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REVIEW ARTICLE

A Nonsteroidal Antiinflammatory Drug: Aceclofenac

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Summary

Aceclofenac (AC) is an effective non-steroidal anti-inflammatory drug, which possesses remarkable anti-inflammatory, analgesic and antipyretic properties. The analgesic and anti-inflammatory efficacy of AC is generally equivalent to that of comparator nonsteroidal anti-inflammatory drugs (NSAIDs) with similar onset of action. AC also shows stimulatory effects on glycosaminoglycan synthesis in human osteoarthritic cartilage. AC appears to be particularly well-tolerated among the NSAIDs with a lower incidence of gastrointestinal (GI) adverse effects. The presence of food does not alter the pharmacokinetic parameters of AC. The peak plasma concentrations (C_{max}), the volume of distribution (V_d), biological half-life and the absorption of AC are not affected by age and therefore dose reductions are generally not necessary in patients. AC is an example of Biopharmaceutical Classification System (BCS) Class II compound. Its oral bioavailability is determined by dissolution rate in GI tract. Therefore, the improvement of AC dissolution is an important issue for enhancing its bioavailability and therapeutic efficacy. A relatively large number of studies have been carried out to formulate different dosage forms of AC, such as tablets, soft capsules, particulate systems and topical systems. In this review, especially the oral, dermal and topical formulations of AC will be discussed.

Key Word: *Aceclofenac.*

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Nonsteroidal Antienflamatuvar İlaç: Aseklofenak

Özet

Aseklofenak (AC) antienflamatuvar, analjezik ve antipiretik özellikleri olan etkili bir nonsteroidal antienflamatuvar ilaçtır. Analjezik ve antienflamatuvar etkileri, genellikle benzer eylem başlangıcı oluşturan nonsteroidal antienflamatuvar ilaçlar (NSAII) ile eşdeğerdir. AC'ın insanda osteoartritik kıkırdağındaki glikozaminoglikan sentezi üzerinde stimulant etkileri de vardır. Aseklofenak düşük gastrointestinal (GI) yan etkileri göstermesiyle NSAII içinde kısmen iyi tolere edilebilirdir. Yiyecek varlığı AC'ın farmakokinetik parametrelerini değiştirmez. Maksimum plazma derişimi (Cmax), dağılım hacmi (Vd), biyolojik yarı ömrü ve emilimi yaştan etkilenmez. Bu nedenle hastalarda doz kısıtlamalarına gerek olmaz. AC Biyofarmasötik Sınıflandırma Sistemi (BCS) Sınıf 2 bileşiktir, oral biyoyararlanımı GI yolaktaki çözünme hızı ile belirlenir. Bu nedenle AC'ın çözünmesinin iyileştirilmesi, biyoyararlılığı ve terapötik etkisini iyileştirmek için önemli bir kriterdir. AC'ın tablet, yumuşak kapsül, partiküler sistemler ve topikal sistemler gibi farklı dozaj şekillerini hazırlamak için birçok çalışma yapılmıştır. Bu derlemede AC'ın özellikle oral, dermal ve topikal formülasyonları tartışılacaktır.

Anahtar Kelime: *Aseklofenak.*

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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). AC was developed in Spain by Grau et al. in 1991 to improve gastrointestinal tolerability (3, 8). AC has shown better gastric tolerance when compared to other NSAIDs (9). The acute gastric ulcerogenic activity of AC 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).

PHYSICOCHEMICAL PROPERTIES AND ANALYSIS

Aceclofenac (CAS 89796-99-6) 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}-phenylacetoxyacetic acid]. The chemical structure is shown in Figure 1 (2). Its molecular formula is $C_{16}H_{13}Cl_2NO_4$ and its molecular weight is 354.188 (7). The solubility of AC, a weakly acidic drug (pKa 4-5), depends on pH. AC is highly soluble in basic conditions but relatively soluble in water and acidic pH conditions. The solubility of AC in different medium is shown in Table 1. It exhibits poor flow and compression characteristics (9, 11, 12).

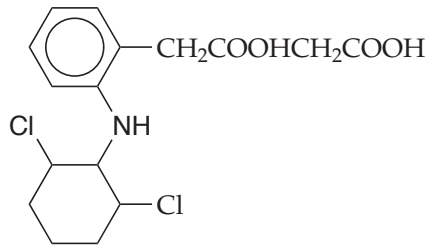

Figure 1. Chemical structure of AC

Table 1. Solubility data of AC in different media (12-17).

Medium	Solubility value	Reference
Water 0.1N HCl pH 6.8	75.59 µg/mL, at 37°C 15.24 µg/mL, at 37°C 10.58 mg/mL, at 37°C	12
Water pH 7.4 pH 8 pH 9	0.018 g/100 mL, at room temperature 0.065 g/100 mL, at room temperature 0.069 g/100 mL, at room temperature 0.075 g/100 mL, at room temperature	13
Water 0.1 N HCl	0.053 mg/mL, at room temperature 0.013 mg/mL, at room temperature	14
Water N HCl pH 4.5 pH 6.8	58.67 µg/mL, at 37°C 21.93 µg/mL, at 37°C 995 µg/mL, at 37°C 1538.7 µg/mL, at 37°C	15
Water pH 1.2 pH 6.8	55.46 µg/mL, at 37°C 11.77 µg/mL, at 37°C 4962 µg/mL, at 37°C	16
Water 0.2 → N HCl pH 4.5	0.076 mg/mL, at 37°C 0.018 mg/mL, at 37°C 6.79 mg/mL, at 37°C	17

Several methods are available in literature to determine the concentration of AC. Techniques used for analysis of AC include titrimetric (2, 18), voltammetric (19), densitometric (20), colorimetric (20, 21), spectrophotometric (22-24), spectroflourometric

(21, 25), polarographic (26), HPLC (19, 20, 22, 27-34), capillary electrophoresis (35), and mass spectrometry (36). Different analytical methods have been developed for the simultaneous determination of AC combinations with various active molecules (19, 21-24, 26, 28-32). Throughout the stability test, AC in plasma has proved stable at room temperature for at least 6 hours (25).

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, 37). Due to short half-life, it is necessary to be administered frequently in order to maintain the desired concentration (38). Therefore, AC is an ideal candidate for sustained release formulation, resulting in more reproducible drug absorption compared to single dosage forms (38, 39). 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 (37).

PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES

AC 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 (C_{max}) of 6.8 to 8.9 mg/L is reached in about 1.25 to 3 hours after ingestion (5, 7, 37). The volume of distribution (V_d) is approximately 25 L, and it is highly protein-bound (>99%) in plasma (2, 7, 37). C_{max} and the area under the plasma concentration-time curve (AUC) increase linearly after the administration of single doses of AC 50, 100 and 150 mg. The presence of food does not alter the pharmacokinetic parameters of AC (5). On the other hand, the presence of food reduces the absorption rate, consequently t_{max} value increases; but the extent of C_{max} or AUC values does not change (37). Moreover, C_{max}, V_d, half-life ($t_{1/2}$) and the absorption of AC is not affected by increasing age and therefore dose reductions are generally not necessary in elderly patients (2).

The pharmacokinetics and metabolism of AC show the species differences. After oral administration to rats, circulating AC rapidly disappears ($t_{1/2}$: 0.08 hr.), while in humans the AC $t_{1/2}$ has been found to be 50 times longer (40). In rats, AC behaves like a prodrug rapidly generating diclofenac by hydrolysis, i.e. ester breakage. The amount of AC found in plasma is low, ever very shortly after its oral administration (40). In contrast, in humans, AC remains more stable and reaches the general circulation without being hydrolyzed; the formation of 4'-hydroxy aceclofenac becomes the major metabolic pathway. AC is metabolized in human hepatocytes and human microsomes to form 4'-hydroxy aceclofenac as the primary metabolite (7, 41). The other minor metabolites, which are about 5% of administered dose, include 5-hydroxy aceclofenac, diclofenac, 5-hydroxy diclofenac and 4'-hydroxy diclofenac (7, 37).

AC is eliminated mainly via the renal route, with a plasma elimination half-life of approximately 4 hours (37). Approximately 70% of the drug is excreted in urine as glucuronide of AC and diclofenac and 20% in feces (5, 42). AC is also more than 99% bound to plasma proteins.

AC has been used to treat >75 million patients worldwide. It has effective therapeutic actions on the painful inflammatory diseases such as osteoarthritis, rheumatoid arthritis and ankylosing spondylitis (2, 5). AC reduces prostaglandin E2 levels in synovial fluid of patients with acute knee pain and suppresses prostaglandin E2 production in patients with severe osteoarthritis. The anti-inflammatory activity of AC has been shown to be similar to that of diclofenac in animal models of acute and chronic inflammation. In contrast to some other NSAIDs, AC shows stimulatory effects on glycosaminoglycan synthesis in human osteoarthritic cartilage (2). Chrondroprotective effect occurs mediated by the suppression of metalloprotease production and proteoglycan release in human rheumatoid synovial cells, namely, AC augments the biosynthesis of extracellular matrix by articular cartilage explants from patients with osteoarthritis. It has been suggested that therapeutic effects of on rheumatoid arthritis and osteoarthritis are due to the chrondroprotective effect of 4'-hydroxy aceclofenac (43, 44).

AC also provides effective analgesia in other indications such as gynecological or dental pain, lower back pain and ear, nose and throat indications. The analgesic activity of AC is similar to that of diclofenac in rodent models and the antipyretic potency of AC is about half that of diclofenac in rats. The treatment with NSAIDs has proven to be effective in the treatment of primary dysmenorrhea, providing significant relief from associated pain (45). Letzel et al. (46) have investigated the analgesic efficacy of a single oral dose of AC 100 mg in woman with primary dysmenorrhea and compared its efficacy with placebo and naproxen, the standard treatment. In this study, peak pain relief scores were statistically better with placebo and appeared comparable for the active treatments. The efficacy of AC has been found to be indistinguishable from naproxen in the treatment of primary dysmenorrhea. Pareek et al. (47) have also evaluated the efficacy and safety of AC-drotaverine combination against AC alone in patients with primary dysmenorrhea. Drotaverine has been used as a smooth muscle relaxant reducing uterine contraction. The combination has provided significantly greater pain relief and significantly decreased peak pain intensity in comparison with monotherapy.

The incidence of GI adverse events with AC has generally been lower that with other NSAIDs in comparative studies (37). Although AC 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 AC is still unclear. A study by Hinz et al. (48) has indicated the action to be due to one of its metabolites, diclofenac that inhibits the enzyme cyclooxygenase (49).

Major pharmacodynamic properties of AC have been presented as following (37):

a) anti-inflammatory activity; *b)* inhibition of production of the inflammatory mediators IL-1β and tumor necrosis factor; *c)* inhibition of basal and IL-1β-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.

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. AC is practically insoluble in water so the improvement of AC dissolution is an important issue for enhancing its bioavailability and therapeutic efficacy. The possibility of improving the solubility and dissolution rate of AC has been investigated by different methods.

One of the approaches used to improve solubility is to use melt granulation and liquisolid techniques. Yadav et al. (50) have prepared the granules of AC with these techniques using PEG 400, HPMC, different diluents and disintegrates. The AC granules prepared by both techniques have shown improvement in solubility, dissolution, wettability and flowability parameters.

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 AC (17, 51-53). The solid dispersion of AC has been prepared using hydrophilic carriers such as urea, mannitol, lactose, PEG, Plasdone-S630, PVP, PVP-VA-64, gelatin hydrolysates, beta-cyclodextrin, sodium lauryl sulphate, Avicel 200 or Sylysia 350 in these studies. The solid dispersions of AC with all carriers have shown considerable increase in the dissolution rate in comparison with pure drug in different dissolution medium.

Lee et al. (54) have demonstrated the excellent dissolution ability and bioavailability of AC powder prepared using the spray-drying. Hydrophilic

solution used for spray drying process has been prepared with acetone, ethanol, water, PVP and Tween 80. Researchers have indicated that the resultant solid powder could be formulated into pellets, granules, tablets or capsules. When orally administered, the developed capsule formulation of AC has increased its bioavailability 2-4 times higher than a commercial tablet; that is, the capsule, which contains small amount of AC (70 mg), has efficacy corresponding to that of the conventional tablet containing 100 mg of AC.

Tran et al. (16) have investigated the dissolution modulating mechanism of pH modifiers (Na_2CO_3) and polymer (Poloxamer 407) in Gelucire-based (Gelucire44/14) solid dispersion for the release of AC. The incorporation of alkalizer combined with polymer has given a promising approach for AC dissolution enhancement. The synergistic effects of alkalizer and secondary polymer in solid dispersion could have modulated dissolution rate of AC without precipitation.

Preparing of AC co-crystals is another approach for dissolution enhancement of AC. Chitosan precipitated on AC 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 AC-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.

Hydrotropes have also tried to increase solubility of AC in aqueous solution. Hydrotropic solubilization for the formulation development of aqueous injection of AC has been demonstrated by Maheshwari et al. (13) by using urea, sodium citrate and their blends. The enhancement in the solubility of AC has been found more than 5 and 25 folds in 30% sodium citrate solution and 30% urea solution, respectively, as compared to its solubility in distilled water. The solubility of AC in a mixed hydrotropic solution containing ≥ 20% urea and 10% sodium citrate solution has also been found more than 250 folds (compared to its solubility in distilled water). This has proved a synergistic enhancement in solubility of AC due to mixed hydrotropy. The problem of inadequate solubility of AC has been overcome by this technique and consequently hydrotropic solubilization has led to the development of lyophilized product of AC for parenteral application.

Chaudhary (9) has also developed a liquid formulation of AC 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 AC.

Soft capsule preparations can be prepared to develop an effective oral system with enhanced solubility and accelerated absorption for poorly water soluble drugs (55, 56). Yong et al. (57) have developed soft capsule dosage form containing ethanolamine, Tween 80 and PEG 400 as solubilizers. The soft capsule content has been put in the gelatin soft capsule and then its dissolution study has been performed. The developed formulation has showed significantly higher dissolution rates than the conventional tablet. The pharmacokinetics of conventional AC tablet and developed formulation containing AC have also been evaluated and compared in humans. The AC-loaded soft capsule gave statistically same plasma concentrations and significantly lower t_{max} value than did the conventional tablet, 1 hr. vs. 0.5 hr., indicating that the drug from soft capsule could be faster absorbed in human subjects. It has been concluded that the soft capsule developed was more effective oral dosage form with fast absorption and similar bioavailability for AC as a poorly water soluble drug.

The use of soft capsule formulation including the self-microemulsifying composition containing the solubilized AC is another and relatively new approach (56). PEG 400, polyoxyethylene hydrogenated castor oil, dimethyl isosorbide and middle chain fatty acid have been used to prepare the self-microemulsifying composition. It has shown that the soft capsule formulation has excellent drug dissolution rate that is higher than that of the commercial tablet.

The dissolution rate of AC from conventional tablets can be increased by increasing the surface area of drug using superdisintegrants in formulation. Setty et al. (42) have prepared fast-dispersible tablets by direct compression method using superdisintegrants. Croscarmellose sodium, sodium starch glycolate and crospovidone have been used as fast disintegrating materials. The most important parameter that needs to be optimized in the development of fast dispersible tablets is the disintegration time. In the study, all the tablets have disintegrated in ≤ 57.5 sec fulfilling the official requirements (<3 min) for dispersible tablets. Since the dissolution process of a tablet depends upon the wetting followed by disintegration of the tablet, the measurement of wetting time has been used as another confirmative test for the evaluation of dispersible tablets. Wetting times of tablets have been ranged as follows: crospovidone ≤ croscarmellose sodium ≤ sodium starch glycolate. It has been concluded that the fast dispersible AC tablets could be prepared by using any of the superdisintegrants used.

Garala et al. (58) have also studied on fast disintegrating AC tablets. The sodium starch glycolate, crosscarmellose sodium and pregelatinized starch have been used in different concentrations. The fast disintegrating tablets of the AC have been formulated using wet granulation method. The disintegration time of all formulations has shown less than 89 seconds. The percentage release of AC from tablets has been found to be 99.5% within 10 minutes.

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 AC necessitates dosing every 12 hours by orally to maintain optimum level of analgesia in chronic pain. Controlled release dosage forms provide an 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. (59) have investigated the efficacy and safety of AC controlled release tablets in the treatment of pain due to knee osteoarthritis (OA). Two hundred and eighty five patients have been randomized to either AC-controlled release tablet once daily or conventional AC tablet twice daily for 6 weeks. The AC-controlled release tablet has been compared to the conventional AC tablet with respect to change in pain intensity. Results have demonstrated the advantages of controlled release AC over the conventional AC tablet. It has been found to be similar to conventional AC in terms of efficacy in knee OA patients with fewer adverse events.

Several research groups have designed the controlled release formulations of AC to maintain effective plasma concentration of drug over a 24-hour interval and consequently improving compliance of patient.

The oral route remains the preferred route of drug administration. Different research groups have attempted to prepare controlled release oral formulation of AC like multiple unit dosage forms or tablets.

Multiple unit dosage forms formulated from several polymers are interesting drug delivery systems and one of the important forms to provide the controlled release. Multiple unit dosage forms such as microparticles (4, 60), microsphres (38, 61-63), or pellets (2) have gained popularity as oral systems because of uniform distribution and absorption of AC in GI tract when compared to single unit dosage forms. Therefore, multiple unit dosage forms of AC have been tried in several studies. For the preparation of these systems, the different methods have been used.

Rao et al. (4) have developed TPP-chitosan microparticles by ionometric gelation method to prolong the release of AC. An increase in TPP concentration, pH and cross-linking time have

decreased the drug release. Similarly, AC-loaded microparticulate system has been prepared by modified solvent evaporation method using cellulose acetate by Dashora et al. (60). The in vitro release study has been carried out and compared with the commercial tablets (the conventional tablet and the SR tablet). The release from the commercial tablets has exhausted within 6 h while microparticles have sustained the release of AC more than 12 hours.

In another study, AC agglomerates have been prepared by spherical crystallization technique using a three solvent system comprising acetone: dichloromethane: water to improve the micromeritic properties of AC and to increase solubility, dissolution rate and hence bioavailability (12). HPMC have been used as hydrophilic polymer. The optimized agglomerates have shown improved micromeritic properties as well as dissolution behavior in comparison to pure drug crystals. The agglomerates prepared have been compressed into tablets by direct compression. The results of solubility studies have revealed that spherical agglomerates have shown increased solubility compared to the pure drug. The dissolution rate of AC from prepared tablets has been found better than that of commercial tablet. The preclinical studies carried out in rats and mice have provided improved pharmacodynamics and pharmacokinetic profiles. The results of in vivo studies of prepared tablets in human subjects have indicated improved pharmacokinetic parameters in comparison with that of commercial tablets. It has been concluded that spherical crystallization technique scaled-up has the potential to provide the directly compressed AC tablets with improved bioavailability.

AC-loaded microspheres have been prepared by the solvent evaporation technique using rosin and poly lactic acid by Lakshmana et al. (38) and Chandiran et al. (61), respectively. The release rate of AC from microspheres has been properly controlled and prolonged. Radhika et al. (62) have also formulated microspheres of AC using enteric polymers (cellulose acetate phthalate and hydroxyl propyl methyl cellulose phthalate) by the same technique and the formulation has shown delayed release. In another study, AC-loaded microspheres have been prepared by using spray-drying technique using carbopol, chitosan, and polycarbophil (63). The prepared AC-loaded microspheres in both studies have shown prolonged drug release.

Shavi et al. (3) have developed an enteric-coated pellets containing AC by using the extrusion/spheronization method. Firstly, core pellets have been prepared using lactose, Avicel PH101 and PVP K-30 and then these have been coated with poly (methyl) acrylate copolymer to achieve site-specific drug release. The enteric-coated pellets have been compared to that of commercial tablets. The formulated pellets have shown better release in comparison with commercial product by preventing releasing in stomach, and it has been concluded that the formulated pellets could be used as an ideal drug delivery system for AC.

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. (39) have developed once-daily sustained release tablets of AC 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.

Kabir et al. (64) have used hydroxypropyl methycellulose (HPMC K15M and HPMC K100M CR) as matrix material to develop once-daily controlled release matrix tablet of AC by direct compression method. Polyvinyl pyrrolidone, microcrystalline cellulose, magnesium stearate and anhydrous colloidal silica have been used for the preparation of tablets. The results of dissolution studies have indicated that the formulations could extend the drug release up to 24 hours. By comparing the dissolution profiles with the commercial sustained release

product, it has revealed that the tablets exhibited similarity to each other.

Basak et al. (65) have also used hydroxypropyl methycellulose as matrix material to prepare matrix core tablet containing AC by wet granulation technique using polyvinyl pyrrolidone, microcrystalline cellulose, magnesium stearate, talc, anhydrous colloidal silica, lactose monohydrate and a ready mix sodium alginate. After being prepared, the core tablets have been treated with coating solution to obtain entering coated tablets. The results of dissolution studies have indicated that the formulation (drug to polymer 1:0.470) exhibited drug release pattern very close to theoretical release profile. AC release from tablets has been extended from 16 to 24 h from formulated batches. Using a similar technique, Ghosh and Barik (66) have formulated matrix tablets of AC and determined if it is bioequivalent to a commercial brand of AC immediate release tablet. The excipients used in the production of the tablets were hydroxypropyl methycellulose, lactose, polyvinyl pyrrolidone, fumaric acid, magnesium stearate, talc, colloidal silicon dioxide and PEG 6000. The t_{max} of the formulated tablet has been found significantly higher than the commercial tablet (2.59 h vs. 2.29 h) due to the controlled release of the drug. There was also no difference in the extent of absorption for both tablets.

Gaikwad et al. (67) have used hydroxypropyl methycellulose as film coating material to formulate controlled release tablet containing AC. The core tablets formulated with polyvinyl pyrrolidone, microcrystalline cellulose and dicalcium phosphate by wet granulation technique have been coated with solution prepared with HPMC, isopropyl alcohol, methylene chloride, diethyl phthalate, polyethylene glycol 4000, titanium dioxide and talc. From the dissolution studies, it has been observed that all batches gave the release by diffusion-dissolution controlled mechanism. A gradual and prolonged release has been obtained and the tablets have shown similarity with the commercial product.

To provide maintain blood concentration, the rectal administration of AC as an alternative to oral route has been thought and the sustained release suppositories containing AC microspheres have been prepared by Baria et al. (68). The release of drug has been evaluated by in vitro dissolution tests and the data have been compared with that of conventional suppository. AC microspheres have been prepared by the solvent evaporation method employing ethyl cellulose as a microsphere forming polymer. PEG 4000, PEG 6000 and stearic acid have been used as a suppository base. The effect of drug: polymer ratio and the stirring rate on microspheres formation, particle size, incorporation efficiency and in vitro AC release have been investigated. It has been concluded that suppository containing AC microspheres has sustained effect up to 8 hours in vitro.

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 (69). Therefore, in some situations topical dosage forms are suggested as alternative to oral preparations or oral formulations taken together. Hence a topical formulations containing AC has an importance for local application. Several research groups have prepared topical formulations of AC using various topical delivery systems, from classic to modern, such as gels, organogels, transdermal patches, vesicular systems, microemulsions and nanoemulsions.

Gels are one of the simple and basic topical dosage forms. Dua et al. (69) have prepared several gel systems using carbopol, HPMC, PEG 4000 and PEG 400. Among gels, the hydroalcoholic carbopol gel formulation has shown maximum AC release. In vitro skin permeation of AC has also been found to be better for this gel formulation compared to the gel formulations containing other gelling materials. Carbopol gel formulation has been evaluated for acute skin irritancy, anti-inflammatory and analgesic effects using the carrageenan-induced thermal hyperalgesia and paw edema method.

The findings have shown that hydroalcoholic carbopol gel formulation is significantly more effective in inhibiting hyperalgesia associated with inflammation. In another study (70) similarly, gel formulations of AC have been produced using Na alginate in addition to carbopol, HPMC and Na CMC and have been evaluated as in vitro. Among all the gel formulations, gel prepared with carbopol has shown better drug release than the other gel formulations.

Besides classical gel systems, organogels have been developed as AC delivery system. Their in vitro and in vivo effects have been compared with hydrogel prepared by using carbopol as a polymer (71). Organogel formulation of AC has been produced with lecithin and ethyl oleate. In vitro skin permeation study has demonstrated that lecithin organogel is effective in providing faster drug release compared to that of hydrogel. Histopathological study has also shown that the organogel does not have any harmful effects on skin. Hence, it has concluded that lecithin organogel seems to be a promising novel topical formulation for AC.

Transdermal patches have also been developed for local action of AC (72). Eudragit L100, L100-55 and S100 have been used as polymer for formulation of AC into patch. The effect of different plasticizers, like propylene glycol and polyethylene glycol (PEG 400) has been investigated on the in vitro drug release. The results of the in vitro release have shown that among investigated patches, the patch prepared with Eudragit L100 had an acceptable percentage drug release after 60 min and the increase of plasticizer concentrations has accompanied by an increase in drug release. The anti-inflammatory activity of AC patch treated rats has shown significant inhibition in edema thickness, produced by carrageenan when compared with the non-treated group.

Vesicular delivery systems such as liposomes, ethosomes, and niosomes are the promising systems for the topical route of administration. They serve as a local depot for controlled drug release. Thus, different research groups have evaluated these dosage forms for the topical use of AC.

Nasr et al. (73) have formulated the AC liposomes and niosomes using a thin film hydration method intended for topical administration. AC liposomes have been prepared using egg phosphatidylcholine and cholesterol; for the formulation of niosomes the surfactants, either Span 40 or Span 60, and cholesterol have been used. Niosomes have shown better stability than liposomes. It has been found that both vesicular systems showed significant sustained anti-inflammatory activity compared to the commercial cream product as manifested by both edema rate and inhibition rate percentages. However, niosomes have showed superior anti-inflammatory activity than liposomes.

Ethosomes, the different type of liposomes, are the promising carriers for the enhancement of topical permeation of drugs through the skin. In contrast to liposomes, these systems allow the transport of significant concentration of drug to the deep layers of skin. AC ethosomes have been prepared by Lewis and Dave (74) using lecithin, ethanol and propylene glycol. Ethosomal suspensions obtained have then mixed with carbopol gel named ethosomal gel system. To evaluate the in vitro skin permeability of AC from ethosomal gel system has been carried out using mouse skin. Drug permeation has been compared with commercial gel; it has shown that ethosomes improved the flux and prolonged the release of the drug.

Niosomes have several problems related to their physical instability such as fusion, aggregation ext.; in order to overcome these problems, proniosomes have been developed. These systems are either powder (water-soluble particles coated with surfactant) or liquid crystalline form. A dry free flowing proniosomes containing AC have been formulated using Span 60 and cholesterol by the slurry method (75). It has been observed that surface of proniosomes was seen rough, thick and uneven. Proniosomes have been found to be stable and have shown no significant difference in percentage of drug retained storage temperatures (refrigerated and at room temperature).

Microemulsions are defined as a dispersed system consisting of an oil, surfactant, co-surfactant and

aqueous phase, which have several advantages such as enhanced drug solubility, ease of manufacturing and enhancement of drug permeation. Lee et al. (76) have formulated oil in water type microemulsion system to enhance the skin permeability of AC. Labrafil® M1944 CS, Cremophor®ELP and ethanol have been used for formulation as oil phase, surfactant and co-surfactant, respectively. The in vitro transdermal permeability of AC has been investigated in rat skin; it has been found that the permeability of AC in microemulsion system was about 5-6 fold higher than that of the ethanol vehicle. This finding has indicated that microemulsion system is a promising vehicle for the percutaneous delivery of AC.

Nanoemulsions are also used to develop topical drug delivery systems of AC (77, 78). Nanoemulsions are dispersions of oil and aqueous phase where the dispersed phase globules are in the nanosized range. The droplets are stabilized with a surfactant film composed of a surfactant or surfactant and co-surfactant mixture. Nanoemulsions themselves act as permeation enhancer. Moreover, they are used for solubilization of poorly water soluble drugs (79). Therefore, nanoemulsions have been investigated as potential delivery system for dermal delivery of AC in the treatment of locally inflamed skin and inflammatory and painful states of bones, joints, tendons and muscles. Shakeel et al. (77, 78) have formulated AC nanoemulsions using Labrafil and Triacetin as oil phase, Tween 80 and Transcutol P as surfactant and co-surfactant by the spontaneous emulsification method. Besides the investigation of characteristic properties of nanoemulsions, dermal permeation of AC through rat abdominal skin has been determined, and in vitro skin permeation profiles of nanoemulsions have been compared with that of AC carbopol gel. A significant increase in permeability parameters has been observed in formulations selected for use in in-vivo studies. The anti-inflammatory effect of AC nanoemulsion has shown a significant increase in percent inhibition value when compared with AC gel on carrageenan induced paw edema in rats. Moreover, no apparent sign of skin irritation has been observed on visual examination of skin treated with nanoemulsions, indicating safe to be used for transdermal delivery.

CONCLUSION

Aceclofenac is an NSAID that is effective in the treatment of painful inflammatory diseases and also provides effective analgesia in several indications. AC 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, AC 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 AC.

The enhancement of AC solubility or dissolution and consequently improving its bioavailability are important issues due to its being practically insoluble in water. Several methods and techniques such as preparing solid dispersion, using hydrotropes, pH modifiers and polymers, preparing soft capsule formulations, using superdisintegrants in tablet formulations have been investigated to improve its solubility and dissolution rate. Topical application is also an important way to provide local action of AC. Therefore, gels, patches, vesicular systems and emulsions have been investigated for the topical formulation of AC.

There are several patents about the formulation of AC to provide enhancement solubility or controlled release. In the near future, new AC formulations will offer a worthwhile alternative to the conventional forms.

In summary, AC has been demonstrated to be effective in the treatment of both chronic and acute inflammatory and degenerative diseases compared with other NSAID therapies. Therefore, AC is the

treatment of choice for patients and physicians in the management of inflammatory pain.

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