CHAPTER III
LITERATURE ON DRUGS INVESTIGATED

NSAIDs: AN OVERVIEW

Inflammation 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. Cyclo-oxygenase (COX) 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. 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 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

I. Non-Selective COX Inhibitors:
1. Salicylates and their congeners
   Aspirin, Sodium Salicylate, Diflunisal, Salsalate, Sulfasalazine
2. Para-aminophenol derivatives
   Acetaminophen
3. Pyrazolone derivatives
   Phenylbutazone, Oxyphenbutazone
4. Indoles and related drugs
   Indomethacin, Sulindac
5. Heterocyclic arylacetic acid derivatives
   Diclofenac, Tolmetin, Ketorolac

6. Propionic acid derivatives
   Ibuprofen, Fenprofen, Naproxen, Ketoprofen, Flurbiprofen.

7. Anthranilic acid derivatives (fenamates)
   Flufenamic acid, Mefenamic acid

8. Oxicams
   Piroxicam, Tenoxicam

II. Preferential COX-2 Inhibitors:
   Nimesulide, Meloxicam, Nabumetone.

III. Selective COX-2 Inhibitors:
   Celecoxib, Valdecoxib, Parecoxib, Etoricoxib

ETORICOXIB – PROFILE

Chemically Etoricoxib is 5-Chloro-6\textsuperscript{1}-methyl-3-[4-methylsulfonyl)Phenyl]- 2, 3\textsuperscript{1} - bipyridine.
Molecular formula : $C_{18}H_{15}ClN_{2}O_{2}S$
Molecular weight : 358.8419
Melting point : 134 – 136°C
UV max : 289nm

**Properties:**

Etoricoxib is white to off-white powder. Etoricoxib is freely soluble in methanol, tetrahydrofuran, dimethyl sulfoxide, methyl ethyl ketone, dimethyl formamide, and chloroform. Etoricoxib is soluble in isopropyl acetate, ethanol and toluene, sparingly soluble in 2-Propanol, and practically insoluble in water. Etoricoxib is an orally administered non-steroidal analgesic and anti-inflammatory agent, analgesic used in the treatment of osteoarthritis and rheumatoid arthritis [Cyclooxygenase [COX-2] inhibitor]$^5-^9$ etoricoxib is used for osteoarthritis (60 mg once daily), rheumatoid arthritis (90 mg once daily), and the pain and signs of inflammation associated with acute gouty arthritis (120mg once daily)$^{10-^11}$

Etoricoxib is a selective COX-2 inhibitor and have analgesic, antipyretic and anti-inflammatory actions, with lesser GIT side effects. It doesn’t have any impact on platelet aggregation and therefore of useful cardio protective effect. It is also used in dysmenorrhoea and familial colonic polyposis, in gouty arthritis and acute musculoskeletal pain.
The mode of action of Etoricoxib is largely based on the inhibition of prostaglandin synthesis. Etoricoxib is a potent inhibitor of the both isoenzymes and the enzyme cyclooxygenase (selective COX-2 being evident) which is involved in the production of prostaglandins, believed that they mediate many of symptoms of inflammation such as oedema and pain.

PHARMACOKINETICS:

Absorption:
Etoricoxib is rather slowly and completely absorbed after oral administration. Dosing with food (a high - fat meal) had no effect on the extent of absorption of etoricoxib.

Distribution:
Etoricoxib is approximately (92%) bound to human plasma protein over the range of concentrations of 0.05 to 5µg/ml. The volume of distribution at steady state is approximately 120 lt.

Elimination:
Elimination of etoricoxib occur almost exclusive log through metabolism followed by renal excretion. Steady state concentrations of etoricoxib are reached within seven days of once daily administration of 120 mg. The mean plasma elimination half life is 20-22 hours. The plasma clearance after a 25 mg I.V dose is estimated to be approximately 50ml/min. Etoricoxib is metabolized to a principle metabolite the 6'- carboxylic acid derivative of
etoricoxib formed by further oxidation of 6’-hydroxymethyl derivative.

**Dosage and administration:**

The usual dose of etoricoxib has not been clearly established in any indication. An oral dose of 120 mg daily has been effective in acute Dental pain, 90 to 120 mg daily in Rheumatoid arthritis. Once, daily dose of 60 mg have shown efficacy in patients with osteoarthritis of the knee. There is no evidence that the dose of etoricoxib needs to be modified in patients with mild renal impairment but as with other NSAIDS caution should be exercised.

**Recent Past Work on Enhancement of Dissolution rate and Bioavailability of Etoricoxib**

Abishek et al.\(^{23}\) prepared and reported on solubility and dissolution enhancement of Etoricoxib by Solid dispersion Technique Using Sugar Carriers. Etoricoxib solid dispersions and their respective physical mixtures using lactose, sucrose, and mannitol were prepared in different ratios by solvent evaporation technique. The XRD and DSC studies indicated the transformation of crystalline etoricoxib (impure drug) to amorphous etoricoxib (in solid dispersions) by the solid dispersion technology. The *in vitro* dissolution studies exhibited improved dissolution in case of solid dispersion using lactose than the solid dispersions using both sucrose and mannitol. The *in vitro* dissolution of etoricoxib from these solid dispersions followed Hixson-Crowell model.
Enhancement of dissolution rate of etoricoxib through solid dispersion technique was studied by Muralidhar et al. In this study Etirocoxib, which is a non-steroidal anti-inflammatory drug, is used to Osteoarthritis, Rheumatoid arthritis and Acute Gouty arthritis. Etirocoxib is practically insoluble in water; hence present study was carried out to enhance dissolution properties of Etirocoxib through the preparation of Solid Dispersions using PEG 6000 as carrier at various proportions by using different techniques like Physical mixtures, Kneading Method and Solvent Evaporation Method. The drug release profile was studied in 0.1N HCl containing 1 % SLS. U.V. Spectrophotometric method was selected for assay as well as in vitro dissolution studies at 234 nm. All the solid dispersions exhibited superior dissolution than pure drug. The drug dissolution studies followed first order kinetics. Solvent evaporation method was found to be superior to other methods.

Kulthe et al. studied and reported on Solubility Enhancement of Etoricoxib by Solid Dispersions Prepared by Spray Drying Technique. Physical transformation of such drugs from crystalline form to its more soluble amorphous form is one of the approaches for improving solubility. Solid dispersions of etoricoxib with non-ionic surfactant as Poloxamer 407 and lipid carrier as Gelucire-50/13 were formulated by spray drying technique. All the proportions of etoricoxib solid dispersions reported enhanced saturation solubility and dissolution rate and only optimized
proportions, decided on the basis of least crystallinity. The study thus reveals tremendous potential of solid dispersions of poorly water soluble drug with Poloxamer 407 and Gelucire-50/13 to enhance its stability and hence solubility.

Chowdary et al.\textsuperscript{26} studied and reported on factorial Study on the evaluation of formulation variables on the dissolution rate of etoricoxib tablets. They studied on the individual main and combined effects of commonly used binders, disintegrants and β-cyclodextrin on the dissolution rate of etoricoxib tablets were evaluated in a $2^3$ factorial study. The individual main effects of binders and beta-cyclodextrin on the dissolution efficiency (DE\textsubscript{10}) were significant ($p < 0.05$). The main effects of disintegrant and all combined effects on DE\textsubscript{10} were not significant ($p > 0.05$). Tablets formulated employing poly vinyl pyrrolidone as binder and potato starch as disintegrant gave highest dissolution rate of etoricoxib, 95\% in 1 h.

Chowdary \textit{et al.}\textsuperscript{27} studied and reported on formulation development studies on enhancement of solubility and dissolution rate of etoricoxib by cyclodextrin complexation. Phase solubility studies indicated that the aqueous solubility of etoricoxib was linearly increased as a function of cyclodextrin concentration and formation of 1:1 M complexes of etoricoxib and cyclodextrins in solution with a stability constant ($K_C$) of 109 and 170 M\textsuperscript{-1} with beta-
cyclodextrin and hydroxypropyl-beta-cyclodextrin, respectively. Etoricoxib-cyclodextrin complexes prepared by kneading method gave rapid and higher dissolution of etoricoxib when compared to etoricoxib pure drug. Thus, cyclodextrin complexation is recommended as an effective and efficient technique for enhancing the solubility and dissolution rate of etoricoxib from tablets.

Fast dissolving etoricoxib tablets containing solid dispersions of etoricoxib was studied and reported by Muralidhar et al.\textsuperscript{28}. Through the preparation of solid dispersions using mannitol as carrier at various proportions (1:1, 1:3, 1:6, 1:9) by using different techniques. Etoricoxib with mannitol (1:6) kneading method gave highest dissolution. The increase in dissolution rate of the drug may be due to increased wettability, hydrophilic nature of the carrier and also possibility due to reduction in drug crystallinity.

Chowdary et al.\textsuperscript{29} studied and reported on factorial study to evaluate the individual and combined effects of beta-Cyclodextrin and Sodium lauryl sulfate on the solubility and dissolution rate of etoricoxib. The individual and combined effects of beta-cyclodextrin and sodium lauryl sulfate in enhancing the solubility of etoricoxib were highly significant ($p < 0.01$). The solubility of etoricoxib was markedly enhanced by beta-cyclodextrin (2.25 fold), sodium lauryl sulfate (32.16 fold) individually as well as combinedly by beta-cyclodextrin and sodium lauryl sulfate (38.82 fold). Solid inclusion complexes of etoricoxib-beta-cyclodextrin
were prepared with and without sodium lauryl sulfate as per $2^2$ factorial design by kneading method. A 2.90 and 3.15 fold increase in $K_1$ and 4.09 and 2.91 fold increase in $\text{DE}_{30}$ of etoricoxib was observed, respectively with beta-cyclodextrin and sodium lauryl sulfate.

Haresh et al.$^{30}$ formulated and reported preparation and characterization of etoricoxib - $\beta$ cyclodextrin complexes prepared by the kneading method. The binary system of etoricoxib with $\beta$ 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 $\beta$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 release in 30 min.

Solubility Enhancement of Etoricoxib by Solid Dispersions Prepared by Spray Drying Technique was reported by Kulthe et al.$^{31}$ Many potent drugs inspite of their therapeutic efficacy are being shelved because of their poor biopharmaceutical properties. Physical transformation of such drugs from crystalline form to its more soluble amorphous form is one of the approaches for improving solubility. Present study utilizes the spray drying technique for physical transformation of a prototype poorly water-soluble drug, etoricoxib. Though metastable amorphous form of
etoricoxib exhibited better solubility characteristics, its stabilization remains a challenge. Hence, solid dispersions of etoricoxib with non-ionic surfactant as poloxamer-407 and lipid carrier as gelucire-50/13 were formulated by spray drying technique and subjected to initial characterization to reveal drug content, saturation solubility, dissolution rate, morphological appearances, crystallinity, molecular interactions and residual solvent content. During initial characterization, all the proportions of etoricoxib solid dispersions reported enhanced saturation solubility and dissolution rate and only optimized proportions, decided on the basis of least crystallinity, were subjected to stability study. During stability study, the solubility characteristics of amorphous etoricoxib dropped drastically, but there was an insignificant decrease in those of the solid dispersions. The study thus reveals tremendous potential of solid dispersions of poorly water-soluble drug with poloxamer-407 and gelucire-50/13 to enhance its stability and hence solubility.

Formulation and Evaluation of Etoricoxib Solid Dispersions employing Starch Phosphate, PVP and PEG 4000 – A Factorial Study was reported by Chowdary et al. 32 Solid dispersion is a widely accepted technique for enhancing the dissolution rate of poorly soluble BCS class II drugs. The objective of the present study is to evaluate starch phosphate - a new modified starch, PVP K-30 and PEG 4000 as carriers in solid dispersions for enhancing
the dissolution rate and efficiency of etoricoxib, a BCS class II drug. The individual main and combined effects of the three factors namely starch phosphate (factor A), PVP K-30 (factor B) and PEG 4000 (factor C) in enhancing the dissolution rate and dissolution efficiency of etoricoxib were evaluated in a $2^3$-factorial study. Starch phosphate (Fa) gave highest enhancement in the dissolution rate of etoricoxib (26.7 fold) followed by PEG 4000 (Fc) (10.54 fold) and PVP (Fb) (8.04 fold). DE$_{30}$ was also increased from 3.03% for etoricoxib pure drug (F1) to 55.28, 46.36 and 36.61 % respectively with solid dispersions Fa, Fc and Fb. Addition of PVP and PEG 4000 to the solid dispersions in starch phosphate has further increased the dissolution rate upto 200.59 fold and dissolution efficiency upto 29.15 fold. Hence addition of PVP and PEG 4000 to the solid dispersions in starch phosphate is recommended to enhance the dissolution rate of etoricoxib, a BCS class II drug.

Effect of Hydrophilic Polymers on the complexation and solubilizing efficiencies of Cyclodextrins was reported by Chowdary et al.\textsuperscript{33} The objective of the present investigation is to study the complexation of etoricoxib with two CDs, β-cyclodextrin and hydroxypropyl β-cyclodextrin for enhancing its solubility. The effect of three hydrophilic polymers namely PVP, HPMC and PEG on the complexation and solubilizing efficiencies of cyclodextrins was also investigated. The aqueous solubility of etoricoxib was
linearly increased as a function of the concentration of βCD and HPβCD alone and in the presence of hydrophilic polymers, PVP, HPMC and PEG. The increase in solubility is due to the formation of a 1:1 M complex in solution in each case. The complexes formed between etoricoxib–CD were quite stable. Addition of hydrophilic polymers has markedly enhanced the complexation efficiency of CDs. PVP has given higher enhancement in the complexation efficiency of both; βCD and HPβCD. The order of hydrophilic polymers in enhancing the complexation efficiency was PVP > HPMC > PEG with both; βCD and HPβCD. Addition of hydrophilic polymers has markedly enhanced the solubilizing efficiency of both; βCD and HPβCD. HPβCD exhibited higher solubilizing efficiency, when compared to βCD, both; alone and in the presence of hydrophilic polymers. PVP has given highest enhancement (11.67-16.75 fold) in the solubilizing efficiency of CDs. Hence, a combination of CDs and hydrophilic polymers is recommended for enhancing the complexation and solubilizing efficiencies of CDs and to enhance the solubility of etoricoxib, a BCS class II drug.

Development and Pharmacological Evaluation of Cyclodextrin complexes of Etrocooxib was reported by Inderbir Singh et al.34 Etoricoxib is an anti-inflammatory drug largely used in a variety of acute and chronic inflammatory diseases, but is associated with low aqueous solubility and poor dissolution leading to a delayed rate of absorption and onset of action. This study focuses on the
development and pharmacological evaluation of a series of binary systems of etoricoxib with cyclodextrins. The binary systems of etoricoxib with β-cyclodextrin (β-CD) and 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) were prepared by the kneading method. Drug-cyclodextrin interactions in solution were investigated by the phase solubility analysis. X-ray diffractometry studies were carried out for the characterization of all binary systems. Invivo studies were performed using the Tail flick and Eddyís hot plate apparatus. The results of the phase solubility studies indicated an increase in etoricoxib solubility upon complexation with β-cyclodextrin (stability constant, $K_c$ value of 198.6 and 209.9 L/mol for 1:1 and 1:2 β-CD complexes of the drug, respectively) and a further increase on complexation with HP-β-CD (stability constant, $K_c$ value of 265.3 and 355.8 L/mol for 1:1 and 1:2 HP-β-CD complexes of the drug, respectively). Results of the invivo drug activity studies also pointed towards an enhanced antinociceptive effect of etoricoxib upon cyclodextrin complexation with 1:2 drug HP-β-CD complex showing maximum effect.

Solubility Enhancement of Etoricoxib by Cosolvency approach was reported by Amit Kumar Nayak et al.\textsuperscript{35} The purpose of this study was to examine and compare the cosolvency using three different cosolvents, namely PEG 400, PG, and Glycerin on the aqueous solubility enhancement of a poorly aqueous soluble drug, etoricoxib, since solubilization of nonpolar drugs constitutes
one of the important tasks in the formulation design of liquid dosage forms. The aqueous solubility of etoricoxib was 0.0767 ± 0.0018 mg/mL, which was significantly improved by the addition of PEG 400, PG, and Glycerin as cosolvents. It was scrutinized that the less-polar solvents were found to increase the aqueous solubility by greater extent, thus accentuating hydrophobic interaction mechanism. Among various solvent-cosolvent blends investigated, water-PEG 400 showed highest solubilization potential. Thus, the study generated an important array of data to compare the effect of these cosolvents on the aqueous solubility of etoricoxib.

Formulation Development of mouth dissolving tablets of a poorly water soluble drug using Sublimation technique was reported by Dagendra Bhatere et al. The purpose of this research was to develop mouth dissolving tablets of etoricoxib. Materials containing etoricoxib, camphor, low substituted-hydroxypropyl cellulose (L-HPC) and lactose were compressed by direct compression technique. Camphor was sublimed from the tablets by exposure to vacuum. The porous tablets were evaluated for percentage friability, wetting time and disintegration time. Sublimation of camphor from tablets resulted in superior tablets. The systematic formulation approach helped in understanding the effect of formulation processing variables. The best results for the batch D3 in terms of crushing strength; friability and disintegration were obtained, when sublimation was carried out of the tablets containing camphor as a
sublimating agent at 5% and L-HPC as disintegrant at the 12% concentration. The drug release data showed that the entire drug was released within 60 min. The best batch prepared using camphor sublimation technique possessed crushing strength (kg/cm²) of 3.5, friability (%) of 0.26, wetting time of 21 sec and disintegration time of 24 sec, respectively.

Formulation and Development of Oral Fast Dissolving Tablet of Etoricoxib was reported by Anup Thakre et al. In this investigation, development of oral fast dissolving tablet of Etoricoxib was developed to overcome solubility problem of Etoricoxib. Dissolution of Etoricoxib enhanced by solid dispersion technique in which Etoricoxib-carrier Urea solid dispersion were prepared by physical mixture (PM), kneading (KN) and by fusion method (FM) techniques, in three molar rations (1:1, 1:2 and 1:3). In formulation Mannitol used to maintain rapid disintegration and Urea added which acts as hydrophilic carrier and super disintegrant. Preparation of tablet by direct compression and evaluation were done. From dissolution study results, method of solid dispersion technique and drug- carrier ratio was optimized. Taste masking of bitter Etoricoxib was done by using Aspartame, In vitro and In vivo taste evaluation was done. Compatibility between drug and excipient examine by FTIR study.
Enhancement of Dissolution rate of Etoricoxib by Solid Dispersion technology was reported by Pragati Kumar et al.\textsuperscript{38} The main aim of the present study is to improve the solubility of highly water insoluble drug Etoricoxib by using solid dispersion technology. Etoricoxib, the drug being studied is a Non steroidal anti- inflammatory drug belonging to “Specific COX-2 inhibitors” classification. It is a drug which is highly insoluble in water, hence dissolution is rate limiting. Therefore the aim is to increase its solubility by using polymers such as PEG 4000, PEG 6000 & Urea. The Solid dispersion technology can be used to improve the dissolution properties of poorly soluble drugs. Etoricoxib is one of the drugs which are practically insoluble in water. Solid dispersions of Etoricoxib in various carriers (PEG 4000, PEG 6000 & Urea) were prepared to enhance its dissolution rate of the drug.

Studies on effect of superdisintegrants on Etoricoxib tablet formulations was reported by Chowdary et al.\textsuperscript{39} Etoricoxib is a selective COX-2 inhibitor, a potent widely prescribed anti-inflammatory and analgesic drug, belongs to Class II under 'BCS' and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Five formulations were developed with various superdisintegrants. The formulations were tested \textit{in vitro} drug release and hardness, friability disintegration and other tablet properties. Hardness of the tablets was in the range 5.5 -6.5 kg / sq.cm in all the batches of tablets. The correlation coefficient (r)
value between log percent undissolved and time was in the range 0.9620 -0.9977 with various tablet formulations. Tablets formulated with Prosolve, modified starch and croscarmellose sodium exhibited higher dissolution rates and dissolution efficiency among all and these tablets also fulfilled all official (I.P) and GMP requirements of compressed tablets.

Modification of Physical and Chemical Properties of BCS II Drug was reported by Patel Ronak N et al. Etoricoxib, a non-steroidal anti-inflammatory drug (NSAID), is highly selective cyclooxygenase-2 (cox-2) inhibitor belongs to class-II under BCS and exhibit low and variable oral bioavailability due to poor aqueous solubility. It has a poor solubility (201µg/ml). The aim of this study was to investigate the effect of the presence of the water soluble polymer polyethylene glycol (PEG) and surfactant (Poloxamer 407) on the complexation of etoricoxib with β-cyclodextrin and hydroxyl propyl β-cyclodextrin. Cyclodextrin which are used as complexing agents to enhance the poor solubility of poorly water soluble lipophilic drugs. The ternary inclusion complexes prepared by physical mixing, kneading method, solvent evaporation and freeze drying method. The formulated complexes were evaluated for drug content and in vitro dissolution studies were performed. The prepared complexes were confirmed and characterized by FT-IR, DSC, SEM, and XRD. The ternary inclusion complex prepared with ETR: HPβCD: Poloxamer407 (1:1:5%) by
freeze drying method were significantly higher than other complexes prepared from different ratio of polymer by physical mixture, kneading and solvent evaporation methods.

A Solid Self-Emulsifying System for Dissolution Enhancement of Etoricoxib was reported by Amit Kumar Nayak et al.\textsuperscript{41} Self-emulsifying drug delivery system offers a solution to improve the oral bioavailability of poorly aqueous soluble drugs. Etoricoxib, a non-steroidal anti-inflammatory drug (NSAID) is a selective cycooxygenase-2 (COX-2) inhibitor. The poor aqueous solubility of etoricoxib results variable dissolution rate, which is the major cause of poor bioavailability. In the current study, formulation of solid self-emulsifying systems for the dissolution enhancement of etoricoxib was attempted. The self-emulsifying tablet of etoricoxib containing goat fat and Tween 60 admixture was formulated by pour moulding technique using a plastic mould. The weight uniformity, drug content, liquefaction time, and \textit{in vitro} dissolution in simulated gastric fluid of the formulated tablets were evaluated. There was increase in \textit{in vitro} drug release with increase in Tween 60 content and decrease in goat fat content. The etoricoxib release in simulated gastric fluid followed the non-Fickian diffusion model (anomalous behaviour).

Design and Evaluation of a new Capsule-type Dosage form for Colon-Targeted Delivery of Etoricoxib was reported by Kiran Kumar GB et al.\textsuperscript{42} A new capsule-type dosage form was investigated
to approximate the chronobiology of rheumatoid arthritis for colonic targeting. The system was designed by imparting a timed-release function and a pH-sensing function to a hard gelatin capsule. The technical characteristics of the system are to contain Succinic acid together with physical mixture of Etoricoxib (1:6 ratio) in a capsule coated with a three-layered film consisting of an acid-soluble polymer, a water-soluble polymer, and an enteric polymer. In order to find the suitable formulation, various formulation factors were investigated through a series of *in vitro* dissolution studies. The ability of colon targeted drug capsule to provide colon specific drug delivery was assessed by *in vitro* drug release studies in buffer solution at pH 1.2 for 2 h, and at pH 6.8 (Simulated colonic fluid) for remaining hour. The results indicated that all the formulations shown no drug release in the stomach but the major portion of the drug was released in the colon and the drug release pattern was found to be F4>F3>F2>F1. From the analysis, it was found that, a predictable timed-release mechanism of a drug can be attained by adjusting the loading amount of Succinic acid. The outer enteric coating with cellulose acetate phthalate provided acceptable acid-resistibility. All these results suggested that this approach can provide a useful and practical means for colon-targeted delivery of drugs.
ACECLOFENAC – PROFILE

Chemically aceclofenac is [2, [(2, 6-dichlorophenyl) amino] phenyl acetoxy acetic acid].

![Chemical Structure of Aceclofenac]

Molecular formula : \( \text{C}_{16}\text{H}_{13}\text{Cl}_{2}\text{NO}_{4} \)
Molecular weight : 354.19
Melting point : 150-155°C
UV max : 275 nm

Properties

Aceclofenac is a white or almost white crystalline powder, practically insoluble in water, freely soluble in acetone and soluble in alcohol. Aceclofenac is an orally administered non-steroidal analgesic and anti-inflammatory agent\textsuperscript{43-44} with a good gastrointestinal tolerability profile\textsuperscript{45-52}. It is official in B.P\textsuperscript{44}. Aceclofenac is used in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and scapulohumeral periarthritis\textsuperscript{53}. It is also indicated for pains of various etiologies, such as musculoskeletal pain, dental pain or post surgical pain\textsuperscript{54}. 
The mode of action of aceclofenac is largely based on the inhibition of prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclo-oxygenase (selectivity to COX-2 being evident)\(^{55,56}\) which is involved in the production of prostaglandins, believed that they mediate many of the symptoms of inflammation such as edema and pain.

**Pharmacokinetics:**

**Absorption:**

Aceclofenac is rapidly and completely absorbed after oral administration. Peak plasma concentrations are reached 1.0 to 3.0 hours following ingestion. The presence of food does not alter the extent of absorption of aceclofenac but the absorption rate is reduced.

**Distribution:**

Aceclofenac is highly protein bound (> 99.7%). The plasma concentration of aceclofenac was approximately twice that in synovial fluid after multiple doses of the drug in patient with knee pain and synovial fluid effusion. The volume of distribution is approximately 30 L.

**Elimination:**

Renal excretion is the main route of elimination of aceclofenac with 70-80% of an administered dose found in the
urine. 20% is excreted in the faecal matter mainly as conjugated hydroxyl metabolites. The mean plasma elimination half-life is 2.0 – 4.0 hours. Clearance is estimated to be 5 liters per hour. Aceclofenac is metabolized to a major metabolite, 4-hydroxy aceclofenac and to a number of other metabolites including 5-hydroxy aceclofenac, 4-hydroxy diclofenac, diclofenac and 5-hydroxy diclofenac.

**Drug Interactions**

Aceclofenac may increase plasma concentrations of lithium, digoxin and methotrexate, increases the activity of anticoagulants, inhibits the activity of diuretics, enhances cyclosporine nephrotoxicity and precipitates convulsions when co-administered with quinolone antibiotics. The co-administration of aceclofenac with other NSAIDs or corticosteroids may result in increased frequency of adverse events. The concomitant administration of aceclofenac and anti-diabetic drugs may result in hypo or hyperglycemia.

**Adverse Drug Reactions:**

Aceclofenac is well tolerated with most adverse events being minor and reversible and affecting mainly the GI system. Most common events include dyspepsia (7.5%), abdominal pain (6.2%), nausea (1.5%), diarrhoea (1.5%), flatulence (0.8%), gastritis (0.6%), constipation (0.5%), vomiting (0.5%), ulcerative stomatitis (0.1%), and pancreatitis (0.1%).
Although the incidence of gastrointestinal adverse events with aceclofenac was similar to those of other NSAIDs in individual clinical trails, withdrawal rates due to these events were significantly lower with aceclofenac than with ketoprofen and tenoxicam. Other adverse effect, which are not common include dizziness (1%), vertigo (0.3%) and in rare cases paraesthesia and tremor.

**Dosage and Administration:**

The usual dose of aceclofenac is 100 mg given twice daily by mouth, one tablet in the morning and one in the evening taken either before or after food. There is no evidence that the dose of aceclofenac needs to be modified in patients with mild renal impairment but as with other NSAIDs caution should be exercised.

Elderly: Generally no dose reduction necessary.

Children: Safety and efficacy not established.

Hepatic Insufficiency: Mild to moderate- 100 mg daily, severe – not recommended.

Renal Insufficiency: Mild – treat with caution.

**Aceclofenac – A Balanced COX Inhibitor:**

Human whole blood assay data shows inhibition of COX-2 by both the parent compound and 4-hydroxy aceclofenac, IC 50 values of COX-1 and COX-2 respectively were > 100 and 0.8 for aceclofenac and > 100 and 36 for 4-hydroxy aceclofenac.
Further evidence of COX-2 selectivity of aceclofenac has been shown by an IC 50 ratio (COX-2: COX-1) of 0.26, which is beyond IC 50 ratios of 0.7 and 0.12 for the COX-2 inhibitors celecoxib and Rofecoxib respectively.

Most recent data have shown aceclofenac to have the highest COX-1: COX-2, IC 50 ratio among a range of agents including rofecoxib, celecoxib, nimesulide, diclofenac and tenoxicam.

Aceclofenac may prevent the degradation of a particular connective tissue in patients with rheumatoid arthritis and osteoarthritis and this should be classified as unique NSAID.

**PAST RESEARCH WORK ON ACECLOFENAC FORMULATIONS**

Dashora, K. *et al.*, 57 investigated the effect of processing variables on microparticulate system of aceclofenac. The systems were prepared by modified solvent evaporation method using different variables such as polymer (cellulose acetate): drug ratios (1: 9, 1: 6, 1: 3 and 1: 1), agitation speed (500 – 1500 rpm) and stirring time (5 – 15 min). The effects of processing variables were evaluated by microparticle size and entrapment efficiency. The *in vitro* drug release study was carried out with prepared microcapsules of various polymer concentrations and optimized processing variables and compared with conventional and SR tablets. The conventional tablet and SR tablets releases maximum
drug within 3 and 6 h respectively while microparticulate system releases more than 12 h. All formulations followed first order release kinetic and diffusion controlled drug release.

Vishal, Y. Joshi et al.\textsuperscript{58} studied on dissolution rate enhancement of poorly water soluble drug, contributions of solubility enhancement and relatively low micelle diffusivity. Aceclofenac is the drug, alkyl polyglucosides and SLS are the surfactants used. Solid dispersion of drug with single and mixed surfactants was prepared using solution method with ethanol as the solvent. Physico-chemical evaluation was conducted by using Du Noux tensiometer method. The results showed that the mixed surfactant system enhances drug solubilization by many folds in comparison of single surfactant.

Dahiya, S. et al.\textsuperscript{59} developed physico-chemical characterization and dissolution enhancement of aceclofenac by preparing solid binary systems of aceclofenac with HPβCD in equimolar ratio, using cogrinding, kneading and co-evaporating methods and compared with a physical mixture. The binary systems were characterized by differential scanning calorimetry, thermogravimetric analysis, mass spectroscopy, \textit{1}H NMR spectroscopy, scanning electron microscopy and \textit{in vitro} dissolution studies. All the binary systems showed superior dissolution and lower dose: solubility ratio (D: S ratio) as compared to pure
aceclofenac. The kneaded product exhibited the best dissolution. Hence, it was suggested that complexation of aceclofenac with HPβCD may be used as an approach to change the drug from BCS class II to BCS class I without changing its intrinsic permeability.

Shaikh, I.M. et al.\(^{60}\) studied the preformulation part and topical delivery of aceclofenac from lecithin organogels. Lecithins and excipients purity was determined. Partition coefficient of the drug was estimated. Effect of water added on the properties of lecithin organogels such as X-ray diffraction pattern, conductivity and viscosity were determined. The permeation study of aceclofenac from different concentrations of lecithin organogels has been determined. Aceclofenac solubility was found to be more in lecithin/oil reverse miscellar system as compared to its solubility in oil. These results showed that organogel exhibits useful pharmaceutical properties.

Yong, C.S. et al.\(^{61}\) carried out trails of clear aceclofenac loaded soft capsules with accelerated oral absorption in human subjects. They prepared five preparations containing various ratios of different solubilizers and their dissolution tests were studied. Among five preparations, a preparation with ethanolamine was selected because of its clear in appearance and showed the fastest dissolution rate. To evaluate and compare the pharmacokinetics of aceclofenac – loaded soft capsules with the conventional tablets,
2 x 2 crossover study was performed. Blood samples were collected and analysed for aceclofenac by HPLC method using UV detector. The results indicated that the soft capsule with ethanolamine was a more effective oral dosage form with fast absorption for poorly water soluble aceclofenac than the conventional tablet.

Lee J. et al.\textsuperscript{62} formulated microemulsion systems for transdermal delivery of aceclofenac. They developed an o/w microemulsion system to enhance the skin permeability of aceclofenac. Eight different formulations with various values of oil, water and the mixture of surfactant and co-surfactant were prepared. The \textit{in vitro} transdermal permeability of aceclofenac from the microemulsions was evaluated using rat skin. The level of aceclofenac permeated was analysed by HPLC and the droplet size of the microemulsions was characterized using a zetasizer nano-ZS. The results indicated that the microemulsion system studied was a promising tool for the percutaneous delivery of aceclofenac.

Yang, J.H. \textit{et al.}\textsuperscript{63} prepared and evaluated of aceclofenac microemulsion for transdermal delivery system. Microemulsion was spontaneously prepared by mixing ingredients and the physicochemical properties were studied. The microemulsion system was physically stable at room temperature at least for 3 months. \textit{In vitro} and \textit{in vivo} performance of microemulsion formulation was evaluated. Skin permeation of aceclofenac from microemulsion formulation was higher than that of cream.
Zema, et al.\textsuperscript{64} studied the application of ultrasonics in assessing a dissolution test with improved discriminating ability towards micronised powders. They prepared two batches of a poorly soluble drug aceclofenac, the known and measurable differences in the dimensions characteristics of the powdered samples, particle size and specific surface area, were not reflected in the \textit{in vitro} dissolution rates assessed according to pharmacopoeial procedures. The test performed by using assembled apparatus enabling ultrasound application, allowed a clear distinction between the dissolution profiles of the two batches. The ultrasonics seems to promote drug particle dispersion, which overcomes their tendency to agglomerate due to the increase in the specific surface area associated with particle size reduction.

Alonso, M.J. et al.\textsuperscript{65} studied aceclofenac – loaded polyepsilon – caprolactone nanocapsules and the effect of coadjuvants on morphometrical, physico-chemical properties and drug entrapment. A central composite design was used to investigate the influence of polymerization adjuvants on these properties and the effect of polymer, oil and drug concentrations in organic phase on the size and encapsulation efficiency has been analysed.

Cordero, J.A. et al.\textsuperscript{66} made a comparative study on the transdermal penetration of a series of NSAIDs namely indomethacin, ketoprofen, diclofenac, Piroxicam, tenoxicam,
ketorolac, and aceclofenac for the determination of the intrinsic transdermal permeabilities and to predict their potential for formulation in a transdermal therapeutic system. *In vitro* studies demonstrated that the used drugs have low intrinsic permeation capacities and therefore, formulation with enhancers would have to be considered in an attempt to increase the fluxes of the NSAIDs.

Perez-Ruiz, F. *et al.*\(^6^7\) carried out the comparative study of the efficacy and safety of aceclofenac and tenoxicam in rheumatoid arthritis. Bioequivalence study data demonstrated that aceclofenac shows similar efficacy to tenoxicam in the treatment of rheumatoid arthritis and better safety profile than tenoxicam, mainly regarding gastrointestinal tolerability.

Arano, A. *et al.*\(^6^8\) studied the comparison of the anti-inflammatory effect and gastrointestinal tolerability of aceclofenac and diclofenac. Single and repeated demonstration for 5 days they reported that both drugs exerted an anti-inflammatory activity and exhibited a similar gastrointestinal tolerability in the rat.

Gowda, K.V. *et al.*\(^6^9\) carried out the evaluation of bioequivalence of two formulations containing 100 mg of aceclofenac. The study was designed as a single dose, fasting, two-period two-sequence crossover study with a washout period of 1 week. The content of aceclofenac in plasma was determined by a validated HPLC method with UV detection. Pharmacokinetic
parameters for both the formulations were found to be in better agreement with reported values. The 90% confidence interval of both the formulations ratio for the parameters were found to be within the acceptable range. They concluded both formulations were equal in terms of rate and extent of absorption.

Naji Najib, *et al.*\(^70\) studied the bioequivalence evaluation of two brands of aceclofenac 100 mg tablets in healthy human volunteers. The drug was administered with 240 ml of water after a 10 hour overnight fast on two treatment days separated by one week washout period. Plasma samples were analysed for aceclofenac by a validated HPLC method with UV-visible detector. Various pharmacokinetic parameters were determined from plasma concentrations for both formulations and found to be in good agreement with reported values. No significant difference was found based on ANOVA. 90% confidence interval of test / reference ratio for these parameters were found to be within the bioequivalence acceptance range of 80-125%. Based on these statistical inferences they were concluded that test aceclofenac is bioequivalent to the reference tablet.

A bioequivalence study of aceclofenac tablets of two brands (Hifenac and Preservex) was conducted by INTAS\(^71\) in 12 healthy adult male Indian volunteers who received each medicine at a dose of 100 mg in a 2 x 2 cross over study. There was a two week washout period between the doses. Plasma concentrations of aceclofenac
were monitored by HPLC over a period of 24 hours after the administration. \( AUC_{\text{inf}} \) was calculated by the linear-log trapezoidal method. \( C_{\text{max}} \) and \( t_{\text{max}} \) were compiled from the plasma concentration – time data. ANOVA was carried out using logarithmically transformed \( AUC_{\text{inf}} \) and \( C_{\text{max}} \), and non-transformed \( t_{\text{max}} \): there were no significant differences between the medications in \( AUC_{\text{inf}} \) and \( C_{\text{max}} \). The point estimates and 90% confidence intervals for \( AUC_{\text{inf}} \) (parametric) and \( C_{\text{max}} \) (parametric) were 91.17% - 105.88% and 85.10% - 109.09% respectively, satisfying the bioequivalence criteria of the European committee for proprietary medicinal products and the US Food and Drug Administration Guidelines. Moreover, the modified Pitman-Morgan’s adjusted F-test indicated that the bioavailabilities of aceclofenac in the 2 medications were comparable regarding intra- and inter individual variability. Therefore, these results indicate that the 2 medications of aceclofenac are bioequivalent and, thus, may be prescribed interchangeably.

Kim, Y.G. \textit{et al.} \textsuperscript{72} studied the bioequivalence of two aceclofenac tablet formulations after a single oral dose to healthy male Korean volunteers, who received each medicine at a dose of 100 mg in a 2 x 2 crossover study. Plasma concentrations of aceclofenac were monitored by HPLC. Pharmacokinetic parameters were determined and found to be in good agreement with reported values. The modified Pitman-Morgan’s adjusted F-test indicated
that the bioavailabilities of aceclofenac in the two medications were comparable regarding intra – and inter individual variability. On the base of the reports they concluded that the two medications of aceclofenac are bioequivalent and, thus, may be prescribed interchangeably.

Zhu Q et al.\(^7\) carried out the Evaluation of the microstructure of semicrystalline solid dispersions. As a result of an increase in the number of emerging therapies with dissolution limited bioavailability, formulation strategies such as solid dispersions that enhance the rate of solubilization are of interest. In this study, the microstructure of solid dispersions prepared with polyethylene glycol (PEG) and four model compounds with different physicochemical properties was evaluated using a variety of experimental techniques. Solid dispersions were prepared by fusion and evaluated using small-angle X-ray scattering (SAXS), powder X-ray diffraction (PXRD), atomic force microscopy (AFM), optical microscopy and differential scanning calorimetry (DSC). SAXS results indicated that aceclofenac and chlorpropamide solid dispersions favored the interlamellar incorporation of the drug in the PEG matrix. Optical microscopy did not show any evidence of interspherulitic accumulation for any of the model compounds. Haloperidol was highly crystalline in the dispersions, whereas evidence of amorphous material was found for the other model compounds. Results indicated that both the crystallization tendency
of the drug and its solubility in amorphous regions of PEG played important roles in determining the location (i.e., interlamellar, interfibrillar or interspherulitic regions) and size of the drug domains within the dispersion.

Kilor VA et al.\textsuperscript{74} prepared an immediate-release enteric-coated pellets of aceclofenac, a poorly soluble nonsteroidal anti-inflammatory drug that has a gastrointestinal intolerance as its serious side effect. Formulation of enteric-coated pellets with improved solubility of aceclofenac could address both of these problems. Pellets were prepared by extrusion-spheronization method using pelletizing agents that can contribute to the faster disintegration and thereby improve the solubility of the drug. Different disintegrants like beta-cyclodextrin, kollidon CL, Ac-Di-Sol, and sodium starch glycolate were tried in order to further improve disintegration time. The pellets were characterized for drug content, particle size distribution, flow properties, infrared spectroscopy, surface morphology, disintegration rate, and dissolution profile. The formulations, which showed best disintegration and dissolution profiles, were coated with Eudragit L100-55, an enteric-coated polymer which does not dissolve at gastric pH but dissolves at intestinal pH, releasing the drug immediately in the dissolution medium. The optimized enteric-coated formulation containing 20% kappa-carrageenan, lactose, and sodium starch glycolate as a disintegrant did inhibit the release of
the drug for 2 h in 0.1 N HCl, whereas 87% of the drug was released within 45 min. The improvement was substantial when it was compared with solubility of pure drug under the same conditions. Thus, dissolution profiles suggested that combination of kappa-carrageenan and sodium starch glycolate resulted into fast-disintegrating, immediate-release pellets, overcoming the bioavailability problem of the poorly soluble drug, aceclofenac, and enteric coating of these pellets avoids the exposure of aceclofenac to ulcer-prone areas of the gastrointestinal tract.

Ranpise NS et al.\textsuperscript{75} was studied on the inclusion complexation of aceclofenac with beta-cyclodextrin by grinding, microwave and spray-drying techniques. A derivative of beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin, was also subjected to the complexation process with aceclofenac by spray-drying technique. The samples were subjected to \textit{in vitro} dissolution studies, fourier transform infra-red spectroscopy, differential scanning calorimetry, nuclear magnetic resonance spectroscopy and X-ray diffraction studies. The \textit{in vitro} dissolution of aceclofenac-hydroxypropyl-beta-cyclodextrin complex was faster as compared to the aceclofenac-beta-cyclodextrin complex and aceclofenac alone. Spray-dried aceclofenac-beta-cyclodextrin complex were subjected to anti-inflammatory and analgesic activity and showed significant anti-inflammatory and analgesic activity.
Chakraborty S et al.\textsuperscript{76} was observed the effects of drug solubility on their release kinetics of water soluble verapamil hydrochloride and insoluble aceclofenac from hydrophilic polymer based matrix formulations. Matrix formulations were prepared by the direct compression method. The formulations were evaluated for various physical parameters. Along with the dynamics of water uptake and erosion, SEM and \textit{in vitro} drug release of the tablets were studied. From an exponential equation, it was found that the kinetics of soluble drug release followed anomalous non-Fickian diffusion transport whereas insoluble drug showed zero-order release. SEM study showed pore formation on the tablet surface that differed depending on drug solubility. t-Test pointed to a significant difference in amount of both drugs released due to the difference in solubility. Solubility of the drug effects kinetics and the mechanism of drug release.

Shavi GV et al.\textsuperscript{77} was developed an enteric-coated multiunit dosage form containing aceclofenac, a nonsteroidal anti-inflammatory drug. The pellets were prepared by using extrusion/spheronization method, and the core pellets were coated with a pH-sensitive poly (meth) acrylate copolymer (Eudragit L100-55) to achieve site-specific drug release. The formulated pellets were characterized for percentage yield, size distribution, surface morphology studies, drug content, and flow properties. \textit{In vitro} dissolution test was used for comparison of drug release profiles of
various coated pellets. The practical yield was found to be 90-95%. The particle size of enteric-coated pellets was found to be in the range of 0.59-0.71 mm. The pellets were spherical in shape and surfaces of pellets were found to be rough and showing micropores. Enteric-coated pellets showed good flow properties and in vitro dissolution profile. Dissolution tests were carried out in a USP type II dissolution apparatus in media-simulating pH conditions of the gastrointestinal tract. The release of the aceclofenac from formulated pellets was established to be minimum in the pH 1.2 (<5%) for a period of 2 h, and at pH 6.8, it shows the maximum release (85 +/- 5% release within 1 h) which indicates gastric resistance of the formulated pellets. The 20% wt/wt enteric-coated pellets were compared to that of marketed product (tablets), it was observed that pellets showed better release profile. The study concluded that the formulated multiparticulate dosage forms can be used as an ideal drug delivery system for the aceclofenac.

Nagda C et al.\textsuperscript{78} was investigated the microencapsulation of the anti-inflammatory drug aceclofenac (ACE) for controlling drug release and minimizing or eliminating local side effects. Microspheres were prepared by a spray-drying technique using solutions of ACE and three polymers, namely, carbopol, chitosan, and polycarbophil, in different weight ratios. The spray-dried mucoadhesive microspheres were characterized in terms of shape (scanning electron microscope), size (6.60-8.40 mum), production
yield (34.10-55.62%), and encapsulation efficiency (58.14-90.57%). *In vitro* release studies were performed in phosphate buffer (pH 6.8) up to 10 hours. The spray-drying process of solutions of ACE with polymeric blends can give prolonged drug release. The *in vitro* release data were well fit into Higuchi and Korsmeyer-Peppas model and followed Fickian diffusion mechanism. *In vivo* data showed that the administration of ACE in polymeric microspheres prevented the gastric side effects. The formulations here described can be proposed for the oral administration of nonsteroidal anti-inflammatory drugs with minimal side effects on gastric mucosa.

Tran TT *et al.* were investigated the dissolution-modulating mechanism of alkalizers and polymers in nanoemulsifying Gelucire 44/14 (GUC)-based solid dispersions (SDs) for controlled release. Aceclofenac (AFC), an ionizable and poorly water-soluble drug, was chosen because of its extremely low solubility at low pH. Nanoemulsifying SD systems containing alkalizers and/or polymers were prepared by the melting method. Drug crystallinity, microenvironmental pH (pH(M)), dissolution rate, and droplet size in the media from nanoemulsifying SD were then characterized. Ternary SD containing alkalizers, mainly Na(2)CO(3) and NaHCO(3), enhanced the initial release rate of AFC in simulated gastric fluid (pH 1.2), but resulted in spring-like precipitation. However, adding a secondary polymer, Poloxamer 407, prevented precipitation in the quaternary SD system. Poloxamer 407 and
alkalizer (Na(2)CO(3)) facilitated nanoemulsion formation (80-140 nm) with a smaller droplet size in a medium of pH 1.2 as visualized by TEM. The surface and inner pH(M) were also modulated by the alkalizers, but not by the polymers. The drug's crystalline structure was further changed to partially or almost amorphous form by the alkalizers and polymers in SD as characterized by instrumental analysis. The synergistic effects of alkalizers and secondary polymers in SD on reduction of drug crystallinity and modulation of pH(M) via molecular interactions could modulate dissolution rates of ionizable and poorly water-soluble model drug without spring-like precipitation by providing more favorable nanoemulsion-forming environment.

Singh AP et al.\textsuperscript{80} carried out the product development studies of amino acid conjugate of Aceclofenac. The prodrugs designed by classical approach increase lipophilicity of the drug, which decreases the water solubility thus decreasing the concentration gradient, which controls drug absorption. To overcome the limitations of traditional prodrug approach, water soluble prodrugs can be designed by adding selected amino acid to the drug moiety that are the substrates for the enzyme located at the intestinal brush border thus overcoming pharmaceutical problem without compromising bioavailability.
ACaa (Amino acid conjugate of Aceclofenac) was synthesized by conjugation with l-phenylalanine by conventional coupling method using N, N-dicyclohexylcarbodiimide and ACaa was characterized by melting point, TLC, photomicrograph, UV, FT-IR, FT-NMR, MS-FAB, XRD and DSC. As a part of product development study ACaa was subjected to studies like \textit{In vivo} in albino rats and \textit{in vitro} like ACaa reversion to AC (Aceclofenac) in aqueous buffers of pH 1.21, 2.38, 3.10, 6.22 and 7.41, at a constant concentration (0.05M), ionic strength (micro = 0.5) and at a temperature of 37 degrees C +/- 0.5 degrees C, ACaa showed negligible reversion (2.15 %) up to 24 hrs study at acidic pH thus suggesting stability in acidic environment of stomach, the rate of reversion increased as pH of medium increased. pH- partition profile, pH- solubility profile and micromeritic studies were also carried out in comparison to pure drug. The solubility and lipophilicity of ACaa exhibited higher values at all pH range when compared to AC. The micromeritic properties also evaluated in terms of particle shape and size, IQCS and kurtosis. Resulting IQCS value approached zero thus suggesting reducing in the degree of skewness.

Patel AR \textit{et al.} \textsuperscript{81} studied the effect of mixed surfactant system of sodium lauryl sulphate (SLS) and alkyl polyglucosides (C(10)APG, C(12)APG and C(12/14)APG) on dissolution rate enhancement of poorly water soluble drug. Aceclofenac-a non-
steroidal anti-inflammatory agent was used as a model drug as it has limited water solubility. The influence of the surfactant concentration in various blends on dissolution rate of Solid Dispersion (SD), prepared using solution method with ethanol as the solvent was studied and the advantage of mixed surfactant systems over the individual surfactants was illustrated by differences in the \textit{in vitro} dissolution profiles of SD. Physico chemical evaluation (critical micellar concentration, zeta potential and beta-parameter calculations) was carried out to study the mixed surfactant systems. Solid mixtures were characterized by Infrared spectroscopy (FT-IR); X-ray diffraction studies (XRD) and scanning electron microscopy (SEM).

It was seen that the dissolution rate of aceclofenac from SD increased with the increase in the APG proportion relative to SLS with the optimum ratio of 0.2 SLS:0.8 APG showing the best effect in all cases. Results obtained from physico-chemical evaluation (the decrease in the value of critical micelle concentration and higher negative value of beta-parameters) suggested the existence of synergism between surfactants blends. The observed results in the dissolution rate enhancement could be attributed to the drug--surfactant interactions as evident from FT-IR, SEM and XRD results.
Nasr M et al.\textsuperscript{82} was studied the vesicular delivery systems, as local depot for sustained drug release. Aceclofenac multilamellar liposomes and niosomes were prepared and a comparative study was done between them through evaluation of entrapment efficiency, particle size, shape, differential scanning calorimetry and in vitro drug release. A stability study was carried out by investigating the leakage of aceclofenac and the change in the vesicles particle size when stored at (2-8 degrees C) for 3 months. The anti-inflammatory effect of aceclofenac vesicles was assessed by the rat paw oedema technique. Results showed that the entrapment efficiency and the \textit{in vitro} release of aceclofenac from the vesicles can be manipulated by varying the cholesterol content, the type of surfactant as well as the type of charge. Niosomes showed better stability than liposomes. Both vesicular systems showed significant sustained anti-inflammatory activity compared to the marketed product, with niosomes being superior to liposomes as manifested by both oedema rate and inhibition rate percentages suggesting their effectiveness as topical anti-inflammatory delivery systems.

Mutalik S et al.\textsuperscript{83} studied the effect of chitosan on improving the dissolution rate and bioavailability of aceclofenac by simple solvent change method. Chitosan was precipitated on aceclofenac crystals using sodium citrate as the salting out agent. The pure drug and the prepared co-crystals with different concentrations of chitosan (0.05-0.6\%) were characterized in terms of solubility, drug
content, particle size, thermal behaviour (differential scanning calorimetry, DSC), X-ray diffraction (XRD), morphology (scanning electron microscopy, SEM), in vitro drug release and stability studies. The in vivo performance was assessed by preclinical pharmacodynamic (analgesic and anti-inflammatory activity) and pharmacokinetic studies. The particle size of the prepared co-crystals was drastically reduced during the formulation process. The DSC showed a decrease in the melting enthalpy indicating disorder in the crystalline content. The XRD also revealed a characteristic decrease in crystallinity. The dissolution studies demonstrated a marked increase in the dissolution rate in comparison with pure drug. The considerable improvement in the dissolution rate of aceclofenac from optimized crystal formulation was attributed to the wetting effect of chitosan, decreased drug crystallinity, altered surface morphology and micronization. The optimized co-crystals exhibited excellent stability on storage at accelerated conditions. The in vivo studies revealed that the optimized crystal formulation provided a rapid pharmacological response in mice and rats besides exhibiting improved pharmacokinetic parameters in rats.

Usha AN et al.\textsuperscript{84} was prepared aceclofenac agglomerates by spherical crystallization technique using a three solvent system comprising acetone: dichloromethane (DCM): water (bridging liquid, good solvent and bad solvent, respectively). Hydroxypropyl methylcellulose-50cps (HPMC) in different concentrations was used
as hydrophilic polymer. The effect of speed of rotation and amount of bridging liquid on spherical agglomeration were studied. The agglomerates were subjected to various physicochemical evaluations such as practical yield, drug content, particle size, loss on drying, porosity, IR spectroscopy, differential scanning calorimetry, X-ray diffraction studies, relative crystallinity, scanning electron microscopy, micromeritic properties, solubility and dissolution studies. The agglomerates showed improved micromeritic properties as well as dissolution behaviour in comparison to conventional drug crystals. The optimized agglomerates (F-9) showed good sphericity as well as high drug release, and hence they were compressed into tablets by direct compression. The tablets were found within the limits with respect to various physicochemical parameters. The dissolution rate of prepared tablets was better than that of marketed tablet and pure drug.

The optimized agglomerates and tablet formulations were found to be stable for 6 months under accelerated conditions. The *in vivo* studies (preclinical pharmacokinetics, pharmacodynamics and toxicity studies, and clinical pharmacokinetics) of optimized agglomerates were carried out. The results of preclinical studies revealed that the agglomerates provided improved pharmacodynamic and pharmacokinetic profiles of drug besides being nontoxic. The results of pharmacokinetic studies of optimized tablet in human subjects indicated improved pharmacokinetic parameters of drug in comparison with that of marketed tablet.
Preparation and evaluation of aceclofenac sustained release formulation and comparison of formulated and marketed product was reported by Santanu Ghosh et al.\textsuperscript{85} The objective of the study was to develop matrix tablets for oral controlled release of aceclofenac. Matrix tablets of aceclofenac, using various viscosity of hydrophilic polymer HPMC in two different proportions, hydrophobic polymer ethyl cellulose and Guar gum were prepared by wet granulation method and subjected to \textit{in vitro} drug release studies. The drug release from all HPMC matrix tablets followed various release kinetics, formulation no -F7 followed higuchi kinetics. Furthermore, the results of the \textit{in vitro} studies in pH 7.5 phosphate buffer medium showed that F7 tablets provided controlled release comparable with market sustained release formulation (Aeroff-SR tablets). F7 tablets showed no change in physical appearance, drug content, or in dissolution pattern after storage at 40°C with 75% RH for 6 months. Based on the results of the \textit{in vitro} studies, it was concluded that the HPMC matrix tablets provided oral controlled release of aceclofenac.

Formulation and \textit{in vitro} evaluation of aceclofenac solid dispersion incorporated gels was reported by Aejaz et al.\textsuperscript{86} Aceclofenac, an analgesic and anti inflammatory drug used in treatment of Osteo arthritis, rheumatoid arthritis and ankylosing spondylitis. Various compositions of aceclofenac solid dispersions were prepared by physical mixing, fusion and solvent evaporation
methods using PVP, PEG 6000, mannitol and urea as carrier to enhance the solubility of drug. The formulations evaluated for drug content, *in vitro* dissolution study and also characterized by IR and DSC studies. There is no interaction between drug and carrier. The general trend indicated that there was a increase in *in vitro* drug release for solid dispersion prepared in the following order Urea > PEG 6000 > PVP > Mannitol. Based on *in vitro* drug release pattern, 1:3 drug carrier ratio was selected as ideal dispersion for gels. Carbopol 940 selected as ideal gel base for preparation of gels and dispersions are incorporated to gel bases by trituration were characterized for rheological studies, drug content estimation and *in vitro* diffusion study, IR spectroscopy. All these properties were found to be ideal. The *in vitro* release of Aceclofenac solid dispersion incorporated gel is significantly improved when compared to pure drug in incorporated gel.

Formulation and Evaluation of Aceclofenac Solid Dispersions for Dissolution Rate Enhancement was reported by AppaRao et al.\(^\text{87}\) Aceclofenac is a novel non-steroidal anti-inflammatory drug (NSAID) having anti-inflammatory and analgesic properties, and is widely used in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Therefore, solid dispersions (SDs) of Aceclofenac were prepared using lactose,
mannitol and urea to increase its aqueous solubility. Aceclofenac SDs was prepared in 9:1, 7:3 and 4:1 ratios of the drug to polymer (by weight). In vitro release profiles of all SDs (F-1 to F-9) were comparatively evaluated and also studied against pure Aceclofenac. Faster dissolution was exhibited by solid dispersion containing 9:1 ratio of drug: lactose. The increase in dissolution rate of the drug may be due to increase in wettability, hydrophilic nature of the carrier and due to reduction in drug crystallinity. The prepared solid dispersion was subjected for % practical yield, drug content and infrared (IR) spectroscopic studies. Absence of significant drug-carrier interaction was confirmed by infrared spectroscopic (IR) data.

Design and Characterization of Aceclofenac Mouth Dissolving Tablets by Effervescent Formulation Approach was reported by Ravikumar et al.\textsuperscript{88} Aceclofenac is a novel non-steroidal anti-inflammatory drug (NSAID) having anti-inflammatory and analgesic properties and is widely used in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly and pediatrics. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Though aceclofenac is well absorbed after oral dosing, there is a first pass metabolism leading to a reduced bioavailability of the
drug (40-50%). Therefore, the present investigation was concerned to develop Mouth dissolving tablets of aceclofenac by effervescent formulation approach to provide patient friendly dosage form. The effervescent excipient system not only aids rapid disintegration of tablets in the oral cavity but also masks the slight bitter taste of medicament. Sodium bicarbonate, heat treated Sodium bicarbonate, tartaric acid, sodium glycine carbonate and citric acid were used as effervescent agents and their ratio in the formulation was optimized. The study revealed that 10:8 ratio of heat treated Sodium bicarbonate and citric acid (F3) in the aceclofenac Mouth dissolving tablets gave a soothing fizz, excellent mouth feel, good palatability and quick dissolution profile. The optimized formulation (F3) was found to be stable during the stability studies conducted as per ICH guidelines, as it showed no significant changes (P<0.05) in the physicochemical properties, disintegration time and in vitro drug release.

Dissolution Enhancement of Poorly Soluble Aceclofenac by Solid Dispersion Technique and its Comparison with Marketed Formulations was reported by Gowthamarajan et al.\textsuperscript{89} The development of a meaningful dissolution procedure for drug product with limited water solubility has been a challenge to both the pharmaceutical industry and the agencies that regulate them. These challenges include developing and validating the test methods, ensuring that method is appropriately discriminatory and addressing
the potential for an \textit{in vivo-in vitro} correlation (IVIVC). Aceclofenac (BCS Class II drug) comes under Non Steroidal Anti-Inflammatory Drugs and widely used as an analgesic. Aceclofenac is poorly soluble in water and aqueous buffers in the gastrointestinal pH range (1.2 – 7.5), which leads to the failure of dissolution of aceclofenac. Here an attempt has been made to enhance the dissolution of aceclofenac by solid dispersion technique. Solid dispersion of Aceclofenac was tried with PEG-6000, Beta Cyclodextrin, Gelatin Hydrolysate, SLS and Croscarmellose. It was found that the aceclofenac – croscarmellose complex has given the best solubility results. The Infra Red spectra revealed that there is no incompatibility between the drug and excipients. The DSC thermogram shows the complete complexation between drug and aceclofenac.

The dispersible tablets of the selected Aceclofenac-Croscarmellose solid dispersions were prepared and compared with \textit{in vitro} dissolution profiles of Aceclofenac without Croscarmellose and marketed tablets. The drug release from the Aceclofenac-Croscarmellose solid dispersions tablets was found to be 94.95% within 10 min. It was comparatively faster than the drug release of Aceclofenac tablets with Croscarmellose and marketed tablets which was found 35.14% and 32.78% within 10 min respectively. The $T_{50}$ values of Aceclofenac-Croscarmellose solid dispersions tablets, Aceclofenac with Croscarmellose tablets and Marketed tablets were...
found to be 3min, 16 min and 21 min respectively. The results showed that the rapid dissolution was the characteristic behaviour of solid dispersion of Aceclofenac-Croscarmellose solid dispersions tablets.

Studies on formulation development of a poorly water-soluble drug through solid dispersion technique was reported by Sunita Dahiya. An attempt has been made to enhance dissolution of aceclofenac (AC) by solid dispersion technique using water soluble carriers PEG 6000 and β-cyclodextrin (β-CD). Solid dispersions of AC with PEG 6000 were prepared by melting solvent method and with β-CD were prepared by co-grinding, kneading and co-evaporation methods. Solid dispersions with both carriers were prepared in drug: carrier (1:1 and 1:2) ratios along with the corresponding physical mixtures. The prepared dispersions were evaluated by differential scanning calorimetry (DSC), scanning electron microscopy (SEM), in vitro dissolution studies. The results from DSC and SEM analysis showed that AC might exist in an amorphous state in the solid dispersion. Considerably improved dissolution profile was obtained by higher PEG ratios (1:2), whereas there was no significant improvement in dissolution of AC along with β-CD at higher carrier ratios. The solid dispersion prepared as AC: PEG 6000 (1:2), exhibited the fastest dissolution among all solid dispersions, was formulated into tablets using direct compression method and further compared with three popular
immediate release marketed brands of AC. Model independent parameters were used for comparing tablets dissolution profiles viz. percentage of drug dissolved in 50 minutes (DP50), dissolution efficiency at 50 minutes (DE_{50}), time for 50% drug release (t_{50%}), similarity factor (f2) and difference factor (f1). The results indicated that formulated tablets displayed better dissolution profiles as compared to existing commercial tablets.

Enhancement of solubility of aceclofenac by using different solubilization technique was reported by Bhupendra Kumar Tiwari et al. The objective of present research is to explore the application of different solubilization technique in the water-insoluble drugs and to reduce concentration of hydrotropic agent produce its own toxicity. In case of synergistic effect in solubility due mixing of hydrotropic agent, say, the toxic level of individual can further be lowered because still less concentration of the hydrotropic agents shall be sufficient for a desired enhancement in solubility.

Formulation Development of Aceclofenac Tablets Employing Starch Phosphate - A New Modified Starch was reported by Chowdary et al. The objective of the study is to prepare, characterize and evaluate starch phosphate, a new modified starch as a carrier in solid dispersions for enhancing the dissolution rate of aceclofenac. The feasibility of formulating solid dispersions of aceclofenac in starch phosphate into compressed tablets with
enhanced dissolution rate was also investigated. Starch phosphate was prepared by reacting starch with di-sodium hydrogen orthophosphate anhydrous at elevated temperatures. Solid dispersions of aceclofenac in starch phosphate were prepared by solvent evaporation method employing various weight ratios of drug: starch phosphate such as 2:1(SD-1), 1:1(SD-2), 1:2(SD-3), 1:3(SD-4) and 1:9(SD-5) and were evaluated for dissolution rate and efficiency. Aceclofenac (50 mg) tablets were prepared employing aceclofenac alone and its solid dispersions SD-3 and SD-4 by wet granulation method and were evaluated. All the solid dispersions prepared gave rapid and higher dissolution of aceclofenac when compared to pure drug. A 51.89 and 107.03 fold increase in the dissolution rate ($K_1$) of aceclofenac was observed with solid dispersions SD-4 and SD-5 respectively. The DE$_{30}$ was also increased from 2.50% in the case of aceclofenac pure drug to 69.43% and 79.83% in the case of these solid dispersions. A 4.01 and 18.35 fold increase in the dissolution rate ($K_1$) was observed with tablet formulations containing solid dispersions SD-3 and SD-4 respectively when compared to plain tablets. Starch phosphate could be used as a carrier to enhance the dissolution rate of aceclofenac from its solid dispersions as well as tablet formulations.

Dissolution rate enhancement of aceclofenac by solid dispersion technique was reported by Shobhit Kumar et al.\textsuperscript{93} The aim of this study was to prepare and characterize solid dispersions
of aceclofenac, employing a mixed excipient system composed of lactose, corn starch as a carrier and to study the effect of a mixed excipient system on rate of dissolution of drug. The solid dispersions were prepared by physical mixture method and solvent wetting method using 1:1 ratios of drug to mixed excipient system. The formulations were evaluated for % practical yield, drug content, bulk density, tapped density, Hausner’s ratio, Carr’s index, angle of repose and in vitro drug release. In this study it was concluded that there was considerable increase in in vitro drug release for solid dispersion as compared to the pure drug taken alone. Based on the drug release pattern, the solvent wetting method showed more in vitro drug release as compared to physical mixture method. It was observed that the dissolution rate of drug from solid dispersions increases with the increase in lactose amount in comparison to corn starch with the optimum ratio of (1.0) lactose:(0.5) corn starch showing the best result.

Effect of lyophilization and polymer compositions on solubility of aceclofenac solid dispersions was reported by Shilpa Gupta et al. Aceclofenac, a non steroidal anti-inflammatory agent is BCS class II drug (highly permeable and low soluble) shows poor aqueous solubility, in order to improve solubility and dissolution rate; solid dispersions of Aceclofenac were prepared using different polymers and effect of polymer compositions on solid dispersion were also investigated. Solid dispersions of Aceclofenac were
prepared using PEG 6000 and Poloxamer 407. Dissolution studies indicated significant enhancement in dissolution of Aceclofenac when dispersed in PEG 6000 and Poloxamer 407. Solid dispersions containing Aceclofenac /Poloxamer 407, 1: 4.5, showed a max. dissolution (97%) after 60 min (D60) and another dispersion containing Aceclofenac /PEG 6000, 1:6, also showed significant enhancement in dissolution rate (D60 value 94%). FT-IR study was also performed to determine the physicochemical properties of the solid dispersions in comparison with the pure drug. It was found that lyophilized solid dispersions of Poloxamer 407 had the maximum effect on the rate and extent of dissolution of Aceclofenac.

A Factorial Study on Formulation Development of Aceclofenac Tablets Employing Starch 1500 and PVP K 30 was reported by Chowdary et al.95 Aceclofenac, a widely prescribed anti-inflammatory and analgesic drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Solid dispersion of aceclofenac in Starch 1500, a modified starch and polyvinyl pyrrolidone (PVP K 30) was investigated to enhance the dissolution rate and to develop aceclofenac tablets with fast dissolution characteristics. The individual and combined (interaction) effects of Starch 1500 and PVP K 30 on the dissolution rate of aceclofenac solid dispersions and tablets were evaluated in a series of $2^2$ – factorial experiments.
Solid dispersions and tablets of aceclofenac were formulated employing selected combinations of Starch 1500 and PVP K 30 as per $2^2$ – Factorial design and were evaluated. The individual and combined effects of Starch 1500 and PVP on the dissolution rate of solid dispersions as well as tablets were highly significant ($P<0.01$). Solid dispersion of aceclofenac in Starch 1500 (a), PVP K 30 (b) and Starch 1500 – PVP K 30 (ab) enhanced the dissolution rate of aceclofenac by 4.89, 4.75 and 4.82 folds respectively when compared to aceclofenac pure drug. Tablets formulated employing solid dispersions of aceclofenac in Starch 1500 (Fa) and PVP K 30 (Fb) gave respectively 2.1 and 2.2 fold increase in the dissolution rate ($K_1$) of aceclofenac when compared to plain tablets (F1). Aceclofenac tablets prepared employing solid dispersions in Starch 1500 – PVP K 30 (Fab) gave highest enhancement (3.0 fold) in the dissolution rate of aceclofenac. Dissolution efficiency ($DE_{15}$) was also increased by 2.12 - 2.42 fold with tablets formulated employing solid dispersions in Starch 1500 (Fa), PVP K 30 (Fb) and Starch 1500 – PVP K 30 (Fab) when compared to plain tablets (F1). Aceclofenac tablets formulated employing all its solid dispersions in Starch 1500, PVP K 30 and Starch 1500 – PVP K 30 gave a very fast dissolution of aceclofenac, NLT 80% in 15 min. Thus, solid dispersions of aceclofenac in Starch 1500, PVP K 30 and Starch 1500 – PVP K 30 could be formulated in to tablets with fast dissolution characteristics.
Solubility enhancement potential of tamarind seed polysaccharide as a solubilizer was reported by Anamika Satle et al. Solubility behavior of a drug is one of the key determinants of its oral bioavailability. In recent years, the number of poorly soluble drug candidates has increased tremendously. The formulation of poorly soluble drugs for oral delivery presents a challenge to the formulation scientists. The present study has shown that it is possible to increase the dissolution rate of poorly soluble drugs like Aceclofenac, Atorvastatin, Irbesartan, by preparing solid dispersion using Tamarind Seed Polysaccharide a water soluble polymer as solubilizer. Physical mixture and Solid Dispersion of Aceclofenac, Atorvastatin, Irbesartan with Tamarind Seed Polysaccharide (TSP) in ratio of 1:1, 1:3, 1:5 were prepared. Solubility study, Drug content and Dissolution profile study were performed for Aceclofenac, Atorvastatin, Irbesartan in Solid dispersions FS1, FS2, FS3, FS5, FS6, FS7, FS8, FS9 as well as in Physical mixtures FP10, FP11, FP12, FP13, FP14, FP15, FP16, FP17, FP18. It was observed that solid dispersions of each drugs showed increase in dissolution rate in comparison with its pure drug in the ratio of 1:3 (Drug: TSP). The selected formulations of Aceclofenac (FS2), Atorvastatin (FS5), Irbesartan (FS8) with TSP were subjected to Accelerated stability study. The prepared Solid Dispersion Formulations of Aceclofenac, Atorvastatin, Irbesartan using Tamarind Seed Polysaccharide as solubilizer were found to be quite stable. It can be concluded that with the careful and proper
use of Tamarind Seed Polysaccharide, solubility of poorly soluble drugs can be improved.

Study the effect of various carriers on the solubility of aceclofenac was reported by Bachhav Devidas et al. Aceclofenac is a new non-steroidal anti-inflammatory drug (NSAID) having fewer side effects as compared to other NSAIDs. The drug suffers from poor bioavailability due to its poor aqueous solubility. Aqueous solubility plays an important role in the dissolution of drug in the gastrointestinal fluid. The present study investigates the use of various carriers like PVP K-30, PEG-6000, Mannitol and Lactose with respect to their effect in increasing the solubility of Aceclofenac and improves its bioavailability.

Dissolution enhancement of poorly soluble Aceclofenac by Complexation with β-Cyclodextrin was reported by Dhamat Khushal et al. Aceclofenac is an effective analgesic and anti-inflammatory drug prescribed widely in recent years for various types of pain and inflammation. Aceclofenac is partially insoluble in water and aqueous fluid and as such it exhibits poor variable oral bioavailability. Aceclofenac needs enhancement of solubility and dissolution rate to improve its oral bioavailability and therapeutic efficacy. Among the various approaches to enhance the solubility and dissolution rate of poorly soluble drugs complexation with cyclodextrin is an effective and industrially accepted technique. In the present investigation, Complexation of aceclofenac with β-CD
was carried out by using various techniques like physical mixture, kneading method, co-precipitate method & solvent evaporation method. From the various characterization studies like drug content, production yield & *in vitro* dissolution study, batch abc-6 by kneading method was selected as optimised batch. Optimised batch was also studied for FTIR.

Solid Dispersion – A Comparative study on the dissolution rate of aceclofenac was reported by Vanitasagar *et al.*\(^99\) Aceclofenac, an analgesic and anti-inflammatory agent used in the management of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. One of the major problems with this drug is its low solubility in biological fluids, which results in poor bioavailability after oral administration. The objective of the present study was to prepare solid dispersions of aceclofenac using PEG 6000, Mannitol and β-cyclodextrine to increase its aqueous solubility. Aceclofenac solid dispersions were prepared in 1:1, 1:2, 1:3, 1:4 w/w ratios of the drug to polymer, using physical mixture and solvent evaporation methods. Prepared aceclofenac solid dispersions were evaluated for particle size, % practical yield, % drug content, and *in vitro* dissolution studies. The highest dissolution was exhibited by solid dispersions containing 1:4 w/w ratio of drug: PEG 6000, prepared by solvent evaporation method. The increase in dissolution rate of the drug may be due to increase in wettability, hydrophilic nature of the carrier, and due to reduction in drug crystallinity.
In vitro dissolution enhancement of aceclofenac using hydrophilic carriers was carried out by Himansu Bhusan Samal et al.\textsuperscript{100} The aim of the present study was to enhance the solubility and dissolution rate of poorly water-soluble drug Aceclofenac (BCS-class II) using its solid dispersions (SDs) with hydrophilic carrier’s polyethylene glycol (PEG) 6000 and Inclusion complex with β-Cyclodextrin. SDs of Aceclofenac with PEG 6000 prepared at 1:1 w/w (Aceclofenac / PEG 6000) ratios by physical mixture (P1), melting (P2) and solvent evaporation (P3) method. Dissolution profile of batch P1, P2 and P3 indicate that solvent evaporation method give better dissolution than physical mixtures and melting method. So other batches (PE1, PE2, PE3, PE4 & PE5) were prepared by solvent evaporation method with ratios 1:3, 1:5, 1:7 and 1:9 respectively. Inclusion complex of Aceclofenac with β-Cyclodextrin was prepared by physical mixture, co-grinding and kneading method at 1:1 w/w ratio. It was clear that kneading method would be the best method for the preparation of inclusion complex of Aceclofenac with β-CD. Hence Kneading method was selected for further study (K1, K2, K3 & K4 in 1:0.5, 1:1, 1:1.5 & 1:2 ratios respectively). Phase solubility study was conducted to evaluate the effect of polymer on aqueous solubility of Aceclofenac. Solid state characterization was evaluated by Fourier-transform infrared spectroscopy (FTIR), and differential scanning calorimetry (DSC). In vitro dissolution study was performed in phosphate buffer at pH 6.8. In vitro dissolution rate of Aceclofenac from solid dispersion (SD) was significantly higher compared to pure Aceclofenac.
Peppermint oil based drug delivery system of aceclofenac with improved anti-inflammatory activity and reduced ulcerogenicity was reported by Anuradha S. Pol et al.\textsuperscript{101} Aceclofenac (ACF), a nonsteroidal anti-inflammatory (NSAID) BCS class II drug belonging to the class of phenyl acetic acid derivatives exhibiting antipyretic, anti-inflammatory and analgesic activities. Many strategies have been employed for improving solubility and thus bioavailability of this drug moiety. But this is a first report on peppermint oil based oral SMEDDS of ACF for achieving a synergistic anti-inflammatory activity by combining NSAIDS with essential oils such as mint oils. Thus, the present investigation was designed with an aim to improve the solubility, dissolution rate, oral bioavailability and eventually anti-inflammatory activity of ACF by incorporating into peppermint oil based SMEDDS. The solubility of ACF was determined in various lipid based excipients viz, essential oils and other lipophiles, surfactants and cosurfactants. Further emulsification studies were carried out in order to select specific oil- surfactant-cosurfactant combinations for plotting the pseudo ternary phase diagrams which were then constructed to identify the existence of microemulsion region. The formulations of ACF-SMEDDS were optimized using pseudo-ternary phase diagrams analysis and studied for drug loading and lipid content. The average globule size of ACF-SMEDDS was less than 100 nm and was confirmed by transmission electron microscopy. The optimized formulation exhibited about 99% release of ACF.
from the SMEDDS filled in capsules. Furthermore, ACF SMEDDS showed 80 ± 7.30 % inhibition after 4 hr of treatment against carrageenan induced paw. In addition to this SMEDDS showed least ulcer score as compared to other treatment group. Thus, the developed SMEDDS were found to exhibit less GI tract toxicity and showed superior anti inflammatory action compared to plain drug.

Dissolution Rate Enhancement of Aceclofenac by Solid Dispersion Technique was reported by Ramana et al.\textsuperscript{102} The aim of this study was to prepare and characterize solid dispersions of aceclofenac, employing a different excipient system composed of PEG 6000, Glycine, and PVP k30 and to study the effect of a mixed excipient system on rate of dissolution of drug. The solid dispersions were prepared by physical mixture method and solvent wetting method using 1:1 ratios of drug to mixed excipients system. The formulations were evaluated for % practical yield, drug content, and \textit{in vitro} drug release. In this study it was concluded that there was considerable increase in \textit{in vitro} drug release for solid dispersion as compared to the pure drug taken alone. Based on the drug release pattern, the solvent wetting method showed more \textit{in vitro} drug release as compared to physical mixture method. Finally it could be concluded that solid dispersion of Aceclofenac using hydrophilic polymers would improved the aqueous solubility, dissolution rate and thereby enhancing its systemic availability.
Enhancement of Dissolution of Aceclofenac Film Coated Tablet by Micronisation Technique was reported by Soni et al.\textsuperscript{103} Aceclofenac is non-steroidal anti-inflammatory drug with marked anti-inflammatory and analgesic properties. It is indicated for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. Aceclofenac is BCS class II drug with low solubility and high permeability. Micronization technique is used to increase the solubility and thus dissolution of Aceclofenac. The micronization was done using jet mill micronizer. The initial particle size of drug is 297.33 micron (D90) which was reduced to particle size 121.87 micron (D90) with single micronization, particle size 116.08 micron (D90) with double micronization and 89.23 micron (D90) with triple micronization of drug. It was observed that the solubility and thus dissolution of Aceclofenac was increased in principle media of 6.8 phosphate buffer and discriminating media 4.5 Acetate buffer with single, double and triple micronization. Thus, it can be justified that micronization is one of the good technique for enhancement of solubility of Aceclofenac by reduction of particle size of drug.

Formulation, Optimization and Evaluation of Solid Dispersion Tablets of Aceclofenac using Kollidon 30 was reported by Panikkarakayil Habeeb \textit{et al.}\textsuperscript{104} The present study was designed to evaluate the effect of Polyvinyl pyrrolidone on dissolution enhancement of aceclofenac from solid dispersion both by \textit{in vitro}
and *in vivo* methods. Aceclofenac binary solid dispersions were prepared using solvent evaporation method. *In vitro* solubility of pure drug and solid dispersions were carried out. Solid dispersion of aceclofenac with PVP showed considerable increase in the solubility in comparison with pure drug in 7.4 pH phosphate buffer, isopropyl alcohol, methanol and acetone. A $3^2$ full factorial design was used in the study. It was noted that the quantity of carrier have considerable effect in the solubility of drug in solid dispersion. Increase in the dissolution of the tablet prepared from solid dispersion was also proved by both *in vitro* dissolution study and *in vivo* pharmacodynamic effects. The amorphous nature of the drug in solid dispersion was confirmed by X-ray powder diffraction and decrease in the intensity of the thermogram compared to the pure drug. FTIR spectroscopy and DSC studies showed that there was no interaction between aceclofenac and PVP in solid dispersion in solid state. Dissolution enhancement was due to decrease in crystallinity of drug and solubilizing effect of the carrier from the solid dispersion of the aceclofenac. In conclusion, the dissolution of aceclofenac can be enhanced by the use of hydrophilic carrier like PVP.
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