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Development and Validation of a Novel Stability Indicating UPLC Method for Dissolution Analysis of Bexarotene Capsules: An Anti Cancer Drug

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Abstract

A novel stability indicating liquid chromatographic method for dissolution analysis of Bexarotene capsules, 75 mg has been developed and validated. Efficient chromatographic separation was achieved on a C18 column (50 mm × 2.1 mm, 1.7-µm particles) with a simple isocratic mobile-phase at a flow rate of 1.0 mL min^{-1}. Quantification was achieved by use of ultraviolet detection at 260 nm. After the determination of the solubility the conditions selected were paddle at 50 RPM, with 900 mL of 0.5% HDTMA (hexadecyltrimethylammonium bromide) in 0.05 M phosphate buffer, pH adjusted to 7.5 with 1 N Sodium hydroxide at 37°C ± 0.5°C. Under these conditions the in vitro release profile of Bexarotene capsules, 75 mg shown good results. The drug release was evaluated by Reverse phase HPLC using mixture of Acetonitrile, water and trifluro acetic acid 70:30:0.1 (v/v/v). The method was validated for linearity, accuracy, precision, ruggedness, solution stability, mobile phase stability as per ICH guidelines to meet requirements for a global regulatory filing.

Keywords: Column liquid chromatography; UPLC; Bexarotene; Dissolution testing; Validation; Stability-indicating

Introduction

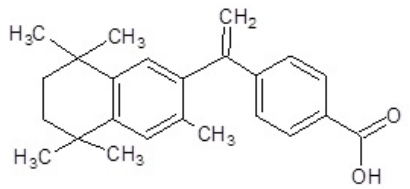

Figure 1a: The structures of Bexarotene and its impurities. Bexarotene. 4-[1-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2-yl)ethenyl]benzoic acid.

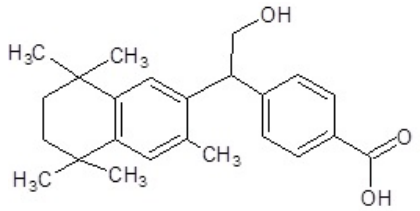

Figure 1b: The structures of Bexarotene and its impurities. 4-[1-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2-yl)ethyl hydroxy]benzoic acid.

Bexarotene is an antineoplastic (anti-cancer) agent. Bexarotene is a retinoid specifically selective for retinoid X receptors, as opposed to the retinoic acid receptors and is chemically known as 4-[l-(3,5,5,8,8-pentamethyltetralin-2-yl)ethenyl] benzoic acid (Figure 1a and Figure 1b). Bexarotene (brand name: Targretin) is approved by the U.S.Food and Drug Administration (FDA) (in late 1999) and the European Medicines Agency (EMA) (early 2001) for use as a treatment for cutaneous T cell lymphoma (CTCL) [1]. It is a third-generation retinoid. Bexarotene is indicated for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in people who are refractory to at least one prior systemic therapy (oral) and for the topical treatment of cutaneous lesions in patients with CTCL who have refractory or persistent disease after other therapies or who have not tolerated other therapies.

Extensive literature survey revealed, few scientific articles have been published in which Bexarotene was quantified in human plasma [2] and rat plasma [3]. Despite this, a literature review reveals the lack of availability of a simple stability-indicating LC method for dissolution analysis of Bexarotene capsules.

The dissolution method conditions are considered from FDA Dissolution data base in which, 0.5% HDTMA (Hexadecyl trimethyl ammonium bromide) in 0.05 M phosphate buffer adjusted to 7.5 with 1 N NaOH/1 N HCl was given as Dissolution media. Since the dissolution medium is in basic side (pH 7.5) and Bexarotene is prone to degradation in basic medium, it is necessary to develop an analytical HPLC method for dissolution analysis which can separate the degradatnts arise due to basic hydrolysis of Bexarotene. As far as we are aware no stability-indicating LC method for dissolution Bexarotene drug product has been developed and validated.

A sensitive, simple, and selective chromatographic method was therefore sought for dissolution analysis of Bexarotene capsules.

Accordingly, the objective of this study was to establish the inherent stability of Bexarotene by use of stress studies under a variety of ICH recommended test conditions [4-6]. By development of a new analytical method for dissolution analysis of Bexarotene capsules [6-8], which could separate Bexarotene from all its related impurities and the various degradation products which could arise during stress testing.

Experimental

Chemicals and solutions

Bexarotene drug substance, standard, was supplied by Gensen Laboratories (Mumbai, India). Targretin capsules generic version was puchased. LC-grade acetonitrile and analytical reagent-grade tri-floro acetic acid were purchased from Merck (Darmstadt, Germany). High-purity water was prepared by use of a Millipore Milli-Q plus water-purification system.

Stock solutions of Bexarotene standard and sample (1.0 mg mL^{-1}) were prepared by dissolving appropriate amounts in ethanol (this solvent will subsequently be denoted 'diluent'). Working solutions of 83 µg mL^{-1} were prepared from this stock solution for analysis of bexarotene capsuels dissolution.

Chromatography

Chromatography was performed with a Waters Aquity UPLC quaternary pump, FTN auto sample manager and a photodiode-array detector (PDA). The output signal was monitored and processed by use of Empower software on a Pentium computer (Digital Equipment). Efficient separation was achieved on a C18 column (50 mm × 2.1 mm, 1.7-µm particles), BEH C18 column by use of a mobile phase isocratic prepared from a degassed 70:30:0.1 (v/v/v) mixture of Acetonitrile, water and trifluro acetic acid. The mobile phase flow rate was 1.0 mL min^{-1}, the column temperature was 30°C, and detection was at 260 nm. The injection volume was 5 µL.

Dissolution test conditions

The solubility study and percentage drug release was determined in 900 ml of 0.5% HDTMA (Hexadecyl trimethyl ammonium bromide) in 0.05 M phosphate buffer adjusted to 7.5 with 1 N NaOH/1 N HCl. Drug release tests were carried out with paddle method (USP apparatus II) at 50 rpm. The temperature of the cell was maintained at 37°C ± 0.5°C by using a thermostatic bath. Sampling aliquots of 10.0 ml were withdrawn at 15, 30, 45 and 60 min and replaced with an equal volume of the fresh medium to maintain a constant total volume. After the end of each test time, sample aliquots were filtered and quantified. The percentage content was calculated by validated stability indicating RP-HPLC method and these contents results were used to calculate the percentage release on each time of dissolution profile. The cumulative percentage of drug released was plotted against time in order to obtain the release profile.

Results and Discussion

Solubility determination and dissolution test condition

When dissolution test is not defined in the monograph of the dosage form, comparison of drug dissolution profiles is recommended on three different dissolution media, in the pH range of 1-7.5. The selection of a dissolution medium may be based on the solubility data and dosage range of the drug product. Hydrochloric acid, phosphate buffer and purified water are typical mediums used for dissolution test and these mediums were evaluated.

Bexarotene was insoluble in aqueous medium. For poorly soluble drugs, a percentage of surfactant can be used to enhance drug solubility and it is also recommended by USFDA. Then different concentrations of HDTMA (Hexadecyl trimethyl ammonium bromide) (0.25%, 0.5% and 1%) were prepared in in 0.05 M phosphate buffer adjusted to 7.5 with 1 N NaOH/1 N HCl and used for dissolution study.

At 25 rpm, the cumulative percentage drug release was considerably less than that at 50 rpm in above said dissolution medium. It was observed that less than 75% of drug was dissolved at 30 min in hydrochloric acid and phosphate buffer at a speed of both 25 rpm and 50 rpm.

In 0.1 N hydrochloric acid medium, pH 4.5 phosphate buffer and pH 7.5 buffer dissolution medium the drug was not completely soluble; some of the drug particles were detected at the bottom of the dissolution vessel. The cumulative percentage drug release obtained was low when compared to 0.5% HDTMA dissolution medium. At the end of 75 min the 0.5 % HDTMA medium showed 100% cumulative drug release at 50 rpm. In 0.25 %, HDTMA solutions showed more than 50% of drug release within 75 min. But in 0.5 %, HDTMA medium, % drug dissolved was nearly 100% within 75 min at stirring rate of 50 rpm. The cumulative percentages of drug in all the above said solutions were recorded. The analysis of variance showed no significant difference between the results obtained at 50 rpm and 75 rpm.

Analytical method development

To establish a selective and sensitive method the primary concern during development was to achieve symmetry of the Bexarotene peak and resolution between the peaks of Bexarotene and degradation peaks. Different types of buffer of different pH, for example phosphate buffer of pH 3–7, citrate buffer of pH 3–5, and ammonium acetate buffer of pH 4–6.5, were studied in combination with acetonitrile and methanol (30, 50, and 70%). The effects of acetonitrile, methanol, and their combinations on peak height and symmetry and on resolution between Bexarotene and degradation peaks were investigated. To improve peak height and peak symmetry, use of different ion-pairing reagents, for example trifluoroacetic acid, and triethylamine, was also investigated. The chromatographic data retention factor (k) and number of theoretical plates (N) were also recorded during these studies.

Solution of Bexarotene was prepared in diluent at a concentration of 100 ppm and the UV–visible spectra were acquired. The first UV absorption maxima of Bexarotene, was at approximately 260 nm, so detection at 260 nm was selected for method-development (Figure 2). Because Bexarotene and its possible degradation impurities are acidic in nature, because of the presence of carboxylic acid groups, a 80:20 (v/v) mixture of disodium hydrogen phosphate monohydrate buffer (0.01 m), pH 3.0, and acetonitrile was chosen for an initial trial with a 25 cm length, 4.6 mm i.d. column containing 5-µm particle size C18 stationary phase.

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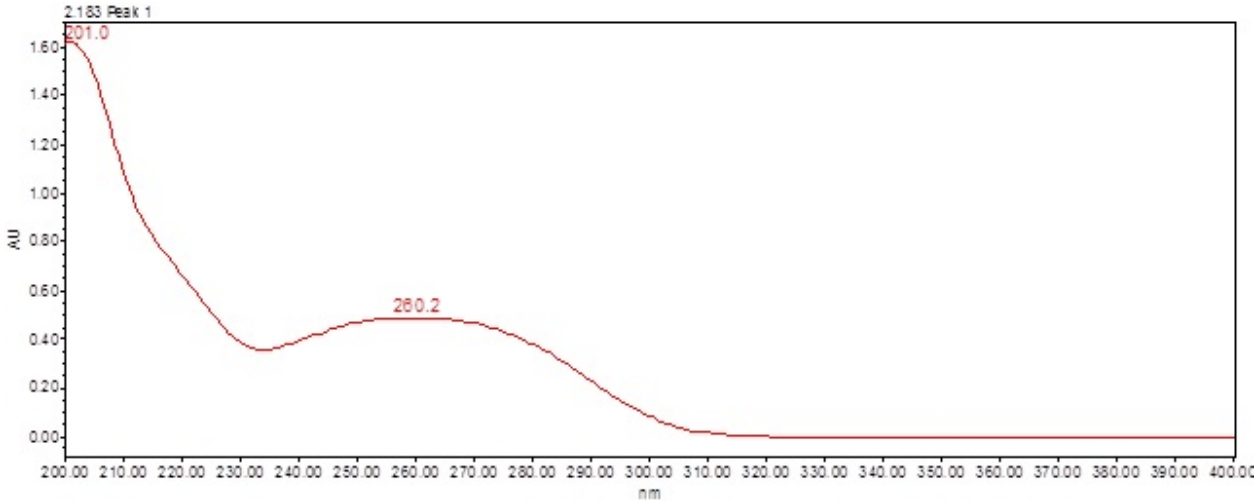

Figure 2: Typical UV Spectrums of Bexarotene and all impurities. Peak-1: imp-1, Peak-2: imp-2, Peak-3: Bexarotene, Peak-4: imp-3 and Peak-5: imp-4.

The flow rate was 1.0 mL min^{-1}. When Bexarotene sample spiked with all the impurities was injected under these conditions, Bexarotene and its impurities, peaks are not eluted even after 60 minutes of run time. To improve the retention time of Bexarotene, to decrease the interactions with stationary phase, acetonirile content has been increased to 40% i.e., buffer: acetonitrile 60:40 (v/v). Even with the increase acetonitrile content in mobile phase, Bexarotene peaks were not eluted before 60 minutes runt time.

To improve the retention times, shifted to UPLC system and submicron C18 column (50 mm × 2.1 mm, 1.7-µm particles). A 60:40 (v/v) mixture of disodium hydrogen phosphate monohydrate buffer (0.01 m), pH 7.5, and Acetonitrile was chosen for an initial trial on UPLC with BEH C18 column (50 mm × 2.1 mm, 1.7-µm particles) because of ionization of the carboxylic acid groups in Bexarotene and its degradation impurities, their polarity increased and interaction with the column was reduced, so all degradation impurities and Bexarotene were co eluted rapidly (~1 min) (Figure 3a).

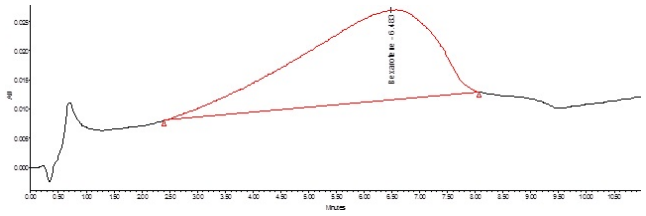

Figure 3a: Bexarotene in mobile phase (Buffer: ACN:60:40 V/V), pH 7.5.

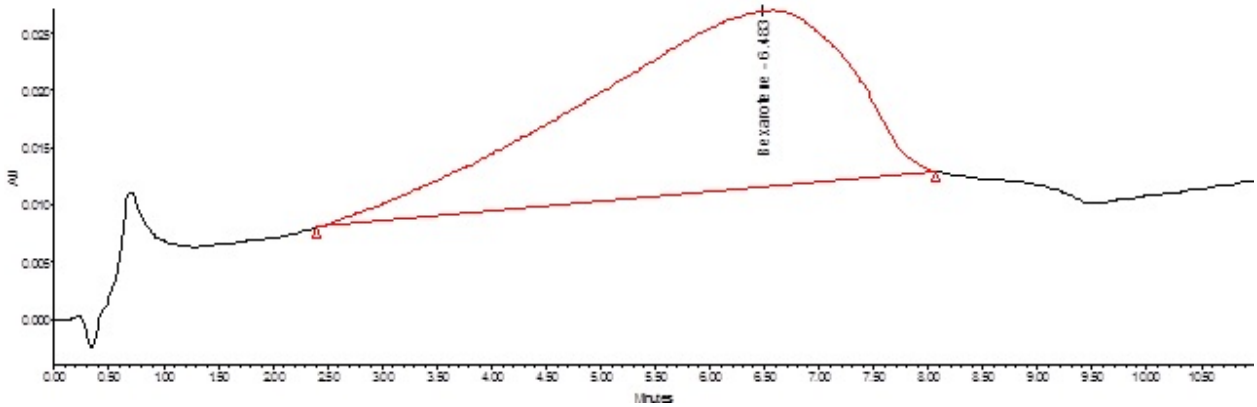

Figure 3b: Bexarotene in mobile phase (Buffer: ACN:80:20 V/V), pH 3.0.

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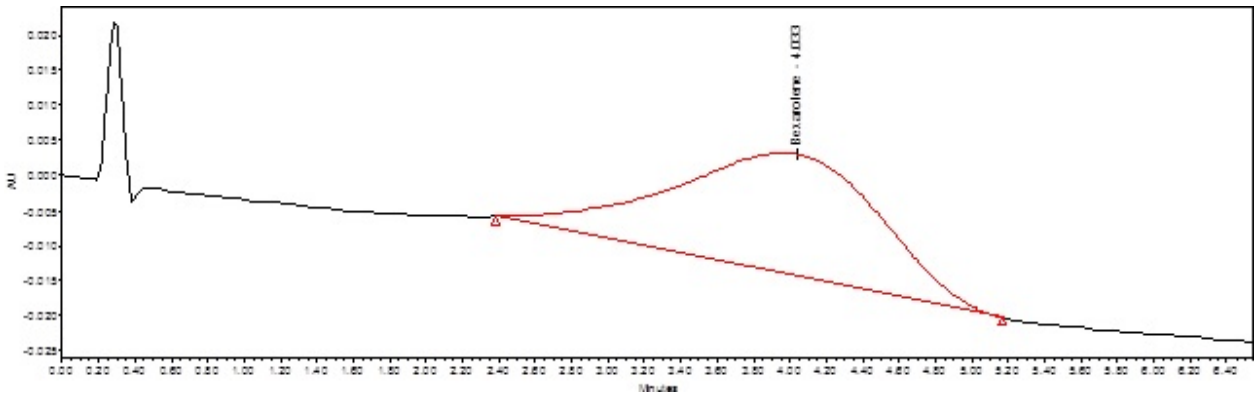

Figure 3c: Bexarotene in mobile phase (Buffer: ACN:70:30 V/V), pH 3.0.

To improve the retention time 80:20 (v/v) mixture of disodium hydrogen phosphate monohydrate buffer (0.01 m), pH 3.0, and acetonitrile was chosen, in acidic environment the ionization of Bexarotene decreases subsequently the polarity also decreased and the interactions with columns got increased, Bexarotene got eluted at about 6 minutes, but the peak shape of Bexarotene is too broad (Figure 3b). To further improve the retention, time a 70:30 (v/v) mixture of disodium hydrogen phosphate monohydrate buffer (0.01 m), pH 3.0, and acetonitrile was chosen Bexarotene got eluted at about 4 minutes but the peak shape of Bexarotene is too broad (Figure 3c).

To have to improve peak shape 0.25 mL trifluoroacetic acid was added to 1000 mL of 70:30 (v/v) mixture of DI water and acetonitrile, the peak shape of Bexarotene was improved, but still the trailing factor is greater than 2.0 observed (Figure 3d). To further improve the peak shape 1.0 mL trifluoroacetic acid was added to 1000 mL of mobile phase (700:300:1.0; water, Acetonitrile and Trifluoroacetic acid) with 1 mL trifluroacetic acid /1000 mL, the peak shape of Bexaroten was improved and the resolution between basic degradation peak and bexarotene is also improved (Figure 3e).

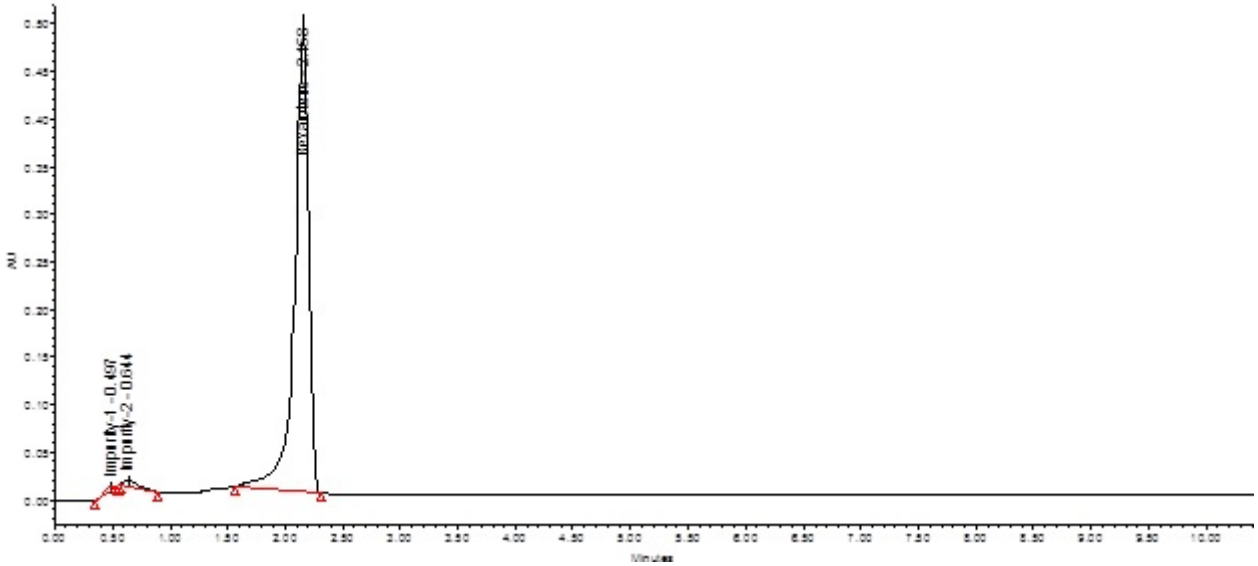

Figure 3d: Bexarotene in mobile phase (Water: AC:70:30 V/V), pH 3.0, 0.25 mL TFA.

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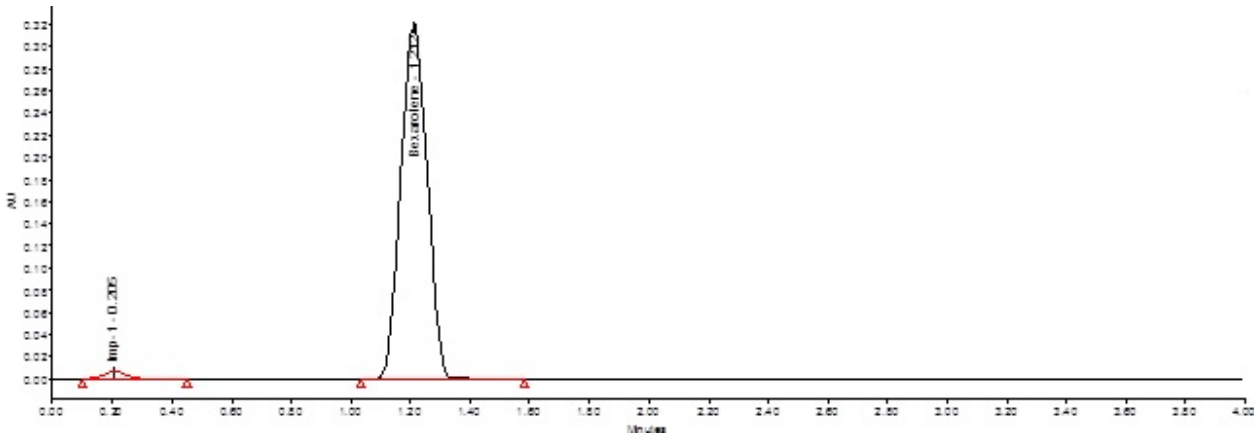

Figure 3e: Bexarotene in mobile phase (Water: ACN:70:30 V/V), pH 3.0, 1.0 mL TFA.

Buffer pH, amount of acetonitrile and amount of trifluro acetic acid all played a major role in achieving a symmetric Bexarotene peak and separation of Bexarotene from degradation impurities.

Method validation

The method was validated for specificity, linearity, range, precision, accuracy, sensitivity, robustness, and system suitability (Table 1).

Name of the parameter	Observed Value	Acceptance Criteria
%RSD of Bexarotene peak in five consecutive injections of standard preparation	0	Not more than 2.0
The tailing factor for Bexarotene peak in all injections of standard preparation	1.1 (mean of 5 injections value)	Not more than 2.0
The number of theoretical plates for Bexarotene peak in all injections of standard preparation	10078 (mean of 5 injections value)	Not less than 2000

Table 1: System suitability results.

Specificity

The dissolution test specificity was evaluated by preparing sample placebo of the commercial formulation of Bexarotene Capsules. These samples were transferred to separate vessels with 900 mL of dissolution medium at 37°C ± 0.5°C and stirred for 45 min at 100 rpm using a paddle (USP apparatus 2). Aliquots of these solutions were withdrawn, filtered through 0.45 µ membrane filters and analyzed by the RP-HPLC method using Bexarotene standard solution of 83 µg/mL.

The specificity [4,6,7] and stability-indicating nature of the method were assessed in the presence of the products obtained during forced degradation studies performed on Bexarotene [8,9]. Stress studies were conducted using a conventional reflux method.

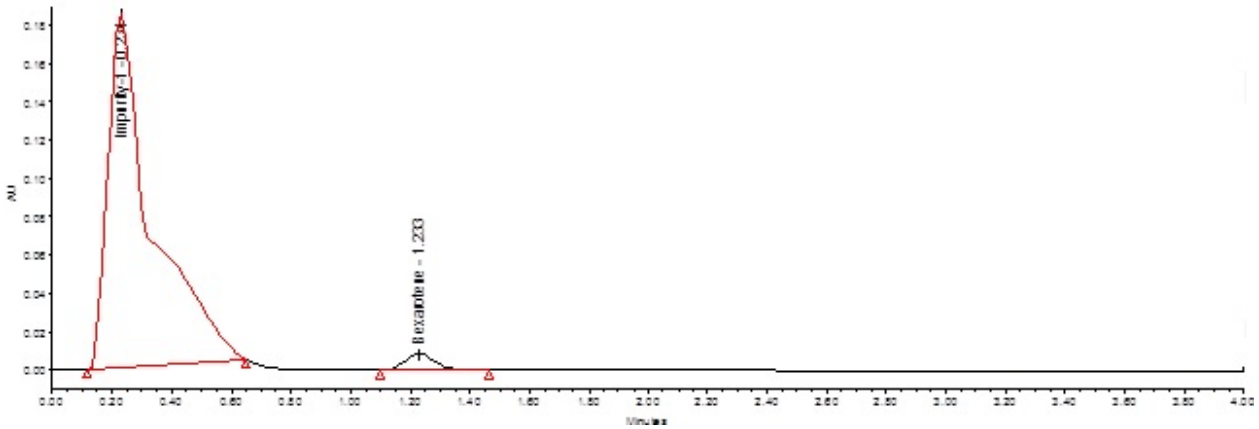

Figure 3f: Bexarotene capsules degradation with 1 m NaOH at Room temperature for 24 h.

All stress studies were performed at an initial drug concentration of 83 µg mL^{-1}. The stress conditions used for the degradation studies included light (exposure of the drug powder to overall illumination of 1.2 million lux hours at an integrated near ultraviolet energy of 200-watt hours/square meter (Whm^{-2}) in a Sanyo (Leicestershire, UK) photostability chamber, conducted in accordance with ICH Q1B), heat (dry heat at 60°C, for 10 days, in a Mack Pharmatech (Hyderabad, India) dry air oven), acid hydrolysis (1 m HCl, at Room temperature, for 24 h), basic hydrolysis (1 m NaOH, at Room temperature, for 24 h) (Figure 3f), and oxidation (10% H_2O_2, at room temperature, for 24 h). For heat and light studies the study period was 7 days. Water baths equipped with MV controllers (Julabo, Seelabach, Germany) were used for hydrolytic studies. Stability studies were conducted in a laboratory humidity chamber (Thermo, India) (Figure 3g and Figure 3h).

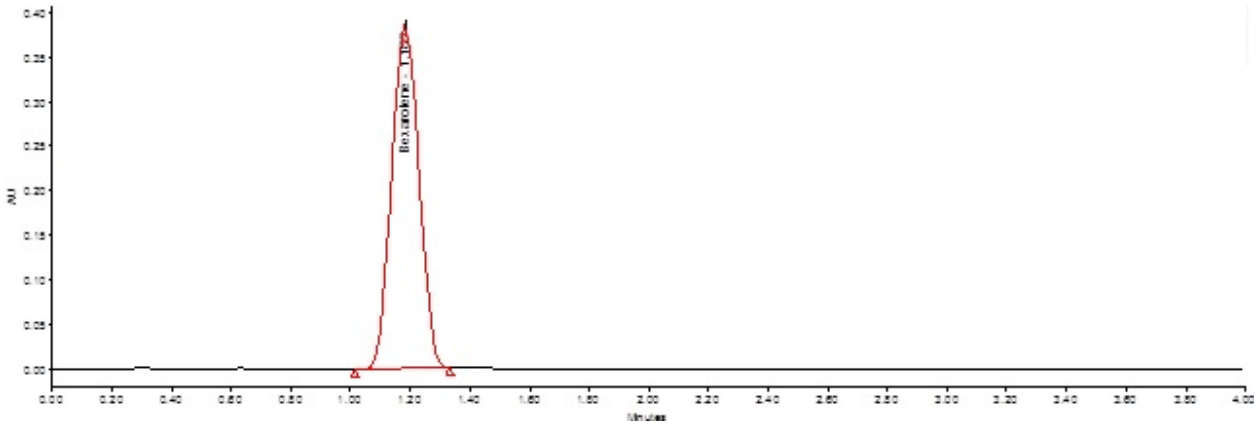

Figure 3g: Bexarotene standard chromatogram in final conditions.

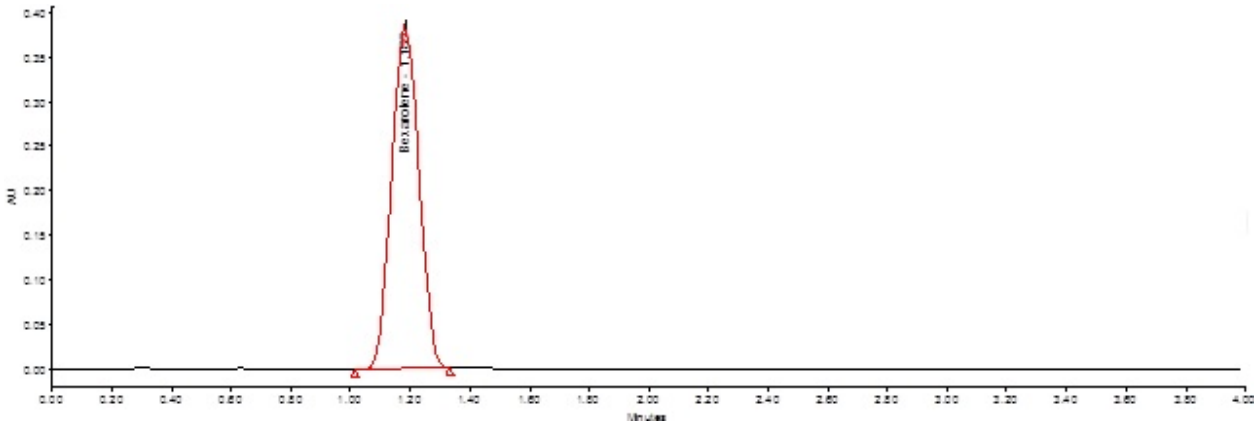

Figure 3h: Bexarotene sample chromatogram in final conditions.

Peak purity of Bexarotene from stressed samples was checked by use of the PDA. The purity angle within the purity threshold limit obtained for all stressed samples demonstrates analyte peak homogeneity. All stressed samples of Bexarotene were analysed for an extended run time of 100 min to check for late-eluting degradation products.

Precision

The precision of the dissolution by HPLC method was evaluated by performing six independent dissolutions of Bexarotene capsules against qualified reference standard. RSD (%) was calculated for the six assay values obtained.

Intermediate precision for the dissolution assay methods was evaluated by performing six independent dissolutions of Bexarotene capsules with the use of a different column (same packing but from a different batch), by a different analyst, using a different instrument (both HPLC and Dissolution), in the same laboratory.

Linear range

Linearity test solutions for the dissolution assay method at different concentrations from 25 to 150% of analyte concentration (i.e., 21, 41, 66, 83, 100, and 125 µg mL^{-1}) were prepared by dilution of the stock solution. Peak area and concentration data were treated by least-squares linear regression analysis and the correlation coefficients, slopes, and Y-intercepts of the calibration plots were calculated.

Accuracy

Accuracy for the dissolution method was studied by triplicate analysis at 50, 100 and 150% of the analyte concentration of 83 µg mL

$^{-1}$. The accuracy was evaluated for the proposed method by adding known amount of bexarotene standard drug (50%, 100%, 150% level) to the tablet placebo powder, which were subjected to dissolution test conditions described above. Each solution was analysed in triplicate. The accuracy was calculated as the percentage of the drug recovered from the formulation matrix.

Robustness

Robustness was studied by making small but deliberate changes in the optimized method conditions and evaluating the effect on the results of Bexarotene capsules. With respect to chromatographic conditions, the mobile-phase flow rate was changed by 0.1 units from 1.0 mL min^{-1} to 0.9 and 1.1 mL min^{-1}. The Trifluro acetic acid was varied by ± 0.1mL units to 0.9 and 1.1 mL. The column temperature was changed from 30°C to 25°C and 35°C. When any changes were made all the other conditions, including the components of the mobile phase, were held constant.

With respect to dissolution conditions; dissolution Media Temperature was changed by ± 2°C from 37°C to 39° and 35°C. The RPM was varied by ± 2 from 50 RPM to 48 RPM and 52 RPM. Dissolution Media volume was changed ± 10 mL from 900 mL to 890 mL and 910 mL.

Solution stability and mobile phase stability

The solution stability of Bexarotene standard and Bexarotene capsules was assessed by leaving a test solution of the sample in a tightly capped volumetric flask at room temperature for 48 h and assay of the solution at 6-h intervals by comparison against freshly prepared standard solution. Stability in the mobile phase was assessed by assay of freshly prepared sample solutions against freshly prepared reference standard solutions at 6-h intervals up to 48 h. The prepared mobile phase was not changed during the study period. Assay was also checked for the test solutions under study.

Validation Results

Precision

RSD for assay of Bexarotene capsules during study of the precision of the dissolution method was within 2.0%. These results confirm the high precision of the method. In the study of intermediate precision the RSD of dissolution results was within 1.0% (Table 2) confirming the ruggedness of the method (Table 3).

Type of precision	Concentration (µg/mL)	%RSD Capsules	
Intra day precision	83	0.2	Acceptance criteria:NMT 2.0%
Inter day Precision	83	0.4	
System precision	83	0.1	

Table 2: Intra day and Inter day system precisions for Bexarotene Drug substance and Bexarotene Capsules.

Experimental parameters for robustness	Prep#	Peak area	% Drug release	% Mean Drug release	% Difference
Normal Conditions	1	1972867	97.65	97.5	N/A
	2	1935733	95.81		
	3	2000993	99.04		
Medium Temperature (-2°C) 35°C	1	2019084	100.11	99.1	1.6
	2	1969414	97.65		
	3	2007052	99.51		
Medium Temperature (+2°C) 39°C	1	2022086	100.26	99.3	1.8
	2	2014261	99.87		
	3	1972777	97.81		
RPM (-2) 48	1	1978283	98.09	97.8	0.3
	2	1962521	97.3		
	3	1977095	98.03		
RPM (+2) 52	1	2027156	100.41	100	2.5
	2	2011941	99.66		
	3	2013872	99.75		
Low HDTMA (-5%)	1	1964706	97.35	98.6	1.1
	2	2005515	99.37		
	3	2002011	99.2		
High HDTMA (+5%)	1	2010462	99.62	99.2	1.7
	2	1991332	98.67		
	3	2007179	99.45		
890 mL Media Volume (-1%)	1	2017873	99.98	99.7	2.2
	2	2035531	100.86		
	3	1981251	98.17		
910 mL Media Volume (+1%)	1	1929052	95.58	96	1.5

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	2	1965033	97.37		

Table 3: Data compilation of robustness study-part-b: sample solution. bexarotene capsules 75mg.

Linear Range

In the dissolution method a linear calibration plot was obtained over the range tested, i.e., 21–125 µg mL^{-1}; the correlation coefficient was>0.999. This result is indicative of excellent correlation between peak area and analyte concentration. The slope and Y-intercept of the calibration plot were 24623.7311 and -105573.0854, respectively (Table 4).

% level	Concentration in µg/mL	Response area	Predicted Response (Y)	Residuals
		(R)		(Y-R)
25	20.95	405310	410294.1	4984.08
50 40	41.1	901753	906462.3	4709.26
80	66.49	1547201	1531659	-15542.2
100	83.01	1934883	1938443	3559.83
125	100.74	2381390	2375022	-6368.42
150	124.92	2961766	2970423	8657.4
Correlation Coefficient				0.999
Slope(m)				24623.73
Intercept(C)				-105573
Residual Sum of Squares(RSS)				4.17E+08
% Y intercept				5.5
Limit value of residuals (±)				38697.66

Table 4: Actual concentrations and chromatographic data of bexarotene linearity solutions.

Accuracy

The individual recovery of Bexarotene is in between 95.7% and 98.9% and the grand recovery (grand mean) value is 97.21%. Over the entire range, 20% to 150% of Bexarotene concentration i.e., 20 µg/mL, the average recovery is 97.21%. This value is well within the validation criteria. Thus the method is valid for the proposed range of concentration. The % RSD of six preparations at different levels (20%-150%) is less than 5.0%, indicating the method is precise.

This study proves that the method is capable of recovering the active drug component Bexarotene from placebo matrix. Thus the method is accurate and precise for the proposed range of concentration (Table 5).

% level	Prep#	Peak area	Amount added (µg/mL)	Amount recovered (µg/mL)	% Recovery	%Mean recovery	SD	% RSD	95% CI
	1	391381	20.15412	19.97899	99.77				Lower
	2	391712	20.15412	19.98236	99.85				99.75
	3	391690	20.15412	19.98213	99.85				
	4	391106	20.15412	19.97619	99.7				Upper
	5	392773	20.15412	19.99314	100.12				100
25	6	391839	20.15412	19.98365	99.89	99.86	0.143	0.1	
	1	1967882	83.31627	83.00657	100.48				Lower
	2	1951794	83.31627	82.84301	99.66				99.83
	3	1955533	83.31627	82.88102	99.85				
	4	1976123	83.31627	83.09035	100.9				Upper
	5	1958333	83.31627	82.90949	99.99				100.6
100	6	1965505	83.31627	82.98241	100.36	100.2	0.4586	0.5	
	1	2947566	125.7886	124.9666	100.34				Lower
	2	2936331	125.7886	124.8524	99.95				100.23
	3	2967968	125.7886	125.174	101.03				
	4	2960372	125.7886	125.0968	100.77				Upper
150	5	2948908	125.7886	124.9802	100.38	100.58	0.4367	0.4	100.9

	6	2968689	125.7886	125.1813	101.05				
Minimum %Recovery					99.7				
Maximum %Recovery					101.1				
Grand Recovery					100.2				

Table 5: Chromatographic data and results of accuracy and precision study.

Robustness

Robustness was studied during the final phase of method development. When the chromatographic conditions flow rate, pH, and column temperature and dissolution conditions RPM, bath temperature, dissolution media volume were deliberately varied there is no changes in the results of Bexarotene capsules dissolution, illustrating the robustness of the method (Table 3).

Solution stability and mobile phase stability

The RSD obtained for assay of Bexarotene was within 1% during studies of stability in the diluent and in the mobile phase, and there was no significant change in Bexarotene content during the studies. These results confirm the compounds were stable in diluent and in the mobile phase used during dissolution assay analysis for a study period of up to 48 h.

Results from Forced Degradation Studies

Basic and acidic hydrolysis

When the drug was exposed to 1 m HCl, significant degradation was observed at RRT ~0.12.

When the drug was exposed to 1 m NaOH, significant degradation was observed at RRT ~0.12, after 24 hours at Room temperature, Bexarotene totally converted to imp^{-1}.

When the drug was exposed to aqueous hydrolysis no major degradation products were observed, so the drug was stable to aqueous hydrolysis.

Oxidizing conditions

When Bexarotene was exposed to 6% hydrogen peroxide at room temperature for 24 h no degradation was observed. The drug was stable to oxidation.

Photolysis

The drug was stable to the effect of photolysis and no degradation was observed.

Thermal degradation

The drug was stable to the effect of temperature and no degradation was observed. All the forced degradation samples were analyzed or assay, and peak purity was calculated.

Peak purity test results obtained by use of the PDA confirmed the Bexarotene and degradation product peaks obtained from analysis of all the stressed samples were homogeneous and pure. Because dissolution assay of Bexarotene was unaffected by the presence of the degradation products (Table 6) the method can be regarded as stability-indicating.

Stress condition	Time	Degradation (%, approx.)
Acid hydrolysis	24 h	0.002
(1 m HCl, Room Temperature)		
Basic hydrolysis	24 h	0.97
(1 m NaOH, Room Temperature)		
Oxidation (6% H_2O_2, room temperature)	24 h	0
Thermal (60°C)	10 days	0
Light (photolytic degradation)	10 days	0

Table 6: Summary of results from forced degradation studies for Bexarotene Capsules.

Conclusion

A new, sensitive, and stability-indicating LC method has been successfully developed for quantitative analysis of Bexarotene capsules dissolution. The method was accurate and precise with good consistent recovery at all the levels studied. The method enables high resolution of degradation products from Bexarotene and from each other. The validated method may be used for routine analysis of Bexarotene capsules dissolution for analysis of other quality-control samples during product development.

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