CHAPTER-2
(LITERATURE REVIEW)

1.18 BRIEF REVIEW OF LITERATURE

Illum et al., 1987[26], developed a nasal delivery system in the form of bioadhesive microspheres. The half life of clearance for starch microspheres was found to be 240 mins as compared to 15 min for the liquid and powder control formulations.

Fisher et al., 1987[7], have studied the relationship between the molecular weight of hydrophilic compounds and their systemic absorption via nasal route and found that although the uptake of drug decreased with increasing molecular weight, polar molecules of quite high molecular weight could be taken up to significant extent.

Morimoto et al., 1987[6], concluded that viscous polymer solutions are suitable dosage form which remain in nasal cavity long enough, increase the contact time with nasal mucosa and thereby increase the bioavailibility.

Hersey et al., 1987[27], studied the effect of absorption enhancers on the permeability properties of nasal mucosa and concluded that enhancer systems could well have an impact on the nasal membrane and hence produce possible permanent damage to the membrane, including cilia, especially when a delivery system is used to treat a chronic disease such as diabetes.

Illum et al., 1988,[28] reported that nasal administration of gentamicin in combination with degradable starch microspheres resulted in bioavailibility of 9.7% as compared to less than 1% for a nasal solution.

Bjork et al., 1988[29]**,** reported that the nasal administration of insulin to rats in combination with degradable starch microspheres or with insoluble starch as a dry powder resulted in a rapid decline in plasma glucose in contrast insulin with soluble starch had no effect.

Ferraj et al., 1990[32] have shown that the bioadhesive microsphere system can be combined with biological absorption promoters such as lysophospholipids to form effective nasal delivery system.

Vyas et.al., 1990,[33] prepared HSA microspheres containing propranolol by emulisification and cross linking method and concluded that controlled drug release following nasal administration of bioadhesive human serum albumin microspheres resulted in sustained and controlled drug absorption and elimination of hepatic first pass metabolism

Ferraj et al., 1990,[34] reported that the use of degradable starch microspheres with insulin for nasal delivery, exhibited a significant change in peak insulin and mean plasma glucose.

Lewis et al., 1990[35] reported the preparation and in vitro characterization of microspheres of polyacrylic acid cross linked with maltose in a w/o emulsification process. It appeared that an increase in curing time of microspheres resulted in an increased release of oxytosin in vitro. This might be due to the fact that an increased curing time leads to heavily cross linked polymeric network inside the microspheres which severely limits swelling on hydration.

Reyden et. Al., 1991[36]**,** evaluated dextran microspheres and polymer solution as potential vehicle for nasal administration of insulin in rats and concluded that a larger reduction in plasma glucose level was observed with insulin carried in the particle system than in the polymer system.

Bjork et al., 1991[37]**,** performed morphological examination of the rabbit nasal mucosa after the nasal administration of starch microspheres for upto 8 weeks has shown that the system can be considered to be biocompatible and not induce serious histopathological changes in the nasal mucosa.

Thanoo et al., 1992[38], prepared cross linked chitosan microspheres containing furosemide and reported that the least cross-linked microspheres released the drug at a faster rate.

Ryden and Edman 1992[39], evaluated dextran microspheres for nasal delivery of insulin in rats. Insulin loaded sephadex and DEAE-sephadex microspheres resulted in maximum glucose reduction of 25% and 9% respectively.

Almedia et al., 1993[40] reported that nasal administration of tetanus toxoid adsorbed into poly-L-Lactic acid microspheres resulted in enhanced immune response compared to free antigen.

Lin et al., 1993[41] studied the correlation between viscoelastic properties of polymeric formulations and nasal residence time .Of the two formulations, 6% HPMC in normal saline and 6% HPMC suspended in propyleneglycol alcohol mixture increase residence time was observed for latter formulation and similar nasal bioavailibility was observed for propranolol in both of the formulation.

Critchley et al., 1994,[42] evaluated bioadhesive starch microspheres as a nasal delivery system for desmopressin, and observed significant improvement in the absorption of drug, both in terms of peak plasma level and bioavailibility.

Durmaz et al.1994,[43] prepared chitosan microspheres containing furosemide from w/o emulsion system using liquid paraffin as the external phase and a solution of chitosan in acetic acid as the disperse phase. The results were examined kinetically and dissolution data indicated that release followed the Higuchi matrix model.

Chiaocs CS, Price JC, 1994,[44] encapsulated Propranolol HCl with cellulose acetate butyrate (CAB) by an emulsion-solvent evaporation method to obtain discrete, spherical microspheres. The effects of drug to polymer ratio and microsphere size on dissolution characteristics were studied. Drug release was faster in simulated intestinal fluid than in

simulated gastric fluid. . For microsphere size fractions between 127 and 359 microns the relationship between the 50 per cent release time and the square of the microsphere diameter was linear (r = 0.9999).

Viven et al., 1994[45], compared the nasal absorption of microspheres containing metoclopramide HCl with that of solution and powder formulation. Compared with solution the relative bioavailibility of the powder was 95%and that of the microspheres was 137%.

Chickering et al, 1995[46], used microbalance based method to measure bioadhesion interactions between individual polymer microspheres and rat intestinal tissue, and concluded that bioadhesion in these bioerodible materials is attributable to hydrogen bonding between hydrophilic functional groups and mucus glycoprotein.

Kriwet et al 1995[47], studied the interaction between bioadhesive polymer poly(acrylic acid) and calcium ions and concluded that chelation of polycarbophil with calcium ion is responsible for increase in bioavailibility of drugs observed with bioadhesive polycarbophil delivery system.

Pritchard et al 1996[48], used hyaluronan of various molecular weight and microspheres made from several of its esters were assessed for its adhesiveness in vitro by means of detachment weight mucociliary transport rate and suggested that inclusion of drug into such biodegradable and biocompatible dosage form is an attractive prospect for transmucosal delivery.

Pereswetoff-Moranth et al., 1996[49], studied the effect of particle size and swellability of dextran microspheres for the improved nasal absorption of insulin in rats. They concluded that the microspheres were non-immunogenic and non-toxic, and conducted measurement of cilia beat frequency and histological studies.

Morel et al., 1997[50], evaluated in vivo transit and bioavailibility study of drug loaded alginate and poly (Fumaric-co-sebacic anhydride)microspheres and concluded that bioadhesive drug delivery system could improve bioavailibility by protecting bioactive molecules from physical and chemical degradation, enhancing absorption rate by decreasing diffusion barrier and increasing the period for absorption by prolonging residence time.

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Ramesh et al, 1998[51], prepared poly(DL) Lactic acid microspheres by oil-in oil emulsion polymerisation method and found that the release of the new anti-inflammatory drug from the poly (DL lactic acid) microspheres followed zero order fashion and lasted for about 14 days.

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Lin et al., 1998[52], studied the effects of magnesium stearate on chitosan microspheres prepared by emulsification-coacervation technique and suggested that the size of the drug-loaded microspheres decreased with increasing magnesium stearate content. The release of propranolol hydrochloride from the microspheres was fast, irrespective of the content of magnesium stearate. Drug encapsulation efficiency was enhanced when a greater amount of magnesium stearate was used.

Gohe et al, 1999[53], studied the factors influencing the characteristics of modified release microspheres of Diclofenac Sodium, and showed that the effect of polymer to drug ratio is more predominant than concentration of ethylcellulose solution.

Illum et al., 1999[54], investigated nasal cavity as a site for systemic drug delivery of leutinizing hormone releasing hormone and calcitonin.

Manmohan et al., 2000[55], evaluated a bioadhesive delivery system for intranasal administration of a flu vaccine in combination with mucosal adjuvant and concluded that bioadhesive microsphere vaccine delivery syetem induced serum immune response.

Davis et al 2001.[56], investigates the effect of starch microspheres on the absorption enhancing efficiency of various enhancer system and were shown to increase synergistically the effect of the absorption enhancers on the transport of insulin across nasal membrane.

Soane et al., 2001[57], evaluated clearance characteristics of two bioadhesive formulations chitosan microsphere and chitosan solution from nasal cavity and it can be concluded that sheep can be considered as a suitable model for in vivo nasal clearance studies of novel bioadhesive drug delivery system.

Varshosaz et al., 2001[58], prepared wax microspheres containing propanolol by a congealable dispersion microencapsulation technique The effects of the process variables; type of wax, speed of emulsification, amount of drug loaded, type and amount of emulsifier, were studied on the entrapment efficiency, angle of repose, dissolution efficiency (DE), in-vitro drug release and mean particle size of (I) microspheres, by a factorial design. All the variables had an effect on the angle of repose and particle size of the (I) microspheres. The only significant parameter affecting the DE was the nature of the wax.

Vasir et al., 2003[59] demonstrated that nasal drug delivery of bioadhesive microspheres offers additional advantage of efficient absorption and enhanced bioavalibility of drug.

Shabaraya et al, 2003[60], concluded that the release of metoprolol tartrate from the chitosan microspheres was found to be sustained. Metoprolol tartrate was formulated as biodegradable microspheres using chitosan by the phase separation emulsification technique.

Arul et al., 2003[61], prepared chitosan microspheres of drug Isoniazid by glutaraldehyde cross-linking method and evaluated the in vitro release pattern of the drug. Stability studies were carried out at different temperatures and found that all the formulations were more stable at 4 degree and room temperature.

Elisabetta et al., 2004[62], prepared mucoadhesive microspheres for nasal administration of an antiemetic drug, metoclopramide and on the basis of in vitro/ex-vivo studies concluded that alginate/chitosan spray-dried microspheres have promising properties for use as mucoadhesive nasal carrier of an antiemetic drug.

Chowdary et al., 2004[63]**,** Ethyl cellulose microspheres of glipizide were prepared by an industrially feasible emulsion-solvent evaporation technique and the microspheres were investigated. These microspheres were found suitable for parentral controlled release.

Patel et al., 2004[64]**,** prepared chitosan microspheres containing Metoclopramide by simple emulsification phase separation technique using glutarldehyde as a cross linking agent and concluded that drug release was diffusion controlled and followed non-Fickian diffusion.

Zhou et al., 2005[65] used water in oil in water (W/O/W) emulsion and solvent evaporation methods to make chitosan/cellulose acetate (CCA) microspheres sized 200–400 μm Ranitidine hydrochloride, as a model drug, was investigated for its release properties in vitro. The optimal condition for the preparation of the microspheres was chitosan concentration 2%, molecular weight 1130 KD. The ranitidine release from the microspheres was 30% during 48 h in phosphate-buffer saline medium.

Martinac et al., 2005[66] concluded that due to the presence of ethyl cellulose the composed microspheres were characterized by improved loroatidine entrapment efficiency in comparison to conventional chitosan microspheres.

Govender et al., 2005[67]**,** statistically optimized the formulation parameters of tetracycline microspheres for maximum bioadhesivity and controlled drug release and concluded that quantitative effects of formulation parameters at different levels on drug release and bioadhesion could be predicted by using a polynomial equation.

Patil et al., 2006[68], prepared mucoadhesive chitosan microspheres of amlodipine besylate by simple emulsification cross linking method for nasal administration with the aim of avoiding first pass effect.

Objective & Plan of Work

Objectives of the study

The aim of this work is to formulate and evaluate bioadhesive microspheres for nasal drug administration of Tizanidine HCl, to prolong the therapeutic effect of the drug as the drug has short half life (2.5 hrs) and poor oral bioavailability (40%).

Need and Importance of the study

1-. Bioadhesive microspheres of Tizanidine HCl increases the contact time with nasal mucosa, its plasma half life which in turn increases the bioavailability

2- They also provide targeted drug delivery.

3- Have a large specific surface, which is indicative of a high interactive potential with biological surfaces.

4- Drug can be administered at lower dose with less side effects.

5-Frequency of administration can be reduced.

Importance of the Proposed Work in Academics / Industry

In Academics, the students will get to know that the nasal route is the best route for administration of systemically active drugs such as proteins, peptides, hormones, and other drugs which are poorly absorbed orally and extensively metabolized in liver and bioadhesive microsphere is the most suitable dosage form for nasal drug administration.

In Industry, work based on this research could be done on large scale.

Proposed Method

Bioadhesive microspheres of chitosan are prepared by simple **"Emulsification Phase Separation Technique."**

- Polymer - Chitosan
- Drug – Tizanidine HCL
- Cross linking agent- Glutaraldehyde
- Type of external phase- Heavy liquid paraffin and light liquid paraffin oil
- Surfactant- DOSS(dioctyl sulfosuccinate)