



STUDY AND IMPROVEMENT OF METHODS FOR THE DETERMINATION OF DICLOFENAC SODIUM IN PHARMACEUTICAL PREPARATIONS

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ABSTRACT

The different assay methods for the determination of diclofenac sodium in pharmaceutical preparations have been reviewed. The determination of percentage purity of diclofenac sodium has been described by non-aqueous titration method. In this study, diclofenac sodium from commercial pharmaceutical preparations was determined quantitatively employing the modified spectrophotometric and HPLC methods and the methods were compared for their accuracy, specificity and rapidity. The results of both methods were reproducible and within official limits however HPLC method has been proved more authentic as it can be used for the determination of percentage purity of raw material of diclofenac sodium and also in combination with other drugs.

Keywords: Diclofenac sodium, HPLC, Spectroscopy

INTRODUCTION

Diclofenac sodium is phenyl acetic acid derivative. It is non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and anti-pyretic activities in both animals and human beings (Todd and Sorkin, 1988). The apparent volume of distribution is 1.4 L/Kg. It is 99% bound to human serum proteins (Brogden *et al.*, 1980; Sheng *et al.*, 2003). It diffuses into and out of synovial fluid. It is eliminated through urinary and biliary excretion of the glucuronide and the sulphate conjugates of the metabolite (Scholer *et al.*, 1986). It has little anti-microbial activity and is under investigation for the treatment of tuberculosis. Diclofenac sodium is used for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. It is often used to treat chronic pain associated with cancer.

It may prevent the development of Alzheimer disease if given daily in small doses for many years. It also acts as anti-uricosuric agent (Tashima and Rose, 1974; Sallmann, 1975; Willis *et al.*, 1979; Davies and Anderson, 1997; Park, 2007).

Dosage form testing, development of the improved dosage form and determination of drug in biological samples is required in pharmaceutical industry and in research. The aim of the present study was to assess the different methods of quantitative analysis of diclofenac sodium and to find out an accurate and rapid method which could be conveniently used for the determination of percentage purity of pharmaceutical diclofenac sodium as raw material and also in combination with other drugs. Therefore, in the present investigations various in-house and modified chemical and instrumental methods of analysis including non-aqueous titration, spectrophotometry and HPLC have been applied keeping in view that the recommended analytical method must be sensitive and should give reproducible results. (Riess *et al.*, 1978; Mascher, 1989; Landsdorp *et al.*, 1990; Reynolds, 1993; Hinz *et al.*, 2005; British Pharmacopoeia, 2008).

MATERIALS AND METHODS

Materials and chemicals

All the following chemicals used in this study were of

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analytical grade:

Methanol, glacial acetic acid, perchloric acid, acetic anhydride, potassium hydrogen phthalate, crystal violet, NaOH, orthophosphoric acid, and sodium dihydrogen orthophosphate.

Raw material and commercial products

Diclofenac sodium raw material (Batch W-502) was purchased from China National Chemical Import and Export Co-operation Shanghai Branch (China). The commercial preparations of diclofenac sodium used in this study were 50 mg tables of each Artifen®, Dyclo®, and Doloflam®.

Assay of diclofenac sodium raw material by non-aqueous titration

About 250mg of diclofenac sodium, accurately weighed was dissolved in 30 ml of glacial acetic acid, and titrated with 0.1N perchloric acid; the end point was determined by using crystal violet as indicator. The end point was blue to green. Each ml of 0.1N perchloric acid was equivalent to 31.81 mg of diclofenac sodium.

Assay of diclofenac sodium tablets by spectrophotometric methods

Preparation of standard solution

For spectrophotometric method 1, the standard sample was prepared as follow. Diclofenac sodium standard 50 mg was taken and made the volume 100 ml with 0.01N NaOH. Sonicated for 10 minutes, filtered the solution and took 2 ml of filtered solution and made the volume 100 ml with 0.01 N NaOH. For the spectrophotometric method 2, in the above method for standard preparation, 0.01N NaOH Was replaced with methanol.

Sample preparation

For spectrophotometric method 1, the sample was prepared as follow. Twenty tablets of diclofenac sodium were grinded and mixed. The powder sample equivalent to 50 mg of the drug was taken and made the volume to 100 ml with 0.01 N, NaOH and sonicated for 10 minutes. The solution was filtered, took 2 ml of filtered solution and made up the volume up to 100 ml with 0.01 N, NaOH. For assay of drug employing spectrophotometric method 2, same method was used as that employed for the spectrophotometric method 1 except the Solution 0.01 N, NaOH was replaced with methanol.

Spectrophotometric assay procedure

All diclofenac commercial preparations were assayed by two spectrophotometric methods, SM1 and SM2. The absorbance of the samples was measured at 276 nm and at 282nm, for SM1 and SM2, respectively.

Assay of diclofenac sodium tablets by modified B.P HPLC Methods

Mobile phase for modified HPLC methods

For HPLC method 1, a mixture containing 30 volumes of, equal volumes of a 0.1% w/v solution of orthophosphoric acid and a 0.16% w/v solution of sodium dihydrogen orthophosphate (adjusted to pH 2.5), was prepared with 70 volumes of methanol. The mobile phase of the HPLC method 2 consisted of a mixture of 25 volumes of the above solutions, adjusted to pH 2.7, and was mixed with 75 volumes of methanol.

Standard solution

Standard solution contained 0.05% w/v and 0.5% w/v of diclofenac sodium in the respective mobile phase for HPLC method 1 and 2, respectively.

Test solution

For HPLC method 1, ten tablets were finely powdered and shaken with 700 ml of methanol (50%) and sonicated for 30 minutes, added sufficient mobile phase to produce 1000 ml. Centrifuged and filtered the supernatant liquid through a 0.45µm filter. The filtrate was diluted with the mobile phase to produce a solution containing 0.05% w/v of diclofenac sodium.

For HPLC method 2, the test solution was prepared by using above procedure except the use of 750ml of methanol (50%). The mobile phase for this method was used to produce 0.5% w/v diclofenac sodium solution.

HPLC procedure for drug determination

Separately injected equal volumes (20µl) of the standard solution and the test solution into the chromatograph, recorded the chromatograms, and measured the responses for the main peaks.

RESULTS AND DISCUSSION

In the present study, various chemical and instrumental methods of quantitative analysis have been evaluated for their accuracy, suitability and simplicity in routine industrial analysis. Analysis of diclofenac sodium raw material was performed by non-aqueous titration. Contents of diclofenac sodium in each tablet were between 95-105 %.The percent recovery of the drug in assay using non-aqueous titration method is shown in Table I.

A linear relationship between the concentration of raw material and the amount of perchloric acid used proves the validity and accuracy of method. However this method is applicable only for diclofenac sodium raw material and cannot be used for tablets formulations as the excipients may contain some fraction of water especially the film coated tablets.

Table I: Percentage recovery of diclofenac sodium raw material using non-aqueous titration method

Weight of Sample (mg)	Volume of HClO ₄	% Purity
50	1.57 ml	99.88
100	3.15 ml	100.2
150	4.7 ml	99.67
200	6.3 ml	100.2
250	7.8 ml	99.22

The UV/Visible spectrophotometer method 1 was implemented on diclofenac sodium tablets using 0.01 N NaOH as diluting medium. The results (Table II) were within the official limits and reproducible. Table III shows a linear relationship between the absorbance and concentration of anylate. UV/Visible spectrophotometer method 2 employed methanol as the diluting agent. The findings shown in Table IV were also within the official limits and reproducible. However, the drug showed more absorption in methanol than in NaOH. The result showed a linear relationship between absorbance and concentration of anylate (Table 5). When both in-house methods were compared (Table 6) the results were quite satisfactory.

Table II: Percentage recovery of diclofenac sodium by spectroscopic method 1

Sample Tablet	Reference Absorption	Sample Absorption	% Purity
Artifen	0.361	0.368	101.9
Doloflam	0.361	0.360	99.72
Dyclo	0.361	0.356	98.61

Table III: Relationship between concentration and absorbance of diclofenac sodium by spectrophotometric method 1

Weight of Sample (mg)	Concentration (%)	Absorbance
40	80	0.286
45	90	0.315
50	100	0.361
55	110	0.402
60	120	0.445

The different brands of diclofenac sodium tablets were analyzed using HPLC. A modified B.P method was used by taking volume of equal mixtures of methanol and phosphate buffer (70:30), and the concentration used was 0.05 w/v. The retention time of diclofenac sodium reduced to 6.5 min as compared to 9.5 min of B.P method where the ratio of mobile phase was (65:35). The

results, shown in Table VII were within official limits and reproducible. In HPLC method 2, B.P method with altered composition of the mobile phase (75:25) and the concentration of diclofenac sodium as 0.5 w/v was used. The retention time was reduced to 4.5 min. The method also showed reproducible results as shown in Table VIII. In this study it was also observed that when the volume of methanol was increased in the mobile phase the retention time for diclofenac sodium was reduced. The findings of the both HPLC methods 1 and 2 were comparable as shown in Table IX.

A comparison of the spectrophotometric and the modified HPLC B.P methods (Table X) did not show any significant variation and proved the accuracy, validity and specificity of these methods.

Table IV: Percentage recovery of diclofenac sodium by spectrophotometric method 2

Sample Tablet	Reference Absorption	Sample Absorption	% Purity
Artifen	0.453	0.459	101.32
Doloflam	0.453	0.470	103.75
Dyclo	0.453	0.471	103.97

Table V: Relationship between concentration and absorbance of diclofenac sodium by spectrophotometric method 2

Weight of Sample (mg)	Concentration (%)	Absorbance
40	80	0.360
45	90	0.430
50	100	0.448
55	110	0.490
60	120	0.531

Table VI: Comparison of % purity of both spectrophotometric methods

Sample Tablet	% Purity by spectroscopic methods	
	Method 1	Method 2
Artifen	101.9	101.32
Doloflam	99.42	103.75
Dyclo	98.61	103.97

Table VII: Percentage recovery of diclofenac sodium by B.P., HPLC modified method 1

Sample Tablet	Reference Area	Sample Area	% Purity
Artifen	2767499	2782055	100.53
Doloflam	2767499	2741357	99.05
Dyclo	2767499	2812921	101.64

Table VIII: Percentage recovery of diclofenac sodium by B.P., HPLC method 2

Sample Tablet	Reference Area	Sample Area	% Purity
Artifen	15490	15635	100.93
Doloflam	15490	15863	102.40
Dyclo	15490	15616	100.81

Table IX: Comparison of % recovery of both B.P., HPLC methods, 1 and 2.

Sample Tablet	% purity by HPLC methods	
	Method No 1	Method No 2
Artifen	100.53%	100.93%
Doloflam	99.05%	102.40%
Dyclo	101.64%	100.81%

Table X: Comparison of results of spectrophotometric and B.P., HPLC methods

Sample Tablet	Spectrophotometer		HPLC Method	
	Method (% purity)		(% purity)	
	1	2	1	2
Artifen	101.9	101.32	100.53	100.93
Doloflam	99.42	103.75	99.05	102.40
Dyclo	98.61	103.97	101.64	100.81

The present findings suggest that by using either method, the percentage purity of the raw material and the commercial products could be determined, accurately and reproducibly. The excipients in the formulation did not interfere with the findings with HPLC. These findings indicated that the above methods are efficient and reliable analytical techniques for routine quality control analysis of raw material and drugs.

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