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SPRAYING DEVICE COMPRISING AQUEOUS BUDESONIDE COMPOSITION

FIELD OF INVENTION

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The present invention relates to a spraying device comprising an aqueous buffered composition of solubilized budesonide having improved storage stability.

10 INTRODUCTION

WO2017009480 discloses a method of substantially increasing the solubility of poorly water-soluble hydrophobic drugs in aqueous solutions. The method comprises dissolving the hydrophobic drug in a suitable
15 organic solvent and mixing the organic solvent with an aqueous buffer solution comprising a saponin component selected from the group of escin, glycyrrhizin and Quillaja saponaria extract, alongwith dexpanthenol and optionally further additives. The solubilization process is based on the formation of saponin micelles in a buffered aqueous environment.

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One such poorly water-soluble drug is budesonide (CAS No. 51333-22-3), a glucocorticoid known inter alia as an agonist of glucocorticoid receptors and for having antiinflammatory activity. It is therefore frequently used to treat inflammatory conditions of the lungs and intestines
25 such as asthma, COPD, Crohn's disease, or ulcerative colitis. The solubility of this drug in water being less than 30 $\mu\text{g/ml}$. Attempts to solubilize budesonide following the method disclosed in WO2017009480, i.e. dissolving budesonide in a phosphate buffered aqueous solvent comprising beta-escin, glycyrrhizin, polypropylene glycol, and dexpanthenol
30 as essential ingredients, resulted in aqueous preparations comprising up to approximately 850 $\mu\text{g/ml}$. While this tremendous increase in solubilized drug was indeed stunning the long-term stability of the preparations was not fully satisfactory and resulted in the formation of undesired degradation and/or reaction products of part of the ingredients.

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Therefore, there was a need to overcome this deficiency and to provide a stable aqueous preparation comprising a reasonably high concentration of dissolved or, more precisely, solubilized budesonide essentially without undesired impurities from decomposition and/or reaction products of
40 some of the ingredients.

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DESCRIPTION OF THE INVENTION

Solubilized budesonide formulations prepared in accordance with the teaching of WO2017009480A1 contain dexpantenol typically in a concentration range of from 0.5 to 5% (w/v). Dexpantenol is used in these formulations to maximize the solubilization capacity and to stabilize the solubilization of budesonide against precipitation during storage at room temperature, i.e. 20 - 25 °C. As indicated above, following the teaching of WO2017009480A1 it is possible to solubilize up to about 850 µg/ml of budesonide and keep it solubilized for long-term storage.

However, evaluating the stability of long-term storage of a hydrophic drug in an aqueous solvent system does not only cover the determination of unimpaired maintenance of drug concentration throughout the storage period but shall also include checking for the chemical stability of the entire solubilization system over the envisaged storage period.

Chemical degradation or decomposition of one or more of the ingredients of an aqueous buffered pharmaceutical composition, including the active pharmaceutical ingredient (API), as well as possible reaction products emerging as the result of chemical interactions between two or more of the ingredients and/or decomposition compounds can be stability limiting. Such degradation, decomposition, and/or reaction products are generally considered undesired impurities and present an impediment to obtaining marketing authorization, potentially limiting the availability of useful therapies.

It is therefore imperative to remove such impurities to the extent possible from aqueous formulations intended for use as pharmaceutical compositions and/or to find ways to avoid the development of such impurities in aqueous solutions comprising solubilized drugs.

In connection with the solubilized budesonide formulations prepared in accordance with the teaching of WO2017009480A1 and including dexpantenol as part of the solubilization system it was found that the long-term storage stability of the formulations was substantially impaired by the gradual development of an initially unknown and unexpected contaminant, hereinafter designated impurity R", and in addition, by a second contaminant, hereinafter referred to as "impurity D".

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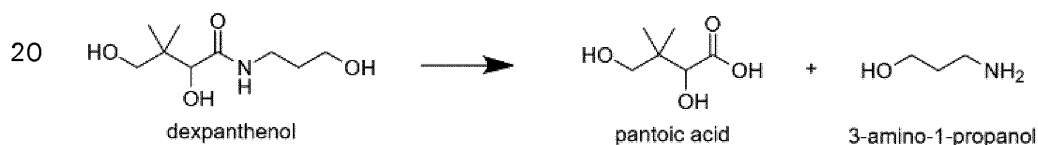
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"Impurity D" is known in the art as 21-dehydro-budesonide, an oxidation product gradually emerging during storage of an aqueous budesonide formulation at ambient temperature. It is not generated by chemical interaction with dexpanthenol or other constituents of the formulation.

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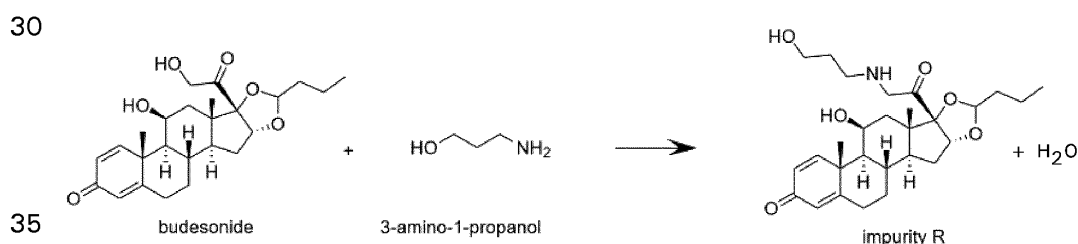
Contrary to impurity D, structural analysis of impurity R revealed that it is a reaction product of budesonide with 3-amino-1-propanol (3AP). 3AP is a known contaminant of commercially available dexpanthenol, the presence of which being acceptable at concentrations of up to 0.5 % in samples conforming to the European Pharmacopoeia (EP), and at concentrations of up to 1.0 % in samples conforming to the United States Pharmacopoeia (USP). Furthermore, during storage of aqueous formulations containing dexpanthenol 3AP forms in a time- and temperature-dependent manner due to hydrolysis, following a reaction scheme indicated by Formula I. This hydrolysis reaction is relatively slow at neutral pH but accelerates at acidic or basic conditions.

Formula I:



Where dexpanthenol is present in an aqueous solvent system together with budesonide the following chemical reaction takes place during prolonged storage (Formula II) resulting in the formation of 21-(3-hydroxypropyl)amino budesonide, i.e. impurity R.

Formula II



In order to limit or prevent the formation of impurity R it was investigated whether or not a reduction of the dexpanthenol concentration in the buffered aqueous composition or even a complete removal of dexpanthenol from the aqueous composition would cause substantial

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losses in drug concentration during storage. From WO2017009480A1 it was known that dexpanthenol has both a solubilizing as well as stabilizing effect on budesonide in a buffered aqueous solvent system.

- 5 Quite surprisingly, however, and contrary to expectations the reduction and even full elimination of dexpanthenol from the present experimental aqueous compositions did not induce precipitation of budesonide during storage at room temperature over several months. This surprising behaviour may be attributed to experimental variations of the present
- 10 aqueous solubilizing system relative to the one disclosed in WO2017009480A1, namely comprising the preferred selection of alpha-escin as opposed to beta-escin as the saponin component, an experimental budesonide concentration of less than 850 $\mu\text{g/ml}$ used in WO2017009480A1, preferably 100 - 400 $\mu\text{g/ml}$, or typically 200 $\mu\text{g/ml}$,
- 15 and adjusting the aqueous formulation to a pH lower than pH 5.65 used in WO2017009480A1, preferably to a pH of from 4 to 5, and typically to a pH of about 4.3.

Escin: While the current nomenclature of escins is based on a differentiation of the individual molecules contained in the mixture of components, the previously used nomenclature distinguished the mixtures of escin components based on their water solubilities. The main fraction of a naturally occurring escin mixture obtainable from horse chestnut extract consists of a compound having a protoescigenin backbone esterified with acetic acid at the C-22 position and with angelic/tiglic acid at the C-21 position (Geisler et al., 2019). This main fraction is called beta-escin. Besides beta-escin, two other fractions are identified in the escin mixture, namely alpha- and crypto-escin, wherein alpha-escin is a mixture of crypto- and beta-escin.

- 30 Beta- and crypto-escin differ in the position of the acetyl group in the backbone. Whereas in beta-escin, in more recent literature also called escin Ia and Ib, this group is located at C-22, it can be found at C-28 in crypto-escin, the latter in more recent literature also called isoescin Ia and Ib, wherein "a" stands for tigloyl and "b" stands for angloyl esterification (Savarino et al, 2023). Both forms can be distinguished by their solubilities in water, their melting points and their hemolytic indices. For example, crypto-escin is soluble in water whereas beta-escin is not readily soluble in water or buffered solutions having a pH of less
- 40 than pH 5 (Geisler et al., 2019). On the other hand, alpha-escin being a

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4:6 mixture of beta-escin and crypto-escin is better soluble in water than pure beta-escin. In addition, whereas alpha-escin remains stable in water or aqueous buffers in the absence of dexpanthenol, beta-escin precipitates in water or aqueous buffers after some hours in the absence
5 of dexpanthenol, but not in the presence of dexpanthenol. It was therefore decided to elect alpha-escin as the preferred saponin component for solubilizing budesonide in the aqueous experimental samples. While commercial escin preparations usually contain both α - and β -escins, α -escins may be formed by simply heating aqueous
10 solutions of β -escins which causes acyl migration involving the hydroxyl groups at positions C21, C22, and C28.

An even further improvement of storage stability was achieved by reducing the development of impurity D. As disclosed hereinbefore,
15 storage stability of aqueous preparations of solubilized budesonide is limited by an oxidation reaction of budesonide, in which 21-dehydro budesonide (designated "impurity D" herein) is formed. The speed and rate of formation of this impurity D can be significantly reduced by preventing permeation of molecular oxygen into the liquid preparations.
20 This can be achieved, for example, by using protective secondary packaging impermeable to oxygen.

During the final steps of preparation of the liquid budesonide formulations, as well as during the subsequent steps of filling the liquid
25 formulations into primary containers and packaging the same into secondary containments under normal atmosphere small amounts of oxygen may still dissolve in the formulations and/or be part of the headspace of the primary and secondary containments. It was experimentally confirmed that even these small amounts are sufficient to
30 generate substantial amounts of impurity D upon storage.

One way of avoiding such undesired oxygen intake into the final preparations is performing the filling process under inert gas atmosphere. Alternatively, or additionally, the oxidation of budesonide can be limited
35 by including inside the secondary packaging containments oxygen absorbing agents commercially available for the protection of oxygen sensitive products.

For pharmaceutical development purposes, the effect of several external
40 parameters on the formation of 21-dehydrobudesonide (impurity D) has

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been tested. It was hypothesized that by reducing the O₂ ingress from the surrounding environment during storage, the formation of impurity D can be reduced even with iron and other metal ions present in the liquid ready-for use formulations.

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Iron ions can leak into the ready-for-use formulations during production from stainless-steel tanks or pipes. Furthermore, primary packaging such as amber glass vials or nasal spray pumps contain iron ions. These iron ions can catalyze the oxidation reaction of budesonide via oxygen

10 radicals. In a first series of experiments it was shown that using HDPE vials instead of amber glass vials as the primary packaging containments, and running an entirely metal free manufacturing and filling process substantially reduced the formation of impurity D.

15 In a follow-up study the content and purity of budesonide in a ready-for-use formulation was monitored over time, wherein the formulation was stored in a primary packaging (HDPE vial) protected by a secondary packaging, i.e. a hermetically sealed, oxygen-impermeable bag additionally equipped with one or more oxygen absorber packets or
20 sachets. For this purpose, a buffered aqueous formulation comprising 200 µg/ml budesonide and adjusted to pH 4.3 was prepared using different equipment for the manufacturing processes, i.e. on one hand solely glass equipment and on the other hand stainless-steel equipment. Samples were stored in HDPE vials (Röchling, Germany) and closed with
25 either APF or Classic Line nasal spray pumps (manufacturer Aptar, Germany). The filled vials were stored either unsealed or sealed in aluminum-coated bags with or without O₂/H₂O absorber sachets at 25 and 40 °C in constant climate chambers with controlled humidity. Samples were analyzed on day 0 and after 2 weeks, 1 month and 3
30 months storage. Budesonide content as well as related impurities were quantified using a validated RP-HPLC method. In addition, pH and appearance of the samples were recorded at each time point.

As a result of the foregoing, excellent storage stability was achieved at
35 substantially reduced formation of impurity D when using oxygen absorbing agents inside the secondary packaging containments. Where such oxygen absorbing agents released water upon absorption of oxygen it proved advantageous to also include a desiccant agent inside the secondary packaging, in order to eliminate developing moisture.

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BRIEF DESCRIPTION OF THE FIGURES

- Figure 1: Representation of relative budesonide concentrations in aqueous buffered formulations containing solubilized budesonide, alpha-escin, and 0%, 2% or 5 % v/v dexpanthenol, expressed as percentage of recovered budesonide in the samples after 12 months of storage at 25°C, relative to the nominal starting concentration (i.e. 100%) of budesonide; analytical determination by HPLC;
y-axis: concentration of recovered budesonide in % of the nominal starting concentration; x-axis: 0%, 2%, 5% v/v dexpanthenol.
- Figure 2: Representation of contents of impurity R in aqueous buffered formulations containing solubilized budesonide, alpha-escin, and 0, 2 or 5 % dexpanthenol, determined by HPLC after 12 months of storage at 25°C;
y-axis: relative concentration of impurity R expressed as % of corresponding recovered budesonide concentrations; x-axis: 0, 2, 5 % v/v dexpanthenol.
- Figure 3: Representation of contents of impurity D in aqueous buffered formulations containing solubilized budesonide, alpha-escin, and 0, 2 or 5 % v/v dexpanthenol, determined by HPLC after 12 months of storage at 25°C;
y-axis: relative concentration of impurity D expressed as % of corresponding recovered budesonide concentrations; x-axis: 0, 2, 5 % v/v dexpanthenol.
- Figure 4: Representation of contents of total impurities (including impurities "D" and "R") exceeding 0.1% in aqueous buffered formulations containing solubilized budesonide, alpha-escin, and 0, 2 or 5 % dexpanthenol, determined by HPLC after 12 months of storage at 25°C;
y-axis: relative concentration of accumulated impurities including impurities R, D, and possible further impurities, expressed as % of corresponding recovered budesonide concentrations; x-axis: 0, 2, 5 v/v dexpanthenol.
- Figure 5: Impurity D content (in percent relative to the budesonide content) of samples prepared in glass containers and stored in the indicated primary and secondary packaging for up to 6 months at 25 °C. Data presented as mean (n = 2);

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- 1 = APF-glass-sealed plus, i.e. glass container equipped with APF spray pump and packaged in sealed bag containing O₂/H₂O absorber material;
2 = Classic-glass-sealed plus; i.e. glass container equipped with classic spray pump and packaged in sealed bag containing O₂/H₂O absorber;
5 3 = APF-glass-not sealed, i.e. glass container equipped with APF spray pump, no secondary package;
4 = APF-glass-sealed, i.e. identical to 1 but without O₂/H₂O absorber;
5 = Classic-glass-not sealed, i.e. glass container equipped with classic spray pump, no secondary package;
10 6 = Classic-glass-sealed, i.e. identical to 2 but without O₂/H₂O absorber.

Figure 6: Impurity D content (in percent relative to the budesonide content) of samples prepared in metal containers and stored in the indicated primary and secondary packaging for up to 6 months at 25 °C. Data presented as mean (n = 2);

- 15 1 = APF-metal-sealed plus, i.e. metal container equipped with APF spray pump and packaged in sealed bag containing O₂/H₂O absorber material;
2 = Classic-metal-sealed plus; i.e. metal container equipped with classic spray pump and packaged in sealed bag containing O₂/H₂O absorber;
20 3 = APF-metal-not sealed, i.e. metal container equipped with APF spray pump, no secondary package;
4 = APF-metal-sealed, i.e. identical to 1 but without O₂/H₂O absorber;
5 = Classic-metal-not sealed, i.e. metal container equipped with classic spray pump, no secondary package;
6 = Classic-metal-sealed, i.e. identical to 2 but without O₂/H₂O absorber.

- 25 Figure 7: Impurity D content (in percent relative to the budesonide content) of samples prepared in glass containers and stored in the indicated primary and secondary packaging for up to 6 months at 40 °C. Data presented as mean (n = 2);

- 1 = APF-glass-sealed plus;
30 2 = Classic-glass-sealed plus;
3 = APF-glass-not sealed;
4 = APF-glass-sealed;
5 = Classic-glass-not sealed;
6 = Classic-glass-sealed.

- 35 Figure 8: Impurity D content (in percent relative to the budesonide content) of samples prepared in metal containers and stored in the indicated primary

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and secondary packaging for up to 6 months at 40 °C. Data presented as mean (n = 2);

- 1 = APF-metal-sealed plus;
- 2 = Classic-metal-sealed plus;
- 5 3 = APF-metal-not sealed;
- 4 = APF-metal-sealed;
- 5 = Classic-metal-not sealed;
- 6 = Classic-metal-sealed.

- Figures 9A, 9B: Budesonide drug contents during storage of dexpanthenol-free samples prepared in glass containers and stored in the indicated primary and secondary packaging for up to 6 months at 25, 30 and 40 °C. Data presented as mean (n = 2);

- a = APF, 25 °C;
- b = Classic, 25 °C;
- 15 c = APF, 30 °C;
- d = Classic, 30 °C;
- e = APF, 40 °C;
- f = Classic, 40 °C;

Fig. 9A: Budesonide contents in absolute values ($\mu\text{g/ml}$);

- 20 Fig. 9B: Budesonide contents in % of initial value at day 0.

- Figures 10A, 10B: Impurity contents during storage of dexpanthenol-free samples prepared in glass containers and stored in the indicated primary and secondary packaging for up to 6 months at 25, 30 and 40 °C. Data presented as mean (n = 2);

- a = APF, 25 °C;
- b = Classic, 25 °C;
- c = APF, 30 °C;
- d = Classic, 30 °C;
- 30 e = APF, 40 °C;
- f = Classic, 40 °C;

Fig. 10A: Impurity D contents in % relative to the budesonide contents;

Fig. 10B: Total impurities contents in % relative to the budesonide contents.

EXAMPLE 1: In situ formation of decomposition and/or reaction products during prolonged storage of aqueous solubilized budesonide compositions

Table 1: Experimental composition

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Ingredient	Concentration [mg/ml]
Budesonide	0.2
Propylene glycol	104 (10% v/v)
Dexpanthenol	0 - 50
EDTA	1.0
alpha-Escin	0.3
Citric acid monohydrate	10.4
Trisodium citrate dihydrate	14.85
Water for injection	q.s.
HCl for pH adjustment	q.s.
pH	4.3

All experimental formulations were stored in capped HDPE vials at 20-25 °C.

10 As can be taken from Fig. 1, formulations comprising 200 µg/mL budesonide dissolved in a buffered aqueous solution comprising the ingredients listed in Table 1 and adjusted to a pH of 4.3, exert a concentration-dependent negative effect on the storage stability of the experimental samples. More specifically, while formulations without
15 dexpanthenol stably maintained budesonide in solution over an observation period of 12 months at 20 - 25 °C, the addition of 2% v/v dexpanthenol caused a decline in recoverable budesonide from about 96% (no dexpanthenol) to about 94% (2% dexpanthenol), and the addition of 5% dexpanthenol caused a further decrease of recoverable
20 solubilized drug down to about 93 % of the nominal starting concentration of budesonide.

At the same time, the concentration of "impurity R" increases with increasing dexpanthenol concentration, as depicted in Fig.2. Or in other
25 words, eliminating dexpanthenol from the experimental samples resulted in the prevention of in situ formation of impurity R during storage at ambient temperature.

Furthermore, the reduction or elimination of dexpanthenol in these formulations not only reduced or eliminated the formation of impurity R

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in the experimental samples but also reduced the formation of impurity D (see Fig. 3). It was quite surprising that a concentration-dependent reduction of the formation of impurity D was observed with the experimental samples.

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Without being bound by theory, this unexpected finding may possibly be due to the formation of impurity R in the presence of dextran, which impurity R, i.e. 3-amino-1-propanol (3AP), is a basic compound bearing a primary amine functional group. With increasing concentrations of 3AP in the experimental samples the pH also slightly increased despite the buffer system used in the solvent. Taking into account that the formation of the budesonide oxidation product (i.e. impurity D) is favored at higher pH, this might explain the observed effect of parallel increase or decrease of impurities R and D.

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From this example it can further be concluded that providing an aqueous solvent system for solubilizing budesonide under the conditions defined in Table 1 allows for completely surrendering dextran as an obligatory ingredient for stably maintaining budesonide in a solubilized state over at least 12 months of storage at room temperature. As a beneficial side-effect of eliminating dextran from the aqueous budesonide formulations the in situ formation of undesired impurities R and D during storage of the liquid formulations is substantially reduced, as can also be taken from Fig. 4, which Fig. 4 is a graphic representation of the sum of all impurities determined by HPLC in the samples including impurities R and D.

EXAMPLE 2: Effect of sealed storage on the stability of liquid budesonide preparations

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Impurity D is formed by oxidation of budesonide at the C21 hydroxyl group yielding an aldehyde group instead. This reaction is effected by molecular oxygen and catalyzed by ions of transition metals such as, e.g., iron, manganese, copper, zinc, nickel, and others.

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Abbreviations used hereinafter:

ACN	Acetonitrile
AD	Aqua destillata
EDTA	Ethylenediaminetetraacetic acid
40 HDPE	High density polyethylene

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HPLC	High performance liquid chromatography
L/N	Lot number
PG	Propylene glycol
RP-HPLC	Reversed phase high performance liquid chromatography
5 RRF	Relative retention factor
SS	Stainless steel
S/N	Serial number
UV/Vis	Ultraviolet/Visible

- 10 The experimental budesonide preparations used for this study comprised the following ingredients:

Budesonide, micronized	0.207 mg/ml
Propylene glycol	10 % (v/v)
15 Dexpanthenol	50 mg/ml
EDTA	1.00 mg/ml
Escin	0.3 mg/ml
Citric acid monohydrate	10.4 mg/ml
Trisodium citrate dihydrate	14.85 mg/ml
20 pH	4.3

Further relevant equipment comprised:

10 ml Snap on bottle, white, sterile	/Röchling Medical Neuhaus GmbH
25 Snap-on nasal spray pump, APF, 50 μ l	/Aptar
Crimp on nasal spray pump, Classic Line, 50 μ l	/Aptar
Sartopore 2	/Sartorius
Bottle Top Filter	/TPP
Aluminum-coated bags	
30 (material: A 20T (12 μ PET/ 12 μ ALU/ 75 μ LDPE)	/Long life for art
O2 Absorber ATCO FT 100 (0.5 Liter)	/Long life for art
H2O Absorber (Minibag 1 g)	/Long life for art
HPLC col. Agilent Eclipse Plus C18 150x4.6mm, 3.5 μ m	/Agilent

- 35 Two experimental preparations with the same composition of ingredients (details see above) were prepared in different containers, i.e. in either glass or stainless steel containers. After sterile filtration, each preparation was filled into two different primary packaging systems – either HDPE vials (Röchling,

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Germany) closed with a 50 μ l APF nasal spray pump (Aptar, Germany), or HDPE vials (Röchling, Germany) closed with a 50 μ l Classic line nasal spray pump (Aptar, Germany). The different primary packaging systems were stored unsealed, sealed in aluminum-coated bags, or sealed in aluminum coated bags additionally containing O₂ and H₂O absorber sachets. The preparations were stored at two different temperatures, i.e. 25 °C at a relative humidity of 65%, and 40 °C at 75% r.h. Samples were taken at day 0 and after 2 weeks, 1, 3 and 6 months of storage and analyzed for the most relevant stability indicating parameters, i.e. budesonide content, impurity D content, impurity R content measured at 240nm, sum of all impurities present, and pH. Furthermore, as a control identical preparations without the drug budesonide were prepared and filled into identical different primary packaging systems and stored unsealed or sealed under identical conditions.

15 Samples of each experimental preparation before final sterile filtration were also taken and subjected to HPLC analysis, in order to check for possible filtration losses.

After filling, vials labelled "unsealed" were directly placed in a crate for storage. Vials labelled "sealed" were placed in aluminum-coated bags and sealed using an appropriate sealing press, and vials labelled "sealed plus" were placed in aluminum-coated bags additionally equipped with O₂ and H₂O absorber sachets and sealed using an appropriate sealing press. For HPLC analysis of the day 0 contents, samples of the experimental preparations were filled directly into HPLC sample vials rather than into the experimental containments.

The experimental preparations were placed in a climate chamber set to either 25 °C / 60 % r.H., or to 40 °C / 75 % r.H., and stored for 6 months. A temperature logger was used to monitor and document the temperature during storage of the samples.

Results:

a) Preparations prepared in glass containers and stored in HDPE vials at 25°C

The budesonide content decreased by 3 – 4.5 % over 6 months. The best results, i.e. lowest drug losses, were achieved when using the APF nasal spray pump for capping and closing the vials, and placing the closed vials (=

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primary packaging) in hermetically sealed oxygen-impermeable bags (= secondary packaging) additionally equipped with O₂/H₂O absorber sachets; the samples still contained 189.4 µg/ml budesonide after 6 months of storage, equivalent to 97 % recovery based on the day 0 values.

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Similarly, using the Classic Line nasal spray pump for closing the experimental vials and having the closed vials sealed in secondary packaging bags including O₂/H₂O absorbers led to fairly low content losses; the samples contained 188.3 µg/ml after 6 months of storage, equalling 97 % recovery based on the day 0 values. Generally, using the Classic Line nasal spray pump, resulted in slightly greater drug content losses compared to respective APF nasal spray pump samples.

On the other hand, the formation of impurity D in the samples packaged using the APF nasal spray pump yielded impurity D values of 0.3 – 0.5 % relative to the budesonide content. The lowest increase of impurity D was found in the sealed samples plus O₂/H₂O absorbers (see Fig. 5).

In comparison, packaging with the Classic Line nasal spray pump led to an impurity D content of around 1.3 % of the drug content after 6 months storage at 25 °C; except for the samples stored in the sealed plus O₂/H₂O absorber secondary packaging, wherein the level of impurity D did not exceed 0.38 % of the drug content. A value comparable to the values obtained with APF nasal spray pump primary packaging.

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The impurity R content in samples stored at 25 °C increases to 2 % of the starting budesonide content regardless of the choice of primary and secondary packaging.

Analytical determination of the sum of all impurities formed over the 6 months storage period at 25 °C revealed that samples stored in sealed packaging plus O₂/H₂O absorbers showed the lowest impurities content regardless of the choice of the nasal spray pump, i.e. 2.5 – 2.6 % of the drug content. The highest overall impurity content was determined in samples packaged using the Classic Line pump (3.4 % - not sealed, 3.5 % - sealed). However, when using the APF nasal spray pump, secondary packaging had no substantial influence on the overall sum of impurities, the total impurities amounting to 2.5 – 2.7 % of the starting drug content.

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b) Preparations prepared in stainless steel containers and stored in HDPE vials at 25 °C

When the experimental preparations were obtained from metal containers of stainless steel, the budesonide drug content decreased by 2 - 4 % over 6 months when stored at 25 °C/60% relative humidity. The lowest content loss was found in samples packaged in HDPE vials using the APF nasal spray pump for closure and sealing bags plus O₂/H₂O absorbers as secondary packaging system; the samples still contained 189.6 µg/ml after 6 months of storage, which is equivalent to 98 % drug recovery based on the day 0 values.

When using vials capped with the Classic Line nasal spray pump and sealed in bags plus O₂/H₂O absorbers the experimental samples contained 188.4 µg/ml after 6 months of storage corresponding to 98 % recovery based on day 0 starting values. Again, using the Classic Line nasal spray pump closure system resulted in a slightly greater drug content loss compared to respective samples using the APF nasal spray pump closure system.

The formation of impurity D in the samples packaged using the APF nasal spray pump yielded impurity D contents of 0.2 – 0.8 % of the budesonide content. The smallest increase of impurity D was found in the samples labelled "sealed plus O₂/H₂O absorbers".

In comparison, primary packaging using the Classic Line nasal spray pump for closure led to impurity D contents of around 2 % of the drug content after 6 months storage at 25 °C; except for the samples in the sealed bag plus O₂/H₂O absorber secondary packaging system which yielded impurity D contents of only up to 0.6 % of the drug content. (Fig. 6)

The impurity R content in samples stored at 25 °C increases to 2 % of the starting budesonide content regardless of the choice of primary and secondary packaging.

Analytical determination of the sum of all impurities formed over 6 months storage at 25 °C revealed that samples stored in sealed packaging plus O₂/H₂O absorbers showed the lowest impurities content regardless of the choice of the nasal spray pump, i.e. total impurities in an amount of 2.4 and 2.8 % of the drug content. Highest overall impurity contents were determined

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in samples packaged using the Classic Line pump (4.3 % - not sealed, 4.3 % - sealed).

c) Preparations prepared in glass containers and stored in HDPE vials at 40 °C

The budesonide content decreased by 10 – 20 % over 6 months in the samples stored at 40 °C / 75% relative humidity. The best results, i.e. the lowest drug content losses were achieved with samples packaged using the APF nasal spray pump for closing the HDPE vials and sealing bags plus O₂/H₂O absorber material as a secondary packaging system; the samples still contained 174.4 µg/ml after 6 months of storage, corresponding to 90 % drug recovery based on the day 0 values.

Surprisingly, the biggest drug losses were detected when using the Classic Line nasal spray pump with vials hermetically sealed in bags plus O₂/H₂O absorbers; the samples contained only 155 µg/ml budesonide after 6 months of storage, corresponding to 80 % recovery relative to the day 0 starting values. Generally, the Classic Line nasal spray pump system caused greater drug content losses than the APF nasal spray pump system.

The formation of impurity D was lowest in the samples stored in sealed secondary packaging plus O₂/H₂O absorbers, resulting in an impurity D content of 0.42% of the budesonide content. Samples stored unsealed or sealed without absorbers contained impurity D in an amount of around 2.6 and 2.5 %, respectively, relative to the budesonide content.

In comparison, packaging using the Classic Line nasal spray pump was accompanied with impurity D contents of 8 – 12.6 % of the budesonide content after 6 months storage at 40 °C. The level of impurity D was much higher compared to the values determined when using the APF nasal spray pump in the primary packaging system (see Fig.7).

Not surprisingly, impurity R contents were only slightly different among the different types of primary and secondary packaging. Samples packaged with APF nasal spray pumps contained 9.3 – 9.8 % impurity R, while samples packaged with Classic line nasal spray pumps contained 8.7 – 9 % impurity R, relative to the budesonide content.

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Analytical determination of the sum of all impurities formed over 6 months storage at 40 °C revealed that samples packaged using APF nasal spray pumps showed the lowest impurities content regardless of the selection of secondary packaging, ie. the total impurities amounting to 10.3 – 12.6 % of the budesonide content. The highest overall impurity content was determined in samples packaged using the Classic Line pump, i.e. 21.2 % - not sealed, 21.9 % - sealed plus O₂/H₂O absorbers.

d) Preparations prepared in stainless steel containers and stored in HDPE vials at 40°C

The budesonide content decreased by 10 - 20 % over 6 months in samples stored at 40 °C / 75% relative humidity. The lowest losses were found in samples packaged using the APF nasal spray pump and sealing bags plus O₂/H₂O absorbers; the samples still contained 174.2 µg/ml after 6 months of storage, corresponding to 90 % drug recovery, relative to the day 0 drug content.

When testing the experimental vials closed with the Classic Line nasal spray pump and sealed in bags plus O₂/H₂O absorbers the samples contained only 171.2 µg/ml after 6 months of storage (89 % recovery based on day 0 values). Again, using the Classic Line nasal spray pump with the experimental vials resulted in slightly greater drug losses as compared to the situation in experimental vials using the APF nasal spray pump closing system.

The formation of impurity D was lowest in samples packaged using the APF nasal spray pump, sealed in bags plus O₂/H₂O absorbers. After 6 months at 40 °C / 75 % relative humidity the samples showed impurity D contents of only 0.9 % of the drug content.

In comparison, primary packaging using the Classic Line nasal spray pump led to impurity D contents of about 1.7 – 13.7 % of the budesonide drug content, greatly depending on the nature of the secondary packaging. The smallest increase in impurity D was found in samples stored in the sealed bags plus O₂/H₂O absorbers secondary packaging, i.e. 1.7 % of the drug content (Fig.8).

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Again, impurity R contents in samples stored at 40 °C were only slightly different among the different types of primary and secondary packaging equipment. Samples packaged using APF nasal spray pumps contained 9.3 – 9.7 % impurity R, while samples packaged using Classic line nasal spray pumps contained 8.7 – 9.5 % impurity R, relative to the budesonide content. Analytical determination of all impurities formed over the 6 months storage period at 40 °C revealed that samples packaged using APF nasal spray pumps and sealed in bags plus O₂/H₂O absorbers showed the lowest total impurities content, i.e. 10.7 % of the budesonide content. Samples packaged using Classic Line nasal spray pumps and sealed in bags plus O₂/H₂O absorbers showed the second lowest total impurities content, i.e. 11.4 % of drug content. The highest overall impurity content was determined in samples packaged using the Classic Line pump, i.e. 22.8 % - not sealed, and 18.0 % - sealed.

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EXAMPLE 3: Effect of sealed storage on the stability of dexpanthenol-free liquid budesonide preparations

Example 2 was repeated except that the aqueous buffered composition did not contain dexpanthenol. The experimental solutions were prepared in metal-free glass containers and filled into HDPE vials, capped with either the classic line spray pump system or with the metal-free APF spray pump system, as described in Example 2. The closed ready-for-use spraying devices comprising the experimental dexpanthenol-free budesonide solution were stored for 6 months as described in Example 2 with the following variations:

- a) storage at 25 °C / 60 % relative humidity (rh)
- b) storage at 30 °C / 75 % relative humidity (rh)
- c) storage at 40 °C / 75 % relative humidity (rh)

Not surprisingly, the best stability results, i.e. the least drug losses, were determined with the samples utilizing the APF spray pump system and the spraying devices sealed in the oxygen-impermeable bags. It can also be derived from the results depicted in Table 2 and Figures 9A, 9B, 10A and 10B, that the storage temperature has a clear yet relatively low impact on the long-term stability of the budesonide preparations provided and stored in metal-free containments in line with the present invention. Also, the dexpanthenol-free preparations come with reduced drug losses and reduced levels of impurities,

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particularly impurity D, as compared with the dexpanthenol-supplemented sample preparations of Examples 1 and 2.

Table 2

40 °C / 75% rH			30 °C / 75% rH		25 °C / 60% rH	
	APF	Classic	APF	Classic	APF	Classic
t [mo]						
	Budesonide [ug/ml]		Budesonide [ug/ml]		Budesonide [ug/ml]	
0	204.07	204.07	204.07	204.07	204.07	204.07
1	200.03	198.02				
2	199.07	196.36				
3	198.42	194.77	200.24	195.83	200.54	198.85
6	192.57	187.08	199.68	197.41	200.12	199.72
	% Budesonide		% Budesonide		% Budesonide	
0	100.00	100.00	100.00	100.00	100.00	100.00
1	98.02	97.04				
2	97.55	96.22				
3	97.23	95.44	98.12	95.96	98.27	97.44
6	94.33	91.64	97.82	97.70	98.03	97.83
	% Impurity D		% Impurity D		% Impurity D	
0	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
1	0.1527	0.5802				
2	0.2353	0.5814				
3	0.2046	0.4664	0.1204	1.2963	0.1062	0.3921
6	0.6943	2.1353	0.1367	0.7512	0.1797	0.4188
	% Total impurities		% Total impurities		% Total impurities	
0	0.1093	0.1093	0.1093	0.1093	0.1093	0.1093
1	0.4846	0.9086				
2	0.7760	1.2010				
3	0.8061	1.2192	0.4548	1.8028	0.3630	0.8534
6	1.9089	3.0433	0.5676	1.3250	0.5263	0.8301

5

Conclusion

From the results disclosed hereinabove it can be taken that the effects of primary and secondary packaging on the formation of impurities in the experimental samples of liquid budesonide preparations were most

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pronounced with regard to the observed formation of impurity D, which is no surprise given that impurity D is an oxidation product of budesonide.

Generally, the levels of impurity D were higher in the primary containers closed with the APTAR Classic Line pump as compared to the primary
5 containers closed with the APF nasal spray pump of the same manufacturer. This observation may be due to the fact that the Classic Line pump contains two metal parts in the fluid path, i.e. a steel spring and the ball of the check valve, which metal parts may get into contact with the liquid budesonide preparation causing leaking out of some metal ions that are known to
10 catalyze and thus accelerate the formation of impurity D. Whereas the APF nasal spray pump is free of metal elements that could possibly get into contact with the liquid material.

Samples that were stored without sealing in oxygen-impermeable bags
15 generally showed the highest levels in impurity D, followed by vials that were sealed in these bags without oxygen absorber. A significant positive effect of sealing the samples in an oxygen impermeable protective bag without removing the oxygen from the atmosphere inside the bag was not observed, however.

20

The lowest levels of impurity D in vials fitted with Classic Line pumps were found in vials that were sealed in impermeable bags together with oxygen- and water absorbing sachets.

25 The levels of impurity D observed in vials closed with APTAR APF pumps were significantly lower than those fitted with Classic Line pumps. As for the Classic line pumps, highest levels of impurity D were observed in vials that were stored without being sealed within the impermeable bags, followed by vials that were sealed in these bags without oxygen absorber. The overall
30 lowest levels of impurity D were found in vials that were sealed in impermeable bags together with oxygen- and water absorbing sachets.

In fact, in APF-closed vials there was no further increase in the impurity D level past the 3-months time point. After 6 months storage at 25 and 40 °C,
35 the relative concentration of impurity D had only risen to 0.18 and 0.42% (relative to budesonide), respectively. With such low impurity D levels it seems possible to provide a packaging system that allows storage of the product for up to 12, or 18, or even 24 months, at room temperature.

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Concomitantly, the data also indicate that unfavorable storage conditions at increased temperatures of e.g. 40 °C, as may, for example, occur during shipping of the ready-for-use preparations to a final destination in a hot and humid region, or during storage in a retailer's shop without cooling facility in s
5 tropic or subtropic region, may not be that detrimental to budesonide preparations as possibly expected, provided suitable packaging is utilized in accordance with the present invention.

The presence of catalytically active metal ions seems to substantially
10 deteriorate the quality of the buffered, slightly acidic, aqueous budesonide preparations during storage even when applying oxygen ingress protection measures. This can be derived from the observation that preparations that came into contact with metal parts of the manufacturing and/or filling equipment generally had higher impurity D levels even in sealed and oxygen-
15 depleted packaging containments. This observation was also confirmed by the fact that inspite of filling the preparations into non-metal glass or HDPE vials it was sufficient for generating increasing impurity D levels to close said vials by metal-containing Classic Line pumps, even if said vials were sealed into oxygen impermeable bags as a secondary packaging.

20

Impurity R levels are, however, not affected by sealing and oxygen depletion. It can be concluded therefrom that the reaction between 3AP and budesonide does not proceed via initial formation of impurity D and the reaction of the primary amine in 3AP with the C21-aldehyde group of impurity D.

25

It can further be derived from the foregoing disclosure and working examples that the best results, i.e. the lowest overall impurity levels in the present aqueous buffered budesonide preparations, are achieved with preparations comprising alpha-escin as the sole saponin component and no dexpanthenol,
30 said preparations prepared in non-metal containments and transferred using metal-free filling equipment, typically after sterile filtration, into metal-free containments preferably made of glass or HDPE, said metal-free containments capped and closed with a spray pump for nasal delivery which is free of metal parts or wherein the sprayable liquid cannot get into contact with any metal
35 parts of the spray pump, such as the APTAR APF nasal spray pump, and further packaged into a sealed, oxygen depleted and preferably also moisture depleted, oxygen impermeable secondary packaging.

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CLAIMS

What is claimed

1. A spraying device comprising a containment and a spray pump
5 system, the containment filled with a buffered aqueous composition comprising budesonide solubilized therein, the buffered aqueous composition comprising
 - a buffer adjusted to a pH of from 4 to 5, preferably adjusted to pH
10 4.3;
 - propylene glycol at a concentration of from 5 to 15 %v/v, preferably of 10% v/v;
 - escin, preferably alpha-escin, as a sole saponin component, at a concentration of from 0.1 - 1 mg/ml, preferably 0.3 mg/ml;
 - 15 - EDTA at a concentration of from 0.5 - 2 mg/ml, preferably 1.0 mg/ml;
 - optionally dexpanthenol at a concentration of from 5 - 50 mg/ml and
 - solubilized budesonide at a nominal starting concentration of at least 100 $\mu\text{g/mL}$, preferably at least 200 $\mu\text{g/mL}$, typically from 200 to 400
20 $\mu\text{g/mL}$;characterized in that the buffered aqueous composition is a mixture of ingredients prepared in a metal-free container and stored in the containment of the spraying device, which containment is made of metal-free material and capped and closed with a spray pump system
25 suitable for nasal or buccal delivery of the aqueous buffered composition, wherein the capped and closed spraying device while being a primary packaging containment for the aqueous buffered composition is hermetically sealed into an oxygen-impermeable and oxygen-free secondary packaging containment, the latter preferably containing an
30 oxygen absorbing agent and optionally also a moisture absorbing agent.
2. The spraying device of claim 1, characterized in that those parts of the primary packaging containment including the spray pump system that are in physical contact with the buffered aqueous composition during
35 storage and/or operation are made of metal-free material.
3. The spraying device of claim 1 or 2, characterized in that the containment comprising the aqueous buffered composition is made of metal-free glass or HDPE.

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4. The spraying device of any one of claims 1 to 3, characterized in that the aqueous buffered composition is free of ions of transition metals selected from the group consisting of zinc, copper, cobalt, manganese, iron, nickel, cadmium, vanadium, molybdenum, titanium, and mercury.

5

5. The spraying device of any one of claims 1 to 4, characterized in that after storage at 20 - 25°C over a period of 12 months the aqueous buffered composition contains at least 90%, preferably at least 95 %, of the nominal starting concentration of solubilized budesonide, and no
10 more than 1%, relative to the solubilized budesonide concentration, of total impurities including impurities R and D.

6. The spraying device of any one of claims 1 to 5, characterized in that the buffer in the aqueous buffered composition is a citrate buffer, a
15 phosphate buffer, or a combination of both.

7. The spraying device of any one of claims 1 to 6, adapted for topical or systemic application, preferably adapted as a nasal spray or a mouth spray.

20

8. The spraying device of any one of claims 1 to 7 filled with a buffered aqueous composition comprising budesonide solubilized therein, for use as a medicament, preferably for use as a medicament in the treatment of inflammatory diseases or conditions.

25

9. The spraying device for use according to claim 8, wherein the inflammatory diseases or conditions are selected from inflammations of the respiratory pathways, of the lungs, of the intestines, of mucosal tissues, and of the skin.

30

10. Use of the spraying device referred to in any one of claims 1 to 7 for the manufacture of a medicament, preferably for a medicament useful in the treatment of inflammatory diseases or conditions, said inflammatory diseases or conditions preferably selected from
35 inflammations of the respiratory pathways, of the lungs, of the intestines, of mucosal tissues, and of the skin.