Chapter 2

Review of Literature
Chapter 2. Review of Literature:

Subramaniam Kannan et al. [1] develop "once daily" sustained release tablets of Aceclofenac (200mg) by wet granulation using hydrophilic polymer like Hydroxy propyl methyl cellulose K-100. The drug excipient mixtures were subjected to preformulation studies. The tablets were subjected to physicochemical studies, in-vitro drug release, kinetic studies and stability studies. FTIR studies shown there was no interaction between drug and polymer. The physicochemical properties of tablets were found within the limits. Aceclofenac is a non steroidal anti-inflammatory agent used in symptomatic treatment of rheumatoid arthritis, osteoarthritis and spondylitis. The drug release from optimized formulations was extended for a period of 24 hrs. The kinetic treatment of selected formulation (F8) showed that the release of drug follows zero order models. The optimized formulations were subjected to stability studies for one month at 45°C temperature with RH 75±5% and showed there were no significant changes in drug content, physicochemical parameters and release pattern. Results of the present study indicated the suitability of hydrophilic polymers in the preparation of matrix based sustained release formulation of Aceclofenac.

Abdul Ahad et al. [2] develop matrix tablets of Aceclofenac with Prosopis juliflora gum and to study its functionality as a matrix forming agent for once daily sustained release tablet formulations. Physicochemical properties of dried powdered Prosopis juliflora gum were studied. Various formulations of Aceclofenac Prosopis juliflora gum were prepared. The formulated tablets found to have better uniformity of weight and drug content with low SD values. The swelling behavior and release rate characteristics were studied. The dissolution study proved that the dried Prosopis
Juliflora gum can be used as a matrix forming material for making once daily Sustained release matrix tablets.

Saravanabhavan et al. [3] develop sustained release matrix tablets of aceclofenac. The tablets were prepared with different ratios of hydroxypropyl methylcellulose K100 M and ethyl cellulose by wet granulation technique. The solubility study of the aceclofenac was conducted to select a suitable dissolution medium for in vitro drug release studies. In vitro dissolution study was carried out for all the formulation and the results compared with marketed sustained release tablets. The drug release from matrix tablets was found to decrease with increase in polymer ratio of hydroxypropyl methylcellulose as well as ethyl cellulose. Formulation F3 exhibited almost similar drug release profile in different dissolution media as that of marketed tablets. From the results of dissolution data fitted to various drug release kinetic equations, it was observed that highest correlation was found for First order, Higuchi's and Korsmeyer equation, which indicates that the drug release occurred via diffusion mechanism.

Indranil Kumar Yadav et al. [4] develop the oral sustained release matrix tablets of aceclofenac using hydrophilic and hydrophobic polymers. Aceclofenac is a non steroidal anti-inflammatory agent used in symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis and its biological half life is 4 hrs. FTIR studies were carried to know the interaction between the drug and polymer. Controlled release formulations of aceclofenac (200 mg) were prepared by direct compression method. The tablets were subjected to physicochemical, in vitro drug release and stability studies. Optimization of the formulation was done by studying effect of drug to polymer ratio on drug release. FTIR studies indicated absence of any interaction between aceclofenac and
polymers. The physicochemical properties of tablets were found within the limits. The drug release from optimized formulations F1, F4 and F7 was extended for a period of 12 hrs. The kinetic treatment to optimized formulations showed that the release of drug follows zero order model and Super Case II transport for F1 and F7 while the drug release of F4 was best explained by Higuchi’s model and Super Case II transport. Release of the drug was retarded with increase in polymer concentrations. The optimized formulations were subjected to stability studies for three months at 45° temperature with RH 75±5%, and showed stability with respect to physicochemical parameters and release pattern. Results of the present study indicated the suitability of hydrophilic and hydrophobic polymers in the preparation of matrix based sustained release formulation of Aceclofenac.

Ghosh et al. [5] examine the pharmacokinetics of a formulated Aceclofenac sustained release tablet formulation and determine if it is bioequivalent to a commercial brand of Aceclofenac immediate release tablet (Zerodol® 100 mg). Each of two groups of twelve fasting volunteers received either the reference standard (Zerodol 100 mg tablets) or the test formulation (200 mg Aceclofenac) orally once, using a cross-over design with a one week wash-out period. Their blood samples were obtained at regular time intervals over 24 h and analyzed by high performance liquid chromatography (HPLC). Using the non-compartmental approach, plasma levels of Aceclofenac were employed to compute their individual disposition kinetics, including peak plasma concentration (Cmax), peak time (Tmax), area under the plasma level-time curve (AUC 0-t), elimination rate constant (Kel) and elimination half life (t 1/2). The Cmax values of 11043 ± 3073 ng/ml and 12301 ± 3000 ng /ml were attained in 2.58 ± 1.22 h and 1.29 ±
Chapter 2 Review of Literature

0.75 h for the test and reference products, respectively, while AUC was 45996 ± 10427 and 50253 ± 8283 ng.h/ml, respectively. On the basis of the pharmacokinetic data, it can be said that the test Aceclofenac sustained release formulation and the reference product were bioequivalent in some respects. However, the test formulation exhibited a longer elimination half-life (t1/2), thus demonstrating sustained release properties, unlike the reference.

Subal Basak et al. [6] formulated enteric coated sustained release aceclofenac matrix tablets were formulated employing hydroxypropyl methylcellulose polymer and the sustained release behavior of the fabricated tablets were investigated. Sustained release matrix tablets containing 200 mg aceclofenac were developed using different drug polymer ratios of hydroxypropyl methylcellulose. Tablets were prepared by wet granulation technique. Formulation was optimized on the basis of acceptable tablet properties and in vitro drug release. The resulting formulations produced monolithic tablets with optimum hardness, uniform thickness, consistent weight uniformity and low friability. Aceclofenac release from tablets was extended from 16 to 24 h from formulated batches. The results of dissolution studies indicated that formulation F-V (drug to polymer 1:0.470), the most successful of the study, exhibited drug release pattern very close to theoretical release profile. Applying kinetic equation models to F-V batch it was found to be followed Higuchi model, as the plots showed high linearity, with correlation coefficient ($R^2$) value 0.9911. Therefore, the formulation F-V tablets showed diffusion dominated drug release. The accelerated stability study showed that the shelf life 40 months (batch F-V) and promising drug storage results.
Gupta et al. [7] prepared sustained release aceclofenac loaded PLGA microspheres by emulsion solvent diffusion technique. The methods used in this components and their concentration necessary for organogels formation were evaluated using phase diagram Solubility of aceclofenac was determined, Characterization of Poly (DL-lactide)-co-glycolide (PLGA) polymer, solubility assessment of aceclofenac, drug-excipients compatibility studies, in vitro analytical method development, preparation of aceclofenac-loaded PLGA microspheres, characterization of the formulations. Prepared microspheres were optimized and evaluated for different parameters and best formulation was subjected to in vitro drug release studies. The prepared microspheres were white, free-flowing and almost spherical in shape. In vitro drug release studies were carried out up to 24 h in three different pH media, i.e., 0.1 N HCl (pH 1.2), phosphate buffer (pH 6.8) and phosphate buffer (pH 7.4). The drug-polymer concentration of dispersed phase influences the particle size and drug release properties. In nut shell it may be concluded that sustained release aceclofenac microspheres can be successfully prepared and used parenterally with increased therapeutic value and reduced side effects.

Parejiya et al. [8] developed Sustained release Aceclofenac matrix tablets constituting Kollidon SR (Polyvinyl acetate- povidone based matrix retarding polymer). Matrix tablets were prepared by direct compression of Kollidon SR varying proportion with fixed percentage of aceclofenac. Tablets containing 50% Kollidon SR demonstrated a rapid rate of drug release with an initial burst effect. Incorporation of more Kollidon SR in the tablet prolonged drug release with subsequent minimization of burst effect as confirmed by mean dissolution time, dissolution efficiency, f2 and drug release kinetic data. The formulation showed close resemblance to commercial product Senafen.
results were explored and explained by the difference of physico-chemical property and micromeritic characteristics. Insignificant effect of various factors e.g. pH, ionic strength, paddle speed was found on drug release. The formulation followed Korsmeyer and peppas kinetic of drug release. Stability study data indicated stable character after short term stability study.

Hindustan Abdul Ahad et al. [9] develop matrix tablets of Aceclofenac with *Prosopis cumanensis* gum and to study its functionality as a matrix forming agent for formulating once-daily sustained release tablets. Physicochemical properties of dried powdered *Prosopis cumanensis* gum were studied. Various formulations of Aceclofenac *Prosopis cumanensis* gum were prepared. They formulated tablets found to have better uniformity of weight and drug content with low SD values. The swelling behavior and release rate characteristics were studied. The dissolution study proved that the dried *Prosopis cumanensis* gum can be used as a matrix forming material for making once daily Sustained release matrix tablets.

Chakraborty et al. [10] prepared microspheres using ionotropic gelation (Aceclofenac) into algino-pectinate bioadhesive microspheres as a potential drug carrier for the oral delivery of this anti-inflammatory drug. Microspheres were investigated in vitro for possible sustained drug release and their use in vivo as a gastroprotective system for aceclofenac. Polymer concentration and polymer/drug ratio were analyzed for their influence on microsphere properties. The microspheres exhibited good bioadhesive property and showed high drug entrapment efficiency. Drug release profiles exhibited faster release of aceclofenac from alginate microspheres whereas algino-pectinate microspheres showed prolonged release. Dunnet’s multiple comparison analysis
suggested a significant difference in percent inhibition of paw edema when the optimized formulation was compared to pure drug. It was concluded that the algino-pectinate bioadhesive formulations exhibit promising properties of a sustained release form for aceclofenac and that they provide distinct tissue protection in the stomach.

Umadevi et al. [11] develop novel colon specific drug delivery of Aceclofenac, a NSAID, was successfully encapsulated into chitosan microspheres. Various formulations were prepared by varying the ratio of chitosan, span-85 and stirring speed and the amount of glutaraldehyde. The SEM study showed that microspheres have smooth surfaces. Microspheres were characterised by Fourier transform infrared spectroscopy and differential scanning calorimetry to confirm the absence of chemical interactions between drug and polymer and to know the formation of microspheres structure. The microspheres were evaluated for particle size, encapsulation efficiency, drug loading capacity, mucoadhesion studies, stability studies, in vitro and in vivo drug release studies. Particle sizes, as measured by the laser light scattering technique, were of an average size in the range 41-80μm. The swelling index was in the range 0.37-0.82 and the entrapment efficiency range was 51-75% for all the formulations. The optimised batch ACM released 83.6% at 8h and 104% at 24h in SCF containing rat caecal content. Eudragit coated chitosan microspheres prevented the release of the aceclofenac in the physiological environment of the stomach and small intestine and released 95.9±0.34% in the colon. With regard to release kinetics, the data were best fitted with the Higuchi model and showed zero order release with non-Fickian diffusion mechanism. The in vivo findings suggest that aceclofenac microspheres exhibit a prolonged effect of aceclofenac in rats and produce a significant anti-inflammatory effect. The findings of the present study
conclusively state that chitosan microspheres are promising for colon targeting of aceclofenac to synchronise with chronobiological symptoms of rheumatoid arthritis.

Kilor et al. [12] prepare 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. To achieve these goals, pellets were prepared by extrusion-spheronization method using pelleting 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

Gaikwad et al. [13] develop a floating, pulsatile, multiparticulate drug delivery system intended for chronopharmacotherapy of arthritis. The floating pulsatile drug delivery has the advantage that a drug can be released in the upper gastrointestinal tract after a definite time period of no drug release, i.e. lag time. Cross-linked beads were prepared using low methoxylated pectin (LM104AS), sodium alginate, and low methoxylated pectin (LM104AS) along with sodium alginate by acid-base reaction during ionotropic gelation. Beads were dried in oven at 50 degrees C for 4 h. Aceclofenac was used as a model drug for encapsulation. Drug loaded multiparticulates were subjected to various characterization and evaluation parameters like entrapment efficiency, surface topography, size analysis and in vitro release study. It was found that calcium pectinate beads show maximum drug entrapment. Hence, pectin containing formulation was further studied for buoyancy, DSC and radio imaging study. Drug release study was performed in acidic environment using pH 1.2 buffer solution for 6 h and then at 7.4 pH for 60 min. The total drug release ranges from 5-10% and 90-94% in acidic and basic media, respectively.

Abul Kalam Lutful Kabir et al. [14] develop a sustained release matrix tablet of aceclofenac using hydroxypropyl methylcellulose (HPMC K15M and HPMC K100M CR) in various proportions as release controlling factor by direct compression method. The powders for tableting were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index, total porosity and drug content etc. The tablets were subjected to thickness, weight variation test, drug content, hardness, friability and in vitro...
release studies. The *in vitro* dissolution study was carried out for 24 hours using United States Pharmacopoeia (USP) 22 paddle-type dissolution apparatus in phosphate buffer (pH 7.4). The granules showed satisfactory flow properties, compressibility index and drug content etc. All the tablets complied with pharmacopoeial specifications. The results of dissolution studies indicated that the formulations F-2 and F-3 could extend the drug release up to 24 hours. By comparing the dissolution profiles with the marketed product, it revealed that the formulations exhibited similar drug release profile. From this study, a decrease in release kinetics of the drug was observed when the polymer concentration was increased. Kinetic modeling of *in vitro* dissolution profiles revealed the drug release mechanism ranges from diffusion controlled or Fickian transport to anomalous type or non-Fickian transport, which was only dependent on the type and amount of polymer used. The drug release followed both diffusion and erosion mechanism in all cases. The drug release from these formulations was satisfactory after 3 months storage in 40°C and 75% RH. Besides, this study explored the optimum concentration and effect of polymer(s) on acelofenac release pattern from the tablet matrix for 24 hour period.

Umesh Shivhare et al. [15] develop “once daily” sustained release tablets of acelofenac by wet granulation using carboxypolymethylene polymer. The drug excipient mixtures were subjected to preformulation studies while the tablets were subjected to physicochemical studies, *in vitro* drug release, stability studies and validation studies. The physicochemical properties of tablets were found within the limits. Formulation F2 & F9 containing Carbopol 971P and Carbopol 974P were found to release the drug in sustained manner upto 24 hour and were stable under accelerated conditions of
Chapter 2

Review of Literature

temperature for 6 months since there were no significant changes in drug content and physical parameters.

Ghosh et al. [16] 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 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 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 in vitro studies, it was concluded that the HPMC matrix tablets provided oral controlled release of aceclofenac.

Nagda et al. [17] developed microencapsulation of the anti-inflammatory drug aceclofenac (ACE) was investigated as a means of 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.

Vadher et al. [18] carried out dissolution of poorly water-soluble BCS-class II drug aceclofenac by co-grinding with novel porous carrier Neusilin US(2.) (amorphous microporous granules of magnesium alumino-silicate. Neusilin US(2) has been used as an important pharmaceutical excipient for solubility enhancement. Co-grinding of aceclofenac with Neusilin US(2) in a ratio of 1:5 was carried out by ball milling for 20 h. Samples of co-ground mixtures were withdrawn at the end of every 5 h. and characterized for X-ray powder diffraction, differential scanning calorimetry, and Fourier-transform infrared spectroscopy. The analysis revealed the conversion of crystalline aceclofenac to its amorphous form upon milling with Neusilin US(2). Further, in vitro dissolution rate of aceclofenac from co-ground mixture was significantly higher compared to pure aceclofenac. The accelerated stability study of co-ground mixture was carried out at 40 degrees C/75%RH for 4 weeks, and it showed that there was no reversion from amorphous to crystalline form. Thus, it is advantageous to use a porous carrier like Neusilin US(2) in improvement of dissolution of poorly soluble drugs

Qureshi et al. [19] The objective of this study was to develop and evaluate an oral chronomodulated drug delivery system for the treatment of rheumatoid arthritis with a distinct predetermined lag time of 6 h (+/- 0.25 h). The basic design of the system consisted of an inner core, an intermediate swelling layer and an external acid-resistant enteric layer applied by pan coating. Croscarmellose sodium was used as a disintegrant and swelling agent to create the desired rupturing pressure. A mixture of hydroxypropyl
cellulose M (175 mg) and ethyl cellulose (25 mg) was used as an intermediate swelling layer. The lag time for the system was found to be independent of the effect of various parameters such as compression load, paddle rotation speed and pH of dissolution medium. For the enteric coating of the press-coated tablet an aqueous dispersion of Eudragit L30 D55 containing 15% of total solid content plasticized with 20 triethyl citrate was applied by conventional pan coater. An in vitro dissolution study of the prepared tablet was conducted initially for 2 h in simulated gastric fluid, and after that medium was changed to simulated intestinal fluid pH 6.8. A pharmacokinetic study was also used to establish in vitro methodology capable of predicting the subsequent in vivo performance of the time-dependent pulsatile-release system. Various pharmacokinetic parameters studied in rabbits as the animal model demonstrated that drug absorption was not influenced by the in vivo behavior of the pulsatile system.

Shavi et al. [20] develop 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. 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.

Achutha Nayak Usha et al. [21] prepared Acelofenac agglomerates by spherical crystallization technique using a three solvent system comprising acetone: dichloromethane: water. Hydroxypropyl methylcellulose-50 cps 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
Chapter 2

Review of Literature

were found to be stable for 6 months under accelerated conditions. The in vivo studies 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.

Radhika et al. [22] formulated delayed release microspheres of aceclofenac using an enteric polymer, cellulose acetate phthalate prepared by solvent evaporation technique. The effects of various other modern enteric polymers such as hydroxyl propyl methyl cellulose phthalate, Eudragit L 100, and Eudragit S-100 on the release of aceclofenac from the CAP microspheres have been evaluated. The microspheres were characterized for particle size, scanning electron microscopy, percentage yield, drug entrapment, and for in-vitro release kinetics. The shape of microspheres was found to be spherical by SEM. The drug entrapment efficiency of microspheres was found to be ranging from 75.65 to 96.52 %w/w. The study was designed in the form of a factorial design in which the effects of HPMCP, Eudragit L 100, and Eudragit S 100 on the release rate of drug from CAP delayed release microspheres were evaluated. The results revealed that the HPMCP exhibits positive influence whereas Eudragit L 100 and Eudragit S 100 exhibits negative effect on the drug release rate of CAP microspheres. In vitro drug release from all formulations followed the first order release kinetics and erosion plot. Formulation with drug: CAP: HPMCP ratio of 1:8:2 was considered best because it showed delayed release.

The Sustained Delayed Release of Anti-inflammatory Drugs 48
Srinivas Mutalik et al. [23] develop a once daily sustained release tablet of aceclofenac using chitosan and an enteric coating polymer (hydroxypropyl methylcellulose phthalate or cellulose acetate phthalate). Overall sustained release for 24 h was achieved by preparing a double-layer tablet in which the immediate release layer was formulated for a prompt release of the drug and the sustained release layer was designed to achieve a prolonged release of drug. The preformulation studies like IR spectroscopic and differential scanning calorimetry showed the absence of drug–excipient interactions. The tablets were found within the permissible limits for various physicochemical parameters. Scanning electron microscopy was used to visualize the surfacemorphology of the tablets and to confirm drug release mechanisms. Good equivalence in the drug release profile was observed when drug release pattern of the tablet containing chitosan and hydroxypropyl methylcellulose phthalate (M-7) was compared with that of marketed tablet. The optimized tablets were stable at accelerated storage conditions for 6 months with respect to drug content and physical appearance. The results of pharmacokinetic studies in human volunteers showed that the optimized tablet (M-7) exhibited no difference in the in vivo drug release in comparison with marketed tablet. No significant difference between the values of pharmacokinetic parameters of M-7 and marketed tablets was observed (p>0.05; 95% confidence intervals). However the clinical studies in large scale and, long term and extensive stability studies at different conditions are required to confirm these results.

Parul Trivedi et al. [24] formulated microencapsule of the anti-inflammatory drug (aceclofenac) to provide controlled release and minimizing or eliminating local side effect by avoiding the drug release in the upper gastrointestinal track. The drug was
Chapter 2 Review of Literature
targeted to the colon and their aligned area for their local effect. Aceclofenac was microencapsulated with Eudragit (S 100, RL 100, and RS 100), using an O/W emulsion-solvent evaporation technique. Aceclofenac microspheres were subjected to micromeritic properties including angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio, and particle size determination. Microspheres were subjected to drug loading, in vitro drug release as well as for scanning electron microscopy. The prepared microspheres were white, free-flowing, and almost spherical in shape. The drug-loaded microspheres show 60-82% drug entrapment, angle of repose was in the range of 16.13 ± 0.621-24 ± 0.590, bulk and tapped densities respectively were in the range of 0.311 ± 0.006-0.562 ± 0.012 and 0.373 ± 0.01-0.735 ± 0.02, Carr's index ranges from 14.04 ± 0.026 to 27.25 ± 1.405, Hausner's ratio was 1.14 ± 0.026-1.37 ± 0.03, and particle size was in the range of 79.7016-144.840 μm. In vitro drug release studies were carried out up to 24 h in three different pH media, i.e., 0.1 N HCl (pH 1.2), phosphate buffer (pH 6.8), and phosphate buffer (pH 7.4). The drug-polymer concentration of dispersed phase influences the particle size and drug release properties. All the formulations at higher pH were followed by the Matrix-Higuchi model.

Sahoo et al. [25] prepared aceclofenac-gelatin micropellets by the cross linking technique using gluteraldehyde as cross linking agent and characterized by X-ray diffractometry, differential scanning calorimetry and scanning electron microscopy. The effect of drug: polymer ratio, temperature of oil phase, amount of gluteraldehyde and stirring time was studied with respect to entrapment efficiency, micropellet size and drug release characteristics. Spherical micropellets having an entrapment efficiency of 57% to 97% were obtained. Differential scanning calorimetric analysis confirmed the absence of
any drug-polymer interaction. The micromeritic studies of micropellets show improved flow property. The entrapment efficiency, micropellet size and drug release profile was altered significantly by changing various processing parameters.

Mutalik et al. [26] develop "once daily" sustained release tablets of aceclofenac by direct compression using hydroxypropyl methylcellulose-K4M. The solubility studies of aceclofenac were conducted to select suitable dissolution media. The drug-exciipient mixtures were subjected to preformulation studies. The tablets were subjected to physicochemical, in vitro drug release and stability studies. Preclinical (anti-inflammatory, analgesic, pharmacokinetic and toxicity studies) and clinical pharmacokinetic studies were conducted for optimized tablets. Based on the preformulation results, microcrystalline cellulose, dicalcium phosphate and spray dried lactose were selected as directly compressible vehicles. Because of the incompatibility with aceclofenac, SOL was excluded from the study. The physicochemical properties of tablets were found within the limits. By comparing the dissolution profiles with the marketed product, the tablet containing HPMC (45%) and MCC (30%) along with talc and magnesium stearate (1% w/w, each) was considered as a better formulation. This tablet exhibited almost similar drug release profile in different dissolution media as that of marketed tablet. Tablet B7 was stable in accelerated conditions for 6 months. The composition of this tablet showed almost similar preclinical pharmacological activities compared to marketed tablet composition and did not exhibit any toxicity in rats and mice with respect to tested haematological and biochemical parameters along with body weight, food and water intake. The pharmacokinetic study in healthy human volunteers
indicated that B7 tablet produced an extended drug release of drug up to 24 h as that of
marketed product with almost identical pharmacokinetic parameters.

Chul Soon Yong et al. [27] developed an effective oral drug delivery system with
accelerated absorption in human subjects for a poorly water-soluble acelofenac, five
aceclofenac-loaded soft capsule preparations containing various ratios of different
solubilizers were prepared and their dissolution tests were carried out. Among five
preparations tested, a preparation with ethanolamine was selected as a formula of
aceclofenac soft capsule, since it was clear in appearance and showed the fastest
dissolution rate due to the solubility-enhancing effect of aceclofenac. To evaluate and
compare the pharmacokinetics of acelofenac-loaded soft capsules with the conventional
aceclofenac tablets in human subjects; 14 normal healthy male volunteers (age 20–25
years old) were divided into two groups and a randomized 2×2 crossover study was
performed. Following oral administration of one tablet or capsule, each containing 100
mg of acelofenac, blood samples were collected at the predetermined time intervals and
the concentration of acelofenac in plasma was determined by HPLC method using UV
detector. The AUC, Cmax, MRT, t1/2 and Kel of acelofenac delivered from soft capsule
were not significantly different from those from acelofenac-loaded conventional tablet.
However, soft capsule gave significantly higher initial concentration and significantly
faster Tmax of acelofenac than did conventional tablet, suggesting that the soft capsule
with ethanolamine showed the faster absorption of acelofenac in human subjects. Thus,
the clear acelofenac-loaded soft capsule with ethanolamine was a more effective oral
dosage form with fast absorption for poorly water-soluble acelofenac.
Hasan et al. [28] describe five new selective, precise and accurate methods for the determination of aceclofenac in the presence of its degradation product; diclofenac are described. Method A utilizes third derivative spectrophotometry at 242 nm. Method B is RSD(1) spectrophotometric method based on the simultaneous use of the first derivative of ratio spectra and measurement at 245 nm. Method C is a pH-induced difference (deltaA) spectrophotometry using UV measurement at 273 nm. Method D is a spectrodensitometric one, which depends on the quantitative densitometric evaluation of thin layer chromatogram of aceclofenac at 275 nm. Method E is RP-HPLC that depends on using methanol: water (60:40 v/v) as mobile phase at a flow rate of 1 ml/min and UV detection at 275 nm. Regression analysis of a beer's plot showed good correlation in the concentration ranges 5-40, 10-40, 15-50, 50-200, 1-50 microg/ml for methods A, B, C, D and E, respectively. These methods are suitable as stability indicating methods for the determination of aceclofenac in presence of its main degradation product, diclofenac. The proposed methods were applied for the analysis of the drug in its pharmaceutical formulation and the results obtained were compared with those obtained with the official B.P. method.

Alonso et al. [29] studied the physicochemical properties of aceclofenac nanocapsules, prepared by interfacial precipitation of poly-e-caprolactone at the oil/water interface, have been studied. A Central Composite Design was used to investigate the influence of polymerization adjuvants on these properties on the elaboration of aceclofenac-loaded poly-e-caprolactone nanocapsules. In this way, the effect of polymer, oil and drug concentrations in organic phase on the size and encapsulation efficiency has been analyzed. The optimized nanocapsule formulation leads to use an initial
concentration of drug (Aceclofenac) of 0.8 mg/ml and 0.6% of oil (Miglyol 812), being the polymer and surfactant concentrations previously fixed.
References:


The Sustained Delayed Release of Anti-inflammatory Drugs
Chapter 2

Review of Literature


