International Journal of Current Trends in Pharmaceutical Research

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Review Article **Open Access**

Aceclofenac: A Review

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A B S T R A C T

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) analog of Diclofenac. It is used for the relief of pain and inflammation in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It should not be given to people with porphyria or breast-feeding mothers, and is not recommended for children. Aceclofenac has higher anti-inflammatory action than conventional NSAIDs. It is a cytokine inhibitor. Aceclofenac works by blocking the action of a substance in the body called cyclo-oxygenase. Cyclo-oxygenase is involved in the production of prostaglandins (chemicals in the body) which cause pain, swelling and inflammation. Aceclofenac is the glycolic acid ester of diclofenac.

Keywords: Aceclofenac, Anti- inflammatory, Diclofenac, Cyclooxgenase, NSAIDs

A R T I C L E I N F O

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Article History: Received 18 February 2016, **Accepted** 19 March 2016, **Available Online** 15 May 2016

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Manuscript ID: IJCTPR2908

PAPER-QR CODE

Citation: Rajiv Kumar, *et al.* Aceclofenac: A Review. *Int. J. Curnt. Tren. Pharm, Res.*, 2016, 4(3): 154-158.

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) form a heterogeneous group of organic acids which have analgesic, antipyretic, anti-inflammatory and platelet inhibitory actions (**1**). The mechanism of action of NSAIDs involves the inhibition of cyclooxygenase (COX), which is a key enzyme in the inflammation cascade **(2)**. The inhibition of COX leads to the suppression of pro-inflammatory prostaglandins and cytokines. Thus, NSAIDs act as analgesic, antipyretic by central as well as peripheral action. The main disadvantage of long-term therapy with NSAIDs is the risk of gastrointestinal disturbances (**3**). Unfortunately, GI side effects have often limited their

clinical utilization. AC is a selective potent inhibitor of COX-2, an inducible enzyme responsible for the generation of inflammatory mediators, and is used in rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and pain management for its analgesic, antipyretic and anti-inflammatory effects (**4-7)**. Aceclofenac was developed in Spain by Grau et al. in 1991 to improve gastrointestinal tolerability **(3, 8**). Acelofenac has shown better gastric tolerance when compared to other NSAIDs (**9**). The acute gastric ulcerogenic activity of Acelofenac was found to be 2-, 4- and 7- fold less than naproxen, diclofenac or indomethacin, respectively (**5**). AC shares structural similarities with another NSAID, diclofenac (**7**). Indeed, the therapeutic index for AC was reported to be four times greater than that of diclofenac, a well established NSAID in clinical use **(2)**. Although AC is similar to other NSAIDs in terms of efficacy, its superior tolerability and compliance indicate that there may be economic consequences (**2**).

2. Physicochemical Properties and Analysis

Aceclofenac is a white or almost white, crystalline powder that is practically insoluble in water, freely soluble in acetone and soluble in alcohol **(6**). The solution in methanol shows an absorption maximum at 275 nm (**10)**. Aceclofenac is a phenyl acetic acid derivative with a chemical designation of [2-{(2,6-dichlorophenyl) amino}-phenyl acetoxyacetic acid]. Its molecular formula is C16H13Cl2NO4 and its molecular weight is 354.188**(7)**. The solubility of Aceclofenac a weakly acidic drug (pKa 4-5), depends on pH. Aceclofenac is highly soluble in basic conditions but relatively soluble in water and acidic pH conditions. The solubility of Aceclofenac in different medium. It exhibits poor flow and compression characteristics **(9, 11, 12)**.

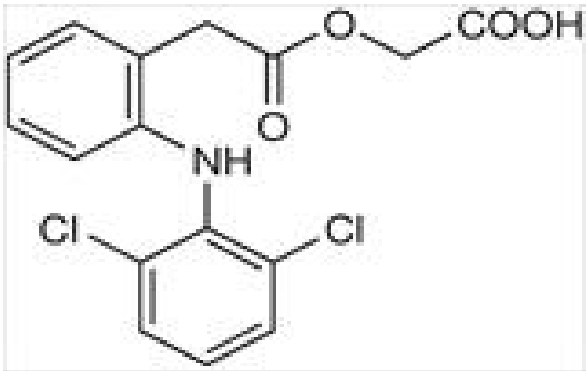

Figure 1: Chemical structure of Aceclofenac

Several methods are available in literature to determine the concentration of AC. Techniques used for analysis of Aceclofenac include titrimetric **(2, 18)**, voltammetric **(19)**, densitometric, colorimetric, spectrophotometric, spectro flourometric, polarographic **(26)**, HPLC capillary electrophoresis and mass spectrometry. Different analytical methods have been developed for the simultaneous determination of Aceclofenac combinations with various active molecules **(19, 21)**. Throughout the stability test, Aceclofenac in plasma has proved stable at room temperature for atleast 6 hours.

Dosage and Administration

The usual dosage of AC in adult patients with arthritic disorders or moderate to severe pain is 100 mg orally twice daily **(5)**. Due to short half life, it is necessary to be administered frequently in order to maintain the desired concentration. Therefore, AC is an ideal candidate for sustained release formulation, resulting in more reproducible drug absorption compared to single dosage forms **(23, 24)**. AC should not be administered to patients with peptic ulcers or GI bleeding, moderate or severe renal impairment, sensitivity to aceclofenac or other NSAIDs. The drug is not recommended in pregnant or breast-feeding women.

Pharmacokinetic and Pharmacodynamic Properties

Aceclofenac is well absorbed from gastrointestinal tract and circulates mainly as unchanged drug. After oral administration of a single 100 mg dose, the peak plasma concentrations (Cmax) of 6.8 to 8.9 mg/L is reached in about 1.25 to 3 hours after ingestion **(5,7)**. The volume of distribution (Vd) is approximately 25 L, and it is highly protein-bound (>99%) in plasma **(2, 7)**. Cmax and the area under the plasma concentration-time curve (AUC) increase linearly after the administration of single doses of Aceclofenac 50, 100 and 150 mg. The presence of food does not alter the pharmacokinetic parameters of Aceclofenac **(5)**. On the other hand, the presence of food reduces the absorption rate, consequently tmax value increases; but the extent of Cmax or AUC values does not change. Moreover, Cmax, Vd, half-life (t1/2) and the absorption of Aceclofenac is not affected by increasing age and therefore dose reductions are generally not necessary in elderly patients **(2)**. Aceclofenac is eliminated mainly via the renal route, with a plasma elimination half-life of approximately 4 hours. Approximately 70% of the drug is excreted in urine as glucuronide of Acelofenac and diclofenac and 20% in feces **(5)**. Acelofenac is also more than 99% bound to plasma proteins.

The incidence of GI adverse events with Aceclofenac has generally been lower that with other NSAIDs in comparative studies. Although Aceclofenac is similar in terms of efficacy to other NSAIDs, its superior tolerability and compliance indicate that there may be economic consequences **(2)**. The mode of action of Acecloefenac is still unclear. A study by Hinz -et al. has indicated the action to be due to one of its metabolites, diclofenac that inhibits the enzyme cyclooxygenase.

Major Pharmacodynamic Charterstics of Aceclofenac

a. Anti-inflammatory activity
b. Inhibition of production of the inflammatory mediators IL-1b and tumor necrosis factor
c. Inhibition of basal and IL-1b-stimulated IL-6 production
d. Inhibition of cyclo-oxygenase activity
e. Inhibition of basal and stimulated prostaglandin E2 production
f. Reduction of stimulated generation of reactive oxygen species
g. Interference with expression of cell adhesion molecules

h. Stimulation of glycosaminoglycan synthesis in osteoarthritic cartilage.

3. Dosage Forms and Formulations

Enhancement of Solubility and Dissolution Rate

The bioavailability of poorly water-soluble drugs depends upon dissolution in GI tract; the major problem is their very low solubility in biological fluids, which results in poor bioavailability after oral administration. Aceclofenac is practically insoluble in water so the improvement of dissolution is an important issue for enhancing its bioavailability and therapeutic efficacy. The possibility of improving the solubility and dissolution rate of Aceclofenac has been investigated by different methods.

The preparation of solid dispersions of drug is another way of dissolution enhancement. Solid dispersions are effective for enhancing dissolution rate via structural changes of crystalline drugs into amorphous forms. Some research groups have used this technique for enhancement of solubility and dissolution rate of Aceclofenac **(17)**. The solid dispersion of Aceclofenac has been prepared using hydrophilic carriers such as urea, mannitol, lactose, PEG, Plasdone-S630, PVP, PVP-VA-64, gelatin hydrolysates, betacyclodextrin, sodium lauryl sulphate, Avicel 200 or Sylysia 350 in these studies. The solid dispersions of Aceclofenac with all carriers have shown considerable increase in the dissolution rate in comparison with pure drug in different dissolution medium. Tran et al. **(16)** have investigated the dissolution modulating mech anism of pH modifiers (Na2CO3) and polymer (Poloxamer 407) in Gelucire-based (Gelucire44/14) solid dispersion for the release of Aceclofenac. The incorporation of alkalizer combined with polymer has given a promising approach for Aceclofenac dissolution enhancement. The synergistic effects of alkalizer and secondary polymer in solid dispersion could have modulated dissolution rate of Aceclofenac without precipitation.

Preparing of Aceclofenac co-crystals is another approach for dissolution enhancement of Aceclofenac. Chitosan precipitated on Aceclofenac crystals using sodium citrate as the salting out agent has been used as vehicle by preparing co-crystals using solvent change method **(14)**. The prepared Aceclofenac-chitosan crystals have exhibited high solubility/dissolution rate of drug from crystals and they have shown high AUC value in mice and rats, indicating the greater bioavailability of AC than the pure drug. Chaudhary **(9)** has also developed a liquid formulation of Aceclofenac using non-aqueous solubilizer components selected from the group consisting of PG, PEGs and optional ethanol. Ready-to-use compositions disclosed in this patent have been prepared by mixing of all components. It has been indicated that a nonaqueous liquid form developed could be used for the parenteral delivery of Aceclofenac.

The use of soft capsule formulation including the self-micro emulsifying composition containing the solubilized Aceclofenac is another and relatively new approach **(24)**. PEG 400, polyoxyethylene hydrogenated castor oil, dimethyl isosorbide and middle chain fatty acid have been used to prepare the self-micro emulsifying composition. It has shown that the soft capsule formulation has excellent drug dissolution rate that is higher than that of the commercial tablet.

Oral Controlled Release Systems

The therapeutic action of NSAIDs should last for 24 hours in order to maintain a high compliance with therapy for patients suffering from painful inflammatory diseases such as osteoarthritis. To reduce the frequency of oral administration and to increase patient compliances, once-daily controlled or prolonged release dosage forms have received more attention. The short elimination half-life of Aceclofenac necessitates dosing every 12 hours by orally to maintain optimum level of analgesia in chronic pain. Controlled release dosage forms provide a extended duration of action and reduce dosing frequency. These dosage forms reduce fluctuations in plasma concentration of drug and they provide favorable efficacy. Controlled release formulations also show a trend toward slightly lower incidences of adverse events compared with the conventional formulations.

Pareek et al**. (22)** have investigated the efficacy and safety of Aceclofenac controlled release tablets in the treatment of pain due to knee osteo-arthritis (OA). Two hundred and eighty five patients have been randomized to either Aceclofenac-controlled release tablet once daily or conventional Aceclofenac tablet twice daily for 6 weeks. The Aceclofenac-controlled release tablet has been compared to the conventional tablet with respect to change in pain intensity. Results have demonstrated the advantages of controlled release over the conventional tablet. It has been found to be similar to conventional Aceclofenac in terms of efficacy in knee OA patients with fewer adverse events. The oral route remains the preferred route of drug administration. Different research groups have attempted to prepare controlled release oral formulation of Aceclofenac like multiple unit dosage forms or tablets. There are a number of techniques applied in the formulation of controlled release tablets. Matrix tablets offer the simplest approach in designing an oral sustained release system. Hydrophilic polymers are widely used in oral tablets to obtain a desirable controlled release profile because of cost effectiveness and broad regulatory acceptance.

Shivhare et al. **(25)** have developed once-daily sustained release tablets of Aceclofenac by wet granulation method using Carbopol 971P and Carbopol 974P, which are hydrophilic matrix materials. Polyvinyl pyrrolidone has been used as binder; magnesium stearate and talc have been added as lubricant prior to compression. In vitro drug release studies have shown that the release has sustained manner up to 24 hour.

Topical Delivery Systems

Topical application is an important route for local action of many therapeutic agents. This route offers many potential advantages such as delivering the drug directly to the side

of action, acting for an extended period of time, helping avoid typical side effect associated with oral administration and using as a supplement to oral therapy for better treatment of conditions such as arthritis **(19)** . Therefore, in some situations topical dosage forms are suggested as alternative to oral preparations or oral formulations taken together. Hence a topical formulations containing Aceclofenac has an importance for local application. Several research groups have prepared topical formulations of Aceclofenac using various topical delivery systems, from classic to modern, such as gels, organogels, transdermal patches, vesicularsystems, microemulsions, nanoemulsions.

4. Conclusion

Aceclofenac is an NSAID that is effective in the treatment of painful inflammatory diseases and also provides effective analgesia in several indications. It is associated with significantly fewer adverse events compared with other NSAIDs. It is a drug with narrow therapeutic index and short biological half-life. A short half-life of AC does not permit once daily administration as monotherapy. Thus, it is necessary to be administered frequently in order to maintain the desired concentration. Therefore, Aceclofenac is an ideal candidate for controlled release dosage forms, resulting in more reproducible drug absorption, reducing the risk of local irritations and maintaining plasma concentration over 24 hours compared to single dosage forms. Microparticles, agglomerates, microspheres, enteric-coated pellets, matrix tablets and film-coating tablets are the approaches investigated to provide controlled release of Aceclofenac.

5. References

[1] JK Aronson. Non-steroidal anti-inflammatory drugs. Meyler's Side Effects of Drugs, 15th edition, The International Encyclopedia of Adverse Drugs Reactions and Interactions, 2006, PP. 2555-2582.

[2] E Legrand. Aceclofenac in the management of inflammatory pain. *Drug Evaluation*, 2004, 5 (6): 1347- 1357.

[3] GV Shavi, U Nayak, RK Averineni, K Arumugam, SR Meka, U Nayanabhirama, P Sureshwar. Multiparticulate drug delivery system of aceclofenac: development and in vitro studies. *Drug Dev Ind Pharm*, 2009, 35(2): 252-258.

[4] NGR Rao, U Kulkarni, A Deshmukh, DK Suresh. Preparation and characterization of ionotropic cross-linked chitosan microparticles for controlled release of aceclofenac. *Int J Pharm Sci Drug Res*, 2(2): 107-111.

[5] RN Brogden, LR Wiseman. Aceclofenac:A Review of its pharmacodynamic properties and therapeutic potential in the treatment of rheumatic disorders and in pain management. *Drug Evaluation*, 1996, 52(1): 113-124.

[6] Aceclofenac. British Pharmacopoeia, 2004 1: 36-38.

[7] NV Chandrasekharan. Aceclofenac.: The comprehensive pharmacology reference. *X Pharm*, 2008, 1-5.

[8] M Grau, JL Montero, J Guasch, A Felipe, E Carrasco, S Julia. The pharmacological profile of aceclofenac, a new nonsteroidal anti-inflammatory and analgesic drug. *Drugs in Inflammation*, 1991, 32(1): 125-129.

[9] LA Chub. Nonaqueous liquid parenteral aceclofenac formulation. US patent 2009/0156670.

[10] Aceclofenac. European Pharma-copoeia, 2008 6.2: 3685- 3686.

[11] HP Zahradnik, A Hanjalic-Beck, K Groth. Nonsteroidal anti-inflammatory drugs and hormonal contraceptives for pain relief from dysmenorrhes: a review. *Contraception, 2010,* 81: 185-196.

[12] AN Usha, S Mutalik, MS Reddy, AK Ranjith, P Kushtagi, N Udupa. Preparation and in vitro preclinical and clinical studies of aceclofenac spherical agglomerates. *Eur J Pharm Biopharm*, 2008, 70: 674-683.

[13] RK Maheshwari, A Indurkhya. Formulation and evaluation of aceclofenac injection made by mixed hydrotropic solubilization technique. *Iranian Pharm Res, 2010,* 9(3): 233-242.

[14] S Mutalik, P Anju, K Manoj, AN Usha. Enhancement of dissolution rate and bioavailability of aceclofenac: chitosan-based solvent change approach. *Int J Pharm, 2008,* 350: 279-290.

[15] T Soni, C Nagda, T Gandhi, NP Chotai. Development of discriminating method for dissolution of aceclofenac marketed formulations. *Dissolution Tech, 2008,* 15(2): 31-35.

[16] TTD Tran, PHL Tran, BJ Lee. Dissolution modulating mechanism of alkalizers and polymers in a nanoemulsifying solid dispersion containing ionizable and poorly water-soluble drug. *Eur J Pharm Biopharm, 2009,* 72: 83- 90.

[17] FA Maulvi, SJ Dalwadi, VT Thakkar, TG Soni, MC Gohel, TR Gandhi. Improvement of dissolution rate of aceclofenac by solid dispersion technique. *Powder Tech*, 2011, 207: 47-54.

[18] RK Maheshwari, S Moondra. A novel method for quantitative determination of aceclofenac in bulk drug and tablets using sodium silicylate as a hydrotropic solubilizing agent. *J Adv Pharm Tech Res*, 2010, 1(1): 78-82.

[19] UD Pawar, AV Naik, AV Sulebhavikar, TA Datar, KV mangaonkar. Simultaneous determination of aceclofenac, paracetamol and chlorzoxazone by HPLC in tablet dose form. *E-journal of chemistry*, 2009, 6(1): 289-294.

[20] NH Zawilla, MAA Mohammad, NME Kousy, SMEM Aly. Determination of aceclofenac in bulk and pharmaceutical formulations. *J Pharm Biomed Anal*, 2002, 27: 243-251.

[21] NME Kousy. Spectrophotometric and spectro fluorimetric determination of etadolac and aceclofenac. *J Pharm Biomed Anal*, 1999, 20: 185-194.

[22] J Jain, R Patadia, D Vanparia, R Chauhan, S Shah. Dual wavelength spectrophotometric method for simultaneous estimation of drotaverine hydrochloride and aceclofenac in their combined tablet dosage form. *Int J Pharmacy Pharm Sci*, 2010, *2*(4): 76-79.

[23] R Shah, C Magdum, SK Patil, DK Chougule, N Naikwade. Validated spectroscopic method for estimation of aceclofenac from tablet formulation. *Research J Pharm and Tech*, 2008, 1(4): 430-432.

[24] MV Bhure, AT Hemke, KR Gupta. UV Spectrophotometric methıds for determination of aceclofenac and diacerein in pharmaceutical formulation. *J Pharm Sci* Res, 2010, 2(7): 426-432.

[25] KV Gowda, DS Rajan, U Mandal, PS Selvan, WD Sam Solomon, A Bose, AK Sarkar, TK Pal. Evaluation of bioequivalence of two formulations containing 100 milligrams of aceclofenac. *Drug Dev Ind Pharm*, 2006, 32: 1219-1225.