CHAPTER – V

LITERATURE ON DICLOFENAC SODIUM
DICLOFENAC SODIUM

Chemical name: 2-[(2,6 dichlorophenyl)-amino]phenyl acetate.

\[
\text{CH}_2\text{COONa Cl}
\]

2-[(2,6 dichlorophenyl)-amino] phenyl acetate.

**Formula:**

\[ \text{C}_{14}\text{H}_{10}\text{Cl}_{2}\text{NaO}_{2}\text{Na} \]

**Molecular wt:**

318.13

**Physical properties:**

Odourless, white to off-white crystalline powder, slightly hygroscopic powder.

**Solubility:**

It is freely soluble in methanol, soluble in ethanol (95%), sparingly soluble in water and in glacial acetic acid, practically insoluble in ether, chloroform and in toluene.

**Pharmacology:**

It is a potent anti-inflammatory and analgesic agent. It inhibits prostaglandin synthesis.

**Absorption:**

It is completely absorbed form the gastrointestinal tract after oral administration. Rectal administration of diclofenac sodium suppositories
produces rapid peak plasma concentration at a rate and level of the same order as oral administration of the drug in solution. In rats and dogs majority of the drug is found in the faeces indicative of biliary excretion whereas in Rhesus monkeys 76% is excreted via the kidneys. In man renal excretion is greater than biliary excretions.

**Tissue Distribution:**

Following rapid absorption the drug is widely distributed with highest concentration in the elimination organs (liver and kidney) and in the blood.

**Metabolism:**

It is metabolized in the liver and excreted primarily by the kidneys and then by the large intestine. The metabolites also appear in bile. Elimination rates in renally impaired patients were comparable to rates in healthy patients. It has a relatively short plasma half-life of approximately 2 hrs and is not likely to accumulate in the plasma with repeated use.

**Adverse reactions:**

Gastrointestinal effects like abdominal pain, constipation, diarrhoea, indigestion, nausea are commonly observed. Peptic ulcer and GI bleeding have been reported in some patients. Other adverse effects include headache, dizziness, rash pruritis and symptoms of hepatotoxicity like jaundice and like symptoms.
Pharmacokinetics of Diclofenac Sodium:

Non-steroidal anti inflammatory drugs are first line drugs in the treatment of painful and inflammatory rheumatic conditions. NSAIDS include salicylates, propionates, indocetates, fenamates, oxicams, pyrazolones, phenylacetates. Diclofenac sodium is phenyl acetic acid derivative with analgesic, anti inflammatory and antipyretic activity. Diclofenac sodium is rapidly absorbed, with excretion occurring through both the urine and bile drug level reaches maximum concentration with the peak ($T_{\text{max}}$) at about 2hr, after oral administration of enteric tablets. Several studies have shown that diclofenac penetrates the synovial membrane and diffuses into synovial fluid. Food delays the absorption of diclofenac, with the enteric formulations and peak plasma concentrations are achieved in 2.5 - 12 hrs after ingestion. Peak plasma concentration ranged from 1.4 µg to 3 µg / ml. No clear peaks are found after a single 100mg dose of sustained release diclofenac. The peak plasma concentration and the area under the plasma concentration time curve are linearly related to dose in the range of 25 mg. to 150 mg after oral, rectal or I.M. routes diclofenac undergoes significant first-pass metabolism and only 60% of the drug reaches systemic circulation. About 99% of drug is reversibly bound to plasma proteins. The half life of the agent is 3 hrs. Diclofenac is a potent inhibitor of cyclooxygenase, thereby decreasing the synthesis of prostaglandin’s prostacyclin and thromboxane products.
Diclofenac sodium has been shown to be a safe, effective drug with a broad range of indications including the treatment of Rheumatoid arthritis, Osteoarthritis, Ankylosing spondylitis, Juvenile arthritis, Acute sprains and strains of ankle or knee. Its high degree of efficacy is comparable with or superior to that of other NSAIDS- Indomethacin, naproxen, ibuprofen, aspirin, phenyl butazone and sulindac etc. The compounds recently described modulatory effect on arachidonic acid metabolism suggests that Diclofenac may have an advantage over other NSAIDS in the treatment of chronic inflammatory diseases. In addition diclofenac appears to be extremely well tolerated. Most adverse effects have been mild or transient.
PAST WORK ON CONTROLLED RELEASE OF DICLOFENAC SODIUM

Design and Evaluation of Matrix-Based Controlled Release Tablets of Diclofenac Sodium and Chondroitin Sulphate was done by Amelia Avachat et al. The purpose of the present study was to develop and characterize an oral controlled release drug delivery system for concomitant administration of diclofenac sodium (DS) and chondroitin sulfate (CS). A hydrophilic matrix-based tablet using different concentrations of hydroxypropylmethylcellulose (HPMC) was developed using wet granulation technique to contain 100 mg of DS and 400 mg of CS. Formulations prepared were evaluated for the release of DS and CS over a period of 9 hours in pH 6.8 phosphate buffer using United States Pharmacopeia (USP) type II dissolution apparatus. Along with usual physical properties, the dynamics of water uptake and erosion degree of tablet were also investigated. The in vitro drug release study revealed that HPMC K100CR at a concentration of 40% of the dosage form weight was able to control the simultaneous release of both DS and CS for 9 hours. The release of DS matched with the marketed CR tablet of DS with similarity factor \( f_2 \) above 50. Water uptake and erosion study of tablets indicated that swelling followed by erosion could be the mechanism of drug release. The in vitro release data of CS and DS followed Korsmeyer-Peppas and zero-order kinetics, respectively. In conclusion, the in vitro release profile and
the mathematical models indicate that release of CS and DS can be effectively controlled from a single tablet using HPMC matrix system.

Design and evaluation of diclofenac sodium controlled drug delivery systems was done by Manjunatha KM\textsuperscript{4} et al. Sustained release dosage form of diclofenac sodium containing immediate and controlled release components was designed. Solid dispersion of immediate release component was prepared using polyvinyl pyrrolidone and mannitol carriers by common solvent method. Controlled release component was prepared in form of spherical beads by ionotropic gelation technique. The beads were prepared based on dispersing drug in solutions of ionic polysaccharides such as chitosan and sodium alginate. These dispersions were dropped into solutions of counter ions such as tetrasodium pyrophosphate and calcium chloride, respectively. The beads were also prepared using agar by dropping agar-drug hot solution into a mixture of chilled liquid paraffin and water. Then, diclofenac sodium controlled release drug delivery systems were prepared by combining the immediate release and controlled release components in different ratios. The formulations were found to be effective in providing controlled release of drug for a longer period of time. The beads were characterized by scanning electron microscopy and X-ray diffraction studies.

Design and evaluation of Xanthan gum-based sustained release Matrix tablets of Diclofenac sodium was done by Yeole PG\textsuperscript{5} et al. In the present investigation, an attempt has been made to increase therapeutic
efficacy, reduce frequency of administration, and improve patient compliance, by developing sustained release matrix tablets of diclofenac sodium. Sustained release matrix tablets of diclofenac sodium, were developed by using different drug: polymer ratios, such as F1 (1:0.12), F2 (1:0.16), F3 (1:0.20), F4 (1:0.24) and F5 (1:0.28). Xanthan gum was used as matrix former, and microcrystalline cellulose as diluent. All the lubricated formulations were compressed using 8 mm flat faced punches. Compressed tablets were evaluated for uniformity of weight, content of active ingredient, friability, hardness, thickness, in vitro dissolution using basket method, and swelling index. All the formulations showed compliance with Pharmacopoeial standards. Among different formulations, F1 showed sustained release of drug for 12 hours with 89.67% release. The effect of other parameters like addition of release modifier (PEG 6000), gum concentration, pH of dissolution medium, rotation speed and dissolution by paddle method, were also studied. Selected formulation (F1) was subjected to stability studies for three months at 0-4°, room temperature (28°), and 45° with RH 75±5%, and showed stability with respect to release pattern. The kinetic treatment showed that the release of drug follows zero order kinetic (R² = 0.9758). Korsmeyer and Peppas equation gave value of n = 0.9409 which was close to one, indicating that the drug was released by zero order kinetic. Thus, Xanthan gum can be used as an effective matrix former, to extend the release of diclofenac sodium.
Nanostructure-coated diclofenac-loaded microparticles: preparation, morphological characterization, in vitro release and in vivo gastrointestinal tolerance was done by Beck et al. This work reports the preparation and characterization of polymeric nanostructure-coated diclofenac-loaded microparticles. After spray-drying, powders presented 80% of yield and encapsulation efficiency of 83%. SEM analyses showed nanostructures adsorbed onto the surface of microparticles presenting surface area (BET) and pore volumes (BJH) (83 m² g⁻¹, 0.10 cm³ g⁻¹) smaller than the uncoated-core (163 m² g⁻¹, 0.25 cm³ g⁻¹). In vitro drug release experiments at pH 5.0 and 7.4 showed dissolution efficiencies of 34% and 78% (uncoated-core), 74% and 83% (physical mixture of raw materials), and 58% and 85% (nanostructure-coated microparticles), respectively. Mathematical modeling of the dissolution profiles fitted a biexponential model at pH 5.0 and a monoexponential model at pH 7.4. Regarding the digestive tolerance experiments, the total lesional indexes were 156.1 ± 48.5 for sodium diclofenac aqueous solution, 132.4 ± 45.7 for uncoated-core, 109.1 ± 35.8 for physical mixture and 29.9 ± 12.1 for microparticles showing a protective effect of these microparticles against the mucosal diclofenac damage. This strategy of coating presents a potential use for oral administration of drugs.

Synthesis of Chitosan Succinate and Chitosan Phthalate and Their Evaluation as Suggested Matrices in Orally Administered, Colon-Specific Drug Delivery Systems was investigated by Khaled Aiedeh and Mutasem
The naturally occurring polymer chitosan was reacted separately with succinic and phthalic anhydrides. The resulting semisynthetic polymers were assessed as potential matrices for colon-specific, orally administered drug delivery. Sodium diclofenac was used as the dispersed model drug. The prepared matrices were incorporated into tablets, which were evaluated in vitro. The evaluation included dissolution studies conducted under simulated gastrointestinal conditions of pH and transit times. The percentage fluid uptake was used to indicate the ability of the matrix to protect an embedded drug from gastric juices. The prepared matrices resisted dissolution under acidic conditions. On the other hand, improved drug release profiles were observed under basic conditions. Therefore, the results suggest the suitability of the prepared matrices in colon specific, orally administered drug delivery system. However, future in vivo testing is planned to fully establish the suitability of the prepared polymers for colon-specific drug delivery.

Rosin derivatives: novel film forming materials for controlled drug delivery was investigated by P. M. Mandaogade et al. Two new rosin derivatives (RD-1 and RD-2) were synthesized in the laboratory and evaluated for physicochemical properties, molecular weight ($M_w$), polydispersity ($M_w/M_n$) and glass transition temperature ($T_g$). Plasticizer free films of the derivatives were produced by casting/solvent evaporation method. The surface morphology (SEM), water vapour transmission and mechanical properties (tensile strength, percent elongation and modulus of
elasticity) of the films were investigated. The derivatives were further evaluated for pharmaceutical film coating by characterizing the release of a model drug (diclofenac sodium) from non-pariel seeds (pellets) coated with the derivatives. Pellet film coating could be achieved without agglomeration of the pellets within a reasonable operation time. Drug release from the coated pellets was sustained up to 10 h with the two rosin derivatives. These findings suggest the possible application of rosin derivatives (RD-1 and RD-2) for film coating.

*In vitro* studies of diclofenac sodium controlled-release from biopolymeric hydrophilic matrices was carried out by Silvina A⁹ et al. The objective of this study was to develop uncoated HPMC matrix tablets, evaluating the relationship and influence of different content levels of microcrystalline cellulose (MCC), starch, and lactose, in order to achieve a zero-order release of Diclofenac Sodium. HPMC matrix tablets of Diclofenac Sodium using microcrystalline cellulose (MCC), starch, and lactose were prepared by wet granulation process. The USP paddle method was selected to perform the dissolution profiles carried out in 900 mL 0.1 N HCl, and phosphate buffer. There was no significant difference in drug release between the hydrophilic matrices when the HPMC concentration was modified in low percentage. Release kinetics of Diclofenac Sodium from these swollen matrices was principally regulated by starch (17 percent) or lactose (17 percent), even on the presence of MCC. When starch (8.5 percent) and lactose (8.5 percent) were mixed at lower concentration in
a ratio 1:1, MCC (5 percent or 7.5 percent) appeared to control the drug release. The release profile remained unchanged after three months storage of tablets. The best-fit release kinetics was achieved with the zero-order plot, followed by the Higuchi and first-order equations. The data obtained proved that the formulations are useful for a sustained release of Diclofenac, due to the percentage released after 8 hours is nearly to 70 percent. The release of Diclofenac Sodium was influenced by the presence of MCC, and by the different concentrations of starch and lactose. Drug release kinetics from these formulations corresponded best to the zero-order kinetics. Compared to conventional tablets, release of the model drug from these HPMC matrix tablets was prolonged; as a result, an oral release dosage form to avoid the gastrointestinal adverse effects was achieved.

Silvina A. Bravo and Maria C\textsuperscript{10} evaluated the effects of hydroxypropyl methylcellulose (HPMC) and carboxypolymer (Carbopol 934) on the release behavior of diclofenac sodium (DS) from a swellable matrix tablet system. Nine different DS controlled-released tablets were compressed by using the wet-granulation technology. The influence of the polymer content, the polymer ratio, the polymeric swelling behavior, and the pH changes on the release rate of DS was investigated. There was no significant difference in drug release when total polymer concentration was 10%. When the tablets were formulated having 20% or 30% of HPMC/carbomer, it was observed that a more rapid release of DS occurred as the carboxypolymer ratio within the matrices increased. The DS release
from all these matrix tablets was pH dependent, being markedly reduced at lower pH, and could be attributed to the poor solubility of DS at this pH value. In HCl 0.1 N solution, HPMC controlled drug release because the carbomer has a low solubility at this pH. As the pH increased, the carbomer became ionized, being able to interact with HPMC to control the drug release.

Preparation and evaluation of sodium diclofenac controlled-release tablets. II. Dibasic calcium phosphate as a retardant in mixtures for direct compression was done by Lin SY et al\textsuperscript{11}. The dissolution behaviour of a direct compression compact prepared with sodium diclofenac and dibasic calcium phosphate (DCP) in different weight ratios with or without Biosoluble polymer (acrylic-based resin) was investigated in distilled water and in a medium with changing pH. The results indicate that the amount of sodium diclofenac released from the compact was dependent on the amount of drug and DCP used in the compact, and was also controlled by the amount of Biosoluble polymer added. A chemical reaction forming diclofenac acid might occur on the surface of the sodium diclofenac compact during exposure to the acidic medium, which was confirmed by diffuse-reflectance spectroscopy. The tablet with a 1:2 weight ratio of sodium diclofenac to DCP exhibited a sustained-release behaviour, similar to commercial sustained-release products (Voltaren SR-100 and Grofenac Retard), but a lower release rate was found as compared to the commercial products. The dissolution behaviour of the study tablet and the commercial
products was found to be dependent on the dissolution medium and the rotating speeds. Glass beads were added to the dissolution assembly to simulate the influence of food, and the enhanced friction between tablet and glass beads might result in a higher dissolution rate of the tablet and the commercial products.

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Controlled release of diclofenac sodium from pH-responsive carrageenan-g-poly(acrylic acid) superabsorbent hydrogel was done by Hossein Hosseinzaadeh\(^\text{13}\). In this paper, controlled release of diclofenac sodium (DS) from pH-sensitive carrageenan-g-poly(acrylic acid) superabsorbent hydrogels was investigated. The hydrogels were prepared by graft copolymerization of acrylic acid (AA) onto kappa-carrageenan, using ammonium persulfate (APS) as a free radical initiator in the presence of methylene bisacrylamide (MBA) as a crosslinker. Infrared spectroscopy was carried out to confirm the chemical structure of the hydrogel. Moreover, morphology of the samples was examined by scanning electron microscopy (SEM). The synthesized hydrogels were subjected to equilibrium swelling studies in simulated gastric and intestinal fluids (SGF and SIF). Hydrogel containing drug DS, at different drug-to-polymer ratios, were prepared by direct adsorption method. The loading yield was found to depend on both the impregnation time and the amount of encapsulated drug. In vitro drug-release studies in different buffer solutions showed that the most important parameter affecting the drug-release behaviour of hydrogels is the pH of the solution. The mechanism involved in release was Fickian
(n ≤ 0.43, n = 0.348) and Super Case II kinetics (n > 1, n = 1.231) at pH 1.2 and 7.4, respectively.

Formulation development and optimization of controlled porosity osmotic Pump tablets of diclofenac sodium was done by Sudeesh Edavalath et al. The porous osmotic pump tablets were designed using D Optimal design and numerical optimization technique was applied to find out the best formulation. Osmotic agent sodium chloride and pore former PEG 400 was considered as independent variables. Drug release rate at 2 h, 4 h, 8 h, 12 h, T50% and release exponent (n) were taken as responses. The increase in concentration of pore former and osmotic agent after a limit, changes the release from zero order to Higuchi based release. The optimized formulation follows non-Fickian release mechanism. The FTIR and DSC studies revealed that no physicochemical interaction between excipients and drug. The influence of pH and agitation intensity on the release of drug was studied and the release mechanism was through osmosis. Stability studies revealed that optimized formulation was stable. The result of D Optimal design and ANOVA studies reveals that osmotic agent and pore former have significant effect on the drug release up to 12 h. The observed independent variables were found to be very close to predicted values of most satisfactory formulation which demonstrates the feasibility of the optimization procedure in successful development of porous osmotic pump tablets containing diclofenac sodium by using sodium chloride and PEG 400 as key excipients.
Preparation and evaluation of ethylcellulose coated microcapsules for controlled release of Diclofenac was done by KPR Chowdary and SB Dana. The objective of the study is to evaluate ethylcellulose as a coat for controlled release microcapsules of diclofenac. Ethylcellulose coated microcapsules were prepared by an emulsion-solvent evaporation method employing different proportions of core and coat and the microcapsules were evaluated for size, drug content and microencapsulation efficiency, wall thickness, surface character by SEM and drug release kinetics. The ethylcellulose coated microcapsules prepared were found to be discrete, spherical, and free flowing. Drug content was uniform (c.v. ≤ 0.11%) in each batch of microcapsules and the microencapsulation efficiency was in the range 98.85-101.81%. Diclofenac release from the ethylcellulose coated microcapsules was slow and spread over a period of 12-16 h and depended on core: coat ratio, wall thickness and size of the microcapsules. Drug release from these microcapsules was by non-fickian diffusion. Good linear relationships were observed between wall thickness of the microcapsules and release rate (K0) and (K1). Microcapsules prepared employing chloroform as solvent exhibited higher release rates when compared to those prepared employing dichloromethane as solvent. Ethylcellulose was found to be an efficient microencapsulating agent and the ethylcellulose microcapsules exhibited good controlled release characteristics and were found suitable for oral controlled release of diclofenac over 12-16 h.
References


