2.1 ANTIHYPERTENSIVE DRUGS

Abnormally high blood pressure is called as hypertension and drugs used to prevent or treat hypertension and associated complications like ischemic heart disease, stroke and myocardial infarction needs antihypertensive class of drugs. [Goodman and Gilman 2003] A very small reduction in blood pressure by 5 mmHg is also helpful in keeping away all possible life threatening complications of high blood pressure like dementia, stroke and ischemic heart disease. [Tortora GJ 2006]

Based on patient history, clinical complications and intensity of associated risks, single or multiple combination anti-hypertensive drug treatment is designed accordingly by physicians. There are different classes of antihypertensive drugs (Figure 2.1 and 2.2) with different mode of actions like diuretics, beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists and vasodilators. [HarshMohan 2000]

Figure 2.1: History of anti-hypertensive drugs
Figure 2.2: Hypertension and modes of action of antihypertensive drugs
2.1.2 Diuretics

Excess salt and water burden present in body's tissues and blood is eliminated by diuretics. [Goodman and Gilman 2003]

<table>
<thead>
<tr>
<th>Loop diuretics</th>
<th>Thiazide diuretics</th>
<th>Thiazide-like diuretics</th>
<th>Potassium-sparing diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bumetanide</td>
<td>Epitizide</td>
<td>Indapamide</td>
<td>Amiloride</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
<td>Hydrochlorothiazide</td>
<td>Chlorthalidone</td>
<td>Triamterene</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Chlorothiazide</td>
<td>Metolazone</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>Torsemide</td>
<td>Bendroflumethiazide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Thiazide and related diuretics are generally more preferred over other diuretics due to their beneficial vasodilation effects. It is choice of medication in treatment of hypertension in a single or in combination with either calcium channel blockers or angiotensin II receptor antagonists.

2.1.3 Calcium channel blockers

Access of calcium into cells of arteries is inhibited by calcium channel blockers. This is also recommended by many physicians from all over the world as first line therapy in treatment of hypertension in a single or in combination with either diuretics or angiotensin II receptor antagonists. [Tripathi KD 2004]

**Dihydropyridines**
- Nitrendipine
- Nimodipine
- Nifedipine
- Nicardipine
- Levamlodipine
- Lercanidipine
- Isradipine
- Felodipine
2.1.4 ACE inhibitors
Angiotensin-converting enzyme inhibitors are called as ACE inhibitors which blocks alteration of angiotensin I enzyme into angiotensin II where later is a potent vasoconstrictor. [Sethi SD 2000; Gales BJ et al., 2010]

These class drugs are found effective more than calcium channel blockers and beta blockers. It is preferred choice in treatment of hypertension associated with chronic kidney disease state.

Captopril  Enalapril  Fosinopril  Lisinopril  Perindopril
Quinapril  Ramipril  Trandolapril  Benazepril

2.1.5 Angiotensin II receptor antagonists
Blockage of rennin-angiotensin system by angiotensin II receptor antagonists produces antihypertensive effects due to vasodilation. It is usually preferred in treatment of diabetic nephropathy and in patients who are not responding to ACE therapy than other drugs. [Gales BJ et al., 2010]

Candesartan  Eprosartan  Irbesartan  Losartan
Olmesartan  Telmisartan  Valsartan

2.1.6 Adrenergic receptor antagonists

<table>
<thead>
<tr>
<th>Beta blockers</th>
<th>Alpha blockers</th>
<th>Mixed Alpha + Beta blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>Doxazosin</td>
<td>Bucindolol</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Phentolamine</td>
<td>Carvedilol</td>
</tr>
<tr>
<td>Nadolol</td>
<td>Indoramin</td>
<td>Labetalol</td>
</tr>
</tbody>
</table>
Beta blockers act on adrenergic beta receptors to lower blood pressure by blocking the action of catecholamines like epinephrine and norepinephrine. It is drug of choice in secondary prevention of hypertension mediated heart attack. [Sethi SD 2000] Alpha blockers act on $\alpha$-adrenoreceptors to give antihypertensive effects especially in patients with prostate disease symptoms.

### 2.1.7 Direct Vasodilators

Vasodilators used to dilates the smooth muscle of arteries by lowering calcium influx or dephosphorylating vaso-constricting myosin enzyme. Due to vessel dialation stored blood quickly gets removed to cause antihypertensive effect.

Sodium nitro-prusside (nitroglycerin) and hydralazine are drugs from this class which gives immediate reduction in blood pressure in emergency conditions like malignant hypertension and gestational hypertension respectively. [Guyton and Hall 1999]

### 2.1.8 GABA-A receptors agonist

Benzodiazepines acts as agonist of the GABA-a receptors as well as hinder the re-uptake of a nucleoside Adenosine and both these actions together produces coronary vasodilation. These come under controversial treatment due to number of well-known side effects. [Herfindel Eric T 2000]

### 2.1.9 Renin Inhibitors

Renin comes one level higher than angiotensin converting enzyme (ACE) in the renin-angiotensin system. Inhibitors of renin can therefore effectively reduce hypertension. Aliskiren (developed by Novartis) is a renin inhibitor,
which has been approved by the U.S. FDA for the treatment of hypertension. [Herfindel Eric T 2000]

2.1.10 Aldosterone receptor antagonists
Aldosterone receptor antagonists or anti-mineralocorticoids eliminate the water content from body similar to diuretics to reduce edema and cardiac workload. These are used as adjunctive therapy along with antihypertensive drugs in treatment of congestive heart failure. [Tripathi KD 2004]

- Eplerenone
- Spironolactone

2.1.11 Alpha-2 adrenergic receptor agonists
Alpha 2 receptors or auto receptors acting drugs reduces blood pressure by stimulating these receptors to ease blood flow. These drugs are generally used in combination with diuretics. [Tripathi KD 2004]

- Clonidine
- Guanabenz
- Guanfacine
- Methyldopa
- Moxonidine

2.1.12 Endothelin receptor blockers
It is newer class of antihypertensive drugs which acts on hormone endothelin receptors. It is preferred in treatment of pulmonary artery hypertension where it blocks receptors of endothelin hormone. [Sethi SD 2000]
2.2 ANGIOTENSIN II RECEPTOR ANTAGONISTS

Renin–angiotensin–aldosterone modulating drugs in treatment of hypertension are known as Angiotensin II receptor antagonists, angiotensin receptor blockers (ARBs), AT1-receptor antagonists or sartans. They are also useful in treatment of diabetic nephropathy and congestive heart failure. [Goodman and Gilman 2003]

ACE inhibitor therapy intolerant patient are treated with Angiotensin II receptor blockers in particular candesartan. They are devoid of ACE inhibitor therapy side effects like persistent dry cough and/or angioedema due to no effect on bradykinin or other kinins. [Tortora GJ 2006; HarshMohan 2000 ]

Patients taking angiotensin receptor blockers (ARBs) are about 35—40% less likely to develop Alzheimer’s disease than those using other antihypertensive. [Gales BJ et al., 2010]

Figure 2.3: Renin–angiotensin–aldosterone modulating system
Pressor inhibition (degree of inhibition of the blood pressure), AT-1 affinity and biological half life at the 24th hour as per US FDA are as follows: [Sethi SD 2000]

<table>
<thead>
<tr>
<th>Pressor inhibition</th>
<th>AT1 affinity</th>
<th>Biological half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azilsartan 32 mg- 60%</td>
<td>Azilsartan-10000-fold</td>
<td>Azilsartan-11 hours</td>
</tr>
<tr>
<td>Irbesartan 150 mg- 40%</td>
<td>Irbesartan-8500-fold</td>
<td>Irbesartan-11–15 hours</td>
</tr>
<tr>
<td>Losartan 100 mg- 25–40%</td>
<td>Losartan-1000-fold</td>
<td>Losartan-6–9 hours</td>
</tr>
<tr>
<td>Olmesartan 20 mg- 61%</td>
<td>Olmesartan-12500-fold</td>
<td>Olmesartan-13 hours</td>
</tr>
<tr>
<td>Telmisartan 80 mg- 40%</td>
<td>Telmisartan-3000-fold</td>
<td>Telmisartan-24 hours</td>
</tr>
<tr>
<td>Valsartan 80 mg- 30%</td>
<td>Valsartan-20000-fold</td>
<td>Valsartan-6 hours</td>
</tr>
</tbody>
</table>

2.2.3 Adverse effects
This is usually well-tolerated class of drugs.

- **Common Adverse effects:** dizziness, headache, and/or hyperkalemia
- **Rare Adverse effects:** orthostatic hypotension after first dose, rash, diarrhea, dyspepsia, atypical liver function, muscle cramp, myalgia, back pain, insomnia, low hemoglobin levels, renal impairment, pharyngitis, and/or nasal congestion [Guyton and Hall 1999; Herfindel Eric T 2000]
2.3 ANTIHYPERTENSIVE MUCO-ADHESIVE FILM DEVELOPMENT

- **Quinteros D et al. 2014** developed and evaluated bioadhesive liposomes to improve ophthalmic chronic topical therapies using melatonin analogue 5-MCA-NAT, sodium hyaluronate or carboxymethyl cellulose or amphiphilic block thermo sensitive poloxamer polymers to prolong hypotensive efficacy in rabbit eyes.

  It is also to avoid side effects due to frequent instillations of eye drops for the treatment of chronic ocular diseases such as glaucoma. Developed formulation exhibited Hypotensive effect more than 8 hours.

- **Meher JG et al. 2013** developed and evaluated mucoadhesive buccal film containing carvedilol and cellulose-polymethacrylate (Eudragit RSPO) by solvent casting technique. Developed formulation showed no drug – polymers interaction in FTIR and DSC analysis, no erosion in 4 h swelling studies, 88 ± 1.15% in vitro drug release, optimum mucoadhesive strength and film strength, 80 ± 2.30% ex vivo drug permeation.

- **Pandey S et al. 2013** developed and characterized bilayered gastro-retentable mucoadhesive patch lercanidipine hydrochloride for stomach-specific drug delivery as lercanidipine hydrochloride is soluble in gastric pH (1-4).

  Bilayered patch was made by using the selected batch of two films by layering method and evaluated for the various parameters like in vitro swelling study and ex vivo mucoadhesive strength. Film was folded into a hard gelatin capsule, evaluated for in vitro drug release in pH 1.2 containing 0.2% (w/v) sodium lauryl sulphate (SLS), and in vivo bioavailability in rabbits. Patches could control the drug release up to 12 h, having mucoadhesion strength in the range of 4.05±0.4 N to 4.52±0.12 N.

  In vivo bioavailability results indicate that the gastro-retentive patch system provides a novel way to retain the drug matrix for the longer period of time
in a stomach, enhance drug absorption and thereby offer a promising strategy for gastro-retentive mucoadhesive drug delivery for the lercanidipine HCl.

- **Fulgêncio Gde O et al. 2012** developed and evaluated mucoadhesive film of timolol maleate and chitosan for ophthalmic drug delivery. Casting and solvent evaporation technique was used to formulate chitosan-coated mucoadhesive film of 0.5% timolol maleate.

  All physicochemical parameters were evaluated and found to be acceptable. In-vivo pharmacodynamics studies were performed in ocular normotensive albino rabbits for 11 weeks. On alternative days, intraocular pressure (IOP) was measured by applanation tonometer. Within first 2 weeks, 85% of the drug was released.

  No signs of ocular discomfort or irritations were observed due to film. Histological analyses were done on the extracted right eyes of three group animals after euthanasia. Histo-pathological studies showed no alterations in ophthalmic structures due to direct film contact.

  Thus results showed that in the treatment and prevention of glaucoma, ocular drug delivery system of chitosan coated timolol maleate film can be safe and efficient.

- **Mandal AS et al. 2012** fabricated and evaluated in vitro bidirectional release and stability studies of mucoadhesive donut-shaped captopril tablets. Objective was to obtain controlled release of captopril in the stomach, coated; mucoadhesive donut-shaped tablets were designed.

  Donut-shaped tablet were made of different ratios of diluents to polymer or combination of polymers by direct compression method. Top and bottom portions of the tablet were coated with water-insoluble polymer followed by mucoadhesive coating.
Time of water penetration, measurement of tensile strength, mucoadhesion studies (static ex vivo and ex vivo wash-off) were taken into account for characterization of respective films. In vitro study has been performed at different dissolution mediums. Optimized batches were also prepared by wet granulation. Stability studies of optimized batches have been performed. The results of time of water penetration and tensile strength indicated positive response against water im-permeation.

Mucoadhesive studies showed that film thickness of 0.12 mm was good for retention of tablet at stomach. At pH 1.2, optimized batch of tablet made with hydroxypropyl methyl cellulose (HPMC) E15 as binder showed 80% w/w drug release within 4–5 h with maximum average release of 97.49% w/w.

Similarly, maximum average releases of 96.36% w/w and 95.47% w/w were obtained with nearly same dissolution patterns using combination of HPMC E5 and HPMC E50 and sodium salt of carboxy methyl cellulose (NaCMC) 500–600 cPs instead of HPMC E15.

The release profiles in the distilled water and pH 4.5 followed the above pattern except deviation at pH 6.8. Stability studies were not positive for all combinations. Coated, mucoadhesive donut-shaped tablet is good for controlled release of drug in the stomach.

- **Aburahma MH et al. 2011** developed and evaluated biodegradable sustained release ocular inserts of potent anti-glaucoma drug-brimonidine to enhance ocular bioavailability. Ocular inserts film was prepared by solvent casting technique using hydroxypropyl methycellulose, carbopol, sodium alginate, and chitosan.

Physicochemical evaluation and drug release showed sustained behavior of (99% at 6 h) sodium alginate film. Ethylcellulose coating to sodium alginate film found to show superior sustainment effect as compared to
Eudragit RSPO when evaluated for intraocular pressure (IOP) lowering effect when inserted in albino rabbit’s eyes.

- **Belgamwar VS et al. 2010** designed and developed oral mucoadhesive multi-particulate system for atenolol by ionic gelation technique using hydroxypropyl methylcellulose (HPMC) K15M and carbopol 971P. Ionic gelation technique involved cross linking of sodium alginate with calcium chloride to slow down the release of drug from the mucoadhesive polymer.

  IR spectroscopy revealed no drug - polymer interactions. Separate, bulky, free flowing multi-particulates with 23-74% average encapsulation efficiency and good swelling index and mucoadhesive strength. Electron microscopic analysis (SEM) showing particle size in range of 561-831 microm. Drug release pattern found to be non-Fickian anomalous transport extended until 12 h. Residence of mucoadhesive microspheres found 6-8 h in upper part of gastrointestinal tract.

- **Belgamwar V et al. 2009** formulated and evaluated oral mucoadhesive multi-particulate system of metoprolol tartarate by ionic gelation technique using polymers like HPMC (K4M, K15M, K100M, E50LV) and Carbopol (971P, 974P) and polycarbophil.

  Ionic gelation technique involved cross linking of sodium alginate with calcium chloride to slow down the release of drug from the mucoadhesive polymer. IR spectroscopy revealed no drug - polymer interactions. Separate, bulky, free flowing multi-particulates with 50-60% average encapsulation efficiency and good swelling index and mucoadhesive strength. Particle size measured by optical microscopy was found to be between 400-650 micron.

  Drug release pattern found to be non-Fickian anomalous transport extended until 12 h. No significant change in the physicochemical properties were observed in stability studies at 40 degrees C /75% RH for 90 days.
Sezgin-Bayindir Z et al 2015 prepared candesartan cilexetil-loaded niosomes and mixed niosomes to enhance the aqueous solubility of the drug, thus improving its oral bioavailability. Surfactants, copolymers, and charge-inducing agents in various combinations used to prepare niosomes. Entrapment efficiency, particle size, zeta potential, sedimentation behavior study, formulation stability, in vitro drug release like parameters were studied. Span 60 and Pluronic P85 added niosomes showed better stability, enhanced drug release and improved oral bioavailability.

Surampalli G et al 2015 developed a novel tablet formulation of amorphous candesartan cilexetil (CAN) solid dispersion involving effective P-gp inhibition for optimal drug delivery by direct compression (DC) method. Interaction studies by FTIR, Carr index, Hausner ratio, flow rate, angle of repose like parameters were evaluated and found compiling.

Average weight, hardness, disintegration time, friability assessments, dissolution kinetics, In vivo pharmacokinetiic and stability studies were performed and found promising. It is found that about 7-10 fold rise in bioavailability observed in candesartan tablet prepared by P-gp inhibition using naringin.

Bao X et al 2014 prepared nanovector low molecular conjugate of chitosan-graft-polyethyleneimine containing candesartan (CPC) and gene for potential targeted cancer therapy. Candesartan used to bind overexpressed angiotensin II type 1 receptor (AT1R) of tumor cells, strengthen endosomal buffering capacity of CPC and suppress tumor.

Particle size, moderate positive charges, superior stability, and efficient in vitro release of drug and gene were found. Flow cytometry and confocal laser scanning microscopy analyses confirmed targeted enhanced intracellular delivery of CPC/pDNA complexes. In vivo investigation on nude mice bearing PANC-1 tumor xenografts revealed that CPC/wt-p53
complexes possessed high tumor-targeting capacity and strong anti-tumor activity. Thus it can be concluded that CPC could be an ideal tumor-targeting nanovector for simultaneous transfer of drug and gene

- **Malakar J et al 2014** developed transdermal candesartan cilexetil delivery using microemulsion containing olive oil, Tween 80 and isopropyl alcohol. Microemulsion was optimized by pseudo ternary phase diagram. Droplet size, viscosity, poly-dispersity index, zeta potential, In vitro skin permeation and stability studies showed promising results of candesartan loaded microemulsion.

- **Dudhipala N et al 2016** developed solid lipid nanoparticles loaded with Candesartan cilexetil (CC) to enhance oral bioavailability. Candesartan cilexetil has poor aqueous solubility and low oral bioavailability. Trimyristin/tripalmitin/tristearin, and surfactants (Poloxamer 188 and egg lecithin E80) were used to prepare solid lipid nanoparticles by hot homogenization followed by ultra sonication method.

  Morphology by DSC and XRD analyses, pharmacokinetic, pharmacodynamic behavior and stability studies were evaluated. Amorphous spherical nanoparticles improved bio-availability of candesartan by 3 fold. In-vivo studies in hypertensive rats showed a decrease in systolic blood pressure for 48 h, while suspension showed a decrease in systolic blood pressure for only 2 h. Thus it is concluded that CC-SLNs significantly enhanced oral bioavailability along with improved pharmacodynamic effect.

- **Gurunath S et al 2015** explored the pharmacokinetic behavior of candesartan solid dispersions prepared by different pharmaceutical interventions using P-gp inhibitor in rabbits to validate the effectiveness of naringin as a pharmaceutical excipient in enhancing the oral delivery of lipophilic candesartan cilexetil.
In-vivo studies in Male albino rabbits (1-1.5 kg) for pure CAN suspensions and various candesartan solid dispersions (10 mg/kg) with and without naringin (15 mg/kg) showed a 3.7-folds increase in apparent bioavailability with freeze-dried solid dispersions with naringin as compared to free CAN suspension administered alone.

- **Sohn Y et al 2012** designed self-microemulsifying tablets for pH-independent fast release of poorly soluble candesartan cilexetil (CDC). Capryol 90, Tween 80 and tetraglycol at a ratio of 5:35:60 used to prepare self-microemulsifying drug delivery system (SMEDDS) in the form of tablets. Pharmaceutical and pharmacodynamic studies showed that SMEDDS overcome low oral bioavailability of CDC due to its limited solubility at physiological pH conditions in the gastrointestinal tract.

- **Sauder MA et al 2012** examined whether acute AT(1)R blockade alters micro-vascular perfusion in skeletal and cardiac muscle in humans. The study was conducted at the Eight overnight-fasted healthy young adults were studied thrice in random order at General Clinical Research Center at the University of Virginia.

Acute AT(1)R blockade with candesartan recruits skeletal as well as cardiac muscle microvasculature in healthy humans without altering insulin-mediated whole-body glucose disposal. This may contribute to the observed improvement in the cardiovascular outcomes in patients receiving prolonged treatment with AT(1)R blockers.

- **Detroja C et al 2011** enhanced the oral bioavailability of practically insoluble Candesartan cilexetil [CC] by preparing nano-suspension. Zirconium oxide beads used to prepare nano-suspension by media milling and spray drying. Particle size, zeta potential, saturation solubility, crystallinity, surface morphology and dissolution behavior were evaluated.

Pharmacodynamic study based on deoxy-corticosterone acetate [DOCA] salt model was performed in rats to evaluate in-vivo performance, which
showed 26.75±0.33% decrease in systolic blood pressure for nano-suspension while plain drug suspension showed 16.0±0.38% reduction, indicating that increase in dissolution velocity and saturation solubility leads to enhancement of bioavailability of SDCN when compared to bulk CC suspension. Thus, the results conclusively demonstrated a significant enhancement in antihypertensive activity of candesartan when formulated as nano-suspension.

- **Lee JE et al 2011** investigated the intravitreal toxicity and pharmacokinetics of candesartan, a selective type 1 angiotensin II receptor blocker, in rabbit eyes. 0.5, 1, and 2 mg in 0.1 mL doses of candesartan were administered in different groups of rabbits for toxicity study. Light microscope and transmission electron microscope is used to examine Retinal histology. 0.5 mg candesartan Intravitreal injection found safe and revealed normal retinal morphology and structures in all eyes.

- **Nekkanti V et al 2010** developed and characterized self-micro-emulsifying drug delivery system (SMEDDS) of candesartan cilexetil. Oils, surfactants, and co-surfactants used to prepare SMEDDS. Pseudo-ternary phase diagrams were constructed to identify the self-micro-emulsification region. Self-microemulsification properties, droplet size, and zeta potential, dissolution characteristics were evaluated. All results showed promising potential use of SMEDDS as a means of improving solubility, dissolution, and concomitantly the bioavailability.

### 2.4 MUCO-ADHESIVE BUCCAL DRUG DELIVERY SYSTEM DEVELOPMENT

Nayanabhirama et al (2004) in his patent disclosed mucoadhesive buccal composition useful for smoking cessation, which comprises hydrophilic polymers, nicotine, starch and excipients, the excipients having the property of controlling the release of nicotine, the resulting composition being provided with a backing membrane to facilitate unidirectional release of nicotine. This invention also relates to a process for the preparation of the said composition.

NilenduSen et al (2004) in their patent disclosed a sustained release mucoadhesive vaginal pharmaceutical composition comprising antifungal agents (triazoles, imidazoles, clotrimazole), prostaglandins, hormones, estrogens, pharmaceutically acceptable salts or esters thereof, isomers, derivatives thereof and the like and combinations thereof. By way of alleviating a fungal infection in the vaginal cavity, any of the antifungal agents heretofore used to alleviate a fungal infection in the vaginal cavity can be used here in.

Sanju Dhawan et al (2004) studied mucoadhesive properties of chitosan microspheres prepared by different methods like thermal cross-linking, glutaraldehyde crosslinking, tripolyphosphate, emulsification and inotropic gelation by NaOH, and ethylcellulose microspheres. The prepared microspheres further evaluated for its size, charge (zeta potential), stability in HCl and adsorption/interaction between mucin and microspheres in aqueous solution.

Emulsification inotropic gelation method produced more mucoadhesive chitosan microspheres. To measure the amount of mucin adsorbed on chitosan microspheres mucous glycoprotein assay and rat gut loop studies were performed. The adsorption of mucin depends on zeta potential of microspsheres, which depends on the method of preparation of microspheres and added amount of mucin.

Park CR et al (2004) evaluated some naturally occurring biocompatible materials like 0-50% w/w of xanthan gum, karaya gum, guar gum, and glycol chitosan as mucoadhesive controlled release excipients for buccal drug
delivery. Tablets of these excipients were prepared and evaluated for swelling, drug release, and mucoadhesion. Result showed xanthan gum as a strong mucoadhesive. Sustained release of drug was evaluated on swelling properties of the tablets, which in turn is an indication of the adhesion values of naturally occurring gum material.

Bandyopadhyay AK et al (2006) developed and evaluated natural mucoadhesive from Tamarindus indica L. containing nasal drug delivery system of diazepam. Mucoadhesive strength, viscosity and gelling property of of mucoadhesive agent from Tamarindus indica L found higher in comparison to synthetic polymers like hydroxy propyl methyl cellulose (HPMC) and carbopol 934. In-vitro drug release determination through franz-diffusion cell were found to be enhanced compared to synthetic polymers.

Anthony AA et al (2007) prepared glibenclamide microspheres using 10% (m/V) mucuna gum. Crosslinking time of 1 hr gave the highest delayed release of the incorporated drug, whereas those without crosslinking showed the fastest release. The Ritger-Peppas case I transport model appeared to have adequately described the release process as about 54% of the batches of microspheres conformed to this model. This implies that a formulation of glibenclamide- loaded mucuna gum microspheres is likely to offer a reliable means of delivering glibenclamide by the oral route.

Basu et al (2009) prepared and evaluated midazolam hydrochloride containing mucoadhesive nasal gels using mucilage of seeds of Linum usitatissimum L. Mucilage properties compared with synthetic polymers HPMC and carbopol 934. Physical parameters like pH, swelling, viscosity and mucoadhesive strength were evaluated. Permeation study by means of excised goat nasal mucosa were performed for gel with and without enhancers. Histological parameters were also evaluated to elaborate local toxicity if any.

Deshmane et al (2009) developed and evaluated sustained release verapamil hydrochloride containing buccal patch using chitosan. Various
parameters like thickness, weight, drug content, pH, swelling index, folding endurance, tensile strength, mucoadhesive strength, mucoadhesive time and in-vitro released were evaluated.

All parameters were found satisfactory and proved a chitosan a good film forming material with strong bioadhesive properties for drug verapamil.

Koland et al (2010) developed and evaluated losartan potassium mucoadhesive buccal films using hydroxypropyl methyl cellulose (HPMC), ethyl cellulose (EC) and eudragit RS 100. Losartan have only 33% oral bioavailability. Chosen drug and polymers were not showed interaction in thermal analysis by DSC.

Various parameters like thickness, weight, drug content, pH, swelling index, folding endurance, tensile strength, mucoadhesive strength, mucoadhesive time and in-vitro released were evaluated. All parameters were found satisfactory. Porcine buccal mucosa used to study ex-vivo permeation and showed slow permeation in HPMC for 7 hr.

It is concluded that HPMC polymer containing films showed more promising result in physical investigations as well as in-vitro and ex-vivo studies.

Kultida Songsurang et al (2011) developed and evaluated sustained release mucoadhesive amoxicillin tablets. Tablets were prepared using ethyl cellulose, chitosan and beta-cyclodextrin. Comparative evaluation of different concentration of chitosan and beta-cyclodextrin containing tablets of cellulose coated amoxicillin were performed. Retardation of amoxicillin release observed for long time with improved protection from stomach acid attack.

Kumar et al (2011) designed, developed and evaluated Nebivolol mucoadhesive tablet using HPMC K4M, HPMC K15M and Carbomer-940 to obtain control release. Direct compression method was used to prepare mucoadhesive tablet. No interaction between drug and polymers were predicted in FTIR analysis. Physicochemical parameters like weight variation,
hardness, friability, drug content, erosion studies swelling index, mucoadhesive strength, in-vitro dissolution and ex-vivo and in-vitro drug release were evaluated.

Kumar Swamy et al (2014) developed and evaluated Candesartan cilexetil mucoadhesive buccal tablets using carbopol-934, sodium carboxy methylcellulose (Na CMC) and hydroxyl propyl methyl cellulose (HPMC) mucoadhesive polymers. Extensive first-pass metabolism and poor oral bioavailability of Candesartan cilexetil are major drawbacks. Direct compression method was used to prepare mucoadhesive tablet.

No interaction between drug and polymers were found in FTIR analysis. Physicochemical parameters like weight variation, hardness, friability, drug content, erosion studies swelling index, mucoadhesive strength, in-vitro dissolution and ex-vivo and in-vitro drug release were evaluated. It is concluded that the bioadhesive buccal drug delivery of Candesartan cilexetil is promising.

Vinay C.H. et al (2015) designed and evaluated Candesartan cilexetil controlled release of mucoadhesive buccal tablets using Carbopol-934, Hydroxy propyl methyl cellulose, Hydroxy ethyl cellulose. Enhancement of bioavailability and reduction in doses to improve patient compliance considered for present work. No interaction between drug and polymers were found in FTIR analysis.

Physicochemical parameters like weight variation, hardness, friability, drug content, erosion studies swelling index, mucoadhesive strength, in-vitro dissolution and ex-vivo and in-vitro drug release were evaluated. 2: 4 ratio of Carbopol-934 and HPMC K4M showed good physiochemical and release results. It is concluded that the bioadhesive buccal drug delivery of Candesartan cilexetil is promising to enhance bioavailability and bypass the extensive hepatic first pass metabolism.
Lindert S et al 2017 reviewed Oromucosal multilayer films. The oral mucosa has recently become increasingly important as an alternative administration route for tailor-made, controlled drug delivery. Oromucosal multilayer films, assigned to the monograph oromucosal preparations in the Ph.Eur. may be a promising dosage form to overcome the requirements related to this drug delivery site. Areas covered of multilayer films are drug delivery tools, and discuss manufacturing processes and characterization methods. We focus on the suitability of characterization methods for particular requirements of multilayer films.

A classification was performed covering indication areas and APIs incorporated in multilayer film systems for oromucosal use in order to provide a summary of data published in this field. Expert Opinion: The shift in drug development to high molecular weight drugs will influence the field of pharmaceutical development and delivery technologies. For a high number of indication areas, such as hormonal disorders, cardiovascular diseases or local treatment of infections, the flexible layer design of oromucosal multilayer films provides a promising option for tailor-made, controlled delivery of APIs to or through defined surfaces in the oral cavity. However, there is a lack of discriminating or standardized testing methods to assess the quality of multilayer films in a reliable way.

2.5 CHITOSAN AS MUCOADHESIVE POLYMER

Ahmed TA et al 2016 have reviewed application of chitosan, chitosan derivatives and chitosan metal nanoparticles as a potential carrier in pharmaceutical drug delivery. Chitosan being biocompatible and biodegradable mucoadhesive polymer is very popular in preparation of stable, permeable, and bioactive micro- or nanoparticles. Preparation and characterization also explained in detail.

Kapanigowda UG et al 2015 developed and evaluated ocular microspheres of ganciclovir by modified water-in-oil emulsification method using chitosan. Conventional eye drops faces lack of corneal permeability due to nasolacrimal drainage and metabolic degradation.
To enhance ocular bioavailability, mucoadhesive ocular microspheres can be advantageous. Prepared microspheres were evaluated for in vitro release study, release kinetics, XRD and stability. Eye irritation studies were performed. In vivo pharmacokinetic study and histopathology were performed in Wistar rats. It is concluded that sustained drug release microspheres of ganciclovir improved bioavailability in Wistar rats.

Sánchez-Sánchez MP et al 2015 developed and evaluated acyclovir containing vaginal formulations using chitosan, carrageenan and HPMC for the prevention of sexually transmitted infections. Sustained release behavior of acyclovir for a period of 8-9 days was observed.

Goldberg M et al 2014 developed and evaluated chemotherapeutic agent cisplatin embedded noninvasive transmucosal drug delivery system using chitosan nanoparticles sponge matrix to increase antitumor efficacy and reduce systemic toxicity.

Salmazi R et al 2015 developed and evaluated curcumin mucoadhesive system for the treatment of vaginal candidiasis. Due to toxicity and resistance of synthetic antifungal agents, natural phytochemicals can be useful in common problem of vaginal candidiasis. From physicochemical evaluation and in-vitro antifungal activity it is concluded that developed curcumin mucoadhesive system can be promising in treatment of vaginal candidiasis.


Kulkarni N et al 2015 developed and evaluated floating chitosan-xanthan beads of controlled release, floating and mucoadhesive beads of glipizide by using the chitosan polyionic-complexation technique. Encapsulation
efficiency, in vitro bioadhesion studies, bioadhesive strength, floating properties, swelling kinetics, scanning electron microscopy, differential scanning calorimetry and drug to polymer interaction parameters were analyzed and found to be promising. It is concluded that chitosan and xanthan gum using prepared mucoadhesive beads showed to possess sustained release effect.

**Gavin A et al 2015** prepared and evaluated mucoadhesive tablet incorporated nanoemulsions of antimitotic genistein as an adjuvant therapy for oral cavity and oropharyngeal cancers. Prepared tablet evaluated for hardness, friability, swelling, ex vivo adhesion and in vitro release assays. It is concluded that nano-mucoadhesive genestein loaded nanoemulsion formulations is potential maintenance therapy for oral cancer patients.

**Samprasit W et al 2015** developed and evaluated mucoadhesive electrospun nanofiber mats containing α-Mangostin using thiolated chitosan (CS-SH) blended with polyvinyl alcohol (PVA) for the maintenance of oral hygiene and reduction of the dental caries.

Swelling index, mucoadhesion strength, Scanning electron microscopy, differential scanning calorimetry, X-ray diffraction, and tensile strength, in vitro drug release, antibacterial activity, cytotoxicity, in vivo performance, and stability were evaluated and found satisfactory. It is concluded that mucoadhesive α-Mangostin loaded nanofiber mats formulations is potential for oral care and the prevention of dental caries.

**Andersen T et al 2015** developed and evaluated mucoadhesive chitosan-coated liposomes and chitosan-containing liposomes using soy phosphatidylcholine with FITC-dextran 4000 and 20,000 fluorescence markers to ensure prolonged residence time at vaginal site.

Size distribution, zeta potential, entrapment efficiency, mucoadhesive behavior and the in vitro release profile were evaluated and compared to plain liposomes. It is found that liposomal chitosan mucoadhesive delivery ensures
prolonged localized residence time on the vaginal mucosa for sustained release of entrapped drug.

**Dhankar V et al 2014** prepared and evaluated ranitidine hydrochloride-loaded mucoadhesive microspheres to improve oral bioavailability of the drug. Water-in-oil emulsion technique is used for preparation of discrete, spherical, free-flowing microspheres with the use of glutaraldehyde as a cross-linking agent. Mucoadhesion, drug loading, particle size and swelling index were examined using a 3(2); factorial design. Peppas' kinetics found in the drug release kinetics.

**Jung IW et al 2014** developed and evaluated mucoadhesive liposomes containing risedronate-using 1,2-distearoryl-sn-glycero-3-phosphocholine and distearoryl-sn-glycero-3-[phospho-rac-(1-glycerol)] and chitosan by freeze-drying method to improve bioavailability. Size distribution, zeta potential, entrapment efficiency, mucoadhesive behavior and the in vitro release profile were evaluated and found satisfactory.

**Szymańska E et al 2014** developed and evaluated vaginal chitosan tablets of clotrimazole to obtain prolonged contact time with mucosa in antimycotic genitourinary tract treatment. Friability, hardness, swelling behavior, residence time, surface morphology, in vitro drug release like parameters were evaluated and found satisfactory.

**Berretta AA et al 2013** developed and evaluated mucoadhesive gels of antimicrobial, anti-inflammatory propolis to treat vulvovaginal candidiasis. Rheological, mucoadhesive, chemical and fungicidal properties were evaluated and found satisfactory.

**Malik RK et al 2013** developed and evaluated mucoadhesive beads of antiemetic drug 5-HT3 receptor antagonist 'Ondansetron Hydrochloride' using sodium tripolyphosphate (Na-TPP) as a cross-linking agent and chitosan as mucoadhesive polymer by ionotropic gelation technique. The particle size, entrapment efficiency, mucoadhesive strength and in vitro drug release were
evaluated and found satisfactory. It is concluded that mucoadhesive ondansetron hydrochloride beads reduces dose as produces sustained release effect.

Dangi AA et al 2012 developed and evaluated melt-in-mouth tablets of carvedilol by direct compression method using different mucoadhesive polymers such as hydroxypropyl methylcellulose (HPMC), chitosan, and sodium carboxymethyl cellulose (Na-CMC) to avoid first-pass metabolism and quick drug entry into the systemic circulation. Prepared tablet evaluated for hardness, friability, swelling, deaggregation time, dissolution test and in vitro release assays and found within acceptable limits.

Manconi M et al 2013 were developed and evaluated metformin-loaded liposomes using chitosan and β-glycerolphosphate to improve bioavailability and control release. Swelling index, mucoadhesive properties, scanning electron microscopy evaluation and transmission electron microscopy evaluation, drug release and in vivo bioavailability were evaluated and found satisfactory.

Jiang L et al 2013 developed and evaluated thiolated chitosan-modified PLA-PCL-TPGS nanoparticles to improve the quality of life of lung cancer patients. Results of in vitro cell viability studies showed nanoparticles effective over Taxol® in terms of cytotoxicity against A549 cells.

Ruiz-Caro R et al 2012 developed and evaluated Mucoadhesive tablets of acyclovir using chitosan and/or hydroxypropyl-methylcellulose to improve oral bioavailability. Prepared tablet evaluated for hardness, friability, swelling, ex vivo adhesion and in vitro release assays. Heterogeneous erosion from tablets displayed in drug release. Gastroretentive behaviors showed by chitosan polymer for release of acyclovir.

Szymańska E et al 2012 developed and evaluated chitosan microgranules of clotrimazole by the wet-granulation method using pentabasic tripolyphosphate (TPP) as an ion cross-linker. Physicochemical and release properties were
found satisfactory and thus it is concluded that developed microgranules producing a sustained-release of clotrimazole for local delivery.

**Veerareddy PR et al 2011** developed and evaluated mucoadhesive microcapsules of cefdinir using chitosan, Carbopol 934P, and methyl cellulose by orifice ionic gelation method. Particle size, encapsulation efficiency, scanning electron microscope (SEM) studies, ex vivo wash-off test, in vitro drug release, FT-IR interaction studies were evaluated and found satisfactory.

**Koland M et al 2011** developed and evaluated ondanestrone buccal films using chitosan, and gelatin to prolong drug release and improve bioavailability. Weight, thickness, drug content, drug loading, uniformity, bioadhesive strength, in vitro mucoadhesion time, degree of swelling, in vitro drug release and kinetic analysis were evaluated and found satisfactory.

**Kawarkhe S et al 2010** developed and evaluated mucoadhesive intravaginal local delivery system in the form of metronidazole by solvent evaporation method using various compositions of Carbopol, hydroxypropylmethylcellulose, chitosan, Polyox and propylene glycol. Weight, thickness, surface pH, folding endurance, mechanical, drug content uniformity, in vitro drug release, swelling, gelling and mucoadhesion property were evaluated and found that all the films possess satisfactory characteristics.

**Sandri G et al 2010** developed and evaluated insulin loaded N-trimethyl chitosan nanoparticles to evaluate the penetration enhancement properties. Both in vitro and ex vivo study revealed insulin permeation to the same extent by -trimethyl chitosan nanoparticles which is due to internalization/endocytosis into duodenum and jejunum epithelial cells.
2.6 GELATIN AS MUCOADHESIVE POLYMER

Padhi JR et al. 2016 developed and evaluated composite hydrogels of gelatin and i-Carrageenan. Developed hydrogels evaluated for internal morphology using optical, scanning electron and confocal microscopy. Chemical interaction between gelatin and i-Carrageenan is evaluated by using X-ray diffraction and ATR-FTIR spectroscopy.

Further antimicrobial drug ciprofloxacin incorporated in hydrogel and evaluated for drug-excipient interaction and antimicrobial activity against nosocomial strains of Bacillus, Vibrio, Pseudomonas and Escherichia coli. Results showed promising uses of hydrogels. Negligible cytotoxicity observed against normal HaCaT and HEK293 cell lines.

Trastullo R et al. 2016 developed and evaluated ondansetron (a selective inhibitor of 5-HT3 receptors) buccal films for paediatric use using hydroxypropylmethylcellulose (HPMC) with chitosan (CH) or sodium hyaluronate (HA) or gelatin (GEL).

Ease of handling, exact and flexible dose, extended duration of activity like advantages lead to transmucosal administration of ondansetron drug in the form of buccal films as an innovation of pediatric dosage forms to prevent and treat nausea and vomiting caused by cytotoxic chemotherapy or radiotherapy and postoperatively. Higher in vitro drug release and drug permeation through porcine buccal mucosa in films of gelatin compared to HPMC film and ensured linear permeation profiles of drug.

Relative uniformity of the gelatin surface with entrapped lysozyme is showed by Scanning electron microscopy images. 100% bactericidal effect against *Staphylococcus aureus* confirmed antimicrobial potential of developed films.

**Hamedi S et al 2016** developed and evaluated mucoadhesive disc containing 70 mg stem bark extract of *Ziziphus jujuba* using polymers like Carbopol 934, PVP k30 and gelatin. Granulation and direct compression methods used to prepare discs. Discs were evaluated for total phenolic content, drug release, in vitro and in vivo mucoadhesion, water uptake and disintegration time. Excellent mucoadhesion and drug release observed during first hour.

**Abruzzo A et al 2015** developed and evaluated propranolol hydrochloride mucoadhesive buccal tablets using chitosan/gelatin microparticles. Micro particles were prepared by spray-drying method with different chitosan-gelatin weight ratios. Micro particles buccal tablets were prepared by direct compression method.

Morphology, drug release and permeation, In vitro water uptake, mucoadhesion strength like parameters evaluated and results confirmed potential of polymers as well as developed tablets in buccal administration of propranolol hydrochloride.

**Kharia AA et al 2015** improved the bioavailability through mucoadhesive nanoparticles mediated controlled delivery of acyclovir (ACV). Nanoparticle formulation optimised by central composite design based on gelatin and Pluronic F-68 as independent variables against responses: particle size, mucoadhesive strength, polydispersity index, entrapment efficiency, loading efficiency and drug release.

Optimised batches of mucoadhesive nanoparticles evaluated for morphology, stability, pharmacokinetic and gastrointestinal tracking. Spherical mucoadhesive nanoparticles showed more than 12 h significant retention in upper gastro-intestinal tract in In vivo mucoadhesion studies in rats.

Results showed potential of selected stabilizer polymers in better redispersibility under different solidification approaches. Different polymers showed significant differences in redispersibility index.

Duggan S et al 2015 synthesized mucoadhesive thiolated gelatin using a novel two-step approach. Amine to carboxylic acid coupling reaction with ethylene diamine used to cause amination of native gelatin and Traut's reagent used for final thiolation. 10-fold increase in thiol content showed improved cohesion and mucoadhesion when compared with unmodified and control gelatin samples.

Temperature and the pH of the amination reaction are key factors responsible for amine content and product yield. 20-25 kDa molecular weight having gelatin is found to be more suitable in production of maximum thiolation.

Borges JG et al 2015 produced and characterized orally disintegrating films of ethanol extract of propolis using gelatin and hydrolyzed collagen. Films were prepared by solvent casting method using different concentrations of hydrolyzed collagen with and without the extract.

Developed films evaluated for swelling index, mechanical properties, mucoadhesive strength, in vitro drug release, pharmacokinetics, stability and antimicrobial activity. FTIR spectroscopic studies performed to observe interactions between the extract and excipients. Satisfactory mucoadhesive properties, elasticity, swelling property and drug release profiles are obtained. Antimicrobial properties of films against Staphylococcus aureus confirmed potential of orally disintegrating films.
Liu CW et al 2014 developed gelatin-based mucoadhesive nanocomposites as skeletons for intravesical gene delivery to the urothelium in the form of hydrogels prepared by chemical crosslinking between gelatin A or B with glutaraldehyde. Hydration ratio, viscosity, size, yield, thermosensitivity, and enzymatic degradation like physicochemical parameters evaluated and 15% gelatin A175 containing optimised hydrogels exhibited 81.5% yield rate, 87.1% hydration ratio, 42.9 Pa·s viscosity, and 125.8 nm particle size.

Pronase degradation and ninhydrin assays performed to determine crosslinking density of the hydrogels. Higher cumulative release from hydrogels containing lentivirus (H-LV) compared to LV alone observed in in-vitro lentivirus (LV) release studies involving p24 capsid protein analysis in 293T cells. In vivo intravesical instillation to rat urothelium also showed enhanced gene delivery in AY-27 cells. Thus results have showed promising prospective of gelatin-based mucoadhesive nanocomposites as gene delivery device.

Kharia AA et al 2014 revealed most influential variable in formulating gastroadhesive nanoparticles of acyclovir. Taguchi standard orthogonal array L8 design used to study effects of formulation and processing variables on various response variables.

Amount of gelatin, glutaraldehyde and Pluronic F-68, acetone addition rate, pH, stirring time and stirring speed were considered as independent variables. Ranges of different evaluation parameters found as: particle size (165 to 1610 nm), PDI (0.360 to 1.00), Q6 (7.31-34.93%), T60% (19.2-37.6 h), entrapment efficiency (15.70 to 83.12%), loading efficiency (39.72 to 80.49%) and mucoadhesive strength (3.959-11.02 g).

Amount of gelatin and amount of Pluronic F-68 found to be two most important affecting factors during Pareto ranking analyses.
Kotagale NR et al 2010 developed ondansetron hydrochloride containing mucoadhesive tablets using varying ratio of different polymers like carbopol-934, sodium alginate and gelatin by direct compression. Tablets were evaluated for hardness, friability, uniformity of weight, disintegration time, microenvironmental pH, bioadhesion and in vitro release. Addition of pH modifiers viz. citric acid and sodium bicarbonate experimented to understand change in microenvironmental pH and bioadhesive strength of tablets.

Desired release profile observed when carbopol-934, sodium alginate, gelatin polymer system used with added pH modifier. Water uptake and in vitro release increased as sodium alginate and gelatin increased. Effect of pH modifiers on microenvironmental pH, bioadhesion, water uptake, in vitro permeation and in vitro release was studied.

Perchyonok VT et al 2013 developed and evaluated occlusive mucoadhesive system for treatment of oral mucositis using chitosan and gelatine through nystatin as a prophylactic agent. Palliative effects of an occlusive dressing, extended the retention time, therapeutic amount of drug release like key benefits of developed prototype delivery systems observed.

Inherent antimicrobial properties of Chitosan offered synergistic activity. Sustained release properties of hydrogels observed from in vitro drug release experiments.

Garg NK et al 2010 reviewed role of mucoadhesive/biodegradable polymers in vaccine mucosal delivery. Mucosal surfaces from gastrointestinal tract, nasal and vaginal tract are major gateway of infectious microorganism to the host. SIgA element in mucosal immune response effectively prevents the attachment and invasion of the microorganism from mucosal surface and thereby serves as an efficient tool against infectious disease.

Both mucosal as well as systemic immune responses against the infectious organisms can be provided by mucosal delivery of vaccine. Mucociliary
clearance, enzymes, pH, low permeation and metabolic degradation like factors are need to be considered.
Natural and synthetic polymers (polylactide-co-glycolide, chitosan, alginate, carbopol, gelatin) as biodegradable and mucoadhesive polymeric carrier system can be promising candidate for mucosal vaccine delivery.

**Shidhaye SS et al 2008** developed and optimized mucoadhesive bilayered buccal patch formulations of sumatriptan succinate by the solvent casting method using chitosan (base matrix), gelatin and polyvinyl pyrrolidone (PVP). Optimisation was done by 3(2) full factorial design using independent variables viz. levels of chitosan and PVP K30, against responses viz. swelling index, in-vitro mucoadhesive strength, in vitro drug release and in-vitro residence time.

Prepared patches evaluated for appearance, thickness, weight variation, drug content, mucoadhesive strength, folding endurance. 3% dimethyl sulfoxide addition in patches showed good permeation of sumatriptan succinate through mucosa. No buccal mucosal damage observed in histopathological studies. Thus, buccal route is best alternatives in administration of sumatriptan succinate.

**Dhaliwal S et al 2008** investigated potential use of mucoadhesive microspheres for gastroretentive delivery of acyclovir using mucoadhesive polymers like chitosan, thiolated chitosan, Carbopol 71G and Methocel K15M. Emulsion-chemical crosslinking technique is used to formulate microsphere. In vitro, ex-vivo and in-vivo physicochemical and biological parameters of prepared microspheres evaluated.

Complete dissolution, prolonged drug release observed in gelatin capsules containing drug powder. Better retention of thiolated chitosan microspheres in duodenal and jejunum regions of intestine observed in mucoadhesion study which leads to significant improvement in oral bioavailability of acyclovir from mucoadhesive microspheres.
Ofokansi KC et al 2007 explored ceftriaxone sodium containing mucin-gelatin mucoadhesive microspheres for rectal delivery. Soluble mucin (S-mucin) was obtained from small intestines of freshly slaughtered pigs and then mixed with type A gelatin. Emulsification cross-linking method used to formulate ceftriaxone sodium-loaded mucoadhesive microspheres in arachis oil as the continuous phase.

Higher and more rapid drug release observed in simulated intestinal fluid (SIF) without pancreatin (pH 7.4) than simulated gastric fluid without pepsin (pH 1.2) by diffusion following non-Fickian transport mechanism. Delivery of acid-labile third generation cephalosporin- ceftriaxone sodium via reactal mucosa is promising.

Bonferoni MC et al 2004 developed ion-exchange based ophthalmic delivery using lambda-carrageenan and gelatin. Anionic polymer when interacts with alkaline drugs leads to slow drug release. Hence, an alkaline anti-glaucoma drug, timolol maleate, was chosen as model drug development of slow release complex formation of lambda-carrageenan and gelatin.

Modulation in the drug release profiles, the rheological and mucoadhesive properties of the hydrated formulations observed from different ratios combination of carrageenan and gelatin in the form of microspheres and films. In-vitro and in vivo studies showed significant high drug concentration and bioavailability.

Wang J et al 2001 evaluated gastric mucoadhesive properties of aminated gelatin microspheres by in vitro and in vivo methods. Two kinds of commercial mucin used to study the interactions of gelatin, aminated gelatin and microspheres in aqueous media. Stronger interaction of aminated gelatin with mucin than either kind of the gelatin observed at a higher mucin concentration.

Significantly larger amount of aminated gelatin microspheres remained in the stomach after perfusion than that of gelatin microspheres due to higher gastric
mucoadhesive ability because of higher amino group content, improved chain flexibility and favorable polymer conformation. Thus in vitro and in vivo experiments showed promising mucoadhesive properties of aminated gelatin microspheres than that of gelatin microspheres.

**Wang J et al 2000** explored use of gastric mucoadhesive drug delivery system containing positively charged gelatin microspheres for eradication of H. pylori. Surfactant-free emulsification in olive oil, followed by a cross-linking reaction with glutaraldehyde used to prepare positively charged biodegradable microspheres using aminated gelatin.

2,4,6-trinitrobenzenesulfonic acid method used in determination of amino group contents of the modified gelatin. In vitro release characteristics of amoxicillin were evaluated for effects of glutaraldehyde concentration, cross-linking reaction time, drug-loading patterns, and type of release media. Significant reduction in Amoxicillin release rate observed from the modified gelatin microspheres compared with that from gelatin microspheres.

Low pH medium fasten amoxicillin release. The improved gastric mucoadhesion of the modified gelatin microspheres was observed compared with that of gelatin microspheres. Thus effective eradication of H. pylori can be expected from modified gelatin microsphere system due to longer mucoadhesion and pH stability.
2.6 MARKET ANALYSIS

Concept of buccal adhesive delivery system was introduced in 1947 when
dental adhesive powder was tested with tragacanth for delivery of penicillin
which became eventually orabase. Orabase is a first generation
mucoadhesive paste local barrier effect for the treatment of mouth ulcers.

Due to ease of administration, accurate dosing and simplicity in production
made mucoadhesive drug delivery a choice system for many drugs (Table
2.1) either for local or systemic effects.

Buccoadhesive dosage forms developed:

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Drug studied</th>
<th>Polymers used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets</td>
<td>Fluconazole, Propranolol,</td>
<td>HPMC, SCMC, CP, CP 934,</td>
</tr>
<tr>
<td></td>
<td>Atenolol, Pravastatin sodium,</td>
<td>Sodium alginate, carbomer,</td>
</tr>
<tr>
<td></td>
<td>Lercanidine HCl, Nystatin,</td>
<td>PVP K 30,</td>
</tr>
<tr>
<td></td>
<td>Ondasteron HCl, Domperidone,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tizanidine HCl</td>
<td></td>
</tr>
<tr>
<td>Films</td>
<td>Propranolol, Fluconazole,</td>
<td>HPMC, SCMC, CP, CP 934,</td>
</tr>
<tr>
<td></td>
<td>Glipizide, Insulin, myoglobin,</td>
<td>Sodium alginate, gellan gum,</td>
</tr>
<tr>
<td></td>
<td>progesterone, Nicotine,</td>
<td>chitosan, ethylcellulose,</td>
</tr>
<tr>
<td></td>
<td>Thiocholchicoside</td>
<td>gelatin, eudragit,</td>
</tr>
<tr>
<td>Patches</td>
<td>Propranolol, Atenolol, Lignocaine, oxytocin,</td>
<td>HPMC, SCMC, CP, CP 934,</td>
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<td></td>
<td>miconazole nitrate</td>
<td>PVA, PVP, chitosan, gelatin,</td>
</tr>
<tr>
<td>Gels</td>
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<td>PVP, HPC, PC, PEG, CP, CP 934,</td>
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<td></td>
<td>Lidocaine, Propolis, Tetracycline,</td>
<td>Hydroxyethyl Methacrylate,</td>
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### Buccoadhesive formulations in market

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Brand</th>
<th>Company</th>
<th>Polymer used / Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-chlorperazine maleate</td>
<td>Buccastem®</td>
<td>Reckitt Banckiser</td>
<td>Xanthan gum, Povidone Tablet</td>
</tr>
<tr>
<td>Pro-chlorperazine</td>
<td>Emezine®</td>
<td>BDSI</td>
<td>Un-disclosed Tablet</td>
</tr>
<tr>
<td>Glyceryl trinitrate</td>
<td>Sucard®</td>
<td>Forest lab</td>
<td>HPMC Tablet</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Fentora®</td>
<td>Cehalon Inc</td>
<td>Oravescent Modified food starch Tablet</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Actiq®</td>
<td>Cehalon Inc</td>
<td>Un-disclosed Tablet</td>
</tr>
<tr>
<td>Miconazole</td>
<td>Loramyc®</td>
<td>Bioalliance pharma</td>
<td>Un-disclosed Tablet</td>
</tr>
<tr>
<td>Miconazole</td>
<td>Tizole®</td>
<td>Tibotec pharmaceutica</td>
<td>CP Tablet</td>
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<td>Miconazole</td>
<td>Daktarin®</td>
<td>Janssen - Cilag</td>
<td>Un-disclosed Tablet</td>
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<tr>
<td>Nicotine</td>
<td>Nicorette®</td>
<td>Leo Pharmaceuticals</td>
<td>Un-disclosed Tablet</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Striant®</td>
<td>Columbia lab</td>
<td>HPMC , CP Tablet</td>
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<tr>
<td>Triamcinolone acetonide</td>
<td>Aphtach®</td>
<td>Teijin Ltd.</td>
<td>HPMC , PAA Tablet</td>
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<tr>
<td>Hydrocortisone sodium succinate</td>
<td>Corlan pellets®</td>
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<td>Acacia gum Oromucosal pellets</td>
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<td>Orabase®</td>
<td>Conva tech</td>
<td>Pectin, gelatin Pral paste</td>
</tr>
<tr>
<td>Chlorhexidine digluconate</td>
<td>Corsodyl gel®</td>
<td>Glaxo-SmithCline</td>
<td>HPMC Oralmucosal gel</td>
</tr>
<tr>
<td>Choline salicylate</td>
<td>Bonjela®</td>
<td>Reckitt Banckiser</td>
<td>HPMC Oralmucosal gel</td>
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</tbody>
</table>

CP, Carbapal, HPMC; Hyromellose, PAA; Polyacrylic acid
2.7 DRUG PROFIL
2.7.1 CANDESARTAN

Systematic (IUPAC) name: 2-ethoxy-1-\{(4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl]phenyl)methyl\}-1H-1,3-benzodiazole-7-carboxylic acid
Candesartan cilexetil is an antihypertensive drug acts as angiotensin II receptor antagonist. [Ardiana F et al., 2012; Khawaja Z and Wilcox CS et al., 2011]

**Patents:** [Barrios V and Escobar C. et al., 2011; Joost A et al., 2011]

<table>
<thead>
<tr>
<th>Products</th>
<th>Country</th>
<th>Patent Number</th>
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<td>Canada</td>
<td>2040955</td>
<td>1998-02-03</td>
<td>2011-04-22</td>
</tr>
<tr>
<td>Atacand,</td>
<td>Canada</td>
<td>2083305</td>
<td>2003-12-09</td>
<td>2012-11-19</td>
</tr>
<tr>
<td>Amias, and</td>
<td>United States</td>
<td>5534534</td>
<td>1994-01-09</td>
<td>2014-01-09</td>
</tr>
</tbody>
</table>

**Indication**
It is usually preferred in treatment of diabetic nephropathy and in patients who are not responding to ACE therapy than other drugs [Mengden T et al., 2009] in the treatment of congestive heart failure, systolic dysfunction, myocardial infarction and coronary artery disease. [De Rosa ML 2010; Suzuki H 2010]

**Dose:** Candesartan cilexetil is linear for oral doses up to 4-32 mg. [Mendis B et al., 2009; Baguet JP et al., 2009]

**Chemistry**
Candesartan cilexetil is used in the form of prodrug Candesartan cilexetil, which is ester of cyclohexyl 1-hydroxyethyl carbonate (cilexetil) ester. [Ardiana F et al., 2012] Esterases in the intestinal wall metabolises Candesartan cilexetil to the active Candesartan cilexetil moiety and improves bioavailability. [Pfeffer MA et al., 2003] But still due to only 15% bioavailability of Candesartan cilexetil tablets, it requires repeated dosing. [Mendis B et al., 2009]

**Mechanism of action**
Blockage of rennin-angiotensin system by angiotensin II receptor antagonists produces antihypertensive effects due to vasodilation. Angiotensin II causes
vasoconstriction. Candesartan cilexetil is 10,000 times more selective for AT1 than AT2 receptors. [Baguet JP et al., 2009; Bader M. 2004]

Figure 2.4: Mode of action of Candesartan

**Pharmacokinetics:**

Uridine diphosphate glucuronosyltransferase mediated N-glucuronidation of Candesartan cilexetil is observed. About 75% of unchanged Candesartan cilexetil excreted in urine and feces. [Stanfield C.L and Germann W.J. 2008]
<table>
<thead>
<tr>
<th>Name</th>
<th>Dosage</th>
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<th>Route</th>
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<tbody>
<tr>
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<td>Apotex Corp</td>
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2.8 EXCIPIENT PROFILE

CHITOSAN

Other names: Poliglusam; Deacetylchitin; Poly-(D)glucosamine; BC; Chitopearl; Chitopharm; Flonac; Kytex [Cheung RC et al., 2015]

Properties:
White or creamy powder or flakes, and odorless, obtained after partial deacetylation of chitin, biocompatible and biodegradable, Sparingly soluble in water; practically insoluble in ethanol (95%), other organic solvents, and neutral or alkali solutions at pH above approximately 6.5.

Source: Chitin is naturally occurring polysaccharide present as exoskeleton element of crustaceans animals like crabs and shrimp and also fungi cell wall. [Jennings JA et al., 2015; Mazzarino L et al., 2014] Deacetylation of chitin in presence of alkali produces linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine called as chitosan. [Costa Idos S et al., 2014; Tang C et al., 2014] Primary amino group present in chitosan is major target for chemical modifications and salt formation with acids. [Boateng JS et al., 2014]

Applications:
Biodegradable, non-toxic and bio-compatible nature of chitosan made it a novel excipient in drug delivery systems. [Castán H et al., 2015; Mortazavian E et al., 2014; Boateng JS et al., 2014] It is popular as excipient in novel pharmaceutical dosage from preparation. [Lv Q et al., 2015; Pongjanyakul T et al., 2013; Park DM et al., 2012; Koland M et al., 2011]

Chitosan exhibits excellent film forming ability, enhances the transport of polar drugs across epithelial surfaces, possesses cell-binding activity due to polymer cationic polyelectrolyte structure that binds to the negative charge of the cell surface.

GELATIN
Gelatin is a high molecular weight heterogeneous mixture of water-soluble proteins derived from collagen. It is extracted by boiling animal skin, tendons, ligaments, bones in water. It is thermo reversible structure. There are two types of gelatin [Row R et al., 2006]

- Type A gelatin: acid-cured tissue
- Type B gelatin: lime-cured tissue.

![Gelatin powder](image)

**Figure 2.5: Gelatin powder**
The pH of a 1.5% solution at 25°C is 3.8–5.5 for Type A and 5.0–7.5 for Type B. Gelatin is soluble in glycerol and acetic acid, and more soluble in hot than
in cold water. It is practically insoluble in most organic solvents such as alcohol, chloroform, carbon disulfide, carbon tetrachloride, ether, benzene, acetone, and oils.

**Properties:**
Appearance: light amber to faintly yellow colored powder
Molecular weight: 15,000–250,000
Solubility: Soluble in glycerin, acid, alkali and hot water
Moisture content: 9–11% (w/w)

**Uses**
- Component of culture media in bacteriology
- Delivery vehicle for the release of bioactive molecules
- Stabilizer, thickener, texturizer in foods
- Suspending agent, encapsulating agent, and tablet binder;
- Plasma expander and hemostatic sponge in veterinary applications
  Stabilize Taq DNA polymerase in PCR,
- Blocking reagent in Western blotting, ELISA, and immunohistochemistry
- It has a very good film forming ability. Useable for preparation of sterile film, ophthalmic film, and sterile sponge

**POLYETHYLENE GLYCOL** [Row R et al., 2006]

**Nonproprietary Names**
- • BP: Macrogols • JP: Macrogols • USP: Polyethylene Glycol

**Synonyms**
Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; PEG; Pluriol E; polyoxyethylene glycol.
Chemical Name
a-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl) [25322-68-3]

Empirical Formula and Molecular Weight
PEG 400, 380–420

Structural Formula

![Chemical structure of polyethylene glycol](image)

Functional Category
Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology
Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations.

It has been used experimentally in biodegradable polymeric matrices used in controlled-release systems. In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.

Description: The USPNF 23 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades
200–600 are liquids; grades 1000 and above are solids at ambient temperatures.

**Typical Properties**

- **Auto ignition temperature**: 371°C
- **Flash point**: 238°C
- **Density**: 1.11–1.14 g/cm³ at 25°C for liquid PEGs
- **Freezing point**: 4–8°C.
- **Refractive index**: 1.465 for
- **Solubility**: all grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher-molecular-weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols

- **Surface tension**: approximately 44 mN/m (44 dynes/cm) for liquid polyethylene glycols;

**Stability and Storage Conditions**

Polyethylene glycols are chemically stable, do not become rancid, do not support microbial growth. These are stable in air and in solution. Glycols with molecular weight less than 2000 are hygroscopic. Antioxidants protect degradation of these glycols from oxidation. Dry heat sterilisation changes their properties like oxidation, darkening and degradation.

**Incompatibilities**

Esterification and etherification of two terminal hydroxyl groups is major concern of reactivity. Again autoxidation exhibits production of secondary products.

**Safety**

Oral LD₅₀ in rat is 0.02 g/kg. Generally polyethylene glycols are regarded as nontoxic and nonirritant and used extensively in pharmaceutical formulations.
HYDROXY PROPYL METHYL CELLULOSE (HPMC) [Row R et al., 2006]

Nonproprietary Names:
Hypromellose, JP: Hydroxypropylmethylcellulose, PhEur: Hypromellosum, USP: Hypromellose

Synonyms
Methocel, methyl cellulose propylene glycol ether, methyl hydroxyl propylcellulose.

Structural formula

Molecular weight
10000-1500000

Viscosity (η): 3–100,000 mPa-s

Description
It is an odorless and tasteless, white or creamy white colored fibrous powder

Solubility
It is soluble in cold water and forming a viscous colloidal solution, soluble in mixtures of ethanol and dichloromethane. Solutions are stable at pH 3.0 to 11.0

HPMC is non-ionic polymer with moderate mucoadhesive properties, has the ability of thickening, anti-salt, water retention, good film-forming, anti-enzyme, dispersing, bonding, and low ash content. Film forming ability is observed at 2–20% concentrations. Generally used for controlled and/or delayed release of the drug substance. Initial burst drug release followed by slow or sustained drug release diffusion observed in buccal bioadhesive system of few drugs.
Ethylenediaminetetraacetic acid (EDTA), also known by several other names, is an aminopolycarboxylic acid and a colourless, water-soluble solid. Its conjugate base is ethylenediaminetetraacetate. It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system. In shampoos, cleaners, and other personal care products, EDTA salts are used as a sequestering agent to improve their stability in air. [Row R et. al. 2006]