II. LITERATURE REVIEW

- **Sato**\(^{11}\) developed hollow microsphere of different drug riboflavin, aspirin, salicylic acid, ethoxybenzamide, indomethacin. Microballoons were prepared by emulsion solvent diffusion method with using enteric acrylic polymer codissolved with drug in mixture of dichloromethane and ethanol. Buoyancy of microballoons decreased with increasing drug ratio. In the case of aspirin, salicylic acid, ethoxybenzamide, the release profile of microballoons proved a linear relationship by Higuchi plot. However indomethacin, riboflavin release did not follow the Higuchi equation, when loading amount of riboflavin was higher than solubility in the mixture of dichloromethane, ethanol, drug release profiles displayed an initial burst release. Insoluble riboflavin absorbed on to the microballoons surface in crystal state. Drug release rate were increases with increased HPMC ratio.

- **Kamel**\(^{12}\) prepared the Ketoprofen floating microparticles by emulsion solvent diffusion technique by using Eudragit RS 100, alone or mixture with Eudragit RL 100. These microparticles were increases the gastric residence time in stomach and minimize the irritant effect in stomach by avoiding direct contact with the mucosa and low dosage for prolonged period. Scanning electron microscopy was examined for surface morphology and size distribution was determined by sieving method. X-ray diffraction, Differential scanning colorimetry
examination shown drug and polymer interaction. Release rates were done in 0.1 N HCL and phosphate buffer 6.8 and floating ability in 0.1 N HCL containing 0.02% Tween 20 for six hours.

- **Sato**\(^{13}\) designed a riboflavin hollow microsphere by emulsion solvent diffusion method using enteric acrylic polymer. It was found that at 20\(^\circ\)C temperature slow rate of evaporation of dichloromethane to formation of porous microsphere as dichloromethane remained in the droplets preventing the formation of hard polymer shell. At high temp. around 50\(^\circ\)C, rapid rate of evaporation provided microspheres exhibiting a single large depression due to drastic evaporation of dichloromethane, shell were conveniently formed by gradual coprecipitation of drug and polymer as well as evaporation of inner solvent (ethanol) at 40\(^\circ\)C. Loading amount of drug is greater, the buoyancy of microballoons decreased, accompanied by increased porosity. So uniform polymer shell was not form, large number of needle – like particles were generated and rough surface, affording reduced buoyancy as rigidity of shell decreased.

- **Kale**\(^{14}\) develop a piroxicam floating microsphere using an enteric polymer and emulsification solvent – evaporation method. The Microspheres remained buoyant continuously over the surface of acidic media (pH 1.2) containing surfactant (Tween 20, 02%) for 8-12 hrs. Differential scanning colorimetry X-ray diffraction study showed
that drug and polymer interaction. Scanning election micrographs indicated that the microsphere is perfect hollow cavity enclosed by rigid shell of polymer. The \textit{in-vitro} drug release study has used pH 7.0 as dissolution medium.

- \textbf{Muthusamy K.}^{15} designed Lansoprazole micropellets by using three drugs to carrier ratio 1:1, 1:2, 1:3 & HPMC, Chitosan, methyl Cellulose as carrier by emulation- solvent diffusion technique (Chitosan 1:1 ratio shown maximum percentage yield of 85\%). \textit{In-vitro} release study in pH 1.2, 6.8, drug to HPMC ratio of 1:3, drug to chitosan vitro of 1:1 shown highest release of 66\% and 72\%.

- \textbf{Sato}^{16} designed the hollow microsphere of riboflavin by emulsion solvent diffusion techniques. The intragastric behaviour of 99M TC labelled. Microballoons (MB) compared with nonfloating microsphere (NF) in vivo using human volunteers; employing gamma scientigraphy. It shows linear correlation between GRT and $41/2$ and total urinary excretion, respectively. In case of MB administration, GRT was longest, $41/2$ and total urinary excretions were high as complain with NR.
Mutalik\textsuperscript{17} develop once daily sustained release tablets of aceclofenac by direct compression using hydroxypropylmethylcellulose-K4M (HPMC). The solubility studies of aceclofenac were conducted to select suitable dissolution media. The drug-excipient mixtures were subjected to preformulation studies. The tablets were subjected to physicochemical, in vitro drug release in 0.1 N HCl and phosphate buffer 6.8 and stability studies. Based on the preformulation results, microcrystalline cellulose (MCC), dicalcium phosphate and spray dried lactose (SDL) were selected as directly compressible vehicles. 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. The pharmacokinetic study in healthy human volunteers indicated that B7 tablet produced an extended drug release of drug upto 24 hrs as that of marketed product with almost identical pharmacokinetic parameters.

Dashora K.\textsuperscript{18} prepared microparticulate of aceclofenac by modified solvent evaporation method using cellulose acetate as polymer & drug and polymer ratio is 1:9, 1:6, 1:3, 1:1, agitation speeds (500-1500rpm) and the stirring time(5-15 min.). The effects processing variables were evaluated by microparticles size and entrapped efficiency. The average microparticles size increases from 80.2 ± 145 to 97.3 ± 2.06 \( \mu \text{m} \) with increase in the polymer concentration while reduces with increase in agitation speed and stirring time and at the higher speed...
gives the irregular shape of particle. *In-vitro* drug release carried out with microcapsules and compare with conventional tablet and SR tablet. The conventional and SR tablet releases maximum drug within 3 and 6 hrs while microparticulate system releases more than 12hrs.

➢ **Dooley**\(^{19}\) Aceclofenac is an orally administered phenylactic acid derivative with effects on a variety of inflammatory mediators. Through its analgesic and anti-inflammatory properties, Aceclofenac provides symptomatic relief in a variety of painful conditions. Aceclofenac reduces joint inflammation, pain intensity and the duration of morning stiffness in patients with rheumatoid arthritis, and is similar in efficacy to ketoprofen, diclofenac, indomethacin and tenoxicam in these patients. It is also effective in other painful conditions (e.g. dental and gynaecological). Aceclofenac is well tolerated, with most adverse events being minor and reversible, and affecting mainly the GI system. It indicates that adverse effects are lower with aceclofenac than with a range of comparator NSAIDs.

➢ **Yamazaki**\(^{20}\) investigate the mechanisms of action of nonsteroidal anti-inflammatory drug aceclofenac in humans, we studied the metabolism of aceclofenac in detail in primary cultured synovial cells of 10 patients with rheumatoid arthritis. Aceclofenac and 4-hydroxyaceclofenac is major compound in human blood after the administration of aceclofenac but they had no inhibitory effects on
cyclooxygenase (COX) activity or COX expression in the rheumatoid cells. In contrast, aceclofenac and 4-hydroxyaceclofenac reduced prostaglandin E2 (PGE2) production by the rheumatoid synovial cells. We also observed that aceclofenac and 4-hydroxyaceclofenac were hydrolyzed into the COX inhibitors diclofenac and 4-hydroxydiclofenac, respectively, by the rheumatoid synovial cells.

- **Legrand**\(^{21}\) investigate the Aceclofenac is oral NSAID that is effective in the treatment of painful inflammatory diseases. It has been proved as effective as diclofenac, ketorolac, indomethacin in patients with rheumatoid arthritis and diclofenac, naproxen, piroxicam in osteoarthritis. It also provides effective analgesia in other indications such as dental or gynecological pain, lower back pain and ear, nose, throat indication. It appears to be particularly well tolerated amongst the NSAIDs, with a lower incidence of gastrointestinal adverse effect.

- **Shakeel F**\(^{22}\) prepared nanoemulsion formulation for transdermal delivery of aceclofenac. Various oil-in-water nanoemulsion were prepared by the spontaneous emulsification method. The nanoemulsion formulations that passed thermodynamic stability tests were characterized for viscosity, droplet size, transmission electron microscopy, and refractive index. The anti-inflammatory effects of formulation F1 compared with aceclofenac conventional gel and nanoemulsion gel on carrageenan-induced paw edema in rats. These
results suggested that nanoemulsion are potential vehicles for improved transdermal delivery of aceclofenac.

- **Yang JH**\(^{23}\) develop novel transdermal formulation for aceclofenac, microemulsion was prepared for increasing its skin permeability. Based on solubility and phase studies, oil and surfactant was selected and composition was determined. Microemulsion was spontaneously prepared by mixing ingredients and the physicochemical properties such was investigated. The mean diameters of microemulsion were approximately 90 nm and the system was physically stable at room temperature at least for 3 months. Aceclofenac in microemulsion was more potent than cream in the alleviation of muscle pain. Therefore, the microemulsion formulations of aceclofenac appear to be a reasonable transdermal delivery system of the drug with enhanced skin permeability and efficacy for the treatment of muscle damage.

- **Muthusamy K.**\(^{24}\) designed Lansoprazole floating micropellets by using three drugs to carrier ratio 1:1, 1:2, 1:3 & HPMC, Chitosan, methyl Cellulose as carrier by emulation- solvent diffusion technique (Chitosan 1:1 ratio shown maximum percentage yield of 85%). *In-vitro* release study in pH 1.2, 6.8, drug to HPMC ratio of 1:3, drug to chitosan vitro of 1:1 shown highest release of 66% and 72%.
Chelladurai S\textsuperscript{25} have developed Gelatin A microspheres were prepared using the emulsification-cross linking technique. The drug was dispersed in polymer gelatin and formulated into a w/o emulsion with liquid paraffin, using glutaraldehyde as a cross linking agent. All the prepared microspheres were evaluated for physical characteristics, such as particle size, incorporation efficiency, swelling ability, \textit{in vitro} bioadhesion on rabbit small intestine and \textit{in vitro} drug release characteristics in pH 6.6 phosphate buffers. All the microspheres showed good bioadhesive properties. Gelatin A and chitosan concentrations, percentage of the cross linking agent and also the drug loading affected significantly the rate and extent of drug release.

Dhawan S\textsuperscript{26} prepared chitosan microspheres by different methods were evaluated by studying the interaction between mucin and microspheres in aqueous solution. The interaction was determined by the measurement of mucin adsorbed on the microspheres. The intensity of the interaction was dependent upon the method of preparation of chitosan microspheres and the amount of mucin added. The extent of mucus adsorption was proportional to the absolute values of the positive zeta potential of chitosan microspheres. The zeta potential in turn was found to be dependent upon the method of preparation of microspheres.
Bytul M\textsuperscript{27} have reported that Ketorolac tromethamine is a member of the pyrrolopyrrole group of non-steroidal anti-inflammatory drug (NSAID) that exhibits analgesic, anti-inflammatory and antipyretic activity. It inhibits the cyclo-oxygenase enzyme system and hence prostaglandin synthesis. It has more pronounced analgesic activity than most NSAIDs prepare and evaluate the ketorolac tromethamine tablets with higher dissolution rates and to compare them with marketed product. Direct compression method was adopted for preparation of tablet using different excipients namely; microcrystalline cellulose, spray dried lactose and starch 1500. The effect of excipients on the drug release from prepared tablets was also studied.