3. LITERATURE REVIEW

3.1. Hypertension

Arterial hypertension is a key cause of morbidity and mortality because of its association with coronary heart disease, cerebrovascular disease and renal disease. The extent of target organ involvement (i.e. heart, brain and kidneys) primarily determines outcome. Current recommendations from international guidelines stated that in all patients with hypertension, it is important to lower BP until systolic and diastolic BP values below 140/90 mm Hg are achieved [12].

Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India. The WHO rates hypertension as one of the most important causes of premature death worldwide. The Global and Regional Burden of Disease and Risk Factors study (2001), in a systematic analysis of population health data for attributable deaths and attributable disease burden, has ranked hypertension in south Asia as second only to child underweight for age [13].

Hypertension is a chronic elevation of blood pressure that causes end-organ damage and results in increased morbidity and mortality. Blood pressure is the product of cardiac output and systemic vascular resistance. It follows that patients with arterial hypertension may have either an increased cardiac output or an increased systemic vascular resistance, or both. In the younger age group, the cardiac output is often prominent, while in older patients increased systemic vascular resistance and increased stiffness of the vasculature play a main role. Vascular tone may be elevated because of increased α-adrenoceptor stimulation or increased release of peptides such as angiotensin or endothelins. Vascular tone refers to the degree of constriction experienced by a blood vessel relative to its maximally dilated state [12].

The final pathway is an increase in cytosolic calcium in vascular smooth muscle causing vasoconstriction. Several growth factors, including angiotensin and endothelins, cause an increased vascular smooth muscle mass termed as vascular remodeling. Both an increased systemic vascular resistance and an increased vascular stiffness raise the load imposed on the left ventricle; this induces left ventricular hypertrophy and left ventricular diastolic dysfunction. In youths, the pulse pressure (difference between the systolic and diastolic pressure) generated by the left ventricle is relatively low and the waves reflected by the peripheral vasculature occur mainly after the end of systole, thus increasing pressure
during the early part of diastole and improving coronary perfusion. With ageing, stiffening of the aorta and elastic arteries increases the pulse pressure [12].

The autonomic nervous system plays an important role in controlling blood pressure. In hypertensive patients, both increased release of, and enhanced peripheral sensitivity to, norepinephrine can be found. In addition, there is increased responsiveness to stressful stimuli. Another feature of arterial hypertension is a resetting of the baroreflexes and decreased baroreceptor sensitivity. The rennin-angiotensin-aldosterone system is a hormone system involved in the regulation of plasma sodium concentration and arterial blood pressure. Plasma Angiotensin II is a potent vasoactive peptide that causes arteriolar constriction, resulting in arterial blood pressure. Angiotensin II also stimulates the secretion of hormone aldosterone from adrenal cortex. The renin–angiotensin system is involved in any case in some forms of hypertension (e.g. renovascular hypertension) and is suppressed in the presence of primary hyperaldosteronism. Elderly or black patients tend to have low-renin hypertension. Others have high-renin hypertension and these are more likely to develop myocardial infarction and other cardiovascular complications [12].

All anti-hypertensive drugs must act by decreasing the cardiac output, the peripheral vascular resistance, or both. The classes of drugs most commonly used include the thiazide diuretics, β-blockers, ACE inhibitors, angiotensin II receptors antagonists, calcium channel blockers, α-adrenoceptor blockers, combined α- and β-blockers, direct vasodilators, and some centrally acting drugs such as α2-adrenoceptor agonists and imidazoline I1 receptor agonists [12].

### 3.2. Calcium Channel Blockers

Calcium channel blockers have been one of the most widely used classes of antihypertensive agents in the last 20 years, based on their effectiveness in reducing BP levels, good tolerability, and abundant evidence on reducing cardiovascular and renal consequences of hypertension [14].

Calcium channel blockers (CCBs) inhibit the flow of extracellular calcium through ion-specific channels that span the cell wall. When inward calcium flux is inhibited, vascular smooth muscle cells relax, resulting in vasodilation and a lowering of blood pressure (BP). Within the drug class, CCBs showed several important differences from the pharmacokinetic and pharmacodynamic point of views as well as for selectivity and duration of pharmacological action, CCBs may be stratified into 3 groups, namely (1) dihydropyridinic agents, which mostly act as dilating agents at peripheral vessel level, (2) phenilalchilaminic...
agents, which predominantly act as negative inotropes and chronotropes at cardiac level, and
(3) benzothiazepinic agents, which have an intermediate profile [14].

All CCBs are peripheral arterial dilators. Dihydropyridines with short elimination half-lives
typically cause reflex tachycardia (an adverse effect that has been largely mitigated by
sustained-release preparations). Verapamil has more negative chronotropic effects than
diltiazem, an effect that makes each useful for acute intravenous treatment and chronic
prevention of atrial dysrhythmias [15].

In the kidney, CCBs produce natriuresis by increasing renal blood flow, dilating afferent
arterioles, and increasing glomerular filtration pressure. Nondihydropyridine CCBs reduce
albuminuria by improving glomerular permselectivity and / or by lowering renal perfusion
pressure. Short-acting dihydropyridines such as nifedipine cause reflex sympathetic
activation and tachycardia. While long-acting drugs such as amlodipine and slow-release
preparations of nifedipine cause less sympathetic activation. Short-acting dihydropyridines
appear to increase the risk of sudden death. Nifedipine is effective in severe hypertension and
can be used sublingually; there is need for caution because of the risk of excessive
hypotension. Dihydropyridine calcium channel blockers can be clinically classified to 1\textsuperscript{st}, 2\textsuperscript{nd}
and 3\textsuperscript{rd} generations. The first generation drugs are nifedipine, nicardipine, verapamil and
diltiazem. Second generation drugs have better pharmacokinetic profile that encompasses
longer action than first generation drugs and enhanced vascular selectivity. They are
subdivided to 2 groups; slow release formulae i.e. nifedipine slow release, felodipine
extended release and second group consist of newer chemical structures like benidipine,
manidipine, nilvadipine and nitrédipine. Third generation drugs comprises long acting drugs,
2 types of calcium channel blockers belongs to this generation. First group is characterized by
a sustained blood concentration with a long half life i.e. amlodipine. Other group is
characterized by lipophilic and highly histotropic properties i.e. lercanidipine which has long
acting pharmacokinetics [15].

3.3. **Lercanidipine in hypertension**

Preclinical studies show lercanidipine is highly selective for vascular tissue and produces
smooth muscle relaxation through competitive binding to L-type calcium channels. It is
highly lipophilic and is stored within cell membranes, which explains its slow onset of action
and persistent smooth muscle relaxant effect. The antihypertensive effect of lercanidipine
primarily occurs by peripheral and coronary vasodilatation. Lercanidipine has greater
vascular selectivity and causes less negative inotropism in vitro than other DHPs including lacidipine, amlodipine, felodipine, and nitrendipine. It does not cause significant reflex tachycardia or other signs of sympathetic activation when given at therapeutic doses to patients with hypertension. Lercanidipine (10 mg/day) produces a smooth antihypertensive effect without unfavorable hemodynamic or sympathetic effects [16].

In addition to its general antihypertensive activity, lercanidipine has a nephroprotective effect in spontaneously hypertensive rats and dilates both afferent and efferent arterioles. Lercanidipine may also have benefits in patients with hypertension and atherosclerotic disease where it is able to reside in cell membranes in the presence of high cholesterol levels. It has well described (in in vitro, animal, and clinical studies) antioxidant effects affecting vasodilatation and reducing oxidation of low-density lipoproteins. Regression of left ventricular hypertrophy has been described with lercanidipine in patients with hypertension, with or without diabetes. Interestingly, lercanidipine exerted a prolonged vasodilatory action in the microcirculation of 19 patients with hypertension, where it might protect against target organ damage. Thus lercanidipine has favorable efficacy and safety profile compared to other calcium channel blockers [16].

However, it is observed that lercanidipine possess highly variable and low bioavailability, around only 10% upon oral administration to GIT. Reasons behind its possessing variable and low bioavailability are (a) It is insoluble in gastrointestinal pH range of 1 to 7.5, (b) lercanidipine has shown low experimental permeability (i.e., permeability co-efficient, $P_{app}$ of $0.5 \times 10^{-7} \text{ cm/s}$ in a Caco2 cell apparatus), (c) it displays extensive presystemic first pass elimination, being a substrate for cytochrome P450 IIIA4 isoenzyme, (d) it possesses “food effect” i.e., lercanidipine administered in the absence of food may remain entirely unabsorbed, (e) oral lercanidipine is maximally absorbed after 2 h of administration. All these factors contribute for highly erratic and low bioavailability, around only 10% upon oral administration to GIT [17].

Therefore, in present research work, delivery strategies of lercanidipine are reconsidered. It is well known that development of poorly soluble and/or permeable drug molecules using nano-suspension formulations results in improved dissolution, permeation and bioavailability. Therefore nanosuspension of lercanidipine was formulated.
3.4. **Nano-suspension**

A nanosuspension is a submicron colloidal dispersion of drug particles which is stabilized by surfactants. A pharmaceutical nanosuspension is defined as very finely dispersed solid drug particles in an aqueous vehicle. The size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm [18, 19].

Preparation of crystalline or amorphous nanoparticles is a smart approach to increase the rate of dissolution and solubility of poorly soluble drugs. Discrete drug particles in the range of 100-1000 nm are defined as pharmaceutical nanoparticles. An increase in the exposed surface area (or surface area-to-volume ratio) by particle size reduction causes an increase in dissolution rate and thus bioavailability. In addition, according to the Kelvin equation, saturation solubility (in terms of vapor pressure) of the drug is dependent on the drug particle size. Theoretically, reduction in particle size will cause an increase in drug solubility. However, it is reported that the actual increase in saturation solubility for “nanocrystalline suspensions” (colloidal size range 100-1000 nm) is subsidiary, approximately 2%-10% compared to unmilled particles. Thus, nanosized crystalline powders may not be a useful approach for solubility-limited drugs (i.e., solubility is rate limiting for oral bioavailability).

In the case of amorphous formulations, the solubility of the drug is increased over the crystalline form due to its high energy state (higher Gibbs free energy). However, amorphous formulations are unstable and will convert to the stable crystalline form over a time period. Theoretically, combining nanotechnology and amorphization approaches may offer absolute or synergistic effects in terms of solubility and dissolution rates. The advantage of amorphous versus crystalline nanoparticles is the significantly higher kinetic solubility of amorphous nanoparticles [18, 19].

Broadly, there are 2 basic methods to manufacture nanoparticles:

1) A “top-down approach” (i.e., milling/grinding of the particles to achieve the required size) and
2) A “bottom-up approach” (i.e., precipitation of drug from a solvent to an antisolvent system).

The top-down approach is very time consuming and usually leads to crystalline particles, whereas the bottom-up approach is less time consuming and usually leads to amorphous particles.
particles due to fast evaporation of the solvent and thus precipitation of the drug as amorphous particles [18,19].

3.4.1. Origin of Pharmaceutical Amorphous Nanoparticles

Amorphous drug nanoparticles were first prepared using HYDROSOL technology (bottom-up to precipitation process) developed by Sucker and coworkers (Sandoz-Novartis), the marketed drug product is called “NanomorphTM” (Abbott/Soliqs, formerly BASF/Knoll). Briefly, the poorly soluble BCS Class II and IV drugs are dissolved in suitable organic solvents, this drug stock solution is rapidly added to a nonsolvent (mainly water containing surfactant), resulting in the formation of a supersaturated drug solution and submicron amorphous drug particles are produced. In addition to their nanosize range, amorphous nanoparticles have short-range order, because the molecules are randomly oriented in a variety of conformational states compared to crystalline drugs (which are characterized by long-range order in compact crystal lattice arrangements). Amorphous nanoparticles have liquid-like properties at the molecular level, but solid-like properties at the macroscopic level. Currently, amorphous drugs are formulated in the form of solid dispersions, which are in the micron size range, using different techniques such as spray drying, freeze drying, or hot melt extrusion. Here, drug stability is assured by the addition of high glass transition (Tg) polymers such as HPMC (hydroxyl propyl methyl cellulose) and PVP [poly (vinylpyrrolidone)]. The advantages of using these polymers are they minimize the molecular motion of the dispersed drug and hence prevent solution facilitated crystal growth and nucleation of the dissolved drug, maintaining the super saturation level for a long period of time and improve the storage stability by inhibiting the recrystallization of amorphous drug. Stabilization of amorphous drug nanoparticles can be achieved by the presence of stabilizers such as polymers, surfactants, and sugars. These excipients are adsorbed on the surface of the nanoparticles via electrostatic or hydrophobic interactions. Excipient adsorption occurs instantaneously following the production of amorphous nanoparticles, inhibiting recrystallization of the high energy sites on the particles, as well as preventing particle growth due to Ostwald ripening [18,19].

A higher amount of stabilizer in amorphous nanoparticulate delivery systems confirms greater stability of the amorphous state; however, the dissolution rate may no longer depend on the amorphous nanoparticles, but also on the nature of the excipient. Furthermore, a lower content of excipients may not have a significant effect on the dissolution rate, but the
formulation may be subject to the risk of recrystallization, affecting the storage stability of the amorphous nanoparticles. Thus, it is necessary to incorporate a suitable concentration of the stabilizer, which is sufficient to improve the storage stability, but yet has a minimal effect on the dissolution rate for the amorphous nanoparticles [18, 19].

3.4.2. Methods of preparation of amorphous nano-particles

Various techniques have been used to prepare amorphous nanoparticles, such as (a) ultrasonication, (b) drug-polyelectrolyte complexation, (c) antisolvent precipitation, (d) solvent evaporation, (e) sonoprecipitation, (f) flash nanoprecipitation, and (g) nanoporous membrane extrusion (NME).

3.4.2.1. Ultrasonication

Ultrasonication is an important top-down processing method for preparation of nano-sized drugs. The generation of crystalline or amorphous nanoparticles depends on the intensity, time of exposure, type and concentration of stabilizer used, and type of drug molecule. Ultrasonication improves the mixing of the precursors and increases mass transfer at the particle surface. This leads to smaller particle size and higher size uniformity.

Mechanism involved in ultrasonication, high and low pressure phases are generated due to the propagation of acoustic pressure waves in the liquid medium. Cavities are created due to the low pressure phase (which is below the saturation vapor pressure of solution). These cavities absorb energy and grow until unstable when they finally collapse violently generating shock waves in the liquid medium. There is interaction between the particles and the shock waves as a result of the localized high temperature and pressure regions created as a result of the implosions of these cavities. Hence, there is fragmentation of matter due to such extreme conditions resulting in the generation of amorphous nanoparticles. These nanoparticles can be spray or freeze dried to obtain dry amorphous nanoparticles [18, 19].

3.4.2.2. Drug-Polyelectrolyte Complexation

In this method, the drug component is mostly an amphiphilic molecule and the complexes are formed due to the simultaneous electrostatic and hydrophobic interactions between the polyelectrolyte and the ionized amphiphile resulting in various structures depending on the nature of the amphiphile. Mechanism involved in this method is described further. Anionic or cationic drug solution is obtained by dissolving a sparingly soluble amphiphilic molecule in acidic or basic medium. Consequently, an oppositely charged polyelectrolyte solution is
added into the ionized drug solution, instigating drug polyelectrolyte electrostatic interaction and concomitant charge neutralization. There is a rapid loss of solubility resulting in instantaneous precipitation when the drug solute is converted back to its sparingly soluble form upon charge neutralization. As a result, drug-polyelectrolyte nanocomplexes are generated. The synergistic effects of strong electrostatic interactions and rapid precipitation between the drug and polyelectrolyte prevent the drug molecules from arranging into an ordered crystal lattice, resulting in the formation of drug-polyelectrolyte amorphous nanoparticles [18, 19].

3.4.2.3. Antisolvent Precipitation

One of the bottom-up nanosizing techniques for the preparation of amorphous nanoparticles is antisolvent precipitation/crystallization technique. This method has been used extensively as a strategy to enhance the dissolution of poorly soluble drugs. It is a simple technique, cost effective, and easy to scale up. Mechanism involved is described further. The drug is dissolved in a solvent and the excipients are dissolved in an antisolvent. The drug solution is added to the antisolvent containing the stabilizers under controlled stirring, resulting in drug precipitation. Drug precipitation is controlled by the presence of stabilizers in the antisolvent, which inhibit crystallization, decrease the nucleation rate, and enhance the formation of a disordered amorphous solid-state form. Antisolvent precipitation may be conducted in combination with sonication. Sonication significantly increases the nucleation rate and hence there is insufficient time to form stable crystal lattices [18, 19].

3.4.2.4. Solvent Evaporation

Solvent evaporation is a popular, relatively straightforward and efficient encapsulation method for many hydrophobic drugs. Solvent evaporation is based on the emulsification of an organic solvent containing polymer in an aqueous phase, following evaporation of the organic solvent, the polymer precipitates in the form nanoparticles. The emulsion droplets which are stabilized by surfactants shrink, but remain relatively stable during solvent evaporation, and these initial emulsion droplets are the basis for the formation of the nanoparticles. Additionally, some emulsion droplets may coalesce during solvent evaporation generating nanoparticles, the size of which is based on the aggregation ratio [18, 19].
3.4.2.5. Sonoprecipitation

Sonoprecipitation is the application of ultrasound during antisolvent precipitation to produce discreet, nonagglomerated, and amorphous nanoparticles to enhance the oral bioavailability of hydrophobic drugs. Poor micromixing during antisolvent precipitation leads to uneven super saturation regions and particle aggregation. Ultrasound in conjunction with antisolvent precipitation provides uniform mixing conditions throughout the vessel. When ultrasound is propagated through a liquid medium, it increases mass transfer and initiates cavitations. The cavitations bubbles formed during the negative pressure phase of the sound waves implode, creating localized hot spots with a high temperature and pressure, releasing powerful shock waves. Ultrasound results in homogenous mixing of the solvent and antisolvent. The solubility of the solute decreases instantaneously achieving maximum super saturation, causing rapid induction of primary nucleation, decrease in crystal size, and prevention of aggregation [18, 19].

3.4.3. Advanced Methods

3.4.3.1. Flash Nanoprecipitation

Flash nanoprecipitation is a relatively fast, simple, scalable process using rapid micromixing to create high super saturation conditions leading to the precipitation and encapsulation of hydrophobic drugs in a polymer-based delivery vehicle. A mixture of an amphiphilic block copolymer along with a highly hydrophobic drug is dissolved in a water miscible organic solvent. This solution is injected into a small chamber at a high velocity along with water; this high velocity produces a turbulent mixing effect resulting in precipitation of the hydrophobic drug and polymer instantaneously, leading to the formation of nanosize range particles. Amphiphilic block copolymers consist of hydrophobic and hydrophilic regions. The hydrophobic region of the polymer and drug is encapsulated in the core of the nanoparticle. The hydrophilic region forms a corona, sterically stabilizing the particles and preventing further aggregation [18, 19].

The hydrophilic regions can be tipped with ligands for specific cell targeting. The flash nanoprecipitation uses a 4-stream multi inlet vortex mixer or a 2-stream confined impingement jet mixer with subsequent dilution [18, 19].
3.4.3.2. Nanoporous Membrane Extrusion (NME)

NME is a novel, simple, low-cost, and efficient technique to prepare uniform 100-nm hydrophobic drug nanoparticles. It is applicable to a wide class of poorly water-soluble drugs and the resulting nanoparticles enhance drug solubility. The nanoparticles are prepared by pumping one liquid containing hydrophobic drug dissolved in a suitable organic solvent into the other liquid containing a buffer solution, through a nanoporous membrane. Membranes with uniform and well-defined nanopores are essential for the preparation of nanoparticles with reduced sizes [18, 19].

3.4.4. Supercritical Fluid Technology

Supercritical fluids (SCFs) are substances that have properties in between that of a gas and liquid (they exists as a vapor and liquid in equilibrium at high temperature and pressure). Substances have superior solubility in the liquid state compared to the gaseous state. The density of substances in the supercritical state is close to that of the same substances in the liquid state. In addition, the diffusivity and viscosity of substances in the supercritical state is close to that of the same substances in gaseous state (providing superior mass transfer rates in the SCF state). There are 6 SCF technologies: (1) rapid expansion of supercritical solutions (RESS); (2) supercritical antisolvent (SAS); (3) gas antisolvent (GAS); (4) solution enhanced dispersion by SCFs; (5) particle from a gas saturated solution; and (6) carbon dioxide assisted nebulization with a bubble dryer® [18,19].

3.4.4.1. Rapid Expansion of Supercritical Solutions

The principal criteria for the application of this technique are that the drug must be freely soluble in the SCF (e.g., supercritical CO2). The SCF is saturated with neat drug or a drug-polymer mixture. This solution is passed under decompression through a hot nozzle which results in sudden expansion of the mixture leading to rapid nucleation and formation of nanoparticles, collected from the gas stream [18, 19].

3.4.4.2. Supercritical Anti-solvent

Drug or a drug-polymer mixture is dissolved in the organic solvent and this mixture is sprayed through a hot nozzle in a chamber containing SCF, which acts as an antisolvent. There is a large volumetric expansion and consequent density drop as a result of solubilization of the SCF in the organic solvent droplets. This results in increased super saturation of the solution leading to the formation of uniform-sized nanoparticles [18, 19].
3.4.4.3. Gas Antisolvent

Drug or a drug-polymer mixture is dissolved in an organic solvent or a mixture of organic solvents. A gas (need not be supercritical) is injected in the solution from the bottom of a closed unit. The gas must be readily soluble in organic solvent, while the drug solubility must be minimal in the gas. The low drug solubility results into super saturation leading to rapid precipitation and formation of nanoparticles [18, 19].

3.4.5. Mesoporous Silica

Tetraethyl orthosilicate (TEOS) is mixed with alcohol, ammonia, and water to form nanoparticles. The particle size of the nanoparticles is optimized by controlling the ratio of solvent/TEOS. Further agitation and heating lead to a pore formation resulting in hollow mesoporous silica nanoparticles. Drug loading is carried out using one of the reported methods: adsorption from organic solution, incipient wetness impregnation technique, melt method, and SCF processing method. Mostly, the solid state of the drug in the mesoporous nanoparticles is amorphous [18, 19].

3.4.6. Electrospinning

A high voltage is applied to a drug, drug-polymer solution or melts resulting in an electrically charged jet stream. A Taylor cone like structure is formed as the voltage is increased, which is due to elongation of the crescent surface of the drug-polymer solution or melt at the tip of the capillary. The solvent evaporates and the mixture solidifies, which is collected in a screen as interconnected nanofibers [18, 19].

3.5. Solid Dosage Form Development of Nanosuspension

Development of poorly soluble and/or permeable drug molecules using nanocrystal formulations results in improved dissolution, permeation and bioavailability. However, long term stabilization of nanosuspension in a dispersion form may become a challenging task. Also considering convenience and consumer preference of solid dosage forms, nanosuspensions have to be dried. Conversion of nanoparticles in patient friendly dosage forms such as tablet, capsules involves unit-operations such as freeze-drying, spray-drying, pelletization and granulation which would likely lead to agglomeration of the nanoparticles, poor re-dispersion and poor recovery of nanoparticles. Further those powders are processed for capsule filling or compressed into tablets. This indicates that conversion of nanoparticles
in patient acceptable dosage form involves several stages which are complicated and time consuming [20].

One of the major concerns with nanosuspension formulations is the preservation of their physical and chemical stability in aqueous medium. Nanosuspensions are more susceptible to both physical instability (due to crystal growth and agglomeration) and chemical instability (due to degradation of the API(s)), when compared to solid dosage forms [21].

In clinical treatment, liquid nanosuspensions are also not convenient to take and carry for storage and shipping. In addition, though stabilizers are used in the liquid nanosuspension to decrease the tendency of aggregation, sedimentation, crystal growth, and crystalline transformation, the liquid nanosuspension with stabilizers still has the tendency at the long-term storage process [21].

Therefore, solid dosage forms are usually more preferred over liquid dosage forms. Liquid nanosuspensions have been explored to be transformed into solid dosage forms for patient convenience reasons and/or long-term stability. Prior to the formulation into solid dosage forms, the liquid nanosuspension DDS is often converted into solid intermediate products. This process is named as solidification of liquid nanosuspension DDS. It is critical to minimize the nanoparticle aggregation during the solidification process. In liquid nanosuspension, stabilizers are used to prevent nanoparticle aggregation by adsorbing onto the surfaces of drug nanoparticles to provide an ionic or steric stabilization. Drying of liquid nanosuspension can cause dry stabilizers, leading to drug nanoparticle destabilization and irreversible aggregation. Therefore, a coherent solidification method should be selected for the dry product preparation of nanosuspension DDS. Several solidification methods have been developed to be applied to transform liquid nanosuspensions into solid powder products such as spray drying, freeze drying, electrostatic spray drying, aerosol flow reactor method, and wet granulation. The spray drying is accomplished using a spray dryer and the liquid nanosuspension is atomized to fine droplets that are evaporated in a warm airflow to form dry nanoparticles. In the freeze drying, the liquid nanosuspensions are lyophilized using liquid nitrogen or a refrigerator, and then the resulted lyophilized substances are freeze dried using a freeze dryer. Electrostatic spray technique has been widely used to deposit nanocrystals in nanosuspensions onto substrate due to its low cost, simple operation and feasibility. The electrostatic force is used for atomization of liquid nanosuspensions. In aerosol flow reactor method, the liquid nanosuspension is atomized using an ultrasonic or a collision-type air jet
nebulizer and the resultant droplets are evaporated in a tubular flow reactor housed in a constant temperature oven [21].

Among these preparation methods of solid powder products, spray drying and freeze drying are two mainstream methods. To reduce time and energy consumption, spray drying is commonly preferred over freeze drying in the pharmaceutical industry. Freeze drying is the most suitable method for thermo-labile drugs such as protein drugs and vaccines. Freeze drying is also generally preferred when the redispersibility of drug nanoparticles after solidification is needed. Different solidification method may induce different dissolution rate of the resultant dry powder in water. Salazar et al. explored the effect of three solidification methods (spray-drying, freeze drying, and wet granulation) on the dissolution rate of dry powder of glibenclamide nanosuspensions. The results demonstrated that, regarding the dissolution rate, the rank order of these three methods was as follows: spray drying > freeze drying > wet granulation. It should be noted that some redispersants (protective agents) are often needed to prevent drug nanoparticle agglomeration during the solidification process and to maintain the redispersion ability in water after the solidification process. These redispersants (protective agents) are mainly polyatomic alcohols such as sucrose, lactose, trehalose, dextran, glucose, β-cyclodextrin, and mannitol. They are often highly water soluble and can form a highly hydrophilic environment around the drug nanoparticles. Among these redispersants, mannitol is found to be the more popular one. The processing parameters during the solidification also have a significant effect on the in vitro and in vivo performance of the dried drug products. Figueroa et al. studied the effects of spray mode, spray rate and atomizing pressure for fluid bed granulation of drug nanosuspensions using naproxen as a model drug. Spray mode had the biggest impact, where top spray yielded smaller re-dispersed particle sizes and faster release rates of drug from granules compared with bottom spray. A higher liquid spray rate resulted in more particle aggregation, while increasing the atomization pressure decreased the re-dispersed particle diameters [21].

Thus, formulation of nanosuspension-based solid dosage forms is a way to overcome instability problems. Liquid nanosuspensions can be converted into solid dosage forms by drying to obtain a powder of nanosized drug particles, which can be processed into conventional dosage forms such as tablets or capsules. Spray and freeze drying are the most common methods of removing water from aqueous systems [21].

In present research, lercanidipine nanosuspension is directly incorporated into ‘fast dissolving oral films’ and ‘thermo-responsible nasal gel’. Transformation of lercanidipine
nanosuspension into trans-mucosal dosage forms was achieved by simple technique which was devoid of lyophilization or spray drying techniques. Hence novelty of this work lies in simple process-integration of drug nanonization and its incorporation into ‘fast dissolving oral films’ and ‘in situ nasal gel’.

3.6. Overview on Fast Dissolving Oral Films

Research and developments in oral drug delivery has evolved to changeover of solid dosage forms from conventional solid tablets/capsules to modified release tablets/capsules, to fast dissolving tablets, to wafers, to recent development of fast dissolving films or strips. The concept of mouth dissolving drug delivery system (MDDDS) arose from the need to provide patients with more conventional means of taking their medication. For the patients suffering from dysphagia, repeated emesis, motion sickness, and mental disorders swallowing a dosage form with large quantity of water is a difficult task. European Pharmacopoeia has used the term orodispersible tablet for a tablet that disperses within 3 minutes in mouth before swallowing. While dissolving or dispersing the tablet in the saliva, some amount of drug may get absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. From this, theory of orotransmucosal drug delivery can be proposed [2, 22, and 23].

3.6.1. Overview of oral mucosa

Oral cavity is made up of the lips, cheek, tongue, hard palate, soft palate and floor of the mouth. Oral cavity is lined by oral mucosa. Surface of the oral mucosa is formed by stratified squamous epithelium lined on basement membrane. (Fig.1). Basement membrane separates epithelium from underlying lamina propria and submucosa layer. Submucosa layer contains blood vessels and nerves. The top quarter to one-third of the oral epithelium is made up of closely compacted epithelial cells. The main function of the oral epithelium is to guard the underlying tissue against potential unsafe agents in the oral environment and from fluid loss. Oral mucosa can be divided into lining mucosa, masticatory mucosa and specialized mucosa. Lining mucosa mainly found on buccal (vestibule of the mouth) and sublingual region (floor of the mouth), masticatory mucosa found on gingiva (gums) and hard palate region, specialized mucosa found on dorsal surface of tongue [24].

Buccal and sublingual mucosae commonly have application in drug delivery as they possess more suitable properties over gingival and palatal surface. Sublingual mucosa is thinner and more superior in terms of permeability compared to buccal mucosa. Therefore sublingual mucosa is more suitable site for drug delivery when rapid onset of action is needed. Tongue
movement and constant washing by saliva makes this site less suitable for retention of dosage form. A thin film fabricated using hydrophilic polymers that rapidly dissolves beneath the tongue or in buccal cavity and dissolved drug gets absorbed through the oral mucosal surface to reach to the systemic circulation [24, 25].

![Figure 1: Schematic Diagram of Buccal Mucosa](image)

Table 2: Comparison of oral mucosa with different mucosae of GIT [24]

<table>
<thead>
<tr>
<th>Absorptive Site</th>
<th>Estimated surface area</th>
<th>Mean fluid volume (mL)</th>
<th>Relative enzyme activity</th>
<th>Relative drug absorption capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>100 cm²</td>
<td>0.9</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.1-0.2 m²</td>
<td>118</td>
<td>high</td>
<td>Moderate</td>
</tr>
<tr>
<td>Small intestine</td>
<td>100 m²</td>
<td>212</td>
<td>high</td>
<td>High</td>
</tr>
<tr>
<td>Large intestine</td>
<td>0.5-1 m²</td>
<td>187</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Rectum</td>
<td>200-400 cm²</td>
<td>-</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

3.6.1.1. Permeability and Barrier properties of the mucosa

Epithelium of the oral mucosa composed of 4 types of cell layers keratinised layer, granular cell layer, spinous cell layer and basal cells. As supra-basal cells differentiate they form strong intercellular desmosomal junctions and form membrane coating granules on their apical surfaces. These membrane coating granules release lipophilic material into the intercellular spaces to ensure epithelial cohesion. This lipophilic material slows the passage
of hydrophilic materials across the epithelium. The charge on the constituents of the basal lamina and high level of hydration of connective tissues may limit the rate of penetration of lipophilic compounds. There are three approaches of diffusion across the oral mucosa's permeability barrier (i) passive diffusion including transcellular (through cells) and paracellular (where material passes through lipid rich domains around the cells), (ii) carrier mediated transport, and (iii) endocytosis/exocytosis where material is actively taken up and excreted by cells via the endocytic pathway [3,7].

Table 3: Characteristics of oral mucosa [1]

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Structure</th>
<th>Thickness (µm)</th>
<th>Surface area (cm²±SD)</th>
<th>Permeability</th>
<th>Blood flow in rhesus monkeys (ml/min/100 g tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buccal</td>
<td>Nonkeratinized</td>
<td>500-600</td>
<td>50.2 ± 2.9</td>
<td>Intermediate</td>
<td>20.3</td>
</tr>
<tr>
<td>Sublingual</td>
<td>Nonkeratinized</td>
<td>100-200</td>
<td>26.5 ± 4.2</td>
<td>Very good</td>
<td>12.2</td>
</tr>
<tr>
<td>Gingival</td>
<td>Keratinized</td>
<td>200</td>
<td>-</td>
<td>Poor</td>
<td>19.5</td>
</tr>
<tr>
<td>Palatal</td>
<td>Keratinized</td>
<td>250</td>
<td>20.1 ± 1.9</td>
<td>Poor</td>
<td>7.0</td>
</tr>
</tbody>
</table>

3.6.2. Advantages of buccal/sublingual films

Oral strips are thin and flexible dosage forms having larger surface area which rapidly wets and dissolves in the moist buccal environment. Drug dissolved in saliva get easily transported from oral mucosal surface to the submucosa layer containing blood vessels ultimately to the systemic circulation. Therefore drugs susceptible for first pass metabolism, degradation in acidic environment can be formulated into oral strips.

The disadvantage associated with most of the ODTs is they are fragile and brittle which demands special packaging during storage and transportation. The films are flexible therefore compared to most of the ODTs they are not as fragile. Hence, there is ease of transportation during consumer handling and storage. Compared to liquid formulations, precision in each dose is more for each of the strips.

Better patient acceptability due to ease of swallowing and no water required while administering therefore can be consumed at anyplace and anytime as per convenience of the individual.

Oral films are convenient dosage form for the patients suffering from dysphagia, repeated emesis, motion sickness and mental disorders. Since the first pass effect can be avoided and
drug directly reaches to the systemic circulation there can be enhanced bioavailability with dose reduction [25].

3.6.2.1. Formulation consideration

Buccal/sublingual films are thin flexible polymeric strips intended to dissolve beneath the tongue or in buccal cavity. So mouth feel, taste masking, rapid dissolution, physical and mechanical characteristics have to be considered while formulating fast dissolving films. All excipients used in the formulation should be approved for use in oral pharmaceutical dosage forms and generally regarded as safe (i.e. GRAS-listed). [25]

3.6.2.2. Film forming polymer

Several polymers can be used for preparation of fast dissolving films (FDF) or oral strips (OS). To obtain the desired properties, polymers can be used alone or in combination. The film obtained should be of enough strength so that there won't be any damage while handling or during transportation, at the same time it should be thin and flexible and should have the property to disintegrate in seconds when placed in mouth to deliver the drug to the oral cavity promptly. As the strip forming polymer is the most crucial and main component of the OS, at least 45%w/w of polymer should be usually present based on the total weight of dry OS. [25] Properties of the commonly used film forming agents have discussed in following Table 4.

<table>
<thead>
<tr>
<th>Table 4 : Properties of the commonly used film forming agents [26, 27]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polymer</strong></td>
</tr>
<tr>
<td>Pullulan</td>
</tr>
<tr>
<td>Lycoat NG 73</td>
</tr>
<tr>
<td>Polymer</td>
</tr>
<tr>
<td>--------------</td>
</tr>
<tr>
<td>Sodium alginate</td>
</tr>
<tr>
<td>Pectin</td>
</tr>
<tr>
<td>HPC</td>
</tr>
<tr>
<td>HPMC</td>
</tr>
<tr>
<td>PVA</td>
</tr>
</tbody>
</table>
Polymer | Source/Composition | Reported Film Properties
--- | --- | ---
Gelatin | Partial acid hydrolysis (type A gelatin) or by partial alkaline hydrolysis (type B gelatin) of animal collagen and/or may also be a mixture of both. | Film made up of gelatin dissolves rapidly, excellent carrier for flavors and possesses a smooth mouth feel
Maltodextrin | It is produced from starch by partial hydrolysis, made up of D-glucose units connected in chains of variable length. The glucose units are mainly connected with each other by α (1→4)glycosidic bond. Malto dextrin is typically composed of a mixture of chains that made up of variable number of (three to nineteen) glucose units. Maltodextrins are classified by DE (dextrose equivalent) and have DE 3-20. Higher the DE value, shorter the glucose chains, higher the sweetness and higher the solubility. | Maltodextrins with lower DE values usually gives higher viscosity and better film formation while higher DE values produce films with more sweetness, solubility, plasticity, and hygroscopicity. Lower DE values offer several processing advantages over higher DE values. Lower DE values improve flexibility of the film which reduces cracking and flaking during slitting and cutting. Being less hygroscopic, lower DE maltodextrins pick up less moisture during slitting and cutting.

3.6.2.3. Plasticizers

Plasticizer is an important ingredient of the OS formulation. It assists in improving the flexibility of the strip and decreases the brittleness of the strip. When Plasticizer added to polymer it gets incorporated in between polymer chains and spaces them apart from each other which results into easy movement of the polymers chains. Plasticizer significantly reduces the glass transition temperature of the polymer therefore polymer chains can slide over each other at lower temperature, thus improves the strip properties. Plasticizer improves
the flow of polymer and enhances the strength of the polymer. The compatibility of plasticizer with the polymer and type of solvent used in the casting of strip determines the selection of plasticizer. Some of the frequently used plasticizer excipients are glycerol, propylene glycol, low molecular weight PEGs, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil. Usually plasticizers should be used in the concentration of 0–20% w/w of dry polymer weight otherwise inappropriate use of plasticizer may lead to film cracking, splitting and peeling of the strip. Use of certain plasticizers may also influence the absorption rate of the drug. The Plasticizer incorporated in the strip should impart long-lasting flexibility to the strip. Generally it depends upon the volatile nature of the plasticizer and type of its interaction with the polymer. Plasticizer should decrease the glass transition temperature of polymer in the range of 40–60ºC for non-aqueous solvent system and below 75ºC for aqueous systems. Plasticizers should have compatibility with drug as well as other excipients used for preparation of strip. Certain drug molecules themselves can act as a plasticizer. For example, ibuprofen interacted with Eudragit RS 30 D and played the role of a plasticizer. In this case, the glass transition temperature of Eudragit RS 30 D decreased and smooth film formation was observed due to the hydrogen bonding between the drug and the polymer. There are two mechanisms proposed for plasticization effect namely internal plasticization (involving chemical interaction) and external plasticizing effect. Formulators prefer the latter mechanism as it does not involve chemical alterations in the product. The chemical structure and concentration of plasticizers play an important role in alleviating the glass transition temperature of the polymers. Cellulosic hydrophilic polymers were easily plasticized with hydroxyl containing plasticizers like PEG, propylene glycol, glycerol and polyols. In contrast, less hydrophilic cellulosic polymers were plasticized with esters of citric acid and phthalic acid. Glycerol acts as a better plasticizer for PVA while diethylene glycol can be used for both HPMC as well as PVA films [25, 28].

3.6.2.4. Active Pharmaceutical Ingredient

Though fast dissolving oral strip dosage form has the capacity to deliver variety of API’s, size of the dosage form limits the use of the drugs to be incorporated. Oral strips are delivered as thin, flexible films with area up to 8 cm² which dissolves within several seconds therefore drug molecules with high dose and low solubility are not preferable. Generally 5% - 30% w/w of active pharmaceutical ingredients can be incorporated in the OS. Water soluble API’s are in the dissolved state in oral strip or they form solid solution means homogenous one
phase system with polymer. Incorporation of water insoluble drug in water miscible polymers can be achieved by micronization or nanonization of drug. Micronization of the drug helps to improve the texture of the film also uniformity and dissolution. Taste masking is an important part while incorporating bitter tasting drugs in fast dissolving films. Complexations with cyclodextrins and resins, polymeric coating, microencapsulation are the important techniques of taste masking [25].

3.6.2.5. Saliva stimulating agents

Saliva stimulating agents increase the rate of production of saliva that would assist in the faster disintegration of the fast dissolving strip. Generally acids like citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid can be utilized as salivary stimulants [2].

3.6.2.6. Sweeteners

Low molecular weight carbohydrates and specially sucrose are most commonly used sweeteners. Sucrose is very soluble in water and being colorless does not impart any undesirable color to the final formulation. It is stable over the pH range 4-8. It masks the taste of both salty and bitter drugs. Polyhydric alcohols such as sorbitol and mannitol also exhibit sweetening capacity and suitable for diabetic patients. Mannitol is half as sweet as sucrose and sorbitol has 50-60% of sweetness of sucrose. Sorbitol and mannitol have negative heat of solution therefore impart cooling sensation in mouth. Artificial sweeteners also termed as intense sweeteners. They are several hundreds to thousands times more sweeter than sucrose. Therefore they are hardly required at a concentration more than 0.2%. Only six artificial sweeteners are permitted for oral use within the European Union, the most widely used is sodium or calcium salts of saccharin. Both the salts exhibit high water solubility and are chemically and physically stable over wide pH range. Less widely used artificial sweeteners are aspartame, acesulfame potassium, thaumatin, sodium cyclamate, neohesperidine. Main disadvantage associated with artificial sweeteners is metallic or bitter aftertaste [29, 30]. A quite new sweetening agent in U.S. market is stevia powder; it is obtained from the extract of the leaves of the plant Stevia rebaudianabertoni. It is natural, nontoxic and safe and 30 times as sweet as sucrose. It is heat stable [29].
Table 5: Comparison of sucrose with saccharin and aspartame [29]

<table>
<thead>
<tr>
<th></th>
<th>Sucrose</th>
<th>Saccharin</th>
<th>Aspartame</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Source</strong></td>
<td>Sugar cane, sugar</td>
<td>Chemical synthesis; phthalic anhydride, a petroleum product</td>
<td>Methyl ester dipeptide of phenylalanine and aspartic acid</td>
</tr>
<tr>
<td><strong>Relative sweetness</strong></td>
<td>1</td>
<td>300</td>
<td>180-200</td>
</tr>
<tr>
<td><strong>Bitterness</strong></td>
<td>None</td>
<td>Moderate to strong</td>
<td>none</td>
</tr>
<tr>
<td><strong>Aftertaste</strong></td>
<td>None</td>
<td>Moderate to strong; sometimes metallic or bitter</td>
<td>none</td>
</tr>
<tr>
<td><strong>Calories</strong></td>
<td>4/g</td>
<td>0</td>
<td>4/g</td>
</tr>
<tr>
<td><strong>Acid stability</strong></td>
<td>Good</td>
<td>Excellent</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Heat stability</strong></td>
<td>Good</td>
<td>Excellent</td>
<td>Poor</td>
</tr>
</tbody>
</table>

3.6.2.7. Flavouring agents

Flavors used in the formulation must be non-toxic, soluble, stable and compatible with the excipients [31].

Table 6: Preferred Flavors used in drugs [31]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Preferred Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>Cherry, maple, pineapple, orange, raspberry, banana-vanilla, butterscotch, coconut-custard, fruit-cinnamon, strawberry, vanilla</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Apricot, cherry, cinnamon, grape, honey, lime, peach-orange, peach-rum, raspberry, wild cherry</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Banana-pineapple, banana-vanilla, cinnamon-peppermint, orange, peach-orange, grenadine-strawberry</td>
</tr>
<tr>
<td>Decongestants &amp; Expectorants</td>
<td>Anise, apricot, butterscotch, cherry, coconut-custard, custard-mint- strawberry, grenadine-peach, strawberry-lemon, gooseberry, orange-lemon, coriander, pineapple, raspberry.</td>
</tr>
<tr>
<td>Electrolyte-solutions geriatrics</td>
<td>Cherry, grape, lemon-lime, raspberry, wild cherry syrup, grenadine-strawberry, lime, port wine, cherry wine, wild-strawberry.</td>
</tr>
<tr>
<td>Salt taste drugs</td>
<td>Butterscotch, maple</td>
</tr>
<tr>
<td>Bitter taste drugs</td>
<td>Wild cherry, walnut, chocolate-mint, licorice</td>
</tr>
<tr>
<td>Sweet taste drugs</td>
<td>Fruit, berry, vanilla</td>
</tr>
<tr>
<td>Acid taste drugs</td>
<td>Citrus</td>
</tr>
</tbody>
</table>
Aromatic oils include caraway, clove, dill, lemon, orange, pepper-mint etc. Synthetic sweeteners, chloroform, vanillin, benzaldehyde etc. and variety of organic compounds like alcohols, aldehydes, esters, ketones, fatty acids and lectones can be used alone or combined with essential oils [31].

Flavor acceptance is also affected by age. In general, children like fruit flavored syrup; adults prefer a more acid taste, while many old people find mint or wine flavors more agreeable. Flavoring agents Flavors used in the formulation must be non-toxic, soluble, stable and compatible with the excipients. Response to the flavor may not be the same in health and disease while a flavor acceptable for a short time may become objectionable if the treatment is prolonged [31].

3.6.2.8. Coloring agents

When drug is present in the film in a suspension or insoluble particulate form, coloring agents have to be incorporated in the oral film. Pigments such as titanium dioxide or FD&C approved coloring agents are generally used (not exceeding concentration levels of 1%w/w) [2,25].

3.6.3. Manufacturing of Oral films

3.6.3.1. Casting Method

It includes mixing of drug, polymers, plasticizers and other components in water, suitable solvent or solvent system. Solvents used for the preparation of solution or suspension should be selected according to ICH solvent classification. Formed solution or suspension is casted on the suitable surface of desired area and dried at appropriate temperature [2].

3.6.3.2. Hot melt extrusion

Hot melt Extrusion is a continuous process. The extruder is usually composed of a feeding hopper, barrels, single or twin screws, the die, screw driving unit and downstream processing equipment (Fig.2). Generally mixed blend of drug, polymer and plasticizers added to the barrel through hopper. The heat required to melt or fuse the material is supplied by the heat created by friction as the material is sheared between the rotating screws and the wall of the barrel in combination with electric or liquid heaters. It facilitates intense mixing and agitation of material which causes distributive and dispersive mixing of drug particles in the molten polymer. Hot melt extrusion processing results in a more uniform dispersion of particles at molecular level [32]. Repka and co-workers used Killion melt extruder to produce HPC
films. PEG 8000 2%, triethyl citrate (TEC) 2%, acetyltributyl citrate (ATBC) 2%, and PEG 400 1% were the plasticizing agents studied. In addition, either hydrocortisone 1% or chlorpheniramine maleate 1% was incorporated into the films as a model drug [33].

![Schematic diagram of hot melt extruder](image)

Figure 2: Schematic diagram of hot melt extruder

3.6.4. Physical Properties of Oral Strips

3.6.4.1. Thickness

The thickness of FDF can be measured by micrometer screw gauge, calibrated electronic digital micrometer, vernier calliper or by SEM images at different locations. This is important to determine thickness because variations in the thickness can directly affect the dose accuracy in the strip. In general, ideally buccal film should possess a thickness between 50 and 1000 μm. Incorporation of plasticizer also influences the thickness of the film [34].

3.6.4.2. Tensile strength

Tensile strength is one of the mechanical properties play significant role in defining physical integrity of the film. Strength of the film can be identified by tensile strength as diametric tension or tearing force. The sample for test is stretched/ stressed until it tears and the stress required represents the tensile strength means maximum stress applied at which the film specimen breaks called as Tensile strength. It is calculated by the applied load (force) at rupture divided by the cross-sectional area of the strip [25, 34]. A TA.XT2 texture analyzer equipment furnished with a 5 kg load cell. Film strips were held between two clamps placed at a distance of 3 cm. Then the strips were dragged by the top clamp at a rate of 2 mm/s and the force at which film breaks is measured. In another method, Palem et al. used a microprocessor based advanced force gauze [25, 34].
3.6.4.3. Percent elongation

When stress is applied, a strip sample stretches or get elongated this is mentioned as strain. Per cent elongation is basically the deformation (increase in the length of strip) divided by original length of the sample. Generally elongation of strip increases with the plasticizer concentration [25, 34].

3.6.4.4. Tear resistance

Tear resistance of a film is a measure of its resistance to rupture and is calculated by subjecting the film to a constant rate of distortion. The maximum stress or force needed to tear the film is recorded in Newton's or pound–force. In a stress strain curve greater the area of stress strain curve, the higher the toughness of the film and amount of energy that a piece of the material can absorb. Mostly very low rate of loading 51 mm (2 in)/min is employed and is intended to measure the force to initiate tearing. The maximum stress or force required to tear the specimen is recorded as the tear resistance value in Newtons (or pounds-force) [25, 34].

3.6.4.5. Young's modulus

Young's modulus or elastic modulus measures the stiffness of film. It is represented as the ratio of applied stress over strain in the region of elastic deformation. The methods used for the measurement of tensile strength could be utilized here. This measures resistance to deformation and can be observed by plotting the stress strain curve wherein the slope measures the modulus. The higher the slope, the greater is the tensile modulus. However, a gentle slope measures a low tensile modulus and low resistance to deformation. Moreover, films which are hard and brittle possess higher tensile strength and higher Young’s modulus values. Hard and brittle strips demonstrate a high tensile strength and Young’s modulus with small elongation [34].

3.6.4.6. Folding endurance

Folding endurance is an important parameter to determine the flexibility of the oral strip. Folding endurance is obtained by repeated folding of the strip at the same place till the strip breaks or folded to 300 times without breaking. The number of times the film is folded without breaking is figured as the folding endurance value [34].
3.6.4.7. Disintegration time

The disintegration time limit of 30 s or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. No official guidance is available about this. Pharmacopoeial disintegrating test apparatus may be used for this study. Typical disintegration time for strips is 5–30 s [25].

Drop Method. In this method one drop of distilled water is dropped by a pipette onto the oral films. The films are placed on a glass slide and then the glass slide is placed planar on a petridish. The time until the film dissolved and caused a hole within the film is measured as disintegration time [35].

Petridish Method. In this method 2ml of distilled water is placed in a petridish and film was added on the surface of the water and the time required until the oral film dissolved completely was measured [35].

3.6.4.8. Dissolution test

In-vitro dissolution of the drug from the film is essential step to determine the permeability of the drug through buccal mucosa. Dissolution testing can be done using the standard basket or paddle apparatus defined in any of the pharmacopoeia or with modification of dissolution apparatus. The dissolution medium selected should mimic the saliva. Many times the dissolution test can be problematic due to tendency of the strip to float onto the dissolution medium when the paddle apparatus is employed [25]. Murata et al. performed dissolution studies in plastic dish. Films were positioned in a plastic dish, and 10mL of the dissolution medium preheated to 37°C was added. The dish was shaken at 300 rpm in a shaker incubator at 37°C [36].

3.6.4.9. Assay/drug content and content uniformity

This is determined by any standard assay method described for the API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85–115% of average drug content. [6] Physical form (crystalline or amorphous) of the drug molecule inside the film can be easily determined by X-ray crystallographic analyses [34].
3.6.4.10. Surface pH

The surface pH of fast dissolving strip should be determined to investigate the chances of any side effects in vivo. An acidic or alkaline pH may cause irritation to the oral mucosa; therefore it should be closer to the pH of the saliva i.e. 6.2–7.4 [34].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Composition of Fast dissolving film</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triclosan</td>
<td>Treating diseases of oral cavity such as plaque, caries and gingivitis</td>
<td>Methocel E5(2.2% w/v), Propylene glycol 1.35% w/v</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Treatment of Nausea and vomiting induced by emetogenic anticancer drugs</td>
<td>Hypromellose (7.4%), L-HPC (1.3%), Microcrystalline cellulose (57%), PEG (15%), Polysorbate 80 (5.4%)</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>Dopamine D2 receptor Antagonists effective in suppressing opioid analgesic-induced nausea and vomiting</td>
<td>Microcrystallinecellulose (57%), PEG (15%), Hypromellose (7.4%), Polysorbate 80 (5.4%) and 5% Low substituted HPC (1.3%).</td>
</tr>
<tr>
<td>Ondansetron Hydrochloride</td>
<td>Antiemetic</td>
<td>Poly vinyl alcohol, Poly vinyl pyrrolidone/ Carbopol 934P, PEG 400</td>
</tr>
<tr>
<td>Tianeptine Sodium</td>
<td>Antidepressant effective against anxiety accompanying mood disorders</td>
<td>Lycoat NG73/Polyvinyl alcohol/HPMC/HEC/Maltodextrin/ Lycoat RS780/PVP K90</td>
</tr>
<tr>
<td>Nicotin</td>
<td>Smoking cessation</td>
<td>Maltodextrin (dextrose equivalent 6 and 12), Sorbitanoleate, Glycerol</td>
</tr>
<tr>
<td>Levocetrizine hydrochloride</td>
<td>Non-sedative antihistamine</td>
<td>Sodium alginate (1.25-1.75 %), Sodium starch glycolate as disintegrating agent</td>
</tr>
<tr>
<td>Levocetrizine di hydrochloride</td>
<td>Third-generation non-sedative antihistamine</td>
<td>HPMC E15/HPMC E 50/PVA (1-2%), Propylene glycol 1%</td>
</tr>
<tr>
<td>Salbutamol sulphate.</td>
<td>Antiasthmatic</td>
<td>HPC/HPMC K100/Sodium Alginate(0.5-2)%</td>
</tr>
</tbody>
</table>
3.7. *In-situ* nasal gel

Nasal cavity has been used from ancient time as a drug delivery route to alleviate diseases and disorders. One of the ‘panchakarmas’ stated in Ayurveda is ‘nasyakarma’, a practice in which a drug is administered through the nostrils [50]. Nasal cavity is an excellent doorway for the entry of the drug moiety to systemic circulation and central nervous system. As mentioned above nasal cavity is lined with mucous membrane with large absorptive surface area, low thickness, high vascularity, porous and thin endothelial basement membrane below the epithelium leads to high permeability of nasal mucosa. Therefore, after absorption through nasal mucous membrane, drug can be directly reach to the systemic circulation with enhanced bioavailability and improved onset of action [5, 6, and 8]. Also it has the potential to target the drug directly across the blood brain barrier via olfactory and trigeminal nerve cells [9].

3.7.1. Nasal Anatomy and Physiology

The human nasal cavity is separated into 2 halves by nasal septum and has the total volume of 15-20 ml. Nasal cavity is divided into 5 regions, nasal vestibule, atrium, respiratory region, olfactory region and extends posteriorly to nasopharynx. Vestibule is the most anterior part of the nasal cavity (Fig.3). Respiratory region occupies most of the volume of the nasal cavity
and lined by respiratory epithelium. If we rank the permeability, vestibule is least, atrium is less and respiratory region is most permeable area of the nasal cavity. Beneath the respiratory epithelium, there is a thin and porous basement membrane. Respiratory mucosa comprises of several types of cells, ciliated pseudo stratified columnar epithelial cells, goblet cells, basal cells and nonciliated cells (Fig.4). Basal cells are thought to be precursors of columnar and goblet cells. Goblet cells are mucosecretory cells. Ciliated pseudo stratified columnar cells are the tall columnar cells which bear 4-6 μm long and 0.3 μm wide hairs like projections called cilia. There are approximately 100 cilia per cell also nonciliated and ciliated cells possess about 300 microvillus each. Cilia are responsible for mucocilliary clearance (MCC) the protective mechanism of respiratory system [8, 51].

![Figure 3](image-url)  
*Figure 3: Schematic diagram of the sagittal section of human nasal cavity*
Mucosa of the nasal cavity is covered with mucus; Mucus is a complex submucosal secretion comprises of about 95% water, 2% mucin, 1% salts, 1% of other proteins for example albumin, immunoglobulins, lysozyme and lactoferrin, and 1% lipids. Nasal mucosa covered with the blanket of mucus which is 5 μm thick comprises of 2 layers, lower sol layer and upper gel layer. The cilia provide sweeping motion into the sol layer by moving back and forth. The entrapped foreign particles along with the gel layer get transported to the nasopharyngeal area for ingestion. The beating action exhibited by cilia at a frequency of 10 to 13 Hz results in the movement of mucus. As mucus moves at a rate of 5 to 6 mm per min, the particles get cleared within 20 min from nose. New mucus layer occupy the epithelium about every 10 min. The MCC can be influenced by environmental and pathological conditions. It specifies that the area of the high permeability characteristics in the nasal cavity where drug should be retained for its higher absorption, from that region only it is clearing rapidly due presence of ciliated cells [8, 52]. However problems associated with the nasal drug administration are anterior leakage if dose volume is not maintained in between 25-200 μl and post nasal drip due to MCC [52]. Therefore it is necessary to enhance the contact time of the drug with nasal mucosal surface or prolong the retention of the drug on mucosal surface.

Now days, various products are available in market to treat local and systemic conditions include nasal sprays and nasal drops [5]. Nasal drops have the problem of anterior leakage.
from nasal cavity. Liquid nasal sprays get spread on the nasal mucosa finely to provide prompt drug absorption but it may get cleared from plasma shortly. Extended or prolonged drug release hardly expected from such systems and formulations with the viscosity more than 0.5 Pa.s are difficult to be sprayed in nasal cavity [53]. Therefore in situ nasal gelling systems with smart polymers (Stimuli responsive polymers) came into the picture, which are liquid at a room temperature, and can be instilled easily or sprayed in nasal cavity and where they attain semisolid or gel form to get retained in nasal cavity. Nasal cavity has the temperature of about 32±2° and pH 5.5-6.5 also mucous secreted by nasal submucosal glands comprises of sodium, calcium and potassium ions. In response to these conditions certain temperature, pH and ion responsive polymers can undergo reversible gelation upon exposure to nasal cavity and can be used in delivering drug in controlled manner [52, 54-56].

3.7.2. Advantages of smart polymers in nasal drug delivery

Along with ease of administration, prolonged retention in nasal cavity and sustainable drug delivery, these systems possess some additional advantages such as, polymers used in stimulus responsive in situ nasal gel may have absorption enhancement effect on drug e.g. chitosan derivatives like trimethyl chitosan enable the paracellular transport of large molecules across the mucosal surface by opening tight junctions. Isoforms of the P450 enzyme, rhodanase, glutathione S-transferases, and carboxylesterases have been detected in the human nasal mucosa. Entrapment of the drug in viscous gel matrix can protect the drug from enzymatic degradation [57].

3.8. Temperature responsive polymers in nasal drug delivery

Certain polymers exhibit sol to gel transition upon exposure to the nasal temperature, for example poloxamer 407, which is a thermosensitive polymer frequently used for in situ gelation. It is a nonionic surfactant consists of polyoxyethylene-polyoxypropylene copolymers. At a given temperature when poloxamer is dispersed in aqueous phase above the critical micellar concentration, there is formation of micelles with hydrophilic shell and hydrophobic core. Micellization is mainly the function of hydrophobic block. At higher concentrations these micelles start arranging themselves in various structures (liquid crystalline phases) like lamellar, cubic and hexagonal. At higher temperature the hydrophilic chains of the copolymer (polyoxyethylene) become desolvated due to the rupture of the hydrogen bonds present between the chains and solvent. This leads to enhanced hydrophobic interactions among the polyoxypropylene chains, and leads to gel formation. At low
temperatures a liquid micellar phase is stable however at high temperature it transforms into the cubic structure. Thermoreversible gelling properties of various poloxamer grades depends upon the molecular weight and ratio of molecular weight of hydrophilic core to molecular weight of hydrophobic core [58, 59]. Poloxamer 407 aqueous solution 16-18% exhibited thermo responsive gelling at 32±2°C, which is closer to nasal temperature [60-62].

Though poloxamer is responsible for in situ gelling comparatively low molecular weight and nonionic nature makes the poloxamer weak mucoadhesive agent. Therefore to enhance the retention, mucoadhesive polymers like carbopol 934P, chitosan, sodium carboxymethyl cellulose (NaCMC), hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose and methylcellulose can be added to the poloxamer gel in the concentration range 0.2-0.5%. As mentioned above mucous comprises of mucin which is anionic polyelectrolyte rich in sulphate groups therefore polymers having ability to interact electronically or to form hydrogen bonds can act as good candidates for mucoadhesion. In general, it has been shown that the bioadhesive strength of a polymer increases with molecular weights above 1 00 000 D. Therefore anionic polymers like Carbopol 934P, NaCMC, HPMC K-15 due to their hydrogen bond forming ability with mucin and cationic polymers like chitosan and its derivatives, aminated gelatin due to their ability to form ionic interaction have proved efficient bioadhesives in nasal drug delivery [63]. Addition of mucoadhesive agents reduces the gelling temperature of the poloxamer [62]. Also other formulation additives can influence gelling time and temperature of poloxamer. Jadhav et al. formulated thermo responsive nasal gel of Nardostachys jatamansi with poloxamer 407-polyethylene glycol (PEG) 400-PEG 4000 [64]. It is reported that as the concentration of the PEG 4000 increases there is increase in the gelling temperature. This can be predicted as; PEG is nonionic, hydrophilic compound, which may establish intermolecular hydrogen bonding with poloxamer chains and water. At the elevated temperature, this hydrophilic interaction has to be weakened and hydrophobic interaction between poloxamer chains should become dominant for gelling. Therefore with increasing concentration of PEG, there is delayed gelation time and temperature [64].

3.8.1. Hydrophobically modified polyelectrolytes

These are the alternatives for above discussed systems. Mucoadhesion of the poloxamers can be enhanced by using copolymers containing both hydrophobic segment (assist the copolymer to aggregate and gel) and a polyelectrolyte segment (provide mucoadhesiveness). Hydrophobically modified polyelectrolytes are the class of polymers where polymers having
ionizable groups are attached to hydrophobic backbone. One of the examples of this is copolymer of pluronic and poly (acrylic acid), which at low concentrations has shown thermogelling property and enhanced mucoadhesion. Poly (acrylic acid) is the standard polymer used regularly as a benchmark for providing mucoadhesiveness. Bromberg worked with different polymers such as Pluronic-poly (acrylic acid) copolymers, Carbomer and Pluronic F127. The study reported enhancement of the residence time of fluorescent labels by the Pluronic-poly (acrylic acid) copolymers compared to other polymers in rat nasal cavity [65, 66].

Actually poloxamer F127 is thermo sensitive polymer and poly (acrylic acid) is pH-sensitive polymer. Due to presence of carboxylic acid in poly (acrylic acid), which get deprotonated at the basic pH and acquire negative charge. Thus polymers possessing similar charged group causes repulsion and the material expand in dimensions leading to gelation. In hydrophobically modified system, in order to achieve adequate mucoadhesion to the polymer, high concentration of the pH sensitive polymer i.e. poly (acrylic acid) has to be used. This makes physical mixture and/or random copolymer of thermostensitive and pH-sensitive polymer only pH-sensitive. It loses its thermo sensitivity. But 1–5% w/v Pluronic-poly (acrylic acid) graft-copolymer (1:1) solution shows $10^3$ fold increase in viscosity at the nasal temperature. Graft-copolymerization retains the thermo sensitivity of Pluronic-poly (acrylic acid) copolymer at physiological pH [67].

3.8.2. Chitosan-based temperature responsive systems in nasal drug delivery

Aqueous chitosan solutions are pH-dependent gelling systems. Amino groups present on chitosan get protonated towards acidic pH (below the pKa value of chitosan 6.2) and repulsion between them causes expansion/swelling of the system thus pH-dependent gelling phenomenon is observed with chitosan [68]. But Nazar et al. synthesized thermo sensitive in situ nasal gel from N-trimethyl chitosan chloride with PEG and glycerophosphate for drug delivery [69]. Basics of this thermo sensitive gelling of chitosan found in U.S. patent 6,344,488 by Chenite et al. [70].

Chenite et al. mixed chitosan acidic solution with glycerophosphate aqueous solution, which can undergo gelling at $37^\circ$ and pH above 6.5 [70]. Mechanism of this gelling was predicted as, at lower temperature strong interaction between chitosan and water prevents the aggregation of hydrated chitosan molecules. But at elevated temperature, (a) chitosan/chitosan inter chain hydrogen bonding; (b) chitosan/organophosphate electrostatic
attractions (between ammonium group of chitosan and phosphate group of glycerophosphate; (c) structuring action of the polyol parts on water molecules facilitates hydrophobic interactions between chitosan chains. Thus chitosan-chitosan and chitosan-phosphate interaction at elevated temperature is responsible for gelling [69].

Any solution of chitosan-glycerophosphate cannot undergo gelation as long as pH of the solution maintained below 6.45. Chitosan-glycerophosphate solution exhibits thermoreversible gelation property in the pH range 6.5-6.9 and above pH 6.9 irreversible gelation occurs [69]. But drawback with this system is chitosan-based thermosensitive gel undergo a slow transition from sol to gel at body temperature because chitosan is soluble in low pH in its protonated form especially in the acidic environments. Therefore, Nazar et al. substituted chitosan with N-trimethyl chitosan chloride, a positively charged, water soluble chitosan derivative and added PEG 4000 which provides additional sites for hydrogen bonding and allows the formation of more extensive gel network [69]. N-trimethyl chitosan of medium average molecular weight and low degree of quaternisation (3.6% w/v) with 5.8% w/v PEG 4000 and 2.5% w/v glycerophosphate undergo thermal gelation at 32.5° within 7 min and exhibit good mucoadhesive properties [70]. Wu et al. formulated temperature sensitive hydrogel using N-[(2-hydroxy-3-trimethylammonium) propyl] chitosan chloride (HTCC) and PEG with a small amount of α, β-glycerophosphate [71]. HTCC is water soluble, mucoadhesive derivative of chitosan which has absorption enhancement effect on nasal mucosa. Role performed by α,β-glycerophosphate and PEG is same as discussed earlier. Insulin loaded this thermogel delivered through nasal route showed enhanced retention, absorption and decreased blood glucose concentration drastically almost 40–50% of initial blood glucose concentration for at least 4 to 5 hours after administration in rats [71]. Incorporation of glycerophosphate responsible for turbid nature of the gel and negatively charged moieties of glycerophosphate may interact with various bioactive components [72].

3.8.3. Chitosan-polyvinyl alcohol

Polyvinyl alcohol (PVA) is water-soluble polyhydroxy polymer. At lower temperature PVA-chitosan exists in a form of liquid solution. At the room temperature there is existence of intermolecular H-bonds between –OH and –NH₂ groups of chitosan and –OH groups of PVA, also H bonding between water and PVA due to hydrophilic nature of PVA. These hydrophilic interactions lead to dissolution of chitosan chains. At lower temperature low mobility of the chitosan chains prevent association of junction chains. At the higher temperature
intermolecular H bond gets ruptured, enhancing mobility of chitosan chains which removes surrounding water molecules and increases association of hydrophobic chitosan chains with each-other. Thus, hydrophobic interaction between chitosan chains is dominant at higher temperature responsible for thermo responsible gelling while at lower temperature hydrophilic interactions of PVA with water and chitosan are dominant. If ratio of PVA to chitosan is exceeded than 10:1, temperature sensitive in situ gelling property vanishes [73]. Agrawal et al. [72] incorporated insulin in chitosan-PVA thermosensitive gel and evaluated in vitro and in vivo. Formulation containing 3% chitosan and 2% PVA showed thermo responsive gelling, high swelling index and the potential of controlling the blood sugar level for 6 h [72].

3.8.4. Poly(N-isopropylacrylamide) (PNiPAAm)

Some copolymers can be considered by their critical solution temperature around which their solubility behavior changes. In other words, hydrophobic and hydrophilic interactions between the polymeric chains and the aqueous media sharply get altered. Polymer is soluble in water at the temperatures lower than the lower critical solution temperature (LCST) and hydrophilic interactions between polymer chains and water are dominant, but as the temperature increases above the LCST hydrophobic interactions between polymer chains become stronger [74]. LCST of (PNiPAAm) is 32° therefore it can be effectively used for localization of drug in nasal cavity. Ryden and Edman [75] observed influence of intranasal administration of insulin on plasma glucose levels in rats by incorporating insulin in particulate systems based on solid epichlorohydrine cross-linked dextran spheres and 2 thermogels namely ethyl (hydroxyethyl) cellulose and (PNiPAAm)-co-polyacrylamide. Ethyl (hydroxyethyl) cellulose also possessed thermogelling characteristics like (PNiPAAm) and having LCST at 30-32°. Addition of small amount of ionic surfactant to ethyl(hydroxyethyl) cellulose leads to the formation of micelle aggregates, which interact with polymer chains at elevated temperature to form stiff gel [75]. Examples of thermresponsible nasal gels are shown in Table 8.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Composition of thermo responsive gel</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine hydrochloride</td>
<td>Dual acting antidepressant</td>
<td>17% poloxamer 407, 1% methocel A4M (mucoadhesive)</td>
<td>[61]</td>
</tr>
<tr>
<td>Fexofenadine hydrochloride</td>
<td>Antihistaminic</td>
<td>Poloxamer 407, chitosan (mucoadhesive)</td>
<td>[76]</td>
</tr>
<tr>
<td>Hydroxypropyl β-cyclodextrin inclusion complex of artemether</td>
<td>Antimalarial</td>
<td>Poloxamer 407 (18%), HPMC K4M (0.5–1.5%)</td>
<td>[77]</td>
</tr>
<tr>
<td>Midazolam hydrochloride</td>
<td>Antiepileptic</td>
<td>Management of nausea and vomiting associated with cancer chemotherapy</td>
<td>[60]</td>
</tr>
<tr>
<td>Ondansetron hydrochloride</td>
<td></td>
<td>18% poloxamer 407, hydroxypropyl cellulose</td>
<td>[62]</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Antiemetic</td>
<td>Poloxamer 407, carbopol, polyethylene glycol 6000, hydroxypropyl cellulose, PVA, chitosan</td>
<td>[78]</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>Antimigraine</td>
<td>Poloxamer 407, carbopol 934P</td>
<td>[79]</td>
</tr>
<tr>
<td>Plasmid DNA</td>
<td></td>
<td>Poloxamer 407 (12% w/w), poloxamer 188 (20% w/w), polycarbophil, polyethylene oxide</td>
<td>[80]</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>Dopamine agonist</td>
<td>Chitosan/β-glycerophosphate, HPMC for mucoadhesion</td>
<td>[81]</td>
</tr>
<tr>
<td>Ellagic acid</td>
<td>Treatment of brain cancer</td>
<td>Chitosan/β-glycerophosphate</td>
<td>[82]</td>
</tr>
<tr>
<td>Insulin</td>
<td>Peptide hormone</td>
<td>i)3.6% HTCC, 5.4% PEG 4000, 3% α,β-glycerophosphate, ii)3% chitosan and 2% PVA, iii)Poly(N-isopropylacrylamide)</td>
<td>[71],[72],[73]</td>
</tr>
</tbody>
</table>

### 3.9. pH-responsive polymers in nasal drug delivery

Generally pH sensitive polymers are the ionisable moieties (weakly basic/weakly acidic) on the hydrophobic backbone. Polymers having acidic groups e.g. carboxylic acid group get...
deprotonated at the (basic) pH and acquire negative charge. Thus polymers possessing similar charged group causes repulsion and the material expand in dimensions. When pH becomes normal the functional groups lose their charge hence the repulsion disappears and the material regains its original shape. Same mechanism expected with the polymers having basic groups which get protonated in acidic pH and causes electrostatic repulsion [68]. Carbopol 934, an acrylic acid derivative showed in situ gelling by deprotonation at nasal pH. Nandgude et al. formulated pH induced in situ nasal gel of salbutamol sulphate using 0.4-0.5% w/v carbopol 934 for sustained release and enhanced bioavailability whereas chitosan exhibit acidic pH-responsive gelation [83]. Amino groups present on chitosan get protonated towards acidic pH and repulsion between them causes expansion/swelling of the system thus pH dependent gelling [68].

Hornof et al. evaluated viscoelastic properties of chitosan-thioglycolic acid conjugates in vitro. Chitosan-thioglycolic acid is also known as thiolated chitosan. This polymer is formed by amide linkage between amino group of chitosan and carboxylic group of thioglycolic acid. In situ pH dependent gelation due to formation of intermolecular and intramolecular disulphide bonds at physiological pH was reported with this polymer. At the physiological pH, concentration of the H⁺ ions decreases due to which thiol groups (-SH) present on the chitosan get converted to thiolated ions (S⁻) which represents active form for oxidation to form intermolecular and intramolecular disulphide bonds. Also thiolated chitosan has superior mucoadhesive properties over unmodified chitosan. This new excipient found promising for gelation at physiological pH because the elastic properties of this gel were found to increase significantly with the degree of thiolation at pH 5.5 [84].

3.9.1. Polymethacrylic acid and polyethylene glycol (P(MAA-g-EG)):

Nakamura et al. formulated mucoadhesive pH sensitive budesonide micro particles of polymethacrylic acid and PEG for nasal delivery. Mechanism behind its swelling at nasal pH is same as that of carbopol i.e. deprotonation at nasal pH and deswelling in acidic pH due to its strong intermolecular interaction with PEG. Following intravenous administration of budesonide, the plasma concentration peaked immediately and decreased rapidly over the next 4 h but with nasal administration of the polymeric formulations, the peak plasma concentration was reached in about 45 min, and the concentration in plasma remained constant for a minimum of 8 h. Thus intranasally administered budesonide-polymer possesses enhanced durability of the drug concentration in plasma [85].
3.9.2. Polyvinylacetal diethylamino acetate

Aikawa et al. incorporated chlorpheniramine maleate and tetrahydrozoline hydrochloride in polyvinylacetal diethylamino acetate pH sensitive gel. Polyvinylacetal diethylamino acetate forms transparent solution at pH 4, which shows abrupt changes at pH 7 by turbidometry studies. This change appeared to be due to precipitation or hydrogel formation. The hydrogel formation on the mucous membranes in the rat nasal cavity was visually confirmed. Dynamic light scattering and scanning electron microscopy indicate there is pore shrinkage of the hydrogel with increase in the temperature from 25-37° at pH 7.4, which potentially responsible for controlling the drug release [86,87]. Examples of pH responsive nasal gels are listed in Table 9.

**Table 9: Examples of pH-responsive Nasal gels**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Composition of pH-sensitive gel</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salbutamol sulphate</td>
<td>β2-adrenergic agonists</td>
<td>0.4-0.5% carbopol 934P, HPMC</td>
<td>[83]</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Glucocorticoid steroid</td>
<td>Polymethacrylic acid and polyethylene glycol</td>
<td>[85]</td>
</tr>
<tr>
<td>Chlorpheniramine maleate,</td>
<td>Antihistaminic</td>
<td>Polyvinylacetal diethylamino acetate 3-7%</td>
<td>[86]</td>
</tr>
<tr>
<td>tetrahydrozoline hydrochloride</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.10. Ion responsive polymers in nasal drug delivery

Ion responsive polymers generally have ionisable groups. These polymeric systems exhibit uncommon rheological behavior upon coulombic interaction with appositely charged species. Gellan gum is anionic polysaccharide composed of 1,3-β-D-glucose, 1,4-β-D-glucoronic acid, 1,4-β-D-glucose and 1,4-α-L-rhamnose repeat units. It has the characteristic property of temperature-dependent and cation-induced gelation. Upon complexation with cations and hydrogen bonding with water, there is formation of double helical junction zones and a three-dimensional network responsible for in situ gelling [88].

Cao et al. developed ion-activated in situ gel of mometasone furoate with 0.2-0.5% w/v gellan gum and 0.15% xylan gum [89]. Sodium, potassium and calcium ions present in nasal mucous interact with anionic groups of the gellan gum which results into sol to gel transition.
to produce prolonged release of mometasone furoate [55]. Also in situ nasal gel formulation of scopolamine hydrobromide with gellan gum was compared with subcutaneous and oral administration in rats, the study exhibited decreased symptoms of motion sickness with nasal gel formulation. Prolonged radioactivity of $^{99m}$Tc in the rabbit nasal cavity indicated prolonged retention of gel in nasal cavity [89].

Krauland et al. modified gellan gum by linking covalently l-cysteine to deacetylated gellan gum. The deacetylated gellan gum-cysteine conjugate displayed superior in situ gelling properties in vitro compared to unmodified polymer [90].

Another famous example of ion responsive in situ gelling nasal drug delivery is PecFent® (fentanyl citrate) nasal spray which uses Archimedes Pharma's patented drug delivery system, PecSys™. PecSys™ is a proprietary pectin-based drug delivery system which delivers fentanyl in controlled manner with fast onset of action and is designed as fine mist spray which forms a gel when it comes in contact with the nasal mucosa. In PecFent® gelling agent is a mixture of sucrose and low methoxyl (LM) pectin. Pectins are heterogeneous polysaccharides comprising a backbone of galacturonic acids units linked by $\alpha$-1,4 bonds, with a component of neutral sugars such as galactose, xylose, rhamnose and arabinose either in the backbone or as side chains. LM pectin has the degree of esterification $\leq 50\%$. High methoxyl (HM) pectins have a degree of esterification (DE) of $>50\%$. Gelling properties of pectin are highly affected by degree of esterification. LM pectins can form gel in the presence of divalent cations, such as calcium following similar mechanism of gellan gum due to the formation of intermolecular junction zones by side by side association of homogalacturonic smooth regions of different chains. Unlike LM pectin HM-pectin forms gel with sugar and acid but in PecFent® sucrose may be added to stabilize the structure of junction zones [91-94].

When nasal fentanyl-pectin spray compared with fentanyl chitosan and fentanyl in chitosan-poloxamer 188 in phase I studies, it exhibited the most favorable tolerability profile and lowest nasal reactogenicity symptom incidence compared to fentanyl chitosan and fentanyl in chitosan-poloxamer 188. In pharmacokinetic studies, PecFent showed superior pharmacokinetic profile compared to transmucosal oral fentanyl citrate [95]. Ion sensitive nasal in situ gels are listed in Table 10.
Table 10: Ion sensitive nasal in-situ gels

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Gelling agents</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl citrate</td>
<td>Management of breakthrough pain in cancer</td>
<td>1% w/v pectin LM</td>
<td>[96]</td>
</tr>
<tr>
<td>Gastrodin</td>
<td>CNS diseases such as vertigo, headache, insomnia, neuralgia, neurasthenia and epilepsy</td>
<td>0.5% w/v deacetylated gellan gum</td>
<td>[97]</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>Anti-inflammatory in the treatment of allergic rhinitis</td>
<td>Gellan gum (0.2–0.5%), xylan gum (0.15%)</td>
<td>[55]</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>Antiemetic</td>
<td>Gellan gum and carbopol 934P</td>
<td>[98]</td>
</tr>
<tr>
<td>Radix bupleuri</td>
<td>Antipyretic, antiinflammatory</td>
<td>0.5% w/v gellan gum</td>
<td>[99]</td>
</tr>
<tr>
<td>Scopolamine hydrobromide</td>
<td>Antiemetic</td>
<td>0.2–1% w/v gellan gum</td>
<td>[89]</td>
</tr>
</tbody>
</table>

3.11. Reported formulation approaches for improved delivery of lercanidipine

1) WO2005053689 discloses a controlled release pharmaceutical composition comprising lercanidipine dissolved or dispersed in a solid vehicle at ambient temperature, thus forming a solid dispersion, achieves delayed release of lercanidine over an extended period of time, reduced food effect and increased bioavailability compared to commercially available lercanidipine containing products [100].

2) US20060073200 discloses a modified release composition of lercanidipine comprising at least one waxy substance [101].

3) US20060134212 discloses an immediate release pharmaceutical composition that achieves rapid release of lercanidipine, i.e. more than 80% drug release within first 60 minutes following entry of dosage form in dissolution media. An immediate release pharmaceutical composition comprising: an inert core; a first layer containing lercanidipine, a surfactant and a binder; and optionally a second layer comprising a film coating [102].

4) US20060165789 discloses a modified release composition containing lercanidipine, which provides for therapeutically effective plasma concentrations of lercanidipine for a period of about 20 to about 25 hours. The modified release composition of the present
invention provides modified release of lercanidipine independent of pH and therefore provides release of lercanidipine even upon exposure to the low pH use environments, such as gastric fluid. Release modifying polymers were chosen from anionic acrylic copolymer composed of methacrylic acid and methacrylate monomers, ethyl cellulose [17].

5) **US20060177507** discloses a simple and improved osmotic device that is capable of providing a controlled release of lercanidipine [103].

6) **KR2006035422** discloses a solubilization method of lercanidipine and a pharmaceutical preparation thereof. Lercanidipine HCl is solubilized in at least one solubilizing agent selected from oleoyl macrogol-6 glycerides, polysorbate, linoleoyl macragol-6-glycerides and diethylene glycol monoethyl ether. This lercanidipine mixture is added with other excipients and transformed into dosage form.

7) **KR2006134727** discloses similar sort of dissolution enhancement technique of lercanidipine as given in KR2006035422. Solubilizing agents used here are Cremophore RH40, poloxamer 407 poloxamer 188.

8) **KR2006126154** discloses the solid dispersion of lercanidipine where lercanidipine and water soluble polymers are dissolved in methylene chloride, and then solution is spray dried or wet granulated and dried.

9) **WO2008068777** discloses stable solid oral dosage form of lercanidipine adsorbate. Adsorbate is prepared by dissolving lercanidipine in organic solvent and this solution is adsorbed over absorbing material, the solvent is then removed [104].

10) **US20060165788** discloses a modified release composition which releases the pulses of lercanidipine based upon the pH of the environment. More than about 80 % of the lercanidipine is released in vitro at a pH about 5-7.5 within about the first 6 hours [105].

11) **Jeong H K et al., (2016)** prepared lercanidipine PVP K-30 solid dispersion via spray drying and rotary evaporation. Results showed that solid dispersion has increased dissolution properties of lercanidipine [106].

performed using dialysis sac showed that drug permeation was enhanced in nanoparticles compared to plain drug. This study is not supported by in-vivo evaluation [107].

13) **Sabir M.D. et al., (2015)** developed oral solid lipid nano-particles of lercanidipine by hot homogenization technique. The gut permeation study across rat intestinal sac showed nearly 4x increment in the permeation of lercanidipine in nano-particles compared to plain lercanidipine. *In vivo* study on male wistar rats showed a significant control in the blood pressure [108].

Table 11: Reported examples of Self-emulsifying Drug delivery system (SEDDS) of lercanidipine [109-112]

<table>
<thead>
<tr>
<th>Excipients used in SEDDS</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peppermint oil (28.71%), Cremophore EL (16.74%), Labrasol (50.23%)</td>
<td>Reddy M.S. et al.</td>
</tr>
<tr>
<td>Gelucire 44/14, labrasol, transcutol-P</td>
<td>Kallakunta V. R. et al.</td>
</tr>
<tr>
<td>Cremophore EL (45%), Caproyl 90, transcutol-HP</td>
<td>Parmar N. et al.</td>
</tr>
<tr>
<td>Miglyol 812, Polysorbate 80, Imwitor 308</td>
<td>Igor L et al.</td>
</tr>
</tbody>
</table>

14) **Shanthakumar G.S. et al., (2015)** developed buccoadhesive compacts of lercanidipine HCl. Bilayered buccoadhesive compacts contain core layer and backing layer by direct compression. From pharmacokinetic study results it was observed that lercanidipine was released and absorbed slowly over longer period of time [113].

15) **Asija R et al.** developed solubility enhanced system of lercanidipine via preparation of lercanidipine-malonic acid co-crystal [114].

16) **Pandey S et al.** developed bilayered gastroretentable mucoadhesive patch for stomach specific drug delivery. Lercanidipine is more soluble in acidic pH than in intestinal pH therefore gastroretentive. Patches could control the drug release up to 12 hours. *In-vivo* study results indicate enhanced absorption of lercanidipine [115].

17) **Balamuralidhara V et al.** developed pH dependent gradient release drug delivery system using pH dependant polymers like Eudragit E100, Hydroxyl propyl methyl cellulose phthalate and Eudragit S100. It was observed by researchers that this drug delivery system efficiently improved uptake of lercanidipine and prolong the Tmax in vivo [116].
18) Vaghani S et al. developed carboxy methyl chitosan hydrogel of lercanidipine which provides pH dependant sustained release of drug for 24 hours. This study is not supported by in-vivo evaluations [117].

Table 12: Reported Transdermal Drug Delivery system of lercanidipine [118-122]

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Excipients</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transdermal Patches</td>
<td>Eudragit RS100, Hydroxypropyl Methyl Cellulose, Ethyl cellulose, Propylene glycol, Di butyl phthalate</td>
<td>Thenge R et al.</td>
</tr>
<tr>
<td></td>
<td>Eudragit RL 100, Hydroxypropyl Methyl Cellulose, d-limonene Propylene glycol</td>
<td>Mamata T et al.</td>
</tr>
<tr>
<td></td>
<td>Ethyl Cellulose, PVP K-30, Hyaluronidase, n-dibutyl phthalate, Tween 60, Dimethyl fumarate, sodium tauro glycolate, cinnamaldehyde, menthol</td>
<td>Subhash P.G et al.</td>
</tr>
<tr>
<td>Micro-emulsion based transdermal gel</td>
<td>Capryol 90, Cremophor EL, ethanol</td>
<td>Dhingani A et al.</td>
</tr>
<tr>
<td>Nano-emulsion based transdermal gel</td>
<td>Capryol 90, Cremophor EL, Transcutol HP</td>
<td>Nafees A et al.</td>
</tr>
</tbody>
</table>