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Topically used corticosteroids: What is the big picture of drug product degradation?

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ABSTRACT

Corticosteroids are widely used in topical formulations such as creams (aqueous) and ointments (non-aqueous). The generally used corticosteroids show large molecular resemblance, where especially the 20-keto-21-hydroxyl group bound to the 17 carbon is important for their chemical stability. Oxidation in both aqueous and non-aqueous environment occurs for triamcinolone acetonide (TCA), hydrocortisone (HC) and desoximethasone (DS). Besides the 20-keto-21-hydroxyl group, TCA, HC and DS have different other moieties attached to the same C17. These moieties are shown to influence not only the type of degradation product formed but also the degradation kinetics. Seven degradation products are found in total and a degradation mechanism is proposed. Furthermore the transesterfication of betamethasone-17-valerate to betamethasone-21-valerate is shown to occur both in aqueous and non-aqueous environment. Finally, a comprehensive scheme of degradation pathways is presented that is applicable for both aqueous and non-aqueous formulations.

1. Introduction

Corticosteroids are anti-inflammatory agents of the steroid hormone class. Corticosteroids bind in the target cell to specific cytosolic glucocorticoid receptors and subsequently interact with glucocorticoid receptor response elements on DNA thereby altering gene expression (Storrs, 1979). The affinity for the glucocorticoid receptor differs for each corticosteroid. Since the 1950's corticosteroids are used for many skin diseases, such as eczema and psoriasis. For these applications, corticosteroids are used in aqueous (creams and lotions) and in non-aqueous formulations (ointments).

One of the concerns with corticosteroid shelf life is the chemical stability. According to the ICH guideline only limited amounts of degradation products may be present in the formulation (Ich, 2005). Furthermore the identification of degradation products is important. Degradation can be studied using stress testing, which is described extensively elsewhere (Baertschi, 2005).

Corticosteroids are prone to oxidative degradation. This degradation predominantly occurs at the 17-side chain of corticosteroid molecules (Hansen and Bundgaard, 1980; Lewbart and Mattox, 1963; Pearlman et al., 1984; Wu et al., 2012). Furthermore degradation of the A ring (Miolo et al., 2003; Ricci et al., 2001; Williams et al., 1980) or hydrolysis of the acetonide moiety (Timmins and Gray, 1983) has been described. A-ring degradation is a photochemical reaction and is considered irrelevant for most pharmaceutical formulations due to UV-protected packaging and is therefore not studied here. The 17-side chain generally consists of a 20-keto-21-hydroxyl group which is identical for the majority of corticosteroids. Nevertheless, several other possible side chains may be bound to the same 17-carbon atom, such as esters, hydroxyl and methyl groups. These extra side chain groups may result in altered potency and degradation mechanisms. The 20-keto-21-hydroxyl containing corticosteroids can be categorized into four groups, based on a different moiety on the 17-carbon atom, namely an acetonide, a hydrogen, a hydroxide or an ester (Fig. 1).

For all in Fig. 1 mentioned corticosteroid groups a small selection of for topical application relevant degradation products is described in literature. For triamcinolone acetonide (TCA) (van Heugten et al., 2018a; Wu et al., 2012) and hydrocortisone (HC) (Hansen and Bundgaard, 1980; Zhang et al., 2016) a 17-carboxylic acid and 21-aldehyde have been reported and for desoximethasone (DS) only a 17-carboxylic acid (Srinivasu et al., 2012). Specifically for HC a 17-ketone and a 17-carboxylic acid and 21-aldehyde without the 17-hydroxide moiety have been described (Hansen and Bundgaard, 1980; Zhang et al., 2016). An overview of these degradation products is presented in

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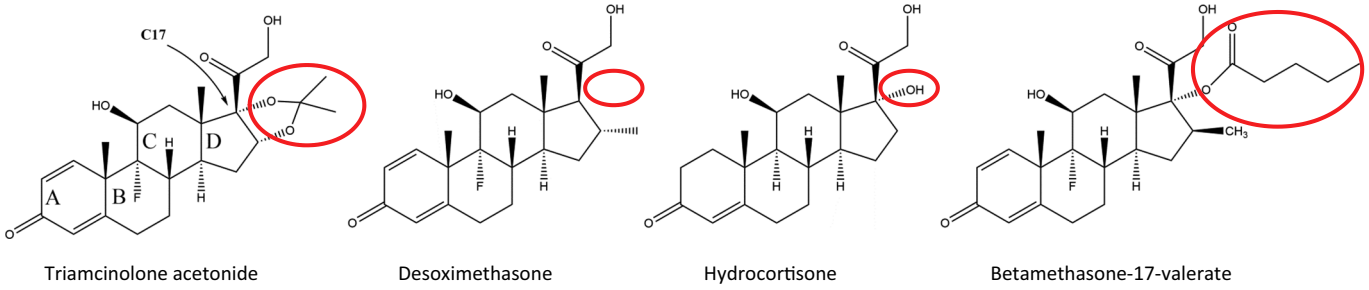

Fig. 1. Overview of the different moieties that may be present on the 17-carbon atom in corticosteroids.

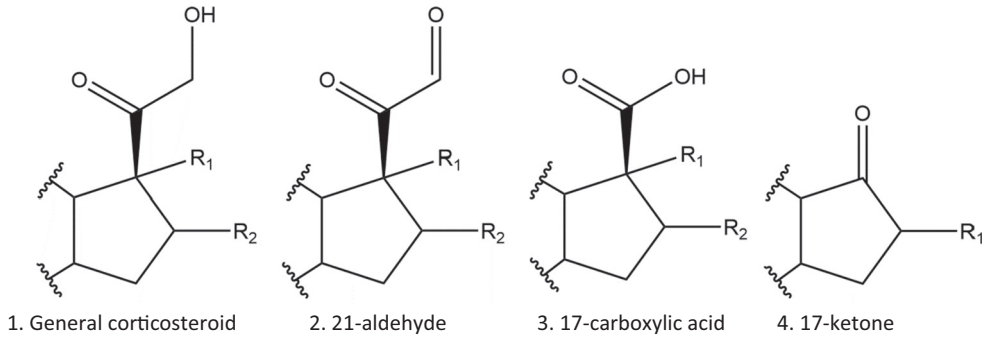

Fig. 2. The four degradation products of 20-keto-21-hydroxy corticosteroids that have been described in literature. R1 = OH, H or OR, R2 = H or OR.

Table 1
Stress conditions in water and PG.

Water	Propylene glycol
0.1 M HCL (25 °C)	
Phosphate buffer pH 9 (60 °C)	
5 mM $FeCl_3$ and $CuCl_2$ (40 °C)	5 mM $FeCl_3$ and $CuCl_2$ (40 °C)
3% H_2O_2 (25 °C)	Peroxide 5% (20 °C)

Table 2
Gradient programs run for triamcinolone acetonide (TCA), desoximethasone (DS), hydrocortisone (HC) and betamethasone-17-valerate (B17V). Percentage of acetonitrile with 20 mM phosphoric acid (ACN) that was used is shown, the rest is water buffered at pH 2 using phosphoric acid.

TCA		DS		HC		B17V	
Time (min)	% ACN	Time (min)	% ACN	Time (min)	% ACN	Time (min)	% ACN
0–12	0–32	0–10	25	0–15	25	0–10	25
12–30	32	10–27	25–45	15–32	25–45	10–27	25–45
30–40	32–70	27–40	45–75	32–45	45–75	27–40	45–75
40–42	70–0	40–41	75–25	45–46	75–25	40–41	75–25
42–47	0					41–46	25

Fig. 2. Betamethasone-17-valerate (B17V) can undergo transesterfication in acidic aqueous environment to betamethasone-21-valerate (B21V) which can subsequently form betamethasone through hydrolysis (Ahmad et al., 2012; Yip and Po, 1979).

In summary, only a limited amount of different degradation products have been described for 20-keto-21-hydroxyl corticosteroids. Unfortunately an overview of the influence of chemical groups near this 17-side chain on the degradation is lacking. Furthermore nearly all previously reported degradation studies were conducted in aqueous environment which does not necessarily apply to degradation in non-aqueous environment.

The aim of this study is to create an overview of the degradation pathways and kinetics of corticosteroid degradation in water and propylene glycol (PG). PG was chosen since it is the major non-aqueous solvent used in ointments, therefore it is considered a model for corticosteroids in non-aqueous environment (ointments).

2. Material and methods

2.1. Reagent and chemicals

The following chemicals were used: HPLC grade acetonitrile (ACN), dichloromethane, methanol (MeOH) and hexane (Avantor

Table 3
Degradation products identified using HPLC-MS for betamethasone 17-valerate (B17V). Amounts are expressed as relative percentage of total degradation, ± %RSD. PG = propyleneglycol.

Stress condition betamethasone 17 valerate					Amount of compound (expressed as relative % of total degradation, ± %RSD)		
Medium		Temp.	Time	% B17V	B21V	Betamethasone	Unknown
Water	0.1 N HCl	60 °C	7d	0.0 (0)	100.0 (0)		
	pH 9	60 °C	1d	50.0 (0.7)	2.0 (0)	48.0 (0.7)	
	3% H_2O_2	60 °C	7d	0.0 (0)	100.0 (0)		
	5 mM $FeCl_3$	40 °C	4d	0.0 (0)	100.0 (0)		
	5 mM $CuCl_2$	40 °C	5d	1.0 (6.7)	99.0 (0.1)		
PG	5% peroxide	60 °C	6d	2.0	98.0		
	5 mM $FeCl_3$	40 °C	7d	92.0 (0.1)	8.0 (0.9)		
	5 mM $CuCl_2$	60 °C	7d	84.0 (0.3)	16.0 (1.3)		4.0 (7.9)