Chapter 2
Review of work done
2.1 Review of work done on stomach specific drug delivery systems

Sheth et al \[1\] developed sustained release hydrodynamically balanced capsules which, upon contact with gastric fluid acquired and maintained a bulk density of less than one and remained buoyant in the fluid and remained so until substantially all of the active ingredients are released. The percent Chordiazepoxide release from capsules in to simulated gastric fluid (pH 1.2) after 1,2,3,7 hrs was 39,61,…100 % respectively.

Du Quing et al \[2\] formulated multiple unit floating sustained release granules of aminophyllin and evaluated. They have reported that increasing quantity of cetyl alcohol and octadecanol could increases the granules floating capability \textit{in-vitro}. Increased concentration of ethyl cellulose delayed the drug release rate.

Stochwell et al \[3\] formulated and evaluated a floating gel system. Buoyancy was achieved by carbon dioxide gas and its subsequent entrapment in to gel network. Sodium alginate, which undergoes gelation in acidic conditions and in the presence of calcium, was used. It was evaluated \textit{in-vitro} as sustained release floating gel system.

Igani et al \[4\] formulated dosage form with specific density less than one in the form of double layer sustained release compressed hydrophilic matrix to achieve a reproducible floatation of a tablet. Carbon dioxide was trapped in to gelled hydrocolloids. The gastric retention of HBS dosage form was found to be significantly more than that of the non-floating dosage form.

Shimpi S et al \[5\] prepared Gelucire 43/01 for the design of multi-unit floating systems of a highly water-soluble drug diltiazem HCl. Diltiazem HCl-Gelucire 43/01 granules were prepared by melt granulation technique. The granules were evaluated for \textit{in-vitro} and \textit{in-vivo} floating ability, surface topography, and \textit{in-vitro} drug release. Aging effect on storage was evaluated using scanning electron microscopy, hot stage polarizing microscopy (HSPM), differential scanning calorimetry (DSC), and \textit{in-vitro} drug release. Granules were retained in stomach at least for 6 hrs. Approximately 65% to 80% drug was released over 6 hrs with initial fast release from the surface. Surface topography, HSPM, DSC study of the aged samples showed phase transformation of Gelucire. The phase
transformation also caused significant increase in drug release. In conclusion, hydrophobic lipid, Gelucire 43/01, can be considered as an effective carrier for design of a multi-unit floating drug delivery system of highly water-soluble drugs such as diltiazem HCl.

Zia et al [6] optimized Sotalol floating and bioadhesive extended release tablet formulation which posses a unique combination of flotation and bioadhesion for prolong residence in the stomach. A new factor factorial design was employed to optimize the tablet formulation containing 240 mg Sotalol HCl, the ratio of NaCMC to HPMC and the ratio of EC to Crosspovidone. The dependent variable was dissolution, bioadhesive capability, tablet disintegration and required compression force for producing 6 kg hardness tablets.

Tossounian et al [7] investigated the in-vivo and in-vitro characterization of hydrodynamically balanced dosage forms. In-vivo visualization was done by using blood level time profiles for diazepam and chlordiazepoxide HBS dosage forms.


Sangekar et al [9] investigated the effect of food and specific gravity on the gastric retention time of floating and non-floating tablet formulations using gamma scintigraphy in humans. No correlation was found between gastric residence time and specific gravity of the dosage form.

Nakamichi K et al [10] prepared a floating dosage form composed of nicardipine hydrochloride (NH) and hydroxypropylmethylcellulose acetate succinate (enteric polymer) was prepared using a twin-screw extruder. By adjusting the position of the high-pressure screw elements in the immediate vicinity of die outlet, and by controlling the barrel temperature, he was able to prepare a puffed dosage form with very small and uniform pores. It was found that the porosity and pore diameter could be controlled by the varying amount of calcium phosphate.
dihydrate. In the shaking test, the puffed dosage form was found to have excellent floating ability and mechanical strength in acid solution (JP First Fluid, pH 1.2). The dissolution profile of NH was controlled by the amount of wheat starch. In the dissolution test using JP Second Fluid (pH 6.8), rapid dissolution of NH and loss of buoyancy were observed.


**Mazer et al** [12] observed intragastric behavior and absorption kinetic of normal and floating modified release capsule of isradipine under fasted and fed conditions. Presence or absence of food rather than buoyancy was the principal determinant of the gastric residence time of the capsule. The drug release and absorption were more by the intragastric interaction with the lipid phase of the meal.

**Inouye,Y et al** [13] prepared buoyant sustained release granules of Prednisolone using ‘H’ or ‘L’ grades of chitosan. The granules were immediately buoyant in both acidic and neutral fluids. Sustained drug absorption from these preparations was noticed in beagle dogs.

**Kawashima et al** [14] prepared hollow microspheres (microballoons) loaded with drug in their outer polymer shell by a novel emulsion solvent diffusion method. The ethanol: dichloromethane solution of drug (ibuprofen) and an acrylic polymer were poured that were thermally controlled at 40°C. The gas phase generated in the dispersed polymer droplet by the evaporation of the dichloromethane formed and the internal cavity in the microballoons of the polymer. The flowability and packability of the resultant microballons were characterized as an entire property and the drug release rate were drastically reduced depending on the polymer concentration at pH 6.8.

**Franz et al** [15] prepared sustained release bilayer buoyant floating dosage form containing Misoprostol, one layer is a drug release layer and other is buoyant or floating layer. The dosage form provided extended gastric retention so that the entire drug is released in the stomach over an extended period. The floating layer
included a polymer i.e. HPMC, which has a property of gelling and which on contact with gastric fluids, hydrates and forms a gelatinous barrier. This dosage form is buoyant on gastric fluid for up to approximately 13 hrs.

Desai et al \cite{16} developed a noncompressed controlled release floating tablets of Thyophylline using agar and mineral oil. Tablets were made by dispersing a drug/mineral oil mixture in warm agar solution, the resultant mixture was poured into tablet moulds which on cooling and air-drying formed a floatable CR tablets. The light mineral oil was essential for the floating property of the tablet since relatively high amount of drug (75%) and low amount of agar (2%) were used into formulation.

Baumgartener et al \cite{17} prepared floating matrix tablets with high dose of freely soluble drugs. Tablets containing HPMC, drug and different additives are compressed. Tablet composition and mechanical strength have greater influence on the floating properties and drug release. With the incorporation of gas generating agent, besides optimum floating time of 30 sec and duration of floating > 8 hr, the drug release was also increased.

Whitehead et al \cite{18} prepared floating alginate beads from alginate solution containing either dissolved or suspending Amoxicillin. The beads were produced by a drop-wise addition of the alginate into calcium chloride solution, followed by removal of the gel beads and freeze drying. Drug release study shows that the beads prepared with the drug in solution provided some sustained release characters and these were improved by the addition of amylase. The beads retained their buoyancy were amylase and amoxicilline were incorporated.

Nur Abubakr O et al \cite{19} prepared captopril floating and/or bio adhesive tablets using two grades of HPMC (400 and 15000 cps.). He compared two conventional tablets; release from floating tablets was apparently prolonged. A 24 hrs controlled release dosage form for captopril was achieved. Tablet hardness was found determining factor with regard to buoyancy of the tablets.

Shoufeng et al \cite{20} illustrated statistical experimental design and data analysis using response surface methodology. A central composite box-Wilson design for the controls release of calcium was used with three formulation variables like
HPMC loading, Citric acid loading and magnesium stearate loading. Sustained release floating delivery of calcium with increased bioavailability was achieved.

Farouk et al \cite{21} developed a programmable controlled release drug delivery system. The device in the form of a non digestible oral capsule was designed to utilize an automatically operated geometric obstruction that keeps the device floating in the stomach and prevents it from passing through the remainder of the GIT. Different viscosity grades of HPMC were used as a model eroding matrices. Zero-order release could be maintained for periods ranging between 5 to 20 days before the geometric obstruction was triggered off.

Talwar et al \cite{22} prepared gastroretentive oral drug delivery system structurally comprised of highly porous matrix having a drug, gas generating component, sugar, release controlling agent and optionally spheronising agents. The pharmaceutical formulation either in the form of pellets, beads, granules or capsules was retained in the stomach while selectively delivering the drug at gastric level or upper part of small intestine for extended period of time.

Joseph et al \cite{23} prepared a floating type dosage form (FDF) of piroxicam in hollow polycarbonate (PC) microspheres capable of floating on simulated gastric and intestinal fluids was prepared by a solvent evaporation technique. Incorporation efficiencies of over 95\% were achieved for the encapsulation. *In-vitro* release of piroxicam from PC microspheres into simulated gastric fluid at 37°C showed no significant burst effect. The amount released increased with time for about 8 h after which very little was found to be released up to 24 hrs. In intestinal fluid, the release was faster and continuous and at high drug payloads, the cumulative release reached above 90\% in about 8 hrs. *In-vivo* evaluation of different dosage forms of piroxicam such as free drug, drug-encapsulated microspheres and microspheres along with a loading dose of free drug in rabbits showed multiple peaking in the plasma concentration-time curve suggesting enterohepatic recirculation of the drug.

Patel et al \cite{24} developed freeze dried chitosan polyethylene oxide hydrogel for the site-specific antibiotic release in the stomach. The freeze dried PEO matrix swollen extensively as compared to air-dried hydrogels. The freeze dried
chitosan PEO could be useful for localized delivery of antibiotic in the acidic environment of the gastric fluid.

**Atybi et al** [25] studied bicarbonate loaded bicarbonate ion exchange resin beads coated with semipermeable membrane. The beads exhibited prolong gastric recidence due to floating. In, addition to bicarbonate, a model drug theophyllin has also been loaded on to the resin. This system gives a controlled release of drug by coating and has potential application as a control release gastric retentive system.

**Yang** [26] developed an asymmetric three-layered tablet. The outer layer consisted of gas generating system. The other outer layer was similar but devoid of gas generating element. The function of these layers was to provide the necessary buoyancy and control the passage of the fluid in to the drug containing layer. Zero-order release of theophylline *in-vitro* was possible for 16 hrs with buoyancy maintained through out the period.

**Timmerman et al** [27] optimized floating and non floating hydrophilic matrix capsule *in-vitro* with regard to their buoyancy or non buoyancy capabilities and their diametric sine evaluation with time. The GRT prolongation is obtained with floating dosage form compared to non floating dosage forms.

**Sheth et al** [28] published a patent for hydrodynamically balance system. This unit consisting of capsule formulation consisting drug, hydrocilloid and other excipients. After emersion in other fluid, the capsule dissolves and hydrocolloid forms a hydrated boundary layer. That gives the formulation floating properties. The drug is subsequently released through this layer is by diffusion.

**Wei et al** [29] formulated a new kind of two-layer floating tablet for gastric retention (TFTGR) with cisapride as a model drug was developed. The *in-vitro* drug release was determined, and the resultant buoyancy and the time-buoyancy curve were plotted. Because of the sodium bicarbonate added to the floating layer, when immersed in simulated gastric fluid the tablet expands and raises to the surface, where the drug is gradually released. The drug release of this kind of two-layer dosage was controlled by the amount of HPMC in the drug-loading layer. Generally the more HPMC, the slower the drug releases. Because
cisapride has greater solubility in SGF than SIF, in vitro drug dissolution in SGF is faster than in SIF.

Soppimath et al. \cite{30} prepared hollow microspheres of cellulose acetate loaded with four cardiovascular drugs (Nifedipine, Nicardipine HCl, Varapamil HCl and Dipyridamole) were prepared by a novel solvent diffusion-evaporation method. The O/W emulsion prepared in an aqueous solution of 0.05% poly (vinyl alcohol) medium with ethyl acetate, a water-soluble and less toxic solvent, was used as a dispersing solvent. The yield of the microspheres was up to 80%. The microspheres had smooth surfaces, with free floating and good packing properties. Scanning Electron Microscopy (SEM) confirmed their hollow structures, with sizes in the range of 350-489 mm. The microspheres were tended to float over the gastric media of more than 12 hrs.

Jayvadan et al. \cite{31} formulated and systematically evaluate in-vitro and in-vivo performances of mucoadhesive microspheres of glipizide. Glipizide microspheres containing chitosan were prepared by simple emulsification phase separation technique using glutaraldehyde as a cross-linking agent. Results of preliminary trials indicate that volume of cross-linking agent, time for cross-linking, polymer-to-drug ratio, and speed of rotation affected characteristics of microspheres. Microspheres were discrete, spherical, and free flowing. The microspheres exhibited good mucoadhesive property in the in-vitro wash-off test and also showed a high percentage drug entrapment efficiency. A $3^2$ full factorial design was employed to study the effect of independent variables, polymer-to-drug ratio ($X_1$), and stirring speed ($X_2$) on dependent variables percentage mucoadhesion, $t_{80}$, drug entrapment efficiency, and swelling index. The best batch exhibited a high drug entrapment efficiency of 75% and a swelling index of 1.42; percentage mucoadhesion after 1 hr was 78%. The drug release was also sustained for more than 12 hrs. The polymer-to-drug ratio had a more significant effect on the dependent variables. In-vivo testing of the mucoadhesive microspheres to albino Wistar rats demonstrated significant hypoglycemic effect of glipizide.

Jayvadan et al. \cite{32} formulated and systematically evaluate in-vitro and in-vivo performances of mucoadhesive amoxicillin microspheres for the potential use of
treating gastric and duodenal ulcers, which were associated with *Helicobacter pylori*. Amoxicillin mucoadhesive microspheres containing chitosan as mucoadhesive polymer were prepared by simple emulsification phase separation technique using glutaraldehyde as a cross-linking agent. Results of preliminary trials indicate that volume of cross-linking agent, time for cross-linking, polymer-to-drug ratio, and speed of rotation affected characteristics of microspheres. Microspheres were discrete, spherical, free flowing and also showed high percentage drug entrapment efficiency. *In-vitro* mucoadhesive test showed that amoxicillin mucoadhesive microspheres adhered more strongly to gastric mucous layer and could retain in gastrointestinal tract for an extended period of time. A $3^2$ full factorial design was employed to study the effect of independent variables, polymer-to-drug ratio ($X_1$), and stirring speed ($X_2$) on dependent variables i.e. percentage mucoadhesion, t80, drug entrapment efficiency, particle size and swelling index. The best batch exhibited a high drug entrapment efficiency of 70% and a swelling index of 1.39; percentage mucoadhesion after one h was 79%. The drug release was also sustained for more than 12 h. The polymer-to-drug ratio had a more significant effect on the dependent variables. The morphological characteristics of the mucoadhesive microspheres were studied using scanning electron microscopy. *In-vitro* release test showed that amoxicillin released slightly faster in pH 1.0 hydrochloric acid than in pH 7.8 phosphate buffer. *In-vivo* *H. pylori* clearance tests were also carried out by administering amoxicillin mucoadhesive microspheres and powder, to *H. pylori* infectious Wistar rats under fed conditions at single dose or multiple dose(s) in oral administration. The results showed that amoxicillin mucoadhesive microspheres had a better clearance effect than amoxicillin powder. In conclusion, the prolonged gastrointestinal residence time and enhanced amoxicillin stability resulting from the mucoadhesive microspheres of amoxicillin might make contribution complete eradication of *H. pylori*.

Myung-Kwan Chun et al [33] prepared mucoadhesive microspheres to increase gastric residence time using an interpolymer complexation of poly(acrylic acid) (PAA) with poly(vinyl pyrrolidone) (PVP) and a solvent diffusion method. The
complexation between poly(acrylic acid) and poly(vinyl pyrrolidone) as a result of hydrogen bonding was confirmed by the shift in the carbonyl absorption bands of poly(acrylic acid) using FT-IR. A mixture of ethanol/water was used as the internal phase, corn oil was used as the external phase of emulsion, and span 80 was used as the surfactant. Spherical microspheres were prepared and the inside of the microspheres was completely filled. The optimum solvent ratio of the internal phase (ethanol/water) was 8/2 and 7/3, and the particle size increased as the content of water was increased. The mean particle size increased with the increase in polymer concentration. The adhesive force of microspheres was equivalent to that of Carbopol. The release rate of acetaminophen from the complex microspheres was slower than the PVP microspheres at pH 2.0 and 6.8. B. Y. Choi et al \cite{34} prepared floating beads from a sodium alginate solution containing CaCO$_3$ or NaHCO$_3$ as gas-forming agents. The solution was dropped to 1% CaCl$_2$ solution containing 10% acetic acid for CO$_2$ gas and gel formation. The effects of gas-forming agents on bead size and floating properties were investigated. As gas-forming agents increased, the size and floating properties increased. Bead porosity and volume average pore size, as well as the surface and cross-sectional morphology of the beads were examined with Mercury porosimetry and Scanning Electron Microscopy. NaHCO$_3$ significantly increased porosity and pore diameter than CaCO$_3$. Incorporation of CaCO$_3$ into alginate solution resulted in smoother beads than those produced with NaHCO$_3$. Gel strength analysis indicated that bead strength decreased with increasing gas-forming agent from 9 to 4 N. Beads incorporating CaCO$_3$ exhibited significantly increased gel strength over control and NaHCO$_3$-containing samples. Release characteristics of riboflavin as a model drug were studied \textit{in-vitro}. Release rate of riboflavin increased proportionally with addition of NaHCO$_3$. However, increasing weight ratios of CaCO$_3$ did not appreciably accelerate drug release. The results of these studies indicate that CaCO$_3$ is superior to NaHCO$_3$ as a gas forming agent in alginate bead preparations. The enhanced buoyancy and sustained release properties of CaCO$_3$-containing beads make them an excellent candidate for floating drug dosage systems (FDDS).
Colombo et al\textsuperscript{[35]} prepared swellable matrices by compression of a powdered mixture of a hydrophilic polymer and a drug. Their success is linked to the established tableting technology of manufacturing. Swellable matrix DDS must be differentiated from true swelling-controlled delivery systems. This review focuses on hydrophilic swellable matrix tablets as controlled DDS. Gel-layer behaviour, front movement and release are described to show the dependence of the release kinetics on the swelling behaviour of the system. \textit{In-vivo} behaviour of matrix systems is also considered.

Alvaro et al\textsuperscript{[36]} developed and characterized the delivery properties of swellable drug-polyelectrolyte matrices (SDPM). Solid complexes \((C–D)_X\) of carbomer \((C)\) neutralized with different proportions of model basic drugs \((D)\), in which \(D\) is atenolol, lidocaine, and metoclopramide, and \(X = 25, 50, 75\) and 100 mol of \(D\) per 100 equivalents of carboxylic groups of \(C\), were prepared and characterized by DSC-TG, IR, and X-ray diffraction studies. Mechanistic studies with hydrophilic and hydrophobic basic drugs were conducted to explore the drug release patterns of SDPM. Besides, release and up-take studies were carried out in water and NaCl solution to examine the influence of ionic effects. The authors concluded that drugs can be loaded in a high proportion on to the polymer and therefore the resulting material could be diluted with other polymers to modulate delivery properties of SDPM. Matrices of atenolol and lidocaine exhibited robust delivery properties with regard to change in proportion of loading \(D\).

J. A. Raval and J. K. Patel\textsuperscript{[37]} investigated the effects of formulation and processing parameters on a floating matrix controlled drug delivery system consisting of a poly (styrene-divinyl benzene) copolymer low density powder, a matrix-forming polymer(s), drug, and diluents (optional). The tablets were prepared by the direct compression technique, using hydrophilic matrix polymers HPMC K4M, HPMC K15M, HPMC K100M, sodium alginate, psyllium, sesbania gum, guar gum, and gum acacia, with or without low density copolymer. Tablets were physically characterized and evaluated for \textit{in-vitro} release characteristics for 8 h in 0.1 mol/l HCl at 37°C. The effect of the addition of low density copolymer and the drug release pattern were also studied. The release rate was
modified by varying the type of matrix-forming polymer, the tablet geometry (radius), and the addition of water-soluble or water-insoluble diluents. At the same time, different concentrations of low-density copolymer were taken to examine any differences in the floating lag-time of the formulation. The \textit{in-vitro} release mechanism was evaluated by kinetic modeling. The similarity factor, floating lag-time, and \( t_{50} \) and \( t_{90} \) were used as parameters for selection of the best batch. The tablet eroded/swelled upon contact with the release medium, and the relative importance of drug diffusion, polymer swelling and tablet erosion on the resulting release patterns varied significantly with the type of matrix forming polymer. The highly porous copolymer provided a low density and, thus, excellent \textit{in-vitro} floating behavior of the tablets at a concentration of 15\% (w/w). It was established that floating behavior of the low-density drug delivery systems could be successfully combined with accurate control and prolongation of the drug release patterns.

\textbf{Anand Kumar} \cite{38} studied preparation and evaluation of floating microspheres with cimetidine as model drug for prolongation of gastric residence time. The microspheres were prepared by the solvent evaporation method using polymers hydroxypropylmethyl cellulose and ethyl cellulose. The shape and surface morphology of prepared microspheres were characterized by optical and scanning electron microscopy, respectively. \textit{In-vitro} drug release studies were performed and drug release kinetics was evaluated using the linear regression method. Effects of the stirring rate during preparation, polymer concentration, solvent composition and dissolution medium on the size of microspheres and drug release were also observed. The prepared microspheres exhibited prolonged drug release (8 hrs) and remained buoyant for \( > 10 \) hrs. The mean particle size increased and the drug release rate decreased at higher polymer concentration. No significant effect of the stirring rate during preparation on drug release was observed. \textit{In-vitro} studies demonstrated diffusion-controlled drug release from the microspheres.

\textbf{Whitehead et al} \cite{39} prepared floating dosage forms of Amoxicillin based on alginate to exhibit prolong gastric residence time. A freeze-dried calcium alginate
multiple unit floating dosage form that demonstrated favorable in-vitro floating characteristics was developed.

**Ganguly S et al** [40] developed a novel chitosan-glyceryl monooleate (GMO) in situ gel system for sustained drug delivery & targeting was developed. The delivery system consisted of 3 % (w/v) chitosan & 3 % (w/v) glyceryl monooleate in 0.33M citric acid. In situ gel was formed at a biological pH and in-vitro release studies were conducted in Sorensen’s phosphate buffer (pH 7.4). Characterization of the gel included the effect of cross-linker, determination of diffusion coefficient and water uptake by thermogravimetric analysis (TGA). Incorporation of a cross-linker (glutaraldehyde) retarded the rate and extent of drug release. Drug release from the gel followed a matrix diffusion controlled mechanism.

**Kubo W et al** [41] developed oral sustained delivery of paracetamol from in situ-gelling gellan and sodium alginate formulations. The potential for the oral sustained delivery of paracetamol of two formulations with in situ gelling properties was evaluated. In-vitro studies demonstrated diffusion-controlled release of paracetamol from the gels over a period of six hrs. The bioavailability of paracetamol from the gels formed in situ in the stomachs of rabbits following oral administration of the liquid formulations was similar to that of a commercially available suspension containing an identical dose of paracetamol.

**Dairaku M et al** [42] developed in situ gel using pectin. Gels formed in situ following oral administration of dilute aqueous solutions of pectin (1.0 and 1.5 %, w/v) containing calcium ions in complexed form to rats was evaluated as vehicles for the sustained release of the expectorant drug ambroxol hydrochloride. A bioavailability of approximately 64 % of that of a commercially available formulation was achieved from gels containing an identical dose of ambroxol formed in situ in the stomachs of rats, with appreciably lower peak plasma levels, diffusion controlled and sustained release of drug over a period of at least six hrs. The influence of added sorbitol (17 %, w/v) on the rheological and drug release properties of the formulations has been examined.
Fujiwara et al\[43\] studied in situ gel from \textit{in-vitro} and \textit{in-vivo} release of paracetamol and ambroxol the influence of different polyhydric alcohols like xylitol, mannitol and sorbitol in different concentration of in situ gelling pectin formulations was examined. 2 % (w/v) pectin gels containing 10 % (w/v) sorbitol showed a sustained release of paracetamol and bioavailabilities of approximately 90 % was seen. Sustained release of ambroxol with pectin concentrations of 1.5 and 1 % (w/v) and a sorbitol concentration of 10 % (w/v) was seen.

Peterson et al\[44\] developed in situ gelling alginites formulations as an alternative to incorporation of various excipients $N^4$-alkoxy carbonyl cytosine derivatives possessing various physicochemical properties and cytosine regeneration rates was being examined to modify release rate and kinetics from in situ gelling alginate formulations. Release rate constants and square root of solubility showed a linear relationship for suspension. A zero order release of parent cytosine was observed from in situ gelling suspension and diffusion coefficients calculated was observed to be similar for suspension and solution.\[10\]

Itoh K et al\[45\] compared the gelation and drug release characteristics of formulations of pectin with high (31%) and low (9%) degrees of methoxylation over a wide pH range (pH 1.2-5.0). Gelation of formulations of pectin with a degree of esterification of 9% (DE9) was observed over the pH range 2.5-5.0 in the presence of 1.6mM Ca $(++)$, but was incomplete in formulations of pectin with a degree of esterification of 31% (DE31). A sustained release of ambroxol was observed following oral administration of pectin DE9 formulations to gastric-acidity controlled rabbits at pH 5.5-5.7 and visual observation of the stomach contents of these rabbits confirmed in situ gelation of these formulations.

Kunihiko Itoh et al\[46\] studied the influence of a variation of gastric pH & addition of a taste masking agent on gelation of pectin solutions and on \textit{in-vitro/in-vivo} release of acetaminophen from gels. Increase of pH above 2.5 and addition of 10% (w/v) D-sorbitol significantly affected ability of 1.5% (w/v) pectin solutions to form coherent gels \textit{in-vitro}. Gelation of sorbitol-free formulations was observed at pH 1.2 and \textit{in-vitro} release of acetaminophen from gel followed diffusion-controlled kinetics; \textit{in-vitro} gelation was incomplete at pH 3.0 resulting in
poor sustained release characteristics. While D-sorbitol inhibited *in-vitro* gelation & noted poor sustained release properties.

Oi H et al \[47\] developed a thermosensitive in situ gelling and mucoadhesive ophthalmic drug delivery system containing puerarin based on poloxamer analogs (21% (w/v) poloxamer 407/5% (w/v) poloxamer 188) and carbopol (0.1% (w/v) or 0.2% (w/v) carbopol 1342P NF). The combined solutions would convert to firm gels under physiological condition and attach to the ocular mucosal surface for a relative long time. *In-vitro* release studies demonstrated diffusion-controlled release of puerarin from the combined solutions over a period of 8 hrs. *In-vivo* evaluation indicated the combined solutions had better ability to retain drug than poloxamer analogs or carbopol alone.

Kashyap et al \[48\] developed biodegradable glucose-sensitive in situ gelling system based on chitosan for pulsatile delivery of insulin was developed. The sols/gels were thoroughly characterized for swelling properties, rheology, texture analysis and water content. Insulin load onto the gels was optimized and was found to affect the rheological behavior of these gels, the final preparation used for *in-vitro* contained 1IU/200ml of the sol. These gels released the entrapped insulin in a pulsatile manner in response to the glucose concentration *in-vitro*. The formulations also evaluated for their *in-vivo* efficacy in streptozotocin-induced diabetic rats at a dose of 3IU/kg.

Escobar-Chavez JJ et al \[49\] developed insitu gel by using Pluronic F-127 PF-127The use of high viscosity hydromiscible vehicles such as hydrophilic gels, is one of various approaches for controlled drug delivery, and represents an important area of pharmaceutical research and development. Of these systems, PF-127 provides the pharmacist with an excellent drug delivery system for a number of routes of administration and is compatible with many different substances. Gels containing penetration enhancers have proven to be especially popular for administering anti-inflammatory medications since they are relatively easy to prepare & very efficacious.

Voorspoels et al \[50\] studied treatment of bacterial vaginosis with a single application of 100 mg metronidazole in a bioadhesive vaginal tablet was found to
be a valid alternative. Further research in relation to tablet shaping and optimal dose finding might increase the cure rate.

**Smart**\(^{[51]}\) developed *in-vitro* method for the assessment of the adhesive force [i.e. the force required to break an adhesive bond] between a disc of test material and a model mucous membrane. This system showed reasonable reproducibility and produced data in agreement with previous studies. Some factors influencing the adhesive force were assessed and only increasing the rate of application of the tensile force was found to have a significant effect. Some putative mucosa-adhesive formulations were evaluated and some buccal tablets found to have minimal adhesive properties. It was concluded that only a small force is required to retain a dosage form within the buccal cavity. The stability of the adhesive bond was assessed for the two most adhesive materials {poly [acrylic acids] carbopol-934P and EX55} by subjecting to a continuous stress for 8 hrs prior to measuring the adhesive force. The carbopol EX55 [polycarbophil] formed the most stable adhesive bond which remained intact for 8 hrs.

**Han-Gon et al**\(^{[52]}\) studied the release and bioavailability of omeprazole delivered by buccal adhesive tablets composed of sodium alginate, hydroxypropyl methylcellulose [HPMC], magnesium oxide and cross-carmellose sodium. Cross-carmellose sodium enhanced the release of omeprazole from the tablets. The tablet was composed of omeprazole, sodium alginate, HPMC, magnesium-oxide, cross-carmellose sodium [20:24:6:50:10 mg]. It may be attached to the human cheek without collapse and it enhanced the stability of omeprazole in human saliva for at least 4 hrs giving a fast release of omeprazole. Results demonstrate that the omeprazole buccal adhesive tablet would be useful to deliver omeprazole which degrades very rapidly in acidic aqueous medium and undergoes hepatic first-pass metabolism after oral administration.

**Codd et al**\(^{[53]}\) developed two novel antifungal bioadhesive lozenges. Both were two-layered with an upper modified-release drug containing layer and a lower bioadhesive layer composed of drum-dried waxy maize starch and carbopol-980P to facilitate application to the oral mucosa. The first type of lozenge contained miconazole nitrate as a spray-dried form containing acacia and
cremophor-RH40 to increase the dissolution of the poorly soluble azole, plus flavorings. The second type also contained chlorhexidine acetate in the drug layer, as both drugs had been reported to act synergistically. In comparison to a proprietary oral gel formulation, the new bioadhesive lozenges produced much more uniform and effective salivary levels of miconazole nitrate over a prolonged period.

Prudat-Christiaens et al [54] studied the bioadhesive systems are new delivery systems used to reduce bioavailability problems resulting from a too short stay of the pharmaceutical form at the activity or absorption site. Aminophylline bioadhesive tablets were made by wet granulation with different polymers: Carbomers-934P, 974P, EX55, sodium carmellose, hypromellose and hydroxypropyl cellulose [HPC]. Wet granulation is a limiting factor for bioadhesion. The combination of polyacrylic acids with hypromellose or sodium carmellose increases bioadhesion and decreases drug release. Carbomer-974P alone had a lower adhesion than carbomer-934P. Combinations of carbomer-934P/hypromellose-100 gave the best adhesion properties and slow release dissolution.

Hosny et al [55] prepared polycarbophil containing diclofenac sodium tablets using two different size of granules. The granules were obtained by evaporation under reduced pressure of polycarbophil particles loaded with alcoholic solution of the drug. The in-vitro release of these bioadhesive containing tablets was evaluated together with that of Ciba-Geigy commercially available enteric coated tablets ‘Voltaren’ in simulated gastric fluid for 2 hrs followed by another 2 hrs in simulated intestinal fluid.

Bouckaert et al [56] studied the use of a bioadhesive buccal tablet containing miconazole nitrate has been shown to be effective in the treatment of oral candidosis and the influence of the application site on the buccal levels of miconazole nitrate. The \( t_{\text{max}} \) the adhesion time and \( T^{\text{MIC}} \) were significantly higher \([P < 0.05]\) when the gingiva was chosen as the application site in comparison with the cheek. The \( C_{\text{max}} \), \( t_{\text{max}} \) and AUC were not significantly different. The
gingiva is the application site of choice in irradiated patients even with a decreased salivary flow.

**Mumtaz et al** [57] prepared bioadhesive buccal tablets from different ratios of poly(acrylic acid-2,5-dimethyl-1,5-hexadiene) [PADH] and HPMC with and without triamcinolone acetonide [TAA] has been investigated in the buccal cavities of healthy human volunteers. The results indicate that tablets with a higher ratio of PADH swell faster, causing the disintegration of the tablets and consequently give rise to more rapid release of drug. The inclusion of higher percentages of HPMC provides more prolonged release of drug through its properties of gelling and slow dissolution. However, adhesion of the tablet was reduced in the excessive flow of saliva and there was also a tendency for the tablet to be dislodged from the mucosa. The tablet with a PADH/HPMC ratio of 50:50 seems to provide a suitable compromise for good bioadhesion and prolonged release of drug.

**Woolfson et al** [58] prepared novel bioadhesive cervical patch drug delivery containing 5-fluorouracil for the treatment of cervical intraepithelial neoplasia [CIN]. The patch was of bilaminar design; with a drug-loaded bioadhesive film cast from a gel containing 2% [w/w] carbopol-981P plasticized with 1% [w/w] glycerin. The casting solvent was ethanol/water 30:70, chosen to give a non-fissuring film with an even particle size distribution. Bioadhesive strength was independent of drug loading in the bioadhesive matrix over the range investigated but was influenced by both the plasticizer concentration in the casting gel and the thickness of the final film. Release of 5-fluorouracil from the bioadhesive layer into an aqueous sink was rapid but was controlled down to an undetectable level through the backing layer.

**Miyazaki et al** [59] prepared oral mucosal bioadhesive tablets of diltiazem by directly compressing the drug with a mixture of chitosan and sodium alginate. In-vitro adhesion studies indicated adhesion properties comparable to those of a commercial formulation. In-vitro release of diltiazem was rapid and could be modified by changing the mixing ratio of chitosan and sodium alginate; increasing the chitosan content in the tablets and/or the viscosity grade of the alginate.
resulted in a decrease in the *in-vitro* release rate. The bioavailability of diltiazem was 69.6% from tablets with a 1:4 chitosan/alginate weight ratio when administered sublingually to rabbits compared with 30.4% by oral administration. Needleman *et al* [60] examined the factors important to prolonged adhesion [adhesion time] in organ culture under standardized conditions. A wide variety of bioadhesive were tested in the model and the effect of mucin was also examined. Whilst many gels adhered for 1–5 hrs, others [chitosan and eudispert] showed no retention loss over 4 days. Histologically, chitosan also showed excellent tissue wetting properties. For most materials, however, mucin significantly reduced adhesion times \([P < 0.05]\). In conclusion, the absence of mucin, the control of gel hydration and swelling, and wetting characteristics were identified as key factors for prolonged adhesion.

Wen-Gang *et al* [61] prepared direct compressed disc systems containing either 10, 15 or 20 mg of propranolol hydrochloride [PL] with a mixture of hydroxypropylcellulose and poly[acrylic acid]. The release data were fitted to the simple power equation and it was found that the release characteristics of PL from these systems were not affected by the amounts of the drug loaded and followed behavior conforming to a non-Fickian mechanism of release. The adhesive bond strength of the systems to the porcine buccal mucosa was evaluated by the tensile strength test and the result showed no significant difference in adhesive bond strength to the porcine buccal mucosa among the three PL-containing discs and drug free discs.

Naffie *et al* [62] investigated different types of mucoadhesive polymers, intended for buccal tablet formulation, for their comparative mucoadhesive force, swelling behavior, residence time and surface pH. The selected polymers were carbopols [CP-934 and CP-940], polycarbophil [PC], sodiumcarboxymethylcellulose [NaCMC] and pectin representing the anionic type, while chitosan as cationic polymer and hydroxypropylmethyl cellulose [HPMC] as a non-ionic polymer. Results revealed that polyacrylic acid derivatives [PAA] showed the highest bioadhesion force, prolonged residence time and high surface acidity. NaCMC and chitosan ensured promising bioadhesive characteristics, while HPMC and
pectin exhibited weaker bioadhesion. Different polymer combinations as well as formulations were evaluated to improve the mucoadhesive performance of the tablets. Bioadhesive tablet formulations containing either 5% CP934, 65% HPMC and 30% spray-dried lactose or 2% PC, 68% HPMC and 30% mannitol showed optimum mucoadhesion and suitable residence time. NaCMC, when formulated individually, exhibited promising bioadhesion, acceptable swelling, convenient residence time and surface pH. In-vivo trials of these formulations proved non-irritative and prolonged residence of the mucoadhesive tablets on human buccal mucosa for 8 to 13 hrs.

Naffie et al\textsuperscript{[63]} studied from the previous work [Part-I\textsuperscript{62}], mucoadhesive formulae containing 5% CP/65% HPMC/30% lactose and 2% PC/68% HPMC/30% mannitol as well as formulae based on sodium carboxymethylcellulose [NaCMC] were selected. Medicated tablets were prepared using diltiazem hydrochloride and metclopramide hydrochloride in two different doses [30 and 60 mg]. The effect of drug and dose on the mucoadhesive properties and in-vitro drug release was evaluated. All formulae produced extended drug release [over 8 to 12 hrs]. Doubling the dose significantly reduced the bioadhesion strength [p < 0.05] with a slight improvement in drug release rate. The formulation of bilayer tablets containing drug-free layer and medicated layer enhanced the drug release without affecting the bioadhesive performance. The bilayer tablet formulated with 2% PC/68% HPMC/30% mannitol was selected for studying the in-vivo metoclopramide release in four healthy volunteers. The tablet ensured controlled drug release for 12 hrs, in addition, good correlation [r = 0.9398] was observed between in-vitro and in-vivo data. Storage at 40\degree C and 75% relative humidity for 6 months didn’t influence the mucoadhesive performance, however, an enhanced released rate was observed.

Shan-chul et al\textsuperscript{[64]} developed the new local anesthetic formulations with a suitable bioadhesive property, hydroxypropylmethylcellulose based gel was formulated. The effects of permeation enhancers on the permeation rate of drug through skin were studied using various enhancers, such as the glycols, the nonionic surfactants, and the bile salts. Among the enhancers used,
polyoxyethylene 2-oleyl ether showed the highest enhancing effects on drug permeation through skin. The analgesic activity was examined using a tail-flick analgesimeter.

Chowdary et al.\cite{65} prepared mucoadhesive tablets with nifedipine alone and its inclusion complexes with $\beta$-cyclodextrin and the mucoadhesive polymers sodium carboxymethyl cellulose and carbopol were investigated with a view to the design of oral controlled release tablets of nifedipine.

Raghuraman et al.\cite{66} prepared propranolol hydrochloride buccal films using three different polymers in various proportions and combinations. The physiochemical parameters like weight variation, thickness, folding endurance, drug content, percentage moisture absorption and percentage moisture loss were evaluated.

Perioli et al.\cite{67} prepared mucoadhesive tablets using different mixture of cellulose and polyacrylic derivatives in order to obtain new formulations containing metronidazole for periodontal disease treatment.

Patil et al.\cite{68} prepared mucoadhesive buccal patches of diclofenac sodium. Patches were fabricated by casting technique with different polymer combinations.

Khurana et al.\cite{69} prepared mucoadhesive films of miconazole nitrate for the treatment of oral candidosis. Films were fabricated by casting technique with different polymer combinations and were evaluated for their in-vitro bioadhesive performance and release characteristics.

Nafee et al.\cite{70} prepared mucoadhesive patches containing 10 mg miconazole nitrate with ionic polymers, sodiumcarboxymethylcellulose and chitosan or non-ionic polymers polyvinyl alcohol, hydroxyethylcellulose and hydroxypropylmethyl cellulose.
Chapter 2

**Review of work done**

### 2.2 References


