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A review on Flurbiprofen: Therapeutic challenges in Emerging Active Metabolizing Biphenyl

Abstract

Flurbiprofen is chemically 2-(3- fluoro-4-Biphenyl) propanoic acid. It is a nonsteroidal anti-inflammatory drug (NSAID) which has also been found effective in the treatment of rheumatoid arthritis and degenerative joint diseases. R-Flurbiprofen has been utilized in the treatment of neoplastic diseases such as breast cancer, lung cancer, prostate cancer as well as cystic fibrosis and Alzheimer's disease. Flurbiprofen has shown an excellent therapeutic action against many diseases and has been reported to acquire anti-inflammatory, analgesic, antipyretic, antimicrobial, antipyretics, antithrombotic, antinociceptive, anti-tumour and radio protective activities. The derivatives of flurbiprofen have been reported to contribute significantly in controlling various diseases. In this context, the present report deals with the summary of therapeutic uses of Flurbiprofen and its various combinations that play an important role in controlling painful and deadly diseases along with reducing serious side effects caused by the typical medical treatment. It is also used in the treatment of rheumatoid arthritis and osteoarthritis.

Keywords: Flurbiprofen (FLB), nonsteroidal anti-inflammatory drug (NSAID), Nitroflurbiprofen, Anti-Alzheimer's disease, analgesic, Antiperiodontitis, arthritis, Antigingivitis, Antirheumatoid Antitumor, Antipyretic, Antiinflammatory and Radio protective properties.

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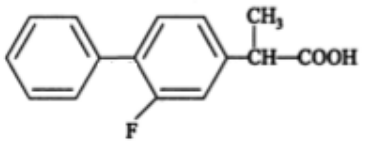
INTRODUCTION

Flurbiprofen (2-fluoro-a-methyl-1, 1'-biphenyl-4-acetic acid), a nonsteroidal anti-inflammatory drug (NSAID) which has also been found effective in the treatment of rheumatoid arthritis and degenerative joint diseases, flurbiprofen has been utilized in the treatment of neoplastic diseases such as breast cancer, lung cancer, prostate cancer as well as cystic fibrosis and Alzheimer's disease. Flurbiprofen and its combinations are cateagorized in the following conversation. In some cases, its derivatives have been found better than flurbiprofen itself, for example:-Several flurbiprofen amides and hydrazones exhibited superior analgesic, antipyretic and anti-inflammatory activities compared to flurbiprofen, Nitroflurbiprofen caused significantly less gastric lesions than flurbiprofen and many

more. Some of the important therapeutic properties of Nitroflurbiprofen are- antiinflammatory, analgesic and antipyretic activitives. Flurbiprofen is an analgesic, antipyretic and anti-inflammatory compound which is practically insoluble in water.



Flurbiprofen

THERAPEUTIC USES OF FLURBIPROFEN

The aqueous solution of flurbiprofen using various hydrotropes has been attempted. The aqueous injections of flurbiprofen were evaluated for antinflammatory and analgesic activities with promising results [1]. The physicochemical, pharmacokinetic and pharmacodynamic properties of flurbiprofen formulate is a worthy member of this series for transdermal drug delivery [2,3]. The anti-inflammatory effect of flurbiprofen tape (FLB-T) by topical application has been investigated to adjuvant arthritic in rats. The gastric damage induced by topical application of FLB-T was found extensively less than that seen in case of oral administration of flurbiprofen [4]. It is mainly metabolized in the liver, which attracts its suitability for percutaneous delivery [5-7].

FLURBIPROFEN AS ANALGESIC, ANTIPYRETIC AND ANTINFLAMMATORY AGENT

Several flurbiprofen amides and hydrazones have been found to exhibit superior analgesic, antipyretic and antinflammatory activities as compared to flurbiprofen [8]. Flurbiprofen axetil (FLB-A) which dissolved in lipid microsphere may encourage aggregation of flurbiprofen granular at inflammatory lesion sites and absorption in a small time, both factors which help to efficiently target therapy. Flurbiprofen has been found to be highly effective in neuroprotection in neuro-degeneration [9]. Flurbiprofen, a non-steroidal anti-inflammatory drug (NSAID) of the propanoic acid class used for the release of pain and inflammation associated with rheumatoid arthritis, osteo-arthritis and for the inhibition of entraoperative miosa [10]. Flurbi-nitroxybutylester a novel anti-inflammatory drug has improved antithrombotic activity. It has been shown that the beginning of a nitroxybutylester moiety into flurbiprofen to form Flurbi-nitric oxide resulted in a compound with distinctly reduced undesired property in the gastrointestinal tract. This effect has been described to be linked to nitric oxide release from the Flurbi-nitricoxide [11].

PHYSIOCHEMICAL-PROPERTIES OF FLURBIPROFEN

The physiochemical-properties of flurbiprofen and its short half-life make it appropriate for administration by oral route. The objective of the study was to prepare gel of Flurbiprofen using different gelling agent. The anti-inflammatory effect of flurbiprofen take place using reversible inhibition of cyclooxygenase (COX), the enzyme liable for the conversion of arachidonic acid to prostaglandin G2 (PGG2) and PGG2 to prostaglandin H2 (PGH2) in the prostaglandin synthesis pathway. This effectively decreases the concentration of prostaglandin implicated in inflammation, pain, swelling and fever. Flurbiprofen is a nonselective COX inhibitor and inhibits the activity of both COX-1 and COX-2. It is also one of the most effective NSAID in terms of prostaglandin inhibitory activity [12]. Flurbiprofen with Eudragit, hydroxylpropylmethyl cellulose and ethyl cellulose combination has been used in design oral controlled release preparations with better anti-inflammatory activity [13]. Flurbiprofen were prepared using hydroxypropylmethylcellulose, carbopol, Lutrol F-127 as gel forming polymers. All gel formulations developed contain ethanol and propylene glycol which in combination enhance permeability of gels [14].

FLURBIPROFEN IN THE FORM OF GEL

In order to decrease systemic side effects following oral administration, flurbiprofen has been formulated as transdermal gels consisting of the drug. Poloxamer 40 and EtOH in buffer solutions [15]. The gels were evaluated for physical emergence, rheological activities, drug release and stability. Flurbiprofen is exhaustively use for the treatment of Rheumatoid arthritis. Rheumatoid arthritis is a form of chronic arthritis which mainly affects young adults, mainly in womens.It also occurs in children (Still's Disease). It generally affects the joints & their synovial membranes, cartilages, capsules and the muscles supplying them [16-18]. The adhesive preparations contain nonsteroidal antinflammatory and analgesic agents like flurbiprofen has also been reported to show superior linkage to human skin and stretchability [19]. Inflammatory activity of 1% flurbiprofen transdermal gel was evaluated using the carrageenan-induced rat paw edema technique [20]. Now-a-days there are better consciousness of the potential consequence of modified-release medium of sparingly soluble drugs such as flurbiprofen. These can be prepared by combination of the drug with hydrophobic polymer. These hydrophobic matrices help to time-consuming the rate of drug dissolution and hence prolong its discharge [21-22].

FLURBIPROFEN AS AN OINTMENT

An ointment base for nonsteroidal antinflammatory agent flurbiprofen has been found effectively helpful in the treatment of periodontitis without impatience. When the ointment was applied to the wet oral tissue such as mucosa, it stays locally with persistent drug release. Such type of an ointment [23] contained carboxyvinyl polymers 2.0, ethanol 30.0, water 15.0, vinyl acetate resion 5.0, flurbiprofen 0.2, IN-NaOH q.s. and glycerol to 100.0%. Similarly, an application of a paste containing flurbiprofen 0.5, hydroxypropyl methyl cellulose-2910-10.0, carboxyvinyl polymer 2.0, glycerine 10.0, EtOH 10.0 wt. % NaOH and water to gingiva hamsters nourish with soft food, suppressed alveoloclasia and gingivitis [24]. In rheumatoid arthritis, the level of C-reactive protein increase early morning leading to enhanced pain and irritation. Chronotherapy for all forms of arthritis using non-steroidal anti-inflammatory drugs (NSAIDs) should be time to make sure that the highest blood levels of the drug coincide with intense pain. Flurbiprofen a NSAID is selected for treatment of rheumatoid arthritis, rheumatoid arthritis requires time-dependent drug liberate for maximum remedial benefits [25].

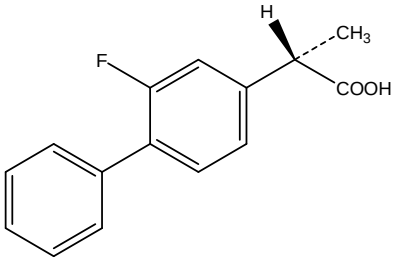
SEMISOLID FORMULATION OF FLURBIPROFEN

A semisolid formulation containing flurbiprofen for the treatment of gingivitis comprise hydroxyethyl cellulose (HEC: 3, 5, 10%), PVP (3, 5%), polycarbophil (PC: 1, 3, 5%) and flurbiprofen (5%) [26]. Administration of nonsteroidal anti-inflammatory flurbiprofen on tissue curing after periodontal surgery has been reported to be very effective [27]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are extensively used to indulgence chronic pain of musculoskeletal disorders such as rheumatoid arthritis (RA) and osteoarthritis (OA). Profens, including ibuprofen, ketoprofen and flurbiprofen are often prescribed for the treatment of articular diseases. In the ancient period, the 2-aryl propionic acid NSAIDs were developed in the form of a racemic mixture, even though they occurred in enantiomeric pairs differing in the COX inhibitory action [28,29].

FLURBIPROFEN AS A NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID)

Flurbiprofen (an effective nonsteroidal anti-inflammatory, analgesic and antipyretic drug) has been reported to be efficient in the treatment of rheumatoid arthritis and degenerative joint diseases. Emulsification-solvent evaporation technique was used for the preparation of flurbiprofen microcapsule to manage the release of flurbiprofen [30]. Flurbiprofen (FLB) is a representative drug of the chiral NSAIDs of the 2- arylpropionic acid class and S(+)-flurbiprofen (SFP) has been exposed to be a more potent COX inhibitor than the R(−)-flurbiprofen (RFP) enantiomer. We earlier showed that SFP inhibits human cyclooxygenase (COX)-1 and COX-2 more potently than other conventional NSAIDs. We showed in an experimental study using rats that the NSAID patch developed by us, the

S-flurbiprofen plaster (SFPP), containing an (S)-enantiomer of flurbiprofen was recognized to quickly suppress inflammatory pain in the rat, AIA model and also to show better absorbability as compare to ketoprofen and loxoprofen patches [31].



S(+)-flurbiprofen

FLURBIPROFEN AS AN ANTI-ARTHRITIC AGENT

It has been described that pyridinoline excretion enhanced specifically in unprocessed adjuvant arthritic (AA) rats, but was significantly normalized by either CMT3 alone or by CMTS with flurbiprofen. CMT3 or CMT8 are chemically modified non-antimicrobial tetracycline derivatives [32]. Recently, flurbiprofen has been reported to decrease the resorption of alveolar bone in naturally occurring chronic destructive periodontal disease in dogs [33]. In addition, we report that the better percutaneous absorption and greater tissue penetration of SFP into the human synovial tissue following significance of SFPP in knee osteoarthritis (OA) patients [34].

OPTICALLY ACTIVE FLURBIPROFEN

R-flurbiprofen has also been found to be very useful in the treatment of neoplastic diseases such as breast cancer, lung cancer, prostate cancer as well as cystic fibrosis and Alzheimer's disease. Interestingly, R-flurbiprofen was revealed to be much less ulcerogenic than its S-enantiomer, however suppresses cell proliferation in the distal colon [35]. Flurbiprofen (FLB) a non-steroidal anti-inflammatory (NSAID) drug is also effective for the treatment of fever, pain and inflammation in the body. The most significant inconvenient reactions that appear after FLB administration contain gastrointestinal tract (GIT) as well as peptic ulcer, dyspepsia, cramping, gastric bleeding substantial in the treatment of liver failure and patient incompliance [36].

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been acknowledged for inhibiting extension of colon tumours in animal models and for declining the risk of colon cancer in humans. R- and S-flurbiprofen considerably reduced colonocyte cataloguing index by 34 and 23% respectively. These findings suggested that R-flurbiprofen mediated control of colonocyteproliferation is self-governing of prostaglandin biosynthesis [37]. FLB requires regular administration round the clock to attain its essential remedial effects due to its short biological half-life (2-6 hrs). Therefore, constant release dosage form of FLB that may have a potential to keep remedial level of FLB in plasma for prolonged phase may avoid its toxic effects on GIT and will recover its area of application. Oral continuous release of dosage forms are known to have numerous advantages over their instantaneous counterpart nevertheless, the drug must be disseminate adequately through well defined polymeric template system [38]. In another report, Chemo preventive effects of R-flurbiprofen (R-FLB), the noncyclooxygenase-inhibiting enantiomer, could be well-known to humans for prophylaxis and in the cure of colon cancer [39].

RADIO PROTECTIVE EFFECTS OF FLURBIPROFEN

Radio protective effects of two nonsteroidal anti-inflammatory drugs (NSAIDs), flurbiprofen (FLB) and its Nobel nitro derivative flurbiprofen-4-nitroxybutylester (Flurbi-NO), which exhibit decreased gastrointestinal toxicity was compared in mice. Because of its lower potential for gastrointestinal damage, Flurbi-NO seemed to be a promising drug, which can find use in the protection of post-

irradiation myelosuppression [40]. Frequent administration of flurbiprofen,{an inhibitor of prostaglandin synthesis (IPS)} has been found to enhance hemopoiesis in mice exposed to sublethal dose of fractionated y-irradiation.The findings show an opportunity to expand the radiation dose range, also to higher lethal radiation doses, by administer flurbiprofen instead of Earlier studied IPS indomethacin or diclofenac [41]. Compounds containg a nitric oxide generator and methods of use for treating dry eye have been now discarded. The compounds of the invention encourage nitric oxide production when administered to the eye. It is believed that Nitric Oxide stimulates mucin production in human conjunctival epithelium and is therefore believed to be useful in treating dry eye [42].

High doses of FLB can be included in microspheres with EC because of its least chances of dose dumping which may result in severe gastric and mucosal irritation. Hydroxypropyl methylcellulose (HPMC) is another semi-synthetic ether derivative of cellulose used in this study. Due to its non-toxic nature, ease of compression and accretion to high levels of drug loading, it has been a leading hydrophilic vehicle used in controlled release dosage forms. The hydration rate of HPMC increases with the increase of hydroxypropyl content and solubility (which is pH independent) [43].

COMPARATIVE STUDY OF R & S FLURBIPROFEN

The doses of R & S-flurbiprofen used in these experiments did not generate any tranquillizing effects in rats subjected to behavioural testing [44]. Flurbiprofen (FLB) is a drug that belong to non steroidal anti-inflammatory drug (NSAID) used for the treatment of colonic pain and inflammation. Regular administration of NSAID like FLB causes the gastric ulceration, bleeding and other gastric problems [45].

In a review with 85 references, the S-enantiomer of flurbiprofen has been revealed to have both antinflammatory and antinociceptive effects, whereas R-flurbiprofen is antinociceptive but not antinflammatory. Significantly, R-flurbiprofen did not undergo considerable chiral inversion to S-flurbiprofen in rats and humans. The findings may be of clinical importance, as it was demonstrated that both enantiomers were also antinociceptive in humans. Because of the less toxic nature of R-flurbiprofen in rats than the S-enantiomer or the racemic mixture, the most significant side effect in the gastrointestinal tract might be achieved with the use of R-flurbiprofen meant for pain therapy [46].

NITROFLURBIPROFEN

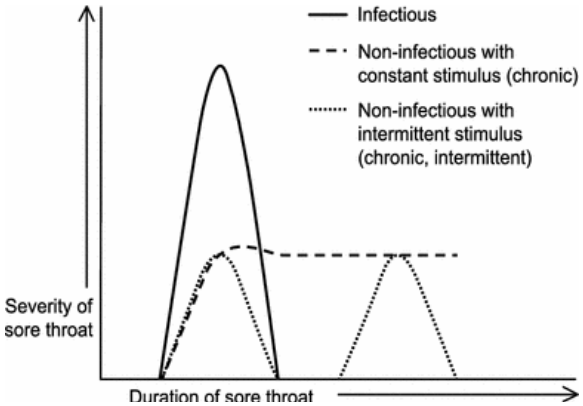
Nitroflurbiprofen caused significantly less gastric lesions than flurbiprofen, perhaps because of its capacity to release nitric oxide (NO) in the stomach [47]. Flurbiprofen (FLB) has been esterifies with a histamine H-antagonist, to acquiesce a chimera drug, FLB-PPA and its protective effect towards gastric lesions, other toxicities and the deposition kinetics were investigated, as compared to those of flurbiprofen. The results obtained here indicated undoubtedly that the chimera drug FLB-PPA scarcely forms any disorder of the gastric mucosa, even after multiple oral administration and thus is a potential medicine for oral use [48]. Some of the recent research examples reported in literature on colon specific FLB tablets are time-dependent sodium alginate compression coated tablets [49], time-dependent pulsatile tablets [50] and controlled release matrix tablets [51].

Nitric oxide (NO) has also been reported to have paradoxical effects in experimental endotoxic shock, contributing to the hemodynamic consequences of endotoxic supervision, but apparently protecting the gastrointestinal mucosa. A Nobel class of NO-releasing nonsteroidal anti-inflammatory drugs (NSAIDs) has recently been described which apply anti-inflammatory activities but create less gastrointestinal injury than the parent nonsteroidal antinflammatory drugs from which they are derived. These results demonstrated that flurbiprofen-4-nitroxybutyl ester is capable of defending the gastrointestinal mucosa from injury probably through conservation of mucosal blood flow [52].

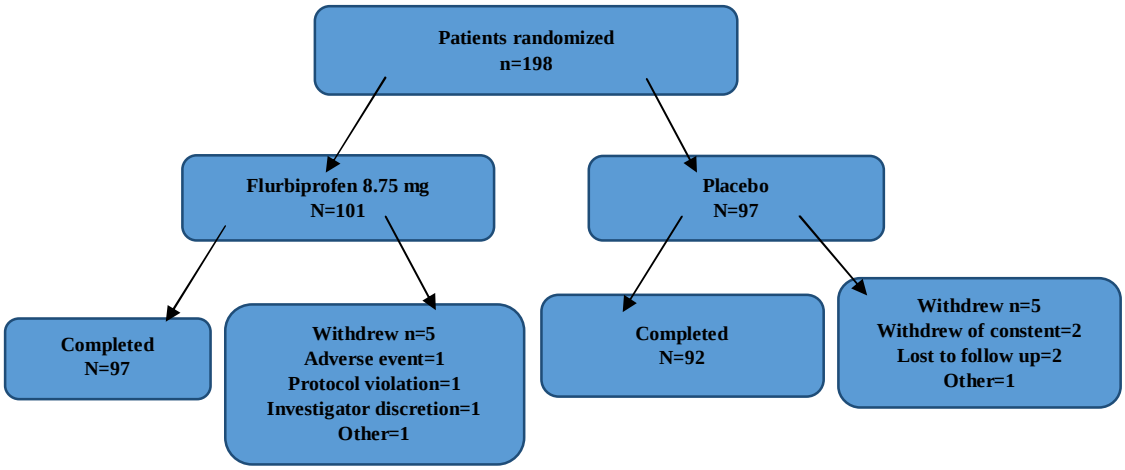
FLURBIPROFEN USED IN THE CATARACT SURGERY AS WELL AS IN THE FORMATION OF OPHTHALMIC SOLUTION

Traditionally, colon target is achieved with approach like prodrug, pH-sensitivity, microbial degradation dependent and time dependent approaches [53]. Development of colon-specific medicine is useful in the treatment of limited disorders of colon as well as to improve the liberation of proteins and peptides [54]. A lot of topical NSAIDs used in the treatment and prevention of ocular inflammation include, indomethacin 0.1% &1.0%, flurbiprofen 0.03%, ketorolac tromethamine 0.4%, 0.45%, 0.5%, diclofenac 0.1%, nepafenac 0.1% and bromfenac 0.09%. The important roles of these are for the prevention of intraoperative miosis during cataract surgery, administration of postoperative inflammation, the diminution of pain, nervousness after cataract, refractive surgery and for the prevention as well as the treatment of cystoid macular edema (CME) after cataract surgery [55].

Many additional therapeutically vital activities of nonsteroidal antinflammatory drugs (NSAIDs) including flurbiprofen are available in the literature. Some of them are - flurbiprofen supported aspirin like drugs (ALD) in protection of human T lymphocytes against benzoquinone (BQ) cytotoxicity [56]. Flurbiprofen 0.03% ophthalmic solution is a propionic acid derivatives used for the prevention of intra operative miosis and is also used for treatment of pain and inflammation subsequent to cataract surgery [57]. Flurbiprofen, a non-steroidal anti-inflammatory drug (NSAID), targets inflammation, a key reason of painful throat symptoms [58,59].



Nonsteroidal antinflammtory drugs resourcefully reduced the transport and cytotoxicity of adefovir mediated by the human renal organic anion carrier. Adefovir is a nucleotide analogue with anti-human immunodeficiency virus (HIV) activity that has been comprehensively studied in clinical trials [60]. Earlier studies have confirmed the effectiveness of flurbiprofen lozenge and granule formulations (8.75mg per dose) for symptomatic reinforcement of painful throat [61-63].



Flurbiprofen has also been found to be useful in controlling the neurovascular deficit in diabetic rats, from which a potential therapeutic advantage could be derived [64].Throat Pain Model is another method which has been used for studies of flurbiprofen 8.75mg lozenge [65,66]. Antibiotics do not provide instantaneous or positive relief and have inequitable impact for bacterial aching throat (symptoms reduced by 16-hours over seven days of sore throat) [67,68]. The importance of flurbiprofen in bone supporting dental implant has also been described [69] etc.

Postoperative pain may effect in patient distress and reduce patient satisfaction [70]. Bone removal orbital decompression, being a multifaceted ophthalmic surgery, can lead to rigorous pain, with considerably advanced postoperative pain scores than other oculoplastic surgeries. Postoperative pain is a major problem subsequent orbital decompression [71,72]. Various topical NSAIDs used in the treatment and prevention of ocular inflammation include, indomethacin 0.1%, & 1.0%, flurbiprofen 0.03%, ketorolac tromethamine 0.4%, 0.45% and 0.5%, diclofenac 0.1%, nepafenac 0.1% and bromfenac 0.09%. The important role of these are-: prevention of intraoperative miosis during cataract surgery, management of postoperative inflammation, the reduction of pain and discomfort after cataract and refractive surgery, the prevention and treatment of cystoid macular edema (CME) after cataract surgery [73].

Flurbiprofen 0.03% ophthalmic solution is a propionic acid derivative approved by FDA for the prevention of intra operative miosis and is also used for treatment of pain and inflammation after cataract surgery [74]. Several studies have demonstrated that the addition of topical NSAIDs to topical corticosteroid treatment leads to less patient discomfort reduced postoperative inflammation, prevention of miosis and improvement in visual acuteness in the early postoperative period relative to patients treat with topical steroids alone [75,76]. Each type of NSAID ophthalmic solution has its own characteristics. Thus, treatment effects may differ among various drugs [77].

FLURBIPROFEN AS A CYCLOOXYGENASE (COX) INHIBITOR

NSAIDs have been shown efficiently decrease in postoperative pain [78]. Flurbiprofen axetil is an injectable nonselective cyclooxygenase (COX) inhibitor that is mainly metabolized into flurbiprofen by hydrolysis; its analgesic effect is assumed to result from the reversible inhibition of COX and the peripheral inhibition of prostaglandin synthesis. Moreover, the drug has shown no irreversible carcinogenic, teratogenic or hepatotoxic effects. However, in this recent study, 45.7% patient's experienced significant postoperative pain with preoperative management of intravenous flurbiprofen axetil [71]. In general,opioid are vital analgesic agents for postoperative pain management. Nalbuphine, a κ-receptor agonist and μ-receptor antagonist, a semisynthetic opioid analgesic that belongs to the phenanthrene family. This drug may give effectual pain relief with less opioid-induced adverse effects than other opioids [79]. Regrettably, Nalbuphine offers a period of analgesia of only 4–5 hours, which is extremely short for postoperative pain management [80]. It is clear that particular flurbiprofen axetil or Nalbuphine is not effective in adequate amount of for postoperative pain control following orbital decompression and there is convincing indication that multimodal analgesia is the best alternative for pain management [81].

Flurbiprofen inhibits both COX enzymes effectively [82]. Prolong oral use of this drug is adversely reported with gastric lesions and inflammation at epithelial lining. In order to avoid above inconvenience, sustained release of flurbiprofen was racked up by amino acid ethyl esters using L-arginine, L-lysine and L- phenylalanine [83]. Amide conjugates of flurbiprofen with various amino acid methyl esters synthesised by Schotten-Baumann method showed increased aqueous solubility, significant activity with reduced ulteration [84]. Dextran prodrug by conjugating N-acyl imidazoles derivative of flurbiprofen and suprofen with dextran40-000, 60-000 and 110000 also displayed the same good results [85]. Increased hydrophlicity, less ulcerotoxicity and colon specificity were achieved by coupling flurbiprofen with L-glysine to form an amide prodrug [86]. Flurbiprofen for transdermal delivery using pronisomers as carrier was tabled in recent past [87]. Novel emulsion of flurbiprofen axetil was prepared by high pressure homoorganisation using tween 80 as an emulsifier and the results proved that it was a promising formulation for ophthalmic anti-inflammatory activity [88]. Lipid nanocarriers containing ester prodrugs of flurbiprofen using pegylated nanostructures

lipid carriers were processed for paternal administration [89]. Flurbiprofen is a potent anti-inflammatory, analgesic, and antipyretic agent belonging to the family of propionates but has not been used as extensively as many of the newer ones, possibly because it requires round the-clock administration due to its shorter half-life (2–6 hours) and has harmful gastric side effects [90].

FURBIPROFEN AS AN ANTI SURGICAL SCRATCHES AGENT

Nonsteroidal anti-inflammatory drug (NSAID) with high similarity to the location of surgical scratches and inflammatory tissues provide postoperative pain relief after dissimilar types of surgeries. The aim of this study was to estimate the postoperative pain, cognitive function and serum levels of pro-inflammatory cytokines in patients undergoing hip arthroplasty surgery with pre- or intraoperative flurbiprofen [91].

FURBIPROFEN AS AN ANTI-DYSMENORRHEA AGENT

"Nonsteroidal antiinflammatory agents," "aspirin," "diclofenac," "flurbiprofen," "ibuprofen," "indomethacin," "ketoprofen," "mefenamic acid," "nimesulide," "piroxicam," "rofecoxib," "tiaprofenic acid" and "valdecoxib" in searching procedure (Supplemental Material) are very valuable against Dysmenorrhea disease. Dysmenorrhea is commonly divided into two types: primary dysmenorrhea (PD) and secondary dysmenorrhea. PD is defined as the hypogastric pain originated from uterine without pathology throughout menstrual period which often occurs with the menarche or after the establishment of the ovulatory cycles of reproductive women and usually lasts two or three days during each period [92]. About 43%–91% adolescent females (under 20 years) are reported with PD and show a deteriorating resemblance as the age grows older [93]. Women experiencing harsh PD will be debilitated to accomplish daily works, even absent from school or job. According to the prior studies, PD is frequently measured to be the consequence of abnormal prostaglandin release which leads to strong contracts of uterus and reduced oxygen supply to the uterus muscles [94]. In addition, unhealthy lifestyle (such as smoking, intemperance and stressfulness) and family history may also have some negative influence on the symptoms of PD [95].

FLURBIPROFEN AS AN ENZYMATIC INHIBITOR/PROMOTER

In previous few years, enzymatic resolution has become more attractive than organic synthesis due to its environmental friendliness, mild reaction conditions and high enantioselectivity [96]. Many optically active pharmaceutical, agricultural and special chemicals can be prepared via enzymatic resolution [97]. (R, S)-Flurbiprofen is one of the most prevalent nonsteroidal antiinflammatory drugs [98]. The therapeutic use of (R, S)-flurbiprofen resides mostly in its S-enantiomer while its R-enantiomer enhances the gastrointestinal toxicity [99]. Consequently, the preparation of (S)-flurbiprofen is strongly recommended. A lot of information has been demonstrated that (S)-flurbiprofen could be obtained via lipase-catalyzed enantioselectivity esterfication [100-103]. However, the comparatively low activity and enantioselectivity were generally found in those studies. Another drawback is the use of organic solvents. Usual organic solvents are volatile and toxic to the environment. In addition, organic solvents also deactivate the enzyme, particularly at high temperatures. Due to the negligible vapour pressure, high thermal stability, reuse and the excellent biocompatibility, room-temperature ionic liquid (IL) has been successfully used as an alternative medium for enzymatic reactions [104-107]. Scientists have reported that the enantioselectivity of lipase for the resolution of 2-methyl-1-butanol was improved about 2.3-fold in an IL than that in organic solvent [108]. Another scientist has also reported that choosing proper combination of cations and anions could boost the activity of lipase by changing the conformation of protein in ILs [109]. Another advantage of ILs is that they can be easily recovered and reutilized as the enzymatic reaction media [110,111].

FLURBIPROFEN AS AN ANALGESIC AGENT

Flurbiprofen axetil cannot only induce preventative analgesia, but also can diminish inflammatory response during extubation [112]. As an analgesic carrier, flurbiprofen axetil has the features of a non-

selective & non-steroidal drug and achieves a targeted effect [113]. Analgesia can be easily induced and the analgesic effect can last for a long period of time. Flurbiprofen axetil achieves its analgesic effect by inhibit epoxidase and reducing the uptake of prostaglandins by prostaglandin synthesis cells [114,115]. Side effects of flurbiprofen axetil, such as important inhibition and gastrointestinal bleeding are comparatively rare [116]. Thus, from the above findings, it seems that flurbiprofen and its various combinations / derivatives are potentially very important for the cause of pharmacological interest.

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