1. **Literature Review**

- Parmar et al (2012), developed mucoadhesive in-situ gels for Metoclopramide hydrochloride an antimigraine drug at concentration of gellan gum 0.2%, 0.4%, 0.6% and 0.8% w/v with Xanthan gum 0.1%, 0.15% and 0.2% w/v as bioadhesive polymer and benzalkonium chloride (0.01%) as preservative. The formulated systems provided sustained release of the drug over an 8-h period in vitro and the developed formulations were devoid of any deleterious effect on the nasal tissues. Hence, this can be viewed as a viable alternative to conventional nasal drops by virtue of its ability to enhance nasal residence time and thereby intranasal bioavailability.

- Dattatraya et al (2012), formulated in situ gel of salbutamol sulphate for improving the bioavailability & sustaining the drug release using poloxamer and Hydroxy Propyl Methyl Cellulose (HPMC). The results revealed that as the increase of bioadhesive polymer HPMC concentration, decrease in gelation temperature (T1) and increase in gel melting temperature (T2). The drug content for all formulation was found to be 96%-100%. The mucoadhesive test indicates that the level of HPMC increases, the mucoadhesive strength also increases.

- Hardikar et al (2012), developed mucoadhesive thermo reversible in situ nasal gel of Amitriptyline HCl. Poloxamer 407 (PF 127) was selected as it has excellent thermo sensitive gelling properties. HPMCK4M was added to impart mucoadhesivity to the formulation and PEG 400 was used to enhance the drug release. Thus release of Amitriptyline HCl can be sustained if formulated in nasal in situ gel containing PF 127 so as to achieve its prolonged action. When drug is released from the dosage form it will permeate easily. Concentration HPMCK4M and PEG 400 in nasal in situ gel can be manipulated to control the release pattern of amitriptyline HCl to prolong its action with faster onset of time.

- Kedanchu et al (2013), prepared Paeonol temperature-sensitive in situ gel composed of poloxamer 407 (P407). The result showed low toxicity to cilia, which allows the gel to be used for nasal administration. The Franz diffusion cell method was used to study the in vitro release of paeonol and the release was in line with the Higuchi equation. Result indicated that the paeonol could be absorbed into the body through mucous membranes and have sustained effect. The paeonol thermosensitive in situ gel can significantly reduce IgE and LTE4 levels and the number of eosinophils, in addition to improving the pathological changes in the nasal mucosa.
• Inayat et al (2013), formulated in situ gels Azelastine hydrochloride using gellan gum in combination with HPMC E4M. Viscosity study of sol and gel formulations indicated that increase in polymer concentration increases the viscosity. Shot weight of the formulations was found to proportionally vary with the viscosity of formulations. Gel strength was found in the range of 22-55 sec. Owing to its increased viscosity after gelation and mucoadhesive characteristics, the formulation displays prolonged nasal residence time.

• Pramod et al (2013), developed Zolmitriptan nasal gels using the mixture of pluronic F-127 (Poloxamer 407) and pluronic F-68 (Poloxamer 188), sodium alginate, sodium carboxymethyl cellulose and polyvinyl pyrrolidone (PVP K–25). These polymers reinforced the gel strength and the bioadhesive force of the prepared nasal gel formulation. The effect was most pronounced with sodium alginate. They prolonged the release of zolmitriptan that may be helpful for migraine treatment.

• Pradnya et al (2013), developed thermoresponsive nasal gel of Nardostachys Jatamansi extract using pluronic PF 127 with dried ethanolic EN. Jatamansi extract, PEG 400, PEG 4000 as gelling point modifiers and methyl paraben as preservatives. Optimized batches showed gelation point at 34°C and 37°C. Spreadability between 0.35-0.8cm, Mucoadhesive strength was 1524.44 and 1720.44 dyne/cm² across freshly excised sheep nasal mucosa. Rheological studies indicated viscous and Newtonian behavior signifies spreadability and increased residence time.

• Vijayakumar et al (2012), formulated in situ gel of Bromhexine hydrochloride with polymers such as Poloxamer (PLX) and Hydroxy Propyl Methyl Cellulose (HPMC). The results revealed that increased bio adhesive polymer HPMC concentration, decrease the gelation temperature( T1) and gel melting temperature (T2). pH of all the formulations were found to be within the range between 6.9- 7.5 ,and the nasal mucosa can tolerate the pH of the above solutions. The drug content for all the prepared formulations was found to be in the range of 96%- 100%. The result of mucoadhesion test indicate that the level of HPMC increases, the mucoadhesive strength also increases.

• Umesh et al (2013), designed pH dependent in situ nasal gel of Beclomethasone Dipropionate using Carbopol 934 and HPMC K4M. The results of a 3² full factorial design revealed that the amount of HPMC K4M and Carbopol 934 significantly affect the dependent variables such as % cumulative drug release, mucoadhesive strength. Optimized formulation of
Beclomethasone dipropionate showed no change in physical appearance, drug content, or in release pattern after storage at 40 °C for 60 days.

- Shah et al (2011), developed nasal in situ gel of Sodium cromoglycate with Carbopol 934 and Hydroxyl Propyl Methyl Cellulose K4M (HPMC K4M). In vitro release data were fitted to various models to ascertain kinetic of drug release. Regression analysis and analysis of variance were performed for dependent variables. The optimized formulation provided sustained in vitro release of drug over an extended period of 8 hrs. As a consequence of its enhanced absorption due to longer residence time, it avoids the first passeffect, mucociliary clearance and reduces the dosing frequency as well.

- Li et al (2014), developed an in situ gel system, based on the combination of poloxamer 407 (P407) and carrageenan (carrageenan–poloxamer 407 hydrogel; CPH) for intranasal delivery of ketorolac tromethamine. Kitorolac tromethamine influenced erosion, drug release, and thermosensitive properties of CPH. CPH containing 15% ketorolac tromethamine showed suitable gelation temperature (~ 35°C) and in vitro sustained release profiles. Pharmacokinetic study of intranasal CPH containing 15% ketorolac tromethamine in rats demonstrated enhanced absolute bioavailability (68.8 ± 23.3%) and prolonged mean residence time (8.8 ± 3.5 h) in comparison with the intranasal solution group (24.8 ± 13.8%, 3.9 ± 0.6 h).

- Qian et al (2014) developed an in situ gel formulation for intranasal delivery of tacrine (THA), an anti-Alzheimer’s drug. Thermosensitive polymer pluronic F-127 was used to prepare The pharmacokinetics and brain dispositions of in situ gel and THA oral solution were compared in rats. The in situ gel exhibited a liquid state with Newtonian fluid behavior under 20°C, while it exhibited a non-flowing gel state with pseudoplastic fluid behavior beyond its Tsol–gel of 28.5°C. Based on nasal mucociliary transport time, the in situ gel significantly prolonged its retention in nasal cavity compared to solution form. Moreover, the in situ gel achieved two- to three-fold higher peak plasma concentration (C_max) and area under the curve (AUC) of THA in plasma and brain tissue, but lowered C_max and AUC of the THA metabolites, when compared to that of oral solution.

- Ravi et al (2013), developed an intranasal thermosensitive gel for rasagiline mesylate Intranasal gels were prepared by combination of P407 and PLX 188 (P188) (1:1) with mucoadhesive polymers [carbopol 934P and chitosan (CH)]. Pharmacokinetic study in
rabbits showed that intranasal gels exhibited significant improvement in bioavailability (four-to six-folds) of the drug, when compared to the oral solution. Chronic exposure studies in Wistar rats showed that these intranasal gels were non-irritant and non-toxic to rat nasal mucosa. Estimation of RM in rat brain tissue showed that intranasal gel formulations exhibited significant improvement in uptake of RM, when compared to that through nasal solution.

- Khan et al (2012) prepared the in situ gel systems of metoprolol tartrate containing carbopol, and hydroxypropyl methylcellulose (HPMC) K4M and K15M. The formulations F10 (0.4% w/v carbopol, 1% w/v HPMC K15M) and F13 (0.3% w/v carbopol, 1% w/v HPMC K15M) showed gel strength of 40.33 ± 0.47 and 43.00 ± 1.41, respectively, and mucoadhesion strength of 31.48 ± 0.14 × 10³ and 32.12 ± 0.05 × 10³ dyne/cm², respectively. In vitro release profiles showed initial burst followed by slow release. F10 and F13 released 88.08 ± 0.98 and 91.18 ± 1.09% drug, respectively in 8 h. R(2) value for F10 (0.9953) and F13 (0.9942) obtained by Higuchi equation and ‘n value’ on treatment obtained by Korsemayer Pappas equation was approximately 0.5, which suggested a release by Fickian diffusion mechanism. The nasal permeability of formulations F10 and F13 were found to be 0.057 and 0.063 cm/s, respectively. Histopathological examination revealed slight degeneration of nasal epithelium with increased vascularity by F10 but no inflammation by F13.

- Farid et al (2013) formulated salbutamol sulfate (SS) as mucoadhesive in situ gelling inserts containing 1.4% SS and 2% gel-forming polymer, HPMC, carboxymethylcellulose sodium (CMC Na), sodium alginate (AL), and CH, were prepared. The weight of inserts, drug content, thickness, and surface pH ranged between 16–27 mg, 3.9–4.2 mg, 15–28 μm, and 5–7, respectively. Cumulative drug released from the inserts exhibited extended release for more than 10 h (the inserts followed a decreasing order of this pattern: CH > AL > CMC Na > HPMC). The drug release from CMC Na and AL inserts followed zero-order kinetics, while HPMC and CH inserts exhibited non-Fickian diffusion mechanism. The inserts exhibited different water uptake (7–23%) with the smallest values for CH.

- Cai et al (2011) developed a novel ion-activated in situ gelling system for the nasal delivery of gastrodin. The best formulation consisted of 10% gastrodin, 0.5% deacetylated gellan gum as the gelatinizer, and 0.03% ethylparaben as the preservative. The rheological properties of
gastrodin nasal in situ gels were also investigated. The viscosity and elasticity sharply increased at temperatures below 25°C. When physiological concentrations of cations were added into the preparation, the mixture gelled into a semi-solid. The results of an accelerated stability test showed that gastrodin nasal in situ gels can remain stable for more than 2 years.

- **Galgatte et al.** (2014), formulated mucoadhesive sumatriptan succinate in situ gel by ion activation mechanism, using deacetylated gellan gum as gelling agent. The maximum drug release (98.57%) was shown by the optimized batch within 5h. The ex vivo studies were performed on sheep nasal mucosa, which showed maximum drug release of 93.33% within 5h. The histopathological study indicated that the optimized batch was safe, and accelerated stability study showed that it was stable for three months. The best formulation, F7 showed absolute bioavailability of 164.70%, and drug targeting index for brain tissues was 1.866; this indicated that sumatriptan can enter the brain via olfactory pathway.

- **Praveen et al.** (2009), developed rizatriptan benzoate sustained release nasal gel, containing pluronic F68, pluronic F127, and bioadhesive polymers like xanthan gum and locust bean gum. The gel was used to manage migraine, to bypass first-pass consequence experienced during oral administration, and to get better bioavailability of the drug, and can be used as secure nasal delivery system.

- **Mehta et al.** (2009), studied about the in situ gelling systems of pheniramine and phenylephrine employing mixture of poloxamer, HPMC, and xanthan gum. The developed gels were stable above a stage of 3 months. In contrast to drug solution, the nasal adhesion period (estimated through gamma scintigraphy) of the in situ formulation was reported to be considerably superior (> 6 h).

- **Meenakshi et al.** (2010), studied about the thermoreversible gel formulations of flunarizine hydrochloride, using P407 as the polymer. β-cyclodextrin were used to prepare the inclusion complexes, with an aim to raise the solubility of flunarizine in nasal secretions. The formulations showed extreme enhancement in the viscosity at 37°C, signifying their promising exploit as in situ gelling systems. Among all the preparations, the β-cyclodextrin formulations exhibited the fastest release and this may be owed to the high dissolution profile of the mentioned drug.

- **Chelladurai et al.** (2008), developed ketoralac tromethamine mucoadhesive in situ nasal gel using CH and pectin as gelling agents. HPMC was added to the above gelling agent to
increase the viscosity and gel force of the prepared gel. All the formulations showed pseudoplastic behavior and diffusion controlled drug release, and there was a mild negligible irritant effect which was evaluated in rats for the selected formulations.

- Gowda (2011) developed mucoadhesive in situ nasal gel of diltiazem hydrochloride (DTZ), using bioadhesive polymers such as PLX and HPMC. The presence of increasing concentration of HPMC in the preparation increased the adhesion strength of the formulations. It was concluded that DTZ in situ gel is suitable to provide a controlled kinetic drug release and was also suitable for minimizing the toxic effects of DTZ.

- Basu and Bandyopadhyay (2010) studied about the bioadhesive in situ nasal gels of midazolam which were developed with different concentrations (0.5%, 1.0% and 1.5% w/v) of mucilage isolated from fig fruits and synthetic polymers such as HPMC and carbopol 934. To study the in vitro permeation characteristics, sodium taurocholate (0.5% w/v) was used as the permeation enhancers in excised goat nasal mucosa. In vivo studies revealed that the prepared formulations showed improved bioavailability of midazolam than the gels prepared with synthetic adhesive polymers and no damage was produced to the nasal mucosa which was utilized for the permeation study.

- Badgajar etal (2010), reported that in situ gel of sumatriptan succinate can enhance the nasal bioavailability of the drug, by providing greater nasal retention time through pluronic F127 and carbopol 974P, and permeation was enhanced by fulvic acid as a new permeation enhancer. Additionally, in situ gels developed with and without permeation enhancer were studied for in vitro drug diffusion. The records of in vitro drug diffusion indicated non-Fickian or anomalous diffusion mechanism.

- Ketousetuo and Bandyopadhyay (2007), developed nasal oxytocin gel with the help of a natural mucoadhesive agent which was extracted from the fruit of Dellinia indica L. When compared to the synthetic polymers, the adhesive force and viscosity of the above mentioned natural mucoadhesive agent was found to be higher and also showed better in vitro drug release profile which was carried out through bovine nasal membrane using a Franz-diffusion cell.

- Chen et al (2010), studied about the temperature-sensitive nasal in situ gel of Radix bupleuri, produced by cold technique using gel base (20% of P407), and the gelation temperature was adjusted with 6% PEG 4000 and subjected to febrile response mechanism. The gel
formulation was in liquid stage at 4 °C and its phase was changed to gel above 30 °C, which is very close to the nasal cavity temperature. The effect created by Radix bupleuri in situ gel was examined in fevered rabbits and this indicated that in situ gel can extend the useful time to 24h, when compared with 4–6 h in Radix bupleuri intranasal solution

Nandgude et al (2008), prepared salbutamol sulphate in situ nasal gels with carbopol as the major polymer with the combination of HPMC. The formulations worn out due to the low concentrations of the polymers, showed poor viscosity, and at high concentrations the gel became rigid and provided controlled release of drug. Finally, some particular concentrations of carbopol 934 and HPMC with the optimized formulation exhibited sol–gel translation, improved bioavailability, and sustained release

Iman et al (2010), prepared chlorpheniramine maleate (CPM), a nasal gel with polymers like CMC Na, HPMC, carbopol 934, and pluronic F127. The most excellent rheological properties and stability were shown by the formulations prepared with CMC Na (3%), and carbopol 934 (0.5%). Furthermore, the above mentioned formulations also provided faster drug release and permeation characters and they delayed mucociliary clearance of the drug, when compared to the control solution. This helped to increase the adhesion nature of the gel in the mucosa and also provided good absorption. When compared with the marketable tablet, the prepared gels provided elevated Cmax and shorter tmax with higher AUC which indicated improved bioavailability.

Bhandwalkar et al (2013), developed thermoreversible venlafaxine hydrochloride, mucoadhesive in situ gel using thermo gelling polymer Lutrol F127 (18%) and adhesive polymers such as carrageenan, PVP K30, carbopol 934, HPMC K4M, tamarind seed gum, and sodium alginate. The optimized formulation T5 showed maximum release of drug (97.86 ± 0.073%) within 150 min with a gelation temperature of 31.17 ± 0.30°C and flux of 0.1545 mg cm(−2) min(−1). Histopathological studies of nasal mucosa exposed that T5 formulation was secure for nasal drug delivery and made no dame to nasal epithelium.

Cao et al (2007), developed a novel in situ nasal gel of scopolamine hydrobromide for motion sickness using 0.2, 0.5, and 1.0% gellan gum concentration (w/v). The viscosity of the formulations improved with increasing concentrations of gellan gum and their vitro release was fair in simulated nasal fluid. The micrographic results indicated that in situ gels
were safe, without nasal ciliotoxicity. In comparison with oral and subcutaneous drugs, scopolamine hydrobromide in situ gel reduced symptoms of motion sickness drastic.