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(54) Titre : SOLUTIONS DE BUDESONIDE STABLES, LEUR PROCEDE DE PREPARATION ET LEUR UTILISATION
 COMME PREPARATIONS POUR LAVEMENT ET MOUSSES PHARMACEUTIQUES
 (54) Title: STABLE BUDESONIDE SOLUTIONS, METHOD OF PREPARING THEM AND USE OF THESE SOLUTIONS
 AS ENEMA PREPARATIONS AND PHARMACEUTICAL FOAMS

(57) **Abrégé/Abstract:**

The present invention relates to stable budesonide solutions with a pH of 6.0 or below, which are dissolved in water, alcohol or a water/alcohol mixture. These solutions preferably additionally contain sodium EDTA, cyclodextrin or mixtures thereof. The stable budesonide solutions according to the invention can be used for producing an enema or rectal foams.



Abstract

The present invention relates to stable budesonide solutions with a pH of 6.0 or below, which are dissolved in water, alcohol or a water/alcohol mixture. These solutions preferably additionally contain sodium EDTA, cyclodextrin or mixtures thereof. The stable budesonide solutions according to the invention can be used for producing an enema or rectal foams.

Stable budesonide solutions, a process for their preparation, and the use of these solutions as enema preparations and pharmaceutical foams

5 The present invention relates to stable budesonide solutions, the process for their preparation, and their use for producing pharmaceutical preparations, in particular enemas and pharmaceutical foams.

10 Budesonide (INN; 16 α ,17-butylienedioxy-11 β ,21-dihydroxy-1,4-pregnadiene-3,20-dione) is a known active substance of the corticoid series which is employed in particular for the treatment of bronchial disorders, but also in cases of inflammatory bowel disorders such as Crohn's disease and, in particular, ulcerative
15 colitis. It has proven particularly suitable for the last-mentioned indication to administer rectal drug forms such as enema preparations or pharmaceutical foams in compressed gas packs, because the active substance is employed directly at the site of the
20 disorder, and budesonide is especially topically effective.

 Budesonide is a racemate consisting of a mixture of the two diastereomers 22R and 22S. The racemate can be employed for the purposes of the
25 present invention, but the 22R diastereomer is preferably employed because this is more active in pharmacological respects by a factor of about 2-3. Processes for fractionating the enantiomers are known, for example from WO92/11280.

30 Because of its lipophilicity, budesonide is virtually insoluble in water but is readily soluble in alcohols. An adequate amount of active substance can be dissolved by the use of solubilizers such as organic, water-soluble alcohols. However, the solutions obtained
35 in this way prove to have too little stability for pharmaceutical use because large amounts of the active substance are decomposed within a short time.

Because of this instability, budesonide preparations which can be used directly by the patient in the administration form ready for use are unknown. Although budesonide-containing enemas are currently marketed in some countries, in these cases the enemas are not ready for use but comprise a type of combination of tablets containing active substance and enema bottles filled with water. Before administration, the patient must in each case remove a tablet, introduce it into the opened enema bottle, wait until the tablet has disintegrated and shake the bottles vigorously before use in order to disperse the active substance as homogeneously as possible in the form of a suspension.

This laborious and troublesome preparation of the enema ready for use can be only inadequately accomplished in particular by frail patients. Homogeneous dispersion of the active substance can be achieved only inadequately by this process, and complete administration of the active substance by squeezing of the enema bottle can scarcely be guaranteed because there is a tendency for the suspended active substance to settle out on the bottom of the bottle in a short time after preparation of the final form.

Although rectal administration of budesonide by means of rectal foams has advantages in respect of convenience of use, the problem here is to provide budesonide solutions which have adequate stability for administration in compressed gas packs. Budesonide-containing rectal foams have therefore not hitherto been disclosed.

One object of the present invention is to provide adequately stable solutions of budesonide.

This object is achieved by budesonide solutions which have a pH of 6 or below.

It has been found, completely surprisingly, that the stability of budesonide-containing solutions depends crucially on the pH. The stability of the solutions increases as the pH decreases. The budesonide solutions according to the invention can be prepared on

an aqueous and/or alcoholic basis, it also being possible to dissolve budesonide in an aqueous, alcoholic mixture.

It has been found, completely surprisingly, in the framework of the present invention that the pH has a crucial influence on the stability of the budesonide solution, specifically in aqueous, aqueous-alcoholic or alcoholic solution.

Table 1 which is shown hereinafter proves the stability of an aqueous solution of budesonide and Table 2 shows the stability of an alcoholic solution (propylene glycol) of budesonide as a function of the storage time and the pH.

15

Table 1

Stability of budesonide solutions according to the invention (2 mg/60 ml of H₂O) as a function of the storage time

pH	Contents ¹⁾ after storage for 14 days at	
	20°C	40°C
7.0	96.5 %	71.2 %
6.5	96.4 %	77.1 %
6.0	97.6 %	84.8 %
5.5	97.4 %	87.6 %
5.0	97.6 %	90.0 %
4.5	97.3 %	93.0 %
4.0	98.7 %	95.2 %
3.5	99.8 %	96.6 %
3.0	100.0 %	97.9 %

20 ¹⁾ Initial value after t = 0 days equal to 100 %

It is evident from Table 1 above that the stability of the solutions increases as the pH decreases. Even after storage at 20°C and pH 3.0 for

14 days, the active substance is still 100 % present. Even on storage at a distinctly higher temperature, that is to say at 40°C and pH 3.0, there is still 97.9 % budesonide in the solution after 14 days.

5

Table 2

Stability of budesonide solutions according to the invention (2 mg/4 g in propylene glycol) as a function of the storage time

Content after storage at				
pH	0 months	3 months 25°C	3 months 40°C	6 months 40°C
7.5	100.0 %	80.6 %	44.4 %	15.3 %
5.0	100.0 %	103.0 %	96.5 %	89.5 %
2.8	100.0 %	99.4 %	98.7 %	95.2 %

10 It is evident from Table 2 above that the stability of the solutions increases as the pH decreases.

The losses of active substance at pH values of 4.0 and below are sufficiently low to be of an acceptable magnitude as a function of the storage time for pharmaceutical products.

15 For pharmaceutical use, the preferred pH values of the form ready for use are ≥ 3.5 for use as enema or else as rectal foam because of the physiological factors and taking account of the amount of about 30 to 20 100 ml to be administered for enemas and of about 4 g in the case of rectal foams.

Any pharmaceutically acceptable organic and inorganic acids can be used to adjust the pH, for example hydrochloric acid, phosphoric acid, citric acid 25 or tartaric acid.

In order to increase the stability further, for example to save transport and storage costs, or else for use as non-rectal administration form, it is also

possible to prepare concentrated budesonide solutions with a pH \leq 3.5. If it is necessary for subsequent use to adjust the pH to a physiologically tolerated value $>$ 3.5, this can take place only shortly before use. 5 This can happen, for example, by dilution or by addition of a base. The dilution process then increases the pH.

In other preferred embodiments, the budesonide solutions according to the invention have an addition 10 of sodium EDTA (sodium ethylenediaminetetraacetic acid; KomplexonTM), which further increases the stability.

In another preferred embodiment of the present invention, the stability of the solution can be increased by using cyclodextrins, preferably hydroxy- 15 propyl- β -cyclodextrin or γ -cyclodextrin. Addition of cyclodextrins also makes it possible to use more concentrated solutions of budesonide.

The invention therefore relates to stable budesonide solutions with a pH of 6.0 or below. The 20 budesonide is dissolved according to the invention in water, alcohol or a water/alcohol mixture.

The alcohols used for the purposes of the present invention are preferably propylene glycol, ethanol or isopropanol.

25 When an alcohol/water mixture is employed, the ratio of alcohol to water is between 100:0 and 80:20, preferably between 98:2 and 93:7.

The budesonide content in the solution ready for use is between 0.001 and 1 % by weight, preferably 30 between 0.01 and 0.1 % by weight and, in the case of enemas, is particularly preferably 0.001 to 0.1 % by weight.

The solutions according to the invention may furthermore contain ancillary substances customarily 35 used in corresponding pharmaceutical formulations. These ancillary substances may be suitable for solubilizing corticoids. The skilled worker is familiar with ancillary substances of this type.

Conventional ancillary substances are those

which influence, normally increase, the viscosity of the solution, preservatives such as ethanol, chlorobutanol, benzyl alcohol, phenylethanol, sorbic acid, benzoic acid, sodium disulfite, p-hydroxybenzoates, phenol, m-cresol, p-chloro-m-cresol, quats, chlorohexidine, thickeners such as gelatin, tragacanth, pectin, cellulose derivatives (for example methylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose sodium), polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acids, xanthan gum, acids such as acetic acid, citric acid, tartaric acid, hydrochloric acid, phosphoric acid; bases such as potassium hydroxide, sodium hydroxide; buffer substances such as hydrochloric acid buffer, phthalate buffer, phosphate buffer, borate buffer, acetate buffer or citrate buffer. In order to increase the solubility of the active substance, it is suitable, for example, to add sufficient amounts of alcohols such as ethanol, isopropanol, glycerol, propylene glycol, polyethylene glycols or to use solubilizers such as, for example, cyclodextrins, preferably β -cyclodextrin, hydroxypropyl- β -cyclodextrin and/or γ -cyclodextrin.

If the budesonide solutions according to the invention are intended for use as rectal foams, it is necessary to add those customary ancillary substances which first make it possible for the dispersion to form. Ancillary substances of this type are emulsifiers known to the skilled worker, such as Eumulgin and various Lanette types. It is furthermore possible to add preservatives such as sorbic acid, parahydroxybenzoates, benzoic acid, acids such as acetic acid, citric acid, tartaric acid, hydrochloric acid and phosphoric acid.

In the case of rectal foams, suitable propellant gases are also introduced into the pressure packs. Even if chlorofluorocarbon gases were suitable as propellant gases, the use of these gases tends to be avoided at present for reasons of environmental protection. The propellant gases preferably used are

therefore hydrocarbons such as isobutane, n-butane or propane/n-butane mixtures.

The pH of the budesonide solutions according to the invention is 6.0 or below. A range between 5.0 and 3.5 is preferred, and the pH range between 4.5 and 4.0 is particularly preferred.

Budesonide is present in the solutions according to the invention in an amount between 0.001 and 1 % by weight, with the concentration in solutions intended to be used as enemas being lower than in solutions intended for rectal foams. The preferred concentration in solutions for enemas is between 0.01 and 0.1 % by weight, and the preferred range for rectal foams is between 0.01 and 0.1 % by weight.

Sodium EDTA is preferably added in an amount of 0.01 to 1.0 % by weight, with a range from 0.01 to 0.1 % by weight being preferred for enemas and a concentration of 0.05 to 1 % by weight being preferred for rectal foams.

Whereas cyclodextrins are added as solubilizers, this preferably takes place in an amount between 0.05 and 0.5 % by weight, with addition of about 0.1 % by weight being preferred.

Solutions for enemas are prepared by processes known per se. It is possible, for example, to incorporate an ethanolic stock solution of budesonide into an aqueous solution of the other ingredients with homogenization. The use of an antioxidant or exclusion of oxygen, and measures in the area of protection from light are not specifically necessary but they may improve the quality and the stability of the resulting products. For rectal use, the finished solution is then dispensed into a conventional flexible enema bottle with applicator tip, both of which are preferably produced from opaque plastic.

The preparation of solutions for rectal foams is also known in the prior art. For example, the preservative and the emulsifiers required for foam formation can be dissolved in the appropriate solution,

preferably the suitable alcohol. The active substance is then incorporated as alcoholic stock solution into this solution. In the last step, Komplexon and the appropriate acid, dissolved in a small amount of water, are stirred into the alcoholic solution with homogenization.

If the budesonide solution according to the invention is used to produce a rectal foam, the finished solution is introduced into suitable compressed gas packs which are provided with commercially obtainable valve systems as single or multiple dose devices, and a propellant gas is added. The packs additionally contain an applicator tip made of plastic. Because of the chemical and physical properties of the stable budesonide solution according to the invention, the foam is inevitably generated in the rectum on administration.

In a preferred embodiment, the stable budesonide solutions according to the invention are used to produce enemas or rectal foams. Other use forms such as, for example, use as metered aerosol, inhalation spray or else as drops, syrup or elixirs are likewise possible and can easily be produced by the skilled worker on the basis of the present description. The invention is explained in detail by means of the following examples.

Example 1

A solution is prepared by the process described above and is dispensed into appropriate plastic bottles and contains the following ingredients per 60 g enema bottle:

budesonide	2	mg
β -cyclodextrin, hydroxypropyl- β -cyclodextrin (0.9) or γ -cyclodextrin	60	mg
sodium EDTA	30	mg
sodium benzoate	300	mg
xanthan gum	360	mg

2N HCl ad pH 4.0

ethanol 400 mg

water ad 60.00 mg

The solution produced in this way proved to be
5 stable even after storage at 40°C for several weeks.

Example 2

Enema produced by the customary process,
10 containing
budesonide 2 mg
sodium benzoate 300 mg
sodium EDTA 30 mg
propylene glycol 500 mg
15 xanthan gum 360 mg
2N hydrochloric acid ad pH 3.5 60.00 mg

The enema produced in this way proved to be
stable after storage at 40°C for several weeks.

20 Example 3

An aqueous solution is produced as in Example 1
and contains the following ingredients:

budesonide 2 mg
25 β -cyclodextrin, hydroxypropyl- β -cyclo-
dextrin (0.9) or γ -cyclodextrin 60 mg
sodium benzoate 300 mg
xanthan gum 360 mg
2N HCl ad pH 4.0
30 ethanol 400 mg
water ad 60.00 mg

The solution produced in this way proved to be
stable even after storage at room temperature for
several weeks.

35

Example 4

An aqueous solution is produced as in Example 1
and contains the following ingredients:

- 10 -

	budesonide	2	mg
	sodium EDTA	30	mg
	sodium benzoate	300	mg
	xanthan gum	360	mg
5	2N HCl ad pH 4.0		
	ethanol	400	mg
	water ad	60.00	mg

The solution produced in this way proved to be stable even after storage at room temperature for several weeks.

Example 5

An aqueous solution is produced as in Example 1 and contains the following ingredients:

	budesonide	2	mg
	sodium benzoate	300	mg
	xanthan gum	360	mg
	2N HCl ad pH 4.0		
20	ethanol	400	mg
	water ad	60.00	mg

The solution produced in this way proved to be stable even after storage at room temperature for several weeks.

25

Example 6

Investigation of the stability of the solutions according to the invention

30

The formulations in the following Table 3 were produced as in Example 1 and investigated for their stability after storage for 1 to 39 weeks. The following results were obtained.

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Table 3

	Content ¹					
	Stress time in ... weeks at 40°C					
	1	4	6	11	16	39
pH 5, without additions	96.1 %	67.6 %	60.2 %	56.6 %		
pH 4, with EDTA, with γ -cyclodextrin			100.0 %	99.6 %	99.8 %	97.3 %
pH 4, with EDTA, with hydroxypropyl- β -cyclodextrin (molar degree of substitution 0.9)			100.0 %	94.7 %	95.0 %	89.4 %
pH 4, with EDTA, with propylene glycol			98.8 %		93.1 %	

¹ Initial value at t = 0 weeks = 100 %

5 The above test results prove that the aqueous budesonide solutions according to the invention with a pH below 6 are still stable even after storage for several weeks. Solutions which contain EDTA and a cyclodextrin are particularly stable. Thus, these
10 solutions still contain 100 % of active substance even after storage at 40°C and pH 4 for six weeks.

Example 7

15 A solution is prepared by the process described above and is dispensed into appropriate compressed gas packs (for example aluminum monoblock can, 55 ml, with liquid valve, shield and metering head) with the addition of a propellant gas (pressure > 1.5 bar, such
20 as, for example, isobutane, n-butane, propane/n-butane mixtures).

The solution contains the following ingredients

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	per 35 g:	
	budesonide	0.01820 g
	Lanette 0	0.45500 g
	Eumulgin B1	0.09100 g
5	Eumulgin B2	0.09100 g
	sorbic acid	0.00845 g
	Komplexon	0.03000 g
	citric acid ad pH 3.5	0.01000 g
	aqua purificata	0.90000 g
10	propylene glycol ad	35.0000 g

The solution produced in this way proved to be stable after storage at 40°C for several months.

Example 8

15	budesonide	0.01820 g
	Lanette 0	0.45500 g
	Eumulgin B1	0.09100 g
	Eumulgin B2	0.09100 g
20	benzoic acid	0.06000 g
	citric acid ad pH 4.0	q.s.
	aqua purificata	0.90000 g
	propylene glycol ad	35.0000 g

The solution produced in this way proved to be stable after storage at 40°C for several months.

Example 9

	budesonide	0.01820 g
30	Lanette 0	0.45500 g
	Eumulgin B1	0.09100 g
	Eumulgin B2	0.09100 g
	Komplexon	0.03000 g
	tartaric acid ad pH 4.5	q.s.
35	aqua purificata	0.90000 g
	propylene glycol ad	35.0000 g

The solution produced in this way proved to be stable after storage at 40°C for several months.

Example 10Investigations of the stability of the solutions
according to the invention

Formulations were produced as in Example 7 with 5 different pH values and were investigated for their stability after storage for 0 - 6 months. The following results were obtained:

Content after storage at

pH	0 months	3 months 25°C	3 months 40°C	6 months 40°C
7.5 without additions	100.0 %	90.4 %	75.0 %	not determined
7.5 with Komplexon	100.0 %	103.0 %	96.5 %	89.5 %
4.5 (94073) with Komplexon, with citric acid	100.0 %	102.5 %	97.8 %	94.6 % (9 months)
4.0 (95030) with Komplexon, with citric acid	100.0 %	97.6 %	98.0 %	-
3.5 (95035) with Komplexon, with citric acid	100.0 %	100.8 %	100.2 %	- -

Table 4

10 The above test results prove that the alcoholic budesonide solutions according to the invention with a pH below 6 are still stable even after storage for several months. Solutions which additionally contain Komplexon are particularly stable. The losses of active
15 substance occurring even after storage at 40°C for 6 - 9 months are extremely small.

CLAIMS

1. A stable sodium-EDTA containing budesonide-solution with a pH between 5.0 and 3.5, wherein the budesonide is dissolved in a solvent selected from the group consisting of water, alcohol or a water/alcohol-mixture, wherein the alcohol is selected from the group consisting of ethanol, isopropanol or propylene glycol and which contains 0.01 to 0.1 % by weight of sodium EDTA.
2. A stable budesonide-solution as claimed in claim 1 which additionally comprises cyclodextrin.
3. A stable budesonide-solution as claimed in any of 1 or 2 claims which comprises 0.001 to 0.1 % by weight of budesonide.
4. A stable budesonide-solution as claimed in any of claims 1 to 3 which comprises 0.05 to 1.0 % by weight of cyclodextrins.
5. A process for producing stable budesonid containing solutions as claimed in any of claims 1 to 4 which comprises dissolving of budesonid and sodium-EDTA in a solvent selected from the group consisting of water, alcohol or a water/alcohol-mixture whereby the alcohol is selected from the group consisting of ethanol, isopropanol or propylene glycol and adjusting the pH of the budesonide solution between 5.0 to 3.5.
6. An enema which comprises a stable budesonide-solution as claimed in any of claims 1 to 4.
7. A rectal foam which comprises a stable aqueous budesonide-solution as claimed in any of claims 1 to 4.
8. The use of a stable budesonide-solution as claimed in any of claims 1 to 4 for producing an enema.
9. The use of a stable budesonide-solution as claimed in any of claims 1 to 4 for producing a rectal foam.