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Stability indicating method development and validation of Dexlansoprazole delayed-release capsules by using RP-HPLC

[1]Santhosh Kumar Ettaboina, [2]Komalatha Nakkala

[1]Analytical Research and Development, Aurex Laboratories Pvt. Ltd. Kukatpally, Hyderabad, Telangana, India, 500072.

[2]Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Mumbai, Maharashtra, India, 400019.

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ABSTARCT: The present study describes the "Stability-indicating Method development and validation of Dexlansoprazole delayed release capsules using RP-HPLC" Isocratic separation was achieved by the use of X-Terra RP18column (250×4.6mm, 5µ), the mobile phase, consisting of a mixture of 10 mm dibasic potassium phosphate buffer, was prepared and the pH of the solution adjusted to 7.20 with dilute orthophospharic acid: acetonitrile: TEA at a ratio of 70:30:1 v/v/v was delivered at a flow rate of 1.2 ml/min and a wavelength detector of 285nm. The retention time for Dexlansoprazole was 6.8 min. The linearity range of Dexlansoprazole was 50µg/mL-150 µg/mL-1 with a regression coefficient (r2) of 0.999, accurate (recovery 97.77-103.94%).Precision (RSD ≤ 1.0 percent), sensitive, specific, simple, fast and robust. Based on the validation parameters performed in accordance with the ICH guidelines, the proposed method was found to be specific, accurate and accurate for the analysis of Dexlansoprazole. The proposed method may be useful in quality control laboratories for the determination of Dexlansoprazole in pharmaceutical dosage form.

Keywords: Dexlansoprazole, Quality control, Reverse-phase high-performance liquid chromatography, Validation.

I. INTRODUCTION

Dexlansoprazole inhibits the H/K ATP ASE enzyme[1-3], which is involved in the secretion of hydrochloric acid, hydrolyzing ATP and exchanging H+ ions from the cytoplasm for K+ ions in the secretary canaliculus, which results in Hydrochloric acid secretion into the gastric lumen. Dexlansoprazole inhibits this effect of H/K ATPase by demonstrating a high degree of activation in the acidic environment[4]. PPIs undergo protonation in the acidic pH setting after passing through the liver and reaching the gastric parietal cells stimulated by a meal, followed by conversion to Sulphenamide, the active form of the drug. Sulphenamide inhibits the activity of the proton pump[5] and hence the transport of hydrogen ions into the gastric lumen via covalent binding to the SH groups of the cysteine residues of H/K ATPase[6]. Dexlansoprazole MR delivery technology is designed to release the drug in two separate pH-dependent phases, the first in the proximal duodenum (25 percent of total drug dose) and the second in the more distal small intestine (75 percent of total drug dose).Dexlansoprazole reduces both basal and stimulated gastric acid secretion[7].Dexlansoprazole has a unique active formulation independent of time-of-day dosing or food[8]. Dexlansoprazole is the R-enantiomer of lansoprazole[9],Dexlansoprazole blocks in the final step of acid production[10].

DexlansoprazoleFor the treatment of acid reflux disorders[11-12] (GERD), Peptic Ulcer disease[13-15], and H. Pylori eradication. Chemical name is (R)-(+) 2-([3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl)-1H-benzimidazole. Dexlansoprazoleis freely soluble in methanol, ethanol & ethyl acetate[16-17], Soluble in Acetonitrile: slightly soluble in ether; very slightly soluble in water; practically insoluble in hexane[18]. Dexlansoprazole is class of Benzimidazoles, Ethers[19].Its Molecular formula is $C_{16}H_{14}F_3N_3O_2S$ &Molecular weight is 369.36 gm/mole.The aim of the current study was to create a highly effective sensitive method for Dexlansoprazole bulk estimation and formulations and validation in compliance with ICH guidelines[20].Dexlansprazole drug substance/drug product LC determinations[21-23], Chemical structures and properties of Dexlansoprazole and related Impurities shown in**Table 1.**

International Journal of Pharmaceutical Research and Applications
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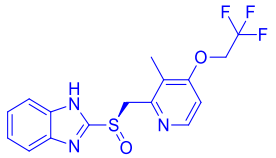
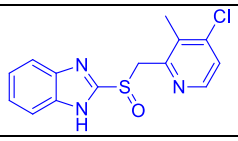
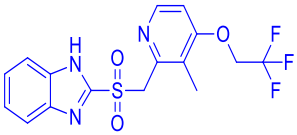
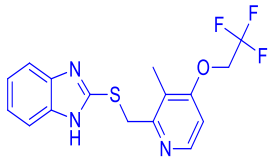
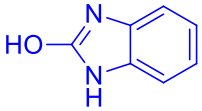
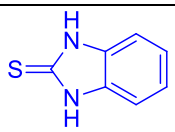
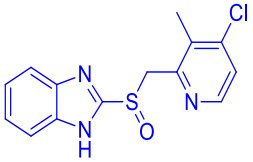
Table 1. Complete profile about the derivatives of Dexlansoprazole

S.No	Name	Chemical Formula	IUPAC Name	M. Wt	Structure
1	DEXP	$C_{16}H_{14}F_3N_3O_2S$	2-[(R)-[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl]-1H-benzimidazole	369.36	
2	DEXP RC-A	$C_{14}H_{12}ClN_3OS$	2-[(4-chloro-3-methylpyridin-2-yl)methylsulfinyl]-1H-benzimidazole	305.78	
3	DEXP RC-B	$C_{16}H_{14}F_3N_3O_3S$	2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfonyl]-1H-benzimidazole	385.36	
4	DEXP RC-C	$C_{16}H_{14}F_3N_3OS$	2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole	353.36	
5	DEXP RC-D	$C_7H_6N_2O$	1H-benzo[d]imidazol-2-ol; 2-Benzimidazolol; 1H-benzimidazol-2-ol	134.14	
6	DEXP RC-E	$C_7H_6N_2S$	1,3-Dihydro-2H-benzimidazole-2-thione	150.20	
7	DEXP RC-F	$C_{14}H_{12}ClN_3OS$	2-[[(4-Chloro-3-methyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole	305.78	

II. MATERIAL AND METHODS

CHEMICAL REAGENTS

The ACS grade of Orthophospharic acid was procured from Macron chemicals, USA. The HPLC grade of Acetonitrile (J.T. beaker) with certified purity of 99.9% was purchased from Avantor performance materials, LLC, Radnor, PA, USA. The ACS grade of Hydrochloric Acid & NAOH pellets was procured from VWR Chemicals, USA. The HPLC grade of Triethyl amine Supplied for Alfa Aesar, USA. The ACS grade of Hydrogen peroxide was purchased from Avantor performance materials, LLC, Radnor, PA, USA. High quality In-House purity water was used for the experiments (TOC<500ppb, pH about 7.0, Conductivity< 1.0 µs/cm, finally exposed to UV radiation and followed filtered through 0.2µm filter). Dexlansoprazole 100% purity was procured from Aspire Life sciences Pvt Ltd. Mumbai, India.

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INSTRUMENTATION AND SOFTWARE

UV-1800 Schimadzu Double beam with UV probe software UV-Visible spectrophotometer with 1cm matched quartz cells.

Waters HPLC system Alliance e2695 separation module with auto injector, temperature controller for sample storage and column was used for current analysis. The signal output was observed through Empower 3 Software Build 3471 SPs Installed: Feature Release 3 DB ID: 2639633283. The LC column is X-Terra RP_{18} column (250×4.6mm, 5µm. manufactured by GL Sciences Inc. Analytical balance model CP225D (make: Sartorius), Top load balance model GP5202 (make: Sartorius) sonicator (make: LIFE CARE), pH Meter (make: ORION 3STAR), Thermal oven(make: NEWTRONIC) were employed in this work.

DETERMINATION OF ΛMAX BY UV-SPECTROSCOPY

The suitable wavelength for the determination of Dexlansoprazole in diluent is identified by scanning over the range 200–400nm with a Shimadzu UV-160 (Shimadzu, Japan) double beam spectrophotometer.

PREPARATION OF SAMPLE SOLUTION BY UV-SPECTROSCOPY

A Sample Stock Solution of DEXP (50 µg mL^{-1}) was prepared by dissolving DEXP (10.0mg), in the Diluent (The Diluent was prepared by 0.1 N sodium hydroxide and Acetonitrile in the ratio of 60:40 v/v) to make 10 mL of solution (Stock Solution 1), Sample working solutions were prepared by quantitatively transferring 0.5 mL of Sample Stock Solution-1 separately into 10 mL volumetric flasks and made to volume with Diluent.

Adjust the baseline to zero using diluent as blank. Take the spectrum forDexlansoprazole as shown in **Fig.1**.

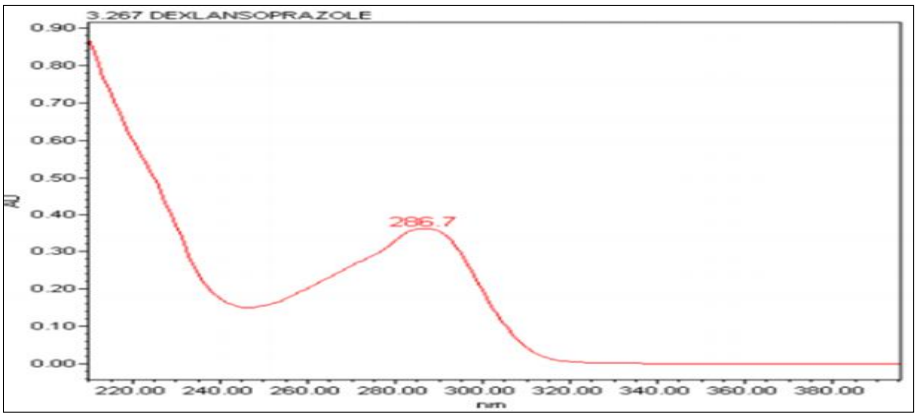

Fig. 1: UV Spectrum of Dexlansoprazole

PREPARATION OF SYSTEM SUITABILITY SOLUTION

A System suitable Stock Solution of DEXP & SULF (240 µg mL^{-1}) was prepared by dissolving DEXP & SULF (30.0mg), in the Diluent (The Diluent was prepared by 0.1 N sodium hydroxide and Acetonitrile in the ratio of 60:40 v/v) to make 50 mL of solution (Stock Solution 1), Standard working solutions were prepared by quantitatively transferring 4.0 mL of System suitable Stock Solution-1 separately into 10 mL volumetric flasks and made to volume with Diluent. System suitability chromatograms are shown in **Fig. 2**.

International Journal of Pharmaceutical Research and Applications
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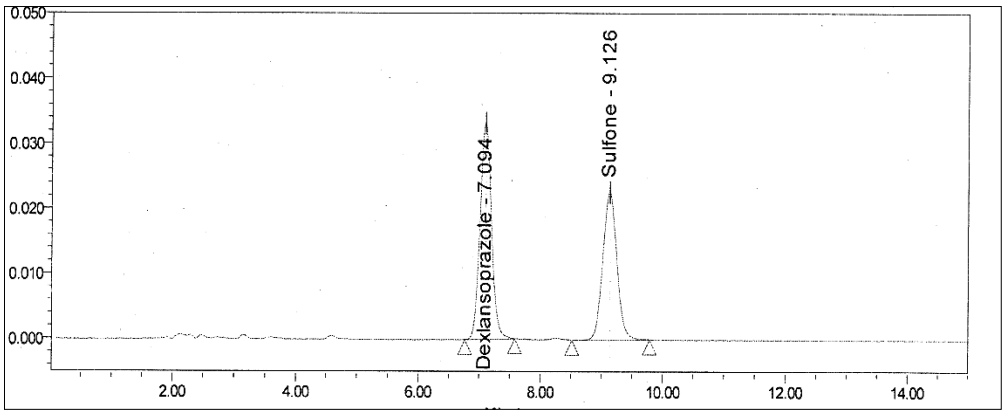

Fig. 2: Chromatogram for System suitability solution

PREPARATION OF STANDARD SOLUTION

A Standard Stock Solution of DEXP (240 µg mL^{-1}) was prepared by dissolving DEXP (30.0mg), in the Diluent (The Diluent was prepared by 0.1 N sodium hydroxide and Acetonitrile in the ratio of 60:40 v/v) to make 50 mL of solution (Stock Solution 1), Standard working solutions were prepared by quantitatively transferring 4.0 mL of Standard Stock Solution-1 separately into 10 mL volumetric flasks and made to volume with Diluent.Standard chromatograms are shown in **Fig. 3**. Results of the System suitability is summarized in **Table 2**.

Table 2. System suitability results

Parameters	Dexlansoprazole	Sulfone	Acceptance criteria
RT(min)	7.09	9.13	±10%
USP Tailing factor	1.12	1.09	NMT 2.0
USP Plate count	7036	7675	NLT 3000
USP Resolution	NA	5.30	NLT 3.0
% RSD	0.3	0.5	NMT 2.0

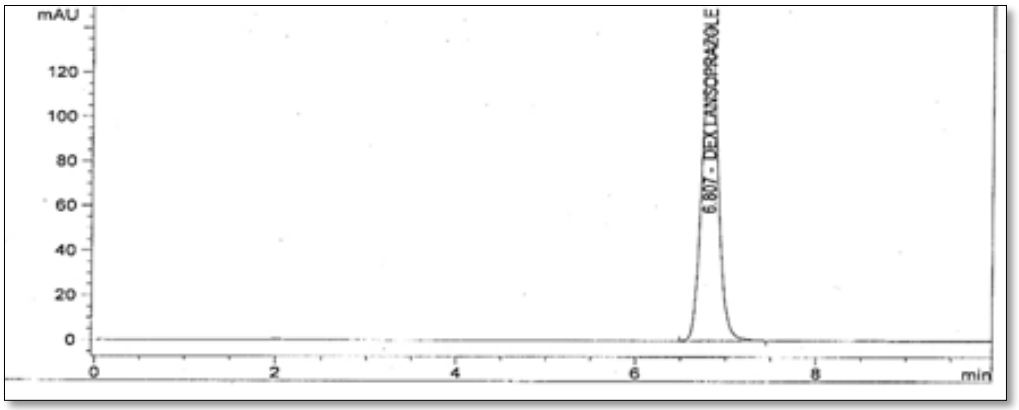

Fig. 3: Chromatogram for Standard

PREPARATION OF SAMPLE SOLUTION

An equivalent weight of 30 mg of Dexlansoprazole was transferred into a 50 mL volumetric flask. To this 30 mL of 0.1 N NaOH was added and sonicate for 15 min till the pellets dissolve completely. Then made up the volume with diluent and centrifuged. From above solution 4 mL was taken in 10 mL volumetric flask and made up to the mark with diluent.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 392-402 www.ijprajournal.com ISSN: 2249-7781

CHROMATOGRAPHIC CONDITIONS

The chromatographic partition was achieved using 10 mm dibasic potassium phosphate buffer was prepared and pH of the solution was adjusted to 7.20 with dilute Orthophospharic acid: Acetonitrile: TEA in the ratio of 70:30:1 v/v/v. As the mobile phase at flow rate 1.2 mL min^{-1}. The LC column was used X-Terra RP_{18}column (250×4.6mm, 5µm). The injection volume was 10µL and detection of components was made at 285 nm.

III. RESULTS AND DISCUSSION

METHOD DEVELOPMENT AND OPTIMIZATION

The analytical method development was initiated based on the chemical structure and functional groups of Dexlansoprazole together with solubility. The component pka of Dexlansoprazole (pKa 8.87).For initial HPLC method development experiment was started based on the structural polarity. Estimation of Dexlansoprazole different mobile phases, solvent–buffer ratios were tried to proposed final chromatographic conditions. The selection of TEA is used to improve the chromatographic retention control and peak shape improvement of the compound. The effects of this amine on the tailing Factor and Theoretical plate count of the compound.Dexlansoprazole is soluble in CH3CN. The peak shapes, the symmetry of Dexlansoprazole were good with mobile phase buffer was selected (pH 7.2) 10 mm dibasic potassium phosphate buffer along with Acetonitrile: TEA in the ratio of 70:30:1 v/v/v. Using X-Terra RP_{18}column (250×4.6mm, 5µm at flow rate 1.2 mL min^{-1}. Selected Diluent was prepared by 0.1 N sodium hydroxide and Acetonitrile in the ratio of 60:40 v/v.The developed method was successfully useful to estimate the amount of Dexlansoprazole.

METHOD VALIDATION

Analytical method validation is essential to ensure that the analytical procedure employed for a specific test is appropriate for its intended. Subsequent to method development, analytical techniques must be validated before and for the duration of routine use. The parameters that were evaluated during contemporary method development include specificity, linearity, range, accuracy, robustness, & precision.

The proposed method was validated based on International Conference on Harmonization (ICH) Q2 (R1) guidelines[24-26].

SPECIFICITY

An essential obligatory as ICH guideline for method validation is specificity or selectivity. In additional words, the specificity is the capability to evaluate the purity of the analyte in the being there of the co-eluting or co-migrating impurity. Neglecting peak purity authentication means, in quality control, an impurity concealed under a peak could fabricate the results. The theory of the photodiode array detector (PDA) compares the spectra involuntarily & report similarity factor for each peak in addition a three-dimensional image helps to verify selectivity without any superfluous workload, consequently, placebo interference was evaluated by using the PDA detector between 200 and 400 nm. The purity of active ingredients was unaffected by the presence of its impurities and thus stability-indicating power of the developed method.

FORCED DEGRADATION

The forced degradation studies were performed to demonstrate whether the analytical method was stability indicating and might unambiguously evaluate the analyte in the presence of impurities and degradation products[27-32]. The solutions of a drug product and placebo were exposed to acid hydrolysis (1N HCl), base hydrolysis (1N NaOH), oxidation (30% H_2O_2), thermal (Heat_105°C) to form degradation products. The liberated degradation products evaluated in terms of co-elution with close eluting with any components in the chromatography and initiate to be selective and unambiguous.The % total degradation (inference of major degradation impurities/products produced with respect to relative retention), mass balance and peak purity results of the stress condition is summarized in **Table 3**. Stressed samples chromatograms are shown in **Fig.4(4A-4D)**.The formula for % mass balance and % degradation is obtainable as follows.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 392-402 www.ijprajournal.com ISSN: 2249-7781

% Degradation = % $Assay_{CtrlSpL}$— % $Assay_{DegSpL}$

$$\% \text{ Mass Balance} = \frac{\%\text{Assay Deg SpL} + \%\text{ Total impurities Deg SpL}}{\%\text{Assay Ctrl SpL} + \%\text{ Total impurities Ctrl SpL}} \text{x } 100$$

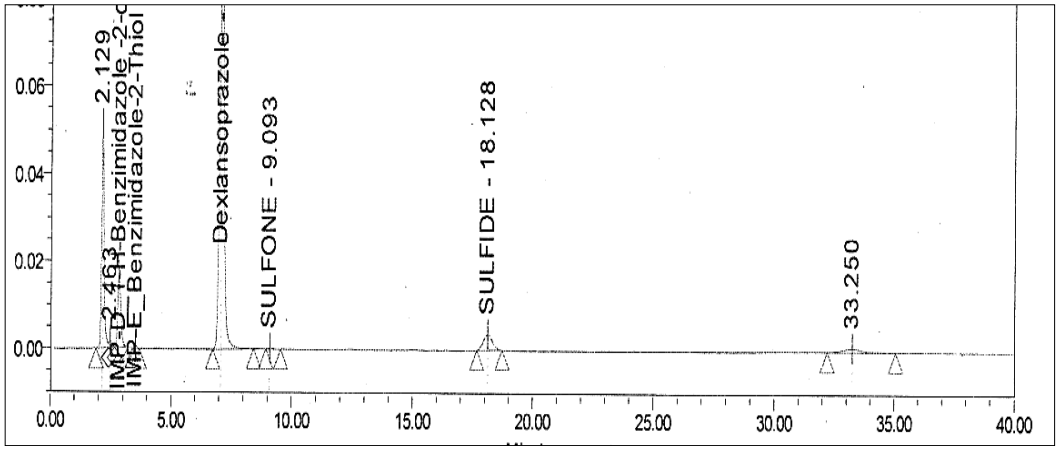

Fig. 4A: Typical Chromatogram of Acid degradation

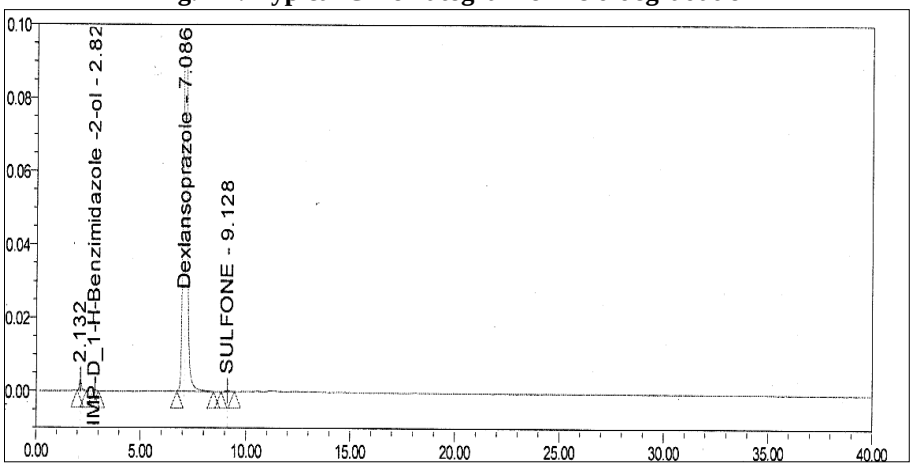

Fig. 4B: Typical Chromatogram of Base degradation

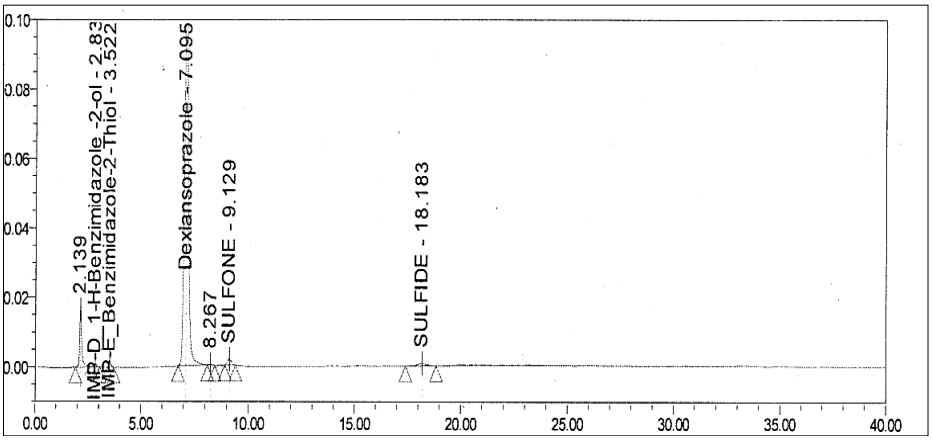

Fig. 4C: Typical Chromatogram of peroxide degradation

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 392-402 www.ijprajournal.com ISSN: 2249-7781

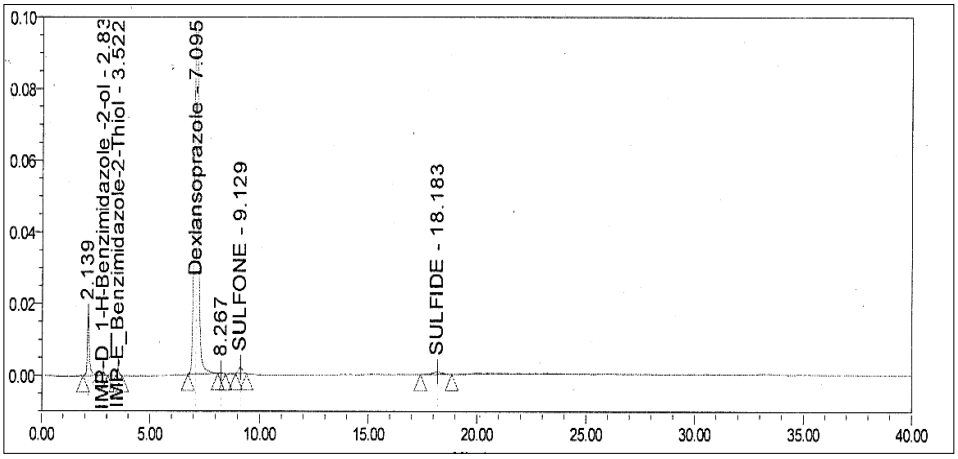

Fig. 4D: Typical Chromatogram of Thermal degradation

Table 3: Summary of forced degradation results

Stress Condition	% Assay of DEXP	% Total Impurities found	% Mass Balance	Dexlansoprazole	
				PA	PT
Control-Sample	99.0			0.127	0.304
1N HCl, refluxed at 80°C for 30min	88.3	10.2	98.6	0.188	0.353
1N NaOH, refluxed at 80°C for 30min	97.1	1.8	98.9	0.166	0.321
30% H_2O_2, refluxed at 80°C for 30min	90.0	8.5	98.5	0.541	0.625
Thermal 105° C for 1 hr	93.3	6.2	99.6	0.222	0.315
PA- Purity Angle, PT- Purity Threshold					

PRECISION

In method precision, a homogenous test of a single batch was analyzed six times. This informs you if a method consistently produces consistent results for a single batch. Calculate the average results(X), standard deviation (SD), and the percent relative standard deviation (%RSD), and the results are presented in **Table 4**.The method was found to be precise since the RSD values method precision was below 1.0.

LIMIT OF QUANTIFICATION & LIMIT OF DETECTION

The LOQ and LOD are determined based on signal-to-noise ratios at analytical responses of 10 and 3 times the and the results are presented background noise, respectively in **Table 4**.

LOD (mg/L) =3 x $=\frac{\text{Noise}}{\text{Signal}}$xLowest concentration of the linearity samples

LOD (mg/L) =10 x $=\frac{\text{Noise}}{\text{Signal}}$xLowest concentration of the linearity samples

LINEARITY

It refers to an assay's ability to yield test results that are proportional to the concentration of analyte in the sample. The range of the analytical assay will be calculated by evaluating this parameter.

Linearity of the method was determined by constructing calibration curves. Standard solutions of Dexlansoprazole of different concentrations levels (50%, 75%, 100%, 125%, and 150%) prepared by serial dilution of standard stock solution) were used for this purpose. The results are presented in **Table 4**.Linearity Curve for DEXP: **Fig. 5**.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 392-402 www.ijprajournal.com ISSN: 2249-7781

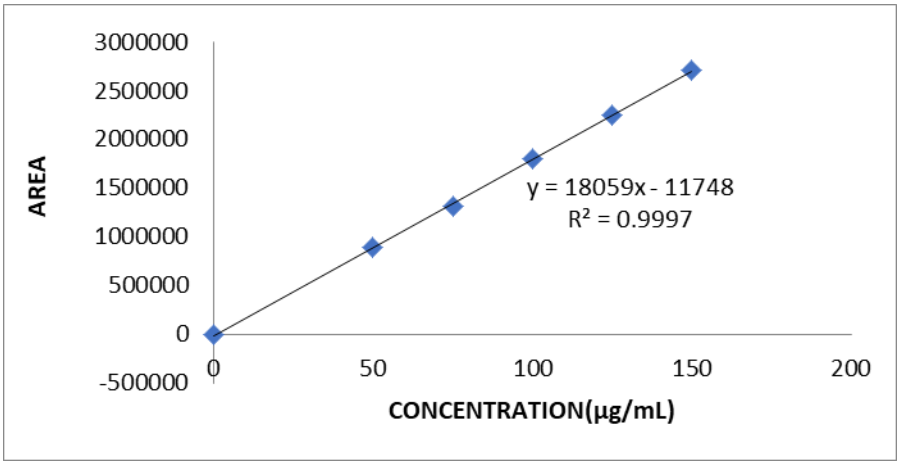

Fig. 5: Linearity plot of Dexlansoprazole

ACCURACY

The accuracy of an experimental data is the degree to which the method's test results are similar to the true value. Accuracy may often be expressed as percent of recovery by the test of known added amounts of analyte. Accuracy was measurement of exactness of the analytical method.

In this HPLC method, the recovery of the samples was verified with three concentration levels (50%, 100% & 150%). The recovery was performed by API+Placebo and injected into the HPLC (triplicate) and the results are presented in **Table 4**.

Table 4. Method validation parameters

Parameters	Dexlansoprazole
Linearity (50-150%)	
Range (µg mL^{-1})	50-150
Slope	18247.456
Intercept	32894.800
Correlation Coefficient	0.9997
STYX SD	17062.002
LOD (µgmL^{-1})	0.14
LOQ (µgmL^{-1})	0.028
Accuracy[(a)](% of Recovery)	
50% Mean ± SD	99.5±0.91
100% Mean ± SD	100.1±0.66
150% Mean ± SD	100.8±1.22
Precision [(b)](%RSD)	
Repeatability	0.5
Intermediate precision	0.8

[a)] Average of three determinations of each concentration level
[b)] %RSD of six determinations of each component
Linearity and other validation parameters results obtained by the proposed HPLC.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 392-402 www.ijprajournal.com ISSN: 2249-7781

ROBUSTNESS

Small deliberate variations in the optimised system parameters were done to test the robustness of the established RP-HPLC method.The effect of change in flow rate, temperature, pH and ratio of Acetonitrile composition in mobile phase on the retention time and tailing factor were studied. The method was found to be unaffected by small changes ± 0.2 ml/min change in flow rate, ± 5ºC change in temperature, ±10% of Organic Phase (Acetonitrile) and Mobile phasepH (±0.2%), the tailing factor and the plate count for the Dexlansoprazolepeak area for five replicate injections of standard were found to be within the acceptable limit of not more than 2.0%, illustrating the robustness of the method.

IV. CONCLUSION

Rapid, simple and stability-indicating HPLC method has been developed effectively forDexlansoprazole delayed-release capsules.The de-veloped and validated HPLC method can accurately quantitate the Dexlansoprazole in finishedProduct.This method provides discriminating quantification of Dexlansoprazolecomponentlacking interference of blank, placebo, im-purities and/or degradation products in that way affirming the stability-indicating character of the method.in addition, this method was environmental, biodegradable and less hazardous. This is for the reason that it spends less quan-tity of toxic organic solvent and therefore produces small amount of toxic waste. The HPLC method was successfully used for the analysis of Dexlansoprazole delayed-release capsules in quality control lab for stability analysis.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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