2. LITERATURE REVIEW

- **A. Amjad et al (2009)**, prepared zolmitriptan–chitosan microparticles by spray drying for nasal delivery & showed spray drying is a suitable technique for preparing spherical microparticles of zolmitriptan of chitosan with a narrow particle size range and high drug loading efficiency.

- **Amit kumar Nayak et al (2010)**, review to compile the recent literature especially for gastroretentive approaches that have become leading technologies in site-specific orally administered controlled release drug delivery.

- **Beatrice Albertini et al (2009)**, prepared the mucoadhesive microparticles and designed an innovative vaginal delivery systems for econazole nitrate (ECN) able to enhance the drug antifungal activity.

- **D. Coucke et al (2009)**, a mucoadhesive spray-dried starch/poly (acrylic acid) powder underwent different heat treatments in order to induce cross-linking between the functional groups of starch (Amioca) and poly(acrylic acid) (Carbopol 974P). After heat treatment the water-absorbing capacity, viscosity and elasticity of the mucoadhesive powder increased. NMR analysis in combination with FT-IR indicated that heat treatment induced a low degree of cross-linking between the polymers.

- **David S. Jones et al (2009)**, described the formulation and characterization of the viscoelastic, mechanical and mucoadhesive properties of thermoresponsive, binary polymeric systems composed of poloxamer (P407) and poly(acrylic acid, C974P) that were designed for use as a drug delivery platform within the oral cavity.

- **Deelipderle et al (2009)**, investigated the effect of tablet excipients on in vitro mucoadhesion combination of two polymers polyoxyethylene and carbopol 971P to make influence on the mechanisms of actions of the mucoadhesives and materials which interact with them.

- **Di Colo G et al (2001)**, A new application of high molecular weight (400 kDa) linear poly(ethylene oxide) (PEO) in gel-forming erodible inserts for ocular controlled delivery of ofloxacin (OFX) has been tested in vitro and in vivo. Inserts of 6 mm diameter, 20 mg weight, medicated with 0.3 mg OFX, were prepared by powder compression.
• **Ehab R. Bendas et al (2008)**, proposed that leaky enteric-coated pellets formulations are able to provide sustained input for drugs that have an absorption window, such as ranitidine hydrochloride, without jeopardizing their bioavailability. Leaky enteric-coated pellets formulations are defined as enteric-coated pellets that allow some of the drug to be released from the formulation in gastric fluid. They used enteric polymer, Eudragit L 30 D-55, combined with soluble compounds including lactose, PEG 8000 and surfactants (Span 60 (hydrophobic) or Tween 80 (hydrophilic).

• **Evangelos Karavas et al (2006)**, prepared pulsatile release formulations consisting of two-layered tablets appropriate for preventing ischemic heart diseases. For this reason the active core was constituted by a FELO/PVP 10/90 w/w solid dispersion while for the adjustment of the drug release time the coating layer was composed of PVP/HPMC blends at different compositions, acting as a stimulus responsible layer. These blends as was found by DSC studies are miscible in the entire composition range, ensured by the interactions taking place between hydroxyl groups of HPMC and carbonyl groups of PVP. The miscibility of the system enhances the mucoadhesive properties of the blends.

• **F. Florian et al (2006)**, developed chitosan-4 thiobutylamidine & showed promising tool for oral administration of P-glycoprotein substrates. Besides the chitosan-4 thiobutylamidine glutathione system other polymers, especially Pluronics have been reported to enhance bioavailability of actively secreted compounds. Multifunctional polymers offer advantages, such as mucoadhesive properties providing an intimate contact with the area of drug absorption and additionally, systemic side effects might be excluded, as polymers will remain in the gut in large part due to their high molecular Weight.

• **FP. Thomas et al (2008)**, developed Thiolated chitosan acyclovir tablets thiolated chitosans was shown to enhance the transport of acyclovir across rat intestinal mucosa and Caco-2 cell monolayers.

• **Ghelardi E et al (2000)**, describes the efficacy of a novel mucoadhesive polymer, the tamarind seed polysaccharide, as a delivery system for the ocular administration of hydrophilic and hydrophobic antibiotics. Healthy rabbits were subjected to repeated ocular instillations with either conventional gentamicin or ofloxacin or these agents
viscosified with the tamarind seed polysaccharide. The increased drug absorption and the prolonged drug elimination phase obtained with the viscosified formulations indicate the usefulness of the tamarind seed polysaccharide as an ophthalmic delivery system for topical administration of antibiotics.

- **Giulia Bonacucina et al (2004)**, Investigated the gelation properties of Carbopol 971e 974 polymeric systems in water-miscible cosolvents like glycerine and PEG 400. Since in these cosolvents, carboxypolymethylene precipitates after neutralisation with a base, in order to obtain Carbops gels avoiding neutralisation and making the dissolution in these gels of insoluble or poorly soluble water drugs. Carbopol is one of the most common thickening agent for water phases.

- **J. Dhananjay et al (2009)**, synthesized chitosan-graft-polyethylenimine using Chitosan (molecular weight 100 kDa; deacetylation degree 87.7%) & showed chitosan-graft-polyethylenimine carrier constituting chitosan and branched polyethylenimine has is a potential candidate for siRNA delivery due to its remarkable *In-vitro and In-vivo* gene delivery success for treating cancer.

- **Jdoao F. Pinto et al (2010)**, considered the most important organs of the digestive system (mouth, oesophagus, stomach, small intestine and colon), their size, physiology and transit patterns of dosage forms while travelling in the digestive tract. For each organ several strategies are considered, namely, adhesion, chemical modification of drug and/or excipient moieties, technological features of dosage forms (e.g. porosity, disintegration time), pH variations or transit times.

- **Ji-Shan Quan et al (2008)**, developed an oral protein drug delivery system, having mucoadhesive and pH-sensitive property. Bovine serum albumin (BSA) as a protein model drug was loaded in thiolated Eudragit-coated CMs (TECMs) to study the release character of the delivery system. It was confirmed that after coating thiolated Eudragit, the percentage of TECMs remained on the isolated porcine intestinal mucosa surface was significantly higher than those of CMs and ECMs. Likewise, gamma camera imaging of Tc-99m labeled microsphere distribution in rats after oral administration also suggested that TECMs had comparatively stronger mucoadhesive characters.
• **K. Pal et al (2009)**, reviewed to provide a good insight on mucoadhesive polymers, the phenomenon of mucoadhesion and the factors which have the ability to affect the mucoadhesive properties of a polymer.

• **K.S Kushwaha Swatantra et al (2010)**, has worked on Chitosan: A Platform for Targeted Drug Delivery & showed the Chitosan - based systems for delivery of therapeutic proteins/peptides and antigens, particularly after administration particles via mucosal (nasal and pulmonary) and parenteral routes. In his study it was found that bio/mucoadhesive chitosans (derivatives) can prolong the residence time of formulations at the mucosal sites, fairly protect the peptide/protein of interest from degradation and enhance its absorption across epithelial barriers.

• **Kavitha K et al (2010)**, reviewed the recent literature and current technology used in the development of floating drug delivery system.

• **KE. Constantia E et al (2001)**, prepared thiolated polymers for mucoadhesion & showed the covalent attachment of chitosan-thioglycolic acid conjugates to the cationic polymer chitosan leads to conjugates exhibiting an up to 10 times improved mucoadhesion. Despite the chemical modification they are still biodegradable and show a good swelling behavior. These properties might be useful in order to prolong the stability and the adhesion of different dosage forms on various mucosal tissues compared to well-established polymers.

• **LK. Mi et al (2009)**, used chitosan microspheres for nasal delivery of vaccines & results suggested that the mannosylation of chitosan microspheres as a nasal vaccine delivery system could enhance immunogenicity of vaccine by targeted delivery to macrophage -inducing receptor mediated endocytosis.

• **M. Prabaharan et al (2008)**, synthesized a novel thiolated carboxymethyl chitosan-g-b-cyclodextrin as drug delivery carrier & showed the covalent attachment of cysteine methyl ester hydrochloride onto carboxymethyl chitosan-g-b-cyclodextrin leads to strongly improved mucoadhesive properties of the polymer by forming inter and/or intramolecular disulfide bonds, which was verified by mucoadhesive studies. This improved mucoadhesive properties could provide stability and prolonged residence time on the polymer-drug molecules on the mucosal tissues.
• **M.Gomez-Burgaz et al (2008)**, formulated the chitosan (CS) and carboxymethylcellulose (CMC) sodium interpolymer complexes using the novel method tablets-in-capsule for stomach drug delivery and investigated the influence of the molecular weight of CS and the proportion CS/CMC on physical properties and clarithromycin (CAM) release.

• **MD. Abd El-Hameed et al (1997)**, formulated mucoadhesive polymeric microspheres as intra-nasal delivery systems from Carbopol 934P, Chitosan, HPMC, and PVA & concluded solvent evaporation technique for the entrapment of FITC-dextran in Carbopol 934P, Chitosan, HPMC, and PVA produced a high yield of discrete microspheres with minimal agglomeration, reproducible drug loading efficiency and release profiles from batch to batch.

• **Mi Lan Kang et al (2009)**, chitosan microspheres have been investigated to determine whether they allow the controlled release of drugs and vaccines. Several researchers have developed modified chitosan microspheres through their concomitant use with adjuvants or immunomodulators for an additive and a synergistic effect, and through the mannosylation of chitosan for receptor-mediated targeting antigen-presenting cells.

• **Mona Semalty et al (2008)**, prepared mucoadhesive buccal films of glipizide by solvent casting technique using hydroxyl propyl methylcellulose, sodium carboxymethylcellulose, carbopol934p and eudragit RL-100. Evaluation was done for weight, thickness, surface pH, swelling index, in-vitro residence time, folding endurance, in-vitro release and drug content uniformity.

• **N. Venkatesan et al (2006)**, studied oral administration of mucoadhesive tablets containing erythropoietin (EPO) and an absorption enhancer labrasol in rats and dogs. Mucoadhesive tablets were prepared using Sylysia 550 holding the absorption enhancer and carbopol 974P as a mucoadhesive agent. Mucoadhesive tablets were covered with a water-insoluble backing layer made of cellulose acetate and a pH-sensitive covering layer made of Eudragit L/Eudragit S. Mucoadhesive tablets showed promising results as an oral drug delivery system for protein therapeutics.

• **Nalini M. Anande et al (2008)**, developed cyst-targeted novel concanavalin-A (Con-A) conjugated mucoadhesive microspheres of diloxanide furoate (DF) for the
effective treatment of amoebiasis. Eudragit microspheres of DF were prepared using emulsification–solvent evaporation method.

- **Pallab Roy et al (2009)**, developed drug delivery system based on combining floating and pulsatile principles for chronotherapy in nocturnal acid breakthrough. This was achieved by using a programmed delivery of ranitidine hydrochloride from a floating tablet with time-lagged coating.


- **Ravinder A. Nath et al (2010)**, the drugs which have local action or those which have maximum absorption in gastrointestinal tract (GIT) require increased duration of stay in GIT. Thus, mucoadhesive dosage forms are advantageous in increasing the drug plasma concentrations and also therapeutic activity. Review the areas of mechanisms and theories of mucoadhesion, factors influencing the mucoadhesive devices and also various mucoadhesive dosage forms.

- **Ray-Neng Chen et al (2010)**, developed gastroretentive drug delivery system (GRDDS) for administering Losartan. Additionally, the influence of optimized GRDDS on the bioavailability of Losartan and the formation extent of active metabolite E3174 by CYP2C9 polymorphism was investigated. Swellable and floatable GRDDS tablets combining hydroxyethyl cellulose (HEC), sodium carboxymethyl cellulose (NaCMC), and sodium bicarbonate were prepared at various compression pressures for evaluating swelling characteristics and floating capacity. The tablets floating over SGF for more than 16 h and swelling to 2 cm in diameter within 3 h.

- **S.H. Park et al (2008)**, Prepared the extended release matrix tablet. Chitosan and Carbopol interpolymer complex (IPC) was formed using a precipitation method in an acidic solution. The chitosan and Carbopol IPC was characterized by Fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), and turbidity measurements. FT-IR demonstrated that the IPC formed a complex through an electrostatic interaction between the protonated amine (NH3+) group of chitosan and the carboxylate (COO–) group of Carbopol. A theophylline tablet was
prepared using the IPC as a matrix material. The drug release profile from this tablet was similar to that from the HPMC tablet and showed a pH-independent release profile. The mechanisms for drug release from the IPC tablet were diffusional release at pH 6.8 and relaxational release at pH 1.2.

- **Sandra Strubing et al (2008)**, investigated the mechanism of floating and drug release behaviour of poly (vinyl acetate)-based floating tablets with membrane controlled drug delivery.

- **Sasa Baumgartner et al (2008)**, xanthan is a well-known biopolymer. It is an anionic polysaccharide. They investigated the relation between the physical properties of a xanthan matrix in the absence or presence of calcium ions and its influence on the release of pentoxifylline. The results indicate that the presence of Ca2+ ions in the solution or in matrices does not cause crosslinking of xanthan polymers, but causes charge screening of ionized groups on the trisaccharide side chains of xanthan, leading to lower inter-molecular repulsion and changing water arrangement. The understanding of the parameters influencing drug release leads to the conclusion that xanthan is suitable for controlled release formulations, especially with the incorporation of certain small counterions.

- **SB. Andreas et al (2003)**, synthesized chitosan–2-iminothiolane conjugates & concluded that modification of chitosan with 2-iminothiolane leads to polymers exhibiting excellent in situ gelling properties and strongly improved mucoadhesive properties. In addition, a controlled drug release can be guaranteed out of thiolated chitosan. Because of these features polymer conjugates were useful polymeric carrier matrix for delivery systems, which provided a prolonged residence time of the drug on the mucosa.

- **Shoufeng Li et al (2003)**, Investigated the effect of formulation variables on drug release and floating properties of the delivery system. Hydroxypropyl methylcellulose (HPMC) of different viscosity grades and Carbopol 934P (CP934) were used in formulating the Gastric Floating Drug Delivery System (GFDDS) employing 2 × 3 full factorial design. Both HPMC viscosity, the presence of Carbopol and their interaction had significant impact on the release and floating properties of the delivery system.
• **Sree Harsha et al (2009)**, prepared lung-targeting albumin loaded ofloxacin microspheres by water in oil emulsion Method. The appearance and size distribution were examined by scanning electron microscopy, and they studied in vitro release characteristics, stability, drug loading, loading efficiency, pharmacokinetics and tissue distribution in albino mice and showed that the microspheres have an average particle size of 11.32 μm. The drug loading and loading efficiency were (66.95 and 94.8%) respectively.

• **T. Selcan Turker et al (2004)**, reviewed on Nasal route and drug delivery systems & concluded that the nasal cavity has a large surface area and a highly vascularized mucosa. Drugs absorbed by the rich network of blood vessels pass directly into the systemic circulation, thereby avoiding first-pass metabolism.

• **Tristan P. Learoyd et al (2008)**, described the preparation of highly dispersible dry powders for pulmonary drug delivery that display sustained drug release characteristics. Powders were prepared by spray-drying 30% v/v aqueous ethanol formulations containing terbutaline sulfate as a model drug, chitosan as a drug release modifier and leucine as an aerosolisation enhancer. The influence of chitosan molecular weight on the drug release profile was investigated by using low, medium and high molecular weight chitosan or combinations thereof.

• **W. Weyenberg et al (2006)**, evaluated different bioadhesive ocular formulations based on drum dried waxy maize starch (DDWM), Amiocaw starch and Carbopol 974P. The concentrations of Carbopol 974P in the mixtures varied between 5 and 25% (w/w). The rheological properties of the non-sterilized and gamma-irradiated physical blends of Carbopol 974P with either DDWM or Amiocaw were compared to those of the corresponding co-spray dried Amiocaw starch/Carbopol powders.

• **Y. Murat et al (2000)**, prepared two types of alginate gel beads capable of floating in the gastric cavity. a) Alginate gel bead containing vegetable oil (ALGO), is a hydrogel bead and its buoyancy is attributable to vegetable oil held in the alginate gel matrix. Metronidazole (MZ), contained in ALGO was released gradually into artificial gastric juice, the release rate being inversely related to the percentage of oil. b) Alginate gel bead containing chitosan (ALCS, is a dried gel bead with dispersed chitosan in the matrix. The drug-release profile was not affected by the kind of
chitosan contained in ALCS. When ALCS containing MZ was administered orally to guinea pigs, it floated on the gastric juice and released the drug into the stomach.

- **Yunying Tao et al (2009)**, developed acyclovir-loaded mucoadhesive microspheres using Ethylcellulose as matrix and Carbopol 974P NF as mucoadhesive polymer for the purpose of improving the oral bioavailability of acyclovir. The release of the drug was influenced markedly by the medium pH and the proportion of Carbopol incorporated in the microspheres. The result of mucoadhesion study showed prolonged residence time of ACV-ad-ms in rats gastrointestinal tract.