

Stability indicating RP-HPLC method of dexibuprofen in nanocream formulation: Identification and quantification

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Abstract: A stability indicating reverse phase-HPLC method was designed for determination of dexibuprofen in drug solution and in nanocream formulation. Chromatographic conditions were optimized simply by adjusting the content and different compositions of reverse phase associated with mobile phases. Different parameters like specificity, limit of quantification (LOQ), limit of detection, linearity, range, system suitability, precision and accuracy were determined. Stability studies of dexibuprofen in nanocream were taken under the stressed situations of alkali, acid, oxidation process, UV and heat degradation. Tailing factor and % RSD were found >2000 and <2% respectively. The method was identified linear over the range of 0.2-1.6mg/ml having co-efficient of correlation 0.9995. Intra-day and inter- day precision and accuracy values for dexibuprofen were $\leq 0.6\%$ and ≤ 1.1032 and $\leq 0.3\%$ and 1.10% respectively. Stability studies showed that dexibuprofen was stable in nanocream against alkali, acid, oxidation, UV light and heat. The developed validated method was precise and accurate for the evaluation of dexibuprofen in solution as well as in nanocream formulation.

Keywords: Dexibuprofen, method validation, RP-HPLC

INTRODUCTION

The quality of pharmaceutical products can be determine by using the analytical techniques that estimate the purity, quality and safety of the product as well as for identification of active pharmaceutical ingredient and impurities or other related substance in that final dosage form are also find out with the help of these analytical techniques (Ohannesian & Streeer, 2001). Different methods such as electrochemical, chromatographic or spectroscopic are used for quantification and identification of active drug and other impurities. Physical and chemical properties of analyte, type of measurement (qualitative or quantitative), sensitivity and selectivity, impurities and active ingredient in the sample are major considerations which can help in selection of an analytical method (Toomula, Kumar *et al.*, 2012).

Dexibuprofen [S-(+) enantiomer] (fig. 1) is more effective than the ibuprofen (recemic) regarding its pain relieving and anti-inflammatory activities (Bonabello *et al.*, 2003), and it shows an equal therapeutic effect as compare to half dose of the racemic ibuprofen (Eller *et al.*, 1998). Various methods for quantification and determination of dexibuprofen was developed like UV spectrophotometric (Pritesh G. D *et al.*, 2011), HP-TLC (M. Selvadurai *et al.*, 2009), RP-HPLC-UV (Hanan A *et al.*, 2011; A. Thenmozhi *et al.*, 2011; P. Balan *et al.*, 2011; Selvadurai and Subramania, 2011; Punnamchand and Madhusudan, 2012).

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The aim of this research work was to develop a simple, fast and reliable method of HPLC for the identification and quantification of dexibuprofen in bulk and nanocream formulation. The novelty and important features of this developed method is simple treatment of the sample at ambient conditions, short retention time, high recovery and stress stability studies.

MATERIALS AND METHODS

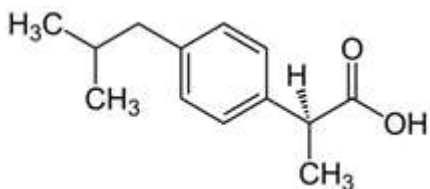
Materials

Dexibuprofen reference standard was gifted from SAMI Pharmaceutical (Pvt) LTD. Karachi (Pakistan). Acetonitrile was purchased from Fisher Scientific (UK). Potassium hydroxide, Sodium hydroxide and hydrochloric acid were bought from Sigma-Aldrich (Germany). Ginger Oil was purchased from Haq Planters International, Karachi, Pakistan. Olive oil, Propylene glycol, Tween 80, Tween 60, Tween 20, Cremophore RH-40, Lecithin, propyl paraben and methyl paraben were received from Daejung Chemicals & metals Co. Ltd. Carbapol-940 was purchased from Sigma-Aldrich, USA. Ortho-phosphoric acid was purchased from Merck (Germany). Hydrogen Peroxide (35%) was purchased from VWR BDH. Polar and ultrapure water was obtained from in-house Smart 2 Pure water purification system obtained from Thermo Scientific (USA). All solvents and chemicals used in this study were of HPLC or analytical grade.

Instrumentation

High-performance liquid chromatography was conducted on Waters Alliance HPLC system (e2695), fitted with

automatic sampler, column oven and 2998 PDA detector and Empower® 3 software (RF-3) was used to obtain the data.



(2S)-2-[4-(2-methylpropyl) phenyl] propanoic acid

Fig. 1: Chemical Structure of dexibuprofen

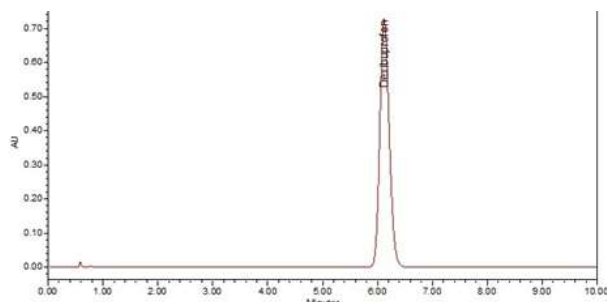


Fig. 2: The chromatogram of dexibuprofen peak obtained for mobile phase containing acetonitrile and purified water at ratio of 45:55 and flow rate of 2.0 mL/min.

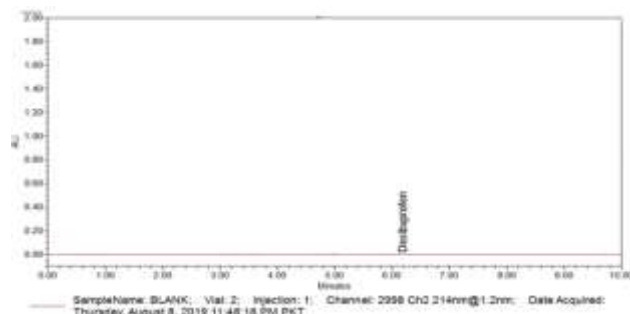


Fig. 3: The chromatogram of blank obtained for mobile phase containing acetonitrile and purified water at ratio of 45:55 and flow rate of 2.0 mL/min.

Chromatographic conditions

HPLC was conducted on C₁₈ column (150× 4.6 mm; 5µm) (Agilent USA) with the flow rate of 2.0 ml/min and 223.5 nm UV detection was used. 10µl sample was injected onto the column at room temperature (Saraji et al, 2020).

Mobile Phase optimization

To observe the response of analyte, short elution time and good resolution, different mobile phase compositions of acetonitrile and distilled water were used over the selected column. pH was adjusted at 2.5 with the help 1.0M ortho-phosphoric acid or 1.0 M potassium hydroxide. Before use, mobile phase was degassed with the help of ultrasonicator and 0.45µm membrane filter was used to filtrate it. The selected mobile phase was also used as diluent (katarzyna et al, 2018).

Preparation of stock and working standard solutions

40 mg of dexibuprofen reference standard powder was dissolved in 25.0 ml of diluent (mobile phase) in 50 ml volumetric flask. The volumetric flask was shaken and sonicated for 5.0 min and made up the final volume with diluent to achieve concentration of 0.8 mg/ml of dexibuprofen.

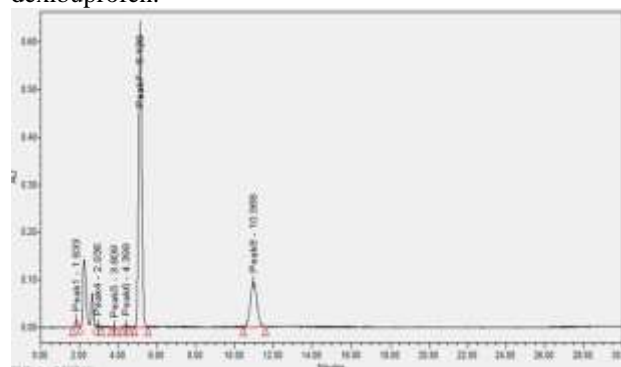


Fig. 4: The chromatogram of placebo (without dexibuprofen) obtained for mobile phase containing acetonitrile and purified water at ratio of 45:55 and flow rate of 2.0 mL/min.

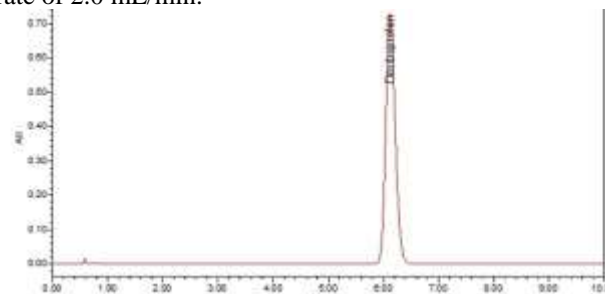


Fig. 5: The chromatogram of dexibuprofen standard (0.8 mg/ml) obtained for mobile phase containing acetonitrile and purified water at ratio of 45:55 and flow rate of 2.0 mL/min.

System Suitability studies

Different system suitability parameters were performed by running at least six injections of a working standard. These parameters such as plate count, relative standard deviation (% RSD) or coefficient of variation, tailing factor and resolution were calculated to determine the system suitability (USP 34, 2010).

Limit of detection (LOD)

LOD was determined in order to find out the lowest concentration of standard solution. LOD is that concentration where highest peak response is obtained, at least 2-3 times more as the base noise level. Limit of detection is calculated by following formula (Jadhav et al., 2007).

$$LOD = 3.3 \times (\sigma/S)$$

Where S= slope of calibration curve, σ = Standard error or standard deviation of residuals

Table 1: Mobile phase composition and observation of dexibuprofen.

Composition (Acetonitrile: Purified water) (v/v)	pH	Flow rate (mL/min)	Observation
45:55	2.5	2.0	Good separation. Long retention time of 6.0 ± 0.2 min.
50:50	2.5	2.0	Good separation. Retention time of 4.25 ± 0.2 min.
60:40	2.5	2.0	Good separation. Retention time of 2.25 ± 0.2 min.
70:30	2.5	2.0	Good separation. Retention time of 1.75 ± 0.2 min.
80:20	2.5	2.0	Good separation. Retention time of 1.60 ± 0.2 min.
90:10	2.5	2.0	Good separation. Retention time of 1.5 ± 0.2 min.

Table 2: System suitability studies of standard preparations of dexibuprofen. Mean \pm S.D, N=6.

Concentration (mg/ml)	Theoretical plate	Tailing factor	Capacity factor
0.2	9078.16 ± 0.68	1.133 ± 0.004	2.359 ± 0.002
0.4	8865.12 ± 0.05	1.141 ± 0.002	2.357 ± 0.001
0.8	5857.89 ± 0.33	1.168 ± 0.003	2.223 ± 0.002
1.2	7212.96 ± 0.10	1.209 ± 0.002	2.305 ± 0.002
1.6	6187.14 ± 0.79	1.238 ± 0.003	2.298 ± 0.002

Table 3: Results of stress degradation studies of dexibuprofen in nanocream formulation Mean \pm S.D, N=3.

Parameters	Exposure time (hr)	
	0	24
Acid degradation (%)	96.08 ± 0.65	77.76 ± 0.64
Alkali degradation (%)	99.82 ± 0.85	89.45 ± 0.74
Oxidative degradation (%)	95.74 ± 0.65	95.44 ± 0.56
Heat degradation (%)	96.93 ± 0.02	94.98 ± 0.36
UV degradation (%)	98.57 ± 1.31	93.34 ± 0.82

Table 4: Within-day and between-day precision and accuracy of dexibuprofen. Mean \pm SD, N= 6.

Added (mg)	Within-day (n=6)			Between Days (n=6)		
	Found \pm SD (mg)	%RSD	Accuracy (%Bias)	Found \pm SD (mg)	%RSD	Accuracy (%Bias)
Dex						
0.2	0.194 ± 0.004	0.1	-0.756	0.201 ± 0.009	0.1	-0.747
0.4	0.382 ± 0.003	0.0	-0.521	0.405 ± 0.032	0.0	-0.492
0.8	0.805 ± 0.037	0.6	0.007	0.837 ± 0.044	0.3	0.046
1.2	1.259 ± 0.004	0.1	0.574	1.229 ± 0.028	0.1	0.537
1.6	1.682 ± 0.004	0.1	1.103	1.682 ± 0.070	0.1	1.103

Lower limit of quantification (LLOQ)

The lowest amount of analyte that can be quantified with precision and accuracy is called LLOQ. It is calculated from following equation (Bushra, 2019).

$$LLOQ = 10 \times (\sigma/S)$$

Preparation of dexibuprofen nanocream

Primary nanocream base was formulated by oil and water phases in two different beakers at 50-60°C with continuous stirring with magnetic stirrer for 30 min. Oil phase was comprised of ginger oil, propyl paraben, tween-80 (hydrophilic surfactant) and propylene glycol (co-surfactant). Water phase was consisted of the hydrophilic surfactant that is carbapol-90 and methyl paraben in water. Dispersed phase was added into dispersion medium (water phase) with continuous stirring. The mixture was stirred at 1500 rpm for 30 min. To

convert the base cream into nanocream, base was homogenized at 20,000 rpm for 20 min with the help of ultra speed homogenizer at room temperature.

Assay of dexibuprofen in drug solution

20 mg of reference standard dexibuprofen drug was taken into volumetric flask (25 ml) and 10 ml of diluent was used to dissolve it. The volumetric flask was shaken for 5 min by using ultrasonicator. Diluent (mobile phase) was used for the purpose of diluting the solution. Dexibuprofen standard stock solution of 1mg/ml was prepared. The % assay of dexibuprofen is calculated by the following equations below (Haroon KS et al, 2015).

$$\% \text{ Assay of dexibuprofen} = A_2 \times C_1 \times P_{DEX} / A_1 \times C_2$$

Where as

A₁= peak area of working standard, A₂= peak area of dexibuprofen in drug solution

C_1 = conc. of working standard in mg/ml, C_2 = conc. of dexibuprofen in nanocream

P_{DEX} = potency of dexibuprofen working standard in %

Assay of dexibuprofen in nanocream

Sample solution was prepared by taking an aliquot of nanocream equivalent to 10 mg of dexibuprofen and 25.0 ml of diluent was added. The sample was heated for 15 min at 60°C and sonicate it for 10 min for proper dispersion. Sample was run through freeze-thaw cycling and 0.45 µm membrane filter was used and analysed via HPLC. To calculate the assay of dexibuprofen, following formula was used (Haroon KS *et al*, 2015)

$$\% \text{ Assay of dexibuprofen} = A_2 \times C_1 \times P_{DEX} / A_1 \times C_2$$

Where as

A_1 = peak area of working standard, A_2 = peak area of sample

C_1 = conc. of working standard in mg/ml C_2 = conc. of target ingredient in cream

P_{DEX} = potency of dexibuprofen working standard in %

Stress degradation studies

To evaluate the standard drug solution with degraded products or impurities during reaction, a good stability indicating technique is needed (Kadi, Mohamed *et al.*, 2011). To analyse the behaviour of dexibuprofen in nanocream formulation, stress degradation studies were conducted. Dexibuprofen stock solution had concentration of 0.8mg/ml.

Alkali and Acid degradation Study

Two sets of flasks of 25 ml were taken and standard stock solution of dexibuprofen (5 ml) was poured into them. In one set of flask, 3M HCl (1ml) and 3M NaOH (1ml) was added and instantly neutralized and made up the volume upto 25 ml with diluent. These samples were considered as 0.0 hour. Another set of flasks were taken and 1.0 mL of both 3M HCl and 3M NaOH was added separately into the each flask which was left on bench at ambient condition (26°C/65%RH) for 24.0 hours. After 24.0 hours, same neutralization procedure was repeated. These neutralized solutions were run in triplicate after passing through 0.45µm syringe filter (Haroon KS *et al*, 2015).

Oxidative degradation

Oxidation degradation was carried out by adding 5.0 ml of stock solution of dexibuprofen into set of two volumetric flasks (25 ml). 344 µl of 35% hydrogen peroxide (H_2O_2) was added in each flask and diluent was used to make the final volume up to 25 ml. One flask was considered at zero hour sample and other was left over the shelf at ambient condition (26°C/65% RH) for 24.0 hour. The final solution of both flasks was passed through 0.45 µm syringe filter and checked in triplicate.

Heat degradation study

Heat degradation test was conducted by taking 5.0 ml of standard stock solution of dexibuprofen in two flasks (25

ml). Diluent was used to make up the final volume and that flask was taken as zero hour samples. The contents of second flask were heated for 2.0 hours at 80°C and after cooling it to ambient temperature, final volume was made up to 25 ml with diluent. The samples were filtered through 0.45 µm syringe filter and injected in triplicate.

UV light degradation

Standard stock solution of dexibuprofen (5 ml) was taken into two flasks of 25 ml. The final volume was made up to 25 ml with diluent and taken as zero hour sample. The second flask was kept in UV cabinet at 223.5 nm for 24 hours after making the final volume of 25 ml and injected. Both samples were filtered through 0.45µm syringe filters before injection.

Linearity

Five different concentrations 0.2, 0.4, 0.8, 1.2 and 1.6 mg/ml of dexibuprofen were prepared in mobile phase and standard calibration curve of dexibuprofen was prepared with the help of peak area and known concentration of dexibuprofen. To determine the linearity and concentration of sample, linear regression line was used. The linearity correlation coefficient (r^2) should be equal to or near to 1.0, which indicates the linear response of the method.

Precision and accuracy

For an analytical method, precision indicates the harmony between a number of measurements obtained after running the sample of same concentrations (multiple times) under the stated condition. Repeatability and intermediate precision were calculated. Repeatability was determined by performing the analysis of six determination of test concentration and it was calculated on two days. For intermediate precision, same procedure was adopted as of repeatability. One concentration (0.8 mg/mL each) of dexibuprofen was used to calculate the precision and accuracy. Six fresh replicates were prepared and analyzed. After that, test concentration was spiked to 50%, 100% and 150% concentration of reference material to calculate the % bias. For precision, the coefficient of variation (% RSD) was determined and for accuracy, the relative percentage error (% bias) was calculated.

Stock solution stability

Dexibuprofen stock solution (0.8 mg/mL) was store at room temperature (26°C) for at least 24.0 hours. Dilution of stock solution was done to a concentration within the standard calibration linear range (0.2-1.6 mg/ml). The HPLC system outputs at 24.0 hours were compared with that of fresh samples at 0.0 hour.

Recovery of dexibuprofen in nanocream formulation

20mg of dexibuprofen was added into a volumetric flask (50 ml) containing nanocream base (total weight 1gm) with diluent. Flasks was heated on water bath at 50°C until the cream base was melted and diluted to the mark

with mobile phase (diluent) and sonicate it for 15 minutes. After sonication, solution was centrifuged for 10 min at 4000 rpm. In order to obtain a concentration of 0.2 mg/ml, 0.5 ml of supernatant was diluted with 10 ml diluent in volumetric flask. To calculate the recovery of dexibuprofen, 25µl of sample was run into HPLC system. The slope and intercept of the calibration curve (0.2-1.6 mg/ml) was used to estimate the dexibuprofen recovery. Following equation was used to calculate the recovery (Kaplan and Pesce, 2019).

$$\% \text{ Recovery} = \text{Amount found} / \text{Amount added} \times 100$$

Where,

Amount found = Amount found in spiked sample, amount added in unspiked sample.

STATISTICAL ANALYSIS

The statistical analysis was performed using SPSS® (version 20, USA). The results were presented in mean ± standard deviation (SD).

RESULTS

Mobile Phase optimization

The response of selected analyte in different mobile phase compositions was summarized in table 1. To observe the behavior of analyte (dexibuprofen), different mobile phase combinations were passed over the selected column C₁₈ (150mm x 4.6: 5µm). Dexibuprofen peak was well resolved and eluted at 6.0 min when mobile phase containing acetonitrile and purified water (45:55 v/v) with flow rate of 2.0 ml/min was used (fig. 2). The retention time of the peak was further reduced to 4.25 min, when the acetonitrile and purified water were in ratio of 50:50 (v/v). Retention time was again decreased up to 1.5 min, as the acetonitrile and water of 90:10.

System suitability studies

The results of system suitability are shown in table 2. Different parameters were determined for system suitability studies like theoretical plates (N), tailing factor (T), capacity factor (K) and % RSD, after injection of 6 replicate of the standard preparations for the concentration of 0.2 -1.6 mg/ml.

LOD and LLOQ of Dexibuprofen

LOD value was 9.9 µg/ml and value of LLOQ was 3.02 µg/ml which can be quantified by this method.

Specificity

In case of blank, no peak was obtained during the retention time of analyte (fig. 3). The chromatograms of placebo and standard (0.8 mg/ml) were presented in fig. 4 and 5 respectively. This method was highly specific for dexibuprofen.

Stress degradation studies

The results of stress condition like alkali and acid hydrolysis, oxidation, heat and UV degradation are shown in table 3 below.

Linearity

The standard calibration curve showed linearity and strong correlation coefficient across the recommended range of 0.2-1.6 mg/mL of dexibuprofen. The linear regression equation of dexibuprofen is $y = 1E + 07x - 44477$, with a correlation coefficient of $R^2 = 0.9999$.

Precision and accuracy

Intra-day precision and accuracy for dexibuprofen ranged from 0 to 0.6% and 0.756 to 1.103, while Inter-day precision and accuracy were 0 to 0.3% and -0.747 to 1.103 respectively as shown in table 4.

Stock solution stability

Dexibuprofen contents remaining at room temperature after 24.0 hour was 100.71 %. The result suggested that the stock solution remained stable at room temperature for 24.0 hours.

Recovery studies of dexibuprofen in nanocream

The accuracy of present method was determined by conducting the experiment for quantification of dexibuprofen sample. The percentage recovery of dexibuprofen was ranged between 95.68 - 105.16% in nanocream sample.

DISCUSSION

In the literature, various studies have been presented like UV spectrophotometric (Pritesh G. D et al, 2011), HP-TLC (Selvadurai et al, 2009), RP-HPLC (Punnamchand and Madhusudan, 2012) for the identification and quantification of dexibuprofen. The present study presents the design and validate an innovative, stability indicating and rapid analysis method for dexibuprofen using RP-HPLC. Dexibuprofen was separated on Waters Alliance HPLC system (e2695) C₁₈ column, using isocratic mobile phase a mixture consisting of acetonitrile and water (45:55, v/v). The retention time of dexibuprofen was 6 min (fig. 2). The developed method of RP-HPLC explores the effect of equipment setting and composition of mobile phase. The proportion of acetonitrile and water (mobile phase) showed a good impact on peak area. The selected mobile phase was more suitable as it has less amount of organic solvent (acetonitrile) and more amount of purified water. The system suitability studies presented that this method is specific and suitable and no interference was found (Cunha et al, 2015, Svorc et al, 2018). It was found that tailing factor was less than 2.0, theoretical plates were more than 2000 and relative standard deviation were also < 2.0 % for dexibuprofen. The capacity factor was within the range of 2.22 - 2.39.

All the values of system suitability were in the range mentioned in USP (USP 34, 2010). These results were similar to the studies performed by Borahan et al, 2019. Stress degradation showed that dexibuprofen was stable against alkali, heat, oxidation reaction and UV light but slightly degraded against acid after 24 hours of treatment. The developed method was successful to distinguish between degradation product and analyte. The results of % RSD were within the recommended range ($\pm 2\%$) (USP-34). Hence, the developed method indicates good process precision and accuracy.

CONCLUSION

A very precise, accurate, cost-effective and simple stability indicating analytical method (RP-HPLC) was designed for the concurrent quantification of dexibuprofen in drug solution and nanocream formulation. The stability studies proposed that dexibuprofen had no considerable effects of alkali, heat, UV light and oxidation but slightly degraded to acid.

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