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Research Article

DEVELOPMENT AND VALIDATION OF SPECTROPHOTOMETRIC AREA UNDER CURVE METHOD FOR SIMULTANEOUS ESTIMATION OF TOLPERISONE HYDROCHLORIDE AND DICLOFENAC SODIUM IN THEIR COMBINED TABLET DOSAGE FORM

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ABSTRACT

Objective: A simple, accurate, precise and specific area under curve method has been developed for simultaneous determination of Tolperisone Hydrochloride (TOL) and Diclofenac Sodium (DIC) in its combined tablet dosage form by using Distilled water as a solvent.

Method: The proposed area under curve method involves measurement of area at selected wavelength ranges. Two wavelength ranges were selected 250.0-270.0nm and 265.0-285.0nm for estimation of Tolperisone Hydrochloride and Diclofenac Sodium respectively.

Result & Discussion: The linearity was found to be 39-54µg/ml and 13-18µg/ml for Tolperisone Hydrochloride and Diclofenac Sodium respectively. The mean % recoveries were found to be 99.65% for TOL and 99.75 % for DIC. For Repeatability, Intraday precision, Interday precision,Reproducibility % RSD were found to be 1.03, 1.024, 1.092,1.114 for TOL and 0.969, 1.07, 1.160,1.104 for DIC respectively. Limit of Detection and Quantitation was found to be 0.172µg/ml and 0.523µg/ml for TOL and 0.486µg/ml and 1.475µg/ml for TOL respectively. Assay results of market formulation were found to be 98.96% and 98.88 % for TOL and DIC respectively. The proposed method has been validated as per ICH guidelines and successfully applied to the estimation of TOL and DIC in their combined Tablet dosage form.

Keywords: Tolperisone Hydrochloride, Diclofenac Sodium, Area under curve method, Analytical Method Validation

INTRODUCTION

TOL is chemically 1-(4-methyl-phenyl)-2-methyl-3-(1-piperidine)-1-propanone-hydrochloride.

Generally piperidine derivative is centrally acting muscle relaxant[1] which is used in the treatment of acute and chronic muscle spasm, In back pain, arthritis of large joints, spastic muscle cramps, paralysis and muscle pain, myelopathy, encephalomyelitis, arthrosis of the large joints obliterating artherosclerosis of the extremity vessels. TOL is official in Japanese pharmacopoeia. Chemically DIC is, sodium {2-[(2,6-dichlorophenyl)-amino]phenyl}acetate, used as analgesic and anti-inflammatory drug used in the treatment of Rheumatoid arthritis, osteoarthritis, acute musculoskeletal disorders (e.g. tendinitis, sprains and dislocations), ankylosing spondylitis, acute gout, postoperative pain, renal colic and control of pain and inflammation in orthopedic, dental and other minor surgery. Diclofenac sodium is official in IP 2010, BP 2009, and USP 30.

The review of literature stated that various analytical methods involving Spectrophotometry, HPLC, and HPTLC have been reported for TOL in single form and in combination with other drugs. Several analytical methods have been reported for DIC in single form and in combination with other drugs including Spectrophotometry, HPLC, HPTLC, LC-MS Methods. However no references have been found for simultaneous estimation of Tolperisone Hydrochloride and Diclofenac Sodium in their combined tablet dosage form by Area under curve method. So, the objective is to develop simple, accurate and precise method for estimation of Tolperisone HCl (TOL) and Diclofenac sodium (DIC) in combined tablet dosage form. The developed method was validated as per ICH guidelines and successfully applied for the assay of TOL and DIC in their combined tablet dosage form.

MATERIALS AND METHODS

Reagents and Chemicals

TOL was kindly gifted by Zydus Cadila Healthcare Ltd, Ahmedabad, Gujarat, India and DIC was kindly provided by Alembic Ltd, Vadodara, Gujarat, India. Tablet of TOL (150 mg) and DIC (50 mg) in combined dosage form (TOLPIDOL-D), Manufactured by Themis Pharmaceuticals was obtained from local market.

Instruments

Double beam UV-visible spectrophotometer (Shimadzu, model 1800) having two matched quartz cells with 1 cm light path and loaded with UV probe software. Electronic analytical balance (Shimadzu, Japan). Ultrasonicator (Sonar, Delhi).

Preparation of standard stock solutions

Accurately weighed TOL (150 mg) was transferred into 50 ml volumetric flask, dissolved and volume made up to mark with Distilled water to give solution containing 3000 µg/ml of TOL. Then, Accurately weighed DIC (50 mg) was transferred into another 50 ml volumetric flask, dissolved and volume made up to mark with Distilled water to give solution containing 1000 µg/ml of DIC.

Area under curve method

For the selection of analytical wavelength solution of TOL (39 µg/ml) and DIC (13 µg/ml) were prepared separately by appropriate dissolution from standard stock solutions and scanned between 200 to 400 nm using Distilled water as blank. From the overlain spectra (Fig.3) of both drugs the area under curve (AUC) is determined at both the selected analytical wavelength ranges. Wavelength range selected were 250 - 270 nm for determination of AUC of TOL and 265 - 285 nm for determination of AUC of DIC. The Calibration curve was prepared in the concentration range of 39-54 µg/ml for TOL at 250 to 270 nm. The Calibration curve was prepared in the concentration range of 13-18 µg/ml for DIC at 265 to 285 nm. The 'X' value is the ratio of AUC at selected wavelength ranges (250-270 nm and 265-285nm) with concentration of component in µg/ml. The concentration of each drug was calculated using following "Cramers and Matrix rule" equation:

$$C_{tol} = \frac{X_{Dic}\,\lambda(265-285)*AUC(250-270) - X_{Dic}\,\lambda(250-270)*AUC(265-285)}{X_{Dic}\,\lambda(265-285)*X_{tol}\,\lambda(250-270) - X_{Dic}\,\lambda(250-270)*Xtol\,\lambda(265-285)}$$

$$C_{Dic} = \frac{X_{tol}\,\lambda(265-285)*AUC(250-270) - X_{tol}\,\lambda(250-270)*AUC(265-285)}{X_{Dic}\,\lambda(250-270)*X_{tol}\,\lambda(265-285) - X_{Dic}\,\lambda(265-285)*X_{tol}\,\lambda(250-270)}$$

Where, C_{Dic} = Concentration of Diclofenac sodium in gm/L;

C_{tol} = Concentration of Tolperisone HCl in gm/L;

$X_{tol}\,\lambda(265-285)$= AUCtol (265-285)/conc. in gm/L;

X_{tol} λ(250-270)= AUCtol (250-270)/conc. in gm/L;

X_{Dic} λ(265-285)= AUCDic (265-285)/conc. in gm/L;

X_{Dic} λ(250-270)= AUCDic (250-270)/conc. in gm/L.

Method Validation

The proposed method has been extensively validated according to ICH guidelines

Linearity

Solutions of TOL ranging from 39-51 µg/ml were prepared by pipetting out 0.13, 0.14, 0.15, 0.16, and 0.17 ml stock solution of TOL into series of 10 ml volumetric flasks and diluted up to the mark with Distilled water. Then, Solutions of DIC ranging from 13-17µg/ml were prepared by pipetting out 0.13, 0.14, 0.15, 0.16, and 0.17 ml stock solution of DIC into series of 10 ml volumetric flasks and diluted up to the mark with Distilled water. The absorption spectra of above solutions were recorded in the range of 200 to 400 nm using Distilled water as blank. Area determined at both wavelengths ranges 250-270 nm and 265-285 nm for TOL and DIC respectively.

Precision (Repeatability)

AUC determined at wavelength range between 250-270 nm for TOL (45 µg/ml) and AUC determined at wavelength range between 265-285 nm for DIC (15 µg/ml) were measured six times and %RSD was calculated and it was within limit (less than 2%)

Intermediate Precision

Intraday precision was determined by analyzing TOL (45 µg/ml) and DIC (15 µg/ml) in combined solution for six times in the same day. Interday precision was determined by analyzing DIC (15 µg/ml) and TOL (45 µg/ml) in for three days. Intraday and interday precision was determined in terms of %RSD. It was within limit (less than 2%)

Reproducibility

Reproducibility expresses the precision between laboratories. It was performed by preparing the standard solution of TOL (45µg/ml) and DIC (15µg/ml) for six times and analyzed as per the proposed method. It was determined in terms of %RSD. It was within limit (less than 2%)

Accuracy (Recovery study)

Accuracy often expressed as % Recovery by the assay of known, added amount of analyte by standard addition method. Known amount of standard solution of TOL and DIC were added at 50%, 100%,120% to pre-quantified sample solution of TOL (45µg/ml) and DIC (15µg/ml). The amount of DIC and TOL were estimated from straight line equation of calibration curve.

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

LOD and LOQ are estimated from the set of 5 calibration curves used to determine method linearity. The LOD and LOQ may be calculated as;

LOD = 3.3 x (SD / Slope)

LOQ = 10 x (SD / Slope)

Where, SD = the standard deviation of Y- intercept of 5 calibration curves

Slope = the mean slope of the 5 calibration curves.

Ruggedness

Ruggedness of the proposed method was determined by analysis of aliquots of sample solution (15 µg/ml DIC and 45 µg/ml TOL) by two analysts and two instrument using same operational and environmental conditions.

Robustness

For the evaluation the robustness of the developed method, small deliberate variation in the optimized method parameter were done (Change in Wavelength ±1 nm.). The effect of change in Wavelength was studied. In term of %RSD which was less than 2% for DIC and TOL.

Determination of TOL and DIC in their Combined Tablet Dosage

Twenty Tablets were weighed and average weight of content was determined & the content of tablets was powdered. The powder equivalent to 150 mg of TOL or 50 mg of DIC was transferred to a 50 ml volumetric flask, dissolved and diluted up to the mark with Distilled water. Aliquots of 0.15 ml of this solution was diluted to 10 ml with Distilled water six times. AUC determined at wavelength range between 265-285 nm and 250-270 nm. The concentration of each drug was calculated using following "Cramers and Matrix rule" equation.

RESULTS & DISCUSSION

Solution of TOL (39 µg/ml) and DIC (13 µg/ml) were scanned separately between 200 to 400 nm using Distilled water as blank. Maximum absorbance obtained at 256nm for TOL and 272nm for DIC. Two wavelength ranges were selected 250.0-270.0 nm and 265.0-285.0 nm for estimation of TOL and DIC respectively (Fig.1 and Fig.2) The Linear regression equations for TOL and DIC was found to be y=0.151x+0.751, R^2 = 0.996 (Fig.4) and y=0.0546x+0.110, R^2 = 0.997 (Fig.5) (in respectively in concentration range of 39-54µg/ml and 13-18µg/ml). Which are within specified criteria of ICH guideline, all data prove that method is linear (Table 1). Linearity data was summarized in Table 3. For Repeatability (Table 4), Intraday precision, Interday precision, Reproducibility (Table 5) % RSD were found to be 1.03, 1.024, 1.092, 1.114 for TOL and 0.969, 1.07, 1.160, 1.104 for DIC respectively. % RSD was found to be less than 2% (which is recommended by ICH guideline) for within a day and day to day variation, which proves that method is precise. Mean % Recovery studies was found to be 99.65% of TOL and 99.75% for DIC. Recovery studies data summarized in Table 6 and Table 7. Recovery greater than 98 % with low standard deviation justifies the accuracy of the method. LOD and LOQ value was found to be 0.172µg/ml and 0.523µg/ml for TOL & 0.486µg/ml and 1.475µg/ml for DIC. LOD and LOQ data were summarized in Table 8. For Ruggedness by Different analyst % RSD were found to be 1.123 and 1.326 for TOL and DIC respectively. % RSD was found to be less than 2% (which is recommended by ICH guideline). Ruggedness by Different analyst was summarized in Table 9. For Ruggedness by Different Instrument % RSD were found to be 1.120 and 1.129 for TOL and DIC respectively. Ruggedness data was summarized in Table 10. % RSD was found to be less than 2% (which is recommended by ICH guideline). For Robustness % RSD were found to be 1.123 and 1.109 for TOL and DIC respectively. % RSD was found to be less than 2% (which is recommended by ICH guideline). Robustness data was summarized in Table 11. Assay value was found to be 98.96% for TOL and 98.88% for DIC. Assay data summarized in Table 12.The proposed validated method was successfully applied for Simultaneous estimation of TOL and DIC.

Table 1: Statistical data of TOL and DIC by Area under curve method

Validation Parameters	TOL	DIC
Linearity Range	39-54 µg/ml	13-18µg/m
Straight line equation	y=0.151x+0.751	y=0.0546x+0.110
Slope	0.151	0.0546
Intercept	0.751	0.110
Correlation Coefficient (r^2)	0.996	0.997

Table 2: Summary of Validation Parameters of TOL and DIC

Validation Parameters	TOL	DIC
Precision (% RSD):		
Repeatability(n=6)	1.03	0.969
Intraday(n=3)	1.024	1.07
Interday(n=3)	1.092	1.160
Reproducibility	1.114	1.1048
Mean % Recovery	99.65	99.75
LOD (µg/ml)	0.172	0.486
LOQ (µg/ml)	0.523	1.475
Ruggedness (% RSD)		
Different Analyst	1.123	1.326
Different Instrument	1.120	1.129
Robustness (% RSD)	1.123	1.109

Table 3: Linearity data for TOL (39-45µg/ml) and DIC (13-18µg/ml)

TOL Concentration (µg/ml)	TOL AUC (250-270nm)*	DIC Concentration (µg/ml)	DIC AUC (265-285 nm)*
39	6.65	13	0.720
42	7.05	14	0.771
45	7.60	15	0.820
48	8.10	16	0.889
51	8.43	17	0.94
54	8.90	18	0.986

*n=6

Table 4: Repeatability Data for TOL(45 µg/ml) and DIC (15 µg/ml)

Solutions	TOL AUC (250–270nm)	DIC AUC (265-285nm)
Mean*	7.615	0.82166
S.D.	0.07905	0.007967
% RSD	1.03%	0.969 %

*n=6

Table 5: Reproducibility by of TOL and DIC

S. No.	TOL Area (250-270 nm)		DIC Area (265-285 nm)	
	Lab.1	Lab.2	Lab.1	Lab.2
1	7.610	7.614	0.816	0.836
2	7.532	7.525	0.821	0.824
3	7.690	7.696	0.834	0.818
Average	7.610	7.611	0.823	0.826
SD	0.079	0.08552	0.009292	0.009165
% RSD	1.038	1.123	1.129	1.109

Table 6: Accuracy data of TOL by Area under curve method

TOL	Test (100%) (µg/ml)	Std. Added (µg/ml	Total Area(250-270nm)	Conc. (µg/ml)	% Recovery	Average	SD	%RSD
80%	45	36	13.396	35.84	99.56	99.09	0.672	0.678
	45	36	13.382	35.79	99.39			
	45	36	13.375	35.75	98.32			
100%	45	45	14.485	44.32	99.39	99.63	0.346	0.347
	45	45	14.874	44.86	99.48			
	45	45	14.952	45.01	100.03			
120%	45	54	16.627	54.59	101.10	100.23	0.777	0.775
	45	54	16.431	53.82	99.59			
	45	54	16.447	54.06	100.02			

Table 7: Accuracy data DIC by Area under curve method

DIC	Test (100%) (µg/ml)	Std. Added (µg/ml)	Total Area(265-285nm)	Conc. (µg/ml)	% Recovery	Avg.	SD	%RSD
80%	15	12	1.459	12	100	99.82	0.185	0.185
	15	12	1.451	11.75	99.84			
	15	12	1.451	11.57	99.63			
100%	15	15	1.611	14.23	99.32	99.63	0.343	0.344
	15	15	1.615	14.51	99.58			
	15	15	1.622	14.99	100			
120%	15	18	1.757	17.73	98.53	98.91	0.349	0.352
	15	18	1.762	17.82	99.01			
	15	18	1.771	17.91	99.21			

Table 8: LOD and LOQ data of TOL and DIC

Parameter	TOL	DIC
Standard Deviation*	0.007905	0.007967
Slope	0.151	0.054
LOD (µg/ml)	0.172	0.486
LOQ (µg/ml)	0.523	1.475

*n=3

Table 9: Ruggedness Data of TOL (45µg/ml) and DIC(15µg/ml)

Parameter	TOL AUC		DIC AUC	
	Analyst – I	Analyt – II	Analyst – I	Analyt – II
Mean*	7.639	7.63	0.825	0.82433
SD	0.08516	0.0865	0.1358	0.00833
% RSD	1.114	1.033	1.636	1.016

*n=3

Table 10: Ruggedness Study for TOL (45µg/ml) and DIC (15µg/ml)

Parameter	TOL Normal Condition	TOL Change Condition	DIC Normal Condition	DIC Change Condition
Instrument change	**UV 1800**	**UV 1700**	**UV 1800**	**UV 1700**
Area	7.618	7.614	0.820	0.821
	7.536	7.525	0.838	0.816
	7.692	7.696	0.827	0.834
Average	7.615	7.611	0.827	0.823
STDEV	0.07803	0.08552	0.009007	0.009292
%RSD	1.024	1.123	1.08	1.129

Table 11: Result of Robustness Study for TOL (45µg/ml) and DIC (15µg/ml)

Parameter	TOL Normal Condition	TOL Change Condition	DIC Normal Condition	DIC Change Condition
Wavelength change	250-270nm	251-269nm	265-285nm	266-284nm
Area	7.618	7.614	0.838	0.836
	7.536	7.525	0.820	0.824
	7.692	7.696	0.827	0.818
Average	7.615	7.611	0.828	0.826
STDEV	0.07803	0.08552	0.00907	0.009165
%RSD	1.024	1.123	1.08	1.109

Table 12: Assay Results of Marketed Formulation

Tablet	Amount of Drug (µg/ml)		Amount Obtained (µg/ml)		% Assay	
TOLPIDOL D	**TOL**	**DIC**	**TOL**	**DIC**	**TOL**	**DIC**
	45	15	44.53	14.83	98.96	98.88

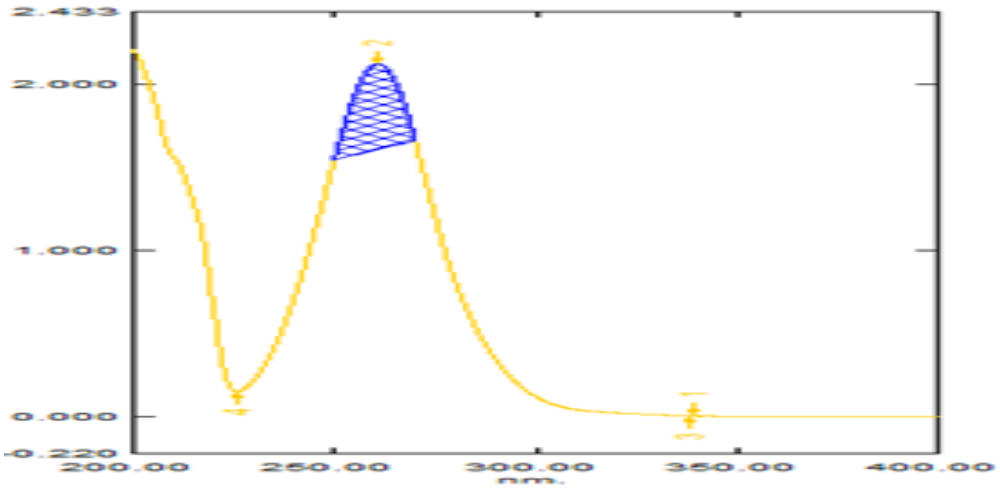

Fig. 1: Spectrum of TOL (39 µg/ml) AUC at 250-270 nm

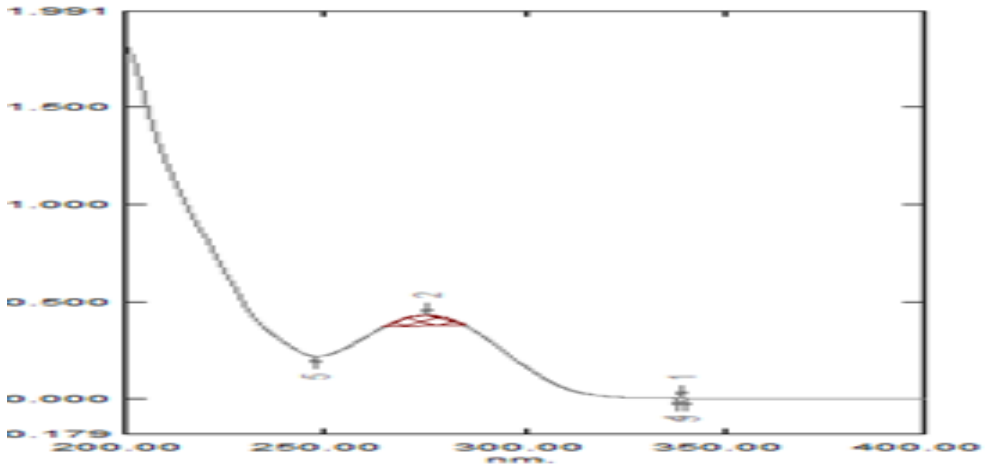

Fig. 2: spectrum of DIC (13 µg/ml) AUC at 265-285 nm

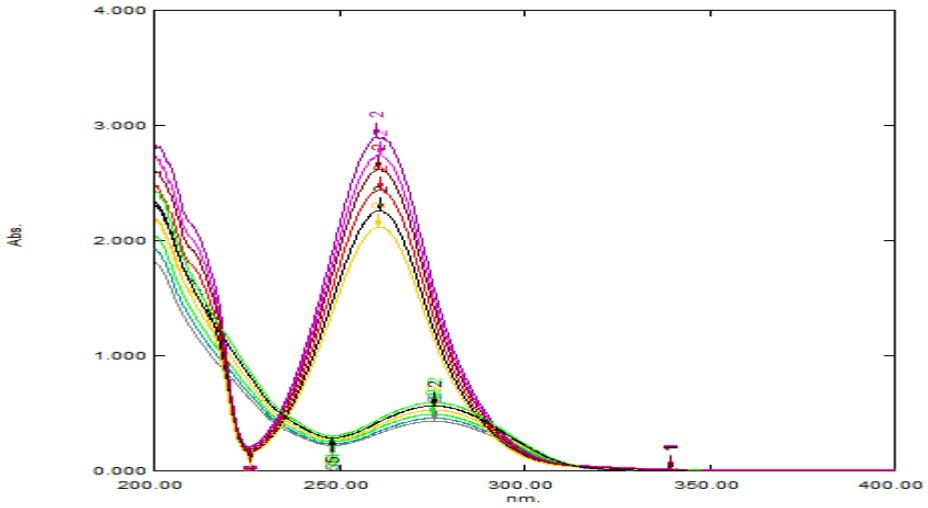

Fig. 3: Overlain spectrum of TOL (39-54 µg/ml) and DIC (13-18 µg/ml) in Distilled water

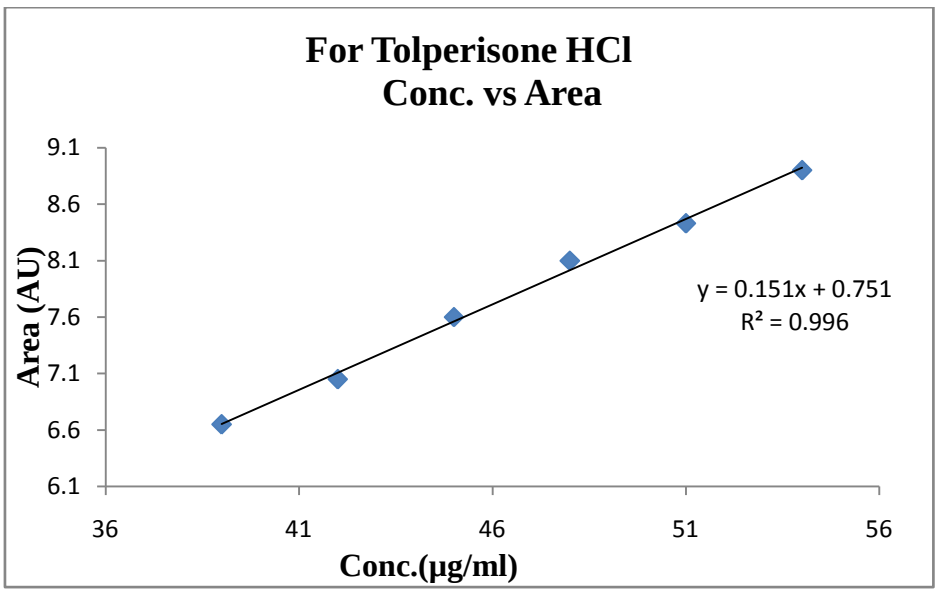

Fig. 4: Calibration curve for TOL at AUC (250-270nm) in Distilled water

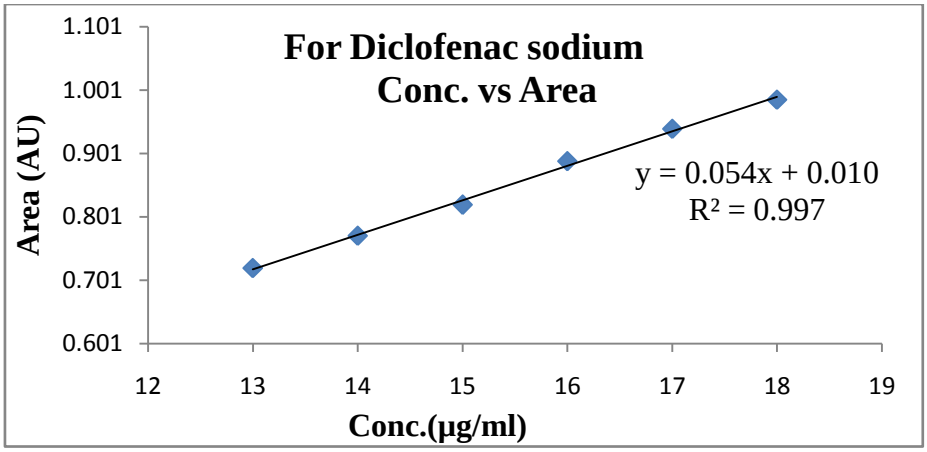

Fig. 5: Calibration curve for DIC at AUC (265-285nm) in Distilled water

CONCLUSION

The proposed area under curve method was found to be Simple, Sensitive, Accurate, precise for Simultaneous estimation of Tolperisone HCl and Diclofenac Sodium. This method utilizes commonly available and cheap solvent, so this method is cost effective method for Simultaneous estimation of Tolperisone HCl and Diclofenac Sodium. The method was validated as per ICH guidelines in terms of linearity, accuracy, precision, reproducibility, limits of detection (LOD) and quantification (LOQ), robustness and robustness. The proposed method can be used for routine analysis and quality control assay of TOL and DIC in combined dosage form.

Abbreviations

AUC-Area under curve, TOL-Tolperisone HCl, DIC-Diclofenac sodium, IP-Indian Phramacopoeia, BP-British Pharmacopoeia, USP-United States Pharmacopoeia, ICH- International Conference on Harmonization, HPLC-High performance Liquid Chromatography, HPTLC- High Performance Thin Layer Chromatography, µg-Microgram(s), mg-Miligram (s), nm- Nanometer (s), ng-Nano gram, Sr.No.-Serial number, %RSD-Percentage Relative Standard deviation, SD- Standard deviation, LOD- Limit of detection, LOQ-Limit of Quantitation.

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