Original Article

Forced Degradation Studies of Drospirenone: Isolation and Characterization of Degradation Products

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ABSTRACT

Aim and Objectives: To remain safe for further processing or human consumption, study of stressed degradation for the identification of feasible degradants is required. The stability indicating high performance thin layer chromatographic method was developed with Camag HPTLC system. **Materials and Methods:** Silica C60F_{254} precoated TLC plates were used as stationary phase for separation of degradation products. The optimized mobile phase system consist of toluene: methanol: diethylamine (7:3:0.1) at 280 nm. **Results:** From the mass details and IR, NMR interpretation, the plausible structure of alkaline degradation product of drospirenone could be 17α (3-hydroxy propyl)-6β, 7β, 15β, 16β-dimethylene-5β-androstane-3β,5,17β triol and acidic degradation product of drospirenone could be 3-oxo-15α,16α-dihydro-3'H-cyclopropa[15,16]-17α-pregna-4,6-diene-21,17-carbolactone. Also *in silico* toxicity studies of the degradation products were performed to assess the toxicity profile of the products using Protox online sever. **Conclusion:** This analytical method can be considered as an alternative practical and inexpensive method for simple, accurate and efficient quantitative detection of drospirenone in the presence of its degraded products.

Key words: Drospirenone, Characterization, Forced degradation studies, *in silico* toxicity study, Degradation products of drospirenone.

INTRODUCTION

Chemically drospirenone (DROS) is 6β, 7β, 15β, 16β-dimethylene-3-oxo-17α-pregn-4-ene 21,17 carbolactone. DROS is a synthesized progestin that is an analog to spironolactone. It is present in number of birth control formulations. As such drospirenone has anti-mineralocorticoid properties, counteracts the estrogen – stimulated activity of the rennin – angiotensin - aldosterone system, and is not androgenic.[1] Stability testing is done primarily to provide the evidence that the drug substance or the drug product maintains its essential features of quality, identity, purity and strength (within acceptable ranges) throughout the time in which, it is expected to remain safe for further processing or human consumption.[2] The ICH Q1A guidelines established that stability-indicating method (SIAM) require for elucidating the inherent stability of the active substance by applying different stress conditions. Stressed degradation studies support for the identification of feasible degradants, the inherent stability of the drug molecules, possible degradation pathways and stability indicated analytical method validation.[3-5] A complete literature survey revealed that most widely high performance liquid chromatography (HPLC) techniques have been published for quantification and pharmacokinetic studies of DROS mostly in combination with ethinyl estradiol or other drugs in pharmaceutical formulations as well as biological fluids.[6-12] While, there is no analytical method accounted for isolation and characterization

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of degradation products of DROS under various stressed conditions. In the present study, we attempted to develop a simple, accurate and precise method for the estimation of drospirenone in the presence of its degraded products and identification of drospirenone degradation products under different stress conditions through IR, NMR and MS characterization.

MATERIALS AND METHODS

Instrumentation

Microsyringe (Linomat (659.004) syringe, Hamilton-Bonaduz Schweiz, Camag,), Silica gel 60 F-254 aluminium plates (pre-coated) (250 µm thickness, 10 × 10 cm; Merck, Germany), Linomat 5 applicator (Camag, Switzerland), saturation pad (Camag, Muttenz, Switzerland), twin trough chamber (20 × 10 cm; Camag, Muttenz, Switzerland), UV chamber (Camag, Switzerland), TLC scanner III (Camag, Muttenz, Switzerland), in this study winCATS version 1.4.0 software (Camag, Muttenz, Switzerland) were used. The FT-IR spectrum was recorded in KBr pellets on a Shimadzu FT-IR PC infrared spectrophotometer in the range as of 4000 to 400 cm^{-1}. The ^{1}H NMR spectrums were recorded on a Bruker spectrometer (400 MHz) using DCM as the solvent. Mass spectrometry was determined in the DI Shimadzu QP-2010 Plus analysis. Microsoft excel was as well used to treat data statistically.

Reference standard substances and reagents

Drospirenone was procured from swapanroop drugs and Pharmaceuticals (Aurangabad India) as a generous gift sample. The pharmaceutical form used in this study was Crisanta (Cipla, India) obtained from the local market as well labelled to contain 3 mg of drospirenone per tablet. Toluene, Methanol, diethylamine, NaOH, HCl, H_2O_2, etc. all solvents as well as reagents used were of analytical grade.

Selection of analytical wavelength for densitometric evaluations

Std.stock solution was applied on TLC plate by means of CAMAG LINOMA-V automatic sample applicator, in order to determine the absorbance maxima. The plate was developed in twin-through glass chamber saturated by means of mobile phase for 10 min. The plate was removed as well dried after chromatographic development. Bands on the TLC plate were scanned in the wavelength range of 200-800 nm. Drospirenone showed absorbance and good resolution at 280 nm which is selected as analytic wavelength.

Selection of mobile phase

Appropriate dilutions of stock solutions were prepared and applied on TLC plates in the form of band (band size: 6mm) and the plates were run into different solvent system. Different mobile phase system consist of - toluene: methanol, toluene: methanol: chloroform, toluene: methanol: GAA, methanol: 1% ammonium acetate solution, chloroform: dimethylamine were tried in different ratios in order to conclude best condition for the effectual separation. Amongst the different mobile phase combinations tested, toluene: methanol: diethylamine (7:3:0.1) was selected as it gives good resolution and peak symmetry for DROS. The R_f value for drospirenone was found to be 0.69 as shown (Figure 1).

Optimized chromatographic conditions

The chromatographic separation were optimized at room temperature (25±2°C) on stationary phase aluminium plates precoated with silica gel 60, plate size 10cm×10cm. Mobile phase toluene: methanol: diethylamine (7:3:0.1) were used. Sample applicator volume 0.6µl, band size 6mm and development chamber twin-through glass chamber, 10 cm × 10 cm with stainless steel lid were used. Wavelength 280 nm selected as analytical wavelength. (Table 1).

Analysis of marketed formulation

Six samples were prepared and analyzed as follows

Accurately weighed extent of tablet powder equivalent to about 3mg of DROS was transferred to 10 ml volumetric flask, few ml of methanol was added as well as ultrasonicated for 10 min, volume was subsequently made up to the mark with methanol. On the TLC plate bands of standard stock solution and bands of sample solution, 0.6µl were applied and the plate was developed and scanned under optimum chromatographic conditions. After scanning, the peak obtained for standard and sample bands were integrated. The amount

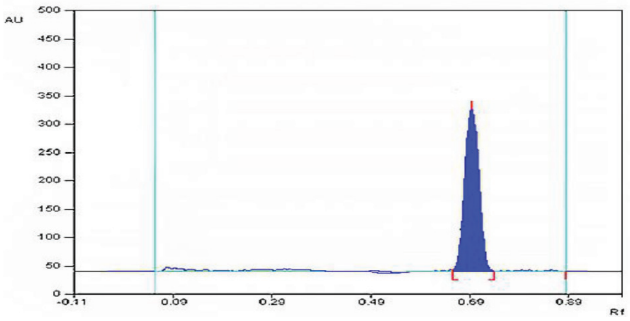


Figure 1: Typical densitogram of drospirenone (R_f Value: 0.69).

Table 1: Optimized Chromatographic conditions.	
Stationary Phase	Aluminium plates precoated with silica gel 60
Mobile Phase	Toluene: Methanol: diethylamine (7:3:0.1)
Plate size	10cm×10cm
Mode of application	Band
Band Size	6mm
Sample applicator volume	0.6µl
Development Chamber	Twin–through glass chamber,10cm×10cm with stainless steel lid.
Saturation Time	10 min
Scanning Mode	Absorbance /Reflection
Slit Dimensions	5×0.45 mm
Scanning Wavelength	280nm

Table 2: Results of analysis of marketed formulation of drospirenone.

Crisanta 3mg								
Sr. No.	**Weight of the Tablet Powder (mg)**	**Peak Area**	**Amount Found Mg/tab**	**% Label Claim**	**Amount of Drug Found**	**% Label claim**	**S.D.**	**%RSD**
1	162.87	4972.41	161.84	99.75	162.29	99.73	1.10	1.78
2	163.10	4971.44	165.01	101.17				
3	162.20	4970.46	161.84	99.66				
4	162.01	4970.46	161.72	99.82				
5	163.03	4970.46	164.54	100.92				
6	162.92	4970.46	159.80	98.08				

of DROS (in mg/tablet) was calculated by comparing mean peak area of sample with that of standard. Result of analysis of tablet of formulation and its statistical evaluation are shown in (Table 2).

Method Validation

The method was validated in fulfilment of ICH guidelines. The subsequent parameters were used for validation of developed method.

Linearity

Linear relationship accompanied by peak area and drug concentration was evaluated over the concentration range expressed in ng band^{-1} by making six repeated measurements in the concentration range of 0.2 to 1.2µl. Densitometric evaluations of the drug were performed at 280 nm (Figure 2). The standard calibration curve for drospirenone is shown in (Figure 3).

Accuracy

To ensure the accuracy of the planned method, recovery studies were carried out with standard addition method at 80, 100, 120% of the test concentration as per ICH guidelines.

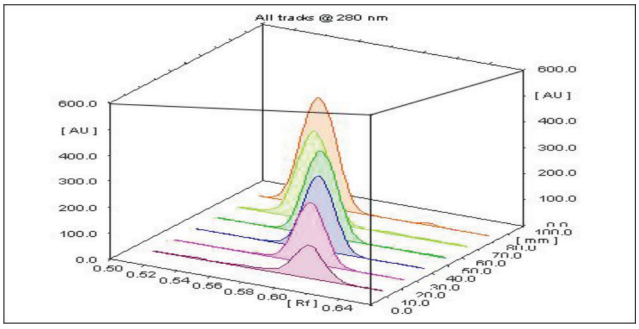


Figure 2: Overlay of drospirenone Linearity at 280 nm.

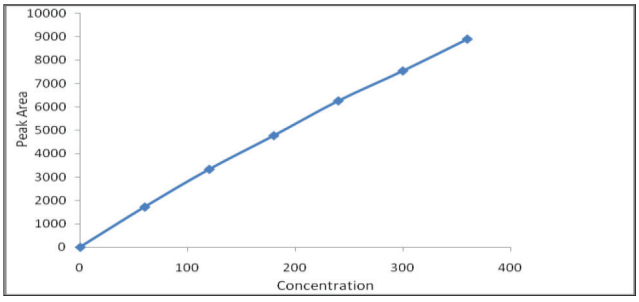


Figure 3: Calibration curve for drospirenone.

Precision

Precision of the developed method was studied by performing repeatability as well as intermediate precision studies.

Repeatability

To verify the degree of repeatability of the method, suitable statistical evaluation was carried out. Six sample of the marketed tablets preparation were analyzed as per the procedure given under the analysis of the same. The standard deviation (S.D.), % relative standard deviation (% RSD) was calculated.

Intermediate precision

Precision (Intraday and Interday) was determined by analysing tablet sample solutions at different time intervals on the similar day and on three different days, respectively. Tablet sample solution was prepared as well as analyzed in the related manner as described in analysis of marketed formulation.

Limit of detection and limit of Quantitation

The LOD and LOQ were determined which is based on the standard deviation of response of the calibration curve.

Robustness study

The effect of intended variations in method parameters like mobile phase composition, mobile phase volume, spotting to development time and time as of development to scanning were evaluated in this study. The effect of these changes on both the R_f values and peak areas was evaluated by calculating the relative standard deviations (RSD) for each parameter.

Forced degradation studies of drospirenone

For forced degradation studies, standard drug was subjected to variety of stress conditions like acidic, alkaline, oxidative, thermal and also neutral degradation.

Acid induced degradation

Acidic degradation involved exposing drug solution to the varying strengths of HCl (0.1N, 0.5N, 1.0N) at 80°C for 1hr. The mixture were refluxed at 80°C for 1hr, cooled and neutralised suitably. Before HPTLC analysis, the acidic stress solutions were diluted up to 300µg/ml with methanol and developed the plate using optimized chromatographic conditions.

Alkali induced degradation

Alkali induced degradation involved exposing drug solution to the varying strengths of NaOH (0.1N, 0.5N, 1.0N) at 60°C for 30 min. The mixtures were refluxed at 60°C for 30 min cooled and neutralised suitably. Before HPTLC analysis, the alkaline stress solutions were diluted up to 300µg/ml in methanol and developed the plate using optimized chromatographic conditions.

Hydrogen peroxide induced (oxidative) degradation

3ml of 3% H_2O_2 was added to volumetric flask containing weighed quantity of drug. The above reaction mixture was heated in precession water bath at 80°C for 1hr. The reaction mixture was well kept in dark to avoid photo-oxidation effect.

Neutral degradation

For neutral condition, drug dissolved in water and heated at 80°C for 1 hr. The neutral stress solution was cooled and diluted to 300µg/ml in methanol and developed the plate using optimized chromatographic conditions.

Isolation of alkaline and acidic degradation products by using HPTLC method

A precisely weighed quantity of 3mg of drug was dissolved in smaller quantity of methanol. Subsequently, 3 ml of 1 N Sodium hydroxide was added and the resultant solution was refluxed in round bottom flask (RBF) on water bath (temperature controlled precision) at 60°C for 30 min. Similarly precisely weighed quantity of 3mg of drospirenone was dissolved in smaller quantity of methanol. Subsequently, 3 ml of 1 N HCl was added and the resultant solution was refluxed in RBF on temperature controlled precision water bath at 80°C for 1hr. The RBF was removed and allowed to cool and volume was made up to 10 ml with methanol. The alkaline as well as acidic degradation of drospirenone was confirmed by means of newly developed method, where the major degradants formed in stressed state was isolated all through preparative HPTLC technique.

For isolation of degradation product, after development of the plate this plate was observed under the UV chamber and the band of standard and degradation product were marked and further scraped and exacted with methanol. The structures of degradant products were determined by IR, NMR, MS studies.

In silico toxicity study of drospirenone degradation products

In silico toxicity studies of the degradation products were performed to assess the toxicity profile of the products. *In silico* toxicity was accessed through the Protox II (http://tox.charite.de/protox_II/). Protox II is based a 33 models for the prediction of various toxicity

as acute toxicity, cytotoxicity, hepatotoxicity, carcinogenicity, immunotoxicity, Mutagenicity.

RESULTS AND DISCUSSION

Method Validation

The proposed method was validated by studying parameters as accuracy, linearity, precision, limit of detection (LOD), limit of quantitation (LOQ) and robustness.[13] Peak areas were found to consist of better linear relationship with concentration than peak heights. For DROS, R^2 was found to be 0.998, calibration graph were construct in the concentration range of 60-360ng band^{-1}. The correlation coefficient, y intercept and slope of the regression line was calculated and present in the (Table 3). At all the three levels percentage recovery was found to be satisfactory (Table 4). The % recovery was found between 100.26% and 100.55%. Repeatability as well as intermediate precision of the developed method were expressed in terms of relative standard deviation (RSD). The coefficients of variation for repeatability, inter-day and intra-day precision of the method was found to be less than 2% (Table 5). The standard deviation of y-intercept and slope of the calibration curves were used to calculate the LOD and LOQ. (LOD (ng/band) 5.38 and LOQ (ng/band) 16.32).

Table 3: Linearity study in physical mixture.

Sr. No.	Concentration (ng/band)	Peak Area*
1	0	0
2	60	1719.13
3	120	3330.76
4	180	4770.46
5	240	6259.24
6	300	7540.18
7	360	8899.93

(Y=1027.179+19.43x) (r^2=0.998).

Forced degradation studies

A minimal of three samples were generated for each stress condition, viz., the blank subjected to stress in the similar mode as the drug, zero time sample containing the drug stored under normal conditions, and the drug solution subjected to stress treatment. This gave the factual assessment of the amount of degradation of the drug molecule. The peak purity analysis was performed to conclude the percentage degradation along with total loss of the API during the formation of forced degradants. The drospirenone was found to be labile to acidic degradation showing degradation peaks at R_f 0.53 (Figure 4A) and highly labile to alkaline as comparative to acidic degradation showing degradation peaks at R_f 0.22, 0.35, 0.38 and majorly 0.51 (Figure 4B). The drug was found to be labile towards oxidative degradation showing degradation peaks at R_f 0.48 and 0.57 (Figure 4C) and no major degradation in neutral conditions, showing degradation peaks at R_f 0.57 (Figure 4D). Table 6 shows summary of degradation of drospirenone in different stress conditions.

Characterization of degradation product of drospirenone

Mass (MS) study

MS study was employed to obtain molecular weight as well fragmentation information of degradation products and it helps to structural information of degradation products. Alkali degradation shows generation of one degradation product. The MS spectrum of degraded drospirenone is shown in (Figure 5A). According to the m/z values and fragmentation pattern, the possible structure for alkaline degradation product was proposed as shown in (Table 7). Acidic degradation shows generation of one degradation product. The MS spectrum of degraded drospirenone is shown in (Figure 6A). According to the m/z values with fragmentation

Table 4: Results of recovery studies.

Sr. No.	Level of Recovery	Actual Concentration level	Amount of Drug present ng/band	Amount of Drug Recovered (ng/band)	% Recovery	% Mean Recovery	% RSD
1	80	2.4mg	144	145.23	100.85	100.55	0.367
			144	144.98	100.68		
			144	144.20	100.13		
2	100	3mg	180	180.46	100.25	100.29	0.182
			180	180.24	100.13		
			180	180.89	100.49		
3	120	3.6mg	216	216.21	100.09	100.26	0.184
			216	216.54	100.25		
			216	217.01	100.46		

Table 5: Results of Intraday and Interday precision of HPTLC Method.

Precision parameters	% Label claim*	S.D.	%RSD
Repeatability	99.10	1.01	1.019
Intraday precision	100.05	1.81	1.80
Interday precision	99.40	1.05	1.05

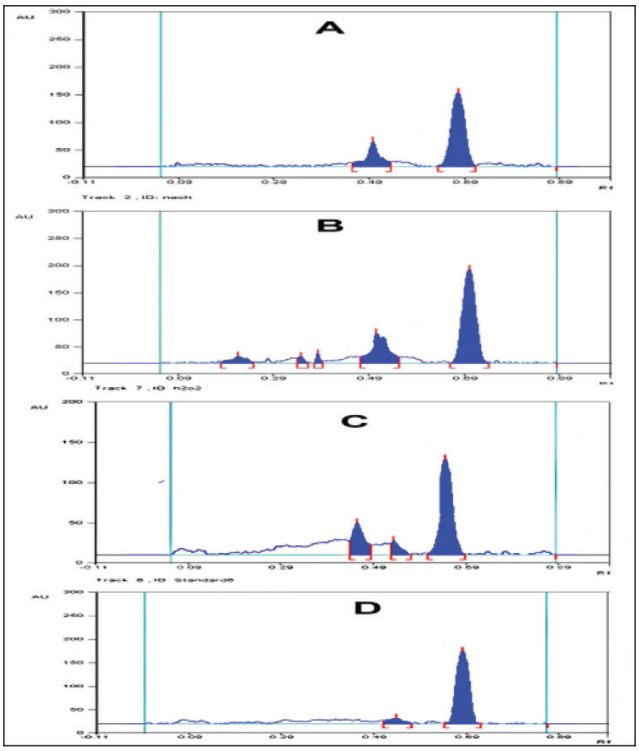


Figure 4: (A) Densitogram of 0.1N HCl stressed drospirenone after 1hr heating at 80°C. (B) Densitogram of 0.1N NaOH stressed drospirenone after 30 min heating at 60°C. (C) Densitogram of 3% H_2O_2 treated drospirenone after 1hr heating at 80°C. (D) Densitogram of drospirenone after 1hr heating at 80°C in DW.

Table 6: Summary of degradation of drospirenone in stress conditions.

Stress Condition	Exposure Condition	Percentage Degradation	Peak Purity*
Alkaline	0.1N NaOH, 60°C for 30 min	43.8	999.771
Acid	0.1N HCl, 80°C for 1hr	16.6	999.658
Neutral	Solid drug in DW 80°C for 1hr	4.23	995.357
Oxidative	1% H_2O_2, 80°C for 1hr	15.23	999.201
	3% H_2O_2, 80°C for 1hr	26.06	999.211

*Peak purity values in the range of 990-1000 indicates homogeneous analyte peak

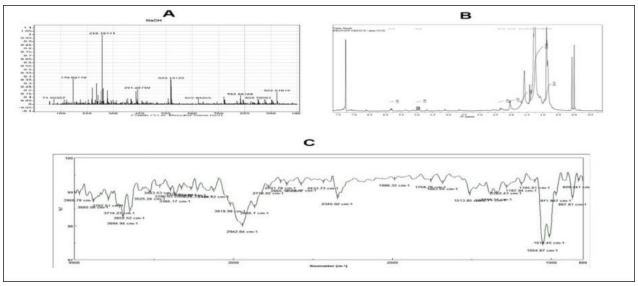
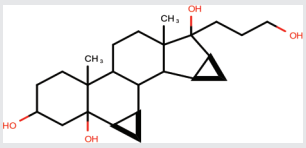
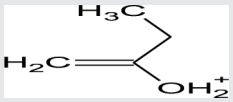


Figure 5: (A) Representation of MS spectrum of alkaline degradation product. (B) Representation of NMR spectrum of alkaline degradation product. (C) Representation of IR spectrum of alkaline degradation product of drospirenone.

Table 7: Interpretation of alkaline degradation product.

Interpretation of MS spectrum of alkaline degradation product		
Sr. No.	**M+1**	**Molecular Fragments**
1.	391.28	
2.	74	
Interpretation of NMR spectrum of alkaline degradation Product		
Sr. No.	**Peak**	**δ ppm**
1.	a	7.54 (s, 3H) OH (steroid)
2.	b	4.5 (3 6H) CH_3
3.	c	0.5-2.0CH steroids CH
Interpretation of IR spectrum of alkaline degradation Product		
Sr. No.	**Range (cm^{-1})**	**Indication**
1.	2942.84	OH stretching
2.	2865.68	CH stretching (Alkane)

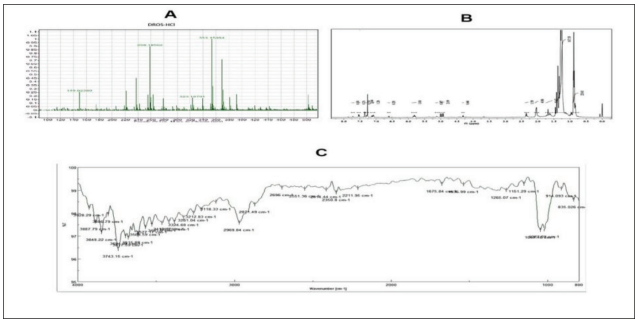


Figure 6: (A) Representation of MS spectrum of acidic degradation product (B) Representation of NMR spectrum of acidic degradation product (C) Representation of IR spectrum of acidic degradation product of drospirenone.

pattern, the possible structure for acidic degradation product was proposed as shown in (Table 8).

NMR study: ^{1H}NMR was recorded at 500 MHz and chemical shifts are derived from TMS peak at δ = 0.00 pm. Extraction procedure: To the aqua solution DCM (10 mL) was added and extracted by using separating funnel. The layers were separated, and the aqueous layer was again extracted with DCM (2x10 mL), combined organic layer were washed by brine (20mL), dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure in rota evaporator to get the desired compound. NMR and IR spectrum of alkaline degraded DROS are shown in (Figure 5B and 5C) respectively. Band interpretation data shown in (Table 9) as well as NMR and IR spectra of acidic degraded drug are shown in (Figure 6B and 6C) respectively.

***The MS value for alkaline degradation product is m/z* 391.28. *The NMR spectrum showed the following signals*:** peak a:(s, 3H) OH (steroid) appeared at 7.54 δ ppm, peak b :(3 6H) CH_3 appeared at 4.5δ ppm, peak C : CH steroids CH appeared at 0.5-2.0 δ ppm. The IR spectra showed OH stretching appeared at 2942.84 cm^{-1} and CH stretching (Alkane) appeared at 2865.68 cm^{-1}. From the mass details and facts given above, the plausible structure of alkaline degradation product could be 17α (3-hydroxypropyl)-6β, 7β, 15β, 16β-dimethylene-5β-androstane-3β, 5, 17β triol.[14,15] The MS value for acidic degradation product is m/z 353.14. The NMR spectrum showed the following signals: peak a: (3 6H) CH_3 appeared at 4.8 δ ppm, peak c: CH steroids CH appeared at 0.5-2.0 δ ppm. The IR spectra showed C=O stretching appeared at 1675 cm^{-1} and CH stretching (Alkane) appeared at 2969 cm^{-1}. From the mass details and facts given above, the plausible structure of acidic degradation product could be 17α (3-hydroxypropyl)-6β, 7β, 15β, 16β-dimethylene-5β-androstane-3β, 5, 17β triol.

Table 8: Interpretation of acidic degradation product.

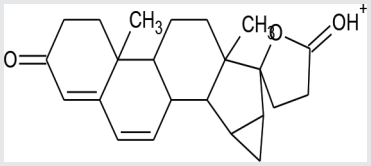
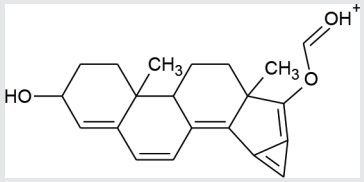
Interpretation of MS spectrum of acidic degradation product		
Sr. No.	**M+1**	**Molecular Fragments**
1.	353.14	
2.	323.18	
Interpretation of NMR spectrum of acidic degradation product		
Sr. No.	**Peak**	**d ppm**
1.	a.	4.8 (3 6H) CH_3
2.	b.	0.5-2.5 CH steroids CH
Interpretation of IR spectrum of Degradation Product		
Sr. No.	**Range (cm^{-1})**	**δ ppm**
1.	1675	C=O stretching
2.	2969	CH stretching (Alkane)
3.	1014	C-O stretching

Table 9: *In silico* toxicity study of drospirenone degradation products.

Molecule Name	Hepato-toxicity	Carcinogenicity	Immuno-toxicity	Mutagenicity	Cytotoxicity	Remark
DROS+ NaOH	0.8	0.84	0.86	0.74	0.87	Immuno toxic
DROS+ HCl	0.6	0.51	0.93	0.94	0.64	Immuno toxic

In silico toxicity study of drospirenone degradation products

Toxicity prediction revealed both degradation products of drospirenone showed only immunotoxic and endpoints as shown in (Table 9).

CONCLUSION

The degradation behaviour of drospirenone under acid, base and neutral, oxidative-as per guidelines was studied. We successfully identify degradation products under acidic and alkaline stress conditions through IR, NMR and MS characterization. Additionally *in silico* toxicity studies of the degradation products were performed to assess the toxicity profile of the products using protox online sever. Hence, this analytical method can be considered as an alternative practical and inexpensive method for simple, accurate and efficient quantitative detection of drospirenone in the presence of its degraded products.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

DROS: Drospirenone; **ICH:** International conference on harmonization; **TLC:** Thin layer chromatography; **HPTLC:** High performance thin layer chromatography; **NMR:** Nuclear magnetic resonance; **IR:** Infrared spectroscopy; **RSD:** Relative standard deviation; **LOD:** limit of detection; **LOQ:** limit of quantitation.

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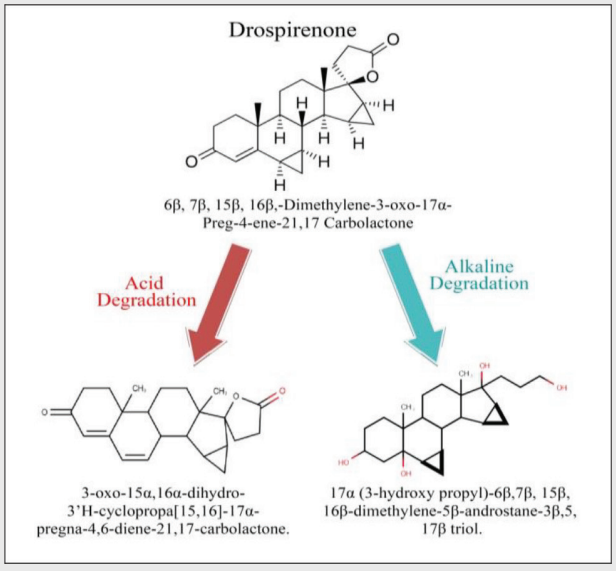
PICTORIAL ABSTRACT



SUMMARY

Drospirenone was found to be degrading in alkaline, acidic and oxidative conditions. Degradation in alkaline condition was more as compared to oxidative and acidic stress conditions. The method was resolving the peak of degradation products from the peak of DROS. Further the characterisation by using IR, NMR, MS were carried out for acidic and alkaline degradation products of DROS. From the mass details and IR, NMR interpretation, the plausible structure of alkaline degradation product of DROS could be 17α (3-hydroxy propyl)-6β, 7β, 15β, 16β-dimethylene-5β-androstane-3β, 5, 17β triol and acidic degradation product of DROS could be 3-oxo-15α, 16α-dihydro-3'H-cyclopropa [15, 16]-17α-pregna-4,6-diene-21,17-carbolactone. *In silico* toxicity studies of the degradation products was performed to assess the toxicity profile of the products by using Protox online server. Toxicity prediction revealed both degradation products of DROS showed only Immunotoxic.

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