CHAPTER 2

REVIEW OF WORK DONE
2.1 REVIEW OF WORK DONE ON SUSTAINED RELEASE FORMULATIONS OF DICLOFENAC SODIUM:

Gayatri Devi and co-workers [43] prepared diclofenac sodium microspheres using egg albumin by chemical cross-linking and inclusion complex with betacyclodextrin. Studies were done on entrapment efficiency, particle size distribution and dissolution pattern.

Chowdary and Vijaya Ratna [44] prepared and evaluated sustained release microcapsules of diclofenac sodium using cellulose acetate as a polymer. The method was based on emulsification of the polymer solution containing the drug in an immiscible liquid medium. Coacervation was achieved by addition of a nonsolvent. The drug release was governed by diffusion rate and followed first order kinetics.

Jani and Gohel [45] employed a computer optimization technique to investigate the key variables affecting the preparation of diclofenac sodium loaded ethyl cellulose microspheres. Contour graphs are presented to visualize impact of independent variables on drug content in the microspheres.

Lin and co-workers [46] prepared enteric coated microcapsules of diclofenac sodium by a spray drying technique using Eudragit L30 D as an enteric coating material. The drug release rate was determined in phosphate buffer pH 6.8, 0.1 N HCl and distilled water by pH change method.

Akigoez and co-workers [47] prepared microspheres of diclofenac sodium using chitosan-H. They discussed the action of diclofenac sodium and effect of various conditions on the drug release kinetics. A $3^3$ factorial design was
used to optimize the variables affecting the t50 and drug content. The release profiles were evaluated kinetically and the best fit was obtained by the Higuchi equation.

Shobha Rani and co-workers [48] prepared microspheres of diclofenac sodium using carriers such as albumin, ethylcellulose, gelatin, calcium alginate and waxes by different techniques of microencapsulation. The yield varied from 65-85 %. Stability of the drug was confirmed by Infra Red Spectroscopy and Thin Layer Chromatography studies. Drug associated with the microspheres was estimated and it ranged from 14.5 to 90%. Morphology was revealed by Scanning Electron Microscopy. Size of the microspheres was determined using optical microscopy and it ranged from 36.3 to 46.6 μm. Short term stability studies at different temperatures were carried out. In-vitro release studies were carried out for a period of 8 h and compared with pure drug and marketed samples.

Hasan and co-workers [49] studied the in vitro and in-vivo evaluation of sustained release and enteric-coated microcapsules of diclofenac sodium. They examined the release of diclofenac sodium from ethylcellulose microcapsules, made up of different drug to polymer ratios. The release process was found to follow the Higuchi square root equation and not the zero order or first order equation. Good agreement between in-vivo and in-vitro results was noticed.

Gursoy and co-workers [50] prepared diclofenac sodium- calcium alginate beads with and without aqueous insoluble polymer dispersions. The morphology and the anti-inflammatory action of the gel beads were studied.
Murata and others [51] prepared cross-linked alginate beads of diclofenac sodium. The sustained release was attributable to the fixation of diclofenac sodium in gel beads. Diclofenac was fixed in the gel by utilizing the lowering of solubility observed with increasing CaCl$_2$ concentration and sustained release could be achieved.

Long and co-workers [52] prepared controlled release diclofenac sodium pellets. The yield was affected by lactose/starch ratio of the granules, viscosity of the binding solution and residence time in the rolling pot. The relative bioavailability was found to be 86% when multiple doses of the controlled release pellets and commercial tablets were administered orally to healthy male volunteers.

Rafiee and others [53] developed controlled release diclofenac sodium granules coated with different polymers like ethylcellulose and Eudragit RS100 by the air suspension technique. Coated granules were compressed into tablets and were enteric coated using a mixture of 1:1 Eudragit L100 and S100. The release profiles were investigated at different pH media and release kinetics were analyzed.

Sujjaareenath and co-workers [54] developed pellets of diclofenac sodium using carrageenan, locust bean, karaya and xanthan gums. The drug release profiles showed sustained release. The mechanism of drug release was found to be of anomalous type.

Okada and co-workers [55] prepared a long acting preparation by mixing uncoated and coated diclofenac sodium beads. The drug release was governed by dissolution of enteric coating and diffusion through the membrane.
Arica and researchers [56] prepared microspheres of diclofenac sodium using carboxy methyl cellulose as a polymer and aluminium chloride as a cross-linker. Different drug to polymer ratios were used to obtain a range of microspheres. They were coated with Eudragit S-100. Increasing the carboxy methyl cellulose concentration led to an increase in encapsulation efficiency, percentage yield, particle size and decrease in release rates. Coating did not alter the size but slowed the drug release rates.

Acikgoz and others [57] prepared microspheres of diclofenac sodium using chitosan as a natural polysaccharide. The independent variable in 33 factorial design were concentration of chitosan, tripolyphosphate concentration and stabilization time. The dependent variables, t50 and the total drug content were investigated by the polynomial equation. The release profile was evaluated kinetically and the best fit was obtained by the Higuchi equation.

Vilivalam and Adeyeye [58] prepared diclofenac wax microspheres using congeable disperse phase encapsulation method. Emulsifiers, glyceryl monostearate and stearic acid were used to improve the efficiency of emulsification. The microspheres showed a high drug content and narrow particle size distribution.

Gohel and co-workers [59] prepared microspheres of diclofenac sodium by coacervation phase separation method using chitosan and glutaraldehyde. The optimum conditions for preparation, factors affecting in-vitro release rate and mechanism of drug release were identified. The in-vivo studies were carried out in rabbits and results show that controlled release formulation could be developed using chitosan. The drug was released according to the Higuchi model.
Guterres and co-workers [60] reported that encapsulation of diclofenac in poly (d,l-lactide) nanocapsules reduced the local tissue damage after a single intra-muscular injection.

Torres and others [61] prepared microcapsules of diclofenac sodium by coating ion-exchange resins with the enteric polymer hydroxypropyl methylcellulose phthalate (HPMCP). A non-aqueous emulsion method was used to microencapsulate the ionic complexes. Anionic resins with different degree of cross-linking (4-6%) were used as the core material. The bioavailability was studied in rabbits using a reference product. In comparison to the uncoated product, the enteric coated product showed a significantly slower apparent rate of absorption.

Chandrashekhar and Udupa [62] prepared and evaluated microspheres and an in situ gel forming system of diclofenac sodium using copolymer of lactic and glycolic acid (PLGA). They concluded that the products can be used as controlled release dosage forms for long term treatment.

Gursoy and co-workers [63] used ionotropic gelation of sodium alginate in an entirely aqueous environment for obtaining controlled release microspheres of diclofenac sodium.

Miyagawa and others [64] prepared wax matrix granules consisting of carnauba wax, diclofenac sodium and rate controlling agents such as hydroxypropyl cellulose (HPC-SL), Eudragit L-100, and NaCl. A wax matrix with high mechanical strength was obtained even at temperatures lower than the melting point of wax. The dissolution behaviour of the drug was strongly influenced by granule formation.
Ono and others [65] prepared a sustained release formulation of diclofenac sodium containing fast and slow acting fractions. Ethylcellulose solution, in 1:1 ethyl alcohol-distilled water, was used for preparing slow acting granules. Fast and slow acting granules were mixed in the ratio of 4:6. The time to reach maximum concentration ($t_{\text{max}}$) was 1 hour and the blood level fell after 10 hours.

Acartuk [66] prepared prolonged release tablet of diclofenac sodium by direct compression using chitin as a retarding agent. Tablets without chitin dissolved within 10 minutes.

Pena and co-workers [67] prepared controlled release inert matrix formulations of diclofenac sodium using ethyl cellulose, pevicon and Eudragit- RS. Dissolution and compressibility of the tablets were tested. Ethylcellulose and pevicon were found to be more effective than Eudragit-RS.

Vyas et. al. [68] prepared bilayer controlled release tablets of diclofenac sodium using Hydroxypropyl methylcellulose (HPMC) -1000 and HPMC-1500. The drug release rate was found to be 8 mg/hour for extended period of time.

Pena Romero and others [69] developed a formulation for sustained release oral tablets of diclofenac sodium. The optimization of tablet weight and composition was carried out by a factorial design. The drug was released by zero order mechanism.

Bhalla and Jather [70] studied the preparation of controlled release spherules of diclofenac sodium by spheronisation. The Eudragit coated cores displayed a satisfactory in-vitro release profile and in-vivo performance.
Nishihata and researchers [71] used hydrogenated soyaphospholipids as a diluent in the preparation of sustained release tablets of diclofenac sodium. They carried out the in vitro release studies at different pH values and at 40 and 100 RPM respectively.

Torres and others [72] prepared and studied the characterization and release properties of diclofenac sodium from enteric coated ion exchange resins. Statistical analysis of the results showed that the degree of the polymer coating significantly retarded the release.

Navarro and co-workers [73] studied the effect of granule size and drug delivery modifier substance such as lactose or hydroxypropyl methylcellulose in prolonged release diclofenac sodium tablets.

Sawayanagi and researchers [74] prepared long acting diclofenac sodium preparations using a copolymer of methacrylic acid and methyl methacrylate. The enteric preparations were prepared in the form of beads, granules, tablets, powders or microcapsules.

Okada and co-workers [75] prepared long acting diclofenac sodium formulations by applying polymer as a coat and an organic acid. The acid decreases the maximum blood concentrations of diclofenac sodium by suppressing and controlling the rate of release and maintaining the blood concentration for a considerable period of time.

Van Wilder and co-workers [76] studied in-vitro dissolution of two oral controlled release preparations of diclofenac sodium. They compared the formulations with different dissolution techniques and at different pH. Faster dissolution was obtained at higher pH values. Acidic digestion generates
slower release. The release was strongly dependent on the method and medium used.

**Bain and co-workers [77]** compared the in-vitro release characteristic between wax based and hydrogel based sustained release diclofenac sodium tablets. The release patterns were compared by employing the release exponent "n" as a method of ascertaining the release mode. The wax matrix exhibited classical diffusion controlled release of drug through tortuous pores. This was confirmed by Scanning Electron Microscopy. The hydrogel tablets exhibited nearly zero order release, a dynamic equilibrium existing between rate of gel swelling and erosion.

**Hirotani and researchers [78]** prepared controlled release granules of diclofenac sodium using hydrogenated soyalecithin. Addition of cholesterol to the granules caused a slower release of the drug. The drug release matched the Higuchi model.

Gel matrix systems which exhibited a bimodal controlled release for oral delivery of diclofenac sodium or ibuprofen were prepared by **Shah and others [79]**. Hydroxypropyl methylcellulose ethers were used as matrixing agents. Initial surface erosion, polymer gelation, a steady state counter current permeation of water, dissolution of drug across the gel layer and subsequent disintegration of gel were noticed. The authors concluded that the uniform drug level was maintained with bimodal release pattern.

**Bozic and co-workers [80]** demonstrated the application of a 2 level back propagation type of neural network for studying and optimizing dissolution of diclofenac sodium from sustained release matrix tablets. The effect of 3 formulation components on the dissolution rate were analyzed by this
The convenience of a formulation study by 2 and 3 dimensional response surface analysis is presented. The authors have stated that the neural network technique is particularly suitable in the pharmaceutical technology of sustained release dosage forms where systems are complex and nonlinear relationship between independent and dependent variables often exists.

The release of paracetamol and diclofenac sodium from inert matrices and its relations with distribution coefficient between matrix and dissolution medium were studied by Zecchi and others [81]. Different systems containing drug and lipid or polymeric inert excipients were used. The drug release was found to be inversely correlated with partition coefficient.

The influence of excipients such as stearyl alcohol, Hydroxypropyl methylcellulose and ethylcellulose on the dissolution rate of diclofenac sodium sustained release tablets was investigated by Hong and co-workers [82] using computer optimization.

Yang and Reza [83] developed controlled release preparations of diclofenac sodium for oral administration. They prepared a directly compressible three layer matrix system which provided an instantaneous dose. Release mechanism followed both biphasic release and zero order release for up to 24 h. They claimed that the drug delivery reduces side effects and provided extended therapeutic effect.

Mohamed [84] used an anion exchange resin to prepare sustained release dosage form of diclofenac sodium. The drug loading and drug release profiles were affected by loading temperature. The drug release was also influenced
by pH and ionic strength of dissolution medium. The drug release kinetics followed diffusion control.

Shibhara and others [85] prepared sustained release formulations of diclofenac sodium. The formulation comprised of (a) granule like nucleus with matrix containing diclofenac sodium, carboxy methylcellulose, hydroxypropyl methyl cellulose acetessuccinate, ethylcellulose or methacrylic acid - methyl methacrylate copolymer as the binder, and carrier micropowders containing silicone dioxide, metasilicate magnesium aluminate or crystalline cellulose coated with, (b)carboxy methylcellulose and or ethylcellulose as the controlled release substances, and (c) the contents similar to granule like nucleus in (a). The weight ratio of (a):(b):(c) was 10:12:15. The tablets were prepared and dissolution rates were tested.

Chattaraj and Das [86] investigated the effects of formulation variables on the release profile of diclofenac sodium from ethylcellulose and hydroxypropyl methylcellulose matrix tablets. An increase in the viscosity of ethylcellulose in granulation led to a decrease in drug release from the tablets. An analysis of kinetics of drug release from hydrophobic ethylcellulose matrix showed Fickian diffusion regulated dissolution. Drug release from hydroxypropyl methylcellulose tablets followed an apparent zero-order kinetics.

Diclofenac sodium and diprophylline with solubilities of 3% and 30% respectively were mixed with Mowlol 40-88 (a soluble poly (vinyl alcohol)) and mannitol in different ratios, granulated with soluble poly vinyl pyrollidone (PVP) and compressed into tablets of different diameters by Colombo and researchers [87]. In-vitro studies indicated that there was a linear relationship between the release rate and area of tablets. Significant
differences were also noted in-vivo when the tablets with different diffusion areas were administered to humans.

**Xiaodong and Huinan** [88] manufactured controlled release tablets of diclofenac sodium. The release was in accordance with zero order kinetics with a release rate of 3 mg/h. The release rate was affected by pH of the medium, speed of rotation and was proportional to the weight gain of film coating.

**E-Sallam and researchers** [89] reported that the sustained release tablets of diclofenac sodium made by hydrogels have to be enteric coated to prevent the dramatic effect of stomach acidity.

**Tabata and others** [90] studied on the sustained release suppositories of diclofenac sodium containing Aerosil. The release rate markedly decreased in suppositories containing Aerosil R972. However, Aerosil Co K 84 and 200 did not affect the drug release rate.

**Iwamoto and others** [91] studied the sustained release characteristic and bioavailability of diclofenac sodium from suppositories containing carbopol 934 and 941. Carbopol 934 produced prolonged effect at 85% w/w while carbopol 941 produced a prolonged effect at 2% w/w.

**Vyas and co-workers** [92] developed prolonged and controlled release of diclofenac sodium using transdermal drug delivery system. To achieve the desired release rates, different combinations of hydrophilic & hydrophobic polymers were used for the preparation of pseudolatex system.
Akira and co-workers [93] studied the effect of nonionic surfactants on percutaneous absorption of diclofenac sodium from gel ointment. In-vitro permeation studies, using excised hairless mouse skin, showed that the amount of diclofenac sodium penetrated into dermis and the receptor phase increased with decreasing polyoxyethylene chain length in surfactant. Similarly as the alkyl chain length decreases, the amount of diclofenac sodium in the dermis and the receptor phase increased.

Ehab and others [94] utilized the principle of interaction of hydrophilic colloids with metallic ions to yield cross-linked insoluble salts in the preparation of diclofenac sodium beads. Beads were prepared from sodium alginate and sodium carboxy methylcellulose. Hard spherical beads of aluminium alginate and aluminum carboxy methylcellulose with a narrow particle size distribution, low friability, high yield and drug content of 70-80% were obtained. The type and concentration of the polymers as well as the pH of the dissolution medium affected the rate of drug release. The higher the polymer concentration, the slower was the rate of drug release. Diclofenac sodium was not released in 0.1 N HCl (pH 1.2) for 2 hr, but was released in pH 6.8 phosphate buffer solution from both the formulations and the commercial Voltaren Retard tablet. The 2 formulations of the beads resulted in a sustained release action of diclofenac sodium for 24 hr. The relative bioavailability of the 2 formulations were 59.01 and 47.96% respectively to that of the commercial tablet.

Pillai and co-workers [95] studied pharmacokinetics and relative bioavailability of commercially available diclofenac sodium tablets in healthy volunteers by employing a sensitive and selective capillary column/Electron Capture Detector assay.
Raz and others [96] studied comparative pharmacokinetic analysis of a novel sustained release dosage form of diclofenac sodium in healthy subjects. The results are compared with the standard formulation.

Saleh and co-workers [97] studied comparative dissolution profiles of five internationally available sustained release diclofenac sodium dosage forms using paddle and the flow through cell methods. The dissolution was found to be pH dependent and flow through cell method showed better dissolution profile than paddle technique.

Thakker and others [98] studied effect of food on relative bioavailability following single dose of diclofenac sodium capsules (150 mg hydrogel bead) in healthy humans. On post-prandial administration, decreased bioavailability was observed.

Sheu [99] studied parameters affecting the dissolution of diclofenac sodium from Voltaren SR and hydroxypropyl methylcellulose (HPMC) based matrix tablets, with addition of NaCl or KCl. Dissolution was inversely related to the rate at which the pH was changed.

Samant and Mehendre [100] performed the bioequivalence study in eight male human volunteers using four different diclofenac sodium enteric coated tablet formulations along with a standard enteric coated formulation marketed in India. All the formulations were containing 50 mg of diclofenac sodium and were evaluated with respect to plasma drug concentration at various time intervals up to 12 hours following administration of 100 mg dose. All the test formulations were compared with the standard formulation by statistical pooled t-test to prove their bioequivalence characteristics.
Inter product variation and inter subject variation were calculated by using analysis of variance.

**Leucuta and co-workers [101]** evaluated the relative bioavailability of diclofenac from enteric sugar coated tablets against a reference enteric film coated tablet. No statistical significant difference was observed for **Cmax**, **tmax**, **t1/2** and **Area Under Curve (AUC)**. The relative bioavailability of diclofenac was 87% against Voltaren.

**Cassidy et. al. [102]** studied the buccal delivery of diclofenac sodium (Voltaren), from a prototype hydrogel in man. After a 30 min delay, plasma levels of diclofenac sodium increased to near steady state levels of 100 ng/ml. The intravenous (iv.) infusion data was used to calculate mean steady state flux of diclofenac sodium (2.1 mg/cm-h) across human buccal mucosa and a lag time of one hour.

**Giungi et. al. [103]** tested a sustained release diclofenac sodium formulation in 25 patients with anti-inflammatory or degenerative osteoarthromuscular affections. Another group of 25 patients was treated with commercially available similar drug formulation. Both the formulations were given once a day for 60 days. The therapeutic activity was evaluated on the basis of intensity of pain, speed of onset of analgesic effect. Both the formulations had comparable bioavailability and tolerability.

Bioavailability of diclofenac sodium from standard and sustained release oral formulations was studied by **Culig and researchers [104]** in healthy volunteers. Blood samples were taken for 12 hours at interval of 30 minutes and analysed by High Performance Liquid Chromatography. Maximum plasma concentration were 2440 and 939 µg/ml in 1.25 and 2.13 hours for
standard and sustained release formulations respectively. Area under concentration time curve were almost the same.

In-vitro and in-vivo release of slow release diclofenac sodium formulations were studied by Moller and his colleagues [105]. Two slow release formulations (tablets and pellets) were compared with oral solutions in humans. Very good correlation between in-vivo and in-vitro results was not obtained.

Pharmacokinetic of diclofenac sodium (Feloran) in experimental animals and human was carried out by Drenska and workers [106]. The data were shown to correspond to a two compartmental model and t max was found to be two hours. The formulations were found to be bioequivalent with other commercial formulations.

Bioavailability and pharmacokinetic study of oral and intramuscular injectable formulation of diclofenac sodium were carried out by Kurowski and others [107]. Intramuscular injections (75 mg) or enteric coated tablets (150 mg) were administered. About 73% of oral dose was absorbed and peak plasma concentration of 2-9 µg/ml was observed after 3.1 hr. The parenteral product showed C max equal to 2.15 µg/ml after 20-30 min and t 1/2 of 1.15 hr. The bioavailability of the three intramuscular formulations was the same.

A study of bioavailability of diclofenac sodium was carried out by Kelly [108]. He found that granules containing diclofenac hydroxyethyl pyrrolidine were bioequivalent to diclofenac sodium enteric coated tablets in humans.
Hooper and co-workers [109] studied the bioequivalence of two 100 mg sustained release formulations of diclofenac sodium. The generic formulation (Xenid LP) showed low bioavailability as compared to standard formulation (Voltaren LP).

Mahmood [110] investigated the pharmacokinetic analysis of an oral sustained release preparation of diclofenac sodium using multisegment absorption models. In this type of model, the gastro intestinal tract is been divided into several segments. The effectiveness of this model has been proved for pharmacokinetic analysis of plasma drug concentration data with irregular or multiple peaks, and for sustained release preparations.

Zmeili and co-workers [111] studied the in-vitro characterization, bioavailability and pharmacokinetics of two different sustained release diclofenac sodium dosage forms i.e. Voltaren and Inflaben. The rate of dissolution of Inflaben was faster as compared to Voltaren, but bioavailability conducted on healthy male volunteers revealed a sustained release pattern for both the products.

Paloma and co-workers [112] reviewed the in-vitro dissolution tests performed by researchers. They established the best conditions to test diclofenac sodium microcapsules. Mathematical adjustments were made in order to establish the most appropriate in-vitro dissolution system.
2.2 REVIEW OF WORK DONE ON MICROSPHERES

2.2.1 Lipid Microspheres

Hernandez and Cerezo [113] used lipid microspheres as carriers to transport and deliver active principles. They are widely used in parenteral nutrition, as fatty emulsions more stable than liposomes, and manifest no adverse effects since they are biodegradable. Vitamin K3 and cyclosporin A were encapsulated in lipid microspheres. The microspheres had mean size of less than 1.20 μm and 90 % of drug encapsulation efficiency.

Domb and co-workers [114] discussed the preparation, physical properties and applications of lipospheres in parenteral delivery of local anesthetics, antibiotics, vaccines and anticancer drugs. They described lipospheres as a new fat based encapsulation system developed for parenteral and topical drug delivery and consists of water-dispersible solid microparticles of particle size 0.2-100 μm.

Mizushima [115] described lipid microspheres as excellent carriers for targeting delivery of drugs to the diseased lesions.

Ohmukai [116] developed a new type of lipid microsphere preparation of flurbiprofen. The lipo-preparation was utilized as drug carrier and was found to be preferentially delivered to lesion tissues, enabling enhancement of drug effects and reduction of adverse reactions.

Khopade and Jain [117] prepared lipospheres of diclofenac diethyl ammonium by microemulsion solidification technique. The study in rats showed improved anti-inflammatory efficacy.
Igarashi and co-workers [118] described lipids as superior carriers for use as a drug delivery system due to their high stability and safety. The drugs exhibited more potent pharmacological activity because of the targeting effect of the lipid microspheres.

Schwarz and co-workers [119] prepared solid lipid nanoparticles by high pressure homogenization of a melted lipid (Dynasan 112) dispersed in water at increased temperatures of 70°C. Soy lecithin and Poloxamer 188 were used as surfactants and stabilizers of the particles. The effect of homogenization parameters was studied and optimized to yield solid lipid nanoparticles for intravenous injection. Particles stabilized with soy lecithin could be sterilized by autoclaving.

Nitrofurantoin bearing microspheres of wax were prepared by Jain and co-workers [120] by wax emulsification and congealing technique. The effects of emulsifier concentration and stirring speed on the drug release and other physical parameters of microspheres were studied.

Thomsen and others [121] studied twelve meltable substances including stearic acid with respect to their ability to form prolonged release pellets in a melt pelletization process using a laboratory scale high shear mixer.

Benita and co-workers [122] prepared 5-fluorouracil carnauba wax microspheres using a meltable dispersion process with the aid of a surfactant. They noted that only hydrophilic surfactants were able to load the 5-fluorouracil. The drug release was governed by a dissolution process.
Dharmadhikari and Joshi [123] microencapsulated salbutamol sulphate for obtaining sustained action. The microcapsules were evaluated for their drug content and in-vitro release. They carried out evaluation of micromeritic properties and stability studies.

2.2.2 Sodium Alginate Preparations

Al-shamkhani and co-workers [124] studied the biological properties of alginates. They were found to be haemocompatible and did not accumulate in any of the major organs.

Masakatsu and co-workers [125] studied the gelling process of alginate. They found that a rapid dehydration occurred initially (1-2 h) and a slow dehydration continued for 3-4 days.

Hodson et al. [126] reported that the structure of surface hydrated alginate gel layer formed in simulated gastric fluid was different from that formed in the simulated intestinal fluid.

Drug encapsulation in calcium alginate microspheres was studied by Wan and co-workers [127]. The efficiency of drug encapsulation was found to increase with drug:polymer ratio.

Lee and co-workers [128] prepared microcapsules composed of alginate and chitosan that released minocycline-HCl for 7 days. The microcapsules proved to be an effective therapeutic modality for the treatment of periodontitis.
The release characteristics of protein from chitosan-alginate microcapsules prepared using an electrostatic droplet generator was evaluated by Okhamafe et. al. [129]. The microcapsule showed unsatisfactory release properties losing 94% of the encapsulated proteins over 24 h period at pH 1.2. Incorporation of a pH sensitive, hydroxypropyl methylcellulose acetate succinate by coating the capsule membrane as well as by blending in emulsion produced significant changes in release profiles.

Cui and co-workers [130] prepared alginate coated microspheres of acebutalol HCl. The drug release was controlled by the amount of powder coating and amount of plasticizer.

Kende and co-workers [131] reported that alginate or chitosan used as hydrogels in vaccine delivery system offers several advantages. These carriers do not require organic solvents for incorporating the vaccines, moreover all the amount of the vaccine added to the hydrogel was loaded into the carrier, which is very useful when the water solubility of vaccine is limited.

Harms and co-workers [132] formulated a toothpaste comprising of zinc stabilized alginate microspheres having a particle size in range of 0.1 to 4 mm.

Suckow and co-workers [133] prepared an oral delivery of alginate microspheres for antigens to vaccinate rabbits against a pathogen Pasteurella multocida.
Chui and co-workers [134] encapsulated glutaraldehyde cross-linked trypsin in a calcium alginate matrix. This microencapsulated controlled release enzyme can be used in enzyme replacement therapy and organic synthesis.

Gohel and co-workers [135] prepared theophylline microspheres of sodium alginate. The process was optimized using computer optimization technique. The microspheres were evaluated for in-vivo studies and a good in-vitro in-vivo correlation was observed.

Bowersock and co-workers [136] used hydrogel microspheres to deliver various vaccines to several animal species by oral administration. Oral delivery of vaccines using alginate microspheres elicited the production of secretory IgA at the mucosal surfaces in mice, rabbits and cattle. Alginate microspheres are effective for the oral administration of vaccine.

2.2.3 Ethyl Cellulose Formulations

Amperiadou and Georgarakis [137] prepared ethylcellulose microcapsules containing theophylline by emulsification of an organic ethylcellulose solution in a oil phase containing a surfactant. Good reproducibility in microcapsule preparation was observed. The microcapsules were uniform in size and possessed free flowing characteristics. The type of agitator (propeller and magnetic) and the drug to polymer ratio exhibited significant influence on the in-vitro dissolution and release of theophylline from microcapsules.

Ethylcellulose embedded prolonged release microparticles containing cimetidine were designed by Chattaraj and Das [138]. Significant reproducibility of the manufacturing process was observed. In-vitro and in-
vivo correlation revealed that the dissolution process is the rate determining step in drug absorption.

A micropellet dosage form was developed using ethylcellulose as a polymer by Chandrashekhare and Gupta [139]. The drug to polymer ratio and stirring speed affected the size distribution of the micropellets. These parameters also affected the in-vitro drug release for obtaining a controlled release oral drug delivery system for theophylline.

Nikolayev and Gebre-Mariam [140] prepared ethylcellulose walled aspirin microcapsules. Drug availabilities from the dosage form were compared with conventional dosage form. Studies in rabbits showed that plasma concentration of the drug was sustained for about 8-10 hours and pharmacokinetics is described by a one compartmental open model. A strong correlation was established between in-vitro and in-vivo tests.

Arabi and co-workers [141] reported that the microencapsulation of drugs is gaining importance in many research activities. A common technique for preparing microcapsules is the solvent evaporation technique which is simple but has a large number of control parameters. The effect of concentration of poly(vinyl alcohol) as a surfactant, molecular weight of ethylcellulose and stirring speed were studied. The effect of molecular weight of ethylcellulose and particle size on drug release were investigated. It has been found that the drug release is decreased with increasing molecular weight of polymer and increasing particle size.

Poj and Puriwat [142] used aqueous ethylcellulose dispersion to prepare sustained release matrixes by spray drying technique. The microspheres were directly compressed. Continuous and uniform drug release patterns
could be obtained. Proper hydrophilic agent might be selected as channeling agent to modify the release characteristics of the matrix product.

El-Helwa and co-workers [143] employed multiple emulsification technique to prepare microspheres of metronidazole using a mixture of ethylcellulose and methyl cellulose. The particle size analysis was influenced by stirring speed and emulsifier concentration. About 80-90% of drug was released within 6 to 8 h.

Nagarajan and co-workers [144] microencapsulated salbutamol sulphate with ethyl cellulose using emulsion solvent evaporation method. Microcapsules were spherical, discrete and free flowing and exhibited slow, sustained and complete release over a 12 h period. The drug release was dependent on core to coat ratio and size of the microcapsules.

Biswanath and co-workers [145] studied the release of sodium benzoate, salbutamol sulfate and caffeine from ethylcellulose microparticles prepared by emulsification solvent evaporation technique. The release followed diffusion process in accordance with the Higuchi equation.

Zhirong and coworkers [146] used an orthogonal test to optimize the preparation conditions and technique for mitoxantrone loaded ethylcellulose microspheres for arterial embolism. The microspheres were regular in morphology with a mean diameter of 110.24 μm. The drug loading was 12.5% and embedding ratio was 55.6%. The release characteristics were in accordance with the single exponential model.

Dashevsky and Zessin [147] prepared microspheres of theophylline by solvent evaporation technique using ethylcellulose of both high and low
molecular weight and also mixtures as a coating material. No permeability through intact isolated polymer films was found. In-vitro dissolution studies exhibited Higuchi model. The size distribution of the microspheres was dependent on the ratio of ethylcellulose with high and low molecular weight.

Zinutti and others [148] worked on the preparation and characterization of ethyl cellulose microspheres containing 5-flurouracil by solvent evaporation technique. In-vitro release was found to be dependent on the drug to polymer ratio.

Puglisi and others [149] prepared tolmetin microspheres by the coacervation process using ethylcellulose. The microspheres were obtained both in presence and absence of protective colloids, such as polyisobutylene (PIB) or ethyl-vinyl acetate copolymers (EVA). The effect of these agents on the preparation, drug content, wall thickness, surface morphology and drug dissolution were evaluated.

Das [150] entrapped theophylline in ethylcellulose microspheres by w/o/w emulsification- solvent evaporation technique. Aqueous solution of the drug was emulsified into a solution of ethylcellulose in toluene containing polyisobutylene as a protective colloid. The primary emulsion was further emulsified into an external aqueous phase to form a w/o/w emulsion. Microspheres were formed after solvent evaporation and precipitation of ethylcellulose. In-vitro dissolution profile and effect of polyisobutylene on the release rate were studied.

Palomo and others [151] investigated the effect of solvent on ethylcellulose microcapsules. Four different solvents ethyl alcohol (an aqueous solvent) acetone, chloroform and toluene (organic solvents) were selected. Diclofenac
sodium was used as an encapsulated substance as it is inactivated in the gastric juices. The polymer and microencapsulation process were selected after an exhaustive study with different polymers and processes. Ethyl phthalate was incorporated in the process to study the influence of the plasticizer on the drug release rate.

*Maysinger and Jalsenjak [152]* studied the in-vitro release and in-situ (rat gut) absorption of free and ethylcellulose microencapsulated cimetidine. The t50 value in-vitro for encapsulated cimetidine was four times greater than the t50 of the free drug. They proposed a physical model to calculate the theoretical value of t50 when microcapsules were used in situ.

*Uchida and co-workers [153]* prepared microcapsules from hydroxypropyl methylcellulose acetate succinate (AS-HG) and ethylcellulose mixture for cefuroxim and theophylline. The microcapsules were prepared by solvent evaporation using liquid paraffin and sorbitan tristearate. The product was evaluated for sustained drug release. The in-vivo of the microcapsules was performed in beagle dogs.

*Manekar and co-workers [154]* microencapsulated nifedipine to avoid photodegradation and to obtain sustained action. The coacervation was achieved by thermal change method using ethylcellulose respectively as a coating material. Microcapsules were evaluated for drug content and in-vitro release pattern.

*Chowdary and Annapurna [155]* prepared microcapsules of aspirin, metronidazole, paracetamol and tolbutamide using ethylcellulose. The microcapsules were studied for encapsulation efficiency, drug release and permeability characteristics. Microencapsulation efficiency was found to be
greater with poorly water soluble drugs. Significant differences were observed in drug release and permeability of various microcapsules. Permeability depended on the method of coacervation employed. Good correlation was observed between solubility of core and release rate.

Chowdary and Rao [156] reported a method based on emulsification of ethylcellulose solution containing sulphanethoxazole in an immiscible liquid medium. Spherical microcapsules were obtained by the addition of a nonsolvent. Sulphanethoxazole release was spread over a period of 5-6 hours. Linear relationship was observed between percentage coat material and $t_{50}$ values.

Chowdary and Rao [157] microencapsulated aspirin with ethylcellulose by a method based on emulsification of the polymer solution containing the drug in an immiscible phase followed by coacervation by the addition of a non solvent. Release of aspirin was spread over 5 h and it depended on, both the percentage of coat material and size of microencapsulation.

Sevgi and co-workers [158] prepared microcapsules of phenylpropanolamine HCl with different core to wall ratios by coacervation phase separation method using ethylcellulose as a coating material. The effects of drug, particle size, the medium pH and core to wall ratio on the dissolution kinetics were studied and evaluated kinetically.

Nixon and Agyilirah [159] tableted microcapsules containing sodium phenobarbital and ethylcellulose. The thickness of the tablets, the break strength and dissolution characteristics were studied and found to be affected by core to wall ratio and size of microcapsule aggregates.
Microcapsules of phenobarbitone with a wall of ethylcellulose have been prepared by Jalsenjak and co-workers [160]. They determined the size distribution and release pattern which had similar characteristics to the release of a drug from an insoluble porous matrix.

Alpar and Walters [161] prepared microcapsules of phenethicillin potassium as model water soluble drug using ethylcellulose as a polymer. The taste was masked, the odour almost eliminated and the release retarded. There was a linear relationship between amount of ethylcellulose and time for 60% release of drug and release pattern was analogous to that from insoluble porous matrices.

Ethylcellulose microspheres containing 5-flurouracil were prepared by Zinutti and co-workers [162] by a oil in oil evaporation/ extraction method. Three drug to polymer ratios of 1:1, 1:2 and 1:3 were used. In-vitro release studies showed that the release was dependent on the drug to polymer ratio and nature of casting solvent. The drug release rate was faster with ethanol than with acetone and could last for 7 days.

2.2.4 Poly(vinyl alcohol) dosage forms

Ficek and co-workers [163] prepared poly(vinyl alcohol) microparticles by a novel freezing-thawing process in the absence of a cross-linking agent. The important parameters affecting the process have been identified.

Kimura and others [164] prepared poly (vinyl alcohol) gel spheres and examined the gastrointestinal transit time in rats following the oral administration by monitoring unabsorbable phenol red contained in the dosage form. While more than 90% of the aqueous solution was transferred
to the large intestine 6 h after administration, about 40% of the poly (vinyl alcohol) gel spheres still remained in ileum. The prolonged plasma concentration time profile of cephalixin was observed and the spheres were found to be useful in controlling the gastrointestinal transit time.

Poly (vinyl alcohol) gel spheres were prepared by Kurosaki and others [165] to prolong contact time of drugs with the gastrointestinal wall. Cephalexin and insulin used as model drugs and improved absorption was noticed.

Gander and co-workers [166] incorporated propoxyphylline and theophylline into three types of cross-linked poly (vinyl alcohol). The firm hydrogels were dried and reduced to the size of 400-630 mm. The drug release from the cross-linked hydrogels was controllable for more than 12 h.

Controlled release dosage forms were prepared by Beltrami et. al. [167] from poly (vinyl alcohol) cross-linked with glutaraldehyde. The effects of inactivation of glutaraldehyde with sodium pyrosulfite to prevent further cross-linking and possible reaction of the glutaraldehyde with added drugs was studied. The loading of proxyphylline was quadrupled by inactivation of the crosslinker and the interaction of glutaraldehyde with phenylpropanolamine was avoided.

Controlled release of drugs like aspirin, griseofulvin and nicotinic acid from cross linked poly (vinyl alcohol) microspheres was studied by Thanoo and co-workers [168]. They used glutaraldehyde for cross-linking the poly (vinyl alcohol) and benzoyl chloride as the catalyst.
Kim and others [169] developed a method for preparing composite poly (vinyl alcohol) beads with a double layer. Acetaminophen and proxyphylline were used as model drugs. Drug diffusion coefficient in the lightly cross-linked poly (vinyl alcohol) core appeared to be at least 10 times larger than that in the highly cross-linked outer shell. At lower cross-linking ratios, the diffusional time lag appeared to be absent and the diffusion profiles were apparently first order in nature.

Bozzay and Torok [170] mixed pharmaceuticals with partially hydrolysed poly (vinyl alcohol), which was cross-linked in situ with glutaraldehyde to give controlled release tablets. In-vitro experiments indicated slow release of the active ingredients.

Minimatrices of poly (vinyl alcohol) and diprophylline were prepared by compression by Colombo and co-workers [171]. The surface was cross-linked by soaking them in an acidic formalin solution and subsequently exposure of the dried matrices to UV light or to heat in an oven. In-vitro studies showed that by optimizing the cross-linking conditions zero order release could be obtained.