Chapter – 2

Review of Literatures
INTRODUCTION TO LITERATURE REVIEW:

Literature review is a systematic and thorough search of all types of published literature in order to identify as many items as possible those are relevant to a particular topic of research. The main objectives to present this chapter are firstly, to provide a justification of the proposed research project and secondly, to develop an argument for the study on the basis of literatures reviewed. This chapter reviews the literatures associated with the areas of interest in present study. The major areas that have been reviewed and presented in different sections of this chapter include:

- Extraction, isolation and purification of natural polysaccharide and their physicochemical characterization.

- Cross-linking of polysaccharide and application of cross-linked polysaccharide in drug delivery system.

- Mucoadhesive drug delivery systems and their evaluation.

- *Hibiscus esculentus* Linn polysaccharide and its pharmaceutical applications.

- Famotidine gastro-retentive drug delivery systems to improve the bioavailability.

2.1. EXTRACTION, ISOLATION AND PURIFICATION OF POLYSACCHARIDE:

Chang et al in their study, extracted polysaccharide from *Ganoderma lucidum* by hot water extraction followed by precipitation with 95% ethanol. The average molecular weight of the isolated & fractionated polysaccharide was carried out by high performance size-exclusion chromatography. The result shows that, 1→3, 1→6-b-D-glucan was the major polysaccharide present in the *G. lucidum*. They also demonstrated
that, 1→3, 1→6-b-D-glucan is responsible for stimulating Mononuclear Cell to release Tumor Necrosis Factor–α for anti-tumor and immune-stimulant activity of *G. lucidum* as in Chinese traditional medicine (1).

Chen *et al* has extracted the water soluble polysaccharide from *Ophiopogon japonicas* by hot water extraction followed by precipitation with 95% ethanol. The extracted polysaccharide was purified DEAE-52 Cellulose ion-exchange chromatography followed by Sephadex G-100 size exclusion chromatography. The high performance gel permeation chromatography analysis showed that the average molecular weight of the polysaccharide was 35.2 kDa. Monosaccharides analysis revealed that the OJP1 is composed of Arabinose, Glucose, Galactose with a relative molar ratio of 1:16:8. Pharmaceutical experiments showed OJP1 can significantly reduce blood glucose level, increase the insulin level and found to be a potential antidiabetic agent (2).

Mu L.X. *et al* has optimized the extraction and purification procedure for polysaccharides from *Astragalus membranaceus* in terms of yield and decoloration. The orthogonal statistical test was used determined in the process optimization of extraction and purification of polysaccharide for its rate of extraction and the effect of deproteinaton and decoloration on the content of polysaccharide. The result of the study established a simple, quick and effective method of extraction of polysaccharide (3).

Jia D. *et al* has reported an effective method of preparative extraction and purification of the polysaccharides from mulberry leaves by gel permeation chromatographic (GPC) method. Orthogonal experimental design was employed to find out optimal condition in terms of temperature, pH, duration and their effect on the yield. The structure analysis indicated that the purified mulberry leaves polysaccharide composed of Mannose,
Galactose and Rhamnose. The molecular weight was approximately 557 062 D. The IR and $^1$H NMR spectra indicated that the polysaccharide mainly pectin type (4).

**Liu Y. et al** has extracted polysaccharide from *Ruditapes philippinarum* and the crude polysaccharide was purified by DEAE-sepharose gel filtration chromatography and Sephacryl S-400 size exclusion chromatography. The purified fraction of polysaccharide found to be composed of aminosugars, uronic acid, fucose and sulfate. FTIR and DSC study revealed that the polysaccharide contain straight chain with –Cho and –COOH functional groups (5).

**Yang et al** has extracted polysaccharide from *Cornus officinalis* a Chinese traditional medicine. An acidic fraction of the polysaccharide was isolated by column chromatography. High performance gel permeation chromatography (HPGPC) showed that the fraction consists of homogeneous polysaccharide with average molecular weight 8.7X10$^4$. Monosaccharide analysis revealed that the polysaccharide fraction composed of rhamnose, arabinose, galactose and galacturonic acid. GC-MS and $^{13}$C-NMR were employed to understand the molecular structure of the polysaccharide chain (6).

**Tian M et al** has isolated a water soluble polysaccharide from *Lycium barbarum* by aqueous extraction followed by purification by DEAE ion exchange chromatography. The structural composition of the polysaccharide was studied by SDS-PAGE gel electrophoresis, GC. The result of the study revealed that the polysaccharide is a kind of complex polysaccharides consisting of acidic heteropolysaccharides and polypeptide or protein. The average molecular weight of the polysaccharide was found to be 1.524 X 10$^5$ (7).
Paik S.Y. et al in their study, have extracted & isolated polysaccharide from *Capsicum annuum* by cold water extraction for 24 hours followed by hot water extraction at 100ºC. Total carbohydrate and uronic acid content of the isolated polysaccharide were determined by the phenol-sulfuric acid and m-hydroxydiphenyl methods using arabinose and galacturonic acid as standards. The isolated polysaccharide was purified & fractionated using DEAE Sepharose by ion-exchange chromatography and Sephadex G-75, G-100, G-200 for gel filtration chromatography (8).

Kharat A.R. et al has extracted the mucilage from seed coat of *Cassia absus* by multiple maceration technique. Extracted mucilage was evaluated in terms of solubility, swelling index, loss on drying, viscosity, and microbial content. The dried mucilage was assessed for binding property in the concentration of 4, 5 & 6% w/w. *Cassia absus* shows promising binding property in compressed tablets in 4 and 5% concentration in comparison to guar gum as standard binder (9).

Li T. et al has studied algal polysaccharide as substitute for gelation in manufacturing of capsule shell and its effect on the bioavailability of drug. The study in human volunteer showed the bioequivalence. The disintegration behavior of the capsule shells formed with polysaccharide was also studied by gamma-scintigraphic study. The result of the study showed that there is not statistical difference between capsule formed with polysaccharide and conventional gelatin. Therefore polysaccharide can be used as vegetable replacement of gelatin in the production of hard capsule shell (10).

Deveswaran R. et al has extracted tamarind seed polysaccharide by non-solvent addition method. The extracted polysaccharide was characterized and evaluated for its suspending properties in Nimusulide suspension. The prepared suspensions were evaluated for rheological & physicochemical parameters. The result of the study showed
the suitability of tamarind seed polysaccharide as suspending agent for pharmaceutical formulations (11).

Enauyatifard R. et al in their investigation, compared Ferula gummosa gum with PVP and acacia as binding agent. The gum was extracted by maceration with distilled water. Acetaminophen and calcium carbonate granules were prepared using the wet granulation method and were evaluated for their micromeritic and flow properties, while the compacts were evaluated for mechanical properties using the hardness, tensile strength and friability. The result obtained in the study indicated that the gum can be used as binding agent for pharmaceutical formulation (12).

Cerqueira M.A. et al has reported a detailed method for extraction, isolation and purification of galactomannan polysaccharide from seeds of Leguminoseae plants. Along with the conventional method of non-solvent addition to isolate polysaccharide, they also employed 1:1 sulphuric acid for the purpose of isolating polysaccharide. The isolated polysaccharide was purified by centrifugation and repeated precipitation with ethanol. This method demonstrated high yield of polysaccharide, yet economic (13).

Hussain K. et al reported a reliable method of estimating total polysaccharide in extracted samples by anthrone reagent method. In this method, colorimetric determination of polysaccharide in terms of glucose unit has been illustrated. The soluble sugars present in the sample were separated by washing with alcohol followed by centrifugation. The polysaccharides present in the sample were hydrolyzed with sulphuric acid. The hydrolyzed polysaccharide gives green (14).

Xiu-zhen N. et al has reported the method of fractionation of polysaccharide isolated from Panax ginseng leaves. Fractionation of polysaccharide was achieved by
combination techniques namely ethanol precipitation, ion exchange and gel filtration chromatography. The method successfully fractionated polysaccharide on the basis on molecular weight and ionic charge. The fractionated polysaccharide was analyzed for monosaccharide composition and molecular weight distribution. The study reported that the polysaccharide of *P. ginseng* composed of arabinose, galactose, xylose, mannose, rhamnose\(^{(15)}\).

### 2.2. CROSS-LINKING OF POLYSACCHARIDE:

**Chaurasia M. et al** has employed the method of glutaraldehyde cross-linking to prepare guar gum microsphere. The cross-linking of guar gum polysaccharide by glutaraldehyde have been achieved in mild acidic condition. Cross-linking of guar gum induced by glutaraldehyde significantly decreases its swellability in aqueous fluid. Reduction of swellability of crosslinked guar gum depends on the concentration of glutaraldehyde used in the process. Results of the study also suggested that, crosslinking of guar gum decreases the drug release rate\(^{(16)}\).

**Barreiro-Iglesias R.** has reported a one-step procedure for cross-linking of chitosan using glutaraldehyde. The optimization of cross-linking procedure was carried out in acetic acid environment with varying concentration of glutaraldehyde, molecular weight of chitosan and reaction temperature. With increase in glutaraldehyde concentration, molecular weight of chitosan and process temperature, reduction of time to achieve gel point was observed. The result of the study suggested that, glutaraldehyde cross-linked chitosan is able to deliver the drug quickly in gastric environment as it inhibits pH sensitive swelling in acidic media\(^{(17)}\).

**Ramachandran S. et al** has biodegradable chitosan microsphere loaded with famotidine to improve bioavailability. The microspheres were prepared by simple
emulsification technique based on glutaraldehyde crosslinking. The microspheres were characterized for entrapment efficiency, drug loading, *in vitro* drug release, surface morphology, as well as by particle size analysis, FTIR spectroscopy and differential scanning calorimetry. Glutaraldehyde cross-linked chitosan microspheres showed prolonged drug release which followed Higuchi model (18).

**Cao Z. et al** has synthesized a series of cross-linked chitosan resigns by forming chitosan coordination of Cu(II) as template in dilute acetic acid solutions under microwave radiation, then reacting the Cu(II)-chitosan complex with glutaraldehyde as cross-linking agent. The cross-linked chitosan showed improved adsorption properties compared to unmodified chitosan (19).

**Singh A. et al** has prepared transparent covalent hydrogels of chitosan by crosslinking with varying amounts of formaldehyde solution used as crosslinking agent. The characteristics of hydrogels were investigated by Fourier transform infrared (FT–IR) spectroscopy and swelling experiments. The effect of crosslinking agent on water absorbency has been investigated. The hydrogels exhibited a relatively higher swelling ratio and equilibrium water content (20).

**Tomihata K. et al** has chemically cross-linked Hyaluronic acid with glutaraldehyde (GA) to produce water-insoluble films having low water contents when brought into contact with water. The crosslinking reaction was performed using uncrosslinked Hyaluronic acid films in acetone–water mixtures. On the basis of the infrared spectra, it was concluded that the cross-linking is due to intermolecular formation of hemiacetal bonds with GA between the hydroxyl groups belonging to different HA molecules led to crosslinking (21).
Shivashankar M. et al has employed glutaldehyde in preparation of microsphere as cross-linking agent. Bupivacaine microspheres were prepared by emulsification technique drug-loaded chitosan microsphere were coated with polyglycolic acid film. Encapsulation yield was 83.1%. SEM studies indicate that the microspheres were spherical and had a relatively smooth surface. XRD and DSC data indicate that there was no interaction between the drug and polymer. The in-vitro dissolution study showed 38% drug release on 11th day (22).

Distantina S. et al has prepared glutaraldehyde-crosslinked kappa carrageenan hydrogel using glutaraldehyde as the crosslinking agent. The cross-linking was carried out by immersing kappa carrageenan in GA solution (1-5 wt%) for 2 min and then cured at 110°C for 25 min. The infrared spectra, thermal analysis, and the value of swelling degree of obtained hydrogel showed that kappa carrageenan was able to be cross-linked using glutaraldehyde without catalyst presence. GA concentration less than 0.027 g GA/g polymer was not able to crosslink hydroxyls group of carrageenan. The cross-linked carrageenan showed decreased in swelling behavior. The cross-linked kappa carrageenan hydrogel was found to be pH sensitive (23).

2.3. MUCOADHESIVE DRUG DELIVERY SYSTEM:

Arora G. et al has formulated oral controlled release mucoadhesive matrix tablets of domperidone using taro gum as mucoadhesive polymer. Tablets were prepared by direct compression and were evaluated for bioadhesive strength and in vitro dissolution parameters. The formulations were optimized using 3² factorial design and response surface methodology. The results of the study indicated concentration dependent mucoadhesive and release retardant potential of taro gum in the formulation of gastro retentive mucoadhesive matrix tablets. Drug release kinetics study revealed that the
formulation follows Higuchi equation and a concentration dependent transformation from fickian to non fickain drug release mechanism was observed. The dependent variables viz. mucoadhesive strength, tensile strength, release exponent and t$_{50}$ could be modulated by varying the critical formulation variables $^{(24)}$.

Madhav N.V.S et al has isolated polysaccharide from seed-coat from Lallimantia royalena by non-solvent addition method. Isolated polysaccharide characterized by solubility, pH, viscosity, colour changing point, UV and IR spectroscopy methods. L. royalena polysaccharide was evaluated for mucoadhesion potential and result obtained was compared with NaCMC and HPMC. Mucoadhesion test by Park and Robinson method showed the isolated polysaccharide possess comparable to NaCMC and similar to HPMC $^{(25)}$.

Patil P et al has formulated ofloxacin mucoadhesive tablet using different types of natural gums such as guar gum, locust bean gum and their combinations for oral administration. Weight variation, Hardness, Friability, Drug content, Swelling index, in vitro drug release study, in vitro mucoadhesive strength study of the prepared tablets were determined. All the formulation found to comply with pharmacopieal standards. The combination of guar gum and locust bean gum in mucoadhesive tablets showed desired in vitro drug release, good swelling and better mucoadhesive strength than single gums and other gum combinations. The drug release of optimized formulation follows the Higuchi kinetic model, and the mechanism is found to be non-Fickian $^{(26)}$.

Takeuchi H. et al has designed particulate drug delivery system with mucoadhesive coating. Chitosan and carbopol were used as mucoadhesive material. The mucoadhesive tests were conducted for the polymers as well as the drug delivery system by quantitative mucin-interaction study. Both the polymer showed excellent mucoadhesive
property. The mucoadhesive polymer coated micro-particles were investigated for gastro-retention in rat intestine by Confocal Laser Scanning Microscopy (CLSM). The CLSM images demonstrated longer retention time for coated microparticles than uncoated particles. The observations of the study suggested that mucoadhesive polymer coated liposomal particles can be used as carrier for oral administration of water soluble drugs \(^{(27)}\).

**Llabot J.M. et al** has investigated *in-vitro* mucoadhesion, water uptake and drug release from the matrices prepared with different ratio of carbopol and lyophilized sodium carbopol. The matrices were prepared by direct compression method. In their investigation, they reported that, with increasing proportion of carbopol in matrices increases the mucoadhesion property. The release behavior of matrices was found to be exhibited a biphasic profile with a first phase characterized by anomolous \((n < 1)\) followed by super case transport mechanism \((n > 1)\) \(^{(28)}\).

**Lee C.H. et al** has developed a mucoadhesive vaginal drug-delivery system using carbopol 934P to achieve dual-controlled delivery of Nonoxynol-9 and EDTA for enhanced fertility control. The effects of mucoadhesive polymers and calcium-related interaction on the residence characteristics of DDS within the vagina and the release kinetic profile were investigated. Prepared DDS was investigated for adhesion force and work of adhesion shear derived from mucin-polymer interaction using lamb vaginal mucosa. The result indicated that mucoadhesive strength of DDS to lamb vaginal mucosa increased with EDTA, but decreased with calcium, indicating that divalent cations play an important role in adhesion of carbopol in mucosal surface. It was also observed that release kinetics was not affected by EDTA, but was reduced in the presence of calcium chloride. These results indicated that mucoadhesive vaginal drug
delivery system seems suitable to achieve controlled release of Nonoxynol-9 for prolonged and enhanced fertility control \(^{(29)}\).

**Jiménez-Castellanos M.R. et al** has designed a unique drug delivery system employing the concept of both bioadhesion and flotation to increase gastric retention time of water soluble drug Sotalol HCl. The floating controlled release bioadhesive drug delivery systems were prepared using different cellulosic polymers. The new oral controlled-release drug delivery device showed acceptable controlled release of the drug, bioadhesiveness in the stomach and intestine of rabbits and buoyancy in an acid medium. This suggests that the dual concept can be successfully employed in achieving enhanced gastric retention time for water soluble drugs \(^{(30)}\).

**Arora G. et al** has developed oral controlled release mucoadhesive matrix tablets of domperidone using natural mucoadhesive material myrrh oleo gum resin. in different concentration (5 to 20 % w/w) employing direct compression technology. The prepared batches were evaluated for post-compression parameters, swelling index, tensile strength, mucoadhesive strength and \textit{in vitro} drug release studies. Result showed that tensile strength and mucoadhesion strength increases with increasing concentration of myrrh oleo gum resin \(^{(31)}\).

**Amin M.L. et al** designed and developed mucoadhesive microsphere of diclofenac sodium using natural gums such as guar gum and tragacanth, sodium alginate as mucoadhesive polymers. Microspheres were formulated using orifice-ionic gelation method. Surface morphology, particle size, swelling behavior and drug entrapment efficiency of the formulated microspheres were determined. \textit{In vitro} evaluation was carried out to assess drug release study kinetics and mucoadhesion properties. The prepared microspheres were discrete and free flowing. With increase in cross-linking,
the rate of drug release found to be delayed. The drug release from all the formulations found to follow Higuchi's model. Overall, the results pointed that mucoadhesive microspheres containing natural gum can be promising alternative for prolonged delivery of drug substances with good mucoadhesive action, targeting the absorption site to thrive oral drug delivery\textsuperscript{(33)}.

\textbf{Alur H.H. et al} has the gum from \textit{Hakea gibbosa} (hakea) as a sustained-release and mucoadhesive component in buccal tablets for a model peptide, namely, salmon calcitonin. The \textit{in vitro} release profiles were sigmoidal in nature and according to a mathematical model indicated super Case II transport as the primary mechanism of release. The resulting plasma salmon calcitonin and calcium concentrations were determined following both intravenous administration and buccal application of mucoadhesive tablets in rabbits. Following the application of the mucoadhesive buccal tablets which contained 40 µg of salmon calcitonin and either 12 or 32 mg of hakea, apparent bioavailability (F) and clearance (CL) were calculated. The mechanism of \textit{in vitro} release is likely to involve peptide diffusion/polymer dissolution. The mucoadhesive strength, as measured by the force of detachment, can be modulated by altering the amount of hakea in the tablet. The mucoadhesive buccal tablets described in the study may be exploited for an improved transbuccal delivery system for therapeutic polypeptides\textsuperscript{(33)}.

\textbf{Mankala S.K. et al} has formulated gliclazide microspheres with sodium alginate and gum kondagogu, gum guar and xanthan gum as mucoadhesive agents, by orifice-ionic gelation and emulsification ionic gelation techniques varying concentrations. Formulations were then evaluated for surface morphology, particle shape, Carr’s index, microencapsulation efficiency, drug release, mucoadhesion studies. Compatibility
studies were performed by FTIR, DSC, and XRD techniques and no interactions were found between drug and excipients used. The microspheres were found spherical and free flowing. All microspheres showed satisfactory mucoadhesive property in in-vitro wash of test. Guar gum found to retard the drug release comparatively better than other gums and concentrations. Drug release from the microspheres was following zero order release kinetics with non-fickian release mechanism and rate of release depends on the coat: core ratio \(^{(34)}\).

**Arora G. et al** has prepared controlled release mucoadhesive matrix tablets of domperidone using a natural polysaccharide *Salvia plebeian* gum. Tablets were prepared by direct compression method employing the *Salvia plebeian* gum in different concentrations (5, 10, 15 and 20% w/w). The prepared batches were evaluated for pre-compression and post-compression parameters. Mucoadhesive strength was determined using texture analyzer. Real-time stability studies were also conducted on prepared batches. drug release data were fitted in various release kinetic models for studying the mechanism of drug release. The *In vitro* drug release kinetic study revealed that the matrix tablets follow zero-order and Higuchi models, which indicates the potential use of the *Salvia plebeian* gum in sustained release mucoadhesive matrix tablets \(^{(35)}\).

**Shah H.V. et al** has designed buccal mucoadhesive compact using natural polymers to increase bioavailability fluvastatin. Mucoadhesive layer of the buccal tablets were composed tamarind seed gum, xanthan gum and thiolated chitosan. The mucoadhesion strength exhibited by thiolated chitosan was many fold higher than that of xanthan gum or tamarind seed gum. Release studies revealed that the sustained release of fluvastatin over several hours may be obtained by combining the thiolated chitosan with natural gums like xanthan and tamrind gum. The bioavailability studies indicated that
bioavailability of fluvastatin was enhanced using the drug delivery system composed of thiolated chitosan along with tamarind seed gum and xanthan gum. Thus, the potential of the mucoadhesive buccal drug delivery device is promising and novel tool in order to improve the therapeutic efficacy of various drugs with shorter half-life and poor bioavailability \(^\text{36}\).

**Singh S.K. et al** designed controlled release mucoadhesive tablet of tramadol HCl to extend gastric residence time for sustaining plasma level. The mucoadhesive matrix tablets were formulated using guar gum, xanthan gum, HPMC K15M and HPMC K100M. Formulated tablets were evaluated for pre-compression parameters, post-compression parameters, *in-vitro* release profile and release kinetics. The release mechanism found to be non-Fickian and followed zero order kinetics. Mucoadhesion strength was studied by modified balance method. The result of the study showed that there is direct influence on the release profile of oral mucoadhesive formulation. It also suggested that combination of synthetic and natural gum can be used to develop successful oral mucoadhesive formulation \(^\text{37}\).

**Patel D.J. et al** has designed mucoadhesive nanosuspension to improve the dissolution rate of famotidine. Polyethylene oxide was employed as mucoadhesive polymer to extend retention time for the famotidine loaded nanosuspension in stomach. Prepared nanosuspensions were evaluated for particle size and distribution, viscosity, mucoadhesion potential, and *in vitro* drug release. Polyethylene oxides of different grades and at varying concentration were found to affect the retention of nanosuspension and controlled the drug release for longer period. The optimized formulation was shown desired dissolution profile with increased gastric retention. It
may be concluded that nanosuspension can be employed as a tool to improve bioavailability of poorly soluble drugs (38).

**Gavaskar B. et al** has formulated mucoadhesive buccal tablets of baclofen using carbopol-974, sodium carboxy methyl cellulose, sodium alginate, methocel as mucoadhesive polymers. The prepared tablets were evaluated for pre-compression and post-compression parameters. The *ex-vivo* mucoadhesion test by modified balance method was performed to assess mucoadhesion strength. The bioadhesion test revealed that, formulations containing carbopol-974 have maximum adhesive strength followed by formulation containing PVP K30 (39).

**Ahmed M.G. et al** has formulated mucoadhesive beads for oral delivery of captopril. The beads were prepared by orifice ionic gelation method. Various ratio of HPMC, carbopol 934p, chitosan, and cellulose acetate phthalate were used in combination with sodium alginate. FT-IR spectroscopy was employed to study the compatibility of polymers with drug. The prepared beads were evaluated for encapsulation efficiency, particle size distribution, drug content and drug release behavior. The adhesiveness of the beads were investigated by wash off method using sheep stomach mucosa. The results of the study suggested that this type of drug delivery system can be potentially applied for sustained release mucoadhesive delivery of drugs (40).

**Santus G. et al** has investigated the effect of bioadhesive polymers in the controlled release behavior of frusemide oral bioadhesive drug delivery system. Gamma scintigraphy study was performed to assess the gastrointestinal transit of drug delivery system *in vivo*. A strong correlation was found between gastrointestinal transit and furosemide absorption. The results showed that the controlled release properties were
not affected by the application of the bioadhesive polymer but that the bioadhesive properties were substantially different \(^{(41)}\).

**Jackson S.J. *et al*\)** has employed Gamma scintigraphy to compare the gastric emptying and residence of this cholestyramine with two formulations known to exhibit bioadhesive properties, Carbopol 934P and sucralfate. Fasted normal subjects received a single radiolabelled dose and gastrointestinal transit was monitored for 6 h. The subjects were fed after 4 h to determine the effects of inducing a fed pattern of motility on the retention of the formulations. The gamma scintigraphic images showed that cholestyramine was distributed widely throughout the stomach whereas Carbopol and sucralfate were concentrated in the body and antrum parts of stomach. The results of the study suggested that, cholestyramine had a comparable emptying time to Carbopol and sucralfate but greater gastric residence and wider distribution, it could provide a potential mucoadhesive drug delivery system targeting the gastric mucosa \(^{(42)}\).

**Sachan N.K. *et al*\)** has formulated ibuprofen loaded micobeads employing Assam bora rice and sodium alginate to modulate the drug delivery by mucoadhesion. The microbeads were prepared by micro-orifice ionic gelation technique. Prepared formulation were characterized for particle size, surface morphology, compatibility studies. *In-vitro* drug release study confirmed extended release of medicament up to 12 hours. *Ex-vivo* mucoadhesion test by wash-off test showed considerable mucoadhesion over a period of 8 hours \(^{(43)}\).

**Goswami D.S. *et al*\)** designed mucoadhesive tablets of Amoxicillin trihydrate to improve patient compliance, using moringa gum as a natural mucoadhesive polymer in combination with other synthetic polymers. Prepared tablets were evaluated for post-compression parameters and mucoadhesive property. The study suggested that moringa
gum can be used as potential candidate for mucoadhesive drug delivery for oral administration \(^{(44)}\).

**Dias et al** has designed Mucoadhesive formulation of acyclovir tablet using carbopol P943 and HPMC K100M. All the formulations shows non-fickian diffusion and complete drug release up to 12 hours. \(^3\) \(^2\) full factorial design employed in the investigation shows both the polymer have significant influence in Mucoadhesive strength of the formulation. *Ex-vivo* study of the formulation has suggested that increased gastric residence time eventually improve the bioavailability of acyclovir \(^{(45)}\).

**Arya et al** has prepared famotidine microspheres by the w/o emulsification solvent evaporation method using mucoadhesive polymers sodium CMC and a release controlling polymer sodium alginate for prolongation of gastric retention time. The prepared microspheres were characterized particle size, shape and drug entrapment efficiency. *In-vitro* drug release study exhibited prolonged release up to 8 hours. It also demonstrated that increasing concentration of sodium CMC increase the mucoadhesion while increasing concentration of sodium alginate decrease the rate of drug release from the matrix \(^{(46)}\).

**Kharwade et al** in their work, has investigated *Aegle marmelos* gum as mucoadhesive material in tablet formulation using diclofenac sodium as model drug. The six tablet formulations were prepared by using 0.25 to 1.50\% w/w of *Aegle marmelos* gum by direct compression. The study shows that *A. marmelos* at a concentration of 1.25\% w/w is a potential for mucoadhesive drug delivery \(^{(47)}\).

**Pund S. et al** has formulated gastroretentive drug delivery of rifampicin. The drug delivery system composed of immediate release rifampicin pallets and mucoadhesive
rifampicin tablet for extended release using carbopol. In their study, they employed Gamma Scitigographic imaging technique to investigate the gastric transit of gastro-retentive formulation. The in-vivo gamma scintigraphic study was carried out in human volunteers using Tc$^{99m}$ as radiolabelling agent. The transit profiles obtained by gamma scintigraphy, demonstrated that the dosage form was retained in the stomach for more than 320 min$^{(48)}$.

Burke M.D. et al has devised a new method for studying gastro-restion study using gamma scintigraphy. The method employs two radio-nucleus namely indium (In$^{111}$) and samarium (Sm$^{153}$). In vitro evaluation revealed significant radionuclide leakage at pH 1.5 while leakage at pH 4.5 was less. The radiolabelling technique was proved to be successful during preclinical and clinical evaluations, allowing evaluation of gastric retention performance as well as complete gastrointestinal transit$^{(49)}$.

2.4. *Hibiscus esculentus* LINN. POLYSACCHARIDE:

Woolfe M.L. et al has extracted and purified polysaccharide from *H. esculentus* by gel chromatography using Sephadex G-100 column. The purified polysaccharide was chemically characterized. FTIR spectra revealed the polysaccharide molecular absorption peaks. The chemical analysis ascertained the presence of rhamnose, galactose, glucose, arabinose, galactouronic acid and glucouronic acid as monomeric unit in the polysaccharide$^{(50)}$.

Sengkhamparn N. et al has extracted and characterized the cell wall polysaccharide of *H. esculentus*. Four fractions of the water soluble polysaccharide was extracted using hot buffer, chelating agent, dilute alkaline and concentrated alkaline. These fractions...
differ in momosaccharide composition but chiefly they consist of rhamnogalactomannan, rhamnose, galactose, galactouronic acid, and arabinose \(^{(51)}\).

**Ndjouenkeu R. et al** has investigated the rheological behavior of *H. esculentus*. The polysaccharide showed typical polyelectrolyte behavior in ionic solution. Concentrated solution of *H. esculentus* polysaccharide gave mechanical spectra that are typical of entangled macromolecular networking. Terminal slopes for okra gum were unusually low, and varied systematically with polymer concentration, which tentatively attributed to compact macromolecular structures, with a strong tendency to self-association \(^{(52)}\).

**Sengkhamparn N. et al** has investigated the physicochemical behavior of two slightly deferent pectin isolated from *H. esculentus*. The viscosity of hot buffer extracted pectin was found to be 5 – 8 times higher than chelating agent extracted pectin. The okra hot buffer extracted pectin showed an elastic behaviour over a wide range of frequencies while okra CHSS and saponified okra pectin showed predominantly viscous responses. The results suggest that the structural variation within the okra pectins greatly affect their rheological behavior \(^{(53)}\).

**Kalu V.D. et al** has compared the *H. esculentus* mucilage with sodium carboxy methyl cellulose and hydroxypropyl methyl cellulose for release retardant in matrix tablet using paracetamol as model drug. Matrix tablets were prepared by direct compression method with and without tablet excipients. The mucilage have found to control the release of paracetamol from the matrix system with as little as 10% of the gum in the formulation. Controlling of drug release increases with increasing concentration of mucilage in the formulation. Paracetamol in okra gum matrix tablets showed non-Fickian release which approached Case II, time-independent release \(^{(54)}\).
Onunkwo G.C. et al has reported a comparative study of *Abelmoschus esculentus* as a binding agent in tablet formulation. The pre-compression parameters (flow property, density, friability) and post compression parameters (weight uniformity, hardness, friability) of the granules & tablets prepared with *A esculentus* was compared with that of acacia, gelatin and PVP. The results indicated that flow of the granules greatly influenced by concentration of gum. While increasing in concentration of the gum severely affect the disintegration time and dissolution rate of the formulated tablets. Which indicate that *A. esculentus* gum may not be a suitable candidate as binding agent for conventional release tablets (55).

Mann et al investigated the mechanical and disintegrating property of *Hibiscus esculentus* mucilage in paracetamol tablets. These properties of *H. esculntus* was compared with gum acacia as standard binder. The effects of the nature and concentration of the mucilage binder and the relative density of the tablet on the tensile strength, brittle fracture index and disintegration time of the tablets were investigated(56).

Ogaji I et al studied okra gum as film coating material on paracetamol tablets. For this study they have extracted the gum from *Abelmoschus esculentus*. The extracted gum was characterized by density, angle of repose, solubility, pH, viscosity study. The coating solution of the gum was prepared in combination with HPMC. The coated tablets were evaluated for weight uniformity, diameter, thickness, hardness, friability, disintegration and water uptake. The coated tablets were found to improve tablet physical properties without significant change in the dissolution profile of the model tablets. The study suggested that okra gum can be used as promising natural, biodegradable, economic film former for aqueous film coating of tablets (57).
Emeje M. et al investigated the fundamental characteristics of gum extracted from *A. esculentus*. The gum was characterized in terms of solubility, swelling index, loss on drying, pH, density and ash value. Elemental analysis, scanning electron microscopy, X-Ray powder diffraction, TGA & DSC, FTIR and NMR spectroscopy were used to characterize the extracted gum. Elemental analysis of the gum showed presence of 39.5%, 7.3%, 51.8% and 1.4% carbon, hydrogen, oxygen and nitrogen respectively. Glass transition temperature was found to be 70°C. The result of the study suggested that the gum can be used as potential candidate for food, cosmetic and pharmaceutical preparations (58).

Shah B.N. et al developed a newer technique to extract mucilage from *A. esculentus* employing microwave radiation. They compared the yield of microwave assisted extraction with conventional method. Microwave extraction at 160 W intensity and 40 min heating duration increase 11.55% in the yield of mucilage when compared to 1 h conventional heating method. The products obtained by both the methods were of similar nature chemically (59).

Deveswaran R et al exploited *H. esculentus* mucilage for suspending agent in liquid preparation and binding agent in tablets. Physicochemical characterization of extracted mucilage shows its suitability as pharmaceutical excipient. In their investigation, it have been demonstrated that at 10% w/w & 20% w/v mucilage of *H. esculentus* exhibits acceptable binding and suspending properties respectively (60).

Ahad H.A. et al formulated matrix tablets of Glimepiride with *Hibiscus esculentus* fruit mucilage and studied its functionality as a matrix forming agent for sustained release tablet formulations. Physicochemical properties of dried powdered mucilage of *Hibiscus esculentus* mucilage were studied. The swelling behavior and release rate characteristics
were studied. This result shows that as the proportion of *Hibiscus esculentus* fruit mucilage increased, the overall time of release of the drug from the matrix tablet was also increased. The dissolution study proved that the dried *H esculentus* mucilage can be used as a matrix forming material for making sustained release matrix tablets (61).

Yao B. *et al* has studied the flocculent activity of *H. esculentus* mucilage to clarify aqueous industrial preparations. 2\(^3\) full factorial design was adopted to determine the effect of concentration of mucilage on reduction on turbidity on sample. The study revealed that, with increasing concentration of *H. esculentus* mucilage turbidity of the sample was reduced. Although the *H. esculentus* mucilage coagulation mechanism is unknown in the actually state of the study, the researchers made two assumptions to explain the phenomenon observed. The mucilage, from its sticky nature, contains polymer molecules. The flocculating activity can be either due to a chemical reaction, or a complex formation (62).

Kotadiya *et al* has investigated the applicability of okra gum as release retardant matrix forming material for colon targeting. The gum has been extracted from fresh okra pods. The tablets of theophylline were prepared with different concentration of gum. Formulated tablets was evaluated for post-compression parameters and found to be satisfactory. *In vitro* drug release study in simulated colonic fluid showed that tablets prepared with 1:2 drug to polymer ration exhibit acceptable drug release profile. The *in vivo* pharmacokinetic study in rat suggests that okra gum can successfully sustain the release of medicaments in stomach and proximal part of intestine (63).

Ahad H.A. *et al* has formulated and evaluated matrix tablets of Gliquidone with *Abelmoschus esculentus* fruit mucilage and Povidone to study its functionality as a matrix forming agent for controlled release tablet formulations. Physicochemical
properties such as solubility, loss on drying, ash value, swelling index, pH, density, microbial content etc. of dried powdered mucilage of *A. esculentus* mucilage were studied. Various formulations containing Gliquidone, *A. esculentus* fruit mucilage and Povidone were prepared. The drug-excipient compatibility studies by FTIR and DSC thermogram was carried out. Pre-compression and post-compression properties were performed and satisfactory results were obtained. The optimized batch of Gliquidone matrix tablets showed zero order release. These results proved that the dried *A. esculentus* mucilage and Povidone combination can be used as a matrix forming material for making controlled release matrix tablets\(^{(64)}\).

### 2.5. FAMOTIDINE GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS:

**Guan J. et al** has developed a gastro-retentive osmotic pump tablet of famotidine to improve bioavailability. Central composite design-response surface methodology was used to investigate the influence of factors, i.e., polyethylene oxide content, NaCl content, iron powder content and weight gain, on the responses including ultimate cumulative release and correlation coefficient of drug release profile. The optimized formulation displays a complete drug delivery and zero-order release rate. The gamma scintigraphic imaging showed extension of gastric residence for a period of 7 hours. The results suggests that poor water soluble drugs can be delivered from single-layer osmotic pump tablets completely in stomach to prolong the drug delivery time in absorption zone\(^{(65)}\).

**Raval J.A. et al** has designed a mucoadhesive drug delivery system to deliver famotidine in stomach. The disc containing mucoadhesive polymers i.e. polyvinyl pyrrolidone (PVP) and polyethylene oxide (PEO) at different ratio were prepared by direct compression method. The prepared disc were evaluated for swelling behavior,
drug release kinetics and mucoadhesion properties. The *in-vitro* gastric retention time was studied using rat stomach mucosa. The result showed that, with increase in the proportion of PEO the mucoadhesion time increased. Drug release from the optimized formulation found to be followed Korsemeyer-Peppas kinetic model with non-Fickian drug release \(^{(66)}\).

**Jaimini M. et al** formulated floating tablets for gastroretentive drug delivery of famotidine. Floating tablets of famotidine were prepared using two different grades of HPMC, i.e. Methocel K100 and Methocel K15M by effervescent technique; these grades of HPMC were evaluated for their hydrogel forming properties. Sodium bicarbonate was incorporated in the formulation as a gas-generating agent. The floating tablets were evaluated for pre-compression and post-compression parameters and *in vitro* buoyancy and dissolution studies. The prepared tablets exhibited satisfactory physicochemical characteristics. All the prepared batches showed good *in vitro* buoyancy. The drug release from the tablets followed non-Fickian diffusion \(^{(67)}\).

**Reddy S.S. et al** has formulated mucoadhesive microspheres of famotidine to prolong gastric residence time. The microspheres were prepared by Orifice Ionic-Gelation method using mucoadhesive polymers like HPMC, CMC, MC, and sodium alginate. *In vitro* drug release study were performed and drug released was evaluated. The effect of polymer concentration on size of microspheres and drug release were observed. As the Sodium HPMC polymer concentration increases the mucoadhesion increased and the drug release rate decreased at higher concentration of sodium alginate \(^{(68)}\).

**Nayak B.S. et al** has prepared sustained release microcapsules of famotidine employing *Terminalia bellerica* The microcapsules were formulated by ionic gelation technique using famotidine as the model drug and were evaluated for particle size, sphericity
measurement, yield percentage, drug entrapment efficiency, wall thickness, swelling property, in vitro drug release profile and drug release kinetic study. The effect of different drug: bhara gum ratio on in vitro drug release profile was examined and compared with guar gum remaining all the parameters constant. The microcapsules with good structure and satisfactory yield were produced. Microcapsules employing bhara gum exhibited slow release of famotidine over 10 hr. Fickian release was observed from most of the formulation with bhara gum \(^{69}\).

**Muqtader M. et al** has reported buoyant drug delivery system (BDDS) of famotidine using natural polymers viz. xanthan gum and guar gum. The prepared BDDS tablets were evaluated for its pre-compression characteristics and post compression parameters. The physical evaluation of all the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality. The floating lag time of all the formulations was less than 10 minutes. All the formulations showed good matrix integrity and retarded the release of drug for 10 hours \(^{70}\).

**Nayak B.S. et al** has designed sustained release microencapsulated drug delivery system of famotidine to enhance gastric residence time by employing mucoadhesive polymers. The microcapsules were prepared by orifice ionic gelation technique using combination of polymers like carbopol-934, HPMC, Na CMC and methyl cellulose. Prepared microcapsules were evaluated for post-formulation parameters. In-vitro drug release study exhibited zero order release up to 9 hours. Ex-vivo mucoadhesion study by wash-off test confirms acceptable mucoadhesion on gastric mucosa \(^{71}\).

**Umarunnisha A.M. et al** Controlled release matrix tablets of famotidine were prepared using a hydrophilic polymer HPMC K100M with three concentrations i.e. drug:
polymers 1:0.5, 1:0.75 and 1:1, by wet granulation method. The granules were evaluated for pre-compression parameters. The tablets were subjected to post-compression evaluation study. *In-vitro* release studies revealed that famotidine formulation with high proportion of HPMC K100M was able to sustain the drug release up to 10 hours. Pharmacokinetic analysis of *in-vitro* drug release data showed, all the formulations followed the mechanism of both diffusion and erosion \(^{(72)}\).

**Modasiya M.K. et al** has formulated *in-situ* gelling system for oral sustained release delivery of famotidine. A \(3^2\) full factorial design was employed to optimize the formulation in-terms of viscosity and drug content. *In-vitro* release study revealed that drug released from the in-situ gel followed non-Fickian diffusion. *In vivo* study for the selected batch of sodium alginate was carried out by pylorus legation method in rats, which showed gel formation in gastric juice and reduction in ulcer index \(^{(73)}\).

**Bakde B.V. et al** has developed gastroretentive controlled release drug delivery system of famotidine to increase gastric retention time for improved bioavailability. Combinations of carbopol 940 P, sodium alginate, guar gum and Kollidon SR were used for the preparation of floating tablets of famotidine. The prepared tablets were evaluated for pre-compression and post-compression parameters. Dissolution study of floating matrix tablets showed controlled release of famotidine following zero order kinetics \(^{(74)}\).

**Zeenath S. et al** has investigated HPMC K4M and HPMC K15M combination to develop floating tablets of famotidine for prolonged gastric residence time to increase bioavailability. Tablets were evaluated for post-compression parameters. Tablets exhibited sustained and prolonged *in-vitro* drug release profiles while floating over the dissolution medium. The release pattern followed was anomalous non-fickian type, indicating that water diffusion and polymer rearrangement played an essential role in
drug release. The selected formulation was subjected for \textit{in vivo} radiographic studies. These studies revealed that the tablets remained in stomach for more than 4.5 h in fed condition indicated that gastric retention time was increased by floating principle \cite{75}.

\textbf{Mishra V. et al} has prepared floating microballoons of famotidine by the Solvent diffusion and evaporation method, using acrylic polymers dissolved in the mixture of dichloromethane, ethanol and isopropyl alcohol. The effect of the various formulation parameters on the morphology, drug incorporation efficiency, \textit{In-vitro} floating behavior, particle size distribution, along with \textit{In-vivo} bioavailability of Famotidine was studied. The release rate of the drug was significantly affected by the type of combination and amount of the polymer used. It was observed that the size of Microballoons was strongly depending on the amount of polymer and the solvent system. \textit{In-vivo} bioavailability study on experimental animals showed significant improvement in bioavailability of Famotidine \cite{76}.

\textbf{Kumar M. et al} has developed a new formulation of buccal patch for systemic administration of famotidine in the oral cavity using HPMC, sodium CMC and polyvinyl alcohol by solvent casting method. FTIR the drug did not show any evidence of interaction with the polymers used. The patches were evaluated for their physical characteristics like weight variation, thickness, drug content uniformity, surface pH, folding endurance, tensile strength, mucoadhesion strength, \textit{In vitro} release studies for famotidine patches in phosphate buffer (pH, 6.6) solution exhibited drug release in the range of 72.58 to 91.91\% in 20 min \cite{77}.

\textbf{Zendelovska D. et al} has reported a rapid, specific and sensitive high-performance liquid chromatographic method for the determination of famotidine in human plasma has been developed. Famotidine and the internal standard were chromatographically
separated from plasma components using a RP HPLC for solid-phase separation with a mobile phase composed of triethylamine in water and acetonitrile using an UV detector at 270 nm. The method was implemented to monitor the famotidine levels in patient samples\(^{(78)}\).

**Akhtar N. et al** has developed a sensitive accurate and rapid reverse phase HPLC method to quantify plasma level of famotidine. Liquid-liquid extraction method was adopted to extract famotidine from plasma sample. A Hypersil ODS C\(_{18}\) column and UV detector was used in the study. The mobile phase consists of disodium hydrogen phosphate, sodium dodecyl sulphate in distilled water and acetonitrile. A calibration curve was conducted in a concentration range of 0.093 – 1.5 µg/ml\(^{(79)}\).

**Ramachandran S. et al** has investigated antiulcer activity of controlled release formulation of famotidine on aspirin induced gastric and duodenal ulcer in rats. The antiulcer activity of pylorus ligated and aspirin induced animals were correlated for the reduction in ulcer levels. The results of the study revealed that controlled release famotidine formulation improved the antiulcer activity than that of conventional famotidine tablets\(^{(80)}\).

**Singh B. et al** has developed floating microspheres of famotidine for the improvement of absorption and bioavailability of famotidine by retaining the system in the stomach for prolonged period of time. The FDDS of famotidine were prepared by different techniques, i.e. polymer phase-separation method, multiple emulsions–water–in-oil-in-water method, oil-in-water emulsion method by using ethyl cellulose and HPMC. Microspheres were evaluated for particle size, drug loading entrapment efficiency and in-vitro drug release. The results obtained from in-vitro dissolution studies were fitted
into various kinetic models. The drug release kinetics was best expressed by Higuchi model<sup>(81)</sup>.

Nalawade P. et al has developed a modified release gastro-retentive drug delivery system of famotidine for 12 h dosage regimen to improve its bioavailability. The optimum formulation was established by statistical optimization technique using $2^3$ full factorial design. Effervescent floating tablets were prepared by direct compression method. The prepared tablets were evaluated for precompression & post-compression parameters. The release of famotidine was found to be influenced by the polymer concentration<sup>(82)</sup>.

Patel D.J. et al has designed famotidine loaded mucoadhesive nanosuspension for the treatment of ulcer. A 3-factor, 3-level Box-Behnken design has been applied to study the effects of amount of the beads (X1), PVPK-30 (X2) and Tween-80 (X3) on the particle size (Y1), and cumulative percentage drug released after 1h (Y2). The optimization was performed using the desirability function and contour plots. The scanning electron microscopy (SEM) showed the nanoparticles as spherical in shape. Ex-vivo mucoadhesion study showed that famotidine mucoadhesive nanoparticles possessed higher mucoadhesion than the famotidine nanoparticles. The in vivo studies on aspirin-induced rats showed better efficacy than the effect of traditional famotidine suspension<sup>(83)</sup>.

2.6. STATISTICAL OPTIMIZATION OF FORMULATIONS:

Mandal et al has employed Response Surface Methodology (RSM) to design and optimize oral sustained release tablet of metformin HCl. A central composite design for $3^2$ was employed to systematically optimize drug release profile. The concentration of HPMC K15M and PVP K30 were taken as independent variables in the study. Contour plots were drawn and optimum formulations were selected. Polynomial mathematical
equations were generated to express various responses using multiple regression analysis. The linear correlation plots drawn between predicted and observed responses demonstrated high regression values and excellent fitness of the model (84).

**Arora G. et al** has formulated oral controlled release mucoadhesive matrix tablets of taro gum incorporating domperidone as model drug. A central composite design for $3^2$, was employed to evaluate the effect of critical formulation variables, namely the amount of taro gum and PVP K 30, on mucoadhesive strength, tensile strength, release exponent and $t_{50}$. The polynomial equation indicates that taro gum has dominating effect on mucoadhesive strength and the independent variables have almost equal and comparable effect on tensile strength (85).

**Singh B. et al** developed oral mucoadhesive matrices of hydralazine hydrochloride. For systematic optimize the drug delivery, a $3^2$ central composite design was employed. Response surface plots were obtained and optimum formulations were selected by extensive grid searches. A very high degree of prognostic ability was indicated by validation of the formulation optimization study. The result of the study revealed that response surface methodology employed was found to be significant. Upon comprehensive evaluation of grid searches, the formulation fulfilled the optimal criteria of best regulation of the release rate and bioadhesive strength (86).

**Arora G. et al** has employed a 2 factor central composite design to optimize the mucoadhesive formulation of domperidone. The effect of two independent variables i.e. concentration of gum ghatti and HPMC K15M on various responses like mucoadhesive strength, tensile strength, release exponent, drug release parameters was investigated. The factors were used in three levels and nine formulations were prepared. Design expert software was used to find the effect of variables on responses. ANOVA shows that the polynomial equation used in the study was significant. Optimized formulations
were found by Grid search with high desirability. Suitable combination of two polymers showed good agreement with predicted values of the responses \(^{(87)}\).

**Nayak A.K. *et al*** has developed and optimized mucoadhesive beads of glibenclamide using a \(3^2\) full factorial design. Effect of two independent variables i.e. ratio of sodium alginate to isapgula mucilage and the concentration of cross-linking agent on the drug entrapment efficiency and cumulative drug release was optimized using response surface methodology. The accuracy and prediction ability of these models was determined using regression analysis. The optimized formulation found after desirability search showed a high degree of agreement with predicted values \(^{(88)}\).

**Bukka R. *et al*** has employed a \(3^2\) full factorial design an intraoral mucoadhesive drug delivery system of rasagiline mesylate. The effect of independent factors i.e. concentration of carbopol P940 and concentration of sodium alginate on mucoadhesion strength and drug release was investigated. Nine formulations were prepared and evaluated. The formulations were optimized by feasibility search using surface response methodology. ANOVA showed the suitability of the model used and high degree of agreement between the predicted values and experimental values \(^{(89)}\).

**Ahuja M. *et al*** has investigated mucoadhesive properties of mimosa seed mucilage as a buccal drug delivery disc. The effects of three factors i.e. drug-excipient ratio, drug concentration and compression force at three levels on bioadhesion strength and drug release rate was observes. Polynomial models including interactions and quadratic terms were generated for all the response variables using a multiple linear regression analysis. Optimum check points were obtained by response surface methodology. The model found to be suitable and showed less prediction error ensuring good agreement for the study. The results of the study showed that there is a little effect of compression force on the mucoadhesive property of the prepared disc \(^{(90)}\).
REFERENCE


Chapter 2


Evaluation and optimization of mucoadhesive drug delivery of famotidine with polysaccharide isolated from *Hibiscus esculentus* Linn. 103


Chapter: 2

Review of Literature


