexes decreases considerably at relatively high temperatures so that the dextrin crystallises out during heating. The sterilisation of the solutions at normal temperatures of 100 to 121°C is rendered much more difficult as a result of this phenomenon.

Surprisingly, it has now been found that certain other beta-cyclodextrin derivatives, while forming inclusion complexes, substantially increase the water-solubility of sparingly water-soluble medicinal substances and the stability of medicinal substances which are instable in water but do not have the disadvantages described above.

Accordingly, the invention relates to pharmaceutical preparations containing inclusion complexes of medicinal substances which are sparingly water-soluble or are instable in water, with a partially etherified beta-cyclodextrin, the ether substituents of which are hydroxyethyl, hydroxypropyl or dihydroxypropyl groups, wherein one portion of the ether substituents may optionally be methyl or ethyl groups and the beta-cyclodextrin ether has a water-solubility of more than 1.8 g in 100 ml of water, wherein inclusion complexes of retinoids with beta-cyclodextrin ethers are excluded insofar as their ether substituents are methyl, ethyl and 2-hydroxyethyl groups.

The use of partially methylated beta-cyclodextrin ethers with 7 to 14 methyl groups in the beta-cyclodextrin molecule, as disclosed by DE-A-31 18 218, does not come within the scope of the invention. Moreover, according to the invention inclusion complexes of retinoids with beta-

cyclodextrin ethers are excluded insofar as their ether substituents are methyl, ethyl and 2-hydroxyethyl groups (cf. WO-A-820051).

Beta-cyclodextrin is a cyclically formed compound of seven anhydroglucose units; it is also known as cycloheptamylose. Each of the seven glucose rings respectively contains three hydroxygroups in the 2-, 3- and 6-position, which can be etherified. In the case of the partially etherified cyclodextrin derivatives used according to the invention, only a part of these hydroxy groups is etherified with the specified hydroxyalkyl radicals and also, optionally, with methyl or ethyl radicals. During etherification with 5-hydroxyalkyl radicals which can be effected by reaction with the corresponding alkylene oxides, the degree of substitution is indicated as a molar degree of substitution (MS), namely in mole of alkylene oxide per anhydroglucose unit, cf. US-A-34 59 731, column 4. In the case of the hydroxyalkyl ethers of beta-cyclodextrin used according to the invention, the molar degree of substitution is between 0.05 and 10, preferably between 0.2 and 2.

A molar degree of substitution of about 0.25 to about 1 is especially preferred.

For etherification with alkyl radicals the degree of substitution (DS) can be indicated directly per glucose unit, which (as already mentioned above) is 3 with complete substitution. Partially etherified beta-cyclodextrins are used within the scope of the invention which, in addition to hydroxyalkyl radicals, contain alkyl radicals, namely methyl or ethyl radicals up to a degree of substitution of from 0.05 to 2.0, preferably 0.2 to 1.5. It is especially preferred if the degree of substitution for the alkyl radicals is about 0.5 to about 1.2.

The molar ratio of medicinal substance to beta-cyclodextrin ether is preferably about 1:6 to 4:1, in particular about 1:2 to 1:1. As a rule it is preferable to use the complexing agent in a molar excess.

The complexing agents which come into consideration include hydroxyethyl, hydroxypropyl and dihydroxypropyl ether

and corresponding ether mixtures thereof and also mixed ethers with methyl or ethyl groups, for example methyl-hydroxyethyl, methyl-hydroxypropyl, ethyl-hydroxyethyl and ethyl-hydroxypropyl ether of beta-cyclodextrin.

The preparation of the hydroxyalkyl ether of beta-cyclodextrin can be carried out according to the process of US-A-34 59 731. Suitable processes for the preparation of beta-cyclodextrin ether are also found in J. Szejtli et al., "Stärke" 32, 165 (1980) and A.P. Croft and R.A. Bartsch, "Tetrahedron" 39, 1417 (1983). Mixed ethers of beta-cyclodextrin can be prepared by reacting beta-cyclodextrin in a basic liquid reaction medium, containing an alkali metal hydroxide, water and, optionally, at least one organic solvent (e.g. dimethoxyethane or isopropanol), with at least two different hydroxyalkylating and, optionally, alkylating etherification agents (e.g. ethylene oxide, propylene oxide, methyl or ethyl chloride).

Medicinal substances, which in the form of inclusion complexes with said beta-cyclodextrin ethers exhibit substantially increased water-solubility and/or greater stability, are those having the corresponding fitting shape, i.e. they have to fit into the cavity of the beta-cyclodextrin cyclic system. For example, non-steroidal antirheumatic agents, steroids, cardiac glycosides and derivatives of benzodiazepin, benzimidazole, piperidine, piperazine, imidazole or triazole.

Benzimidazole derivatives which come into consideration are thiabendazole, fuberidazole, oxibendazole, parabendazole, cambendazole, mebendazole, fenbendazole, flubendazole, albendazole, oxfendazole, nocodazole and astemisol [sic]. As piperidine derivatives there may be considered fluspirilene, pimozide, penfluridole, loperamide, astemizole, ketanserine, levocabastine, cisapride, altanserine and ritanserine. Suitable piperazine derivatives are lidoflazine, flunarizine, mianserine, oxatomide, mioflazine and cinnarizine. As imidazole derivatives there are named metronidazole, ornidazole, ipronidazole, tinidazole, isoconazole, nimarazole, burimamide, metiamide, metomidate,

enilconazole, etomidate, econazole, clotrimazole, carnidazole, cimetidine, docodazole, sulconazole, parconazole, orconazole, butoconazole, triadiminole, tioconazole, valconazole, fluotrimazole, ketoconazole, oxiconazole, lombazole, bifonazole, oxmetidine, fenticonazole and tubulazole. The triazole derivatives under consideration include virazole, itraconazole and terconazole.

Particularly valuable pharmaceutical preparations are obtained if etomidate, ketoconazole, tubulazole, itraconazole, levocabastine or flunarizine are converted into water-soluble form by means of the complexing agents used in accordance with the invention. Therefore, these preparations in particular form the subject-matter of the present invention.

The invention also relates to a process for the preparation of pharmaceutical preparations of medicinal substances which are sparingly water-soluble or are instable in water, which is characterised in that the beta-cyclodextrin ether is dissolved in water and the corresponding medicinal substance is added and, optionally, the resultant solution of the inclusion complex is dried in accordance with per se known methods. The formation of the solution can take place at temperatures of between 15 and 35°C.

The medicinal substance is preferably added in portions. The water can contain, for example, physiologically compatible substances, such as common salt, potassium nitrate, glucose, mannitol, sorbitol, xylitol or a buffer, such as a phosphate, acetate or citrate buffer.

Using the beta-cyclodextrin derivatives used according to the invention it is possible to prepare medicinal forms both for oral, parenteral and local application, e.g. infusion and injection solutions, drops (e.g. eye drops, nose drops), sprays, aerosols, syrups and baths.

The aqueous solutions can also contain suitable physiologically compatible preservatives, e.g. quarternary ammonium soaps, chlorobutanol.

To prepare solid preparations the solutions of the inclusion complexes are dried in accordance with conventional methods; for example, water can be removed in a rotary evaporator or by freeze-drying. The residue is powdered and, optionally after the addition of further adjuvants, is transformed into tablets, sugar-coated pills, suppositories, capsules or creams and ointments.

The following examples illustrate the invention which, however, is in no way limited to the examples given below.

The phosphate buffer solution indicated in the examples has a pH value of 6.6 and the following composition:

KH_2PO_4	68.05 g
NaOH	7.12 g
demin. water to	5000.0 g

All indications of percent are percent by weight.

Example 1

Starting from a 7 % stock solution of hydroxyethyl-beta-cyclodextrin (MS 0.43) in a phosphate buffer solution, a dilution sequence is prepared so that the complexing agent concentration is present graduated in 1% steps. 3 ml of these solutions are transferred by pipette into 5 ml snap cover glass vessels containing the appropriate medicinal substance. After agitation for 24 hours at 25°C, the solution is filtered off via a membrane filter (0.22 μm) and the content of dissolved medicinal substance is determined by spectrophotometry. Figures 1, 3 and 4 show the increase in the concentration of medicinal substance in solution as a function of the amount of added complexing agent for indomethacin (Fig. 1), piroxicam (Fig. 3) and diazepam (Fig. 4). The maximum possible concentration of medicinal substance is limited by the saturation solubility of the cyclodextrin derivative in the buffer, which in the case of hydroxyethyl-beta-cyclodextrin (MS 0.43) is at 7.2 g/100 ml.

If, for example, the results with indomethacin are compared with those indicated for 2,6-di-O-methyl-beta-cyclodextrin in DE-A-31 18 218 (Fig. 2), the hydroxyethyl

derivative exhibits a distinctly higher complexing constant (cf. the different gradients in Figs. 1 and 2).

Example 2

Using a 10 % hydroxypropyl-beta-cyclodextrin solution (MS 0.35) in a phosphate buffer solution, the saturation solubility at 25°C is determined for various medicinal substances under the same conditions as in Example 1. Table 1 indicates saturation solubility S_1 in a phosphate buffer solution and S_2 in a phosphate buffer solution with the addition of 10 % hydroxypropyl-beta-cyclodextrin.

Table 1

Medicinal substance	S_1 (mg/ml)	S_2 (mg/ml)	ratio S_1 to S_2
indomethacin	0.19	5.72	1: 30.1
digitoxin	0.002	1.686	1: 842.5
progesterone	0.0071	7.69	1: 1083.0
dexamethasone	0.083	14.28	1: 172.0
hydrocortisone	0.36	21.58	1: 59.9
diazepam	0.032	0.94	1: 29.4

In a similar manner the solubility of medicinal substances is investigated in a 4 % aqueous solution of hydroxypropyl-methyl-beta-cyclodextrin (DS = 0.96; MS = 0.43). The results obtained are set out in the following Table 2, wherein for each medicinal substance there is indicated the ratio R of saturation solubility in water, with and without addition of the beta-cyclodextrin derivative, and at the pH value indicated. Moreover, in all cases the solutions prepared according to the invention are found to be substantially more stable compared to aqueous solutions.

Table 2

<u>Medicinal substance</u>		<u>R</u>
itraconazole	at pH 5.0	96.0
	at pH 2.5	75.0
flunarizine		18.0
levocabastine	at pH 9.5	18.0
	at pH 7.4	8.0
ketoconazole		85.0
flubendazole		30.0
tubulazole		43.0
cisapride		3.0
loperamide		62.0
etomidate		8.5
cinnarizine	at pH 5.0	28.0
	at pH 3.0	12.0

Example 3

0.7 g of hydroxyethyl-beta-cyclodextrin (MS 0.43) and 0.04 g of indomethacin are worked into 10 ml of phosphate buffer solution at 25°C until a clear solution is formed. The latter is filtered through a membrane filter (0.22 µl) and is poured in laminar flow into a previously sterilised injection bottle which has been stored at 21°C (B). In parallel therewith a saturated indomethacin solution in a phosphate buffer solution (0.21 mg/ml) is stored under the same conditions (A). The active substance concentrations determined by high-pressure liquid chromatography are set out in Table 3. The substantially improved stability of the preparation according to the invention is quite apparent.

Table 3

<u>Storage time in weeks</u>	<u>indomethacin content (%)</u>	
	<u>A</u>	<u>B</u>
0	100.1	99.7
2	91.2	99.9
4	79.1	98.1
6	69.8	98.6
8	64.8	98.4

Example 4 (injection preparation)

0.35 g of hydroxypropyl-beta-cyclodextrin (MS 0.35) is dissolved in 5 ml of physiological saline solution warmed to a temperature of about 35°C and 3 mg diazepam are added. After brief stirring a clear solution is obtained which, after filtration through a 0.45 μ m membrane filter, is poured into an ampoule.

Example 5 (tablet)

7 g of hydroxyethyl-beta-cyclodextrin (MS 0.43) and 0.5 g of medroxyprogesterone acetate are dissolved in 100 ml of water. Subsequently, the water is removed in a rotary evaporator. The residue (75 mg) is powdered and is mixed with 366 mg of calcium hydrogen phosphate·2H₂O, 60 mg of maize starch, 120 mg of cellulose powder (microcrystalline), 4.2 mg of finely dispersed silicic acid (Aerosil^R 200) and 4.8 of magnesium stearate to form tablets having a final weight of 630.0 mg and 5 mg of active substance per individual dose. The dissolution rate of the medroxyprogesterone acetate from this preparation is approximately 21 times higher than when using the same tablet adjuvants without the addition of beta-cyclodextrin ether.

Example 6

5 g of hydroxyethyl-beta-cyclodextrin (MS 0.43) and 14 g of vitamin A acetate are dissolved in 100 ml of water or sugar solution (5 % aqueous solution) by stirring for about 2.5 hours under a nitrogen atmosphere. After filtration through a 0.45 μ m membrane filter, the solution is either poured into ampoules and sterilised or poured into dropping bottles using 0.4 % chlorobutanol as preservative.

Example 7

5 g or 7.5 g of hydroxyethyl-beta-cyclodextrin (MS 0.43) and 0.5 or 0.75 g of lidocaine is dissolved in 100 ml of physiological saline solution at 30°C (B). Injection solutions, eye drops and solutions for cutaneous application are prepared therefrom analogously to Example 6. If the anaesthetising

effect of these solutions in an animal experiment are compared with an aqueous lidocaine HCl solution (A) a prolongation of the effect by 300 % is observed. Experiment: rat, injection of 0.1 ml into the tail root in the vicinity of the right or left nerve cords and electrical stimulation. The results of the experiment are set out in Table 4.

Table 4

active subst. conc. (%)	duration of effect (min.)		prolongation (%)
	A	B	
0.5	56	163	291
0.75	118	390	330

Example 8

6 mg of dexamethasone and 100 mg of hydroxyethyl-beta-cyclodextrin (MS 0.43) are dissolved in 5 ml of water, are filtered under sterile conditions through a 0.22 μ m membrane filter and are packed in a dosing aerosol can which allows 0.1 ml per dose to be released.

Example 9

The acute intravenous toxicity of a number of beta-cyclodextrins was tested on rats, whereupon the following results were obtained. Surprisingly, it was found that the toxicity of the derivatives used according to the invention is a whole order of magnitude lower.

Table 5

LD ₅₀ in rats (i.v.) in mg/kg body weight	
beta-cyclodextrin	453
dimethyl-beta-cyclodextrin (DS = 2.0)	200-207
hydroxypropyl-methyl-beta-cyclodextrin (DS = 0.96; MS = 0.43)	> 2000*

* a higher dose was not tested. In mice the value was > 4000 mg/kg.

In a further series of experiments the haemolytic effect of methyl ether according to DE-A-31 18 218 was compared with that of an ether used in accordance with the invention. For this purpose, 100 μ l of a physiological saline solution with a cyclodextrin content of 10 %, 800 μ l of a buffer (400 mg MOPS, 36 mg $\text{Na}_2\text{HPO}_4 \cdot 2 \text{H}_2\text{O}$, 1.6 g NaCl in 200 ml H_2O) and 100 μ l of a suspension of red blood corpuscles (human origin, washed three times with saline solution) are mixed together for 30 min. at 37°C. Subsequently, the mixture was centrifuged and extinction at 540 nm was determined. Controls:

- a) 100 μ l of saline solution + buffer $\rightarrow$ 0 % haemolysis
- b) 900 μ l of water $\rightarrow$ 100 % haemolysis

The results obtained are set out in the following Table 6, which indicates the concentrations at which 50 % and 100 % haemolysis took place.

Table 6

substance	C_{50} %	C_{100} %
dimethyl-beta-CS (DS = 2.0)	0.33 %	0.5 %
methyl-beta-CD (DS = 1.79)	0.53 %	0.8 %
hydroxypropyl- methyl-beta-CD (DS = 0.96 MS = 0.43 %)	1.5 %	4.0 %

The results show that the haemolytic effect of hydroxypropyl-methyl ether is about 5 to 8 times lower than that of the dimethyl ether according to the state of the art.

Animal experiments have also demonstrated that, in contrast to methyl ethers, hydroxyalkyl ethers do not cause any irritation of the mucous membranes and the eyes.

CLAIMS:

1. A pharmaceutical preparation containing inclusion complexes of medicinal substances which are sparingly water-soluble or are instable in water, with a partially etherified beta-cyclodextrin, the ether substituents of which are hydroxyethyl, hydroxypropyl or dihydroxypropyl groups, wherein one portion of the ether substituents may optionally be methyl or ethyl groups and the beta-cyclodextrin ether has a water-solubility of more than 1.8 g in 100 ml of water, wherein inclusion complexes of retinoids with beta-cyclodextrin ethers are excluded insofar as their ether substituents are methyl, ethyl and 2-hydroxyethyl groups.
2. A preparation according to Claim 1, characterised in that it contains a partially etherified beta-cyclodextrin which has a molar degree of substitution for the hydroxyalkyl substituents of from 0.05 to 10 and a degree of substitution for the alkyl substituents of from 0.05 to 2.0.
3. A preparation according to either Claim 1 or Claim 2, characterised in that it contains the medicinal substance and the beta-cyclodextrin ether in a molar ratio of from 1:6 to 4:1.
4. A preparation according to any one of Claims 1 to 3, characterised in that as medicinal substance it contains a non-steroidal antirheumatic agent, a steroid, a cardiac glycoside or derivatives of benzodiazepin, benzimidazole, piperidine, piperazine, imidazole or triazole.
5. A preparation according to any one of Claims 1 to 4, characterised in that as medicinal substance it contains etomidate.
6. A preparation according to any one of Claims 1 to 4, characterised in that as medicinal substance it contains ketoconazole.



7. A preparation according to any one of Claims 1 to 4, characterised in that as medicinal substance it contains itraconazole.

8. A preparation according to any one of Claims 1 to 4, characterised in that as medicinal substance it contains levocabastine.

9. A preparation according to any one of Claims 1 to 4, characterised in that as medicinal substance it contains flunarizine.

10. A preparation according to any one of Claims 1 to 4, characterised in that as medicinal substance it contains tubulazole.

11. A process for the preparation of a pharmaceutical preparation according to any one of Claims 1 to 10, characterised in that the beta-cyclodextrin ether is dissolved in water and the appropriate medicinal substance is added and, optionally, the resultant solution of the inclusion complex is dried in accordance with per se known methods.

12. A process according to Claim 11, characterised in that the residue obtained after removal of the solvent is pulverised and, optionally after the addition of further adjuvants, is converted into a solid administration form.

13. A process according to Claim 11 or Claim 12, characterised in that further physiologically compatible substances are added to the water.

14. A process according to Claim 13, characterised in that common salt, glucose, mannitol, sorbitol, xylitol or a phosphate or citrate buffer is added to the water.

