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Spectrophotometric, chromatographic and spectrofluorometric methods for the determination of diclofenac: A review

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ABSTRACT

Diclofenac is a Non-steroidal anti-inflammatory drugs (NSAIDs) are the group most widely used in human and veterinary medicine, since it is available without prescription for treatment of fever and minor pain. The clinical and pharmaceutical analysis of these drugs requires effective analytical procedures for quality control and pharmacodynamics and pharmacokinetic studies. An extensive survey of the literature published in various analytical and pharmaceutical chemistry related journals has been conducted and the instrumental analytical methods which were developed and used for determination of diclofenac (an aryl acetic acid derivative) in bulk drugs, formulations and biological fluids have been reviewed. This review covers the time period from 1989 to 2010 during which 43 methods including spectroscopic, chromatographic titrimetric methods were reported. The application of these methods for the determination of diclofenac in pharmaceutical formulations and biological samples has also been discussed.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of drugs of diverse chemical composition and different therapeutic potentials having a minimum of three common features: identical basic pharmacological properties, similar basic mechanism of action as well as similar adverse effects. Moreover, all drugs in this group exhibit acidic character. Most NSAIDs are weak acids, with a pKavalues in the range of 3.0–5.0 (acids of medium strength)[1].

Diclofenac is easily available and effective and thus are extensively used by patients. The growing demand for this agents calls for higher level of quality control of these its preparations, so that they are in the highest possible degree free from any impurities that may come from the production process, as well as from decomposition products of active or auxiliary substances. Therefore, it seems appropriate to develop new analytical methods regarding their qualitative and quantitative analysis[2].

Introduction of new methods, enabling carrying out determinations with maximum accuracy, contributes to increased interest in analytical methods as such. They should enable to

simultaneously determine the individual components in multicomponent preparations and in biological material.Development and validation of analytical methods are of basic importance to optimize the analysis of drugs in the pharmaceutical industry and to guarantee quality of the commercialized product**[3]**. The present review comprises references covering the period from 1989 to 2011 that have been used for the determination of diclofenac in individual dosage form or in the combination with other drugs.

Various analytical methods developed for diclofenac

➢ An accurate and precise spectrophotometric method was described for the determination of diclofenac sodium in bulk samples and pharmaceutical preparations. With *p-N*, *N*-dimethylphenylenediamine as solvent and maximum absorbance at 670nm. The reaction is sensitive enough to permit the determination of 2.0–24μg/ml[4].

➢ A spectrophotometric method was described for the determination of diclofenac sodium in bulk samples and pharmaceutical preparations. The method is based on the reaction of diclofenac sodium with pN,N-dimethylphenylenediamine in the presence of Sor Cr(VI) whereby an intensely coloured product having maximum absorbance at 670 nm is developed. The reaction is sensitive enough to permit the determination of 2.0–24 μg /ml [5].

➢ The determination ofdiclofenac was done by two methods. In the first method diclofenac reduces iron(III) to iron(II) having a maximum absorbance at 520nm. The reaction obeys Beer's law for concentrations of 10–80μg/ml. In the second method, diclofenac is treated with methylene blue in the presence of phosphate buffer (pH6.8) and the complex is extracted with chloroform. The complex has a maximum absorbance at 640nm and linearity was in the range 5–40μg/ml[6].

➢ Diclofenac sodium, famotidine andketorolac tromethamine were determined by FIA with spectrophotometric detection. The sample solution 5.0–50 μg/ml of diclofenac sodium, in methanol was injected into a flow system containing 0.01% (w/v) of 2,4,dichloro-6-nitrophenol (DCNP) in methanol. The colour produced due to the formation of a charge transfer complex was measured with a spectrophotometric detector set at 450 nm. A sampling rate of 40 per hour was achieved with high reproducibility of measurements RSD 6 1.6% [7].

➢ A procedure for simultaneousestimation of diclofenac sodium, chlorzoxazone andparacetamol in three component tablet formulations has beendeveloped. The method is based on the native ultravioletabsorbance maxima of the three drugs in 0.02 mol/ Lsodiumhydroxide. Diclofenac sodium has absorbance maxima at276 nm[8].

➢ A validated method has been developed for estimation of diclofenac in bulk and formulation. With 0.5%w/v sodium hydroxide as solvent and maximum absorbance at 450nm. Method obeys Beer's law in the concentration range of 2.0–12μg/ml [9].

➢ The methods employ first derivative ultraviolet spectrophotometry, simultaneous equations and the program in the multicomponent mode of analysis of the instrument used, for the simultaneous estimation of the two drugs. In 0.02 mol / L sodium hydroxide, diclofenac sodium has maxima at 276 nm [10].

➢ A new accurate, precise and reproducible method has been devised for the determination of diclofenac sodium in bulk and in pharmaceutical preparations using Eu(III) ions as the fluorescent probe. In aqueous solution the measurement was performed at 616nm and 592nm. A linear relationship between bound Eu(III) and the concentration of diclofenac sodium was found from 10- 200µg/ml[11].

➢ A new accurate and precise spectrophotometric method in which diclofenac sodium is analyzed and determined as it is Fe(III) complex, with chloroform as solvent and maximum absorbance at 481nm. Beer's law was found up to 1.57–15.7 Mmol/L [12].

➢ A colorimetric method was developed for the quantitative determination of diclofenac sodium in pure form and in pharmaceutical preparations. It was based on the interaction of the secondary aromatic amine with *p*-dimethylaminocinnamaldehyde in acidified absolute methanol medium to form very stable red products [λ_{max} at 538 nm]. Beer's law was obeyed over the range of 10–80µg/ml[13].

➢ The spectrofluorometric determination of diclofenac sodium in pharmaceutical tablets and ointments was described. It involves excitation at 287 nm of an acid solution (HCl 0.01 M) of the drug and measurement of the fluorescence intensity at 362 nm. The linear range is 0.2–5.0 µg/ml[14].

➢ Two economic and reproducible methods for the determination of the diclofenac salts [sodium or diethylammonium] in three pharmaceutical formulations (tablets, suppositories and gel) were presented. In the first, diclofenac salt is determined both by measuring the absorbance of the solutions at a fixed wavelength (λ =276nm) and using a multiwavelength computational program to process the spectrophotometric data in a selected range (λ 230–340 nm). In this case, the analysis is performed measuring the peak-to-peak amplitude in the first-derivative UV spectrum (^{1}D 261- 296). In the second method, diclofenac is precipitated in acid medium and determined by the analysis of the endothermic peak (t_p = 182°C) in the DSC curve obtained in nitrogen atmosphere[15].

➢ A accurate, economic and reproducible second derivative spectrophotometric method has been developed for the determination of the degradation products of diclofenac sodium from gel-ointment. The amplitudes in the second derivative spectra at 260 and 265 nm were selected to determine diclofenac sodium in 0.1M NaOH solution[16].

➢ A rapid, accurate and reproducible spectrophotometric method for the determination ofdiclofenac sodium was developed. In 3.0×10^{-2} mol/L H_2SO_4 medium. Using the peak height as a quantitative parameterdiclofenac was determined at 580 nm over the range 0.2–8.0µg/ml[17].

➢ A rapid, accurate and reproducible flourimetric and spectrophotometric methods was proposed for the determination of diclofenac in bulk samples and pharmaceuticals with sodium hydroxides solvent and measured at 455nm. The calibration graphs are linear over 0.20–20 µg/ml[18].

➢ A accurate and reproducible method was developed for the determination of diclofenac in human serum by HPTLC. Standard diclofenac sodium was spotted on silica gel 60 F_{254} precoated plates, which were developed using the mobile phase toluene: acetone: glacial acetic acid (80:30:1v/v/v). Densitometric analysis of diclofenac sodium was carried out at 280nm

with diclofenac being detected at an R_f of 0.58. The extraction efficiency was found to range from 76 to 80%. The calibration curve of diclofenac sodium in serum was found to be linear in the range of 200–800ng[19].

➢ A sensitive, accurate and reproducible method was developed for the determination of synthetic precursors which could be remained as impurities in raw drug materials. HPLC was used to detect and separate diclofenac from its usual precursors. The chromatographic conditions were as follows: column, C_{18}, mobile phase, methanol: water (55:45), flow rate 1ml/min, wavelength of detection 254nm[20].

➢ Two modified methods were developed for assaying sodium diclofenac by GLC and HPLC. GLC was equipped with flame ionization detector. SE-30/chrom W-HP (80-100 mesh) was used as a column in GC. For reversed phase HPLC, the mobile phase was methanol: water (55:45). The separation was performed on an analytical 300×3.9 mm internal diameter µ-bond pack phenyl column using UV detection at 274 nm with flow rate of 1.0ml/min. O-(4-chlorobenzoyl) benzoic acid and mefenamic acid were used as internal standard for GLC and HPLC method respectively[21].

➢ A economic and reproducible spectrophotometric method was developed for the determination of diclofenac sodium in pure form and in pharmaceutical formulations was developed. Measured at 510 nm against a reagent blank of ortho- phenanthroline pH 4.4. Beer's law is valid within a concentration range of 1.0–32 µg/ml[22].

➢ An effective method was developed for the determination of sodium or potassium diclofenac is proposed in its pure form and in their pharmaceutical preparations. The method is based on the reaction between diclofenac and tetrachloro-*p*-benzoquinone (*p*-chloranil), in methanol medium. This reaction was accelerated by irradiating of reactional mixture with microwave energy (1100 W) during 27 s, producing a charge transfer complex with a maximum absorption at 535nm with methanol: water 60:40v/v. Beer's law is obeyed in a concentration range from of 1.25×10^{-4} to 2.00×10^{-3} mol /L [23].

➢ A economic, accurate and reproducible spectrophotometric method was proposed for determination of sodium diclofenac in pharmaceutical preparations based on its reaction with concentrated nitric acid (63%w/v). The reaction product is a yellowish compound with maximum absorbance at 380 nm. The corresponding calibration curve is linear over the range of 1.0–30 µg/ml [24].

➢ A modified procedure was developed for the visible spectrophotometric determination of diclofenac in pharmaceutical preparations using aqueous solution of copper (II) as reagent. Concentration was measured at 680 nm. The beer's law was obeyed between 1mg/ml to 25mg/ml [25].

➢ A method was developed for the evaluation of diclofenac sodium in tablet, injectable and gel type formulations. The diclofenac sodium was analyzed by reverse phase column (SGX C_{18} (150mm × 3mm internal diameter 7µm)) using mobile phase methanol and phosphate buffer (pH 3.2) and detection was done at 282 nm[26].

➢ A colorimetric assay method for diclofenac sodium tablets was developed. The method was based on a simple aromatic ring derivatization technique using newly developed 4-carboxyl-2, 6-dinitrobenzenediazonium ion (CDNBD) as chromogenic derivatizing reagent with subsequent

formation of an azo dye. The diazo coupling reaction was carried out between CDNBD and diclofenac. The UV absorption spectrum was recorded and absorption λmax at 470nm by using glacial acetic acid as solvent. The assays were linear over 1.35 -10.8µg/ml of diclofenac[27].

➢ A rapid, economic and accurate spectrofluorometric method was developed for diclofenac sodium. Method for the micro determination was based on its reaction with cerium(IV) in an acidic solution and measurement of the fluorescence of the Ce(III) ions produced. The aborbance was measured at 356nm and 250nm with double distilled water as solvent. The range of application is 124.3–600 ng/ml and the limit of detection is 72.7ng/ml[28].

➢ A sensitive, stable and reproducible high performance thin layer chromatographic method was developed for the determination of diclofenac sodium in pharmaceutical formulations. The drug was extracted from the sample then various aliquots of this solution were spotted automatically by means of Camag Linomat IV on a silica gel 60 F_{254} aluminium plate, using a mixture of toluene : ethyl acetate : glacial acetic acid (60:40:1, v/v/v) as mobile phase. The spot areas were quantified by densitometry at 282 nm. Linear calibration curve was obtained over the range 5-80 µg/ml (r^2 = 0.9993)[29].

➢ A reversed-phase high-performance liquid chromatographic method with electrochemical detection was developed for the quantitative determination of diclofenac potassium in plasma. Naproxen was used as the internal standard. Chromatographic separation was performed on a C_{18} column with methanol: water (68:32 v/v). The flow rate for diclofenac was 1.0 ml/min with detection wavelength of 275 nm. Linearity of the method was confirmed in the range 5-2000ng/ml[30].

➢ A rapid, reproducible and precise method was developed for determination of diclofenac released from suppositories using UV spectrophotometry and HPLC. The solvent used were methanol and phosphate buffer pH7.3 for UV and HPLC. 275nm was used wavelength of detection for both the methods with a flow rate of 1.5 min/min in HPLC detection [31].

➢ A rapid, accurate and reproducible HPLC method to quantitate plasma levels of diclofenac sodium in human plasma was developed. The internal standard was naproxen analyzed on µ-bond pack C_{18} (150×4.6mm) in acetonitrile: deionized water: orthophosphoric acid 45:54.5:0.5 (pH3.5) at 276nm and linearity of 0.005-4µg/ml [32].

➢ Developed a simple accurate and precise reverse phase HPLC method for simultaneous estimation of diclofenac and rabeprazole. The method was developed using HQSiC_{18} column 250×4.6mm internal diameter consisting solvent methanol: water in 80:20 v/v ratio at a flow rate of 1.25ml/min and detection at 284.0 nm[33].

➢ A kinetic method was developed for the determination of micro quantities of diclofenac sodium. The method was based on a ligand-exchange reaction. The reaction was followed spectrophotometrically by monitoring the rate of appearance of the cobalt diclofenac complex at 376 nm in acetic acid as solvent[34].

➢ A rapid, economic, accurate and reproducible new spectrophotometric method has been developed for the determination of diclofenac sodium in pharmaceutical preparations. This method is based on the reaction of diclofenac sodium with reagent and detection of the produced coloured complex. This ion associate complex was detected and extracted with toluene and an

absorption maximum at 566.2 nm against a blank reagent. The calibration graph was linear from 0.9 to 11 µg/ml of diclofenac[35].

➢ An extractive-spectrophotometric method for the preconcentration and determination of diclofenac was developed. In a strong nitric acid medium, diclofenac produced a yellowish compound in a water/tetrahydrofuran/perfluorooctanoic acid homogeneous phase that could be extracted into a sediment micro droplet. The concentration of the extracted coloured compound in the micro droplet was determined by measuring its absorbance at 376 nm. The absorbance of diclofenac solutions in water: methanol 50:50v/v obeyed Beer's law, over the range of 1.0–30 and 0.5–40 µg/ml[36].

➢ A flow-through sensor for the determination of diclofenac sodium was developed, based on retention of the analyte on a Sephadex QAE A-25 anion-exchange resin packed in a flow-cell of 1.0mm of optical path length, and monitoring of its intrinsic absorbance by UV-spectrophotometry at 281nm in 0.1M NaOH as solvent[37].

➢ A simple, accurate, precise and reproducible method for simultaneous estimation of rabeprazole and diclofenac was done by simultaneous equation method and graphical absorbance method using methanol: 0.1M NaOH (70/30v/v). The λmax of rabeprazole and diclofenac found to be 294.0nm and 281.2nm[38].

➢ A accurate, sensitive and reproducible HPLC assay was developed for diclofenac measurement in human plasma. Naproxen as internal standard and diclofenac eluted at 3.9 and 8.3 minutes, respectively, on a Nova-Pak C_{18} 4µm cartridge, and were detected using a 996 photodiode array detector set at 276nm. The mobile phase, 0.2% glacial acetic acid (pH 3.0): acetonitrile (51:49, v/v), was delivered at 2.0ml/min. Calibration curves were linear in the range 0.02–1.92 µg/ml[39].

➢ A simple, accurate and reproducible method for simultaneous chromatographic estimation of diclofenac and rabeprazole was developed in tablet formulation by using phenomenex luna (C_{18}) column with the help of mobile phase containing potassium dihydrogen phosphate buffer (pH 7.4 adjusted with 1M sodium hydroxide) and acetonitrile in 60:40 ratio by keeping the flow rate of 1.0 ml/min and detection wavelength 280.0 nm. Linearity was found between concentration ranges of 10-50 µm/ ml for both of drugs [40].

➢ A rapid, accurate, precise and reproducible UV spectrophotometric method was developed for determination of diclofenac sodium in human stratum conium by skin stripping method using marketed diclofenac sodium topical formulations. Diclofenac exhibited distinct λmax in methanol at 285nm with linear relationship (r^2=0.9787) in between 5-25µg/ml [41].

➢ A accurate, rapid and precise flow extraction spectrophotometric method was developed for determination of trace amounts of diclofenac sodium. Detection performed at 282 nm against phosphate buffer pH 6.4 as blank. The method was linear in the range of 3.0–80 µg/ml [42].

➢ Six simple, accurate, precise and reproducible methods for simultaneous estimation of rabeprazole and diclofenac were performed in capsule dosage form. The concentration of individual compound was determined by simultaneous equation method, absorbance ratio method, dual wave length method, area under curve method, first order derivative spectrophotometry method and multicomponent method. The λmax of rabeprazole sodium and diclofenac sodium was found to be 292nm and 276nm in 0.01N NaOH solution. Rabeprazole and

diclofenac obeys the Beer's law in concentration range of 5-30 µg/ml and 5-35 µg/ml respectively [43].

➢ A simple, sensitive, accurate and precise RP-HPLC method was developed for the simultaneous estimation of rabeprazole sodium and diclofenac sodium in tablet dosage form. The method was developed by using a HiQ SiL C18 (250 mm×4.6mm internal diameter) column with a mobile phase consisting of water: methanol: acetonitrile (20:40:40 v/v), at a flow rate of 1.2 ml/ min and detection was carried out at 284 nm[44].

➢ A stable, simple, rapid and precise RP-HPLC method for simultaneous analysis of diclofenac sodium and rabeprazole sodium was developed. Separation was carried out using C_8 column with triethyl amine buffer (pH 5): acetonitrile (50:50 v/v) as mobile phase with flow rate 2ml/min. The detection was carried out at 284nm [45].

➢ A stability indicating reverse phase high performance liquid chromatography for the simultaneous determination of rabeprazole and diclofenac was developed in solid dosage form. The method was based on HPLC separation of both drugs in reverse phase mode using Phenomenox C_{18} column with Waters HPLC system by using mobile phase composition of acetonitrile and 50mM ammonium acetate buffer (pH 3.6) (60:40 v/v) at flow rate 1ml/min. Detection wavelength used at 254 nm. Loratidine was used as internal standard. Linearity was obtained in the concentration range of 1.0-3.2 µg/ml for rabeprazole and 6.0-16.0 µg/ml diclofenac [46].

➢ A simple, rapid, economic and precise UV spectroscopic method for simultaneous analysis of diclofenac sodium and rabeprazole sodium was developed. Analysis was carried out using water: methanol (80:20 v/v) as mobile phase. The detection was carried out at 284nm for rabeprazole and at 277.5nm for diclofenac sodium, respective absorption maximum of each other [47].

Applications

The above mentioned methods have applications in the determination of the diclofenac in various pharmaceutical formulationslike tablets, injections, capsules. These methods give results which are comparablewith the official pharmacopoeial methods used for thedetermination of diclofenac;hence, these methods can be successfully used for routine analysisand quality control of diclofenac. The methods have been used for the quantitative determination of the drug in pure form and commercial preparations. The commonly occurring excipients do not interfere in the determination of the drug in the case of commercial samples. The methods have been validated and results have been found to be accurate, precise and comparable to the official methods.

CONCLUSION

This review presents spectrophotometric, chromatographic and spectrofluorometricas well as fluorometricanalytical methods applied for the determination of confirmation of diclofenac. Despite wide availability of the equipment, their use is however still limited, especially with a complicated matrix. The ultimate goal is to obtain results with more and more precision and accuracy and at increasingly lower concentration levels of the substances being determined. Comparing validation parameters of already researched methods, it can be concluded which one of them is more sensitive (low LOD and LOQ values), accurate (precision and recovery) and allows markings in a broad linearity scope.

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