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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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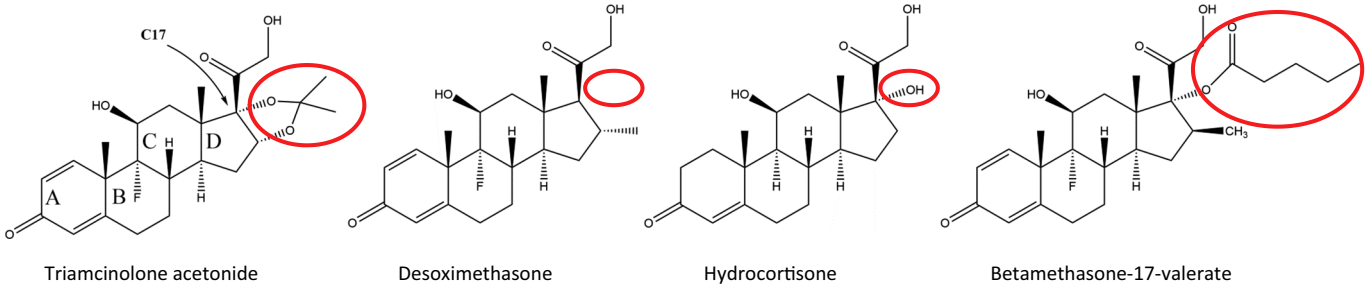


Fig. 1. Overview of the different moieties that may be present on the 17-carbon atom in corticosteroids.

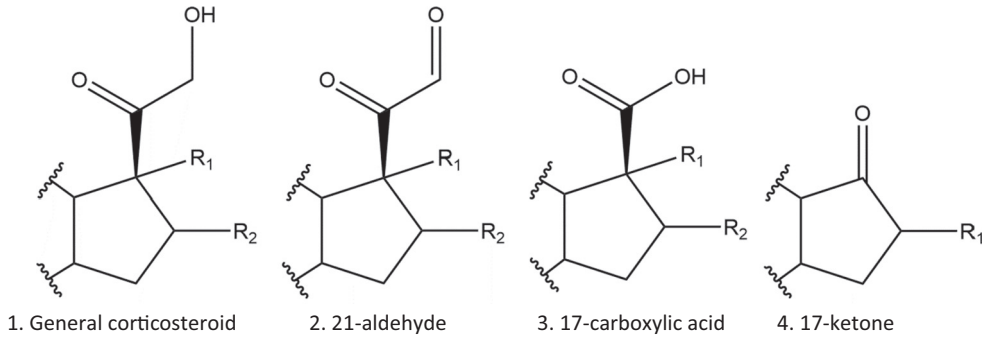


Fig. 2. The four degradation products of 20-keto-21-hydroxy corticosteroids that have been described in literature. R1 = OH, H or OR, R2 = H or OR.

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)

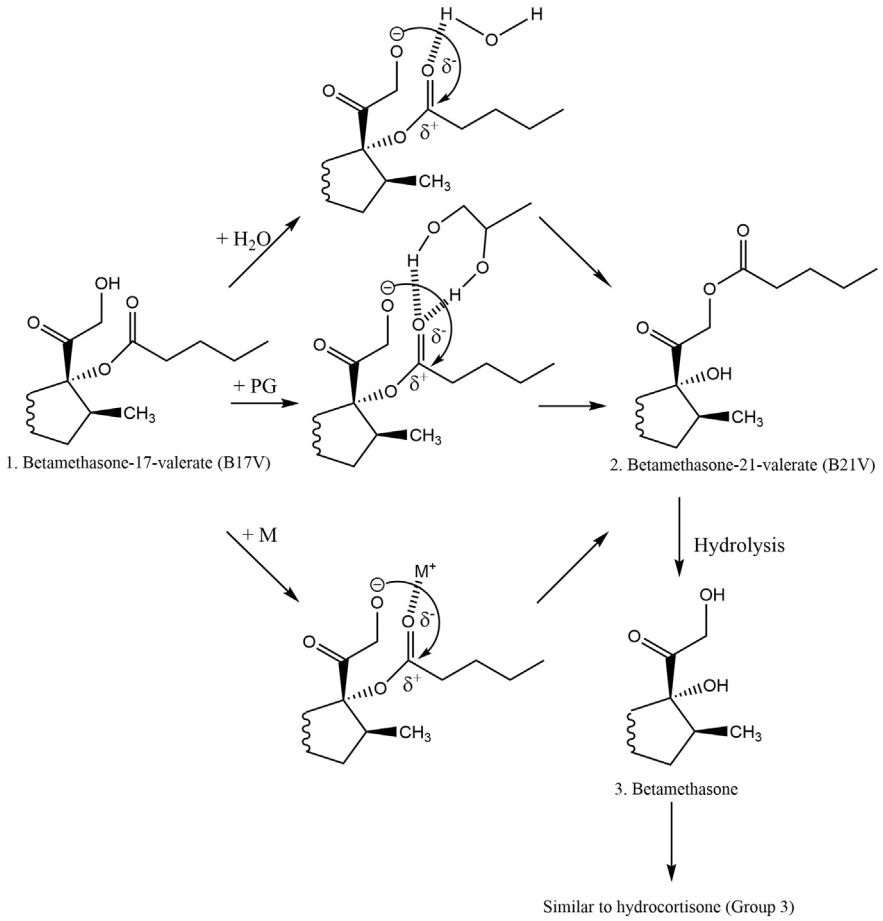


Fig. 3. Proposed degradation mechanism of betamethasone-17-valerate (B17V) to betamethasone-21-valerate (B21V) and betamethasone in both aqueous and non-polar environment.

Performance, Center Vally, Pennsylvania, USA), copper(II) acetate (Alfa Aesar, Havehill, Massachusetts, USA), disodium edetate, hydrogen peroxide (H_2O_2), iron(III) chloride ($FeCl_3$), copper(II) chloride ($CuCl_2$) and tert-butyl peroxybenzoate (Merck, Darmstadt, Germany), propylene glycol (PG) (Brenntag, Dordrecht, The Netherlands), hydrocortisone (Sanofi Aventis, Buckingham, UK), triamcinolone acetonide and betamethasone-17-valerate (Newchem, Milan, Italy) and desoximethasone (Farmabios, Pavia, Italy). 1 M hydrogen chloride (HCl) was prepared on site. Distilled, deionized water was prepared by a Elga Centra R 60/120 system (Woodridge, Illinois, USA).

2.2. Synthesis of the 21-aldehyde of TCA

The synthesis of the 21-aldehyde (compound 2, Fig. 2) was based on a method described in literature (Pearlman et al., 1984; van Heugten et al., 2018a). The 21-aldehyde was synthesized by dissolving 600 mg TCA and 31.5 mg copper(II)acetate in 150 mL methanol. Air was bubbled through the solution for 60 min. The reaction was quenched by adding 20 mL of 2.5 mg/ml disodium edetate. The solution then was concentrated to 30 ml under cold air and extracted twice with 200 ml dichloromethane. The dichloromethane was evaporated under cold air. The formed 21-aldehyde was characterized using LC-MS.

2.3. Stress testing in water

Stress testing was performed on 0.05% solutions of the corticosteroid in a mixture of ACN:water (50:50). These solutions were exposed to the conditions described in Table 1. Storage temperature and time were chosen based on a degradation target of 5–20%. HCl and phosphate buffer at pH 9 were used to simulate acid and base catalyzed degradation. H_2O_2, $FeCl_3$ and $CuCl_2$ were used for peroxide and trace metal mediated oxidation respectively. Compounds were included in the results when their presence was in a concentration of ≥0.5%.

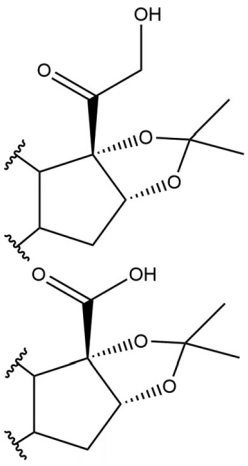
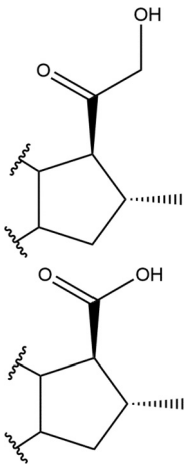
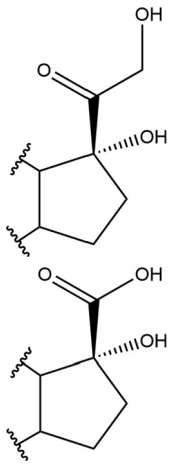
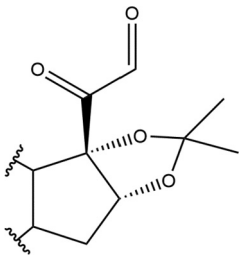
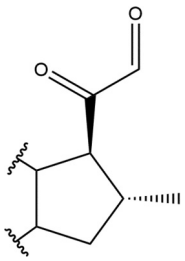
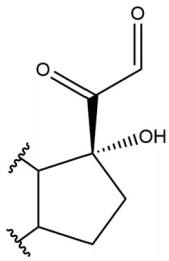
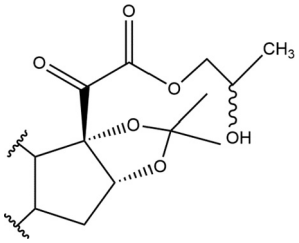
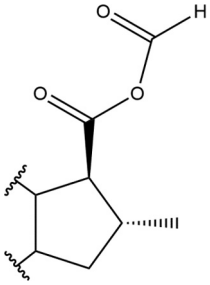
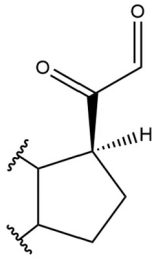
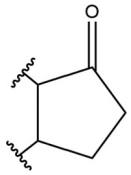
2.4. Stress testing in propylene glycol (PG)

The corticosteroids (0.05%) and reagents were dissolved in PG. For water free peroxide catalyzed degradation an organic peroxide, tert-butyl peroxybenzoate, was used (further referred to as 5% peroxide in PG). The other conditions were identical to the stress conditions in water (Table 1). Degradation constants (day^{-1}) were calculated assuming first order kinetics and expressed as average ± %RSD. Experiments were conducted in duplicate and expressed as average (% RSD) except for 5% peroxide in PG, this was tested on a single sample.

2.5. HPLC-UV

Chromatography was conducted on a Shimadzu Prominence-iLC-2030C 3D liquid chromatograph with diode array detector (Kyoto, Japan) and an Altima C18 RP18 column (250 × 4.6 mm^2, with 5 µm particles) (Mandel Scientific Company, Ontario, Canada). The flow rate was 1.5 ml/min and UV detection was at 241 nm. Mobile phase components were ACN with 20 mM phosphoric acid and water buffered at pH 2 using phosphoric acid. Injection volume was 20 µL. Chromatograms were obtained and analyzed with Shimadzu LabSolutions software version 5.5.7. For the four corticosteroids different gradient programs were run, these are shown in Table 2.

Table 4
degradation products identified using HPLC-MS for triamcinolone acetonide (TCA), desoximethasone (DS) and hydrocortisone (HC).

TCA	DS	HC
 17-carboxylic acid of TCA (van Heugten et al., 2018a; Wu et al., 2012) m/z = 420.4	 17-carboxylic acid of DS (Srinivasu et al., 2012) m/z = 362.5	 17-carboxylic acid of HC (Hansen and Bundgaard, 1980) m/z = 348.5
 21-aldehyde of TCA (van Heugten et al., 2018a; Wu et al., 2012) m/z = 433.5	 21-aldehyde-DS m/z = 376.5	 21-aldehyde of HC (Hansen and Bundgaard, 1980) m/z = 361.5
 21-glyoxilic PG ester (van Heugten et al., 2018a) m/z = 507.5	 Anhydride of DS m/z = 404.5	 17-deoxy-21-alhyde of HC (Hansen and Bundgaard, 1980) m/z = 345.5
		 17-ketone of HC (Hansen and Bundgaard, 1980) m/z = 319.5

2.6. LC-MS analysis

MS was conducted on a Micromass Quattro Ultima TQD system equipped with an electrospray ionization (ESI) source (Waters Chromatography, Etten-Leur, The Netherlands). Masses were scanned from m/z 50–1100, gas flow to 530 L/h, gas temperature to 350 °C and voltage 3 kV. Data was analyzed with Masslynx version 4.0 software. The mobile phase components were ACN and water buffered at pH 2 using formic acid.

3. Results and discussion

3.1. Betamethasone-17-valerate (B17V) degradation

Corticosteroids containing an C17 ester moiety are known to degrade freely in aqueous environment (Ahmad et al., 2012; Yip and Po, 1979). Degradation of these corticosteroids in non-aqueous environment has however not been described before. Therefore this was studied in more detail, results are shown in Table 3.

Table 5
Overview of the degradation products formed in different stress conditions for triamcinolone acetonide (TCA), desoximethasone (DS) and hydrocortisone (HC). Amount of degradation product is expressed as relative percentage of total degradation.

Medium		Amount of compound (expressed as relative % of total degradation ± %RSD)						
		1. 21-Aldehyde	2. 21-Aldehyde without OH	3. 17-Carboxylic acid	4. Anhydride of DS	5. 17-Ketone	6. 21-Glyoxilic PG ester	7. 7. unknown rrt 21.5 min DS
Water	0.1 N HCl	–	–	–	–	–	–	–
	pH 9	12.0 ± 0.0 (TCA) 14.0 ± 26.8 (HC)	20.0 ± 5.4 (HC)	24.0 ± 6.6 (TCA) 50.0 ± 4.7 (DS) 13.0 ± 0.0 (HC)		18.0 ± 21.1 (HC)	51.0 ± 1.5 (TCA)	49.0 ± 1.5 (DS)
	3% H_2O_2		–	14.0 ± 0.0 (HC)	–	86.0 ± 0.7 (HC)	–	–
	5 mM $FeCl_3$	58.0 ± 0.15 (TCA) 10.0 ± 0.0 (HC)		34.0 ± 0.0 (DS) 15.0 ± 0.0 (HC)	64.0 ± 0.0 (DS)	76.0 ± 1.0 (HC)	42.0 ± 0.0 (TCA)	
	5 mM $CuCl_2$	100.0 ± 6.7 (TCA) 100.0 ± 0.0 (DS) 93.0 ± 0.0 (HC)	–	–	–	–	–	–
PG	5% peroxide	–	45.0 (HC)	100.0 (DS)		55.0 (HC)	–	–
	5 mM $FeCl_3$	98.0 ± 1.4 (TCA)	–	16.0 ± 7.0 (DS)	84.0 ± 1.7 (DS)	100.0 ± 2.1 (HC)	–	–
	5 mM $CuCl_2$	91.0 ± 8.7 (TCA) 18.0 ± 6.6 (DS) 59.0 ± 15.5 (HC)	–	46.0 ± 1.3 (DS)	17.0 ± 0.0 (DS)	42.0 ± 8.6 (HC)	–	–

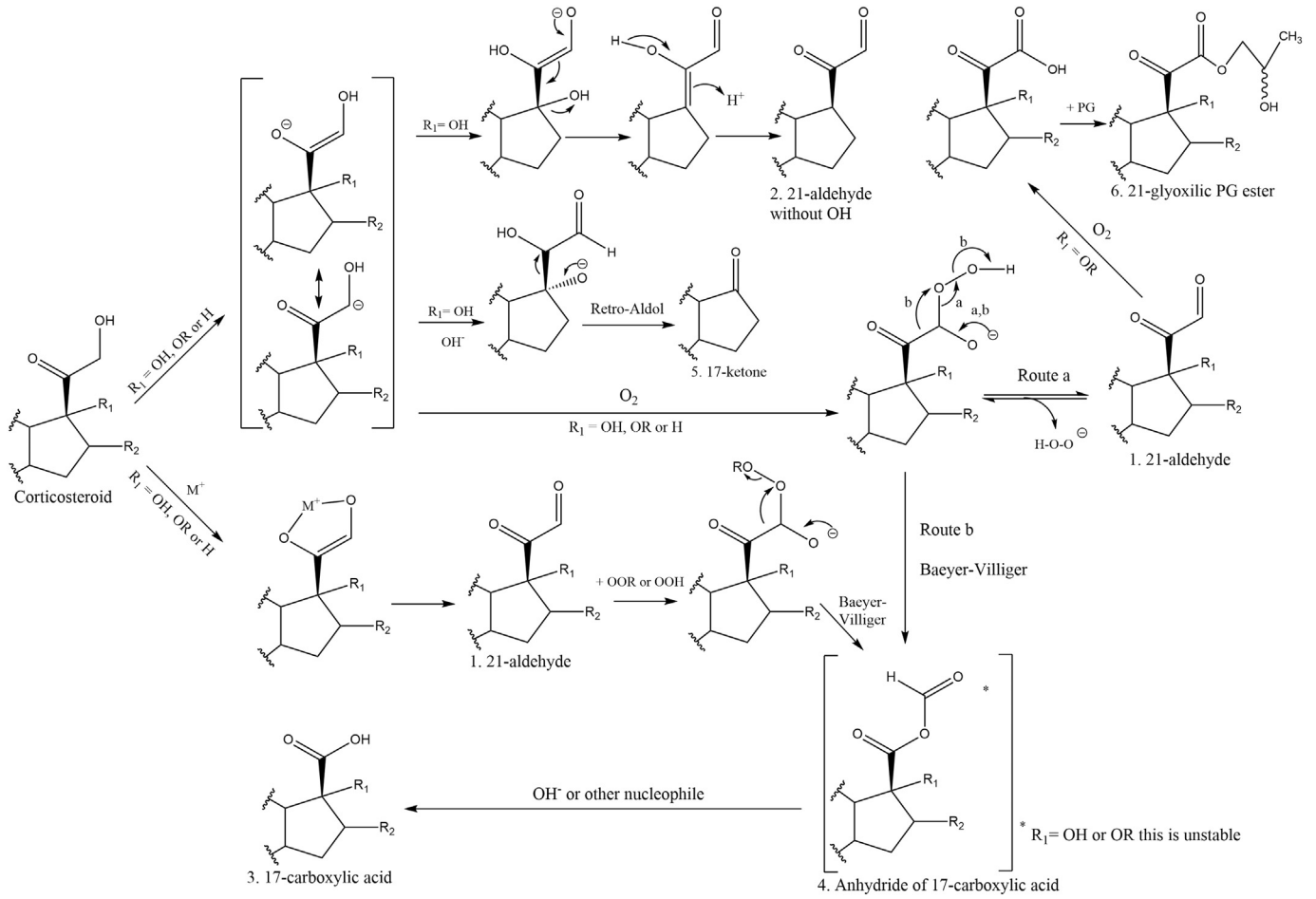


Fig. 4. Proposed degradation mechanism for corticosteroids containing a 20-keto-21-hydroxyl side chain.

As can be seen in Table 3, transesterfication occurred to a large extent under all conditions. This conversion has been described before for aqueous formulations (Ahmad et al., 2012; Yip and Po, 1979), but not for non-aqueous environment. It is possible that the PG contained small amounts of water due to its hygroscopic nature. Another explanation can be the effect of PG or metal ions on transesterfication. Fig. 3 proposes this degradation mechanism.

20-Keto-21-hydroxyl corticosteroids are prone to oxidative degradation. However, the primary degradation product B21V did not undergo oxidative degradation under the conditions studied here. Thus, the ester moiety on the C21 apparently protects the compound against further oxidative degradation. Only after hydrolysis of the ester moiety to form betamethasone similar oxidative degradation to HC will occur (Li et al., 2009).

Table 6
Degradation constants of triamcinolone acetonide (TCA), hydrocortisone (HC) and desoximethasone (DS) in water and propylene glycol (PG) in the presence of different stress conditions (± %RSD).

Degradation constant day^{-1}	TCA	HC	DS
In water			
0.1 N HCl (20 °C)	0.001 (0.0)	0.001 (0.0)	0.001 (0.0)
pH 9 (60 °C)	0.123 (± 2.8)	0.100 (± 0.4)	0.014 (± 1.0)
3% H_2O_2 (20 °C)	0.001 (0.0)	0.018 (0.0)	0.001 (0.0)
5 mM $FeCl_3$ (40 °C)	0.002 (± 7.9)	0.049 (± 0.3)	0.022 (± 1.0)
5 mM $CuCl_2$(40 °C)	0.005 (± 15.1)	0.018 (± 0.0)	0.001 (± 0.0)
In propylene glycol			
5% peroxide (20 °C)	0.001	0.006	0.009
5 mM $FeCl_3$ (40 °C)	0.076 (± 3.3)	0.068 (± 2.3)	0.109 (± 0.8)
5 mM $CuCl_2$ (40 °C)	0.007 (± 37.5)	0.064 (± 22.0)	0.011 (± 2.0)

3.2. TCA, DS and HC degradation

Using mass spectrometry the *m/z*-ratio's of compounds in degradation study samples were studied. These were compared with *m/z*-ratio's of degradation products mentioned in literature. Table 4 presents the degradation products that were identified in the samples.

3.3. Quantitative overview of the degradation products

In Table 5 an overview is presented of the identity and relative amount of degradation product formed for TCA, HC and DS under oxidative stress conditions in water and PG.

The profiles of degradation products formed in aqueous and non-aqueous environment are similar among all DS, HS and TCA. An 21-aldehyde and 17-carboxylic acid were found for HC, TCA and DS. However, clear differences in the degradation profile of the corticosteroids were also found. For example, HC was the only corticosteroid that degraded to compound 2 and 5; a 21-aldehyde lacking the C17-hydroxyl and a C17-ketone respectively, both compounds for which the C17-OH participates in the degradation mechanism. This is in accordance with literature (Hansen and Bundgaard, 1980; Zhang et al., 2016). Furthermore, only TCA degraded to compound 6; a 21-glyoxilic PG ester which has been described in a study on a TCA ointment (van Heugten et al., 2018a). Solely DS degraded to compound 4; an anhydride which has been described in literature as an intermediate (Srinivasu et al., 2012). Interestingly, also a previously unreported 21-aldehyde was found for DS. Since the 21-aldehyde was also found for TCA and HC and reported in literature for other corticosteroids it seems logical that it will also form for DS. Furthermore the 21-aldehyde was reported as precursor for the 17-carboxylic acid for betamethasone before (Li et al., 2009).

Degradation profiles for corticosteroids under trace metal stress depended on the type of metal salt used. In water, the presence of copper led predominantly to the degradation into compound 1 (the 21-aldehyde) while the presence of iron resulted in a wider range of degradation products.

The data described above was combined with all relevant literature to propose an overview of 20-keto-21-hydroxylcorticosteroid degradation in general (Hansen and Bundgaard, 1980; Li et al., 2009; Srinivasu et al., 2012; van Heugten et al., 2018a, b). Fig. 4 presents this overview.

3.4. Degradation kinetics of corticosteroids in water and PG

HC, TCA and DS were exposed to identical degradation conditions and first-order degradation constants were calculated. Table 6 presents these constants.

In Table 6 it can be seen that degradation constants vary greatly dependent on the studied stress condition, indicating that the corticosteroids are not equally susceptible to every type of stress condition. Some results stand out. First, HC degraded faster than TCA and DS under aqueous stress conditions. Second, acidic and peroxide stress did not cause rapid degradation in any corticosteroid studied here. Third, aqueous alkaline environment and trace metals (especially iron) caused rapid degradation. This is more profound in PG than in water. Thus, both the solvent and the type of trace metal determine the degradation profile and the degradation rate as well.

3.5. General discussion on corticosteroid degradation

From this study a number of conclusions can be drawn. First of all it is clear that when an ester group is bound to the 17 carbon atom first transesterfication to a 21-ester and subsequently hydrolysis occurs. When no ester is present oxidation is the predominant degradation mechanism. These corticosteroids form only a small selection of degradation products. A 17-carboxylic acid and a 21-aldehyde were found for all these corticosteroids. Interestingly when a hydroxide group (HC) is bound to the 17 carbon atom a wider range of degradation products can be formed. Furthermore for HC in general faster degradation was observed.

Metal salts show higher reactivity in non-aqueous environment compared to aqueous environment. $FeCl_3$ shows higher degradation constants compared to $CuCl_2$ and other degradation products are formed. Iron and copper are transition metals which can be involved in diverse chemical reactions. Copper has a more filled electron shell (i.e. d-shell) and hence is less reactive. This is why iron can bind six ligands while copper can only bind two ligands (Crabtree, 2005). Therefore potentially more reactions with iron may occur compared to copper.

Interestingly TCA shows a different degradation pattern compared to DS. TCA and DS both have a relatively non-reactive group bound to the 17-carbon (an acetonide and hydrogen respectively) in common. Therefore it is remarkable that unique degradation products were found for both TCA and DS such as the 21-glyoxylic PG ester for TCA and an anhydride for DS. Also a not identified degradation product was found for DS in alkaline conditions. Apparently the acetonide and hydrogen group influence corticosteroid degradation. Potentially this can be explained by the fact that an acetonide is more electron rich which may influence the degradation.

4. Conclusion

An overview of the quantitative and qualitative degradation of a wide range of corticosteroids is presented in both aqueous and non-aqueous environment for the first time. Corticosteroids containing a 20-keto-21-hydroxyl group bound to the 17 carbon atom degrade predominantly by oxidation. The other group (i.e. a hydrogen, hydroxide or acetonide) bound to the 17 carbon atom not only influences degradation kinetics but also the type of degradation product formed. When an ester group is bound to the 17 carbon first transesterfication and hydrolysis occur before it further degrades by oxidation. By using this overview degradation of corticosteroids can be predicted and potentially inhibited through the understanding of the degradation mechanisms presented here.

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