UV Spectrophotometric Estimation of Diclofenac Potassium and Omeprazole Magnesium in Bulk and Combined Tablet Dosage Form

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Abstract : The aim of the present work is to develop simple, sensitive, accurate, precise and economic UV-spectrophotometric methods for the simultaneous estimation of diclofenac potassium and omeprazole magnesium in bulk and pharmaceutical tablet dosage form. The absorbance maxima (λ_{max}) for detection of diclofenac potassium and omeprazole magnesium were selected as 282.2 nm and 301.8 nm respectively for simultaneous equation method while wavelength range for detection of diclofenac potassium and omeprazole magnesium were selected as 280 nm - 285 nm and 300 mm - 305 nm respectively for area under curve method. Both the methods were found to be linear over the range of 5-30 μg/ml and 1-6 μg/ml for diclofenac potassium and omeprazole magnesium respectively and exhibited the correlation coefficient (r^2) of 0.999.The developed methods were validated statistically according to ICH guidelines in terms of linearity, accuracy, precision, limit of detection and limit of quantitation.The degradation behavior of the diclofenac potassium and omeprazole magnesium were studied by subjecting to an acid, alkaline, neutral, oxidative, photolytic, sunlight and thermal degradation.
Keywords: Diclofenac potassium, omeprazole magnesium, UV spectrophotometric method, validation, forced degradation.

Introduction

Diclofenac potassium (DICLO) is chemically potassium-2-[[(2,6-dichlorophenyl)-amino] phenylacetate (Fig. 1a) is a non-steroidal anti-inflammatory agents (NSAID) shows anti-inflammatory, antipyretic, analgesic activity and acts by inhibiting both leukocyte migration and the enzyme cylooxygenase (COX-1 and COX-2), leading to the peripheral inhibition of prostaglandin synthesis. Also, reduces the neutrophil chemotaxis and superoxide production at the inflammatory site. It is used as a drug of choice in conditions requiring potent anti-inflammatory action like ankylosing spondylitis, rheumatoid and osteoarthritis, dysmenorrhoea and management of acute pain. It is official in British Pharmacopeia[1-2].

Omeprazole magnesium (OME) is chemically (RS)-5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole, magnesium salt (2:1) (Fig. 1b) is a antiulcerative (proton pump inhibitor) acts by suppressing gastric acid secretion by specific inhibition of the proton pump (H^+/K^+-ATPase

pump) in the gastric parietal cell. It also inhibits gastric mucosal carbonic anhydrase. It is used to treat peptic ulcer. It is official in United State Pharmacopeia[3-4].
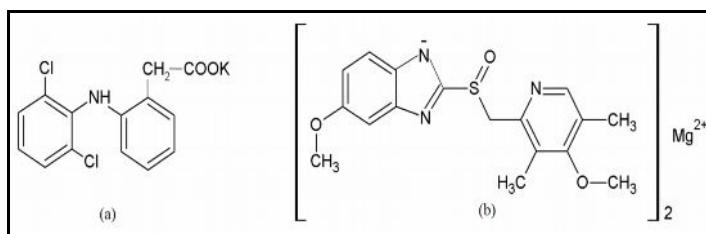

Fig. 1: Structure of (a) diclofenac potassium and (b) omeprazole magnesium

Literature survey revealed that spectrophotometric[5-6], HPLC[7-8], HPTLC[9], LC-MS[10], capillary electrophoresis[11] methods have been reported for estimation of DICLO and spectrophotometric[12-13], HPLC[14-15], UHPLC[16], HPTLC[17], LC-MS[18-19], capillary electrophoresis[20], voltammetry[21] methods have been reported for estimation of OME from its formulation or biological fluids in single or combination with other drugs.There was no any method reported for the simultaneous estimation of DICLO and OME from their combined tablet dosage form. This paper is in continuation with our work,[26-33] where we studied spectrophotometric method for single or multicomponent drugs.The aim of the present work is to develop and validate two spectrophotometric methods for estimation of DICLO and OME in bulk and tablet formulation and to perform forced degradation studies on the drugs as per ICH guidelines.

Materials and Methods

Instruments

The Spectrophotometric measurements were carried out using UV-visible double beam spectrophotometer (Model: UV-1800, Shimadzu Corp., Japan) with spectral bandwidth of 2 nm and 10 mm matched quartz cells used for development of analytical method. The absorption spectra of reference and test solution were carried out over the range of 200 - 400 nm using methanol as blank solution. Data acquisition was made by using computer operated software UV-probe version 2.33. The weighing was made on digital analytical balance (Model: AA-2200, Anamed); and sonication was carried out using Ultra Sonic Bath (Model: CD-4820, HMG India).

Chemicals and Materials

Working standards of DICLO and OME were pursued as a gift sample from Wockhardt Ltd., Aurangabad, India and the marketed formulation, Gi-Nac tablet (Diclofenac potassium 50 mg and Omeprazole magnesium 10 mg) was pursued as a gift samples from Ordain Health Care Global Pvt. Ltd. Kanchipuram, Tamil Nadu, India. All chemicals and solvents of AR grade were purchased from MERCK Ltd, Mumbai, India.

Selection of Solvent System

Methanol was selected as solvent system because both the APIs were found to be soluble in it. The selection of solvent was made after assessing the solubility of both the drugs in different solvents like water, ethanol, 0.1 M NaOH, 0.1 M Hcl etc.

Preparation of Standard Stock Solution

An accurately weighed quantity of about 10 mg of pure drug of DICLO and OME were taken and transferred into two different 100 ml volumetric flasks. Both drugs dissolved separately in methanol to give stock solution of concentration of 100 μg/ml respectively and the flasks were sonicated for about 15 min to solubilize the drugs.

Method- I: Simultaneous Equation Method

For the simultaneous equation method development, the wavelength absorbance maxima (λ_{max}) of both drugs are required. The working standard solutions containing 10 µg/ml of DICLO and 10 µg/ml OME were scanned separately in the range of 200-400 nm for absorbance maxima (λ_{max}) against methanol as blank solution. DICLO shows maximum absorption at 282.2 nm while OME at 301.8 nm. From the overlain spectra of both the drugs wavelength selected for quantification were 282.2 nm for DICLO and 301.8 nm for OME. The absorptivity coefficients of these two drugs were determined at selected wavelength and the concentrations of both drugs are calculated by using the equations (1) and (2)[22]. The absorption spectrum was obtained for DICLO, OME and their overlay is shown in Fig.2 and 3.
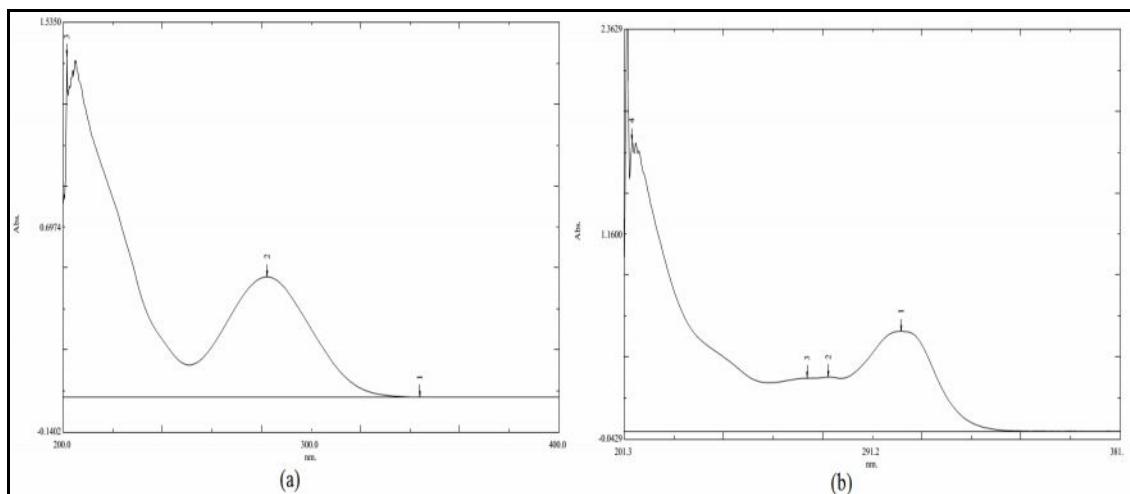

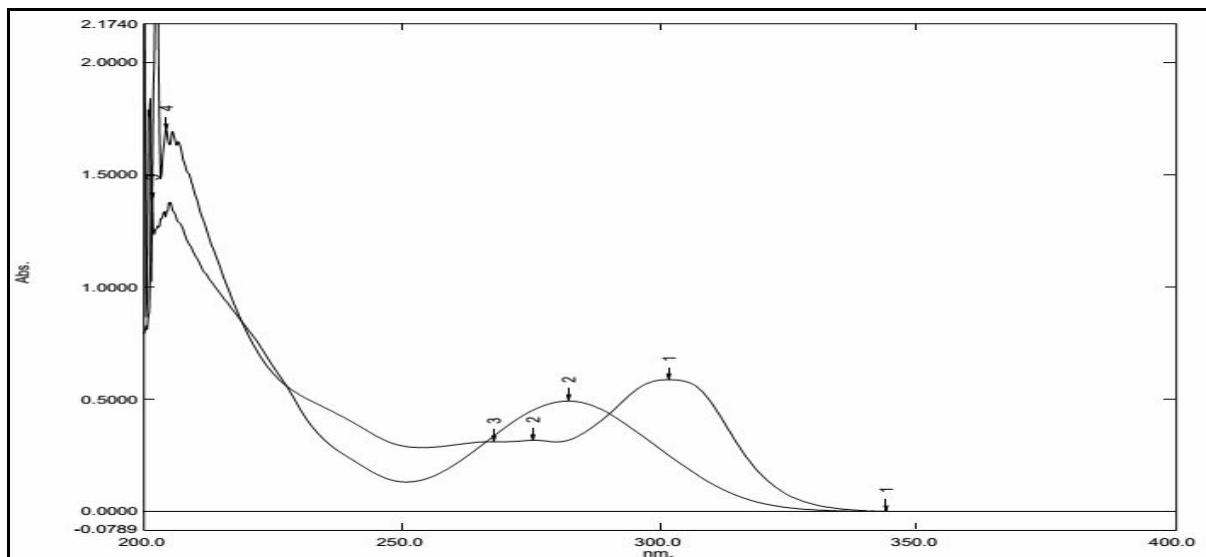**Fig. 2: Absorption spectrum of (a) DICLO and (b)OME**

Fig.3: Overlay spectrum of DICLO and OME

$$C_x = \frac{A_2 ay_1 - A_1 ay_2}{ax_2 ay_1 - ax_1 ay_2} \quad \text{................................} \quad (1)$$

$$C_y = \frac{A_1 ax_2 - A_2 ax_1}{ax_2 ay_1 - ax_1 ay_2} \quad \text{................................} \quad (2)$$

Where, C_x and C_y = the concentrations of DICLO and OME respectively in gm/100 ml; A_1 and A_2 = the absorbance of mixture at λ_1 (282.2 nm) and λ_2 (301.8 nm) respectively; ax_1 and ax_2 = the absorptivities of DICLO at λ_1 (282.2 nm) and λ_2 (301.8 nm) respectively; ay_1 and ay_2 = the absorptivities of the OME at the λ_1 (282.2 nm) and λ_2 (301.8 nm) respectively.

Method- II: Area under Curve

For the simultaneous estimation using the area under curve (AUC) method, the working standard solutions containing 10 µg/ml of DICLO and 10 µg/ml OME were scanned separately in the range of 200 - 400 nm for absorbance maxima (λ_{max}) against methanol as blank solution. DICLO shows maximum absorption at 282.2 nm while OME at 301.8 nm. The area under curve of the both the drugs were determined at the selected wavelengths in the range of 280 nm - 285 nm (DICLO) and 300 nm - 305 nm (OME). The absorptivity coefficients of these two drugs were determined at selected area under curve (AUC) and the concentrations of both drugs are calculated by using the equations (3) and (4)[23]. The AUC spectrum was obtained for DICLO and OME is shown in Fig.4.
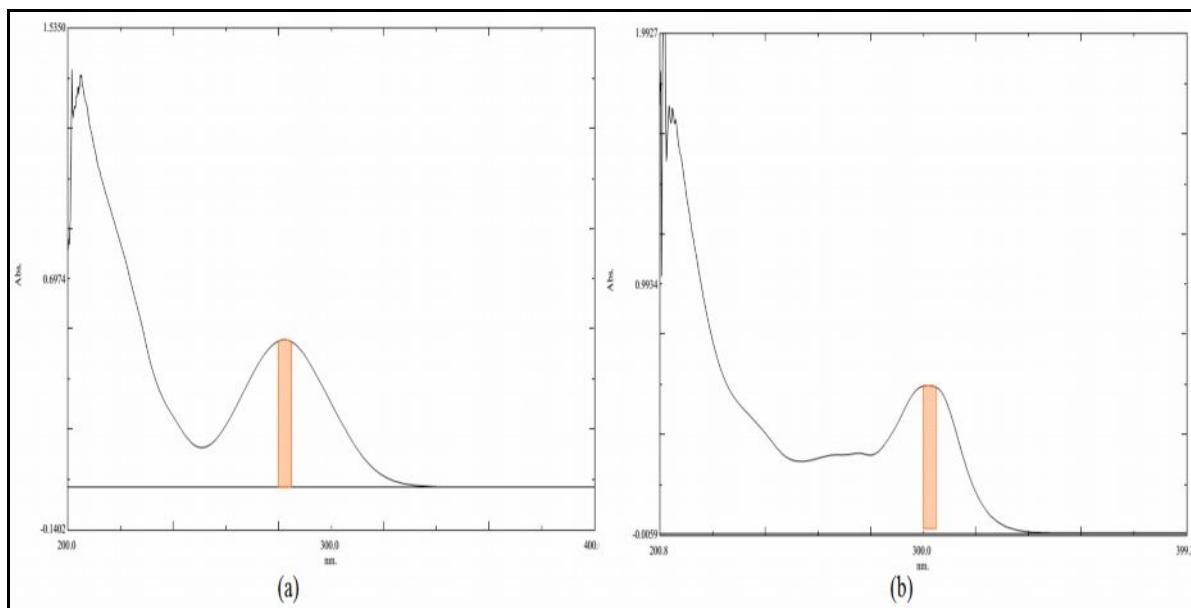

Fig. 4: AUC spectrum of (a) DICLO and (b)OME

$$C_x = \frac{AUC_{(\lambda_3-\lambda_4)} \cdot X_{B(\lambda_1-\lambda_2)} - AUC_{(\lambda_1-\lambda_2)} \cdot X_{B(\lambda_3-\lambda_4)}}{X_{A(\lambda_3-\lambda_4)} \cdot X_{B(\lambda_1-\lambda_2)} - X_{A(\lambda_1-\lambda_2)} \cdot X_{B(\lambda_3-\lambda_4)}} \quad \dotsm \quad (3)$$

$$C_y = \frac{AUC_{(\lambda_1-\lambda_2)} \cdot X_{A(\lambda_3-\lambda_4)} - AUC_{(\lambda_3-\lambda_4)} \cdot X_{A(\lambda_1-\lambda_2)}}{X_{A(\lambda_3-\lambda_4)} \cdot X_{B(\lambda_1-\lambda_2)} - X_{A(\lambda_1-\lambda_2)} \cdot X_{B(\lambda_3-\lambda_4)}} \quad \dotsm \quad (4)$$

Where, C_x and C_y= the concentrations of DICLO and OME respectively in gm/100 ml; $AUC_{(\lambda_1-\lambda_2)}$ and $AUC_{(\lambda_3-\lambda_4)}$ = the area of the mixture; $X_{A(\lambda_1-\lambda_2)}$ and $X_{A(\lambda_3-\lambda_4)}$= the absorptivities of DICLO; $X_{B(\lambda_1-\lambda_2)}$ and $X_{B(\lambda_3-\lambda_4)}$ = the absorptivities of OME.

Preparation of Calibration Curve

Stock solutions of 100 µg/ml of DICLO and 100 µg/ml of OME respectively were prepared in methanol. Appropriate aliquots of DICLO and OME from stock solution further diluted with methanol to obtain 5, 10, 15, 20, 25, 30 µg/ml and 1, 2, 3, 4, 5, 6 µg/ml concentration of DICLO and OME respectively for both the methods. For the method- I, the absorbance of solution was measured at 282.2 nm and 301.8 nm and the calibration curves were plotted for these concentrations against absorbance value obtained at respective λ_{max} and they are shown in Fig. 5 respectively and data are given in Table I. For the method- II, wavelength range for detection of DICLO and OME were selected as 280 nm - 285 nm and 300 mm - 305 nm respectively and the calibration curves were plotted for these concentrations against area under curve (AUC) obtained at respective

wavelength range and they are shown in Fig.6 respectively and data are given in Table II. The optical characteristics and other parameters are shown in Table III.
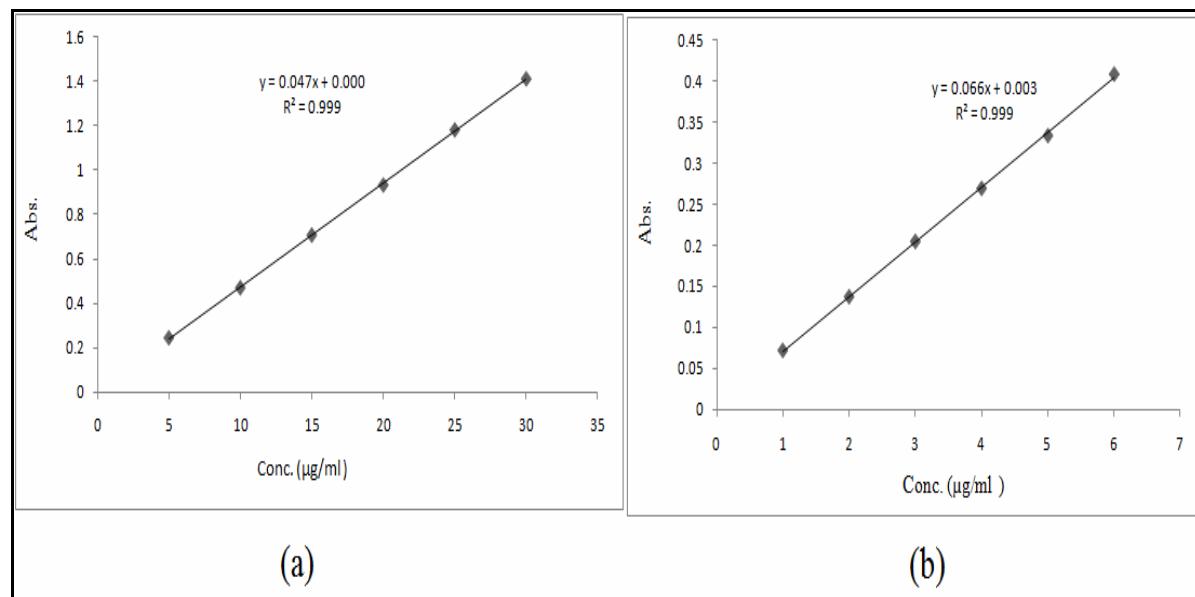

Fig. 5: Calibration curve of (a) DICLO and (b) OME [Method – I]

Fig. 6: Calibration curve of (a) DICLO and (b) OME [Method – II]

Table I: Standard calibration data for DICLO and OME (Method – I)

Sr. No.	DICLO			OME	
	Conc. (µg/ml)	Abs. at 282.2 nm		Conc. (µg/ml)	Abs. at 301.8 nm
01.	5	0.2408		1	0.0718
02.	10	0.4675		2	0.1373
03.	15	0.7060		3	0.2047
04.	20	0.9323		4	0.2694
05.	25	1.1821		5	0.3336
06.	30	1.4131		6	0.4086

Table II: Standard calibration data for DICLO and OME (Method -II)

Sr. No.	DICLO		OME	
	Conc. (µg/ml)	Peak area (280 nm - 285 nm)	Conc. (µg/ml)	Peak area (300 nm - 305 nm)
01.	5	1.1983	1	0.3568
02.	10	2.3268	2	0.6831
03.	15	3.5250	3	1.0195
04.	20	4.6397	4	1.3428
05.	25	5.8870	5	1.6623
06.	30	7.0310	6	2.0360

Table III: Optical characteristics and other parameters

Parameters	Method- I		Method- II	
	DICLO	OME	DICLO	OME
Wavelength range (nm)	282.2 nm	301.8 nm	280 nm – 285 nm	300 nm – 305 nm
Linearity range (µg/ml)	5 - 30 µg/ml	1 – 6 µg/ml	5 - 30 µg/ml	1 – 6 µg/ml
Limit of detection (µg/ml)	3.0895	0.6249	3.0878	0.6176
Limit of quantitation (µg/ml)	9.3624	1.8936	9.3569	1.8716
Regression equation ($y = mx + c$)	y = 0.047x + 0.000	y = 0.066x + 0.003	y = 0.234x + 0.005	y = 0.333x + 0.017
Slope (m)	0.047	0.066	0.234	0.333
Intercept (c)	0.000	0.003	0.005	0.017
Regression coefficient (r^2)	0.999	0.999	0.999	0.999

Analysis of Marketed Formulation

Twenty marketed tablets of DICLO and OME, Gi-Nac were accurately weighed and average weight was calculated, then these tablets were crushed into a fine powder using a Pestle and Mortar. The quantity equivalent to 50 mg of DICLO and 10 mg of OME were weighed and transferred into 50 ml volumetric flask, then volume was made up to the mark with methanol and this mixture was sonicated for about 20 min. After sonication, it was filtered through Whatmann filter paper no. 41 and the filtrate was further diluted with methanol to get a final concentration of 10 µg/ml and 2 µg/ml of DICLO and OME respectively. For method- I, the absorbance of these solutions were measured at 282.2 and 301.8 nm respectively and the concentrations of the two drugs in the sample solutions were determined by using equation (1) and (2). For method- II, wavelength range for detection of DICLO and OME were selected as 280 nm - 285 nm and 300 mm - 305 nm respectively and the concentrations of the two drugs in the sample solutions were determined by using equation (3) and (4). The analysis procedure was repeated six timeswith tablet formulation. The results of analysis of marketed tablet formulation are given in Table IV.

Table IV: Assay of marketed formulation: Gi-Nac (DICLO-50/ OME-10)

Parameters	Method- I		Method- II	
	DICLO	OME	DICLO	OME
Label claim (mg/tab)	50	10	50	10
Amount found (mg/tab)*	49.95	9.92	50.01	9.95
% Label claim*	99.91	99.17	100.02	99.51
S. D.	1.1503	1.5972	0.9658	0.9387
% R. S. D.	1.1513	1.6105	0.9655	0.9434

* Indicates average of six determinations

Validation of Analytical Method

The developed method was validated for following parameters as per ICH guideline[24].

Linearity

The linearity of measurement was evaluated by analyzing different concentrations of the standard solution of DICLO and OME respectively. For both the methods, the Beer-Lambert's law was obeyed in the concentration range 5-30 µg/ml and 1-6 µg/ml for DICLO and OME respectively. The proposed methods were evaluated by its regression coefficient (r^2) value which was calculated by statistical method. For both methods, the regression coefficient (r^2) was found to be 0.999 for DICLO and OME respectively.

Accuracy

To ascertain the accuracy and reliability of the proposed methods, recovery studies were performed at three different levels i.e. 80%, 100% and 120% by standard addition procedure as per ICH guidelines. The recovery studies were carried out by adding a known amount of standard of DICLO and OME to pre-analyzed powder of tablet formulation and each determination was repeated three times at each level. Total amount of drug found and percentage recovery were calculated. Results of recovery studies are reported in Table V and VI for method- I and method- II respectively. Each determination was repeated three times.

Table V: Results of recovery study (Method - I)

Drug	Amount present	Amount added	Amount recovered*	% Recovery*	SD	% RSD
DICLO	50	40	89.46	99.40	0.9644	0.9702
	50	50	98.77	98.77	1.5175	1.5365
	50	60	109.13	99.21	0.9560	0.9636
OME	10	8	17.79	98.85	1..4283	1.4449
	10	10	19.71	98.57	1.1805	1.1976
	10	12	21.66	98.49	0.5786	0.5875

 Indicates average of three determinations

Table VI: Results of recovery study (Method – II)

Drug	Amount present	Amount added	Amount recovered*	% Recovery*	SD	% RSD
DICLO	50	40	89.43	99.37	1.1764	1.1838
	50	50	98.77	98.77	0.4190	0.4243
	50	60	109.80	99.82	0.3878	0.3885
OME	10	8	17.88	99.32	1.1347	1.1425
	10	10	10.02	100.21	1.1804	1.1778
	10	12	21.90	99.54	0.5970	0.5996

Indicates average of three determinations

Precision

The precision of the method was verified by using stock solutions in the ratio of 10:2 containing 10 µg/ml and 2 µg/ml of DICLO and OME respectively.

The repeatability was evaluated by analyzing the six replicates of sample solution of DICLO and OME respectively in both the methods.The intermediate precision of the methods were studied to find out intraday and interday variation in the test method of DICLO and OME respectively. In the intraday variation study, three different sample solutions were prepared and analyzed thrice in a day (morning, afternoon, and evening). In the interday variation study, the sample solutions were prepared and analyzed thrice, for three consecutive days.

Results of repeatability is reported in Table VII for method- I and method- II respectively and results of intermediate precision study is reported in Table VIII and IX.

Table VII: Repeatability data of mixture of standard drugs

Parameters	Method- I			Method- II	
	DICLO	**OME**		**DICLO**	**OME**
% Amount found*	99.20	99.79		99.68	99.61
S.D.	0.7135	1.5295		1.3384	0.8048
% R.S.D.	1.6726	1.5321		1.3428	0.8079

Indicates average of six determinations

Table VIII: Data for intra-day and inter-day precision (Method – I)

Drug	Intra-day precision				Inter-day precision		
	% Found*	**SD**	**% RSD**		**% Found***	**SD**	**% RSD**
DICLO	100.55	1.4032	1.3956		99.21	1.6594	0.1978
OME	98.49	0.4800	0.4874		99.07	1.5179	1.2895
Indicates average of three determinations							

Table IX: Data for intra-day and inter-day precision (Method – II)

Drug		Intra-day precision				Inter-day precision		
		% Found*	**SD**	**% RSD**		**% Found***	**SD**	**% RSD**
DICLO		100.24	0.6385	0.6370		99.74	0.7580	0.7599
OME		99.21	0.5137	0.5179		99.33	1.2149	1.2231
Indicates average of three determinations								

LOD and LOQ

The limit of detection (LOD) is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value. The limit of quantitation (LOQ) is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The several approaches are used to determine the detection and quantitation limits as per ICH guideline. This includes the use of standard deviation of the response and the slope of the calibration curve, visual evaluation, and signal to noise ratio. In the present work, the LOD and LOQ of DICLO and OME were determined by using standard deviation of the response and slope approach and calculated with use of the following equations (5) and (6):

$$LOD = \frac{3.3 \cdot \sigma}{S} \quad \text{...........................} \quad (5)$$

$$LOQ = \frac{10 \cdot \sigma}{S} \quad \text{...........................} \quad (6)$$

Where, σ = the standard deviation of the response; S = the slope of the corresponding calibration curve.

Force Degradation Studies

The ICH guidelines entitled stability testing of new drug substances and products that required stress testing to be carried out to elucidate the inherent stability characteristics of the active substance[25]. The aim of stressed degradation studies was to check the stability of the DICLO and OME on different conditions. The stress conditions applied for degradation study involved acid, base, neutral hydrolysis, oxidative, thermal and photolytic degradation with timely interval of 0.5, 1, 1.5, 2, 3, 4, 6, 8 hrs in acid, base, neutral hydrolysis and oxidative degradation while in thermal and photolytic degradation 0.5, 1, 1.5, 3, 6, 12, 24 hrs and degradation study was stopped after sufficient degradation.

To perform acid hydrolysis, 10 ml of stock solution containing 1 mg/ml of DICLO and OME was refluxed at 60ºC with 10 ml of 0.1 M Hcl for 6 hrs and 0.5 hr respectively; To perform base hydrolysis, 10 ml of stock solution containing 1 mg/ml of DICLO and OME was refluxed at 60ºC with 10 ml of 0.1 M NaOH for 8 hrs and 6 hr respectively; To perform neutral hydrolysis, 10 ml of stock solution containing 1 mg/ml of DICLO and OME was refluxed at 60ºC with 10 ml of distilled water for 8 hrs and 1.5 hr respectively; To perform oxidative degradation, 10 ml of stock solution containing 1 mg/ml of DICLO and OME was refluxed at 60ºC with 10 ml of 3% H_2O_2 for 4 hrs and 1hr respectively; while the thermal and photolytic degradation study was carried out by exposing pure drugs of DICLO and OME to dry heat at 80ºC for 24 hrs in thermal degradation, UV radiations for 24 hrs and 12 hrs respectively in photolytic degradation. These solutions were further diluted with methanol to form10 µg/ml and 2 µg/ml of DICLO and OME respectively.

Finally, change in absorbance (method - I) and peak area (method - II) of samples were compared with standard absorbance and peak area to calculate percent degradation and percent assay.The results of forced degradation study indicates that the both the drugs are sensitive to acid, alkali, neutral hydrolysis, oxidative, thermal and photolytic conditions but OME is more susceptible than DICLO in all these stressed conditions. Summary of the forced degradation of DICLO and OME are given in Table X and XI.

Table X: LOD & LOQ

Parameters		Method- I			Method- II	
		DICLO	**OME**		**DICLO**	**OME**
LOD (µg/ml)		3.0895	0.6249		3.0878	0.6176
LOQ (µg/ml)		9.3624	1.8936		9.3569	1.8716

Table XI: Data of forced degradation study (Method – I)

Sr. No	Condition	% Degradation			% Assay	
		DICLO	**OME**		**DICLO**	**OME**
01.	Acid hydrolysis	7.76	19.97		92.23	80.02
02.	Base hydrolysis	6.26	12.30		93.74	87.70
03.	Neutral hydrolysis	8.55	10.57		91.45	89.43
04.	Oxidative degradation	6.28	18.25		93.72	81.74
05.	Photolytic degradation	9.62	19.81		90.37	80.19
06.	Thermal degradation	11.85	14.28		88.15	85.71

Table XII: Data of forced degradation study (Method – II)

Sr. No	Condition	% Degradation			% Assay	
		DICLO	**OME**		**DICLO**	**OME**
01.	Acid hydrolysis	9.44	21.37		90.56	78.63
02.	Base hydrolysis	6.28	11.51		93.71	88.49
03.	Neutral hydrolysis	8.63	12.36		91.36	87.64
04.	Oxidative degradation	6.47	19.29		93.52	80.71
05.	Photolytic degradation	10.11	13.94		89.89	86.05
06.	Thermal degradation	8.59	16.73		91.41	83.27

Results and Discussion

The validated stability indicating spectrophotometric methods for estimation of DICLO and OME in tablet formulation has been developed using methanol as solvent. DICLO and OME show maximum absorbances at 282.2 nm and 301.8 nm, respectively. For both the methods, DICLO and OME follow Beer's law in the concentration range of 5-30 µg/ml and 1-6 µg/ml (r^2= 0.999). Method-I employs the simultaneous equation method using 282.2 nm and 301.8 nm as two analytical wavelengths, while method-II employs the area under curve method, which uses 280 nm - 285 nm and 300 nm - 305 nm as two analytical wavelength

ranges for estimation of DICLO and OME. The optimized methods showed mean recovery with 99.12 ± 1.1460 and 98.64 ± 1.0625 in method-I and 98.99 ± 0.6610 and 99.69 ± 0.9707 in method-II for DICLO and OME, respectively. Results within the range indicate non-interference with the excipients of formulation.

The mean percent label claims of tablet formulation were found to be 99.91 ± 1.1503 and 99.17 ± 1.5972 in method-I and 100.02 ± 0.9658 and 99.51 ± 0.9387 in method-II for DICLO and OME, respectively. The standard deviation, coefficient of variance and standard error were obtained for DICLO and OME were satisfactorily low. The precision was calculated as repeatability, inter and intraday variations and results was found to be within acceptable limits (i.e. % RSD < 2). The LOD and LOQ values of DICLO and OME were found to be 3.0895 and 0.6249 µg/ml and 9.3624 and 1.8936 µg/ml respectively for method- I, while 3.0878 and 0.6176 µg/ml and 9.3569 and 1.8716 µg/ml respectively for method- II. The forced degradation studies showed DICLO and OME undergoes degradation in acidic, alkaline, neutral, oxidative, photolytic and thermal condition and the percentage degradation was found to be 7.76, 6.26, 8.55, 6.28, 9.62, 11.85 % and 19.98, 12.30, 10.57, 18.25, 19.81, 14.28 % in method-I, 9.44, 6.28, 8.63, 6.47, 10.11, 8.59 % and 21.37, 11.51, 12.36, 19.29, 13.94, 16.73 % in method-II for DICLO and OME respectively.

Conclusion

The two spectrophotometric methods were developed and validated as per ICH guidelines and suitable for simultaneous estimation of diclofenac potassium and omeprazole magnesium in bulk and tablet dosage form. The developed methods are simple, sensitive, accurate, precise and also economic in time as well as cost for the analysis as compared to chromatographic methods. Application of these methods for analysis of diclofenac potassium and omeprazole magnesium tablet formulations was showed that there is no interference of excipients in estimation. The degradation behaviour of diclofenac potassium and omeprazole magnesium was determined by subjecting them in various stress conditions as per ICH guidelines. Hence, these developed methods can be successfully employed in quality control and routine analysis of the diclofenac potassium and omeprazole magnesium containing dosage form.

Acknowledgement

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