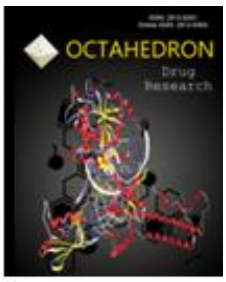
Octahedron Drug Research 3 (2023) 12-17 ISSN: 2812-6351

Online ISSN: 2812-636X

OCTAHEDRON
Drug Research
Vol. 3

Review Article



Spectrophotometric Investigations of Some Non-steroidal anti-inflammatory drugs (NSAIDs): A Brief Review

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ARTICLE INFO

Article history:
Received 5 May 2023
Received in revised form
26 May 2023
Accepted 26 May 2023
Available online 26 May 2023

Keywords: NSAIDs; Spectrophotometric Analysis; Aspirin; Ibuprofen; Diclofenac; Indomethacin

ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs), are one of the most commonly used drugs around the world for the treatment of pain, fever, and inflammation. They are a group of synthetic drugs that act as cyclooxygenase (COX) enzyme inhibitors, so inhibit the formation of PGs which are important mediators in pain & inflammation. According to their chemical structure, they are classified into groups: acetylated salicylates (aspirin), non-acetylated salicylates, propionic acids (naproxen, ibuprofen, acetic acids (diclofenac, indomethacin), enolic acids (meloxicam, piroxicam) anthranilic acids the polyketide class of natural products. Different qualitative and quantitative methods have been reported for the determination of NSAIDs such as chromatographic methods, flow injection methods, spectrofluorometric methods, spectrophotometric methods, and capillary electrophoresis methods. It was found that spectrophotometric methods are sensitive and low-cost for the analysis of different NSAIDs in pharmaceutical formulations as well as biological samples. This article reviews different spectrophotometric methods effective for the determination of some NSAIDs like aspirin, ibuprofen, diclofenac, and indomethacin.

1. Introduction

When the human body is exposed to damaging agents, inflammation occurs to protect the body by inactivation or removal of these agents and promoting healing. The signs of inflammation in Latin are Dolor (pain), Calor (heat), Rubor (redness), Tumor (swelling), and Functio laesa

(Loss of function) [1]. Mediators of inflammation include Prostaglandins, Bradykinin, Serotonin, Histamine, Interleukins, Platelet-activating factor etc. Pain Is a hard sensory and bad emotional experience associated with actual and potential tissue damage [2]. It is one of the human body's defense mechanisms that indicates the person is exposed to the problem. Analgesics are used for relieving pain, inflammation, and fever. Analgesics are classified into opioid analgesics -narcotics like morphine and non-opioid analgesics – NSAIDS like aspirin. Here, this article talks about the non-steroidal anti-inflammatory drugs NSAIDs like aspirin, ibuprofen, diclofenac, and Indomethacin. They are used as antiplatelet, analgesic, anti-inflammatory, and antipyretic. Aspirin was the parent one in this group and was produced in 1897 by Felix Hoffman of the Bayer company [3]. Later, phenylbutazone and indomethacin were introduced. All NSAIDs inhibit prostaglandin PG synthesis. Prostaglandins, prostacyclin (PGI2), and thromboxane A2 (TXA2) are produced from arachidonic acid. Cyclooxygenase (COX) is the enzyme responsible for prostaglandins synthesis in the human body. There are two forms of COX, constitutive COX-1, and inducible COX-2. COX-1 is responsible for housekeeping function while COX-2 is generated by cytokines and is responsible for PG synthesis during inflammation [4]. Most NSAIDs inhibit COX-1 and COX-2 nonselective. Aspirin acetylated COX irreversibly while other NSAIDs are competitive reversible inhibitors.

1.1 Classification of NSAIDs drugs

According to chemical structure, NSAIDs are classified into Salicylates: aspirin, Sodium salicylate & diflunisal. Propionic acid derivatives: ibuprofen, ketoprofen, naproxen. Aryl acetic acid derivatives: diclofenac, ketorolac. Indole derivatives: indomethacin, sulindac. Alkanones: Nabumetone. Oxicams: piroxicam, tenoxicam. Anthranilic acid derivatives (fenamates): mefenamic acid and flufenamic acid. Pyrazolone derivatives: phenylbutazone, oxyphenbutazone, azapropazone (apazone) & dipyrone (novalgin). Aniline derivatives (analgesic only): paracetamol.

Aspirin (Fig 1A) is commonly known as acetylsalicylic acid (ASA). Aspirin is very effective as an antiplatelet agent and so it is used in cases of blood clots and heart attacks. Aspirin is a white, crystalline, mildly acidic chemical with a melting point of 136 °C (277 °F) and a boiling temperature of 140 °C (284 °F), and PKa is 3.5. It is available in the form of Capsule, Extended Release, 24 HR Tablet, Chewable, Capsule, Liquid Filled Tablet, and Enteric Coated Tablet. Aspirin is slightly soluble in water and slightly soluble in organic solvents such as ethanol, DMSO, and dimethylformamide [5].

Ibuprofen (Fig 1B) is 2-(4-isobutyl phenyl) propionic acid It was developed in 1960 and used as a safer alternative to aspirin. It was used in the treatment of rheumatoid arthritis in the UK in 1969 and the USA in 1974 [6]. Ibuprofen has two enantiomers, the R-enantiomer and S-enantiomer. I*n vivo, the* alpha-methyl acyl-CoA converts the R-enantiomer into the biological active S-enantiomer [7]. For the maximum management of mild to moderate pain related to dysmenorrhea, headache, migraine, postoperative dental pain, spondylitis, osteoarthritis, rheumatoid arthritis, and soft tissue disorder, ibuprofen is administrated with its enantiomer dexibuprofen in a racemic mix. Ibuprofen acts as an antiplatelet agent by inhibiting thromboxane synthesis. It prolongs gestation and labor by inhibiting the synthesis of prostaglandin. It is available in the form of tablets, oral suspensions, gel, or lotion. Ibuprofen is a colorless crystalline solid with a melting point of 217–220°C and a dissociation constant pKa = 8.99. It is soluble in acetone and slightly soluble in ethanol, methanol, and acetonitrile [5].

Diclofenac, (Fig 1C) is 2-[2-(2,6-dichloroanilino)phenyl]acetic acid, used to treat mild to moderate pain, or signs and symptoms of osteoarthritis or rheumatoid arthritis. Diclofenac is important to manage the pain in ankylosing spondylitis and menstrual cramps [8]. Ibuprofen is administered as a capsule, tablet, enteric Coated, tablet, extended-release tablet, powder for solution, capsule, and liquid filled. Should avoid the administration of diclofenac in the long term due to increasing the risk of fatal heart attack or stroke. Diclofenac sodium is an odorless, white to off-white crystalline, slightly hygroscopic powder. Diclofenac (sodium salt) is soluble in organic solvents such as ethanol, DMSO, and dimethylformamide [5]. Diclofenac is a weak

acid, poorly soluble in water in its un-ionized form, and mainly formulated as a salt.
Indomethacin, (Fig 1D), 2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid is a synthetic nonsteroidal indole derivative with anti-inflammatory activity and chemo-preventive properties. It is effective in the cases of multi-drug resistant tumors by inhibiting the expression of multidrug-resistant protein type 1 [9]. Indomethacin can cause cell apoptosis (NCI04) by inhibiting the migration and proliferation of cancer cells [10]. It is a potent nonsteroidal anti-inflammatory drug (NSAID) typically used for chronic inflammatory arthritis. It is administrated as a capsule, suspension, capsule, and extended-release tablet. Indomethacin is a white to yellow crystalline powder and its pKa is 4.5. It is practically insoluble in water and sparingly soluble in alcohol [5]. Indomethacin is stable in neutral or slightly acidic media and decomposes in strong alkalis.

1.2. Pharmacology of NSAIDs

Prostaglandins are the main mediators of pain, inflammation, and fever in the human body, and play an important role in protecting the stomach from ulcers. They are formed during the metabolism of arachidonic acid by the cyclo-oxygenase (COX-1 and COX-2). Thromboxane causes platelet aggregation, and prostacyclin produces vasodilation. The mechanism of action NSAIDs is based on inhibiting cyclo-oxygenase (COX-1 and COX-2) and this results in preventing the formation of prostaglandins, thromboxane, and prostacyclin. NSAIDs make irreversible inhibition to cyclo-oxygenase enzymes, except aspirin acetylated COX-1 irreversibly [11].

Therapeutic Applications of NSAIDs

NSAIDs are analgesics, antipyretics, and anti-inflammatories, so are used to relieve pain, and inflammation in the following cases: arthritis, backache, cold or flu, headaches, period pain, joint or bone injuries, sprains, and strains, muscle or joint complaints and toothache [12]. Aspirin is used in the long term to prevent blood clots. The main side effects of NSAIDS are ***erosions, ulcerations*** in GIT due to inhibition of the formation of cytoprotective PGE_2, PGI_2, ***increased bleeding*** due to inhibition of thrombocytes aggregation, ***renal failure*** due to inhibition PGE_2, PGI_2 that regulates renal functions, ***asthma attack*** due to - LT production induces in predisposed people bronchoconstriction [13].

1.3. Analysis of NSAIDs

NSAIDs are extremely important agents in the management of pain, inflammation, and fever, so they have been analyzed by different techniques. Among these different techniques, spectrophotometric methods are considered very advantageous due to low cost, rapid, simple and validity. Other methods that have been reported to analyze NSAIDs are high-performance liquid chromatography, spectrofluorometer, voltammetry, and capillary electrophoresis.

1.4. Spectrophotometric Methods for the Analysis of NSAIDs

Ibrahim B. et al [14] reported a spectrophotometric method for the determination of aspirin in authentic powder and its tablets. Potassium permanganate forms a stable complex with aspirin measured at 350 nm. The linearity of the method was found to be ranged between 1.0 to 44.0 mg/ml of aspirin with molar absorptivity 8.815 × 10 3 L mol^{-1} cm-1 and a detection limit 0.8 mg/ml. The method was used for the analysis of aspirin in drug formulations in different proprietary tablets.
Manal E. et al [15] developed a spectrophotometric method for the determination of aspirin and omeprazole in the presence of salicylic acid as a degradation product. Different univariate/multivariate post-processing algorithms are used to analyze ASP, OMP, and SAL quantitatively, without any prior separation. The univariate/multivariate algorithms include double divisor ratio difference and double divisor mean centering as the univariate approaches while the multivariate methods include principal component regression (PCR) and partial least squares (PLS) models. Mohamed et al [16] developed a spectrophotometric method for the determination of Ibuprofen (IBU) and Lornoxicam (LOR). Copper tetramine and copper sulfate react with Ibuprofen and Lornoxicam and form stable complexes measured at 265 and 260 nm respectively. The

method was linear from 2.063 to 103.14 and 3.72 to 74.36 μg mL^{-1} of recovery values 99.95 to 100.40 and 99.98 to 100.00 %, for IBU and LOR respectively.

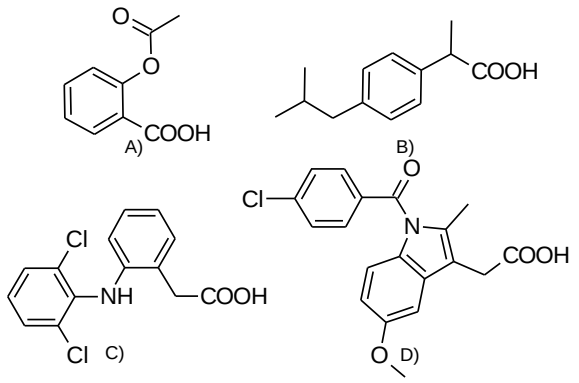

Figure 1. The chemical structure of A) aspirin B) ibuprofen C) diclofenac D) indomethacin.

Jalbani N. et al [17] proposed gas chromatographic and spectrophotometric methods for the determination of diclofenac Sodium, ibuprofen, and mefenamic acid in urine and blood samples. For the spectrophotometric method, the absorbance was measured against methanol at a wavelength of 200-500 nm. The linearity range was 2-10 mg./mL with limits of detection of 0.4-0.6 mg./mL of each drug. Souza R. et al [18] reported a spectrophotometric method for the determination of diclofenac in pharmaceutical preparations. The method is based on using the aqueous solution of copper (II). A green color com plex is formed between copper(II) and diclofenac with maximum light absorption at 680 nm.
The optimal pH of the solution was 5.3. The solution was 50.0 mg mL^{-1} (copper (II) acetate in 0.01 mol L1 acetic acid solut ion). The mixture was extracted three times with chloroform using a total volume 5 mL. The linear range was from 1.0 to 25.0 mg mL 1 in the working solution. Matin A. et al [19] proposed a simple spectrophotometric method for the determination of sodium diclofenac in pharmaceutical formulations. The method is 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 method was linear over the range of 1-30 mg l(-1), while the limit of detection is 0.46 mg l(-1).

Nagaraja P et al [20] proposed a sensitive spectrophotometric method for the determination of indomethacin in authentic powder and capsules. The coupling reaction of hydrolyzed INM with diazotized p-phenylenediamine dihydrochloride (PPDD) gives a red product measured at 510 nm. The reaction needs an acidic medium (sulfuric acid). The method was valid and linear in the range of 0.2-10 mg/mL. Maheshwari R et al [21] reported a spectrophotometric estimation of indomethacin capsules with niacinamide as a hydrotropic solubilizing agent. In the present investigation, a hydrotropic solution of 2 M niacinamide was employed as the solubilizing agent to solubilize the poorly water-soluble drug, indomethacin, from the capsule dosage form for spectrophotometric determination in the ultraviolet region. The hydrotropic agent used did not interfere with the spectrophotometric analysis. In preliminary solubility studies, it was found that there was more than a fivefold enhancement in the aqueous solubility of indomethacin (poorly water-soluble drug) in 2M niacinamide solution as compared to its aqueous solubility at 28 ± 1°C. Noreen F et al [22] developed a spectrophotometric method for the determination of indomethacin using the partial least square method. The method used ammonium oxalate as the reagent that reacts with the drug and gives violet colored product measured at 578nm. The reaction needs concentrated sulfuric acid and heating for 17 min at 80 °C. The reaction is selective for indomethacin with a detection limit of 0.05 mg/10 mL. The reaction obeys Beer's Law from 0.05 mg to 4 mg/10 mL of indomethacin. Sayed M. et al [23] studied pH-induced difference spectrophotometric methods for the determination of Indomethacin. Based on the spectral changes of indomethacin induced by changing the pH of the solvent medium, a method for its determination has been developed. The latter involves absorbance measurement of both acid and alkaline solutions of the compound at 260 nm: the difference between both values is linearly related to concentration in the range 0.4-1.4 mg/100 mL.

Table 1: Spectrophotometric analysis of some NSAIDs.

Drug	Reagent	Linearity range μg L^{-1}	LOD μg mL^{-1}	λ max nm	Applications	Ref.
Aspirin	Potassium permanganate	1-44	0.4	350	tablets	[14]
Aspirin	Salicylic Acid	2.5-30	0.738	224	tablets	[15]
Ibuprofen	Copper tetramine and copper sulphate	2.063- 103.14		265	tablets	[16]
Ibuprofen	Methanol	2-10	0.4-0.6	240	urine and blood samples	[17]
Diclofenac	Copper (II)	1.0 -25.0	0.2	680	tablets and ampoules	[18]
Diclofenac	Conc. nitric acid (63% w/v)	1-30	0.46	380	tablets	[19]
Indomethacin	*p*-Phenylenediamine dihydrochloride (PPDD)	0.2-10	0.066	510	capsules	[20]
Indomethacin	Niacinamide	10-50	0.023	320	capsules	[21]
Indomethacin	Ammonium oxalate	0.05- 4 mg/10 mL	0.05 mg/10mL	578	capsules	[22]
Indomethacin	pH of the solvent medium	0.4-1.4 mg/100 mL	0.133 mg/mL	260	capsules	[23]

2. Conclusion

NSAIDs have been determined by different analytical techniques, but here we are concerned with spectrophotometric methods for the determination of some NSAIDs in pure form or pharmaceutical dosage form. The importance of spectrophotometric methods appears in the fast, simplicity, low cost, and validation. Aspirin, ibuprofen, diclofenac, and Indomethacin were determined spectrophotometrically in different methods in pure and pharmaceutical preparations without interfering with excipients. The results have been found to be accurate, precise, and validated statistically.

Conflict of Interest: The authors declare and state that this research was conducted in the absence of any potential or source for conflict of interest.

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