CHAPTER 2

LITERATURE SURVEY

The several investigations have been carried out in the past on the development of oral sustained/controlled drug delivery systems for NSAIDs. The survey of literature was carried out on such investigations support to research protocol for fabrication of oral sustained/controlled drug delivery dosage forms of aceclofenac sodium and dexibuprofen microbeads and matrix tablets.

2.1 Review on oral microspheres/microbeads

Roland Bodmeier et al\(^5\) was developed water insoluble drugs like griseofulvin, ibuprofen, indomethacin and tolbutamide spherical agglomerates by dropping the chitosan or sodium alginate drug polymeric dispersion into calcium chloride solution as counter ion. The results revealed that the ionic character of the polymers resulted in pH dependent disintegration of the beads in variation pH environments.

Kulkarni et al\(^5\) have prepared diclofenac sodium loaded sodium alginate controlled release beads by precipitation with alcohol and cross-linking with glutaraldehyde in acidic medium. The investigations suggests that the increasing in the concentration of sodium alginate which influences the percentage entrapment efficiency but the beads expose longer time to the cross-linking agent have shown lower entrapment efficiency with extended release.

Kakkar AP, et al\(^5\) developed and characterized ibuprofen loaded microspheres by ionotropic gelation technique. The results report that the mean diameter, recovery encapsulation efficiency, wall thickness, size distribution and release characteristics of the microspheres were influenced by concentration of sodium alginate.

Gohel MC, et al\(^5\) developed diclofenac sodium microspheres prepared by coacervation-phase separation method by using chitosan and glutaraldehyde were used
as coating material and cross-linking agent respectively. The obtained results suggests that the optimum formulation conditions such as stirring time and stirring speed in the manufacturing process which are affecting the sphericity and in vitro release of drug from hard gelatin capsules containing microspheres in phosphate buffer (pH 6.5) and mechanism of drug release according to the Higuchi model.

Kennedy R.A et al\textsuperscript{56} were studied release of paracetamol (sparsely soluble) from calcium and zinc alginate beads. The results reveals that the rapid release in the acidic environment and other media, entrapment of water-soluble drugs in the conventional style alginate gel beads does not provide a satisfactory oral sustained release system.

Roland Bodmeieret al\textsuperscript{57} studied sustained release sodium alginate polymeric microspheres containing water insoluble drugs (Ibuprofen, Theophylline, Guaifenasan, and Pseudoephedrine HCl). The study suggests that the drug release profile of drugs depends on the polymer ratio and type of polymer dispersion used in different concentration of curing medium.

Pin G Liu et al\textsuperscript{58} prepared theophylline, clorthiazide and indomethacin drug delivery particulate by using alginate, poly lysine and pectin by ionotropic gelation method. The results revealed that the sodium microbeads coated with pectin are more resistant in acidic pH and modulated the release profiles in the alkaline pH. The poly lysine increases the mechanical strength and modulates the drug release of the alginate/pectin beads for prolonged time period.

Bodmeier R et al\textsuperscript{59} developed micro or nanoparticles by ionotropic gelation using chitosan or sodium alginate solution cross-linked with triphosphate or calcium chloride respectively. The results explain that the ionic characters of the polymers show pH dependent release of the microparticles. Chitosan beads (I) shows rapid
disintegrated and drug release in 0.1N HCl and while calcium alginate (II) beads disintegrate slowly in 0.1N HCl but rapidly disintegrated in simulated intestinal fluids.

Sriamornsak P et al\textsuperscript{60} investigated the effect of certain processing variables on the physical properties and in-vitro drug release of poorly water soluble indomethacin from calcium pectinate gel (CPG) beads. The results explain that the processing variables affected the bead size, entrapment efficiency and the slower release of indomethacin from CPG beads. The mechanism of indomethacin release from CPG beads followed the diffusion controlled model.

Pillay CM et al\textsuperscript{61} studied indomethacin alginate micro discs by using ionotrophic gelation of sodium alginate with calcium chloride. The results conclude that the maximum degree of swelling of calcium alginate micro discs in phosphate buffer pH 6.2 and mechanism of drug release from the swellable micro discs was modulated by swelling or diffusion processes.

Maria Luisa Torre, et al\textsuperscript{62} studied the characterization of ampicilllin calcium alginate beads by using aqueous sodium alginate dispersion is added drop wise to the solution of calcium chloride, the droplets immediately converted into gel beads. The study suggests that the viscosity of polymer solution which influences the morphology, drug content, in-vitro release, and erosion of the prepared beads. The release of drug in different time intervals depended on the molecular weight of the polymer and the pH of the dissolution medium.

Fathy, et al\textsuperscript{63} developed sustained release tiaramide sodium alginate microbeads. The study revealed that a calcium alginate bead was found to be release rapidly in higher pH level due higher porosity. Therefore, calcium alginate beads coated with hydroxy methyl cellulose acetate succinate (HPMCAS) which forms an
extra diffusion barrier on the beads shows lowest release at pH 1.2 acidic buffers and then drug release was slowly increase in higher pH level of the dissolution medium.

Lim LY, et al\textsuperscript{64} investigates the sulfadiazine chitosan beads was prepared by ionotropic gelation and to determine drug loading and release profiles. The study suggests that the proportion chitosan in the formulation influences drug loading efficiency, bead size, opacity and sphericity of the beads. A longer period of contact with counter ions decreased bead size and efficiency of loading. Release depended on drug loading and pH of the dissolution medium.

Gheorghe Fundueanu et al\textsuperscript{65} investigate a new technique for the preparation of calcium alginate microspheres treated with an excess amount of sodium hydroxide added into curing medium containing various concentration of calcium chloride. This investigation explains presence of sodium hydroxide in the curing medium influences the shape, morphology and significantly decreases of swelling followed rapid drug release from the microspheres.

Rastogi R. et al\textsuperscript{66} have developed theophylline spherical microspheres by modified emulsification method, using sodium alginate as the hydrophilic carrier. The results indicate that the mean particle size and entrapment efficiency of the microspheres increased with an increase in the concentration of polymer and the cross-linker as well as the cross-linking time. The higher level of drug released in the SIF due to prolonged retention and bio-adhesive property of particles in the small intestine.

Yagnesh L. Patel et al\textsuperscript{67} have prepared metronidazole calcium alginate beads using $3^2$ factorial designs with variable concentration drug and curing time. The result suggests that the size of the beads and entrapment efficiency increases with increasing the concentration of polymer and decreases with increase in curing time. The drug
solubility influences the swelling behavior of drug loaded microspheres, in acidic medium is very less swelling and whereas in PBS higher swelling observed by the gelling nature of polymer.

Takka S.et al\textsuperscript{68} investigated the release rate of nicardipine hydrochloride from various alginate gel beads adopted by utilizing $2^3$ factorial designs. The investigations revealed that the drug: polymer weight ratio and CaCl\textsubscript{2} concentration had a significant effect on the drug entrapment efficiency and drug release profile. The drug release from the alginate gel beads by both diffusion through the swollen matrix and relaxation of the polymer with increasing pH level.

Gupta B.K et al\textsuperscript{69} was designed nimesulide oral controlled release microparticulate drug delivery system by ionotropic gelation technique using sodium alginate and HPMC used as polymers and CaCl\textsubscript{2} as a counter ion. The microspheres formulated with HPMC shows higher entrapment efficiency and more sustaining release of drug compared to sodium alginate microspheres.

Arica B. et al\textsuperscript{70} prepared controlled release alginate beads of ibuprofen by ionotropic gelation method. The study explains that the concentration of sodium alginate influences particle size and entrapment efficiency followed to stirring speed. The in-vivo study carried out in six healthy mice by administration of sodium alginate beads by orally. This indicates that the administer beads of ibuprofen prevents gastric lesions.

A. H. El-kamel et al\textsuperscript{71} have prepared ibuprofen microbeads by the ionotropic gelation method by using sodium alginate and methyl cellulose as coating polymer. The result reveals that the release of drug from alginate beads followed by diffusion and relaxation of the polymer at pH1.2, while diffusion and erosion at pH6.8 PBS. The in vitro drug release from MC-alginate beads showed an extended release pattern
which was compared with commercially available sustained-release and fast release tablets.

Rajesh K.S., et al\textsuperscript{72} was prepared ketoprofen alginate microparticles by dropping alginate-drug suspension with or without aqueous colloidal polymer dispersions into calcium chloride solution. The investigation suggests that the increase in concentration of sodium alginate and aqueous polymer dispersions (Acrycoats) prolong the drug release from the microparticles depended only on the concentration of alginate and nature of aqueous colloidal dispersion.

Agrawal S, et al\textsuperscript{73} developed aceclofenac sodium microspheres by ion-gelation method using a polymeric mixture of sodium alginate and further coated with cellulose acetate phthalate. This suggests that the sodium alginate influences particle size, drug content, drug entrapment efficiency and morphology of microspheres and rapid drug release in higher pH level but slower release was observed from sodium alginate coated with cellulose acetate phthalate.

Malay K. Das et al\textsuperscript{74} studied furosemide alginate microspheres prepared by the ionotropic external gelation technique using Ca\textsuperscript{2+}, Al\textsuperscript{3+} and Ba\textsuperscript{2+} ions. This study suggests that the mean particle size, entrapment efficiency and in vitro release profile could be altered significantly by changing various formulation parameters to give a sustained release of drug from the microspheres. The kinetic modelings of the release data indicate that furosemide release from the alginate microspheres followed to be Fickian diffusion mechanism.

FarhanaYesmin et al\textsuperscript{75} have been designed aceclofenac loaded agarose beads by dropping the hot aqueous solution into a different percentages of chilled CaCl\textsubscript{2} solution followed by drying at room temperature. The results report that the increase
concentration of agar influences the entrapment efficiency and swelling index and the aceclofenac release was decreased followed by swelling of agar in higher pH level.

Brice Moulariet al\textsuperscript{76} developed sulindac calcium alginate beads by ionotropic gelation technique. The investigation reports reveals that the polymer to drug ratio was influences the percentage of yield and entrapment efficiency. An in-vivo study suggests that the sulindac loaded alginate beads shows a significant reduction of macroscopic histological damage in the stomach and duodenum and increases the muco-protective effect in mice compare to the pure drug.

Mayur G. S. et al\textsuperscript{77} examines the influence of various process parameters on papain entrapped in ionotropically cross-linked alginate beads. The results explain that the percentage entrapment and particle size were found to be directly proportional to sodium alginate concentration and inversely proportional to calcium chloride concentration and hardening time. The inability of beads to dissolve in acidic environment, with complete dissolution in PBS of pH 6.8 result the complete release of papain into the small intestine.

Trivedi Pet al\textsuperscript{78} developed microencapsulate the anti-inflammatory drug of aceclofenac sodium with EudragitS100 using an O/W emulsion-solvent evaporation technique. The increasing polymer concentration could influence the drug entrapment efficiency, particle size and rapid drug release potential at higher pH level followed by the matrix-higuchi model.

Kamlesh Dashora et al\textsuperscript{79} developed aceclofenac microparticulate systems of by modified solvent evaporation method. This investigation explains that the increasing the concentration of polymer influences entrapment efficiency, size uniformity, angle of repose and compressibility index and slowest drug release up to 12 hours followed to first order release kinetic and diffusion controlled drug release.
Thaned Pongjanyaku et al\textsuperscript{80} studied the calcium alginate (CA) beads loaded with intercalated complexes of propranolol HCl (PPN) and magnesium aluminum silicate (MAS), which serve as micro-reservoirs, were prepared by ionotropic gelation method. The results indicate that the increased MAS content caused an increase in PPN entrapment efficiency, thermal stability, and the strength of the CA beads and could significantly reduce the initial burst of PPN release and modulate drug release in a sustain manner.

2.2 Review on solid self microemulsification technique

Paradkar. A. et al\textsuperscript{81} formulate a self-emulsifying system (SES) containing a lipophilic drug, loratadine, and converted into solid porous polystyrene beads (PPB) by solvent evaporation method. This suggests that the concentration of polystyrene influences the loading efficiency and minimizes the leakage of SES from micro-pores that was acts as rate-limiting barrier for drug release.

Pradip Kumar Ghosh et al\textsuperscript{82} has developed an acyclovir oral microemulsion formulation by using Labrafac with Labrasol as surfactant and Plurol Oleique as co-surfactant. The study suggests that the microemulsion formulations increase the solubility of drug. The \textit{in-vitro} intra-duodenal diffusion and in-vivo study of microemulsion formulation as compared with the commercially available tablet increases the oral bioavailability.

Vijay Kumar N et al\textsuperscript{83} have reported self-microemulsifying drug delivery system (SMEDDS) of sparingly soluble drug candesartan cilexetil filling into hard gelatin capsules. The optimized liquid SMEDDS formulation was converted into free flowing powder by adsorbing onto a solid carrier for encapsulation. The study reported that the solid powder of SMEDDS filled into hard gelatin capsules shows the
rate and extent of drug dissolution was significantly higher than commercial tablet formulation.

Abdalla A, Kleinet al\textsuperscript{84} developed a new pellet based self-emulsifying (SE) drug delivery system for the oral delivery of poorly soluble drugs using microcrystalline solid material by extrusion/spheronization. This result describes that the influence of physiological dissolution media and enzymatic digestion on the solublization capacity of the formulation increases with increase concentration of microcrystalline cellulose.

Wang Z et al\textsuperscript{85} have prepared and investigate the new solid self-emulsifying (SE) pellets of nitrendipine poorly soluble drug and then the liquid SEDDS were converted in to pellets with adsorbents such as porous silicon dioxide, crospovidon, microcrystalline cellulose and lactose by extrusion or spheronization technique. The uniform size, round shape and low friability pellets was obtained with 30% liquid SEDDS and the in-vitro release profiles was similar for the liquid self emulsion.

A. Gal et al\textsuperscript{86} was prepared diltiazem hydrochloride hydocolloid beads based on agarose, alginate or gellan carriers and talc, kaolin, calcium carbonate, potato, or corn starch as fillers. The overall results explain that the concentration of fillers influences to the stability of the beads and prolonged the time of drug release compare with beads formulated with no fillers.

Dong Wuk Kim et al\textsuperscript{87} prepared solid-self microemulsion drug delivery system (SMEDDS) formulations were prepared by spray-drying the solutions containing liquid SMEDDS and solid carriers such as hydrophilic dextran and hydrophobic colloidal silica (SMEDDS). The result suggests that the colloidal silica produced an excellent conventional solid SMEDDS in which the liquid SMEDDS was absorbed onto its surfaces. The physicochemical properties of solid microemulsion
microcapsules modulate with respect to type of solid carriers included in the manufacturing process.

Prabagar Balakrishnan et al\textsuperscript{88} prepared dexibuprofen solid form of lipid-based self-emulsifying drug delivery system (SEDDS) by spray drying liquid SEDDS with an inert solid carrier Aerosil 200. The particle size analysis revealed no difference in the z-average particle diameter of the reconstituted emulsion between liquid and solid-SEDDS. In-vivo results of solid SEDDS and dexibuprofen powder in rats at the dose of 10 mg/kg was significantly higher than those of dexibuprofen powder.

Yi T, et al\textsuperscript{89} was developed a solid form of self-microemulsifying drug delivery system (Solid-SMEDDDS) of poorly water soluble drug fenofibrate by spray-drying with dextran as the inert solid carrier. The results reveal that the dissolution rate was significantly increases from solid SMEDDDS than the drug powder.

Ghanshyam V. Joshi et al\textsuperscript{90} investigated the advantageous effect of clay mineral as drug carrier for timololmaleate (TM). The different concentration of clay intercalated with TM into the interlayer of montmorillonite (MMT). The results suggests that increasing the concentration of MMT retard the drug release in SGF pH 1.2 and increases the release in SIF pH 7.4 followed by sustained up to 12 hours.

2.3 Review on sustained release matrix tablets

Libo Yang, et al\textsuperscript{91} has been developed controlled release three-layer matrix system of diclofenac sodium for oral administration using poly (ethylene oxide) and hydroxy propyl methylcellulose [HPMC] as retardants by directly compressed technique. The results suggest that the concentration of polyethylene oxide and HPMC could influence the dissolution rate and shows that both biphasic release and zero-order release kinetics for up to 24 hours was based on both dissolution and swelling/erosion for linear portion of release profile.
Efentakis et al. have reported the effects of hydrophilic and hydrophobic polymeric matrices containing flurbiprofen on swelling and releases kinetics. The investigated data suggests that the release kinetics were influenced by polymer hydration and swelling. In non-swelling hydrophobic matrices of acrylic resins, drug release was slow when a hydrophobic drug was incorporated.

Nath BS et al. have worked on formulation and evaluation of sustained release dosage form of theophylline using a combined hydrophobic and hydrophilic matrix by wet granulation. The results reveal that the proportion of polymeric materials influences the rate and extend of drug release and show anomalous diffusion followed by first order rate kinetics.

Peppas et al. have prepared indomethacin matrix tablets were compressed by wet-granulation and investigate the influence of polymer molecular weight, matrix porosity, pH and ionic strength of the dissolution medium. It was noted that the drug release was influenced by polymer molecular weight. The higher molecular weight polymers induces higher swelling and produce thick gel layer where the out word movement of un-dissolved drug boundary formed which displaces from the gel layer.

Md. Selim Reza et al. was prepared matrix tablets of theophylline, diclofenac sodium and diltiazem HCl using Kollidon SR, carnauba wax and hydroxy propyl methylcellulose (HPMC-15cps) by direct compression process. The results suggest that the higher polymeric content (75%) in the matrix decreased the release rate of drug because of increased tortuosity and decreased porosity. The Kollidon SR shows an intermediate release profile but HPMC matrix shows zero-order.

M.L. Vuebaa et al. have prepared ketoprofen tablets by wet-granulation by adding methylcellulose, hydroxy propyl cellulose and hydroxypropylmethylcellulose as retardants and lactose monohydrate and β-cyclodextrin as diluents. The analysis of
the release profiles show distinct kinetic models (zero-order, first-order, Higuchi and Korsmeyer–Peppas) that were influenced by polymer and also the type of diluents present in tablet.

Panna Thapa et al.\textsuperscript{97} investigated the influences of diluents and concentration of carbopol 934P and granulation techniques in the release of poorly water-soluble drug (Ibuprofen) from matrix tablets using lactose, dibasic calcium phosphate (DCP), microcrystalline cellulose (MCC) and starch as diluents. The result suggests that the drug release rate decreased with increasing the polymer diluent ratio followed to higuchi matrix kinetics.

M. Harris shoaiib et al.\textsuperscript{98} develop a once-daily sustained release matrix tablet of ibuprofen using hydroxypropylmethylcellulose (HPMC) as release retardant by direct compression technique. The drug release data were fit into different dissolution models and shows best fit to the Higuchi matrix followed to diffusion, swelling and erosion of polymeric matrix.

S. Mutaliket et al.\textsuperscript{99} develops sustained release tablets of aceclofenac by direct compression using hydroxy propyl methylcellulose (HPMC). The results explain that the tablets exhibited almost similar drug release profile in different dissolution media as that of marketed tablet. The pharmacokinetic study in healthy human voluntaries, the tablets shows an extended drug release up to 24 hours as that of marketed product with almost identical pharmacokinetic parameters.

M. P. Venkatarajua et al.\textsuperscript{100} have investigated the synergistic activity of locust bean gum (LBG) and xanthan gum (X) of propranolol hydrochloride controlled delivery matrix tablets. The result explains that the synergistic effect of LBG and X influence physicochemical properties of tablets and highest burst release was found in
case of X and LBG but XLBG matrices predicted excellent controlled release for extended period of time.

Reza MS et al \textsuperscript{101} were developed sustained release theophylline matrix tablets by direct compression of Kollidon SR powder blends and different concentration of Kollidon SR and HPMC-15cps. The study suggest that the tablets containing only Kollidon SR was exhibit a fast drug release in initial lag time but the combination HPMC-15cps and Kollidon SR matrix tablets evident to prolonged the release of drug with subsequent minimization of burst release pattern and followed to zero-order or case II release.

Mukesh C. Gohel et al \textsuperscript{102} investigated the functions of super-disintegrants such as croscarmellose sodium, crospovidone, and sodium starch glycolate in ibuprofen tablet formulation. It has been reported that the crospovidone exhibit significantly higher hardness than croscarmellose sodium. The wicking action of crospovidone influences the water uptake by the tablet and the disintegration of the tablet is facilitated by the swelling efficiency of croscarmellose sodium.

Achutha Nayak, Usha et al \textsuperscript{103} have prepared aceclofenac agglomerates by using acetone, dichloromethane (DCM) and hydroxy propyl methyl cellulose-50 cps (HPMC) in different concentrations was used as hydrophilic polymer by spherical crystallization technique The optimized agglomerates were compressed into tablets by direct compression. The formulated tablets were shows prolonged drug release than that of marketed tablet and pure drug. The in-vivo studies were carried out of optimized agglomerates and preclinical studies revealed that the agglomerates provided improved pharmacodynamics and pharmacokinetic profiles of aceclofenac.

Beom-Jin Lee et al \textsuperscript{104} developed melatonin matrix tablets using of hydroxy propyl methyl cellulose (HPMC) and investigate the effects of HPMC viscosity, drug
loading, type and amount of disintegrant, lubricant and glidant, and aqueous polymeric coating level and was compared with two commercial products. The results suggest that the HPMC polymer viscosity increased, the release rate significantly decreases in different intervals of time and the drug loadings increased, the release rate slightly decreased. The tablets containing super-disintegrants such polyplasdone XL, Primojel, and Ac-Di-Sol were predominantly increases the drug release.

Muralidharan Selvadurai, et al\textsuperscript{105} developed single-unit of oral sustained release dosage form of dexibuprofen using xanthan gum with diluent Avicel PH101 by the wet granulation method. The study reveals that the varying proportion of polymer and diluent could have modulate the drug release in a controlled manner followed to higuchi and Peppas kinetics compare with dexibuprofen marketed tablet.

Punit B. Parejiya et al\textsuperscript{106} have formulated aceclofenac sustained release matrix tablets constituting varying proportion of Kollidon SR by direct compression. The study reveals that the faster drug release is observed with initial burst effect from tablets containing less amount of Kollidon SR but in higher level of Kollidon SR in the tablet is prolonged drug release with subsequent minimization of burst effect as followed Korsemeyer and Peppas kinetic mechanism.

YIN Hui et al\textsuperscript{107} establish a method to determination of dexibuprofen content from sustained release tablets by using high performance liquid chromatography and in-vitro release characteristics were evaluated by UV spectrophotometry. This result explains that the release of dexibuprofen from the tablets was extended up to 12 hours, exhibited zero-order kinetics. The HPLC technique can be used for the quality control of dexibuprofen sustained release tablets because of its accuracy, good reproducibility and high sensitivity.
Bendgude NT et al.\textsuperscript{108} developed diltiazem hydrochloride matrix tablets by direct compression containing HPMC as retardant and lactose, MCC, and dicalcium phosphate as diluents. The addition of lactose in the tablet containing high soluble drug showed remarkable swelling and erosion and the best sustained drug release, compared to matrices containing microcrystalline cellulose and dicalcium phosphate.

Evren Algin et al.\textsuperscript{109} were prepared Verapamil HCl matrix tablets and evaluate the effects of direct tableting agents like AvicelPH101®, Cellactose80®, Ludipress LCE®, Pharmatose200M®) and Hydroxypropyl-methylcellulose (HPMC) on release profiles and swelling behaviors of the tablets. The results suggest that the proportion of HPMC and lactose in the formulation increases the swelling and significantly decreases the drug release. The \textit{in-vitro} release data was mainly fitted to the non-Fickian transport mechanism followed to diffusion and erosion due increase of swelling of hydrophilic polymer in the presence of diluents.

Silvina A. Bravo et al.\textsuperscript{110} was prepared HPMC matrix tablets of diclofenac sodium using microcrystalline cellulose (MCC), starch, and lactose as diluents by wet granulation technique and to evaluating the relationship and influence of different content levels of diluents. The result suggests that the release of diclofenac sodium was influenced by the different concentration of polymer to diluent ratio in the formulations. The drug release kinetics from these formulations was followed to zero-order kinetics compared to conventional marketed SR tablets.
2.4 Review of protocol drugs

A. Aceclofenac sodium\textsuperscript{111-112}

![Structural formula of Aceclofenac sodium]

**Official status:** Official in I.P., B.P and U.S.P.

**Structural formula:** Aceclofenac is chemically \(2-[(2, 6\text{-Dichlorophenyl})\text{ amino}]\) \(\text{phenyl}\) \(\text{acetyl}\) \(\text{oxy}\) \(\text{acetic acid sodium. (CAS No- 89796-99-6)}\)

**Molecular formula:** \(\text{C}_{16}\text{H}_{12}\text{Cl}_{2}\text{NO}_{4}\text{Na.} \quad \text{Molecular weight: 354.2}\)

**Anatomical Therapeutic Chemical (ATC):** M01AB16M02AA25

**Category:** Analgesic, anti-inflammatory

**Description:**

Aceclofenac sodium is phenyl acetic acid derivatives contains not less than 99.0% and not more than the equivalent of 101.0 percent of \(2-[(2-(2-[\text{2, 6-\text{dichlorophenyl}}\text{ amino}]\text{ phenyl}\) acetyl] oxy] acetic acid sodium. It is a white or almost white crystalline powder having melting point 144.6 °C practically insoluble in water, freely soluble in acetone and alcohol.

**Pharmacology**

Aceclofenac sodium is non-steroidal anti-inflammatory drug used extensively in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The anti-inflammatory, analgesic and ant-pyretic action of aceclofenac sodium mainly inhibits the COX-2 enzyme at site of inflammation with subsequent reduction in the synthesis of certain prostaglandins from their arachidonic acid precursors which
inhibit the migration of leucocytes including polymorph nuclear leucocytes into inflammatory sites.

**Pharmacokinetics**

<table>
<thead>
<tr>
<th>Oral bioavailability: 100%</th>
<th>Urinary excretion: 70-80%;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bound in plasma: &gt;99.7%</td>
<td>Clearance: 5 L/min</td>
</tr>
<tr>
<td>Volume of Distribution: 30 L/Kg;</td>
<td>Half-life: 3-4 Hours</td>
</tr>
</tbody>
</table>

Aceclofenac sodium is rapidly and completely absorbed after oral administration, peak plasma concentrations are reached 1 to 3 hours after an oral dose. The drug is highly protein bound > 99.7%. The plasma concentration of aceclofenac sodium was approximately twice that in synovial fluid after multiple doses of the drug in-patient with knee pain and synovial fluid effusion. Renal excretion is the main route of elimination of aceclofenac sodium with 70 to 80% of an administered dose found in the urine and 20% is excreted in the faces. The plasma elimination half-life of the drug is approximately 3-4 hours.

**Drug Interactions**

Aceclofenac sodium may increase plasma concentrations of lithium, digoxin and methotrexate, increase the activity of anticoagulant, inhibits the activity of diuretics, enhance cyclosporin nephrotoxicity and precipitate convulsions when co-administered with quinolone antibiotics.

**Adverse effects**

Aceclofenac sodium is well tolerated; with most common GI disorder adverse effects include dyspepsia, abdominal pain, nausea, diarrhea, gastritis, constipation, vomiting, ulcerative stomatitis, and pancreatitis.
Therapeutic dose

The usual dose of aceclofenac sodium is 75-100 mg given twice daily for the treatment of acute and chronic pain. The maximum dose recommended 200 mg per day.

B. Dexibuprofen

![Structural formula of Dexibuprofen](image)

**Official status:** Official in I.P., B.P and U.S.P.

**Structural formula:** Dexibuprofen is (2S)-2-[4-(2-methylpropyl) phenyl] propionic acid

**Molecular formula:** C13 H18 O2  **Molecular weight:** 206.28

**Category:** Analgesic, anti-inflammatory

**Anatomical Therapeutic Chemical (ATC) code:** M01AE14

**Description:**

Dexibuprofen is an orally administered propionic acid derivatives contain not less than 98.0% and not more than 102.0% of percent of (2S)-2-[4-(2-methylpropyl) phenyl] propionic acid. Dexibuprofen is a slightly white to off-white, crystalline powder having melting point 49-53 0C and practically insoluble in water, but is
readily soluble in most organic solvents like methanol, methylene chloride, and acetone, and is soluble in aqueous solutions of alkali hydroxides and carbonates.

**Pharmacology**

Dexibuprofen[S (+)-Ibuprofen] is considered as pharmacologically active enantiomer of racemic Ibuprofen. It is a nonsteroidal ant-inflammatory drug with analgesic action which acts by inhibiting the binding of arachidonic acid to the cyclooxygenase sub-unit of prostaglandine synthetase.

**Pharmacokinetic properties**

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<td>Bound in plasma : &gt;99. %</td>
<td>Clearance: 5 L/min</td>
</tr>
<tr>
<td>Volume of Distribution: 28 L/Kg;</td>
<td>Half-life: 1.8-3.5 Hours</td>
</tr>
</tbody>
</table>

Dexibuprofen is rapidly and extensively absorbed after oral ingestion followed too primarily from the small intestine and extensively metabolites in the liver forms the therapeutically inactive metabolites. These inactive metabolites are completely excreted by the kidneys (90%) followed in the bile. The elimination half-life is 1.8-3.5 hours; the plasma protein binding is about 99 %. Maximum plasma levels are reached about 2 hours after oral administration.

**Dosage and administration**

The dosage should be adjusted to the severity of the disorder and the complaints of the patient. During chronic administration, the dosage should be adjusted to the lowest maintenance dose that provides adequate control of symptoms. The maximum single dose is 400 mg and recommended up to 600 to 900 mg daily, divided three single doses. The dose may be temporarily increased up to 1200 mg dexibuprofen per day in acute disease conditions.
Adverse effects

The onset of symptoms usually occurs within 4 hours. Mild symptoms are most common, including abdominal pain, nausea, vomiting, drowsiness, headache, tinnitus and ataxia. Rarely, moderate or severe symptoms include gastrointestinal bleeding, metabolic acidosis, seizures, impaired kidney function and distress syndrome.

Contraindication:

Dexibuprofen is contraindicated in patients with previous history of hypersensitivity to other NSAIDs and those suffering from asthma, bronchospasm, acute rhinitis, or cause nasal polyps, urticarial or angioneurotic edema and suspected gastrointestinal ulcer or bleeding disorders.

Therapeutic indications

Dexibuprofen was used in the symptomatic treatment for the relief of pain and inflammation associated with osteoarthritis, acute symptomatic treatment of pain during menstrual bleeding (primary dysmenorrhea) and muscular-skeletal pain or dental pain.

2.5 Review of polymers

Polymers have been successfully employed in the formulation of solid dosage forms and are specifically useful in the design of oral sustained / controlled release drug delivery systems. Both synthetic and natural polymers have been investigated extensively for this purposes but the use of natural polymers for pharmaceutical applications is attractive because they are economical, readily available, non-toxic, and capable of chemical modifications, potentially biodegradable. Natural
polysaccharides hydrogels have been widely used as drug release modifiers in several controlled drug delivery systems of their advantageous properties over synthetic polymers such as biocompatibility, biodegradability ability to modify the properties of aqueous environment capacity to thicken, emulsify, stabilize, encapsulate, swell and to form gels. It is well known that polysaccharides can respond to surrounding conditions such as pH, ionic strength, and temperature. The pH-sensitivity of hydrogels is an important factor in designing for controlled drug delivery systems for water insoluble drugs having pH sensitivity in the GI-tract.

2.5.1 Sodium alginate

Empirical formula: $\text{(C}_6\text{H}_7\text{O}_6\text{Na)}_n$

Synonym: Algin and alginic acid

Chemical properties

It is the sodium salt of alginic acid and high molecular weight linear polymer envelops of D-mannuronic acid and L-glucuronic acid residues that are composed of M and G homopolymeric region. The M/G ratio of sodium alginate dictates the physical properties such as viscosity and swelling behavior and gelling nature of alginate.
The chemical structure of alginate with β-D-mannuronic (M) acid blocks and α-L-gluronic (G) acid blocks

**Solubility**

Sodium alginate is slowly soluble in water and forming a viscous colloidal solution. It is insoluble in alcohol, other organic solvents. The rate of dissociation of alginate molecules in water is demonstrating the solubility of alginates. In contrast, the M and G-helices could precipitate as alginic acid at low pH (< 3) while in higher pH level induces the protonation of phosphate ions in the alkaline pH and alternating M/G forms viscous polymeric gel. This pH dependent property of alginates is very much important in pharmaceutical dosage forms to minimize the release drugs in GI tract especially that those are the drugs having higher GI-disorders.

**Thickening**

Sodium alginate having good thickening properties depends upon molecular weight and viscosity. This viscosity could be affected by interaction with certain crosslinkers such as Ca$^{2+}$, Ba$^{2+}$ and Al$^{3+}$ cations among all that calcium ions interacting with alginates even small concentrations will produces very viscous gel than alginate alone. These types viscous solutions have thixotropic flow properties are very use full in situ-gel formulations.

**Swellability**

The rate of swelling is mainly depends on the type alginate and pH of the solvent medium. The swelling alginates are very less in acidic solution but it gradually increases at neutral solutions. Swelling properties of alginates have been used in sustained release products to control the release of drug for an extended period of time in various physiological conditions.
Gel formation

The alginates produce viscous gel with certain monovalent, divalent and multivalent cations. The presence of monovalent cations in the alginate solution produces soluble salts whereas divalent and multivalent cations induce viscous gels or precipitates. The gelation of alginic acid forms high viscous acid gel by intermolecular binding with calcium ion. During the crosslinking process the water molecules will entrapped inside the polymeric gel and free to migrate throughout the gel layer. These property of alginates are much importance in many applications for cell immobilization / microencapsulation.

Applications

In the pharmaceutical field, sodium alginate has been used as excipient in certain novel drug delivery products such as microspheres or microbeads, matrix tablets, situ-gel formulations and transdermal patches. Sodium alginate is used as suspending and thickening agents in water miscible pastes, creams, gels, lotions. They are also used as stabilizers for oil in water emulsions and as binding and disintegrating agents in tablets.

Due to the intrinsic properties of alginate calcium gels like biocompatibility, mucoadhesive and ease of manipulation that are recently been focused on the delivery of proteins, cell encapsulation, and tissue regeneration.

Alginates are also been used for the applications for oral and ocular drug delivery. In situ gel formation has also been used to study the oral administration of NSAIDs. When the swallowed solution reached the stomach, the acidic environment allowed the calcium ions to interact with alginate leading to the gel formation which protects the gastric mucosa.
2.5.2 Hydroxy propyl methylcellulose (HPMC)\textsuperscript{123-125}

Hydroxy propyl methylcellulose (HPMC) is the cellulose ethers are commonly used to design of certain novel drug delivery products either oral or per-oral administration. HPMC polymers hydrate in water forming a gel layer at the matrix periphery which controls the release of drug from the formulated system.

**Empirical formula:** \( C_8H_{15}O_6-(C_{10}H_{18}O_6)\ n-C_8H_{15}O_5 \), **Molecular weight:** 86,000

**Synonyms:** Methylhydroxypropylcellulose, Propylene glycol ether of methyl cellulose, Methylcellulose propylene glycol ether (Methocel)

**Chemical names:** Cellulose-2-hydroxypropylmethyl ether, Cellulose hydroxy propyl methyl ether

**Properties**

HPMC is a white to off-white fibrous powder swells in water to produce a viscous colloidal non-ionic solution. It was dissolves slowly in water, soluble in most polar solvents, insoluble in anhydrous alcohol, ether, and chloroform but soluble in mixtures of methyl alcohol and methylene chloride. The pH of 1\%w/w aqueous solution ranges from 5.5 to 8.0. Apparent density: 0.25 – 0.70g/cm\(^3\) and pH: 5.5-8.0

**Functional Categories:**

**USP:** Suspending and or viscosity increasing agent, tablet binder, coating agent.

**BP:** Viscosity increasing agent, adhesive anhydrous ointment, ingredient.

**Others:** Film former, emulsion, stabilizer.

**Stability and storage conditions**

Very stable in dry condition, solutions are stable at pH 3.0-11.0. Aqueous solutions are liable to be affected by microorganisms stored in a tight container; in cool place. The recommended storage temperature is 5-35 °C.
**Pharmaceutical applications:**

HPMC is used as a coating agent, stabilizing agent, tablet binder, viscosity modifier and suspending agent in various pharmaceutical products. The 2 to 10%w/w of concentration used as binder in tablet granulation and 2-5% high viscosity grades are used as release retardant of water-soluble drugs.

The HPMC polymer mainly used in sustained release oral products because of adequate swelling behavior in the aqueous medium to form thick gel layer which entrapped more drug and retards slowly for extended time period.