CHAPTER III

3.1 AIM AND OBJECTIVE

- The Aim of the study is to develop various strategies like Microemulsion and Microspheres for brain targeting of an Anti-parkinsonism drug Ropinirole hydrochloride by Nasal administration.

- To design drug delivery systems that can bypass the hepatic first pass metabolism and achieve rapid delivery of the drug directly to brain, thereby increasing its bioavailability.

- To minimize anosmia (loss of sense of smell), nasal irritation and interference/damage to nasal mucosal layers which is a major disadvantage after frequent administration through nasal route by using hypoallergenic materials.

- To achieve the desired drug levels in brain in treatment of Parkinson’s disease.

- To evaluate the effect of various BBB permeation enhancer like Propylene glycol, Cyclodextrins & polyethylene glycol on the permeation and delivery of GDNF to the brain.

- To evaluate the effect of various mucoadhesive agents Chitosan, Carbopol, Eudragit & Sodium alginate on the residence time of the formulation in the nasal cavity which increases the drug delivery to the brain.

- Compatibility Studies between drug and excipients by FTIR, DSC and XRD.

- Comparative Evaluation of two strategies for particle size analysis, Morphological studies by SEM and Zeta potential, Swelling Index, Drug Entrapment efficiency, In Vitro mucoadhesive strength determination, Invitro diffusion studies and In vivo animal models.

- To optimize the various parameters in the preparation of Nasal drug delivery systems successful treatment of Parkinson’s disease.

- To compare the extent of drug reaching the brain by nasal drug delivery system.

- To achieve good correlation between the in vitro and in vivo results.

- And there by improve compliance and quality of life of the patients suffering from Parkinson’s disease.
3.2 CRITERIA FOR SELECTION DRUG

Criteria for brain targeting

Chemical form

For determination of absorption parameter the chemical form of drug is taken into consideration. Moreover if drug is converted into its salt or ester form its absorption predominately also increases. For example, the carboxylic acid ester of L-tyrosine showing better absorption as compared to unmodified L-tyrosine if given as in-situ nasal formulation.

Polymorphism: Polymorphism generally affects the dissolution rate and solubility of drugs so in indirect way it effects the absorption of drugs through biological membranes.

Molecular weight: There is an inverse relation in between the molecular weight and absorption of drug if molecular weight is up to 300 Daltons. Absorption of drug gets decreased as the size increases mostly if more than 1,000 Daltons but the absorption can be increased by using absorption enhancers.

Particle size

It has been reported that particles greater than 10μm in size are deposited in the nasal cavity. Particles that are 2 to 10μm can be retained in the lungs, and particles of size less than 1μm are exhaled.

Solubility and Dissolution Rate

The amount of fluid available for dissolution of drug Particles in nasal cavity or mucosa is very less while in the gastrointestinal tract for oral drug delivery the amount of fluid is more. That is why deposition in the nasal cavity need to first to dissolve prior to absorption.

Partition Coefficient and pKa: According to the pH partition theory, unionized form of drug is well absorbed compared with ionized form of drug and the same theory is suitable in the case of nasal drug absorption.

Lipophilicity: On increasing lipophilicity, the nasal absorption of the compound normally increases. For example, number of lipophilic drugs such as naloxone, buprenorphine and testosterone have been shown to be completely or almost completely absorbed nasally.
pH of the formulation
The drug should be in unionized form and pH should be in between 4.5 to 6.5 so that nasal irritation can be minimized when given nasally. Only the limited volume can be delivered to nasal cavity because of small size. The volume and dose for nasal cavity is 0.1-0.2 ml and 25mg per nostril respectively.

Osmolarity
Drug absorption can also be affected by tonicity of the formulation. For example, the effect of osmolarity on the absorption of secretin in rats and found that absorption reached maximum at a sodium chloride concentration of 0.462 M, because shrinkage of the nasal epithelial mucosa occurs if kept in presence of hypertonic solutions.
Buffer capacity: Nasal secretion may alter the pH of the administered dose. This further can affect the concentration of unionized drug that is available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH of drug in-situ.

Criteria of Drug (Ropinirole Hydrochloride)
Molecular Weight : 296.84 (260.38 as the free base).
Melting Range : 2430 to 2500
Solubility : 133 mg/ml in water. In other solvents it is partially soluble
pKa (Strongest acidic) : 13.24
pKa (Strongest basic) : 10.17
Bioavailability (%) : 50%
Protein Binding (%) : >40% bound to plasma proteins with a blood-to-plasma ratio of 1:1
Elimination half life (hrs) : 5-6hrs
Metabolism : hepatic (extensive)
3.3 STRATEGIES

Strategy is a high level plan to achieve one or more goals under conditions of uncertainty. Strategy is important because the resources available to achieve these goals are usually limited. Strategy generally involves setting goals, determining actions to achieve the goals, and mobilizing resources to execute the actions. A strategy describes how the ends (goals) will be achieved by the means (resources). This is generally tasked with determining strategy.

Strategies of this present work as follows:

1. Microemulsion
2. Microspheres

MICROEMULSION

Microemulsion is commercially feasible, simple and convenient vehicles for delivery of medicaments which can enhance the drug absorption with reduced systemic Microemulsion side effects. Intranasal drug delivery system is a promising alternative route of administration for poor bioavailability drugs and it has advantages in term of increase patient acceptability and compliance. So, an intranasal microemulsion is one of the important delivery system for noninvasive drug delivery to systemic circulation.

Challenges in nasal drug delivery via microemulsion

- The main problem in a microemulsion application is a high concentration and a narrow range of physiologically acceptable surfactants and co-surfactants.
- Large surfactant concentration (10-40%) determines their stability.
- Selection of components: if the systems are to be used topically, selection of components involves a consideration of their toxicity, irritation and sensitivity.
- Nasal congestion due to cold or allergies may interfere with absorption of drug through nasal mucosa.
- Delivery is expected to decrease with increasing molecular weight of drug.
- Some therapeutic agents may be susceptible to partial degradation in the nasal mucosa.
- Concentration achievable in different regions of the brain and spinal cord varies with each agent.
- Fluidity of interfacial film should be low to promote the formulation of microemulsion.
Selection Oil Phase
The oil component influences curvature by its ability to penetrate and swell the tail group region of the surfactant monolayer. Following are the different oil is mainly used for the formulation of microemulsion:
- Castor oil, Sesame oil, oleic acid, turpentine oil etc.

Aqueous phase
The aqueous phase may contain hydrophilic active ingredients and preservatives. Buffer solutions are used as aqueous phase by some researchers.

Selection of Surfactants
The role of surfactant in the formulation of microemulsion is to lower the interfacial tension which will ultimately facilitates dispersion process during the preparation of microemulsion and provide a flexible around the droplets. Generally, low HLB surfactants are suitable for w/o microemulsion, whereas high HLB (>12) are suitable for o/w microemulsion. Following are the different surfactants are mainly used for microemulsion.
- Polysorbate (Tween 80 and Tween 20), Lauromacrogol 300, Lecithins, Decyl polyglucoside (Labrafil M 1944 LS), Polyglyceryl-6-dioleate (Plurol Oleique), Dioctyl sodium sulfosuccinate (Aerosol OT), PEG-8 caprylic/capril glyceride (Labrasol).

Selection Co-surfactants
Co-surfactants are mainly used in microemulsion formulation for following reasons:
- They allow the interfacial film sufficient flexible to take up different curvatures required to form microemulsion over a wide range of composition.
- Short to medium chain length alcohols (C3-C8) reduce the interfacial tension and increase the fluidity of the interface.
- Surfactant having HLB greater than 20 often require the presence of cosurfactant to reduce their effective HLB to a value within the range required for microemulsion formulation.
  Eg: sorbitan monoleate, sorbitan monostearate, propylene glycol, propylene glycol monocaprylate (Capryol 90), 2-(2-ethoxyethoxy) ethanol (Transcutol) and ethanol.

Methods for the preparation of Microemulsions
1. Phase Titration Method
2. Phase Inversion Method
MICROSPHERES

All types of microspheres that have been used as nasal drug delivery systems are water-insoluble but absorb water into the sphere's matrix, resulting in swelling of the spheres and the formation of a gel. The building materials in the microspheres have been starch, dextran, albumin and hyaluronic acid, and the bioavailability of several peptides and proteins has been improved in different animal models. Also, some low-molecular weight drugs have been successfully delivered in microsphere preparations. The residence time in the cavity is considerably increased for microspheres compared to solutions. However, this is not the only factor to increase the absorption of large hydrophilic drugs. Microspheres also exert a direct effect on the mucosa, resulting in the opening of tight junctions between the epithelial cells. Starch and dextran microspheres have been administered repeatedly and can be classified as safe dosage forms.

The present study is planned with the following objectives:

- To design nasal microspheres for brain targeting of Ropirinole HCl using different mucoadhesive polymers by adopting suitable technique.
- To study the influence of formulation and process variables on microsphere formation and release characteristics.
- To perform the physicochemical characterization of the prepared microspheres.
- To carry out in vitro drug release studies and to explore the release behavior using various kinetic models.
- To determine the mucoadhesive strength and Ex vivo permeation of the optimized microspheres using mucus membranes of suitable animals adopting suitable methods.
- To carry out stability studies for selected formulations as per ICH guidelines.
3.4 METHOD OF DATA COLLECTION

The data for the study is planned to collect from the laboratory-based experiments:

- Preformulation studies like solubility, melting point and characterization of the drug and polymers will be carried out employing suitable methods and compatibility of drug with excipients will be determined by using Infra-Red Spectroscopy instruments adopting reported methods.
- Microemulsion will be prepared by using different Oil, Surfactant and Co-surfactant by employing suitable technique.
- and Microspheres will be prepared by using different mucoadhesive polymers like chitosan, carbopol, gaur gum, etc. by employing suitable technique.
- Influence of formulation and process variables like concentration of polymer (s), surfactants, dispersion medium, temperature and speed on microsphere formation and release characteristics will be studied.
- The prepared microemulsion and microspheres will be characterized for different parameters.
- In vitro release studies will be carried out and the drug release data will be subjected to various kinetics models.
- In-vivo permeation studies will be carried for the optimized microemulsion and microspheres using animal.
- Integrity of drug in the optimized microspheres will be investigated by FT-IR instruments using suitable methods.
- Stability studies on the selected formulations will be carried out using stability chamber as per ICH guidelines.