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STABILITY INDICATING RP-HPLC METHOD FOR SIMULTANEOUS DETERMINATION OF OXYCODONE AND IBUPROFEN IN BULK AND ITS DOSAGE FORMS

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ABSTRACT:

A Stability indicaiting, simple, sensitive and rapid reverse phase high performance liquid chromatographic method was developed for the estimation of Oxycodone and Ibuprofen in Bulk and its dosage forms. The isocratic method was developed on Inspire C_{18} (4.6x150 mm,5 µm) column with potassium dihydrogen orthophosphate buffer (pH 3.0):Acetonitrile mobile phase in ratio of 35:65 delivered at 0.8 ml/min and effluents were monitored at 220 nm. The mobile phase was used as a diluent. The Injection volume was 20 µl. The analytical procedure was validated as per ICH guidelines. The selected chromatographic conditions were found to separate Oxycodone (Rt=3.9 min) and Ibuprofen (Rt=2.96 min).Calibration curve was plotted with a range from 4.0 -6.0 µg/ml and 320-480 µg/ml for Oxycodone and Ibuprofen respectively. Results of the analysis were statistically as per ICH guidelines. The percentage recoveries for Oxycodone and Ibuprofen ranged from 99.82% and 99.85 % respectively. The limit of detection was found to be 3.05µg/ml and 3.14µg/ml for Oxycodone and Ibuprofen respectively. Limit of quantification was found to be 9.95µg/ml and 10.02 µg/ml for Oxycodone and Ibuprofen respectively. The method represents a fast-analytical procedure and stability indicating analytical method for the simultaneous estimation of Oxycodone and Ibuprofen in bulk and its dosage forms. No interference from any component of pharmaceutical dosage form was observed. Validation studies revealed that the method is specific, rapid, reliable, and reproducible. The method is amenable to the routine analysis of large numbers of samples with good precision and accuracy.

KEY WORDS: Oxycodone, Ibuprofen, Reverse Phase HPLC, Stability Indicating Method.

INTRODUCTION:

Oxycodone, (5R,9R,13S,14S)-4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one (Molwt: 315.364 g/mol). It is a semisynthetic opiod synthesized from poppy derived thebaine. It is a narcotic analgesic generally indicated for relief of moderate to severe pain.It acts on k-receptors and appears to be k_{2b}-opiod agonist.Ibuprofen(RS)-2-(4-(2 methylpropyl)phenyl)propanoicacid (Molwt.: 206.29 g/mol) is a nonsteroidal anti-inflammatory drug (NSAID). It works by reducing hormones that cause inflammation and pain in the body.it is used to reduce fever and pain or inflammation caused by many conditions such as headache, toothache, back pain, arthritis, menstrual cramps,or minor injury. Ibuprofen work by inhibiting the enzyme cyclooxygenase(COX) which converts arachidonic acid to prostaglandin H_2(PGH_2),this inturn is converted by other enzymes to several other prostaglandins and to thromboxane A_2. Chemical structures of Oxycodone and Ibuprofen are shown in **Fig. 1& Fig 2.** respectively.

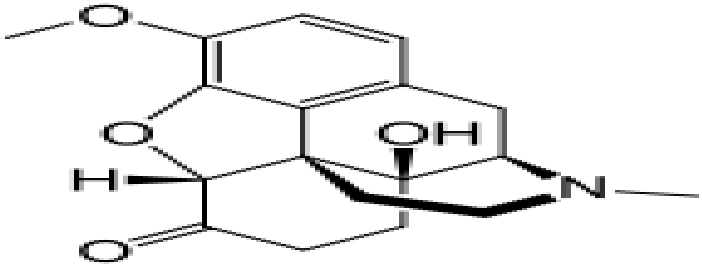

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Figure 1: Chemical Structure of Oxycodone

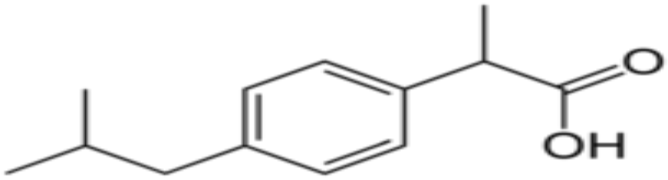

Figure 2: Chemical Structure of Ibuprofen

The review of literature reveals that methods including RP-HPLC[3,17,18,19], LC-MS, RP-UPLC[8], HPTLC and spectrophotometric [5,7,10]methods were reported for the simultaneous estimation of Ibuprofen with other combinations.RP-HPLC[4] method was developed for the analysis of Oxycodone in pharmaceutical dosage forms.LC-MS method was developed f or the simultaneous estimation of Oxycodone with other combinations. HPLC methods were developed for the estimation of Oxycodone[14],[15] and Ibuprofen individually in human plasma UPLC[2] meothod for Ibuprofen for determination in human plasma was developed. The present work resolves the need of a method for simultaneous estimation of Oxycodone and Ibuprofen in tablet dosage form by RP-HPLC method under isocratic conditions and at lower pH. Quality control study of Dexibuprofen[20] through RP-HPLC estimate for the routine analysis. This method has been successfully used for quality-control analysis and for other analytical purposes for the combination.

MATERIALS AND METHODS:

Photo diode array Detector 2996 was used for wavelength determination.Method was developed on Waters e2695 separation Module. Inspire C_{18} (4.6X150 mm,5 µm) column was used. Treasure Fast clean ultra sonic cleaner Sonicator were used at different stages of method development. All the chemicals used were of HPLC grade. Data acquisition was performed by Empower software . Standards of Oxycodone and Ibuprofen were procured with thanks from PHARMA TRAIN LABS (Kukatpally,Hyderabad A.P, India).

Selection of wavelength

220 nm wavelength was selected for the simultaneous estimation of Oxycodone and Ibuprofen by RP-HPLC method.

Preparation of standard solution

Accurately weigh and transfer 400 mg of Ibuprofen & 5 mg of Oxycodone working standard into a 100ml clean dry volumetric flask add Diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. Further pipette 1 ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with diluent.

Preparation of sample solution

Accurately weigh 515 mg of powder and transfer equivalent to 400 mg of Ibuprofen & 5 mg of Oxycodone sample into a 100ml clean dry volumetric flask add about 70ml of Diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. Further pipette 1 ml of the above stock solution into a 10 ml volumetric flask and dilute up to the mark with diluents.

Preparation of Phosphate Buffer

Weighed 7.0gms of potassium dihydrogen orthophosphate into a 1000 ml beaker, dissolved and diluted to 1000 ml with HPLC water. Adjust the pH to 3 with orthophosporic acid.

Preparation of Mobile phase

Mix a mixture of above buffer 350 ml (35%) and 650 ml of Acetonitrile HPLC (65%) and degas in ultrasonic water bath for 5 minutes. Filter through 0.45 µ filter under vacuum filtration.

Assay

20 µl of standard and sample solutions were injected into the injector of HPLC, and the peak areas of the drugs in standard and sample were compared and the assay was performed. The chromatograms are shown in Fig.3 & 4. Oxycodone and Ibuprofen show the purity percentage values of 99.22 % w/v and 99.81 % w/v respectively.

The retention times of Ibuprofen and Oxycodone in the standard solution having the concentration of 400 µg/ml of Ibuprofen and 5 µg/ml of Oxycodone were found to be around 2.98 min and 3.68 min respectively.

Ibuprofen and Oxycodone shows the percentage purity values are 99.34 % w/v and 99.93 % w/v respectively.

Validation of the developed method

The validation of developed method was performed on the basis of criteria given in ICH guidelines, viz., specificity, linearity, range, precision, accuracy, detection and quantitation limit. The criteria are discussed as follows.

RESULTS AND DISCUSSION:

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A series of trials for optimization of chromatographic conditions were run with variations in composition of mobile phase. This resulted in the selection of phosphate buffer (pH=3):Acetonitrile in the ratio of 35:65 as mobile phase. A flow rate of 0.8 ml/min, wavelength of 220 nm and run time of 8 min was used. Using such conditions, as shown in **Table 1**, the peaks were separated more prominently and showed a better resolution. Thus proposed chromatographic conditions were found to be appropriate for the quantitative determination of the drugs.

Table 1: Chromatographic conditions

Parameters	**Description**
Flow rate	0.8 ml/mim
Column	InspireC_{18}(4.6x150mm,5µm,Make:ACE)or equivalent
Detector wavelength	220 nm
Column temperature	Ambient
Injection volume	20 µl
Run time	8 min
Mobile phase	Buffer: Acetonitrile 35:65

System suitability

Six replicate injections of the mixed standard solution of Oxycodone & Ibuprofen were injected. System suitability parameters such as resolution, tailing factor, no. of theoretical plates were calculated. The results are reported in **Table 2** and chromatograms are shown in **Fig 3**.

Table 2: System Suitability Data for Oxycodone and Ibuprofen

	Peak Name	RT	Area	Height	USP Plate Count	USP Tailing	USP Resolution
1	Ibuprofen	2.983	721235	82848	2716	1.29	
2	Ibuprofen	2.984	716440	82026	2687	1.31	
3	Ibuprofen	2.985	718012	81916	2680	1.30	
4	Oxycodone	3.903	129380	13860	3919	1.19	3.73
5	Oxycodone	3.903	128314	13633	3848	1.20	3.68
6	Oxycodone	3.903	129640	13738	3830	1.22	3.68

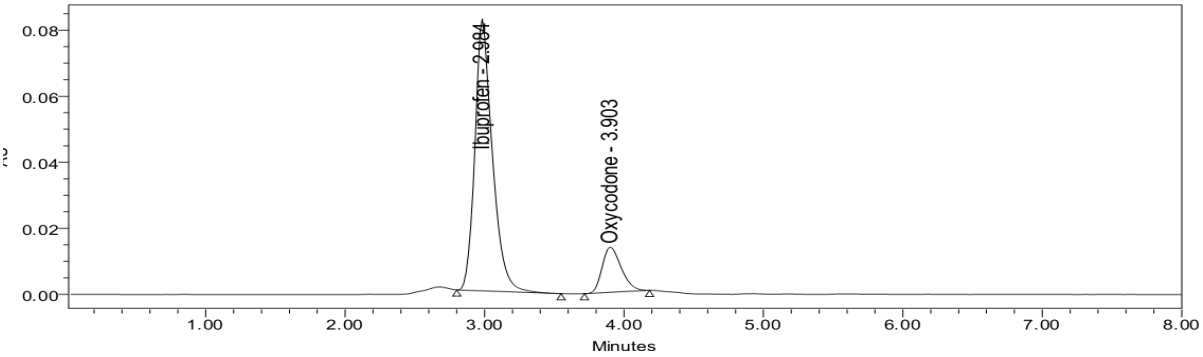

Figure 3: Chromatogram of Standard Solution of Ibuprofen and Oxycodone

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Specificity

It was confirmed by injecting the placebo and placebo spiked standard and observed that there was no shift in wavelength interference due to placebo. Specificity studies indicated that the excipients did not interfere with the analysis. The chromatogram obtained after injecting the placebo and placebo spiked standard in HPLC system is shown in **Fig 4 & 5**. .No peaks were found at the retention time of Oxycodone and Ibuprofen. The retention times were found to be 3.903 min and 2.983 min respectively.

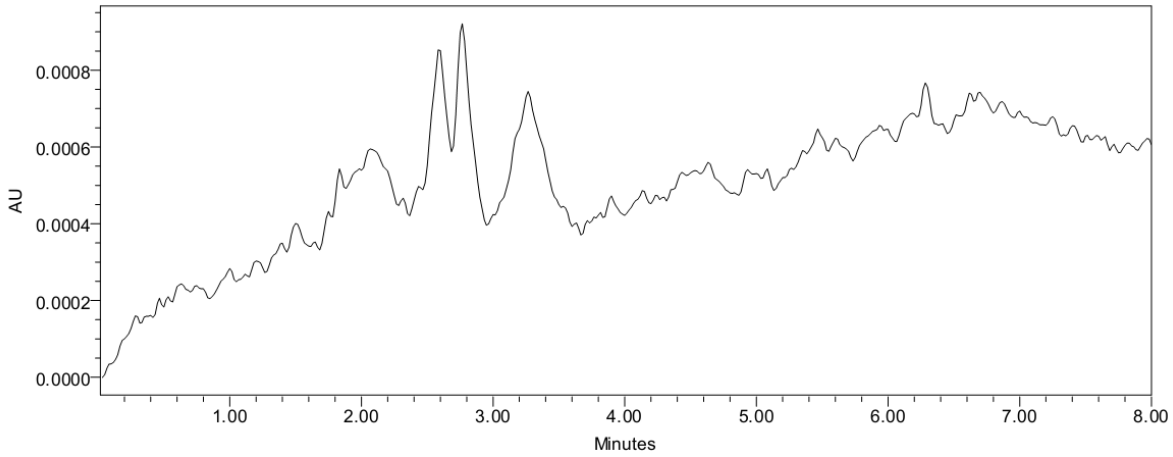

Figure 4: Chromatogram of Placebo

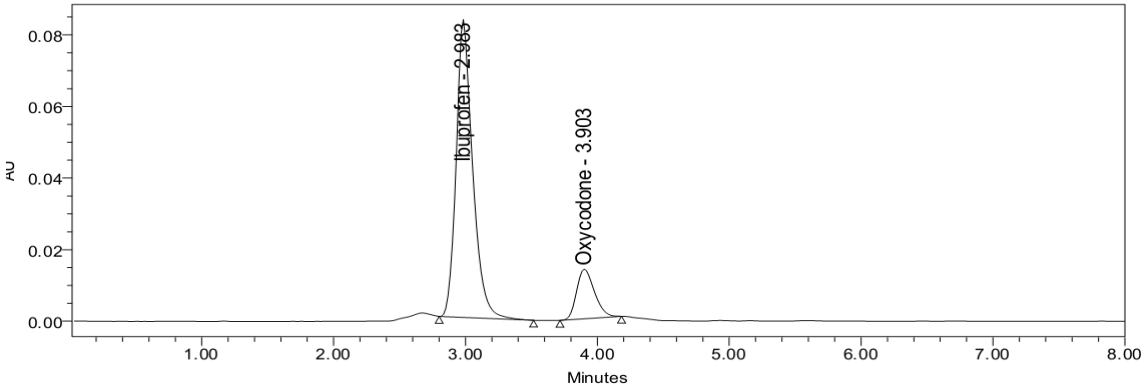

Figure 5: Chromatogram of Placebo Spiked Standard

Linearity

In the linearity study, calibration curves were plotted between different concentrations of the drug and their corresponding mean peak areas. The linearity ranges were found to be 4.0 - 6.0 µg/ml for Oxycodone and 320-480 µg/ml for Ibuprofen. The calibration curves are shown in **Fig 6 and 7**. Linearity Results for Oxycodone and Ibuprofen shown in **Table 3.**

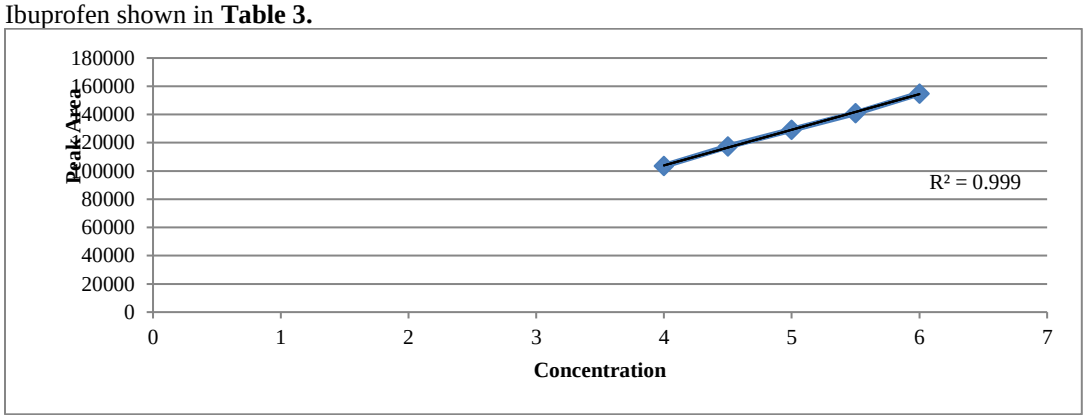

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Figure 6: Calibration curve of Oxycodone

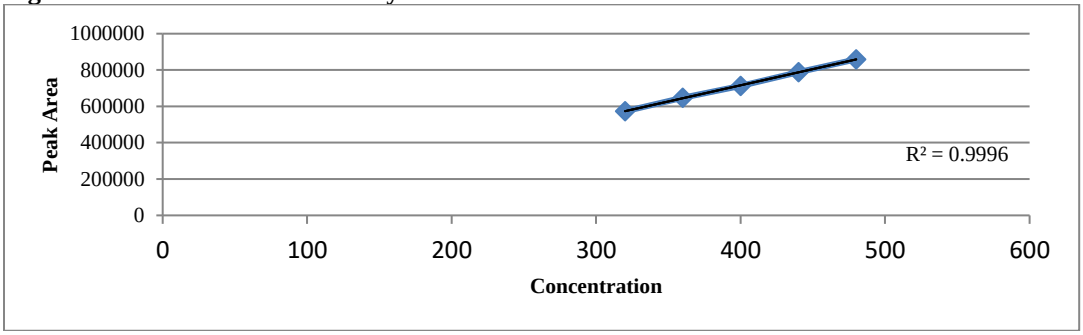

Figure 7: Calibration curve of Ibuprofen

Table 3: Linearity Results for Oxycodone and Ibuprofen

Oxycodone		Ibuprofen	
Conc. µg/ml	**Mean peak area*(mV*sec)**	**Conc. µg/ml**	**Mean peak area*(Mv*)**
4.0	103593	320	572976
4.5	117289	360	647517
5.0	129183	400	712672
5.5	140950	440	788026
6.0	154874	480	858730
Correlation coefficient	**0.999**		**0.999**

Accuracy

Recovery studies were used to evaluate the accuracy of the analytical method. It was verified by recovery studies. Oxycodone and Ibuprofen working standards were spiked with Placebo and made up with diluent to give the target concentrations. The data of recovery study are shown in **Table 4**. The mean recovery was found to be 99.82% for Oxoycodone and 99.85% for Ibuprofen. The limit for the mean of % recovery is 98-102% and as both the values are within the limit, hence it can be said that the proposed method was accurate.

Table 4: Data of Recovery Studies of Oxycodone and Ibuprofen

% Concentration	Peak Area	Amount added(mg)	Amount found(mg)	%recovery
50% oxycodone				
Ibuprofen	**70795**	**2.5**	**2.48**	**99.2%**
	345911	**200**	**199.2**	**99.6%**
100% oxycodone				
Ibuprofen	**131604**	**5**	**5.02**	**100.4%**
	691298	**400**	**399.6**	**99.9%**
150% oxycodone	**195023**	**7.5**	**7.49**	**99.86%**
Ibuprofen	**1038819**	**600**	**600.4**	**100.06%**

Precision

System precision

In system precision the standard solution of oxycodone and Ibubrofen was injected for 6 times and measured the peak area of all 6 injections in HPLC. The %RSD for the area of 6 replicate injections was found to be with in the acceptance criteria of 2%.The results are reported in **Table 5** and overlay chromatograms of system precision of Oxycodone and Ibuprofen is shown in **Fig 8.**

Table 5: System Precision Data for Oxycodone and Ibuprofen

Oxycodone		Ibuprofen	
Injection	**Peak Area**	**Injection**	**Peak Area**

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Injection-1	129270	Injection-1	707728
Injection-2	128130	Injection-2	712769
Injection-3	128756	Injection-3	715103
Injection-4	129843	Injection-4	714129
Injection-5	128774	Injection-5	712863
Injection-6	127481	Injection-6	712774
Average	128709	**Average**	712561
Standard Deviation	830.7028	**Standard Deviation**	2547.866
%RSD	0.65	**%RSD**	0.36

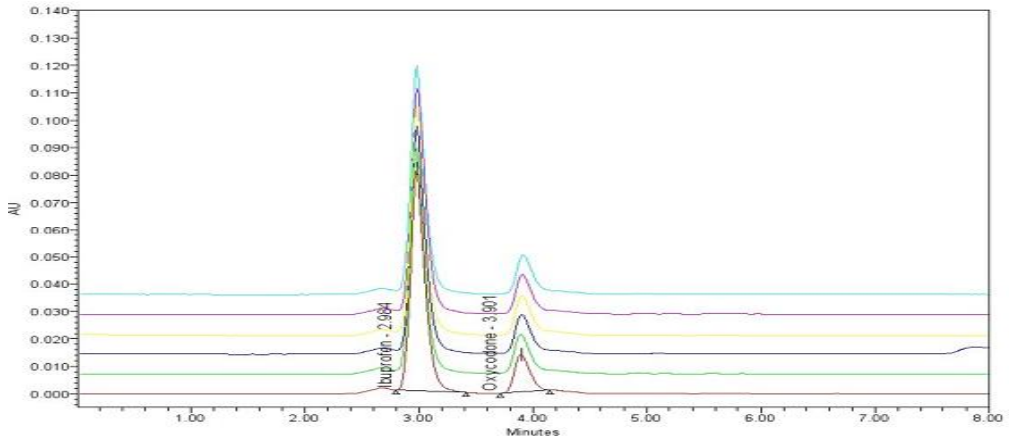

Figure 8: Chromatogram of System Precision Overlay of Oxycodone and Ibuprofen

Method precision

The sample solution of Oxycodone and Ibubrofen was injected for 6 times and measured the peak area of all 6 injections in HPLC. The %RSD of peak area is present with in the acceptance criteria of 2%. The results are reported in **Table 6** and overlay chromatograms of method precision of Oxycodone and Ibuprofen is shown in **Fig 9.**

Table 6: Method Precision Data for Oxycodone and Ibuprofen

Oxycodone	**Ibuprofen**	**Oxycodone**	**Ibuprofen**
Injection	**Peak Area**	**Injection**	**Peak Area**
Injection-1	130624	Injection-1	710634
Injection-2	129997	Injection-2	710927
Injection-3	131727	Injection-3	714206
Injection-4	130802	Injection-4	713339
Injection-5	130058	Injection-5	715920
Injection-6	130255	Injection-6	711789
Average	130577.2	**Average**	712802.5

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Standard Deviation	645.7211	Standard Deviation	2060.268
%RSD	0.49	%RSD	0.29

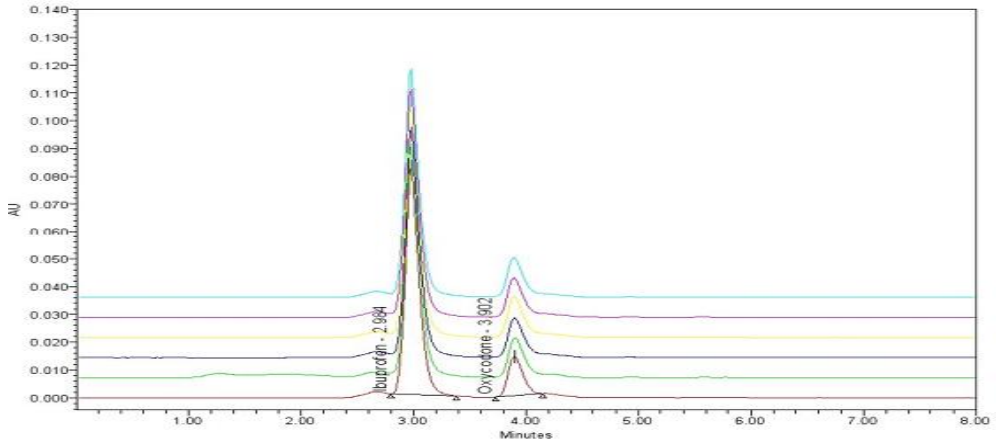

Figure 9: Chromatogram of Method Precision Overlay of Oxycodone and Ibuprofen

Intermediate Precision

To evaluate the intermediate precision (also known as Ruggedness) of the method, Precision was performed on different day by using different column on same dimensions. The standard solution was injected for six times and measured the area for all six injections in HPLC. The % RSD for the area of six replicate injections was found to be within the specified limits. The results are reported in **Table 7** and overlay chromatograms of intermediate precision of Oxycodone and Ibuprofen is shown in **Fig 10.**

Table 7: Results of Intermediate precision for Oxycodone and Ibuprofen

Oxycodone		Ibuprofen	
Injection	Area	Injection	Area
Injection-1	130137	Injection- 1	717258
Injection-2	129825	Injection-2	715405
Injection-3	129580	Injection-3	721691
Injection-4	130939	Injection-4	718264
Injection-5	129431	Injection-5	717138
Injection-6	129137	Injection-6	718153
Average	129841.5		717984.8
Standard deviation	636.445		2085.322
%RSD	0.49		0.29

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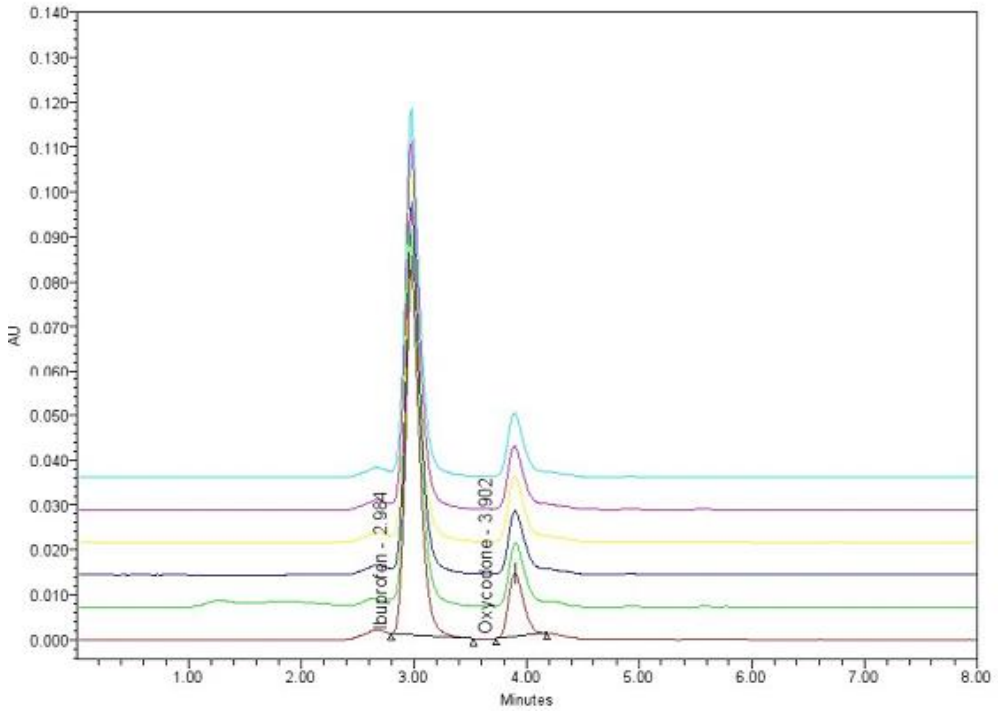

Figure 10: Chromatogram of Intermediate Precision Overlay of Oxycodone and Ibuprofen

Robustness

Robustness was determined by carrying out the assay during which flow rate and organic phase were altered slightly. The results are reported in **Table 8 and 9.**

Table 8: System Suitability Results of Change in Flowrate for Oxycodone and Ibuprofen

Drugs	Flow rate(ml/min)	USP Plate count	USP Tailing
Oxycodone	0.6	3876	1.21
Ibuprofen	0.6	2620	1.25
Oxycodone	0.8	3848	1.2
Ibuprofen	0.8	2687	1.31
Oxycodone	1.0	3800	1.23
Ibuprofen	1.0	2586	1.29

Table 9: System Suitability Results of Change in Organic Composition in Mobilephase for Oxycodone and Ibuprofen

Drugs	Change in Organic composition in Mobile phase	USP Plate count	USP Tailing
Oxycodone	10% less	3887	1.22
Ibuprofen	10% less	2696	1.3
Oxycodone	*Actual	3848	1.2
Ibuprofen	*Actual	2687	1.31
Oxycodone	10% more	3776	1.22
Ibuprofen	10% more	2579	1.29

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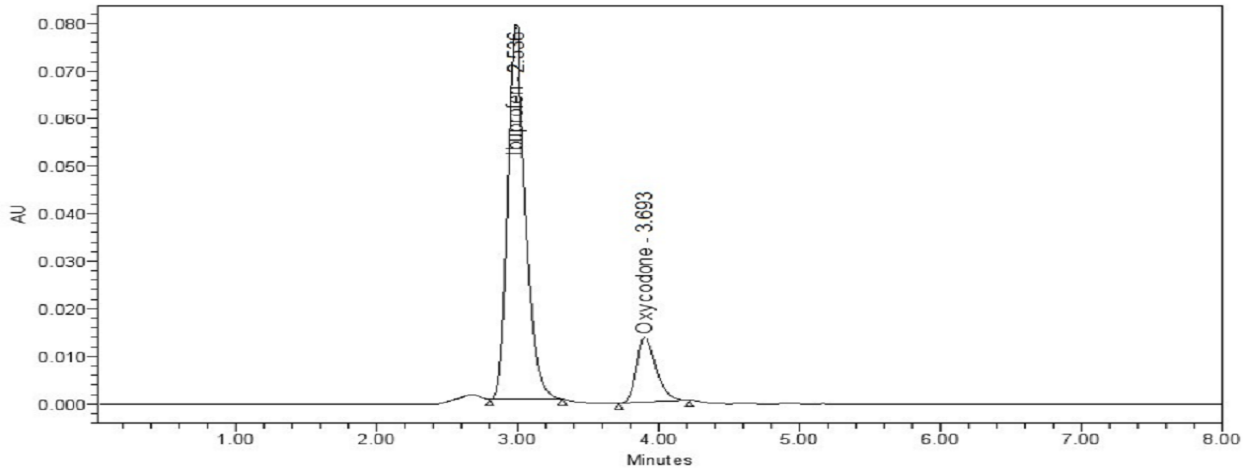

Figure 11. Chromatogram showing robustness solution of decreased mobile phase flowrate (0.6 ml/min) of Oxycodone and Ibuprofen.

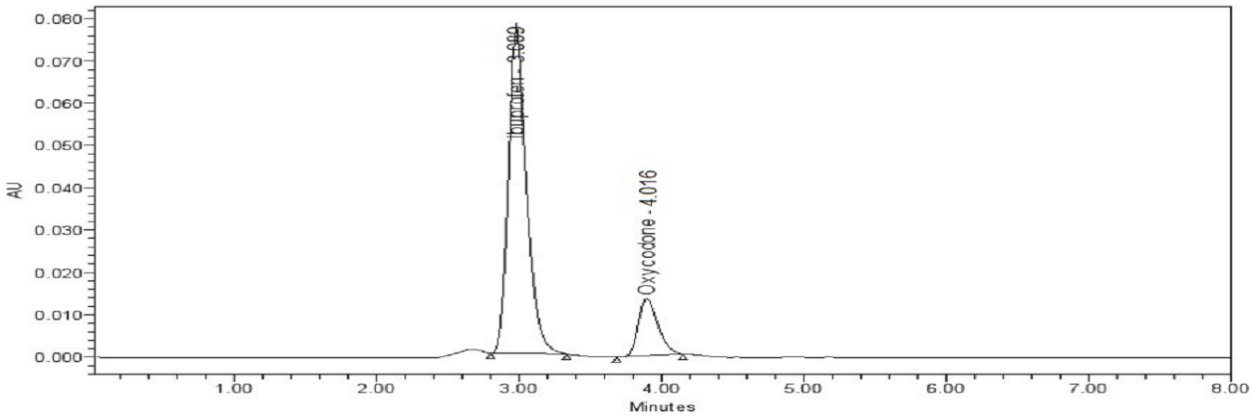

Figure 12. Chromatogram Showing Robustness Solution of Increased Mobilephase Flowrate (1.0 ml/min) of Oxycodone and Ibuprofen.

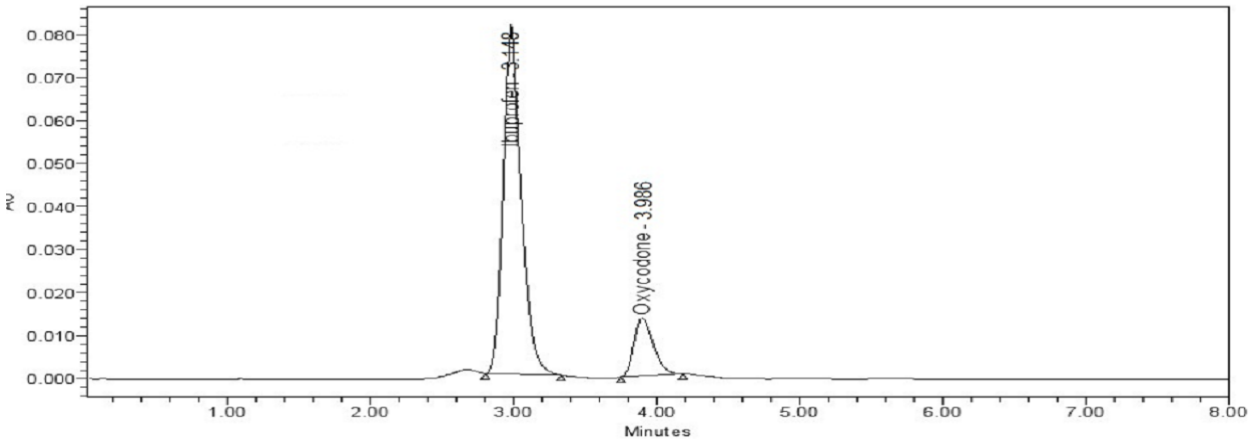

Figure 13. Chromatogram Showing Robustness Solution of Less Organicphase Ratio of Mobile phase (-10 %) of Oxycodone and Ibuprofen.

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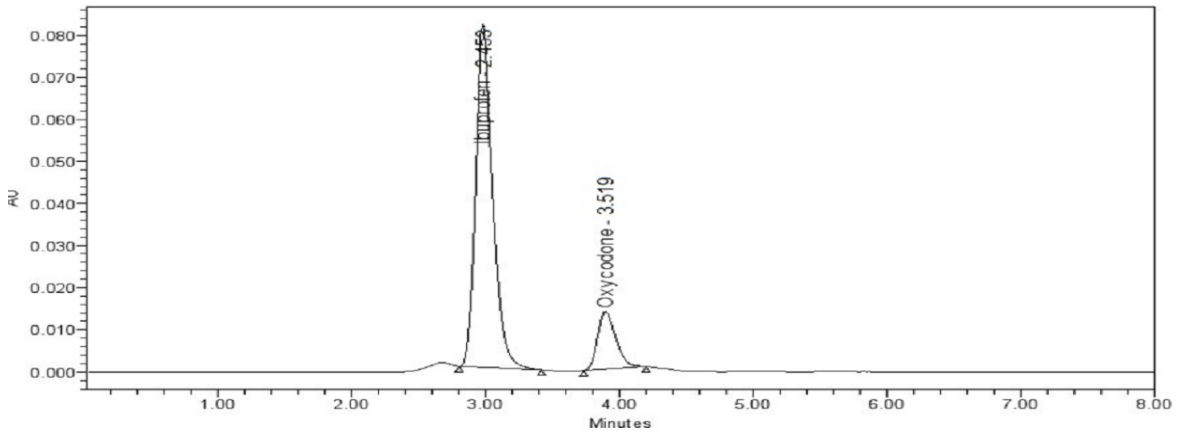

Figure 14. Chromatogram Showing Robustness Solution of More Organicphase Ratio of Mobile phase (+10 %) of Oxycodone and Ibuprofen.

Detection limit and Quantitation limit

LOD's can be calculated using the response standard deviation (σ) and the calibration curve slope (S).
Formula:

$$\text{LOD} = 3.3 \text{ X } \frac{\sigma}{S}$$

The Limit of detection (LOD) was found to be 3.05 µg/ml and 3.1 4 µg/ml for Oxycodone and Ibuprofen respectively.

LOQ's can be calculated using the response standard deviation (σ) and the calibration curve slope (S).
Formula:

$$\text{LOQ} = 10 \text{ X } \frac{\sigma}{S}$$

Limit of quantitation (LOQ) was found to be 9.95µg/ml and 10.02 µg/ml for Oxycodone and Ibuprofen respectively.

Degradation Studies

The sample solutions of Oxycodone and Ibubrofen were subjected to acidic, basic, peroxide, temperature and light. The results were reported in the **Table 10** and chromatograms shown in **Fig 15-18.**

Table 10: Results of Degradation Studies for Oxycodone and Ibuprofen

	Oxycodone			Ibuprofen		
	Area	%Assy	% Degraded	Area	%Assay	% Degraded
	117586	93.16	6.84	645865	94.08	5.92
Acid	105862	83.87	16.13	623586	90.83	9.17
Base	110245	87.34	13.67	635425	92.56	8.05
Thermal	108965	86.33	18.81	631245	91.95	18.89
Peroxide	102475	81.19	12.66	625475	91.11	7.44
Photolytic						

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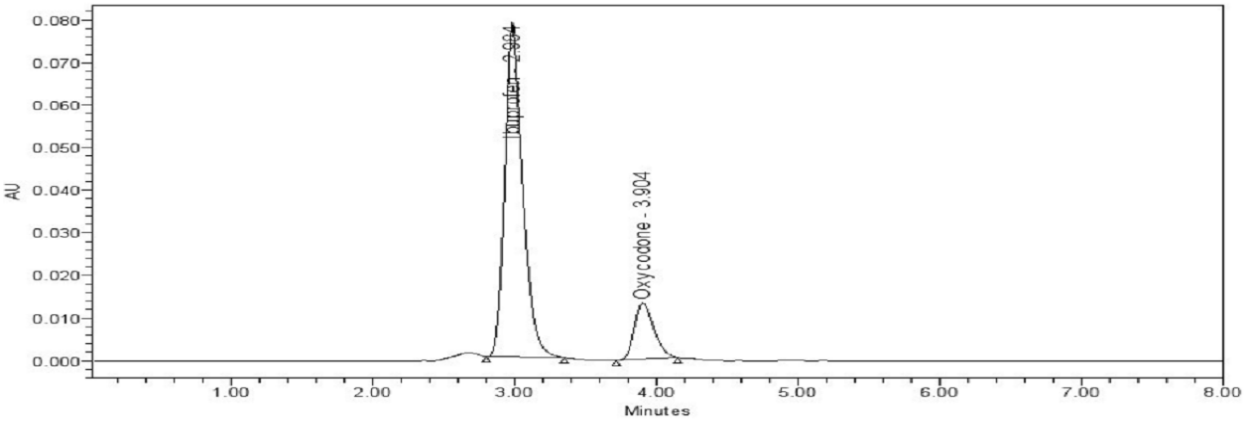

Figure 15. Chromatogram Showing Hydrolytic Degradation by Acid for Oxycodone and Ibuprofen.

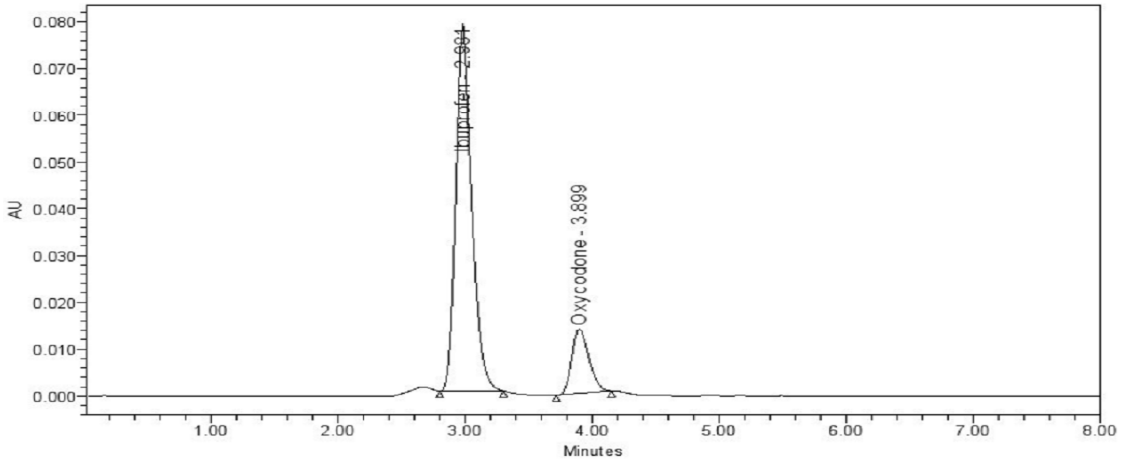

Figure 16. Chromatogram Showing Hydrolytic Degradation by Alkali for Oxycodone and Ibuprofen.

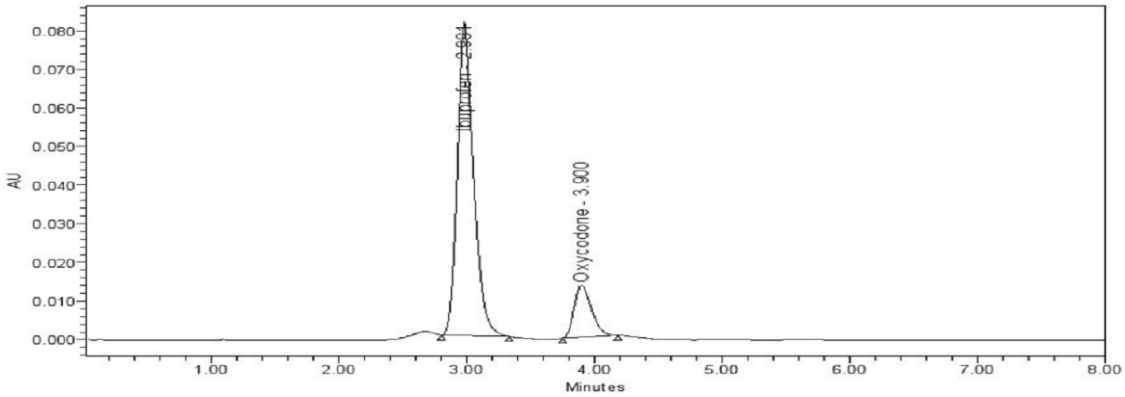

Figure 17. Chromatogram Showing Oxidative Degradation by 3% Hydrogen Peroxide for Oxycodone And Ibuprofen.

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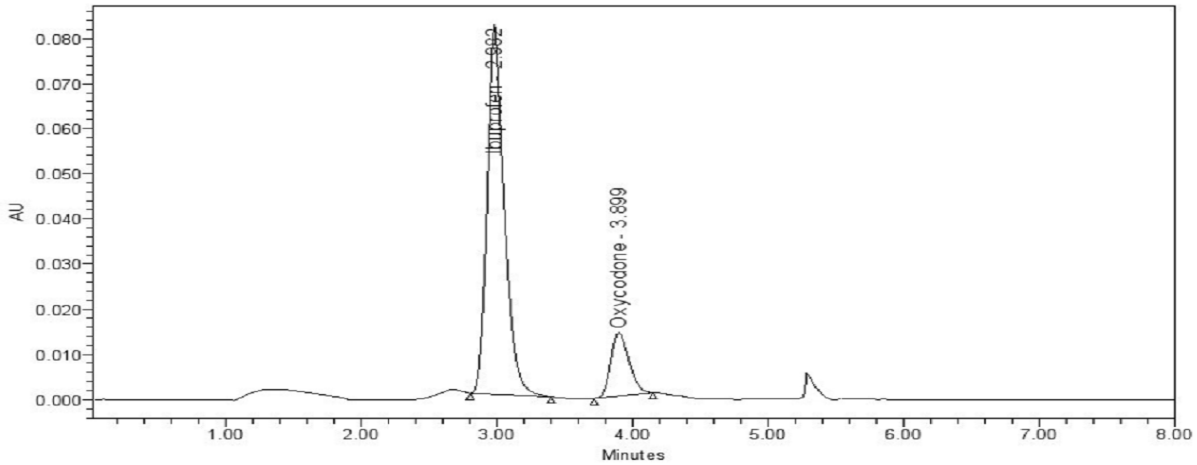

Figure 18. Chromatogram Showing Photolytic Degradation for Oxycodone and Ibuprofen.

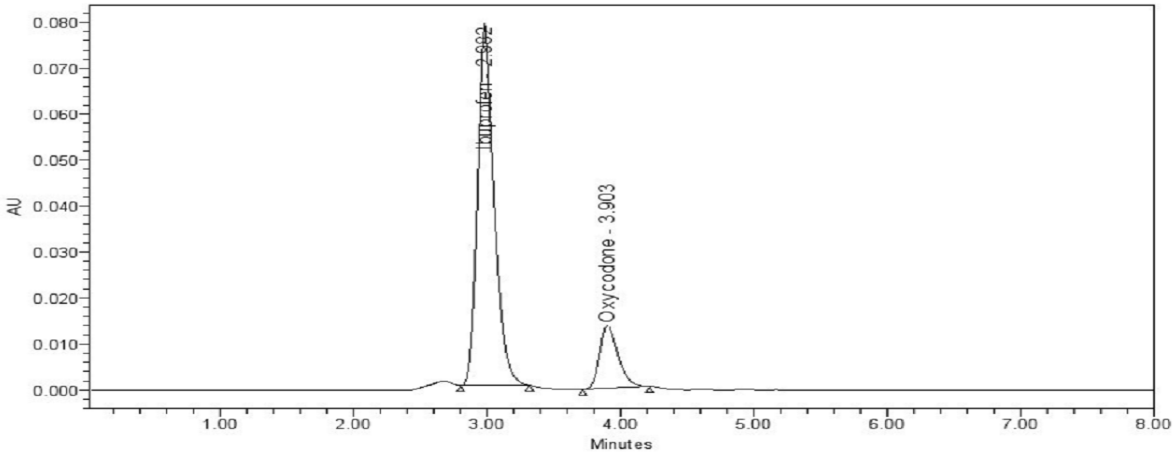

Figure 19. Chromatogram Showing Thermal Degradation for Oxycodone and Ibuprofen.

Degradation studies were carried out as per ICH guidelines. The sample solutions were subjected to acidic, basic, peroxide, thermal and light. whereas in acidic, basic the % degradations were found to be – 6.84 %, - 16.13 % and - 5.92 %, -9.17 % for Oxycodone and Ibuprofen respectively. The % degradation by peroxide was found to be -18.81 % and -18.89 % for Oxycodone and Ibuprofen respectively. The % degradation by thermal was found to be -13.67 % and -8.05 % for Oxycodone and Ibuprofen respectively. The % degradation by photolytic was found to be -12.66 % and -7.44 % for Oxycodone and Ibuprofen respectively. Thus, Oxycodone is not stable in basic, oxidative, thermal and photolytic conditions and stable in acidic degradation. Ibuprofen is not stable in photolytic conditions and stable in acidic, basic, oxidative and thermal degradation. So far there is no stability indicating analytical method reported for the determination of Oxycodone and Ibuprofen in bulk and its dosage forms. The proposed method was helpful in the separation of the two compounds without the interference of degradants, estimate the active contents. Hence the developed method can be used for quality control analysis and accelerated stability studies.

4. Conclusion:

A new stability indicating analytical method was developed and validated by RP-HPLC technique. The sample preparation is simple, consumes less amount of mobile phase and the required time for analysis is very short, the information given in the study will be very useful for the quality monitoring of Oxycodone and Ibuprofen in bulk and its dosage forms. The method was applied for the determination of potency of the commercial product of Oxycodone and Ibuprofen and potency was found within the limit. The results of assay analysis of two drugs from a combined dosage form using this developed method were found to be close to 100 %. Recovery studies were satisfactory which shows that there is no interference of excipients.

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The developed analytical procedure has shown satisfactory results for all the validation parameters. The proposed method was specific as no interference of excipients was found. The information given in the study will be very useful in quality control, content uniformity test, in-vitro dissolution of the combination of Oxycodone and Ibuprofen drug products. The proposed method can be efficiently applied for the separation of the drugs from its excipients and its degradation components in the pharmaceutical formulation. It can be used to check rapid and accurate drug quality during stability testing.

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