Chapter 3

NON–STEROIDAL ANTI-INFLAMMATORY DRUGS
AN OVERVIEW
NON–STEROIDAL ANTI-INFLAMMATORY DRUGS: AN OVERVIEW

Nonsteroidal anti-inflammatory drugs, usually abbreviated to NSAIDs or NAIDs, are drugs with analgesic, antipyretic (fever-reducing) and, in higher doses, with anti-inflammatory effects (Reducing inflammation). The term "nonsteroidal" is used to distinguish these drugs from steroids, which (among a broad range of other effects) have a similar eicosanoid-depressing, Anti-inflammatory action. As analgesics, NSAIDs are unusual in that they are non-narcotic. NSAIDs are sometimes also referred to as nonsteroidal anti-inflammatory agents/analgesics (NSAIAs) or nonsteroidal anti-inflammatory medicines (NSAIMs). The most prominent members of this group of drugs are aspirin, ibuprofen, and naproxen partly because they are available over-the-counter in many areas.

Mechanism of action

Most NSAIDs act as nonselective inhibitors of the enzyme cyclooxygenase (COX), inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. COX catalyzes the formation of prostaglandins and thromboxane from arachidonic acid (itself derived from the cellular phospholipid bilayer by phospholipase A2). Prostaglandins act (among other things) as messenger molecules in the process of inflammation. This mechanism of action was elucidated by John Vane (1927-2004), who later received a Nobel Prize for his work. A newly discovered COX-3 may also have some role.

NSAIDS have antipyretic activity and can be used to treat fever. Fever is caused by elevated levels of prostaglandin E2, which alters the firing rate of neurons within the hypothalamus that control thermoregulation. Antipyretics work by inhibiting the enzyme COX, which causes the general inhibition of prostanoid biosynthesis (PGE2) within the hypothalamus. PGE2 signals to the hypothalamus to increase the body's thermal set point effective as an antipyretic than acetaminophen.

Classification

NSAIDs can be broadly classified based on their chemical structure.

**Propionic acid derivatives:** Ibuprofen, Naproxen, Fenoprofen, Ketoprofen, Flurbiprofen, Oxaprozin

**Acetic acid derivatives:** Indomethacin, Sulindac, Etodolac, Diclofenac
**Enolic acid (Oxicam) derivatives**: Piroxicam, Meloxicam, Tenoxicam, Dricoxam, Lornoxicam, Isoxicam

**Fenamic acid derivatives**: Mefenamic acid, Meclofenamic acid, Flufenamic acid, Tolfenamic acid

**Selective COX-2 inhibitors (Coxibs)**: Celecoxib, Rofecoxib, Valdecoxib, Parecoxib, Lumiracoxib, Etoricoxib

NSAIDs within a group will tend to have similar characteristics and tolerability. There is little difference in clinical efficacy among the NSAIDs when used at equivalent doses. Rather differences among compounds tend to be with regards to dosing regimens (related to the compound’s elimination half-life), route of administration, and tolerability profile. Some more common examples are given below.

**Sulphonanilides**: Nimesulide

**Others**

Licofelone; Licofelone acts by inhibiting LOX (lipooxygenase) & COX and hence known as 5-LOX/COX inhibitor.

**Uses**

NSAIDs are usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present. Research continues into their potential for prevention of colorectal cancer, and treatment of other conditions, such as cancer and cardiovascular disease. NSAIDs are generally indicated for the symptomatic relief of the following conditions:

- Rheumatoid arthritis, Osteoarthritis, Inflammatory, arthropathies (e.g. ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome), Acute gout, Dysmenorrhoea (menstrual pain), Metastatic bone pain, Headache and migraine, Postoperative pain, Mild-to-moderate pain due to inflammation and tissue injury, Pyrexia (fever), Ileus, Renal colic. They are also given to neonate infants whose ductus arteriosus is not closed within 24 hours of birth. Aspirin, the only NSAID able to irreversibly inhibit COX-1, is also indicated for inhibition of platelet aggregation. This is useful in the management of arterial thrombosis and prevention of adverse
cardiovascular events. Aspirin inhibits platelet aggregation by inhibiting the action of thromboxane -A.

**Pharmacokinetics**

Most nonsteroidal anti-inflammatory drugs are weak acids, with a pKa of 3-5. They are absorbed well from the stomach and intestinal mucosa. They are highly protein-bound in plasma (typically >95%), usually to albumin, so that their volume of distribution typically approximates to plasma volume. Most NSAIDs are metabolized in the liver by oxidation and conjugation to inactive metabolites which are typically excreted in the urine, although some drugs are partially excreted in bile. Metabolism may be abnormal in certain disease states, and accumulation may occur even with normal dosage. Ibuprofen and diclofenac have short half-lives (2–3 hours). Some NSAIDs (typically oxicams) have very long half-lives (e.g. 20–60 hours).

**Adverse effects**

The widespread use of NSAIDs has meant that the adverse effects of these drugs have become increasingly prevalent. The two main adverse drug reactions (ADRs) associated with NSAIDs relate to gastrointestinal (GI) effects and renal effects of the agents. These effects are dose-dependent, and in many cases severe enough to pose the risk of ulcer perforation, upper gastrointestinal bleeding, and death, limiting the use of NSAID therapy.
LITERATURE ON LORNOXICAM FORMULATIONS

Syed Namath Ulla et al.,\(^1\) worked to develop lornoxicam sustained release matrix tablets to provide complete drug release which starts in the stomach and continues in the intestine to maintain analgesic effect. They found that the maximum absorption occurred at wavelength 373nm in 0.1N HCl and at 379nm and in pH 6.80. They developed various formulations using polymers like HPMC (K4M, K15M, K100M) and studied interaction between drug and selected polymers. They found that there is no interaction between polymers and the drug and it followed zero order kinetics as the correlation coefficient (R2 value) was higher for zero order release. They also found that the formulation satisfied physicochemical parameters and in vitro drug release profile requirements for a sustained drug delivery system.

Yassin El-Said Hamza et al.,\(^2\) worked on to develop new directly compressed, double layer tablets (DLTs) of lornoxicam which works on initial burst drug release in the stomach and comply with the release requirements of sustained-release products. This double layer tablet composed of a fast-release layer and a sustained-release layer which gives rapid drug release that starts in the stomach to rapidly alleviate the symptoms and continues in the intestine to maintain protracted analgesic effect. They tried with an amorphous, freeze-dried complex of lornoxicam with hydroxypropyl-\(\beta\)-cyclodextrin in 1:2 molar ratio for fast-release layer and Xanthan gum a hydrophilic matrix-forming agent for sustained-release layer. They found that the drug contained in the fast-release layer showed an initial burst drug release of more than 30% of its drug content during the first 30min of the release study followed by gradual release of the drug for a period of 8 hours.

Metker Vishal et al.,\(^3\) developed Oro dispersible tablets of Lornoxicam for fast disintegration in the mouth in seconds without chewing and the need of water. They worked with the use of Kyron T-314(Polacrillin Potassium) which acts as a super disintegrant and menthol as subliming agent. They found that there is a lot of potential for rapid absorption, improved bioavailability, effective therapy and patent compliance.

Senthil Selvi et al.,\(^4\) worked on formulation and evaluation of lornoxicam orodispersible tablets using natural superdisintegrants. They used Ispagol’s mucilage, powder and husk powder etc. for the preparation of lornoxicam oral dispersible
tablets. They found that natural superdisintegrants can be used instead of synthetic superdisintegrants for the formulation of oro dispersible tablets.

Supriya C.Patil et. al., worked to develop oral disintegrating tablet of lornoxicam using croscarmellose as super disintegrating agent and using kneading technique. They prepared kneading mixture with croscarmellose in the weight ratios of 1:0.5, 1:1, and 1:1.5. They found that mixture of 1:1.5 ie, drug: croscarmellose showed highest dissolution rate and the tablets were prepared using kneading mixture by wet granulation method. They found disintegrating time as 12 sec., hardness of 3.6 kg/cm², friability of 0.8% and cumulative percent drug release of 99.62% in 30 minutes.

Sanjay Wasudeo Upare et. al., developed a taste masked oral disintegrating tablet of poorly soluble lornoxicam by direct compression technique with β-cyclodextrin (βCD) complexes using various superdisintegrants like sodium starch glycolate, crospovidone and L-Hpc. They found that disintegrating time between 21 to 33.66 sec., 97.79% drug release time between the ranges of 5 to 30 min.

Ravi KumarNayak et. al., studied on formulation and evaluation of fast dissolving tablets of lornoxicam. They prepared orodispersible tablets of lornoxicam by using superdisintegrants viz; crospovidone, croscarmellose sodium and sodium starch glycolate using the direct compression method. They evaluated the tablets for thickness, uniformity of weight, hardness, friability, wetting time, invitro disintegrating time and invitro dissolution time. They found different formulations disintegrating time between 18 to 75 sec.’s and drug release between the ranges of 10 to 12 min. Formulation containing 4% showed 99% drug release within 12min and least disintegrating time 18 sec.’s and stable as per the ICH guidelines.

Taksande JB et. al., worked on formulation and characterization of lornoxicam fast dissolving tablet using natural superdisintegrants. They used natural superdisintegrants like banana powder, soy polysaccharide and synthetic superdisintegrant crospovidone. The prepared formulations were evaluated for properties like drug content, hardness, disintegration time, wetting time, water absorption ratio, dispersion time and in vitro release study. They found that there is no incompatibility of excipients with drug, with the help of FTIR and DSC studies.
They found that the formulation with soy polysaccharide showed disintegration time as 10sec.’s and 12 sec.s and 90% drug release in 15 min.

Patil A.L. et. al.,\(^9\) worked on modification of physicochemical characteristics of lornoxicam using cyclodextrin as modulator. They prepared inclusion complex using HPβCD to modify the physicochemical properties of lornoxicam for dissolution enhancement. They performed phase solubility study as per Higuchi and Connors and found the stability constant value as 130M. They used kneading method for the preparation of solid state complex. They found that the kneaded product showed significant enhancement in solubility when dissolution study was performed using phosphate buffer pH7.4 and as per USP apparatus type II compared to pure drug. The complex gave \(t_{90}\) value < 5min.

S.Z.Chemate et. al.,\(^10\) worked on enhancement of solubility and dissolution rate of lornoxicam employing Hydroxy propyl β-cyclodextrin (HPβCD) and two surfactants (SLS and Tween 80) alone and in combination. The individual main effects and combined(interaction) effects of HPβ-cyclodextrin and surfactants on the solubility and dissolution rate of lornoxicam were evaluated in a series of 22 factorial experiments. The complexes were evaluated for dissolution rate and dissolution efficiency. They found that ANOVA indicated that the individual main effects of HPβCD,SLS and Tween 80 as well as the combined effects in enhancing the solubility and dissolution rate of lornoxicam are highly significant (P,0.01). They found that the dissolution rate \((k_1)\) was increased to 9.50 folds when a combination of HPβCD with Surfactants SLS and Tween 80 is used.

Saurabh Sharma et.al.,\(^11\) worked on preparation of taste masked orodispersible tablet by direct compression method and optimizing the effect of sodium starch glycolate as a super-disintegrating agent and camphor as sublimating agent. They prepared orodispersible tablet batches and evaluated for pre-compression parameters, post-compression parameters and then characterized by differential scanning calorimetry, powder X-ray diffraction, Fourier transform infrared and in-vitro release study in pH 1.2 at 37\(^\circ\)C ± 0.5\(^\circ\)C and found drug release in 105min. They conducted stability of optimized formulation for 4 weeks at stress and temperature and normal humidity conditions and found no major changes.
K B Bini et al., \cite{kbbini12} worked on Development and Characterization of Non-Ionic Surfactant Vesicles (Niosomes) for Oral delivery of Lornoxicam. They prepared lornoxicam loaded niosomes by lipid film hydration method with different surfactant to cholesterol ratio. They evaluated niosome formulations for FT-IR study, microscopy for entrapment efficiency, In vitro release study, Kinetic data analysis, stability study. They found one of the formulations showed higher entrapment efficiency of 80.54 ± 0.99. They found that the release followed the zero order kinetics, and kinetic analysis showed that the drug release followed super case II transport diffusion and the formulation showed appropriate stability for 90 days.
LITERATURE ON MEFENAMIC ACID FORMULATIONS

Ashtamkar Joel et. al.,\textsuperscript{13} worked on Formulation and Evaluation of sustained release tablets of mefenamic acid using hydrophobic polymers. He prepared controlled release matrices by direct compression and performed the in-vitro drug dissolution studies to find out the drug release rate and patterns. He used Ethyl cellulose, polyvinyl acetate and their combination as rate controlling polymers. He studied the effect of addition of ethyl cellulose and polyvinyl acetate on in-vitro drug dissolution. He formulated tablets using various polymer content percentages and carried out \textit{in-vitro} drug release using USP type II at 50 rpm in 900 ml of acidic dissolution medium (pH 1.2) for 2 hours, and then by 900ml. alkaline dissolution medium (pH 7.4) up to 24 hours. He used mean dissolution time to characterize drug release rate to study the drug release retarding efficiency of polymer. He concluded that retarding efficiency of polymer. He found that the ethyl cellulose and polyvinylacetate in combination in the matrix gave both the uniform retardation effect as well as desired physical properties to the formulation.

Rachit Khullar et. al.,\textsuperscript{14} investigated on formulation and evaluation of mefenamic acid emulgel for topical delivery. They prepared emulgel of mefenamic acid using carbapol 940 as a gelling agent and mentha oil and clove oil were used as penetration enhancers. The formulations were subjected for evaluation for rheological studies, spreading coefficient studies, bioadhesion strength, skin irritation studies, \textit{in vitro} release, \textit{ex vivo} release studies, anti-inflammatory activity and analgesic activity and found comparable analgesic and anti-inflammatory activity with marketed NSAID gel formulations and concluded that topical emulgel of mefenamic acid posses an effective anti-inflammatory and analgesic activity.

Ozyazici M.et.al.,\textsuperscript{15} worked on sustained release spherical agglomerates of polymethacrylates containing mefenamic acid. They prepared spherical agglomerates with various polymethacrylates like Eudragit RS 100, Eudragit RL 100 and Eudragit L 100 which are having different permeability characteristics separately and in combination of Eudragit RS 100 and Eudragit L 100 and in different ratios. They used spherical crystallization method using ethanol/dichloromethane solvent (crystallization) system in preparing the spherical agglomerates. They investigated on the influence of various formulation factors on the encapsulation efficiency. They
found that the yields of preparation and the encapsulation efficiencies were high for all formulations. They also found in the histological studies that the administration of mefenamic acid in spherical agglomerates containing Eudragit RS/L provided a distinct tissue protection in the stomach and duodenum. They also found in the DSC, XRD studies that mefenamic acid particles crystallized in the presence of polymethacrylates did not undergo structural modifications.

Pooja Patel et. al.,\textsuperscript{16} worked on formulation and evaluation of time-controlled triple-concentric mefenamic acid tablets using Carbopol and Ethocel polymers. The burst dose was programmed to release immediately after an ingestion of tablet to be followed by a lag period of 2-4 hours, and thereafter an 8 hours controlled release of mefenamic acid from core tablet. They prepared core tablets using various concentrations of Carbopols 971P, 974Pm 71G or 907. They found that different carbopols gave different release rates of mefenamic acid. They also found that the extent of uptake of dissolution medium by core tablets was inversely related to the rate of release of mefenamic acid from the tablets. They also found that the compression forces applied during compression coating with Ethocel for lag period, and immediate-release drug coating for burst release did not affect the integrity of core tablet.

Taro Kojima et. al.\textsuperscript{17} investigated on stabilization of a supersaturated solution of mefenamic acid from a solid dispersion with Eudragit. They prepared solid dispersions by cryogenic grinding method. They were characterized by using powder x-ray diffractometry, in vitro dissolution test, in vivo oral absorption study, infrared spectroscopy, and solid- and solution-state NMR spectroscopies. They found 200 fold higher concentration of mefenamic acidin dissolution test using acetate buffer (pH 5.5), Gavin P. Andrews et. al.,\textsuperscript{18} investigated on the solubility of mefenamic acid in a copolymer of polyoxyethylene-polyoxpropylene (Lutrol F68), and the drug polymer solubility has on invitro dissolution of the drug. They prepared solid dispersions of mefenamic acid by a hot melt method using Lutrol F68. The solubility of the drug in molten and solid polymer was assessed using PXRD and hot-stage/fluorescence microscopy. Drug dissolution studies were conducted on single-phase solid solutions and biphasic SD using phosphate buffer pH6.8 as dissolution media. They found that the complexity of drug-polymer binary blends and in particular defining the solubility of a drug within a polymeric platform. They also
found the significant effect drug solubility within a polymeric matrix has upon the
\textit{invitro} dissolution properties of solid polymer/drug binary blends.

Tarek A.Ahmed \textit{et. al.,}^{19} investigated on In vitro release, rheological, and
stability studies of mefenamic acid coprecipitates in topical formulations. They
prepared drug coprecipitates with different polymers at various drug-to-polymer
ratios. They found PVP polymers (ratio 1:4) gave best results. They prepared
aqueous ionic cream, ointments of absorption and water soluble bases and gels of
methylcellulose, carboxymethylcellulose sodium, HPMC, Carbopol 934 and 940, and
Pluronic F127 bases containing 1-10\% drug as coprecipitates of PVP polmers (1:4).
They found that highest drug release was achieved from 1\% drug concentration from
water soluble base and methylcellulose among cream/ointment and gel bases,
respectively. Gels, in general yielded better release than creams/ointments. Stability
studies showed that HPMC and methylcellulose had the smallest changes in drug
content, viscosity, and pH among the formulations. Methylcellulose gel containing
1\% drug as coprecipitates of PVP K90 was the best among the studied formulations,
showed improved bioavailability of mefenamic acid.

S.Cesur \textit{et. a.l.,}^{20} worked on Crystallization of mefenamic acid and
polymorphs. Mefenemic acid crystals were recrystallized from five different solvents
of \text{N, N-dimethylformamide (DMF), acetone, N,N-dimethylacetamide (DMA),
Dimethylsulfoxide (DMS) and Ethyl Acetate (EA). They studied the crystal structure
and the polymorphic forms of the crystals obtained by recrystallization by using SEM,
Raman diffractometry and X-ray patterns. They studied the crystal size distribution,
the crystal shape, the polymorphic form which effects the quality and bioavailability
of the drug.}

M.V.Nagabhushanam \textit{et.al.,}^{21} worked on dissolution enhancement of
mefenamic acid using solid dispersions in crospovidone. They prepared solid
dispersions of mefenamic acid with a water soluble polymer PVP and a super
disintegrant crospovidone by using common solvent evaporation method with the help
of methanol as solvent. They evaluated the solid dispersions thus prepared for
dissolution rate and dissolution efficiency and compared with the pure drug. They
found Solid dispersions with a marked enhancement in dissolution rate and
dissolution efficiency. The order of increasing dissolution rate was found with
increase in crospovidone ratio. They found that the superdisintegrants alone or in combination with PVP could be used to enhance the dissolution rate of poorly soluble drug mefenamic acid.

Sanjeev Kumar et.al.,\textsuperscript{22} worked on some novel techniques for solubility enhancement of mefenamic acid. They used evaporative precipitation into aqueous solution (EPAS), spherical agglomeration (SA) and solid dispersion using solvent evaporation and melt mixing. They investigated for drug content studies, solubility studies, in vitro study and in vivo evaluation of anti-inflammatory activity and they characterized the formulations by differential scanning calorimetry (DSC) and X-Ray powder diffractionmetry (XRID). They found that the formulations with SLS and HPMC showed a significant increase in solubility in case of spherical agglomeration technique and in case of solid dispersion, all carriers showed improvement in the dissolution rate of the drug and there is no change in the polymorphism, and in the crystalline form. They also found that the formulation containing HPMC & SLS as drug carrier showed better anti-inflammatory effect with comparison to pure drug confirming the improved bioavailability of the drug.

Bani-Jaber A et. al.,\textsuperscript{23} investigated on sodium mefenamate as a solution for the formulation and dissolution problems of mefenamic acid. They prepared sodium salt of mefenamic acid by reacting mefenamic acid powder with equimolar sodium hydroxide in an aqueous phase. The resultant solution was lyophilized and sodium-mefenamic acid powder was collected. The salt formation was confirmed by FTIR and DSC studies. The tablets were compressed using the salt form of the drug using minimum amount of Avicel pH 101 and these tablets were studied for drug dissolution which showed much higher dissolution rate and extent than tablets with pure drug.

Pradnya B Patil et. al.,\textsuperscript{24} worked on development of dissolution medium for poorly water soluble drug mefenamic acid. They developed a dissolution medium which is water consisting of 2\% w/v sodium lauryl sulphate on the basis of solubility data of mefenamic acid at 37\textdegree C. They evaluated the discriminating power of the selected dissolution medium (2\% w/v sodium lauryl sulphate in water.) relative to the other dissolution medium. They found that the 2\% w/v sodium lauryl sulphate in water serves as most suitable dissolution medium for mefenamic acid.
K.P.R. Chowdary *et. al.*,\(^2\(^5\) worked on solid dispersions of mefenamic acid in superdisintegrant promojel alone and with PVP. They prepared solid dispersions of mefenamic acid with a water-soluble polymer (PVP) and a superdisintegrant primojel (PJ), by common solvent and solvent evaporation methods using methanol as solvent. They evaluated the solid dispersions thus prepared for dissolution rate and dissolution efficiency in comparison to the corresponding pure drug. They found that the solid dispersions showed enhanced dissolution rate and dissolution efficiency. The order of increasing dissolution rate was observed with an increase in primojel ratio. They found that the solid dispersions in combined carriers gave much higher rates of dissolution than super disintegrants alone.

Mudit Dixit *et. al.*,\(^2\(^6\) did investigations on preparation and characterization of spray dried microparticle and spray chilled particle of mefenamic acid by spray drying method. They produced microparticles containing mefenamic acid by spray drying using isopropyl alcohol and water in the ratio of 40:60 (v/v) as solvent system and spray chilling technology by melting the drug and chilled by atomized with nozzle to enhance dissolution rate. They were evaluated for in vitro dissolution and solubility. The dissolution of the spray dried microparticle and chilled particles were improved compared with recrystallized and pure sample of mefenamic acid. They found that spray drying of mefenamic acid is a useful tool to improve dissolution.

Sevgi F *et. al.*,\(^2\(^7\) worked on histological study of alginate beads for controlled release delivery for mefenamic acid. In this study they prepared mefenamic acid-alginate bead formulation by ionotropic gelation method using 3 x 2(2) factorial design. They evaluated the thus prepared drug on rat gastric and duodenal mucosa suspended in 0.5% (w/v) sodium carboxymethylcellulose solution and loaded in alginate beads for irritation effects. They evaluated biodegradable controlled release mefenamic acid beads and free mefenamic acid for the degree of gastric or duodenal damage following oral administration in rats. The gastric and duodenal mucosa was examined for any hemorrhagic changes. They found that the administration of mefenamic acid in alginate beads prevented the gastric lesions.

Andrews GP *et. al.*,\(^2\(^8\) worked on characterization of the thermal, spectroscopic and drug dissolution properties of mefenamic acid and polyoxyethylene-polyoxypolypropylene solid dispersions. They prepared solid dispersions of mefenamic
acid by a hot melt method using copolymer of polyoxyethylene-polyoxypropylene (Lutrol F68) as a thermoplastic polymeric platform. Drug dissolution studies were conducted on single-phase solid solutions and biphasic SD using phosphate buffer pH 6.8 as dissolution media. They found that the dissolution properties of mefenamic acid were significantly influenced by the solubility of the drug in the polymer matrix.
LITERATURE ON CELECOXIB FORMULATIONS

Punitha S. et al.,\textsuperscript{29} worked on Enhancement of Solubility and Dissolution of Celecoxib by Solid Dispersion Technique. They prepared solid dispersion with urea by solvent evaporation and fusion method in the ratios of 1:1, 1:3, and 1:5. They found that the prepared dispersion showed marked increase in the saturation solubility and dissolution rate of celecoxib than that of pure drug. The dispersion with urea (1:5) by fusion method showed faster dissolution rate (79.08\%) and excellent physicochemical characteristics as compared to other dispersions with urea (1:1 and 1:3). There were no interactions found when subjected to FT-IR studies.

Vikram M. Pandya et al.,\textsuperscript{30} investigated on formulation, characterization and optimization of fast dissolve tablets containing celecoxib solid dispersion. They prepared solid dispersion of celecoxib with polyvinyl pyrrolidone K30 (PVP –K30) using a solvent-evaporation method. They studied dissolution profiles of developed formulations in distilled water containing 1\% SLS. They investigated drug-polymer interactions using differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR). They formulated celecoxib fast-dissolve tablets, using 1:2 solid dispersion with PVP-K30, and used croscarmellose sodium as a superdisintegrant and pearlitol 200 SD (pearlitol) as a pore-forming agent. A 32 full-factorial design was employed to study the effect of independent variables, the amounts of croscarmellose sodium (X\textsubscript{1}) and pearlitol (X\textsubscript{2}), on dependent variables, disintegration time, percentage friability, wettability, and percentage of drug released after 20 min (Q\textsubscript{20}). They found that a dispersion of the drug in polymer considerably enhanced the dissolution rate. They also found no chemical incompatibility between the drug and PVP-K30, and celecoxib in the amorphous form only.

Punitha S et al.,\textsuperscript{31} investigated on enhancement of celecoxib solubility by solid dispersion using mannitol. They prepared solid dispersion of celecoxib by physical trituration, solvent evaporation and fusion method using 1:1, 1:3 and 1:5 ratios of drug and polymer (mannitol). They found that all the prepared dispersions showed marked increase in the saturation solubility and dissolution rate of celecoxib than that of pure drug. The dispersion with mannitol (1:5) by fusion method showed faster dissolution rate (82.46\%) as compared to other solid dispersions with mannitol.
(1:1 and 1:3) whichever prepared by physical mixture and solvent evaporation method. The FT-IR shows the complexation and there were no interactions. They found that the solid dispersions of celecoxib:mannitol prepared as 1:5 ratio by fusion method showed excellent physicochemical characteristics and was found to be described by dissolution kinetics and was selected as the best formulation in the study.

S. Muralidhar et al., studied to enhance dissolution properties of celecoxib. They made solid dispersions of celecoxib using PVP K30 as carrier at various proportions (1:1, 1:2, 1:4 and 1:6) with different techniques like physical mixtures, kneading method and solvent evaporation method. They studied release profiles in water containing 2% SLS. The dispersions were evaluated for drug content uniformity, dissolution rate study, T50, DE20, ANOVA. They found a marked increase in the dissolution rate with all solid dispersions, among that celecoxib with PVP K30 by solvent evaporation method showed maximum drug release.

Meka Lingam et al., worked on enhancement of solubility and dissolution rate of poorly water soluble drug celecoxib using cosolvency and solid dispersion techniques. They prepared solid dispersions with different polymers like PVP, PEG and subjected to physicochemical characterization using FTIR spectroscopy, X-ray diffractometry, differential scanning calorimetry, solubility and visolution studies. They used cosolvents like PEG 400, ethanol and propylene glycol. Highest solubility (791.06±15.57 mg/ml) was observed with cosolvency technique containing the mixture of composition 10:80:10%v/v of water : PEG 400 : ethanol. The celecoxib existed mainly in amorphous form only in prepared solid dispersions thus prepared.

J Thimmasetty et al., worked on solubility parameter estimation of celecoxib by current methods. The solutions containing excess drug were shaken in a water bath for 72h at 25°C. The solutions attained equilibrium were then filtered and analysed. The extended Hildebrand solubility approach was used to process the solubility data of celecoxib. For understanding the solute-solvent interactions, partial solubility parameters concept was utilized. A multiple regression method using the extended Hansen’s partial solubility parameters was applied to verify the solubilities of celecoxib in polar and nonpolar solvents and to predict its solubility in untested solvents. The three parameter approach and the Flory-Huggins size correction term
‘B’ give the prediction of solubility with correlations up to 92%. The four-parameter approach give appreciable correlations (96%). They found considerable evidence to suggest that celecoxib is soluble in solvents, through acid - base parts of molecule. They also found a criteria of the ideal mole fraction solubility intersecting the mole fraction solubility curve is proved to be successful in deciding the solubility parameter of celecoxib. The total solubility parameter of celecoxib determined from the different methods of data analysis is finally assigned at 11 H. The partial solubility parameters obtained from four-parameter approach give insights into the interaction capability of celecoxib and are consistent with its chemical structure.

Vijay Tiwari et. al., 35 worked on preparation and evaluation of fast dissolving tablets of celecoxib. They prepared fast dissolving tablets of celecoxib by hot melt extrusion process using sorbitol, and superdisintegrants (sodium starch glycolate), binder (polyvinyl pyrrolidone), sweetner (saccharine sodium), flavor (menthol). They prepared six different formulations of solid dispersions and evaluated for drug release profiles of the same. They found that the bioavailability of celecoxib is increased by fast dissolving dosage form.

Ali J. et. al., 36 investigated on formulation and development of floating capsules of celecoxib: in vitro and in vivo evaluation. They developed a hydrodynamically balanced system for celecoxib as single-unit floating capsules. Various grades of low-density polymers were used for formulation of these capsules. The capsules were prepared by physical blending of celecoxib and the polymer in varying ratios. The formulation was optimized on the basis of in vitro buoyancy and in vitro release in citrate phosphate buffer pH 3.0 (with 1% sodium lauryl sulfate). Capsules prepared with polyethylene oxide 60K and Eudragit RL100 gave the best in vitro percentage release and were used as the optimized formulation.

Andrej Dolenc et. al., 37 worked on the advantages of celecoxib nanosuspension formulation and transformation into tablets. They prepared a nanosuspension tailored to increase drug dissolution rate and its transformation into dry powder suitable for tableting. Nanosuspensions of celecoxib, were produced by the emulsion-diffusion method using three different stabilizers (Tween® 80, PVP K-30 and SDS) and
characterized by particle size analysis, dissolution testing, scanning electron microscopy imaging, differential scanning calorimetry and X-ray powder diffraction. Spray-dried nanosuspension was blended with microcrystalline cellulose, and compressed to tablets, and their tensile strength, porosity and elastic recovery of tablets were investigated. The crystalline nano-sized celecoxib alone or in tablets showed a dramatic increase of dissolution rate and extent compared to micronized.

Ram R. Patlolla et al., worked on formulation, characterization and pulmonary deposition of nebulized celecoxib encapsulated nanostructured lipid carriers. They encapsulated celecoxib (Cxb) in the nanostructured lipid carrier (Cxb-NLC) nanoparticles and evaluated the lung disposition of nanoparticles following nebulization in Balb/c mice. Cxb-NLC nanoparticles were prepared with Cxb, Compritol, Miglyol and sodium taurocholate using high-pressure homogenization. In-vitro cytotoxicity studies were performed with A549 cells. The particle size and entrapment efficiency of the Cxb-NLC formulation were 217 ± 20 nm and > 90%, respectively. The Cxb-NLC released the drug in controlled fashion, and in-vitro aerosolization of Cxb-NLC formulation showed an FPF of 75.6 ± 4.6%, MMAD of 1.6 ± 0.13 µm and a GSD of 1.2 ± 0.21. Cxb-NLC showed dose and time dependent cytotoxicity against A549 cells. Nebulization of Cxb-NLC demonstrated 4-fold higher AUCt/D in lung tissues compared to the Cxb-Soln. The systemic clearance of Cxb-NLC was slower (0.93 l/h) compared to the Cxb-Soln (20.03 l/h). Cxb encapsulated NLC were found to be stable and aerodynamic properties were within the respirable limits. Aerosolization of Cxb-NLC improved the Cxb pulmonary bioavailability compared to solution formulation.

Mohamed Nasr et al. worked on in vitro and in vivo evaluation of proniosomes containing celecoxib for oral administration. He prepared celecoxib proniosomes and evaluated the influence of proniosomal formulation on the oral bioavailability of the drug in human volunteers. Proniosomes were prepared by sequential spraying method, which consisted of cholesterol, span 60, and dicetyl phosphate in a molar ratio of 1:1:0.1, respectively. The average entrapment percent of celecoxib pronosome-derived niosomes was about 95%. The prepared proniosomes showed marked enhancement in the dissolution of celecoxib as compared to pure drug powder. The bioavailability of 200 mg single dose of both celecoxib proniosomal
formulation and a conventional marketed celecoxib capsule was studied in human volunteers. They found that the proniosomal formulation significantly improved the extent of celecoxib absorption than conventional capsule.

Faiyaz Shakeel et. al.,\textsuperscript{40} worked on nanoemulsion of celecoxib. They prepared celecoxib (CXB) nanoemulsion, solid lipid nanoparticle and solid dispersion. The solubility of CXB in each formulation was determined using the reported HPLC method at the wavelength of 250 nm. Dissolution studies of pure CXB and its formulations were performed using USP dissolution apparatus in distilled water. The highest solubility (228.24 mg/mL) as well as % dissolution (99.9) of CXB was obtained with nanoemulsion technique. The results of solubility and dissolution were highly significant using the nanoemulsion technique as compared to other techniques (P < 0.01). All three formulations showed a sustained type of drug release. The best sustained type drug release was obtained with nanoemulsion. They found that nanoemulsion is a promising vehicle for solubility and dissolution enhancement of CXB.

Mohmoud M. et.al.,\textsuperscript{41} investigated on effect of buffer species on the inclusion complexation of acidic drug celecoxib with cyclodextrin in solution. They investigated the interaction of celecoxib (CeloX) with cyclodextrins (CDs) by phase solubility techniques. They examined the influences of CD type, pH, buffer type, buffer concentration and temperature on the tendency of Celecoxib to form inclusion complexes with CDs. The tendency of Celecoxib to complex with CDs is in the order HP-β-CD > β-CD > γ-CD > α-CD, where the complex formation constants ($K_{11}$) were 1377, 693, 126 and 60 M\textsuperscript{-1}, respectively.

Erdog A. et. al.,\textsuperscript{42} worked on in vitro characterization of a liposomal formulation of celecoxib containing 1,2-distearoyl-sn glycerol-3-phosphocholine, cholesterol, and polyethylene glycol and its functional effects against colorectal cancer cell lines. They prepared a liposomal formulation of Celecoxib using 1,2-Distearoyl-sn-glycero-3-phosphocholine, cholesterol, and polyethylene glycol. Encapsulation efficiency of the drug was greater than 70%; the release was slow and sustained with only 12%-20% of Celecoxib released in the first 12 h.
Malik P et al.,\(^{43}\) worked on hydrophilic prodrug approach for reduced pigment binding and enhanced transscleral retinal delivery of celecoxib. They developed soluble prodrugs of celecoxib with reduced pigment binding and enhanced retinal delivery. Three hydrophilic amide prodrugs of celecoxib, celecoxib succinamidic acid (CSA), celecoxib maleamidic acid (CMA), and celecoxibacetamide (CAA) were synthesized and characterized for solubility and lipophilicity. In vitro melanin binding to natural melanin (Sepia officinalis) was estimated for all three prodrugs. In vitro transport studies across isolated bovine sclera and sclera-choroid-RPE (SCRPE) were performed. Prodrug with the highest permeability across SCRPE was characterized for metabolism and cytotoxicity and its in vivo transscleral delivery in pigmented rats. Aqueous solubilities of CSA, CMA, and CAA were 300-, 182-, and 76-fold higher, respectively, than celecoxib. Melanin binding affinity and capacity were significantly lower than for celecoxib for all three prodrugs. Celecoxib succinamidic acid, a soluble prodrug of celecoxib with reduced melanin binding, enhances transscleral retinal delivery of celecoxib.

Bragagni M. et al.,\(^{44}\) worked on liposomes, transfersomes and ethosomes as carriers for improving topical delivery of celecoxib. They have developed an effective topical formulation of celecoxib, to promote drug skin delivery, providing its in depth penetration through the skin layers. Three kinds of vesicular formulations have been investigated as drug carriers: liposomes containing a surfactant, or transfersomes and ethosomes, containing suitable edge activators. They found Tween 20-ethosomes as most promising one as carrier for topical celecoxib applications aimed to prevent skin cancer development and increase the anticancer drugs effectiveness against skin tumors.

Liu Y et al.,\(^{45}\) investigated on mechanism of dissolution enhancement and bioavailability of poorly water soluble celecoxib by preparing stable amorphous nanoparticles. They produced celecoxib nanoparticles by combining the antisolvent precipitation and high pressure homogenization (HPH) approaches in the presence of HPMC E5 and SDS (2:1, w/w) and the suspensions were spray dried. SEM revealed spherical celecoxib nanoparticles. The DSC and XRPD results indicated that the
antisolvent precipitation process led to the amorphization of celecoxib. The XPS data indicated the amorphous celecoxib nanoparticles exhibited different surface property compared to raw celecoxib. celecoxib nanoparticles increased the saturation solubility of celecoxib fourfold. celecoxib nanoparticles completely dissolved in the dissolution medium of phosphate buffer (pH 6.8, 0.5% SDS) within 5 min, while there was only 30% of raw celecoxib dissolved. The C (max) and AUC(0-24h) of celecoxib nanoparticles were approximately threefold and twofold greater than those of the celecoxib Capsules, respectively. They found by combining the antisolvent precipitation under sonication and HPH as a promising method to produce small, uniform and stable celecoxib nanoparticles with enhanced dissolution rate and oral bioavailability due to an increased solubility because of the combination of amorphization and nanonization with increased surface area, improved wettability and reduced diffusion pathway.
LITERATURE ON NAPROXEN FORMULATIONS

Mehta R. et. al.,\(^{46}\) worked on formulation and in vitro evaluation of Eudragit S-100 coated naproxen matrix tablets for colon-targeted drug delivery system. They prepared matrix tablets of naproxen using a hydrophobic polymer i.e., Eudragit RLPO, RSPO, and combination of both, by wet granulation method. Eudragit S-100 coated matrix tablets of naproxen showed promising site-specific drug delivery in the colon region.

Chawla A. et. al.,\(^{47}\) studied on Eudragit S-100 coated sodium alginate microspheres of naproxen sodium: Formulation, optimization and in vitro evaluation. They prepared Core microspheres of alginate by a modified emulsification method followed by cross-linking with CaCl\(_2\), which was further coated with the pH dependent polymer Eudragit S-100 (2.5 or 5 %) to prevent drug release in the upper gastrointestinal environment. Drug release from all sodium alginate microsphere formulations followed Higuchi kinetics and drug release from Eudragit S-100 coated microspheres followed the Korsmeyer-Peppas equation with a Fickian kinetics mechanism.

Sheha M et. al.,\(^{48}\) worked on pharmacokinetic and ulcerogenic studies of naproxen prodrugs designed for specific brain delivery. The synthesis and preliminary in vitro and in vivo investigations of Nap prodrugs with dihydropyridine (I) and ascorbic acid (II) through an ester spacer to target specific brain delivery of Nap were done. They studied the brain bioavailability of Naproxen after oral administration of the prodrugs in rats. They found moderate oral bioavailability of prodrugs (AUC = 53-94 h \(\cdot\) \(\mu\)g/mL) in rats compared with parent Naproxen (AUC = 155 h \(\cdot\) \(\mu\)g/mL) at equimolar doses. Contrarily, there was a twofold increase in Naproxen levels in the brain with the prodrugs compared to parent Naproxen. The enhanced brain bioavailability may be attributed to the specific carrier system in addition to the reduced percentage of plasma protein binding of Naproxen. Plasma protein binding of the tested prodrugs was investigated in vitro using equilibrium dialysis. They also found that the percentage of plasma free fraction of prodrugs (9-15%) was significantly greater than that of Naproxen (about 5%) when tested at 20 \(\mu\)M, illustrating more available prodrug to cross the blood brain barrier. A significant decrease in gastric ulcerogenicity of the prodrugs compared with parent Naproxen was also noted. They found that oral dihydropyridine and ascorbate prodrugs for brain
site-specific delivery of Naproxen may be used in the treatment of neurodegenerative diseases.

Bhoyar PK et al.,\textsuperscript{49} investigated on encapsulation of naproxen in lipid-based matrix microspheres: characterization and release kinetics. Naproxen was microencapsulated with lipid-like carnauba wax, hydrogenated castor oil using modified melt dispersion (modified congealable disperse phase encapsulation) technique. They found \textit{In vitro} drug release from all the batches better fitting with the Korsmeyer-Peppas model, indicating the possible mechanism of drug release to be by diffusion and erosion of the lipid matrix.

Calija B et al.,\textsuperscript{50} investigated the feasibility of chitosan treated Ca-alginate microparticles for delivery of naproxen in lower parts of GIT and evaluated influence of formulation factors on their physicochemical characteristics and drug release profiles. Investigated factors were drug/polymer ratio, chitosan molecular weight, chitosan concentration in hardening medium, and hardening time. Sixteen microparticle formulations were prepared utilizing 24 full factorial design (each factor was varied at two levels). Microparticles size varied between $262.3 \pm 14.9$ and $358.4 \pm 21.7 \mu m$ with slightly deformed spherical shape. Low naproxen solubility and rapid reaction of ionotropic gelation resulted in high encapsulation efficiency ($> 75.19\%$). Under conditions mimicking those in the stomach, after two hours, less than $6.18\%$ of naproxen was released. They found significant influence of all investigated factors on drug release rate was observed in simulated small intestinal fluid and experimental design analysis revealed that chitosan molecular weight and its concentration had the most pronounced effect on naproxen release. They also found that the release data kinetics has predominant influence of a pH-dependent relaxation mechanism on drug release from microparticles.

Wang-Smith L et al.,\textsuperscript{51} worked on pharmacokinetics and relative bioavailability of a fixed-dose combination of enteric-coated naproxen and non-enteric-coated esomeprazole magnesium. They found that there are no pharmacokinetic drug interactions between naproxen and esomeprazole and the NAP/ESO tablet is bioequivalent to EC naproxen, and and the bioavailability of non-EC esomeprazole from the NAP/ESO tablet is lower than the EC esomeprazole formulation.
Rodrigues MR et. al.,\textsuperscript{52} worked on preparation, in vitro characterization and in vivo release of naproxen loaded in poly-caprolactone nanoparticles. Naproxen was loaded in poly-caprolactone (PCL) nanoparticles as an implantable sustained release system to prolong its anti-inflammatory activity. They prepared Naproxen-loaded nanoparticles with the following characteristics: Nanometric size (< 300 nm), negative zeta potential, low polydispersity index (< 0.1), satisfactory encapsulation efficiency, low water content (< 1%), and spherical shape. In vitro naproxen release profile was sustained and the kinetics followed the Higuchi model. They chose PCL nanoparticles containing about 12.5% (w/w) of the naproxen (sample A3) for complementary studies of stability and in vivo release in rats. They found that Nanoparticles did not suffer alteration during stability studies and In vivo release was sustained by one month.

Puglia C et. al.,\textsuperscript{53} evaluated the percutaneous absorption of naproxen from different liposomal formulations constituted of different lipids: stratum corneum lipids (SCL) and phosphatidylcholine/cholesterol (PC/CHOL). They found that the liposomes create a drug reservoir mixing with SC lipids, whilst PC/CHOL liposome promoted Naproxen permeation through the skin and Liposome lipid composition seems to affect Naproxen permeation through the skin.

Tiong N et. al.,\textsuperscript{54} worked on effects of liquisolid formulations on dissolution of naproxen. They evaluated the effects of different formulation variables, i.e. type of non-volatile liquid vehicles and drug concentrations, on drug dissolution rates. They formulated liquisolid tablets with three different liquid vehicles, namely Cremophor EL (polyoxyl 35 castor oil), Synperonic PE/L61 (poloxamer 181, polyoxyethylene-polyoxypropylene copolymer) and poly ethylene glycol 400 (PEG400) at two drug concentrations, 20\%w/w and 40\%w/w and Avicel PH102 was used as a carrier material, Cab-o-sil M-5 as a coating material and maize starch as a disintegrant. They applied empirical method of Spireas and Bolton (1999) \cite{1} to calculate the amounts of coating and carrier materials required to prepare naproxen liquisolid tablets. Quality control tests, i.e. uniformity of tablet weight, uniformity of drug content, tablet hardness, friability test, disintegration and dissolution tests were performed to evaluate each batch of prepared tablets. They studied In vitro drug dissolution profiles of the liquisolid formulations and compared with conventional formulation, in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.2) without
enzyme. They did stability studies to evaluate the stability of the tablets under humid conditions. Differential scanning calorimetry and Fourier transform infrared were used to investigate physicochemical interaction between naproxen and the excipients. They found that liquisolid tablets formulated with Cremophor EL at drug concentration of 20%w/w produced high dissolution profile with acceptable tablet properties. They found that the dissolution profiles of liquisolid tablets prepared with Cremophor EL were not affected by ageing significantly and also found from DSC that drug particles in liquisolid formulations were completely solubilised.

Maghsoodi M et. al., worked on preparation of microparticles of naproxen with Eudragit RS and talc by spherical crystallization technique. They prepared Microparticles of naproxen with Eudragit RS and talc by the spherical crystallization technique, i.e. quasi-emulsion solvent diffusion method. They evaluated them by micromeritic properties, yield, encapsulation efficiency, drug physical state and dissolution rate of drug. The influence of formulation factors and preparation condition (drug: polymer ratio, talc: polymer ratio, SLS concentration, stirring speed) on the properties of the microparticles were also examined. The resultant microparticles were finely spherical and uniform with high incorporation efficiency and yield. Greater encapsulation efficiency was obtained by increasing the drug: polymer ratio and talc: polymer ratio and by reducing the SLS %. They could enhance dissolution rate of naproxen from microparticles significantly with increasing the ratio of drug: polymer and stirring rate, and sustained by increasing SLS % in crystallization medium.

Corti G et. al., worked on dissolution and permeation properties of naproxen from solid state systems with chitosan. They prepared Drug-chitosan systems by simple physical mixing, kneading, cogrinding, or coevaporation using five types of chitosan (base and glutamate or hydrochloride salts, both at two different molecular weights). They tested the products for drug-dissolution behavior and for permeation properties through both Caco-2 cell monolayers and artificial lipophilic membranes. They found that all combinations with chitosan base were significantly (p < .01) more effective in enhancing drug-dissolution rate than those with both its salts, because of its higher amorphizing effect toward the drug, as observed in solid-state studies.

Maghsoodi M et. al., investigated on physicomechanical properties of naproxen-loaded microparticles prepared from Eudragit 100. They preared
Microparticles of naproxen with Eudragit L100 and Aerosil by the emulsion solvent diffusion method to avoid local gastrointestinal irritation. They used ethanol as solvent, dichloromethane as a bridging liquid, water as poor solvent, Aerosil as anti-adhesion agent, and sodium dodecyl sulfate to aid in the dispersion of the drug and excipients into the poor solvent. The obtained microparticles were evaluated for micromeritic properties, yield, encapsulation efficiency, drug physical state, and drug release properties. The resultant microparticles were finely spherical and uniform with high incorporation efficiency (>79%) and yield (>71%). They could enhance the incorporation efficiency with increasing the ratio of excipients to drug and the initial difference of temperature between the solvent and nonsolvent. They Studied characteristics of the micromeric properties of formulations, like flowability and packability, found that microparticles were suitable for further pharmaceutical manipulation (e.g., capsule filling). They found the microparticles as gastroresistance, and the drug release followed a Hixon and Crowell kinetic.

Maghsoodi M et. al., worked on particle design of naparoxen-disintegrant agglomerates for direct compression by a crystallo-co-agglomeration technique. They characterized them by differential scanning calorimetry (DSC), powder X-ray diffraction (XRPD) and scanning electron microscopy. The agglomerates were compressed at different compression pressures and dissolution studies were carried out for the tablets produced at lowest compression force. They found that the increase in particle size and the spherical form of the agglomerates resulted in formation of products with good flow and packing properties. DSC and XRPD studies showed that naproxen particles, crystallized in the presence of HPC and disintegrant did not undergo structural modifications. They could enhance the dissolution rate of naproxen by the amount of disintegrant.