3 LITERATURE REVIEW

3.1 Ethosome and its Formulations

Rakesh R et al (2012) investigated the feasibility of transdermal delivery of cromolyn sodium using ethosomes a novel lipid vesicular carrier. *In-vitro* drug release studies of optimized ethosomal formulation through cellophane membrane showed an enhanced and sustained delivery of drug when compared to conventional liposomes. Results recorded suggest that ethosomes can be a promising tool for transdermal delivery of cromolyn sodium [1].

Saxena Gk et al (2010) carried out the work to develop transdermal delivery of hydrophobic drug (stavudine) for the treatment of AIDS, through the ethosomes. The optimized ethosomal formulation showed transdermal flux of 25.01 ± 0.34 µg/cm²/hr across rat skin as compared to 2.98 ± 0.21µg/cm²/hr for plane drug solution, 4.28 ± 0.54 µg/cm²/hr for hydroethanolic solution and 9.7 ± 0/21 µg/cm²/hr for classical liposome. From the results it can be concluded that ethosomes can increase the transdermal flux and prolong the release and serve as attractive route for sustained delivery of stavudine [2].

Nikalje AP et al (2012) focused on the review of ethosomes: A Novel Tool for Transdermal Drug Delivery. The review illustrated the broad concept of ethosomes, mechanism of penetration, preparation, advantages, composition, its characterization and evaluation. Review was more broadly specified by the applications of ethososmes. Ethosomal carrier enables the opportunities for the development of novel improved therapies [3].

Zhen Z et al. (2012) proposed the study to characterize a novel transdermal delivery carrier, ethosomes containing 5-fluorouracil. The penetration of ethosomes in Hypertropic Scar (HS) and skin was analyzed by ethosomes fluorescently labeled with rhodamine 6GO using confocal laser scanning microscopy. After application for 24 h the fluorescence intensity was highest in ethosome-Scar, followed by Ethosome-Skin,
Hydroethanolic solution-Scar, and Hydroethanolic -Skin, which indicates the penetration of ethosomes in HS was greatest. From the reports generated it can be consider that ethosomes are a highly efficient carrier in HS [4].

**Chaurasia MK et al (2011)** developed the nanosized ethosomes bearing ketoprogen for enhanced transdermal delivery. *In-vitro* drug permeation across human skin noted the improved drug permeation and higher transdermal flux with ethosomal formulations as compared to hydroethanolic drug solution. The estimated steady state *In-vivo* plasma concentration from ethosomes attained therapeutic drug levels whereas hydroalcoholic drug solution exhibited sub therapeutic drug concentration [5].

**Ferrara et al (2004)** have focused on the comparative preformulation evaluation of ethosomes and liposomes of Azelaic acid. From the results observed it was found that the release rate was more rapid from the ethosomal system than from the liposomal systems. It was concluded that ethosomes produced by the highest ethanolic concentration released more rapidly as compared to others [6].

**Xingyan Liu et al (2011)** developed a stable formulation with good entrapment efficiency, release rate, and transdermal absorption. Considering the data generated it can conclude that ligustrazine ethosomes patches could encourage better drug absorption and increase bioavailability as compared with conventional ligustrazine administration [7].

**Maheshwari RG et al (2012)** focused on the formulation and evaluation of Clotrimazole an anti-fungal agent by loading into the different nanocarriers (ethosomes and ultra deformable liposomes) and compared their transdermal potential. Skin interaction and FT-IR studies revealed greater penetration enhancing effect of Ethosomal formulation than that of the ultra deformable liposomes. Results also suggested ethosomes to be the most proficient carrier system for dermal and transdermal delivery of clotrimazole [8].

**Sarat CC et al (2012)** examined the comparative assessment sonicated and un-sonicated Ketoconazole encapsulated ethosomes Drug encapsulated ethosomes were prepared using...
“Hot” method technique. *In-vitro* drug release of Ketoconazole was improved in case of ethosomes containing 30% ethanol with sonication. From evaluation studies, the developed ethosomes of Ketoconazole demonstrated enhanced properties with increasing concentrations of ethanol as well as by subjecting vesicles for sonication [9].

### 3.2 Selection of Route of Administration for Proposed Dosage Form

*Kumar S et al (2012)* have focused on the recent developments in targeted drug delivery systems. The review has broadly illustrated the strategic approaches that have been proposed for brain drug delivery system. The review applies for the understanding the concepts and challenges for targeted drug delivery systems [10].

*Kaur P et al (2015)* have envisaged on the *in-situ* drug delivery. Author focused on the novel approach for brain targeting through the mucosal membrane. The review revealed the concepts of barriers involved in the nasal drug delivery, factors influencing nasal drug absorption, mechanism of nasal absorption and strategies to overcome the factors. Moreover the article provides the knowledge to identify and know the gelling systems for intranasal drug delivery and the choice of polymers involved in the formulations [11].

### 3.3 Selection of Polymers for Nasal Drug Delivery

*Hamed AS et al (2012)* developed phospholipid based colloidal nanocubic vesicles encapsulating olanzapine for its brain targeting through the nasal route where the nanocubic vesicles were prepared by incorporating non-ionic copolymers, poloxamer 188 or 407, in the lipid bilayer. The results recorded illustrated that the intranasal nanocubic vesicles were significantly more efficient in targeting olanzapine to the brain compared to the liposomal vesicles with drug targeting efficiency values of 100% and 80%, respectively, and absolute bioavailability of 37.9% and 14.9%, respectively [12].

*Gabal YM et al (2014)* investigated the influence of the nanocarrier surface charge on brain delivery of a model hydrophilic drug via the nasal route. Anionic and cationic
nanostructured lipid carriers (NLCs) were prepared and optimized for their particle size and zeta potential. The absolute bioavailability of both drug loaded anionic and cationic NLCs in situ gels was enhanced compared to that of the intranasal solution of the drug with values of 44% and 77.3%, respectively. Cationic NLCs in situ gel showed a non significant higher $C_{\text{max}}$ in the brain compared to the anionic NLCs in situ gel. Anionic NLCs in situ gel gave highest drug targeting efficiency in the brain (DTE %) with a value of 158.5 which is nearly 1.2 times that of the cationic NLCs in situ gel [13].

Joshi S (2011) mainly focused on the Sol-gel transformations in HPMC (hydroxypropyl methylcellulose) and its applications. This article contains investigations on the effects of salt additives in Hofmeister series on the HPMC gelation. Explanations are provided based on the chemical structure and the molecular binding/association of HPMC in a media. The test results at the body temperature helps in understanding the progress of the gelation process within the human body environment. The detailed interpretation of various molecule level interactions unfolded the sol-gel mechanisms and the influence of a few other factors. The obtained test data and the established mathematical models are expected to serve as a guide in customizing applications of HPMC hydrogels [14].

Yadav D et al (2012) formulated nasal drug delivery system containing Salbutamol Sulphate for improving the bioavailability & sustaining the drug release. The study was aimed to enhance the bioavailability. Thermoreversible, bioadhesive polymers such as poloxamer and Hydroxy Propyl Methyl Cellulose (HPMC) were loaded in the form of in situ gel by cold technique. The results revealed that as the HPMC concentration was inversely proportional to gelation temperature whereas mucoadhesive strength also increases with increase of bioadhesive polymer HPMC. The optimized formulation showed the controlled drug release [15].

De A et al (2013) designed and optimized the nasal insitu gel of Ondansetron by using factorial design. In-situ nasal gel of the Ondansetron was prepared using Pluronic F-127 as the thermoreversible polymer and HPMC E15 and Chitosan as the mucoadhesive polymer. The formulated system provided a sustained release of the drug over a 5- hour
period *In-vitro* and the developed formulations showed marked increase in permeation rate. The formulation has facilitated to improve the residence time which makes the dosage form an alternative for oral drug delivery [16].

**Wei Z et al (2009)** developed and optimized a Paclitaxel (PTX) loaded Pluronic P123/F127 mixed polymeric micelles. The developed formulation were optimized using Doehlert matrix design to investigate the effect of four variables, namely P123 mass fraction, amount of water, feeding of PTX and hydration temperature on the responses including drug-loading coefficient (DL %), encapsulation ratio (ER %) and the percentage of PTX precipitated from the drug-loaded mixed micelles after 48 h. The results obtained for the optimum formulation displayed a low CMC, a high entrapment efficiency and micelle stability. PTX release profile was identified to be sustained due to encapsulation into the inner core of the micelles. PTX encapsulation by mixed micelles also confirmed an increased *In-vitro* cytotoxicity compared to Taxol [17].

**Makhlof A et al (2008)** enlighten the concept of mucoadhesion for the design of non-invasive drug delivery systems. Review has been elaborated to design a more effective drug delivery by choosing the right mucoadhesive drug carriers and polymers. Efforts have been to made emphasis on the development of mucoadhesive formulations, and in particular on recently developed micro- and nanoparticulate systems. Moreover, the applications of the mucoadhesive carrier systems for different administration routes such as the oral, nasal, pulmonary and ocular route have been discussed [18].

**Pisal SP et al (2004)** examined the preformulation aspects of Pluronic gels for nasal delivery of Vitamin B₁₂. The major concern of the investigation was to improve absorption and patient compliance. The results of this study reveal that addition of drug alone or the formulation additives results in alteration of gelation properties. From the results generated it reveals that Thermodynamic properties of PF 127 gels are significantly altered with polymer concentration and water-soluble formulation additives [19].
Cho HJ et al (2010) made the efforts to enhance permeation and solubility of an intranasal delivery system of fexofenadine hydrochloride, by incorporating it into the poloxamer 407 (P407) / hydroxypropyl-β-cyclodextrin (HP-β-CD) based thermoreversible gels with chitosan. The In-vitro permeation profile and bioavailability studies suggested the feasibility that thermosensitive gels could be used as an effective dosage form to enhance the nasal absorption of fexofenadine hydrochloride [20].

Majithiya RJ et al (2006) investigated the thermoreversible mucoadhesive in-situ gel of Sumatriptan using thermoreversible polymer Pluronic F127 (PF127) and mucoadhesive polymer Carbopol 934P (C934P). Formulations were designed so as to have gelation temperature below 34°C to ensure gelation at physiological temperature after intranasal administration. Considering the evaluated observations and histopathological examination it was concluded that PF127 based gel formulation of sumatriptan with in-situ gelling and mucoadhesive properties with increased permeation rate is promising approach for prolonging nasal residence time and thereby nasal absorption [21].

Mahathi K et al (2014) prepared nasal in-situ gel of Levofloxacin hemihydrate was prepared for the treatment of nasal infections to provide sustained release of drug and to attain site specific action. Carbopol 934 was used as a pH triggered polymer using different concentrations alone and in combination with different grades of HPMC. The results obtained concluded that Levofloxacin hemihydrate nasal in situ gel produces prolonged and site specific drug delivery for the treatment of respiratory tract infections especially for sinusitis and bronchitis [22].

Jun Loh X et al (2007) revealed the potential of biodegradable thermo gelling copolymer hydrogels in areas such as sustained drug release, gene delivery and tissue engineering. This review was focused to provide a widespread summary of the recent developments in this field of study and highlights the most recent intellectual property and research papers [23].
3.4 Method Selection for Intranasal Drug Delivery

**Kumar A et al (2015)** developed the combinational Zolmitriptan (ZMT) and ketorolac tromethamine (KT) intranasal drug delivery system for the management of migraine. Study was designed to formulate ZMT and KT loaded thermo reversible in-situ mucoadhesive intranasal gel formulation with the bioadhesive polymer (Xyloglucan). Optimization was confirmed by the Box-Behnken design. Obtained record concludes that optimized formulation would be helpful to mitigate migraine associated symptoms much better over the currently available formulations [24].

**Chen X et al (2013)** demonstrated the brain targeting of curcumin by intranasal administration of a thermosensitive poloxamer hydrogel in improving the brain targeting efficiency. Prepared gels were evaluated for hydrogel gelation temperature, gelation time, drug release and mucociliary toxicity characteristics as well as the nose-to-brain transport in the rat model. The results recorded concluded that the developed thermosensitive curcumin nasal gel was having the favorable gelation, release properties, biological safety and enhanced brain-uptake efficiency [25].

**Sharma S et al (2013)** formulated intranasal mucoadhesive nanoparticulates and thermo-reversible gel of levodopa for brain targeting through the intranasal route. chitosan nanoparticles loaded with levodopa (CNL) were prepared and were loaded in a thermo-reversible gel using PF127, (CNLPgel) and were optimized for different parameters. In-vitro release studies from CNL obeyed Higuchi kinetic model, whereas the drug release from CNLPgel followed the Hixson–Crowell model. In-vivo studies indicated a maximum recovery of the drug in brain following intranasal administration of CNL suspension in saline followed by the drug dispersed in plain pluronic gel [26].

**Bhandwalkar MJ et al (2012)** developed the thermo reversible nasal in-situ gel of venlafaxine hydrochloride using Lutrol F127 (18%) as a thermo gelling polymer wheras, Mucoadhesion was modulated by using carbopol 934, PVP K30, HPMC K4M, sodium alginate, tamarind seed gum, and carrageenan as mucoadhesive polymers. Results revealed that as the concentration of mucoadhesive polymer increased the mucoadhesive
strength increased but gelation temperature decreased. Formulation was optimized for various parameters and examine for histopathology of nasal sheep mucosa. Pharmacodynamic study concluded that Venlafaxine hydrochloride was more effective as an antidepressant by nasal route as in-situ gel nasal drops in comparison to oral administration of equivalent dose [27].

**Dondeti P et al (1996)** focused on the on the nasal absorption through varios dosage forms. The core review was to discuss the factors affecting the nasal absorption by bioadhesive and formulation parameters. Nasal administration of drugs especially peptides along with bioadhesive polymers in combined with a nontoxic enhancers can provide the promising potential as alternative therapy to the injections [28].

**Bonacucina G et al (2004)** determined the Rheological, mucoadhesive and release properties of carbopell gels in hydrophilic co-solvents. The basic idea of the investigation was to study the gelation properties of Carbopol 971 and 974 polymeric systems in water-miscible cosolvents such as glycerine and PEG 400. The results obtained creates the challenge for designing PEG 400-Carbopol systems as a first-rate alternative to traditional water gels [29].

**Ved PM et al (2011)** prepared the nasal formulation by dissolving Zidovudine in pH 5.5 phosphate buffer solution comprising of 20% polyethylene oxide/propylene oxide (Poloxamer 407, PLX) as thermoreversible gelling agent and 0.1% n-tridecyl-β-D-maltoside (TDM) as permeation enhancer. The proposed study was intended to investigate the olfactory transfer of zidovudine after intranasal (IN) administration and to assess the effect of thermoreversible gelling system on its absorption and brain uptake. The evaluation results and the pharmacokinetic and brain distribution studies revealed that a polar antiviral compound, Zidovudine could preferentially transfer into the CSF and brain tissue via an alternative pathway, possibly olfactory route following intranasal administration [30].
Jose S et al (2012) investigated thermo-sensitive gels containing lorazepam microspheres for intranasal brain targeting. Pluronics (PF-127 and PF-68) were used as thermoreversible polymers. Box Behnken design was employed to optimize microsphere formulations. From the record it showed that the concentration of 21% PF-127 and 1% PF-68 were found to be promising gel vehicles whereas the prolonged profile for dispersion of the microspheres in the viscous media was observed, in comparison to the microspheres alone [31].

Patil PR et al (2015) formulated ion-sensitive in-situ gels of Zolmitriptan. The study was conducted for the formulations of in-situ gels by using gellan gum as gelling agent and HPMC K100 as controlled or sustained release polymer. All the formulations were evaluated for various parameters and optimized for the concentration of gelling agent and mucoadhesive agent. In-vitro release data revealed that the optimized formulation showed controlled and sustained drug release pattern. When applied for kinetic studies it obeyed fickian diffusion. Thus considering the results thermoreversible gel can be the better alternative for the present oral dosage form [32].

Chand R et al (2015) formulated the thermoreversible formulation containing rizatriptan benzoate for intranasal administration. Combination of chitosan and aqueous \( \beta \)-glycerolphosphate were used to provide the thermoreversible systems. Both In-vitro release and ex-vivo permeation of rizatriptan from gels were measured at 37°C using Franz diffusion cells. Formulations were tested In-vivo in mice for reduction in locomotor activity using digital actophotometer and nasal mucosal tissues were examined histopathologically, where the results displayed were supporting the investigation [33].

Mahalkar NG et al (2013) demonstrated the gelling properties and drug delivery via nasal route for zolmitriptn by using natural polymers from bark of Sterculia foetida Linn. The mucoadhesive strength and viscosity of this natural mucoadhesive polymer was found to be higher in comparison to the synthetic polymers, namely HPMC and carbopol 934. The in-situ gelation was achieved by the use of pluronic F127 which exhibit
thermoreversible gelation property. The research suggest the in-situ gel as preferred the drug delivery for brain targeting by using natural polymers [34].

**Patel M et al (2010)** designed the thermoreversible formulations of flurazinize hydrochloride for nasal delivery. The purpose of investigation was to improve the drug residence time in the nasal cavity. Formulations were developed by forming the complex of drug and β-cyclodextrin (β-CD). The formulations so prepared were in the liquid state at 4°C while turned into a gel at the temperature of the nasal cavity. Poloxamer 407 was used as the polymer which exhibited the phase transition behavior. Results studied indicated fast release suggesting the increase in the solubility and dissolution rate of flunarizine hydrochloride [35].

**Kolsure P et al (2012)** investigated Zolmitriptan formulations for nasal administration. Mixture of pluronic F-127 (Poloxamer 407) and pluronic F-68 (Poloxamer 188) were used to confer temperature sensitive gelation property. To modulate the gel strength and bioadhesive force for zolmitriptan nasal gel, bioadhesive polymers such as sodium alginate, sodium carboxymethyl cellulose and polyvinyl pyrrolidone (PVP K–25) were investigated. Histopathological examination of sheep nasal mucosa with control and optimized formulation did not show any histological damage to the nasal tissue. Considering the results it can be concluded that Zolmitriptan can be safely provided in the poloxamer based dosage form to sustain the release and imorove the therapeutics and patient compliance [36].
3.5 References


