CHAPTER-II

Literature Review
2.1 Past work done using *Saccharomyces Cerevisiae*

*Bishop et al.,* (1998) have developed a method for encapsulation of essential oils into baker’s yeast(*Saccharomyces cerevisiae*). They recovered the essential oils from the cells using water/ethanol extraction procedure and analysed by gas chromatography and rate of permeation of oil into yeast cells was found to increase significantly at higher temperature due to phase transition of lipid membrane.

*Branko et al,* (2007) have developed a rheological mechanism to elucidate the mechanism of Calcium alginate microbead deformation in the course of cell growth within. The volumetric deformation of beads with yeast cells as a function of time and cell concentration per bead. In this case the elastic forces are dominant, indicating different mechanisms of relaxation without the influence of the cells.

*Soo Hwan Cheong et al.,* (1993) have investigated *Saccharomyces cerevisiae* in calcium alginate membrane and cultured swellings of the capsules were prevented. The influx of carbon dioxide through the capsule membrane increased approximately twice by adding non ionic surfactant to the calcium chloride solution.

*Zhi-jie Sun et al.,* (2007) have studied the physiology and stress tolerance of *Saccharomyces Cerevisiae* using alginate-chitosan microcapsules with liquid core and solid core. The suspended cells showed a two fold increase in intracellular glycerol content, trehalose content and superoxide dismutase activity. This was studied for osmotic stress, oxidative stress, ethanol stress and heat shock stress and significant tolerance was reported.

*Khan et al.,* (2000) have prepared semi permeable polyamide microcapsules by interfacial polymerization by cross linking polymers and used for encapsulating baker’s yeast. The size and distribution of cells were investigated by a combination of laser confocal, electron scanning and transmission electron microscopy.
Weiwang et al., (2006) have studied microencapsulation as a simple and cost effective way to enclose bio-active materials, such as drugs and cells and releasing the enclosed substances in a controlled form.

Tetusa Ozeki et al., (2003) have studied the application of acid treated yeast cell wall as binder functioning as a disentegrant, acetyl salicylic acid was granulated using various polymers and the ungranulated and the granulated products were compared.

Takeo Imai et al., (1995) have studied the intracellular pH of yeast and was determined using fluorescense microscopic image processing technique, the results indicated that the yeast proton pump was activated during growth from the point of view of pH in vivo.

Petr Cimprich et al., (1995) examined a layer of suspension of yeast cells which was made using pH sensitive fluorescent dyes and checked on the distribution curves with various phases of growth of the cells which did not change significantly.

Guorong Shiet et al., (2007) have encapsulated the water soluble antioxidant, chlorogenic acid in a lowest high volume yeast cells for the first time and characterised by FT-IR Spectra and fluorescence micrographs of yeast cells and the storage stability was investigated.

Marko Mancini et al., (2000) have assessed yeast suspensions by using rheometric instruments to check on the Newtonian properties and the effect of temperature versus viscosity was also studied.

Spilimberg sara et al., (2007) have investigated the yeast survival in apple juice using Nitrous oxide.

Raman Saraswathi et al, (2006) have assessed the yeast cells which were used to microencapsulate terbutaline sulphate and formulated dry powder inhalation to
target inflamed bronchial epithelial cells. The freeze dried samples were evaluated for parameters such as: yield, entrapment efficiency and bifocal microscopy. Among the 12 samples, the 6th sample constituted with 0.2 gm of drug maintained at 35°C showed higher encapsulation yield. The release of the drug from the microcapsules showed first order kinetics sustained action. The dry powder mixture of the encapsulated yeast with spray dried lactose was prepared and powder characteristics studied.

*Otero et al.,* (2002) have studied the kinetics of thermal denaturation of yeast protein in intact cells of *Saccharomyces Cerevisiae.*

2.2 Past work done using guar gum

*Chourasia et al.,* (2004) have studied a formulation consisting of cross linked microspheres of guar gum for colon targeted delivery of metronidazole and studied the various parameters in simulated gastric fluid and colonic fluid using rat cecal contents.

*Mohini Chaurasia et al.,*(2006) have made guar gum microspheres containing methotrexate and characterised for local release of the drug in the colon, simulated gastric fluid was used and *in vitro* and *in vivo* studies were done.

*A.Dharamsi et al.,* (2004) have investigated the release kinetics of theophylline agar-guar gum micro beads. The results indicated the surface adhering drug was found to release immediately and a constant release was obtained upto 5 hours from all the batches. The added guar gum improved the gel strength of agar and the release rate was controlled significantly.

*Chowdary et al.,* (2006) have studied olibanum resin as a microencapsulating agent for controlled drug delivery. Resin coated microcapsules of nifedipine were prepared by emulsification solvent evaporation method. Microencapsulation
efficiency was in the range of 98-105%. Drug release was by non fickian diffusion mechanism.

Krishnaiah et al., (2005) have formulated and studied guar gum matrix tablets for oral controlled release of water soluble diltiazem hydrochloride based on the results of the \textit{in vitro} and \textit{in vivo} studies it was concluded that the guar gum matrix tablets provided oral controlled release of water soluble diltiazem hydrochloride.

Reddy et al., (2006) have formulated blend microspheres of chitosan and guar gum by water in oil emulsification method and cefadroxil was loaded and crosslinked with glutaraldehyde. The microspheres were characterised using SEM, X-ray diffraction, and Differential Scanning Calorimetry. The \textit{in vitro} release was performed at pH 3.4 buffer medium indicated sustained and controlled release of cefadroxil from semi-IPN microspheres up to 10 hours.

Soppimath et al., (2002) have investigated the water transport and drug release study from crosslinked polyacrylamide grafted guar gum hydrogel microspheres for controlled release and was prepared by water in oil emulsification method and the microspheres were loaded with verapamil hydrochloride and nifedipine were studied for controlled releases.

Qu F et al., (2006) have investigated on modified guar gum microspheres as protein drug carrier, bovine serum albumin was loaded with various concentrations and studied for their controlled release.

Patra et al., (2004) have investigated controlled release formulation of propranolol hydrochloride using guar gum as carrier and also studied the influence of cellulose ethers like sodium carboxy methyl cellulose, hydroxyl propyl methyl cellulose and ethyl cellulose on the \textit{in vitro} release of propranolol hydrochloride from
guar gum matrix tablets. The *in vitro* dissolution kinetics followed a first order release via Fickian diffusion controlled mechanism.

*Jaleh Varshosaz et al.,* (2006) have formulated matrix tablets with Tramadol hydrochloride using xanthan and guar gum and compared with hydrophilic matrices like HPMC and CMC with respect to *in vitro* drug release.

*Reddy et al.,* (2002) have formulated ionic crosslinked sodium carboxy methyl guar gum for encapsulating proteins and investigated the release of the protein with that of the metal ion in simulated gastric fluid.

*Krishnaiah et al.,* (2002) have examined administration of 5-fluorouracil as tablet for colon cancer using guar gum and the study was done and estimated by HPLC method, the results showed that tablets with 80% of guar gum was most likely in targeting 5-fluorouracil in the colon.

*Thomas Durig et al.,* (2002) have investigated the matrix tablets of verapamil hydrochloride with guar gum and studied the effect of ionic and non-ionic excipients and additives as modulators of swelling and erosion kinetics of verapamil hydrochloride tablets. The release followed the fickian diffusion method.

*Krishnaiah et al.,* (1998) have used guar gum and indomethacin and formulated as tablets and evaluated by *in vitro* and *in vivo* methods. The study indicated that guar gum is a potential carrier for drug targeting to colon.

*Rama Prasad et al.,* (1998) have studied the colon specific drug delivery by *invitro* methods using guar gum and indomethacin and demonstrated the susceptibility of guar gum to the colonic bacterial enzyme and subsequently the drug release.

*Krishnaiah et al.,* (2001) have studied the colon targeted drug delivery of mebendazole using guar gum formulated as a tablet and was done for various parameters and dissolution study was done.
Krishnaiah et al., (2004) have developed matrix tablets of metoprolol tartarate with guar gum and made in the form of three layer matrix tablets and studied various parameters like hardness, thickness, drug content uniformity and *invitro* drug release studies, the results indicated that the three layer matrix tablets exhibited a controlled release.

Krishnaiah et al., (2002) studied the pharmacokinetic evaluation of guar gum based matrix tablets with metoprolol tartarate. An *invivo* study was done and the two way cross over design was followed and was compared with the immediate release tablets.

Sinha et al., (2001) have studied the influence of natural polysaccharides for colon specific drug delivery as the colon is inhabited by a large number of variety of bacteria which secretes many enzymes.

Aminabhavi et al., (2004) have formulated three different ratios of guar gum to acryl amide and incorporated diltiazem hydrochloride and carried out release in simulated gastric and intestinal conditions. The drug release was found to be diffusion controlled. The nature of the drug transport through the polymer matrices was studied by comparing with Higuchi and Hixon Crowell equation.

Judith Feitosa et al., (2007) have obtained the commercial guar gum and purified by four different methods and characterized by gel permeation chromatography. They worked on various parameters and concluded that guar gum has a variety of biological applications.

Nicholas Peppas et al., (2009) have studied the mucoadhesive device process and biomaterials for mucoadhesion which can protect the drug from absorption process in addition to protecting it on the route to the site of delivery.
Andrew and Metters, (2006) have studied the advances of hydrogel technologies and facilitated the hydrogel network design by identifying the key parameters and molecule release mechanism.

Paolo Colombo, (1993) wrote a review on hydrogel matrices or swelling controlled delivery systems for drug delivery for oral use. The release mechanism, modelling and mathematical analysis of release data are described by him.

### 2.3 Past work done using egg albumin

Susana Torrado et al, (1996) have studied the drug release from the micro aggregates of egg albumin and was confirmed by jetting the dissolution data to the equation of Peppas and showed a zero order release kinetics.

Torrado Santiago et al., (2001) have developed albumin micro aggregated oral formulation for controlled release. Acetaminophen was taken as the drug and albumin microaggregates were formulated into matrix tablets. Dissolution and bioavailability studies were done and the extent of drug absorption was compared for all the formulations.

Masumi Koishi et al., (2006) have studied phenacetin microcapsules with egg albumin for the size and size distribution and percentage of fine particles were determined.

Kim et al., (2001) have formulated and evaluated chitosan microspheres containing indomethacin made by coacervation phase method. As the pH of the encapsulation media was increased, the incorporation efficiency, particle size and flowability decreased, along with increase of drug release rate.

Mathew et al., (2007) have prepared Ketorolactromethamine loaded albumin microspheres by emulsion cross linking method and studied the drug entrapment, particle size and release characteristics.
Sudha Rathod et al., (2008) have used thermal denaturation process to prepare pilocarpine loaded egg albumin microspheres, entrapment efficiency, in vitro release studies showed spherical matrix mechanism.

Gayatri Devi et al., (1992) have formulated egg albumin microspheres using diclofenac sodium and evaluated for entrapment efficiency, particle size, diffusion and dissolution pattern.

Katti, (1999) has prepared albumin microspheres using chlortohiazide by suspension cross linking method and was evaluated for particle size and surface morphology by scanning electron microscopy.

Rajesh Dubey et al., (2003) have formulated albumin microspheres and found that both heating temperature and heating time effects the albumin microspheres and has a significant effect on the drug entrapment efficiency.

Gupta et al., (1989) have studied physio-Chemical characteristic of albumin microspheres.

Torrado et. al., (1999) have evaluated the in vivo characteristic of egg albumin microspheres containing paracetamol and the organoleptic characteristics could be improved using egg albumin.

Gennadios et al., (2006) have determined the concentration of sulfhydryl groups using aqueous egg white solution with polyethylene glycol.

Vural et. al., (1990) have formulated albumin microspheres with cyclophosphamidade and the particle size and the entrapped drug was determined.

Mahdy et al., (1998) have used Chemical and thermal hardening process to prepare mono-dispersed albumin microspheres and it was found to be dependent on albumin and emulsifier concentration.
Murthy et al., (2005) have investigated celecoxib loaded albumin microspheres and distribution of technetium$^{99m}$ labelled celecoxib as well as its microspheres for intravenous administration. The *invitro* release studies indicated sustained release for 6 days and radioactivity was measured in different organs and showed significant amount of radioactivity in the liver, spleen, and lungs.

Henry et al., (2006) have prepared bovine serum albumin and used as a matrix and vancomycin loaded microspheres were more effective in killing staphylococcus aureus.

Naveen et al., (2008) have prepared four formulations of bromophenol blue loaded albumin microspheres and the surface characteristics were studied.

Green et al., (2004) have prepared microcapsules of primaquine diphosphate with albumin and heated with vegetable oil and performed the pharmacokinetic evaluation.

### 2.4 Past work done using ethyl cellulose

Morkhade Dinesh et al., (2007) have prepared ethyl cellulose microcapsules containing diclofenac sodium. Increase in drug concentration showed increase in porosity and decrease in particle size and wall thickness of microcapsules and thus showed a faster drug release. The temperature and stirring speed of the external phase and the pressure affected the properties of the microcapsules.

Chowdary et al., (2004) have formulated and evaluated ethyl cellulose microspheres of glipizide using solvent evaporation technique and the release was slow and diffusion controlled and dependent on the core: coat ratio.

Das et al., (2007) have used double emulsion solvent diffusion method to microencapsulate zidovudine using ethyl cellulose, the effect of polymer-drug ratio,
surfactant concentration of the secondary emulsification process, the volume of the processing medium and the stirring speed was evaluated.

Ajaykumar patil et al. (2001) have formulated diclofenac sodium microcapsules using pectin complex and the coating agent was ethyl cellulose and this was evaluated for controlled release of the drug which was obtained due to complexation and microencapsulation.

Handa et al., (2000) have formulated pellets of isosorbide-5-mononitrate and carbamazepine by suspension and powder layering techniques using ethyl cellulose as a coating agent and in vitro release and stability studies were done and were found to be stable under different conditions of storage.

Pratim.Choudhury et al., (2009) have formulated metformin hydrochloride using ethyl cellulose and evaluated the release characteristic invitro and invivo and the results were treated statistically to validate the findings.

Das et al., (2007) have formulated and evaluated zidovudine-ethyl cellulose microcapsules using water-in-oil-in-oil double emulsion solvent diffusion method. Evaluation was done for entrapment efficiency, volume of the processing medium, surfactant ratio and the correlation was observed using Higuchi model.

Rama et al., (2005) have formulated and evaluated controlled release preparations of zidovudine using ethyl cellulose and w/o/w double emulsion solvent diffusion method was used and evaluation was done for entrapment efficiency and characterised using IR spectra, SEM and DSC. The data obtained from in vitro studies was fitted in various kinetic models and high correlation was obtained in the Higuchi model.

Mastiholimath et al., (2008) have formulated ranitidine microparticles using ethyl cellulose for gastroretentive delivery and was made by solvent evaporation
technique and it showed excellent buoyancy and was characterised using various parameters.

Cheu et al., (2001) have prepared sustained release microcapsules of acyclovir using ethyl cellulose and studied the encapsulation efficiency and dissolution characteristics. The sustained release characteristic was more prominent in simulated intestinal fluid than simulated gastric fluid. The decomposition of acyclovir significantly decreased when stored at 37 and 50°C.

Homar Mina et al., (2007) have prepared microcapsules of celecoxib using various polymers and cellulose derivatives and invitro and invivo characteristics were investigated.

Yi-Hung Tsai et al., (2003) have prepared potassium chloride microcapsules using ethyl cellulose and studied the encapsulation efficiency and sustained release characteristics.

Martinac et al., (2005) have prepared spray dried chitosan microspheres using ethyl cellulose having various weight ratios and used loratidine for nasal delivery. The microcapsules were evaluated with respect to particle size, entrapment efficiency, physical state of the drug, swelling properties and in vitro drug release profile.

Nean et al., (2003) have investigated the effect of water on ethyl cellulose and evaluated the effect of particle size and the moisture absorption profiles were analyzed.

Chen et al., (2005) have used emulsification and solvent evaporation technique to prepare biodegradable poly(lactide-co-glycolide)microspheres loaded with ganciclovir and the burst characteristics and other parameters were studied using gel permeation chromatography, SEM, DSC and Ultra violet spectroscopy was used to study the hydrolytic degradation.
Graves et al., (2005) have studied the release of insulin from ethyl cellulose microcapsules using cyclodextrins and mathematical models were proposed.

Sajeev et al., (2003) have prepared microcapsules of diclofenac sodium using various concentrations of ethyl cellulose and these microcapsules were compressed to tablets to obtain controlled oral release formulations. The formulations were evaluated for appearance, drug content uniformity, hardness, thickness, weight variation and friability, reproducible release kinetics of all the batches could be produced.

Carmen Remunan Lopez et al., (1998) have prepared buccal bilayered device having nifedipine and propanolol hydrochloride and cross linking polymers with a backing membrane made of ethyl cellulose. The crosslinked chitosan containing devices absorbed large quantities of water and gelled and eroded allowing drug release.

Sengel Ceyda et al., (2006) have prepared diltiazem HCl loaded ethyl cellulose microspheres by solvent evaporation technique and evaluated for particle size, encapsulation efficiency, surface morphology and their release characteristics.

Lavasanifar et al., (1997) have used the coacervation phase technique of microencapsulation to coat theophylline with ethyl cellulose, the in vitro release studies were done and the kinetic studies suggests that the prepared microcapsules and followed Higuchi’s model for drug release.

Yamaguchi et al., (1997) have microencapsulated renin inhibitor by phase separation of ethyl cellulose in cyclohexane to obtain a sustained release of the drug for once in a day application. The release was found to be pH dependent.

Choong-Kook Kim et al., (1991) have prepared ethyl cellulose microcapsules of Isoprinosine, an antiviral agent with a bitter taste and the drug release from microcapsules was influenced by the ratio of the core to wall, the viscosity grade of
ethyl cellulose and the overall microcapsule size and the release characteristics were checked with respect to the first order and diffusion controlled process.

*Nimmnnit et al.*, (1996) have prepared microcapsules of cephalexin using ethyl cellulose and Eudragit RL and RS and was done by coacervation phase technique and the release characteristics were studied.

*Arabi et al.*, (1996) have prepared microcapsules of allopurinol using ethyl cellulose by solvent evaporation method, the effect of molecular weight of ethyl cellulose and stirrer speed was studied and it was concluded that by increasing the molecular weight and particle size the rate of release of the drug decreased considerably.

*Zhi-yan Zhang et al.*, (2000) have prepared tramadol hydrochloride microcapsules by resin complex using spray drying method and with various viscosities of ethyl cellulose and the release rate was evaluated with respect to the viscosities of the polymer.

*Cortesi Rita et al.*, (2007) have prepared Eudragit micro particles loaded with acyclovir for ophthalmic administration. The microparticle morphology was characterised by optical and electron microscopy. The release kinetics of the drug from the microspheres was determined by a dialysis method.

*Ranendra Narayan Saha et al.*, (2007) have prepared oral controlled release tablets of Lamivudine with hydroxylpropyl methylcellulose as a retardant polymer and studied the various formulation factors such as polymer proportion, polymer viscosity and compression force on the *in vitro* release of the drug, no incompatibility was observed between the drug and excipients used in the formulation of matrix tablets.
Murthy et al., (2006) have prepared micro emulsion drug delivery system of acyclovir for improved oral bioavailability and was evaluated for surface tension, viscosity, pH, refractive index, diffusion and bioavailability. The in vitro intraduodenal diffusion and in vivo study revealed increase of bioavailability (12.78 times) after oral administration of the micro emulsion formulation as compared with the commercially available tablets.

Jain et al., (2006) have prepared extended release matrix tablets of zidovudine using hydrophilic Eudragit and with hydrophobic ethyl cellulose. In vitro and In vivo drug release was done. Eudragit could sustain the drug release for only 6 hours but when combined with ethyl cellulose it could sustain the drug release upto 12 hours. Fitting the drug release data to Korsermeyer equation indicated that the diffusion along with erosion could be the mechanism of drug release.

Jain et al., (2005) have formulated and evaluated multivesicular liposomal depot delivery system for controlled systemic delivery of acyclovir sodium and showed a very high drug loading and controlled release of acyclovir for an extended period of time.

2.5 Previous methods used for microencapsulation

Das et al., (2007) have used double emulsion solvent diffusion method to microencapsulate zidovudine using ethyl cellulose, the effect of polymer - drug ratio, surfactant concentration of the secondary emulsification process, the volume of the processing medium and the stirring speed was evaluated.

Stulzer Hellen et al., (2008) have prepared acyclovir in cross linked chitosan microspheres by spray drying technique and quantified the acyclovir and validated using HPLC method, the linearity presented a perfect correlation coefficient.
Obeidat Wasfy et al., (2007) have used the emulsion solvent evaporation method to find the effect of the dispersion of Eudragit S100 powder on the properties of cellulose acetate butyrate microspheres containing theophylline. Microencapsulation of different polymer solution concentration of different viscosities were prepared, evaluated and compared to microspheres of a constant concentration of the drug containing different amounts of Eudragit S100 Powder as filler. The release study in the acidic and alkaline media was studied.

Tony Whateley et al., (1997) have prepared stable water in oil in water multiple emulsion of Pluronic F 127: PAA complexes of theophylline and insulin and studied the release rates and this was dependent on the droplet size of the emulsion which in turn was dependent on the particle size of the complex.

Tedajo et al., (2001) have formulated pH compartmented water in oil in water multiple emulsion to do a diffusion study and investigated the release mechanism, pH and conductivity showed that the acidic species transport takes between the two aqueous compartments. The release mechanism responsible for transport across the oil phase was investigated and breakdown of oil globules facilitated transport by surfactant micelles across the oil phase or by fickian diffusion.

Biswanath Sa et al., (2006) have used oil in water emulsion solvent evaporation method to prepare polystyrene-coated diltiazem-resin complex and did the in vitro evaluation. The effect of various formulation parameters on the characteristics of microcapsules was studied. Mean diameter and encapsulation efficiency of the microcapsules increased with an increase in the concentration of the emulsion stabilizer and the core/coat ratio. Kinetic studies revealed the desorption of drug from the resinate obeyed the typical particle diffusion process, whereas the drug
release from the microencapsulated resinate followed the diffusion-controlled model in accordance with the Higuchi equation.

_Ciombor Deborah et al.,_ (2006) have used modified water in oil in oil emulsion solvent removal method to encapsulate protein using polylactic-co-glycolic-acid. Various factors were studied, including composition of the suspension medium and the relative amounts of aqueous phase containing protein to polymer solution. High yields of microsphere fabrication were achieved using silicon oil containing methylene chloride as a suspension medium instead of pure silicon oil with a minimum loss of polymer and the protein encapsulation was found to be 98%.