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Simultaneous Estimation of Paracetamol and Dexibuprofen by Using UV- Spectroscopy and RP-HPLC Methods in Tablet Dosage Form

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Abstract

Simple and economical spectrophotometric methods have been developed for simultaneous estimation of dexibuprofen (DXB) and paracetamol (PCM) from tablet dosage form. Ethanol (95%) was used as solvent. Method-I involves, formation of Q-absorbance equation at 235.5 nm (isoabsorptive point) and 249.5 nm (max of paracetamol); Method-II simultaneous equation method involves the measurement of absorbances at two wavelengths 223 nm (max of dexibuprofen) and 249.5 nm (max of paracetamol) and Method-III multicomponent mode of analysis involves the measurement of absorbances at two wavelengths 223 nm (max of dexibuprofen) and 249.5 nm (max of paracetamol); The linearity lies between 2-7 g/ml for dexibuprofen and 4-14 g/ml for paracetamol for all the three methods. The accuracy and precision of the methods were determined and validated stastically. All the methods showed good reproducibility and recovery with % RSD less than 1. All method were found to be rapid, specific, precise and accurate and can be successfully applied for the routine analysis of dexibuprofen and paracetamol in bulk and combined dosage form.

Key words: linearity, validation, Accuracy, Precision

Abbreviations: LOD: Limit of detection, LOQ: Limit of quantization, DXB: dexibuprofen; PCM: paracetamol; RP-HPLC, reverse phase high performance liquid chromatography.

Introduction

Paracetamol is official in Indian Pharmacopoeia 1996 and in British Pharmacopoeia (1998), monograph of PCM disclose the detail information along with its degradation profile and UV and HPLC determination. Paracetamol [*N*-(4-hydroxyphenyl) acetamide /acetaminophen] is an analgesic-antipyretic agent which inhibits prostaglandin biosynthesis by blocking the enzyme cyclooxygenase. It is effective in treating mild-to-moderate pain such as headache, neuralgia, and pain of musculo-skeletal origin.[1] Widespread use of paracetamol in different kinds of pharmaceutical preparations, accurate, rapid, selective and sensitive methods for the determination of paracetamol individual and in combination are being validated.

Dexibuprofen [(+)-ibuprofen] is the dextrorotatory (s (+)), active enantiomer of racemic ibuprofen. it is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. Dexibuprofen is a non-steroidal anti-inflammatory (NSAID), analgesic (pain relieving), and antipyretic (fever reducing) drug. NSAIDs inhibit the body's production of prostaglandins and other compounds such as cyclooxygenase, lipoxygenase, leukotrienes, and lysosomal enzymes that sensitize pain receptors and stimulate inflammatory responses.

Literature survey revealed that several analytical methods have been reported for the Godse *et al.* (2005)[7] have reported a RP-HPLC method for simultaneous estimation of paracetamol and aceclofenac in tablets.

A simple, selective, rapid, precise and economical reverse phase HPLC method has been developed for the simultaneous estimation of paracetamol and aceclofenac from pharmaceutical dosage forms. The method was carried out on a Hichrom C18 (25 cm×4.6 mm i.d., 5 µ) column with a mobile phase consisting of acetonitrile: 20 mM phosphate buffer (pH 5.0) (60:40 v/v) at a flow rate of 0.8 ml/min. Detection was carried out at 265 nm. Etoricoxib was used as an internal standard. The retention time of paracetamol, aceclofenac and etoricoxib was 4.75, 6.44 and 8.83 min, respectively. The developed method was validated in terms of accuracy, precision, linearity, limit of detection, limit of quantitation and solution stability. The proposed method can be used for the estimation of these drugs in combined dosage forms.

Academiae et al. (2004)8 developed a determination of Dexibuprofen Concentration and Pharmacokinetics in Ventricle Succus by RP-HPLC Method.

The RP-HPLC method for determination of dexibuprofen in ventricle succus and for observing the changes of dexibuprofen concentration in ventricle succus with the time elapsing. Methods We injected the dexibuprofen directly to the rabbit's ventricle succus. The chromatographic separation was achieved on a Kromasil C 18(150 mm×4.6 mm,7 µm), the mobile phase was consisted of methanol:0.02 mMol/L KH2PO4:acetonitrile(65:30:5), the velocity of flow was 1.0 ml/min, the temperature of the chromatographic separation was the lab temperature and the detection wavelength was at 225 nm. The internal standard was phenylbutazone. Results A good linearity was obtained from 0.5 to 80 µg/ml in ventricle succus with a correlation of 0.9994. Tmax of the dexibuprofen in ventricle succus was 1.1 h, Cmax was 9.9 µg/ml,T 1/2 was 3.5 h,AUC was 61.0 µg·h/ml. Conclusion The test provided a useful method for measuring the dexibruprofen concentration in ventricle succus. The results demonstrat that the pharmacokinetics model of dexibuprofen in ventricle succus is one-compartment model.

This paper describes simple, accurate, precise, and sensitive reversed-phase (RP)-HPLC methods for Simultaneous Estimation of Paracetamol and Dexibuprofen by Using UV-Spectroscopy and RP-HPLC Methods in Tablet Dosage were optimized and validated according to International Conference on Harmonization (ICH) guidelines.

Materials and Methods

Drugs and chemicals

The entire chemicals used throughout project were AR grade. Laboratory glassware of Borosilicate and Whatman grade filter papers were used. UV spectrophotometer was Shimatzu, make model-1601,Japan was used.

The gift sample of the dexibuprofen and paracetamol were obtained from Glenmark pharmaceutical ltd satpur, Nasik (Maharashtra) and promed pharmaceutical laboratory, Indore (M.P.) respectively. The tablet dosage dosage form BRUTEK-P Manufactured by Emcure pharmaceuticals ltd. Pune (M.H), India (Label claim: 300 mg Dexibuprofen , 500 mg Paracetamol) was procured from the local market. Methanol AR was obtained from Merck Limited, Mumbai, India.

Instruments

The instrument used for the entire analysis was SIMADZU UV 1601 UV-VIS recording spectrophotometer. It is a double beam high speed scanning spectrophotometer with advanced quantitative software and provides full facilities for monochromator, a CRT display and a parallel head printer. Therefore it permits high seed absorption sectrophotometry, data processing and presentation without addition of any expensive option. The software for this instrument basically comprises 8 modes for measurement.

Preparation of stock solutions

To prepare stock solution of paracetamol , (1000 µg/ml) 100mg of paracetamol was placed in 100 ml volumetric flask and dissolved in 75 ml of methanol and the volume was made up to the mark with methanol, to obtain the solution of 1000 µg/ml . 10 ml of the solution was diluted up to 100ml with methanol to produce final stock solution of 100 µg/ml of paracetamol. Standard stock solution of

dexibuprofen was prepared similarly as that of paracetamol.

Preparation of Standard for test of linearity

From the stock solution of 100µg/ml of paracetamol and, dexibuprofen appropriate dilution with methanol was made to prepare the solution having concentration as shown in table1 and table 2. The absorbance was measured at 249nm and 221 nm for paracetamol and dexibuprofen respectively. The calibration curves were plotted from mean values of observation.

Selection of appropriate wavelength

Appropriate dilution (100µg/ml) was prepared using standard stock solution of 100µg/ml each of paracetamol and dexibuprofen respectively. Both the solution were scanned over range of 390-190nm, using medium scan speed.

The sampling wavelength for analysis includes,

Absorption maxima (λmax) of paracetamol=249 nm .

Absorption maxima (λmax) of dexibuprofen= 221 nm.

The required absorptivity value was calculated from the mean of six independent reading.

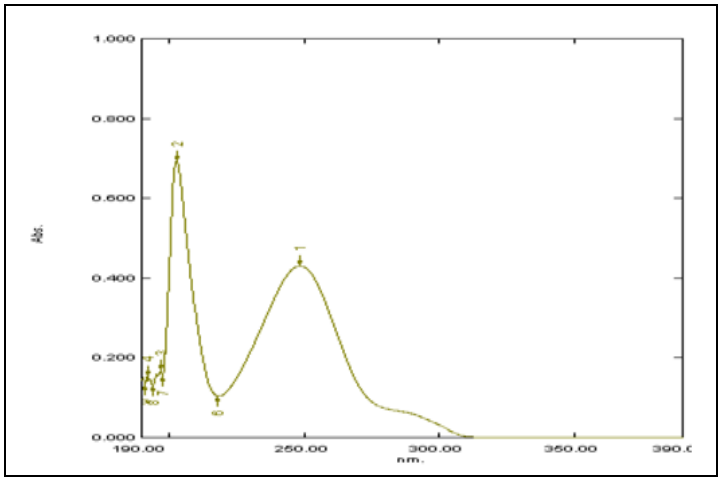

Figure 1: UV spectra of paracetamol at 249nm

Table 1: Linearity studies of PARACETAMOL 249 nm

S.No.	Conc (µg/ml)	Replica1	Replica2	Replica3	Replica4	Replica5	Mean	SD(±)	RSD
1.	2	0.200	0.188	0.268	0.184	0.188	0.205	0.03	0.14
2.	4	0.376	0.351	0.431	0.411	0.324	0.378	0.04	0.10
3.	6	0.575	0.528	0.626	0.591	0.501	0.564	0.04	0.07
4.	8	0.773	0.688	0.804	0.794	0.653	0.742	0.06	0.08
5.	10	0.960	0.825	0.938	0.985	0.818	0.905	0.07	0.07
6.	12	1.020	0.985	1.162	1.160	1.001	1.065	0.08	0.07

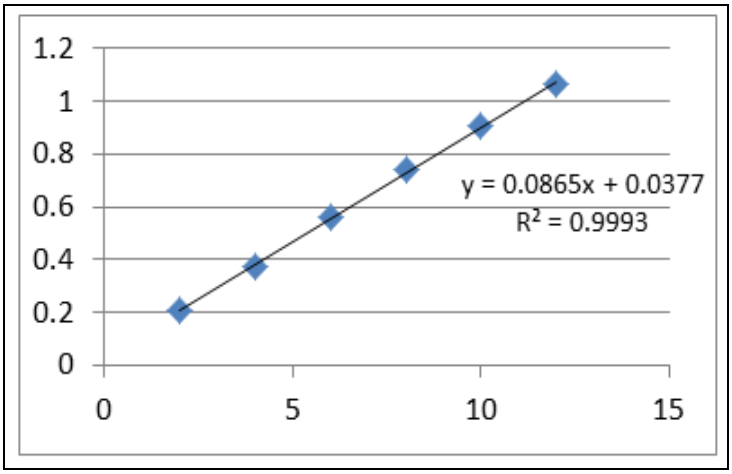

Figure 1: Linearity studies of paracetamol at 249nm

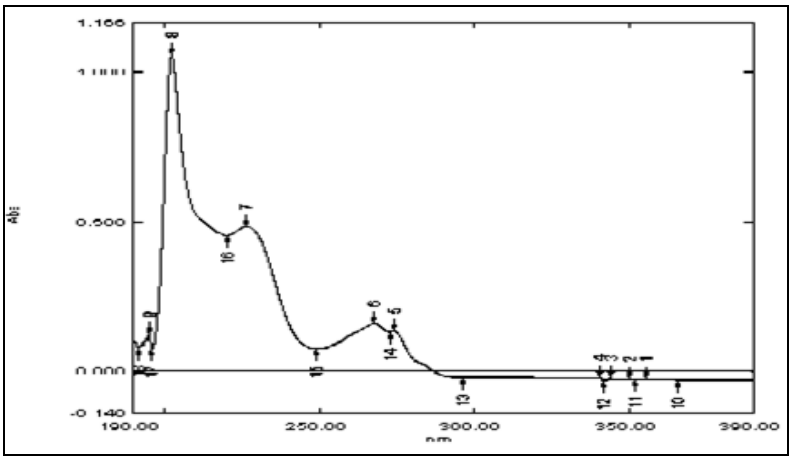

Figure 2: Absorbance of dexibuprofen at 221nm

Table 2: Linearity studies of DEXIBUPROFEN 221nm

S. No.	Conc (µg/ml)	Replica1	Replica2	Replica3	Replica4	Replica5	Mean	SD(±)	RSD
1	2	0.223	0.213	0.225	0.212	0.234	0.221	0.009	0.04
2	4	0.425	0.411	0.418	0.416	0.422	0.418	0.005	0.01
3	6	0.600	0.625	0.620	0.626	0.612	0.616	0.010	0.01
4	8	0.833	0.812	0.829	0.812	0.837	0.824	0.011	0.01
5	10	1.037	1.028	1.065	1.023	1.022	1.03	0.017	0.01
6	12	1.247	1.256	1.236	1.224	1.234	1.23	0.012	0.008

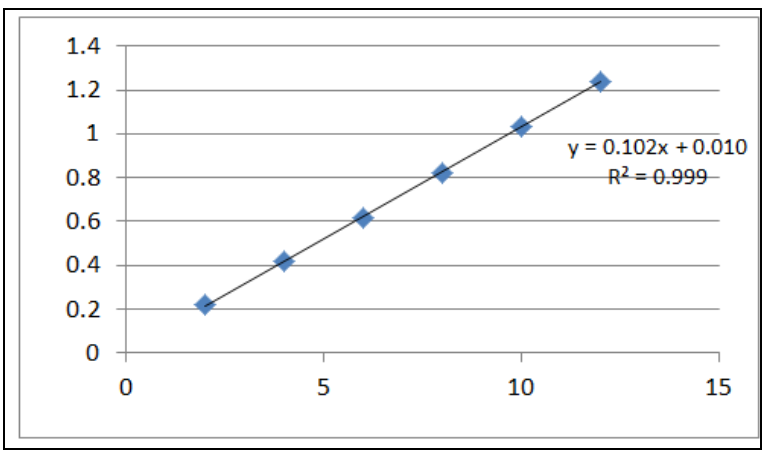

Figure 3: Linearity studies of dexibuprofen

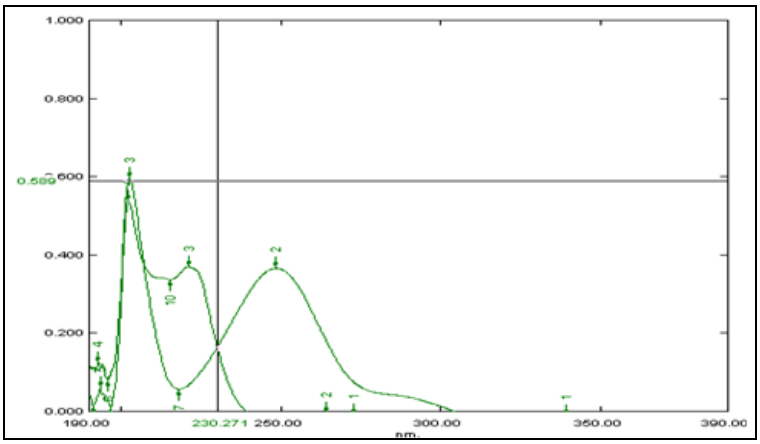

Figure 4: Overlain spectra of paracetamol and dexibuprofen at 230 nm

Analysis of commercial formulation

20 tablets brand "Brutec-p" manufactured by Glenmark pharmaceutical ltd procured from local market and their average weight was calculated. Twenty tablets were crushed and equivalent weight was transferred to 100 ml volumetric flask, dissolved in 30 ml methanol and sonicated for 10 min. The volume was then made up to the mark using same solvent. The resulting solution was filtered through Whatmann filter paper grade 41 and from filtrate 10mL was taken which was equivalent to average weight of one tablet i.e., it contains 300 mg/10ml of dexibuprofen and 500 mg/10 ml of paracetamol, From the above two stock solution appropriate dilution were made to prepared different solution containing both the drugs in the proportion 3:5 for Dexibuprofen and Paracetamol respectively. Then the absorbencies of these solutions were noted at 221nm and 249 nm.

Table 3: Assay of tablet formulation

S.NO.	Labelled Concentration		Concentration observed		Percentage(%) Label claim observed	
	PCM	DIB	PCM	DIB	PCM	DIB
1	500	300	499.89	299.89	98.91	99.63
2	500	300	499.96	299.92	99.68	99.73
3	500	300	499.98	300.16	99.80	100.53
4	500	300	499.89	299.91	98.98	99.70

Table 4: statistical validation of recovery

%	Drug	Mean %	± S.D.	% RSD
80	PCM	99.34	0.517	0.52
	DIB	99.92	0.035	0.035
100	PCM	99.68	0.295	0.29
	DIB	99.98	0.130	0.13
120	PCM	100.1	0.117	0.117
	DIB	99.75	0.713	0.714

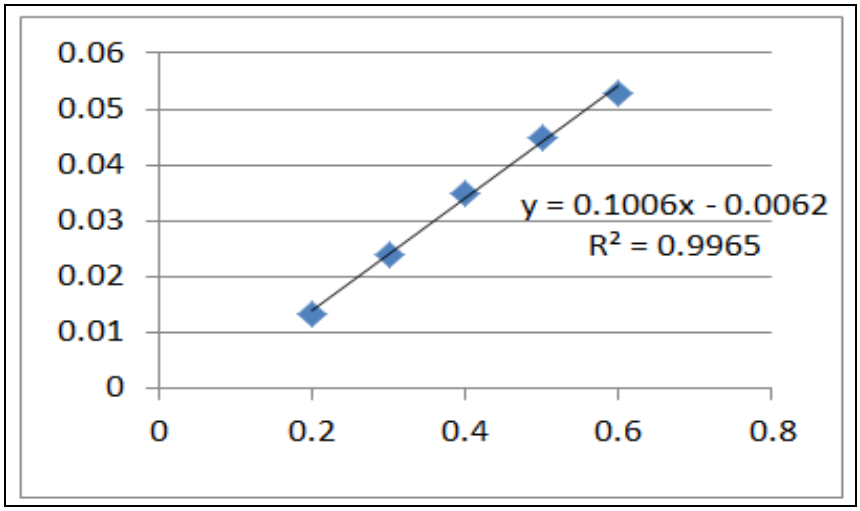

Figure 5: LOD and LOQ of paracetamol

Table 5: LOD and LOQ of DEXIBUPROFEN

Replicate No.	**Absorbance of DIB at concentration (µg/ml)**				
	0.2 µg/ml	**0.3 µg/ml**	**0.4 µg/ml**	**0.5 µg/ml**	**0.6 µg/ml**
Replicate 1	0.009	0.016	0.025	0.034	0.045
Replicate 2	0.011	0.015	0.024	0.035	0.044
Replicate 3	0.010	0.014	0.028	0.038	0.046
Replicate 4	0.0149	0.018	0.029	0.036	0.048
Replicate 5	0.011	0.017	0.029	0.033	0.047
Mean	0.011	0.020	0.027	0.038	0.046
S.D.	0.0018	0.0015	0.0023	0.001	0.0015
RSD	0.09	0.05	0.07	0.02	0.02

Mean standard deviation 0.0004
Slope of curve 0.088
LOD 3.3 x 0.0004/0.088 = 0.015µg/ml
LOQ 10 x 0.0004 /0.088 =0.045µg/ml

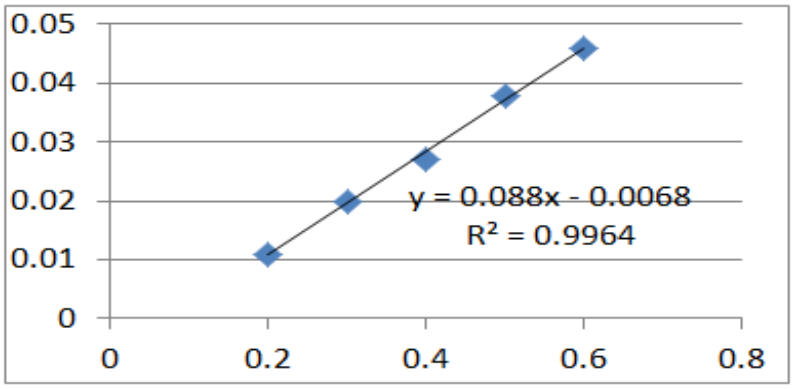

Figure 6: LOD and LOQ of dexibuprofen

Analysis of commercial formulation

20 tablets brand "Brutec-p" manufactured by Glenmark pharmaceutical ltd procured from local market and their average weight was calculated.

Table 5: Assay of tablet formulation

S.No.	Conc. as per Label (mg / tablet)		Conc Found (mg / tablet)		%Content	
	PCM	DIB	PCM	DIB	PCM	DIB
1	500	300	500.12	299.95	101.12	99.83
2	500	300	500.11	300.11	101.11	100.36
3	500	300	499.98	298.99	99.81	96.63
4	500	300	499.93	299.97	99.32	99.91
5	500	300	499.89	300.12	98.91	100.4

Recovery Study

Table 6: Statistical validation of recovery study

%	Drug	Mean %	± S.D.	% RSD
80	PCM	99.98	0.123	0.12
	DIB	99.27	1.031	1.04
100	PCM	99.59	0.707	0.71
	DIB	99.37	0.760	0.76
120	PCM	100.02	0.110	0.11
	DIB	99.23	1.054	1.06

Intermediate Precision

(Inter-day and Intra-day precision)

The intra and inter-day precision was calculated by assay of the sample solution on the same day and on different days at different time intervals respectively.

Table 8: Intra and inter day precision study of Paracetamol

S. No.	Intraday			Interday		
	Percentage obtained			Percentage obtained		
	1st hr	2nd hr	3rd hr	Day 1	Day 2	Day 3
Replicate-1	100.01	99.98	100.04	100.01	98.77	98.62
Replicate-2	100.13	99.87	100.12	100.13	99.34	99.01
Replicate-3	99.98	100.01	99.97	99.98	98.62	98.01
Replicate-4	100.02	99.79	100.01	100.02	99.87	98.02
Replicate-5	100.12	99.86	99.98	100.12	99.98	98.95
Mean	100.05	99.90	100.02	100.05	99.31	98.52
S.D.	0.0683	0.0909	0.0602	0.0683	0.619	0.486
%RSD	0.07	0.09	0.06	0.07	0.63	0.49

Table 9: Intra and inter day precision study of Dexibuprofen

Replicate No.	Intraday			Interday		
	Percentage obtained			Percentage obtained		
	1st hr	2nd hr	3rd hr	Day 1	Day 2	Day 3
Replicate-1	99.87	98.77	99.86	99.87	99.98	100.01
Replicate-2	99.07	99.42	99.24	99.17	99.87	98.16
Replicate-3	100.11	100.09	99.98	100.01	99.89	99.01
Replicate-4	100.03	100.03	100.12	99.79	98.97	97.99
Replicate-5	99.86	99.98	100.22	99.86	98.12	98.14
Mean	99.78	99.65	99.88	99.74	99.36	98.66
S.D.	0.415	0.564	0.385	0.328	0.809	0.854
%RSD	0.42	0.57	0.39	0.33	0.81	0.87

Limit of Detection and Limit of Quantitation (LOD and LOQ)

Solutions for the measurement of LOD and LOQ were prepared as per the procedure discussed in section 3.3.8. The absorbances were measured at 230 nm (isobestic point) and 249 nm for PARACETAMOL and DEXIBUPROFEN respectively. This was repeated five times and the standard deviation of the analyte was calculated.

Table 10: LOD and LOQ of PARACETAMOL

Replicate No.	Absorbance of PCM at concentration (µg/ml)				
	0.2 µg/ml	**0.3 µg/ml**	**0.4 µg/ml**	**0.5 µg/ml**	**0.6 µg/ml**
Replicate 1	0.010	0.014	0.025	0.034	0.045
Replicate 2	0.011	0.018	0.024	0.035	0.044
Replicate 3	0.025	0.016	0.026	0.033	0.046
Replicate 4	0.034	0.015	0.029	0.036	0.042
Replicate 5	0.045	0.017	0.029	0.033	0.047
Mean	0.025	0.016	0.026	0.034	0.044
S.D.	0.0015	0.0015	0.0023	0.0013	0.0019
RSD	0.06	0.09	0.08	0.03	0.04

Mean standard deviation 0.0017
Slope of curve 0.082
LOD 3.3 x 0.0017 / 0.082 = 0.67 µg/ml
LOQ 10 x 0.0017 / 0.082 = 1.01 µg/ml

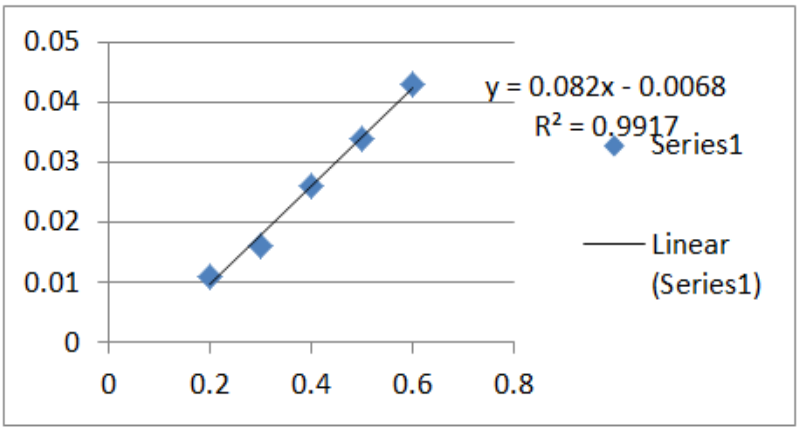

Figure 7: LOD & LOQ curve of paracetamol

Replicate No.	Absorbance at concentration (µg/ml)				
	0.2 µg/ml	**0.3 µg/ml**	**0.4 µg/ml**	**0.5 µg/ml**	**0.6 µg/ml**
Replicate 1	0.009	0.016	0.025	0.033	0.043
Replicate 2	0.011	0.015	0.024	0.035	0.044
Replicate 3	0.010	0.015	0.028	0.037	0.046
Replicate 4	0.014	0.018	0.027	0.036	0.048
Replicate 5	0.011	0.017	0.029	0.033	0.047
Mean	0.011	0.017	0.026	0.034	0.045
SD	0.0018	0.0013	0.0020	0.0017	0.0020
RSD	0.016	0.07	0.07	0.05	0.04

Mean standard deviation 0.0017
Slope of curve 0.085
LOD 3.3 x 0.0017 /0.085 = 0.68 µg/ml
LOQ 10 x 0.0017 / 0.085 = 1.08 µg/ml

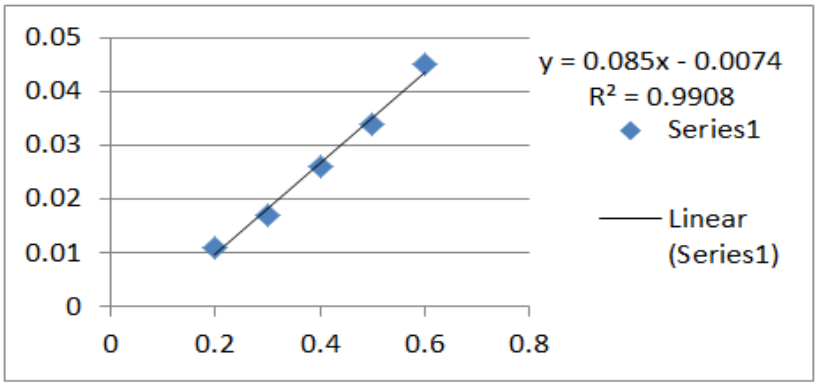

Figure 8: LOD & LOQ curve of Dexibuprofen

Table 12: Statistical validation of recovery study

%	Drug	Mean %	± S.D.	% RSD
80	PCM	99.54	0.501	0.50
	DBI	99.37	0.371	0.37
100	PCM	99.56	0.501	0.50
	DIB	99.37	0.501	0.37
120	PCM	99.09	0.490	0.49
	DEX	98.42	0.587	0.60

Table 13: LOD and LOQ of Paracetamol

S.No.	Absorbance of PCM at concentration (µg/ml)				
	0.2 µg/ml	0.3 µg/ml	0.4 µg/ml	0.5 µg/ml	0.6 µg/ml
Replicate 1	0.029	0.04	0.052	0.066	0.081
Replicate 2	0.032	0.044	0.053	0.067	0.082
Replicate 3	0.039	0.051	0.061	0.074	0.081
Replicate 4	0.038	0.050	0.056	0.073	0.082
Replicate 5	0.041	0.053	0.062	0.078	0.087
Mean	0.035	0.048	0.056	0.0720	0.082
SD	0.0050	0.0054	0.0045	0.0050	0.0025
RSD	0.014	0.11	0.08	0.06	0.03

Mean standard deviation 0.0044
Slope of curve 0.118
LOD 3.3 x 0.0044 /0.118 = 0.12 µg/ml
LOQ 10 x 0.0044 / 0.118= 0.37 µg/ml

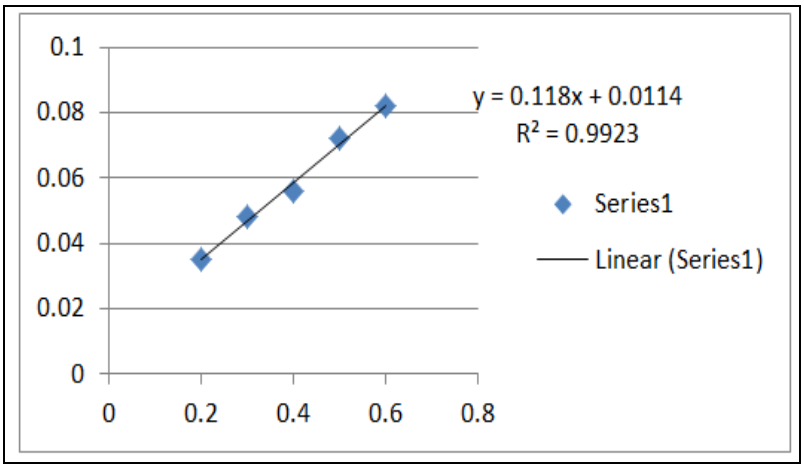

Figure 9: LOD and LOQ of Paracetamol

Table 14: LOD & LOQ curve of Dexibuprofen

Replicate No.	Absorbance of DIB at concentration (µg/ml)				
	0.2 µg/ml	**0.3 µg/ml**	**0.4 µg/ml**	**0.5 µg/ml**	**0.6 µg/ml**
Replicate 1	0.009	0.016	0.025	0.033	0.043
Replicate 2	0.011	0.015	0.024	0.035	0.044
Replicate 3	0.010	0.015	0.028	0.037	0.046
Replicate 4	0.014	0.018	0.027	0.036	0.048
Replicate 5	0.011	0.017	0.029	0.033	0.047
Mean	0.011	0.017	0.026	0.034	0.045
SD	0.0018	0.0013	0.0020	0.0017	0.0020
RSD	0.016	0.07	0.07	0.05	0.04

Mean standard deviation 0.0017
Slope of curve 0.085
LOD 3.3 x 0.0017 /0.085 = 0.67 µg/ml
LOQ 10 x 0.0017 / 0.085 = 1.09 µg/ml

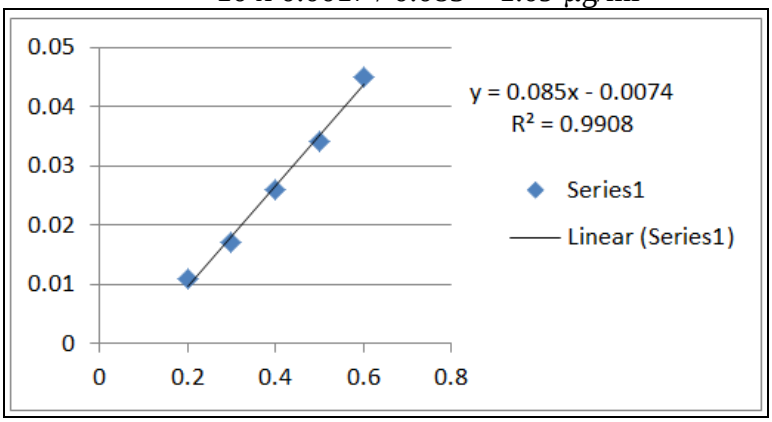

Figure 9: LOD and LOQ of Dexibuprofen

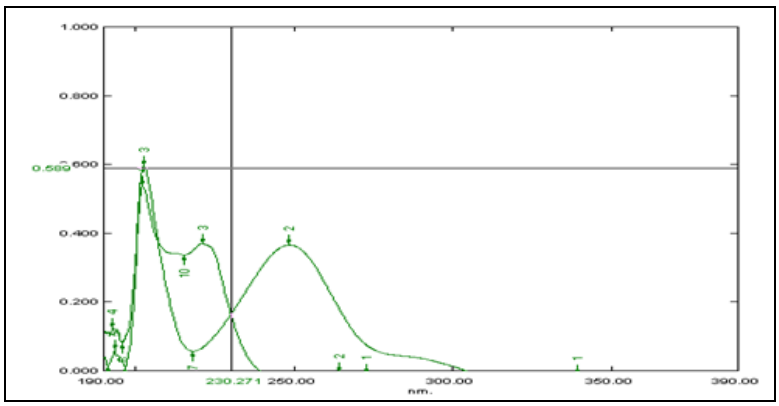

Figure 10: Overlain spectra of Paracetamol and Dexibuprofen

Result and Discission

Table 15: Comparison of statistical data for linearity

Methods	Mean SD		RSD	
	PCM	**DBI**	**PCM**	**DBI**
Simultaneous Equation Method	0.0533	0.0050	0.0092	0.83
Absorbance Ratio Method	0.020	0.0023	0.0092	0.0013
Multi-component Analysis	0.0207	0.0016	0.0092	0.009

Table 16: Comparison of statistical data for accuracy

Methods	Mean SD		RSD	
	PCM	DIB	PCM	DIB
Simultaneous Equation Method	0.8736	1.179	0.8993	1.175
Absorbance Ratio Method	0.7823	1.099	0.7820	1.00
Multi-Component Method	0.6016	0.6952	0.6056	0.6966

Table 17: Comparison of statistical data for precision (intermediate precision)

Methods	S.D.		RSD	
	PCM	DIB	PCM	DIB
Simultaneous Equation Method	**0.439**	**0.804**	**0.443**	**0.863**
Absorbance Ratio Method	**0.232**	**0.559**	**0.235**	**0.565**
Multi-Component Method	**0.375**	**0.474**	**0.375**	**0.476**

Table 18: Comparison of LOD and LOQ values

Methods	LOD		LOQ	
	PCM	DIB	PCM	DIB
Simultaneous Equation Method	**0.013**	**0.015**	**0.04**	**0.045**
Absorbance Ratio Method	**0.67**	**0.68**	**1.01**	**1.08**
Multi-Component Method	**0.12**	**0.61**	**0.37**	**1.09**

Conclusion:

According to the concept of UV-spectrophotometric method for estimation of PCM and DIB was developed and based on validation data the method was found to be simple, accurate, rapid, reproducible and convenient for routine analysis. In the present work, a successful attempt has been for developing a spectrophotometric method for Simultaneous equation method, isoabsorbance ratio method and multicomponent method of Paracetamol and Dexibuprofen respectively. Absorbance are measured at two wavelengths. One was being the λmax (λ_1= 249nm) of paracetamol and other being λ max (λ_2= 221nm) and obey Beer's-Lambert's Law in the concentration range 2-12µg/ml.The method was validated as per ICH Guidelines.The recovery studies were carred out by standard addition method at 80,100.120% and % recovery was found to be 99.34, 99.68, 100.1 respectively.the low % RSD indicates high precision of method.

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