LITERATURE REVIEW OF NSAIDs AND DRUGS SELECTED

Inflammation\(^1\) is defined as a directed tissue response to noxious and injurious, external and internal stimuli. Cell damage associated with inflammation acts on cell membranes to cause leukocytes to release lysosomal enzymes; arachidonic acid is then liberated from precursor compounds and various eicosanoids are synthesized. Cyclooxygenase (COX)\(^2\) pathway of arachidonate metabolism produces prostaglandins, which have a variety of effects on blood vessels, on nerve endings and on cells involved in inflammation. Among the COX isoforms, COX-1 is constitutively present in nearly all cell types at a constant level and tends to be homeostatic in function\(^3\). It produces the prostaglandins necessary for the autocrine/paracrine responses and for the maintenance of normal renal functions, integrity of gastric mucosa and hemostasis. High concentrations of COX-1 are found in platelets, vascular endothelial cells, stomach and collecting tubules in kidneys. COX-2 activity is normally absent from cells (except those of kidneys and brain), but is induced\(^3\) during inflammation and tends to facilitate the inflammatory response.

Anti-inflammatory activity of NSAIDs is mediated chiefly through inhibition of biosynthesis of prostaglandins by inhibiting COX enzymes either non-selectively (inhibition of both COX-1 and COX-2) or selectively (inhibition of COX-2). Inhibition of COX-2 is thought to mediate the anti-pyretic, analgesic and anti-inflammatory actions of NSAIDs, but the simultaneous inhibition of COX-1 results in unwanted side effects, particularly those leading to gastric ulcers, most common side effect associated with non-selective COX inhibitors. NSAIDs are characterized by their ability to relieve pain without interacting with opioid receptors. They possess anti-platelet activity to varying degree and are non-addicting. These drugs are chemically diverse, but most are organic acids with ionization constants...
ranging from 3.0 to 11.0. They have varying degrees of lipid solubility and are absorbed almost completely orally. They are highly protein bound and have small volumes of distribution. They are classified as

4.1 Non-Selective COX Inhibitors:

A. Salicylates and their congeners

Aspirin, Sodium Salicylate, Diflunisal, Salsalate, Sulfasalazine

B. Para-aminophenol derivatives

Acetaminophen

C. Pyrazolone derivatives

Phenylbutazone, Oxyphenbutazone

D. Indoles and related drugs

Indomethacin, Sulindac

E. Heterocyclic arylacetic acid derivatives

Diclofenac, Tolmetin, Ketorolac

F. Propionic acid derivatives

Ibuprofen, Fenprofen, Naproxen, Ketoprofen, Flurbiprofen.

G. Anthranilic acid derivatives (fenmates)

Flufenamic acid, Mefenamic acid
H. Oxicams

Eterocoxib, Tenoxicam

4.1.1. Preferential COX-2 Inhibitors:

Nimesulide, Meloxicam, Nabumetone.

4.1.2. Selective COX-2 Inhibitors:

Celecoxib, Eterocoxib, Parecoxib, Etoricoxib
4.2. ETORICOXIB DRUG PROFILE

Chemical Name: 5-chloro-2-[6-methyl pyridin-3-yl]-3-[4-methylsulfonylphenyl] pyridine.

Molecular Formula: C₁₈H₁₅Cl N₂O₂ S

4.2.1. Structure:

4.2.2. Molecular Mass: 358.84

4.2.3. Therapeutic Category: Non-steroid anti-inflammatory drug (high selective COX-2 inhibitor)

4.2.4. Pharmacopoeial Status: Not recommended in any pharmacopoeia
4.2.5. PHYSICAL PROPERTIES

4.2.5.1. Description: It is a white of off-white crystalline powder.

4.2.5.2. Solubility:

A) Freely soluble in

- Methanol, Tetrahydrofuran, Dimethyl-sulphoxide, Methyl-ethyl ketone, Dimethyl formamide chloroform.

B) Soluble in

- Isopropyl acetate, Ethanol, Toluene.

C) Sparingly soluble in

- 2-propanol

D) Practically insoluble in water.

4.2.5.3. Storage: Store in a tight container.

4.2.6. Therapeutic indication:

- Symptomatic relief of osteoarthritis (OA).
- Rheumatoid arthritis (RA).
- The pain and signs of inflammation associated with acute gouty arthritis.
4.2.6.1. Dosage:

Etoricoxib is administered orally and may be taken with or without food. The onset of drug effect may be faster when Etoricoxib is administered without food. This should be considered when rapid symptomatic relief is needed.

\(a\) Osteoarthritis

- The recommended dose is 60 mg once daily.

\(b\) Rheumatoid arthritis

- The recommended dose is 90 mg once daily.

\(c\) Acute gouty arthritis

- The recommended dose is 120 mg once daily. Etoricoxib 120 mg should be used only for the acute symptomatic period. In clinical trials for acute gouty arthritis, Etoricoxib was given for 8 days.

Doses greater than those recommended for each indication have either not demonstrated additional efficacy or have not been studied. Therefore, the dose for each indication is the maximum recommended dose:

- The dose for OA should not exceed 60 mg daily
- The dose for RA should not exceed 90 mg daily
- The dose for acute gout should not exceed 120 mg daily, limited to a maximum of 8 days treatment.

As the cardiovascular risks of Etoricoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used.

**Elderly:** No dosage adjustment is necessary for elderly patients.
**Hepatic insufficiency:** In patients with mild hepatic dysfunction (Child-Pugh score 5-6) a dose of 60 mg once daily should not be exceeded. In patients with moderate hepatic dysfunction (Child-Pugh score 7-9) the recommended dose of 60 mg every other day should not be exceeded.

Clinical experience is limited particularly in patients with moderate hepatic dysfunction and caution is advised. There is no clinical experience in patients with severe hepatic dysfunction (Child-Pugh score 2:10); therefore, its use is contra-indicated in the patients given below.

**Renal insufficiency:** No dosage adjustment is necessary for patients with creatinine clearance $\geq 30$ ml/min. The use of Etoricoxib in patients with creatinine clearance $<30$ ml/min is contra-indicated.

**Pediatric use:** Etoricoxib is contra-indicated in children and adolescents under 16 years of age.

**4.2.7.CONTRA-INDICATIONS:**

1. History of hypersensitivity to the active substance or to any of the recipients.
2. Active peptic ulceration or active gastro-intestinal (GI) bleeding.
3. Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria, or allergic-type reactions after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors.
4. Pregnancy and lactation.

5. Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥10).

6. Estimated renal creatinine clearance <30 mL/min.

7. Children and adolescents under 16 years of age.


9. Patients with hypertension whose blood pressure has not been adequately controlled.

10. Established ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease,

4.2.7.1. OVERDOSE:

- No overdoses of Etoricoxib are reported during clinical trials.

- In clinical studies, administration of single doses of Etoricoxib up to 500 mg and multiple doses up to 150 mg/day for 21 days did not result in significant toxicity.

- In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the GI tract, employ clinical monitoring, and institute supportive therapy, if required.

- Etoricoxib is not dialyzable by haemodialysis; it is not known whether Etoricoxib is dialyzable by peritoneal dialysis.
4.2.8. MECHANISM OF ACTION:

- ARCOXIA™ (Etoricoxib) selectively inhibits cyclooxygenase (COX)-2, the isoform associated with pain and inflammation.
- COX occurs in COX-1 and COX-2 isoforms.
- COX-1 is constitutively expressed in various tissues as part of normal cellular function.
- COX-2, believed to be induced by proinflammatory cytokines, is increased in inflamed tissues.
- Both newer and older NSAIDs inhibit COX, but newer NSAIDs selectively inhibit COX-2, the isoform associated with pain and inflammation.

4.2.9. PHARMACOKINETICS:

4.2.9.1. Absorption

Orally administered Etoricoxib is well absorbed. The absolute bioavailability is approximately 100%. Following 120 mg once-daily dosing to steady state, the peak plasma concentration (geometric mean Cmax = 3.6 µ/ml) was observed at approximately 1 hour (Tmax) after administration to fasted adults. The geometric mean area under the curve (AUC:0-24hr) was 37.8 µg-hr/ml. The pharmacokinetics of Etoricoxib is linear across the clinical dose range.
Dosing with food (a high-fat meal) had no effect on the extent of absorption of Etoricoxib after administration of a 120-mg dose. The rate of absorption was affected, resulting in a 36% decrease in Cmax and an increase in Tmax by 2 hours. These data are not considered clinically significant. In clinical trials, Etoricoxib was administered without regard to food intake.

4.2.9.2. Distribution

Etoricoxib is approximately 92% bound to human plasma protein over the range of concentrations of 0.05-5 µ/ml. The volume of distribution at steady state (Vdss) was approximately 120 l in humans. Etoricoxib crosses the placenta in rats and rabbits, and the blood-brain barrier in rats.

4.2.9.3. Metabolism

Etoricoxib is extensively metabolized with <1 % of a dose recovered in urine as the parent drug. The major route of metabolism to form the 6'-hydroxymethyl derivative is catalyzed by CYP enzymes. CYP3A4 appears to contribute to the metabolism of Etoricoxib in vivo. In vitro studies indicate that CYP2D6, CYP2C9, CYPIA2 and CYP2CI9 also can catalyse the main metabolic pathway, but their quantitative roles in vivo have not been studied. Five metabolites have been identified in man. The principal metabolite is the 6'-carboxylic acid derivative of Etoricoxib formed by further oxidation of the 6'-hydroxymethyl derivative. These principal metabolites either demonstrate no measurable activity or are only weakly active as COX-2 inhibitors. None of these metabolites inhibit COX-1.
4.2.9.4. Elimination

Following administration of a single 25-mg radio-labeled intravenous dose of Etoricoxib to healthy subjects, 70% of radioactivity was recovered in urine and 20% in faces, mostly as metabolites. Less than 2% was recovered as unchanged drug. Elimination of Etoricoxib occurs almost exclusively through metabolism followed by renal excretion. Steady state concentrations of Etoricoxib are reached within seven days of once daily administration of 120 mg, with an accumulation ratio of approximately 2, corresponding to a half-life of approximately 22 hours. The plasma clearance after a 25-mg intravenous dose is estimated to be approximately 50 ml/min.

4.2.10. Drug Interactions:

1. **ACE inhibitors**: May diminish the antihypertensive effect of ACE inhibitors.

2. **Aspirin**: Concomitant administration of low doses of Aspirin with Etoricoxib may lead to increased risk of GI ulceration or bleeding.

3. **Digoxin**: Patients should be carefully monitored for any toxicity, as there is an increase in Cmax of Digoxin by 33%.

4. **Diuretics**: NSAIDs can reduce natriuretic effect of Furesemide and thiazides because of inhibition of renal prostaglandin synthesis.

5. **Lithium**: NSAIDs cause increase in lithium levels in plasma and reduction in renal lithium clearance.

6. **Warfarin**: Anticoagulant activity should be carefully monitored particularly during first few days, when Etoricoxib is prescribed to patients on Warfarin therapy.
4.2.11. PRECLINICAL SAFETY DATA:

In preclinical studies, Etoricoxib has been demonstrated not to be genotoxic. Etoricoxib was not carcinogenic in mice. Rats developed hepatocellular and thyroid follicular cell adenomas at >2-times the daily human dose [90 mg] based on systemic exposure when dosed daily for approximately two years. Hepatocellular and thyroid follicular cell adenomas observed in rats are considered to be a consequence of rat-specific mechanism related to hepatic CYP enzyme induction. Etoricoxib has not been shown to cause hepatic CYP3A enzyme induction in humans. In the rat, gastrointestinal toxicity of Etoricoxib increased with dose and exposure time. In the 14-week toxicity study Etoricoxib caused gastrointestinal ulcers at exposures greater than those seen in man at the therapeutic dose. In the 53- and 106-week toxicity study, gastrointestinal ulcers are also seen at exposures comparable to those seen in man at the therapeutic dose. In dogs, renal and gastrointestinal abnormalities are seen at high exposures.

Etoricoxib was not teratogenic in reproductive toxicity studies conducted in rats at 15 mg/kg/day (this represents approximately 1.5 times the daily human dose [90 mg] based on systemic exposure). In rabbits, no treatment-related external or skeletal foetal malformations are seen. A non-dose-related low incidence of cardiovascular malformations was observed in Etoricoxib-treated rabbits. The relationship to treatment is not established. In rats and rabbits, no embryo/foetal effects are seen at systemic exposures equal to or less than those at the daily human dose [90 mg]. However, there was a decrease in embryo/foetal survival at exposures greater than or equal to 1.5 times the human exposure. Etoricoxib is excreted in
the milk of lactating rats at concentrations approximately two-fold those in plasma. There was a decrease in pup body weight following exposure of pups to milk from dams administered Etoricoxib during lactation.

4.2.12. PAST WORK ON ETORICOXIB SOLID DISPERSIONS

Shamkant Shimpil\textsuperscript{17} et al. Evaluated the ability of (gelucire) in protection of amorphous etoricoxib Polymorphic transition and stability problems during amorphous drug formulation are the major limiting factors in pharmaceutical technology. The purpose of the study was to evaluate the ability of polyglycolized glycerides (Gelucire) in protection of amorphous form of drug during compression and shelf life with lower proportion. Amorphous etoricoxib (AET) was prepared by spray drying technique. Tablets of AET and melt granmes of AET (MG-AET) with Gelucire 50/13 were prepared. Tablets parameters like hardness, disintegration and content uniformity were evaluated. Tablets were evaluated immediately after compression and on storage for 3 months at ambient conditions to determine degree of transformation using X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) and dissolution profiles. Spray drying yielded the amorphous etoricoxib. Content uniformity in the tablet was in between 95 to 105%. Other parameters like disintegration and hardness were well within the limits. The results showed significant difference in the degree of crystallinity between AET tablet and MG-AET tablet. MG-AET tablet showed absence of crystallinity after 3 months storage. Polyglycolized glycerides (Gelucire 50/13) are able to protect amorphous etoricoxib during compression. As excipient required is low, it became possible to prepare tablet formulation as compared to other excipient like polyvinylpyrrolidon (PVP).
Poonam Karekar\textsuperscript{18} Etal. Solid dispersion systems of a poorly water-soluble drug, etoricoxib were prepared with poloxamer 188 in 1:0.5, 1:1.5 and 1:2.5 ratios and evaluated by FTIR, powder XRD and dissolution studies. Physical studies demonstrated strong hydrogen bonding with significant decrease in the crystallinity and formation of amorphous etoricoxib in its binary systems. All binary systems of etoricoxib showed faster dissolution than pure drug alone ($P < 0.001$). However, 1:2.5 proportion of etoricoxib: poloxamer 188 showed superior performance (DE$_{45}$: 71.27\% ± 3.85) in enhancing solubility and dissolution rate of etoricoxib suggesting optimum ratio of the carrier.

Shamkant Laxman Shimpi\textsuperscript{19} Etal: Studied the Methods of preparation and application of amorphous form are well established but it is equally important to note that devitrification of amorphous drugs has limited their applications. Present study was performed to investigate mechanism for amorphous drug stabilization using Gelucire in comparison with polyvinylpyrrolidone (PVP). Etoricoxib and celecoxib were taken as model drugs for this study, as etoricoxib has only proton accepting site for hydrogen bonding in comparison with celecoxib, which has both proton accepting and donating site. Solid dispersion of celecoxib with polyvinylpyrrolidone and Gelucire was prepared by spray drying and melt-granulation technique respectively. Dissolution of melt-granulation of amorphous celecoxib was improved significantly as compared to amorphous celecoxib and Celecoxib-PVP solid dispersion. Melt-granulation with lipid seemed to be more dominant than amorphization of drug for improving dissolution. Stability data revealed that PVP was significantly advantageous for amorphous form stabilization whereas Gelucire failed in case of Celecoxib. In contrast to this, our previous study revealed the stabilization ability of Gelucire for amorphous etoricoxib.
Bhaskar chauhan\textsuperscript{20} et.al has prepared and characterized Etoricoxib solid dispersions using hydrophilic lipid carriers polyglycolized glycerides (Gelucire) by spray drying technique and the in vitro dissolution test showed a significant increase in the dissolution rate of solid dispersions as compared with pure Etoricoxib and physical mixtures of drug with lipid carriers.

Bhanu Bhai N. Suhagia\textsuperscript{21} et.al: Studied the influence of polyethylene glycol 4000 (PEG) and polyvinylpyrrolidone K30 (PVP) on in \textit{vitro} dissolution of Etoricoxib from solid dispersions. Preliminary studies were carried out using a physical mixture of the drug and carriers. Solid dispersions were prepared using the solvent evaporation method. Improved dissolution was attributed to decreased crystallinity of the drug, improved wetting and solubilizing effects of carriers such as PEG and PVP from the solid dispersion of etoricoxib. In conclusion, dissolution of etoricoxib can be modulated using appropriate levels of hydrophilic carriers.

Haresh M. Patel\textsuperscript{22} et al: Studied the complexation of etoricoxib with cyclodextrin binary system of etoricoxib with (3-cyclodextrin (\(\beta\)-CD) was prepared by the kneading method. Drug-cyclodextrin interactions in solution were investigated by the phase solubility analysis. The results indicate partial interaction of the drug with (3-CD in the physical mixture and complete interaction in the kneaded complex. The dissolution of etoricoxib was notably increased as compared to pure drug as well as its physical mixture. The complex showed more than 75\% drug released in 30 min.
4.3.CELECOXIB – DRUG PROFILE

Celecoxib is used in the present study because it is a poorly soluble and highly permeable drug\textsuperscript{23}. It is a suitable drug for preparing suspensions. It was the first specific inhibitor of cyclooxygenase-2 (COX-2) to be approved by United States Food and Drug Administration (US FDA) in 1998\textsuperscript{24}. It was synthesized with a major clinical goal of producing an NSAID with little or no effect on the gastrointestinal tract and kidney.

4.3.1.Structure :

![Structure of Celecoxib]

4.3.2.Chemical Name : 4-[5-(4-methyl phenyl)-3(trifluoromethyl)-1H-Pyrazol-1-y1] benzene sulfonamide\textsuperscript{25}.

4.3.3.Empirical Formula : \( \text{C}_{17}\text{H}_{14}\text{F}_{3}\text{N}_{3}\text{O}_{2}\text{S} \)

4.3.4.Molecular weight : 381.38

4.3.5.Therapeutic category : Analgesic & Anti-inflammatory

4.3.6.Description : “Celecoxib” occurs as a white to off-white odorless crystalline powder.

4.3.7.Melting Point : The melting point of “celecoxib” was found to between 157\textdegree-159\textdegree C.

4.3.8.Dissociation constant : pKa of about 11.1
4.3.9. Solubility: Free soluble in Methanol, Acetone, Thyl Acetate and Acetonitrile\(^1\).

Solubility in water at 25\(^\circ\)C is = 0.007 mg/ml

4.3.10. Stability: Celecoxib was found to be practically stable under the stress conditions tested\(^26\).

4.3.11. INDICATIONS AND DOSAGES

Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory analgesic and antipyretic actions\(^27\). It is used in the treatment of osteoarthritis, rheumatoid arthritis, acute painful conditions\(^28\), primary dysmenorrhoea\(^29\) and ankylosing spondylitis\(^30\).

The mechanism of action of celecoxib is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of COX-2, and at therapeutic concentrations in humans, celecoxib does not inhibit the cycloxygenase-1 (COX-1) isoenzyme\(^31\). It comparatively exhibits lower incidence of symptomatic gastrointestinal ulcer complications that other NSAIDs\(^32\).

4.3.12. PHARMACOKINETICS\(^33\):

The important pharmacokinetic parameters are as follows:

\[
\begin{align*}
C_{\text{max}} \text{ (peak plasma concentration)} & : \quad 705 \pm 268 \text{ ng/ml after a single oral dose of 200mg} \\
\text{Peak time (Time to reach } C_{\text{max}}) & : \quad 28 \pm 1.0 \text{ after a single oral dose of 200mg.}
\end{align*}
\]
Oral biavaiability$^{34}$ : 59%

Plasma protein bound : 97%

Volume of distribution : $455 \pm 166$ liters/kg

Plasma Clearance : $6.60 \pm 1.85$ ml. Min$^{-1}$ kg$^{-1}$

Half life : $11.2 \pm 3.47$ hours

Metabolism$^{31}$ : “Celecoxib” metabolism is primary mediated via cytochroma p450 2C9.

Excretion : Less than 3% of celecoxib is excreted unchanged in urine. Excreted primarily as hydroxylated metabolite.

### 4.3.13.DRUG – DRUG INTERACTIONS$^{35}$:

Aluminium and Magnesium antacids : May decrease plasma levels of celecoxib. These agents must be given at least 1hour apart.

Angiotensin converting enzyme inhibitors : Diminish antihypertensive effect. Blood pressure monitoring of cardio vascular events

Aspirin : Increases risks of ulcers; low aspirin dosages can be used safely for prevention of cardio vascular events.

Fluconazole : Decreases metabolism of celecoxib and increase the AUC by two folds.
Itraconazole\textsuperscript{36} No change in metabolism of celecoxib.

Ketoconazole\textsuperscript{37} No change in metabolism of celecoxib

Lithium : Increased concentration may occur. Close monitoring of Lithium plasma to sodium retention.

Warfarin : A direct interaction has not been reported; however patient is observed for signs and symptoms of bleeding

4.3.14.AVERSE REACTIONS\textsuperscript{35}

Central Nervous system : Dizziness, headache, insomnia

Gastro intestinal : Abdominal pain, diarrhea, dyspepsia, flatulence, nausea.

Gastro urinary : Elevated blood urea nitrogen level

Metabolic : Hyperchloremia, hypophosphatemia

Respiratory : Upper respiratory tract infection

Skin : Rash

Other : Back pain, peripheral edema
4.3.15.OVER DOSAGE AND TREATMENT

Common clinical signs of over dose include lethargy, drowsiness, nausea, vomiting, epi-gastric pain and gastro intestinal bleeding. Other possible symptoms include hypertension, acute renal failure, respiratory depression and coma. Although there is no antidote for treatment of overdose, symptomatic and supportive case is usually sufficient. If a patient is seen within 4 hours of the over dose, emesis, activated charcoal, an osmotic cathartic, or a combination of these can be used.

4.3.16.PAST WORK ON CELECOXIB

Gupta et al.\textsuperscript{38} co-processed celecoxib, PVP and meglumine by spray drying technique for generation of a ternary amorphous system. An amorphous drug product that provided enhanced solubility and stability was obtained. The spray drying process parameters were optimized to provide an amorphous product with required characteristics.

Sinha et al.\textsuperscript{39} studied inclusion complexation between celecoxib and $\beta$CD in solution and solid state. NMR studies suggested a strong interaction between celecoxib and $\beta$CD prepared by spray drying. Celecoxib entrapped in spray dried complexes dissolved much faster than the uncomplexed drug and physical mixtures.
Nagarsenker et al.\textsuperscript{40} prepared celecoxib – HP-βCD complexes and carried out in vitro and in vivo evaluation. The dispersions exhibited faster rates of dissolution and the kneaded dispersion was found more effective in inhibiting rat paw edema.

Ventura et al.\textsuperscript{41} investigated celecoxib – DM-βCD complex characterization and its in vitro permeation. They reported a 1:1 inclusion complex formation between celecoxib – DM-βCD. They prepared the solid inclusion complexes by kneading and freeze drying methods. Freeze-dried complexes showed higher rates of dissolution. Enhanced celecoxib permeation through CaCo-2 cells monolayer was observed.

Chowdary et al.\textsuperscript{42} studied molecular modeling, characterization and dissolution of βCD complexes of celecoxib. They observed a 1:1 stoichiometric inclusion complex formation between celecoxib and βCD. Among the solid inclusion complexes prepared by various methods (freeze-dried systems, co-vaporated systems and kneaded systems), freeze-dried complexes showed highest dissolution rate.

Chandrasekhararao et al.\textsuperscript{43} studied the improvement of physical stability and dissolution rate of celecoxib suspensions by complexation with βCD. They prepared celecoxib suspensions employing its solid dispersions with βCD prepared by physical mixing, slugging and kneading methods, with sodium carboxymethylcellulose as the suspending agent. They observed highest improvement in physical stability and dissolution rate for celecoxib-βCD (1:2) solid dispersions prepared by kneading method.
Swati Rawat et al.\textsuperscript{44} studied the effect of $\beta$CD inclusion complexation on the solubility of celecoxib. Enhancement of dissolution rates with increasing quantity of $\beta$CD in the complex was observed. It was also observed that the complexes exhibit higher dissolution rates than the pure drug and physical mixture.

Subramanian et al.\textsuperscript{45} studied topical delivery of celecoxib by using microemulsion as the vehicle for the treatment of UV B induced skin cancer. Formulation consisting of 3\% celecoxib, 22\% propylene glycol dicaprylate/dicaprate + caprylic/capric mono-/di-glycerides (2:1), 30\% polysorbate 80 and water showed higher permeation rate and significant anti-inflammatory activity.

Babu et al.\textsuperscript{46} studied the applicability of tamarind kernel powder (TP) as a carrier in the dissolution enhancement of celecoxib. They reported 1:4 as the optimum weight ratio of drug:TP for enhancing drug dissolution.

Spherical crystallization of celecoxib was carried out by Paradkar et al.\textsuperscript{47} using solvent change method and found that the particle size, bulk density, mean yield pressure and drug release were significantly affected by changing the solvents.
Saha et al.\textsuperscript{48} studied the design and evaluation of controlled release polymeric discs for ocular delivery of celecoxib, and found that controlled release using polymeric discs of HPMC and PVA for celecoxib is feasible with near zero order release profile.

Yener et al.\textsuperscript{49} compared three different formulations (gel, o/w emulsion, oleaginous cream) and two penetration enhancers (oleic acid and methanol) as vehicle systems for celecoxib in respect of release and penetration through excised human skin in vitro using Franz diffusion cell. Influence of vehicle on release rate was studied in vitro using a cellulose acetate membrane. They concluded that among all the formulations tested, celecoxib was released and penetrated into human skin more quickly and to a greater extent from gel formulations.

Krishnaiah et al.\textsuperscript{50} developed colon targeted delivery systems for celecoxib in the prevention of colorectal cancer. They concluded that the matrix tablets containing either 20 or 30\% of guar gum are most likely to target celecoxib for local action in the colon.

Neelam Seedhar et al.\textsuperscript{51} studied the solubility and solubility enhancement of celecoxib and rofecoxib using various solvent systems like water, alcohols, glycols, PEG 400 and mixed solvents and formulated liquid oral of these drugs employing various solvent systems.

Thakkar et al.\textsuperscript{52} prepared microsphere formulations of celecoxib using a natural polymer, chitosan as a carrier for intra-articular administration to extend the retention of the drug in the knee joint. Significant difference in arthritic lesions post therapy in rats was
observed in the group treated with celecoxib solution compared to the group treated with celecoxib loaded chitosan microspheres.

Subramanian et al.\textsuperscript{53} developed self microemulsifying drug delivery system (SMEDDS) of celecoxib. The SMEDDS formulation optimized via mixture design consisted of 49.5\% PEG-8 caprylic/capric glycerides, 40.5\% mixture of Tween 20 and propylene glycol monocaprylic ester (3:1) and 10\% celecoxib, showed significantly higher rate and extent of absorption than conventional capsule. The relative bioavailability of the SMEDDS formulation to the conventional capsule was 132\%.

Chawla et al.\textsuperscript{54} studied the effect of major energy imparting pharmaceutical unit processes, like size reduction, wet granulation, consolidation and compression on solid state transformation of celecoxib and its N, N-dimethyl acetamide and N. N-dimethyl formamide solvated forms.
REFERENCES:


