



CHAPTER 1

INTRODUCTION

It is well known that contraceptive needs change during a couple's reproductive life, because of changing cultural, religious and reproductive needs. In addition, many couples do not use modern methods for the fear of side effects. To meet the unmet needs of the couples a wider range of fertility regulation methods should be made available. Research is going on worldwide for the development of improved versions of existing technologies as well as the development of new methods.

Oral contraceptives (OCs) allow effective and convenient family planning for women and couples worldwide, and have revolutionized the reproductive lives of millions of women since their introduction in the 1960s. However, all oral contraceptive drugs interfere with the production and action of endogenously synthesized steroid hormones (Kent et al, 2002).

Also induction of hepatic enzymes by oral contraceptives may interfere with potency and duration of other medications such as anticoagulants (Ellison et al, 2000), antibiotics, or anticonvulsant drugs. In addition, orally administered steroids interfere to different degrees with hepatic protein synthesis of procoagulatory and fibrinolytic proteins (Rosing et al, 1999) and fatty liver as a consequence of long-term treatment. It is also likely that factors originating from or due to hepatic metabolism of exogenous steroids play a role in hypertension and dyslipidaemia, side effects frequently observed with oral contraceptive treatment. Therefore there is a need of development of female contraceptives other than presently available oral contraception without compromise of safety and user compliance.

Throughout history, family planning has been a shared responsibility, with most methods requiring male involvement (Handelsman, 2001). During the last century, convenient and highly reliable contraceptive methods were developed for women, yet not a single new male contraceptive method was introduced (Anderson and Baird, 2002). The shifted burden of contraceptive responsibility can only be rebalanced by the availability of comparably attractive methods for men, allowing them to share more equitably the burdens and benefits of effective family planning. There are currently no systemic methods of contraception for use by men, the development of a male-use equivalent of oral, injectable and implantable female steroid hormone methods of contraception has been the subject of research for the past 30 years or more. A number of studies in animals and men have shown that the administration of

androgens alone, androgen and progestin combinations, and combinations of androgens with gonadotrophin-releasing hormone receptor ligands can suppress gonadotrophin secretion and thereby reduce spermatogenesis to render men infertile.

New materials and new technologies have stimulated pharmaceutical researchers to identify and use alternatives to the classical oral and injectable routes. One of the routes currently being studied is the nasal way. The intranasal administration provides a useful way of taking a range of systemic drugs. The compliance of patients who require long-term medication has been shown to be better due to the simplicity and ease of administration when compared to the parenteral route (Pontiroli et al., 1985, Hirai et al., 1981). Also, the rate of absorption, plasma concentration and pharmacokinetics following nasal route of administration is often compares well to that obtained by intravenous medication because of rich vasculature and high permeability of nasal mucosa. In selected drugs the pharmacokinetics relating to drug absorption and metabolism via the nose are more favorable (Chien et al., 1989, Wuthrich and Buri, 1987, Pontiroli et al., 1989). It has recently been shown that the bioavailability of the steroidal drugs progesterone, 17- β -oestradiol, 17 α -ethinyloestradiol when given via nasal route in rats is greatly superior to that via the oral route (Bawarshi-Nassar et al., 1989). Also, study involving nasal administration of norethisterone shows superiority of this route (Anand Kumar et al., 1991). The bioavailability of Testosterone was found similar to that of i.v. route when given nasally (Hussain et al., 1984). The large number of fenestrated capillaries just below the surface epithelium may well contribute to absorption (Fisher, 1990). However, for the drugs of very short biological half life, the rapid absorption is unfavourable to sustain the drug level in the systemic circulation, and the large mucociliary clearance of the nasal mucosa (Schipper et al., 1991) may cause poor absorption of certain drugs. The mucociliary clearance under normal conditions rapidly clears the applied material since there is a little time of contact between the drug and the mucosa. Therefore, employing nasal delivery for prolonged release required the development of particular strategies in order to keep the substance on the mucosa for a long time without altering the functionality of the nose. Prolonging the contact of the drug with the absorptive surfaces by means of an appropriate delivery system can increase the bioavailability of intranasally administered drug. It was reported that bioavailability of drug with the bioadhesive compound such as carbopol and chitosan was increased

by durability of the drug concentration in plasma by broadhesivity of polymer to the mucus

Weakly cross-linked polyacrylates as carbomers (which are FDA approved) by Ca^{2+} complexation are able to trigger the reversible opening of the tight-junction between the cells and to allow the paracellular transport of peptides (Luessen et al., 1996, Junginger and Verhoef, 1998). Chitosans have been shown to have similar properties to reversibly open the tight junctions. This mechanism is thought to occur by ionic charge transfer between the positive charge of chitosan molecule and the negative charges (sulfate and sialine groups) of the glycocalix (Thanou et al., 2000).

The pulmonary route is also being used for the effective delivery of drugs into the systemic circulation. For a long time, the lung has been used for the administration of drugs for the treatment of local conditions. However, more recently, spurred on by the advent of novel delivery devices, there is a growing interest in the use of the lung for the systemic delivery of challenging molecules, such as peptides and proteins, as well as analgesic agents and even vaccines (Vyas and Khar, 2002). The larger surface area of the lung is well known; although, interestingly, the permeability of the lung tissue in itself is not that different from other mucosal surfaces, it is the large area that provides for the rapid absorption. The challenging aspect still remains unanswered are the mode of delivery for liposomally encapsulated drug to lungs. Metered dose inhalers (MDI) are currently being reformulated as a result of the ban being implemented throughout the world by the United Nations on the use of chloro-fluoro carbons (CFCs). To meet this challenge, one such alternative is the development of new and improved "Dry Powder Inhaler (DPI)" system that will allow inhalants administration of all drugs presently delivered with MDIs.

Liposomes are phospholipid vesicles composed of lipid bilayers enclosing one or more aqueous compartments. Liposomes are attracting considerable interest in the area of drug delivery because of their biocompatible, biodegradable and relatively nontoxic nature (Shek and Barber, 1986). Liposomes are also known to sustain the release of the entrapped drug(s) (Knepp et al., 1988, Arrowsmith, 1983; Akhtar and Juliano, 1992) and to decrease the mucociliary clearance of the drug(s) due to their surface viscosity (Harris, 1988). Therefore, more effective and sustained systemic absorption of a drug would be attained by administering the drug containing

liposomes in respiratory tract. As a drug delivery system, liposomes can significantly alter the pharmacokinetics and pharmacodynamics of entrapped drugs, for example, by enhancing drug uptake, delaying rapid drug clearance, and reducing drug toxicity (Kimelberg and Mayhew, 1978, Szoka and Papahadjopoulos, 1981, Poznansky and Juliano, 1984).

There have been many fewer studies on the safety of long-term use of the progestogen only pill (POP) than of the combined oral contraception (COC), but the existing data are largely reassuring (McCann and Potter, 1994). Levonorgestrel (LN) has been used for many years both alone (in low doses) in the POP and in combination with eströgen in COC preparations.

Unlike steroid hormones, gonadotropin releasing hormones exerts specific action on the pituitary gonadotrophs and the human reproductive tract. This specificity reduces the likelihood of secondary adverse effects such as gynecomastia, thromboembolism, edema, liver and gallbladder involvement. Although clinical application of these peptides is highly promising, their potential may be restricted by difficulties involved in self-medication.

The aim of the present study was to develop a carrier based nasal and pulmonary drug delivery for contraception both in male and female using two different approach i.e., steroidal contraception using a second generation progesterone derivative Levonorgestrel and peptide contraception using a potent gonadotropin releasing hormone agonist, Leuprolide acetate. It was an objective to enhance and maintain effective therapeutic concentrations of the drug for prolonged period of time in development of pharmaceutically rational drug-delivery systems using liposomes and/or mucoadhesives for maximizing the therapeutic index, reducing the dose/frequency of dosing, and systemic side-effects and, thereby, reducing the cost of therapy.

RESEARCH ENVISAGED

The project focuses on the preparation and characterization of formulations for nasal and pulmonary delivery based on liposomes and/or mucoadhesives and the evaluation of the selected formulations for *in vitro* diffusion studies and *in vivo* studies in animals.

The proposed plan of work include

- I Literature reviews covering various aspects of contraception, nasal and pulmonary delivery especially with mucoadhesives, liposomes, dry powder inhaler and profiles of selected drugs
- II To find an ideal liposomal form as far as encapsulation efficiency is concern Liposomes containing drugs will be prepared by reverse phase evaporation and thin film hydration method The prepared liposomes will be characterized with respect to, encapsulation efficiency, size and size distribution and lamellarity
- III. To prepare nasal formulations with and/or without liposomes and /or mucoadhesive agents and characterize the developed formulations with respect to pH, viscosity and mucoadhesive properties Comparative evaluation of the formulations will be conducted for *In vitro* diffusion studies and *In vivo* studies including pharmacokinetics/pharmacodynamics Liposomal formulations will also be subjected to drug retention studies
- IV To prepare dry powder inhaler formulations by lyophilization and optimized with regard to percent drug entrapment by proper selection of cryoprotectant and diluent Characterization of the prepared Liposomal DPI will be carried out for encapsulation efficiency, size and size distribution, lamellarity, and drug retention at different storage conditions Flow and dispersion properties will also evaluated including, angle of repose, bulk density, moisture content, compressibility, dispersibility and fine particle fraction. Comparative evaluation of the formulations will be conducted for *In vitro* diffusion studies and *In vivo* drug bioavailability studies.

REFERENCES

- Akhtar, S and Juliano, R E , 1992 Liposome delivery of antisense oligonucleotides adsorption and efflux characteristics of phosphorothioate oligodeoxy-nucleotides, *J Control Rel*, 22, 47-56
- Anand Kumar, T C , Shah, R S , Chitlange, S M , Hazari, K T , Gopalkrishnan, K , Vadi goppula, A D., Vernekar, V.J., Borkar, D M , Puri, C P . 1991 Effects of intranasal administration of norethisterone on folliculogenesis, cervical mucus, vaginal cytology, endometrial morphology and reproductive-endocrine profile in women *Contraception*, 245-265
- Anderson, R A and Baird, D T., 2002. Male contraception. *Endocr Rev*, 23, 735-762
- Arrowsmith, M., Hadgraft, J and Kellaway, I.W , 1983. The in vitro release of steroids from liposomes, *Int J Pharm*, 14, 191-208
- Bawarshi-Nassar, R N , Hussain, A , Crooks, P A , 1989 Nasal absorption and metabolism of progesterone and 17 β -oestradiol in the rat *Drug Metab Dispos*, 17(3), 248-54
- Bawarshi-Nassar, R N , Hussain, A , Crooks, P.A , 1989. Nasal absorption of 17 α -ethinyloestradiol in the rat *J Pharm Pharmacol*, 41, 214-215
- Chien, Y W., Si, K.S.E. and Chang, S , 1989 Nasal systemic drug delivery In YW Chien, eds *Drugs and the pharmaceutical sciences* New York. Marcel Dekker, pp. 1-26
- Ellison, J., Thomson, A J , Greer, I.A. and Walker, I D., 2000 Drug Points Apparent interaction between warfarin and levonorgestrel used for emergency contraception. *BMJ*, 1321-1382
- Fisher, A.N , 1990 Absorption across the nasal mucosa of animal species compounds applied and mechanisms involved. In: Gibson, G G (Ed.), *Progress in Drug Delivery* London: Taylor and Francis, pp. 87-143.
- Handelsman, D. J , 2001. Male contraception, in: L.J. DeGroot, (Ed), *Endocrinology*, 4th Ed., Saunders, Philadelphia, pp. 2344-2349.

Harris, A S , Svensson, L , Wagner, Z G , Lethagen, S and Nilsson, I M , 1988 Effect of viscosity on particle size, deposition, and clearance of nasal delivery systems containing desmopressin J Pharm Sci, 77, 405-408

Hirai, S et al , 1981 Absorption of drugs from the nasal mucosa of rat Int J Pharm , 7, 317-325

Hussain, A A , Kimura, R. and Huang, C H , 1984 Nasal absorption of testosterone in rats Nasal absorption of testosterone in rats J Pharm Sci, 73(9), 1300-1

Junginger, H.E and Verhoef, J C , 1998. Macromolecules as safe penetration enhancers for hydrophilic drugs—a fiction? Pharmaceutical Sciences and Technology Today, 1, 370-376

Kent, U M , Mills, D E , Rajnarayanan, R V , Alworth, W L and Hollenberg, P F . 2002 Effect of 17-alphaethynylestradiol on activities of cytochrome P450 2B (P450 2B) enzymes: characterization of inactivation of P450s 2B1 and 2B6 and identification of metabolites. J Pharmacol Exp Ther, 300; 549-558

Kimelberg, H K and Mayhew, E.G., 1978 Properties and biological effects of liposomes and their uses in pharmacology and toxicology CRC Crit. Rev Toxicol . 96, 25-79

Knepp, M , Hinz, R S , Szoka, F.C and Guy, R H , 1988 Controlled drug release from a novel liposomal delivery system I. Investigation of transdermal potential, J Control Release, 5, 211-221

Luessen, H L , de Leeuw, B.J., Langemeyer, M.W , de Boer, A B , Verhoef, J C and Junginger, H E , 1996 Mucoadhesive polymers in peroral peptide drug delivery VI. Carbomer and chitosan improve the intestinal absorption of the peptide drug buserelin in vivo. Pharm Res, 13(11), 1668-72.

McCann, M F. and Potter, L.S., 1994. Progestin-only oral contraception: A comprehensive review. Contraception, 50(suppl 1), 1-195.

Pontiroli, A.E., Calderara, A., Pozza, G., 1989 Intranasal drug delivery: potential advantages and limitations from a clinical pharmacokinetics perspective. Clin Pharmacokin, 17(5), 299-307.

Pontiroli, A E , Secchi, A. and Alberetto, M , 1985 Alternative routes of peptide hormone administration. Special Topic in Endocrinol Metab, 7, 77-99

Poznansky MI, Juliano RL. Biological approaches to the controlled delivery of drugs: a critical review. *Pharmacol Rev* 1984;36:277-336.

Rosing, J, Middeldorp, S, Curvers, J et al., 1999. Low-dose oral contraceptives and acquired resistance to activated protein C: a randomised cross-over study. *Lancet*, 354(9195), 2036-2040.

Schipper, N G M, Verhoef, J C and Merkus, F W H M, 1991. The nasal mucociliary clearance: Relevance to nasal drug delivery. *Pharm Res*, 8, 807-814.

Shek, P.N., and Barber, R.F. 1986. Liposomes: a new generation of drug and vaccine carriers. *Modern Med Canada*, 41, 314-326.

Szoka, F., and Papahadjopoulos, D., 1981. Liposomes: preparation and characterization. In Knight, CG, (Ed.) *Liposomes: From Physical Structure to Therapeutic applications*. Elsevier/North-Holland Biomedical Press, New York, pp. 51-82.

Thanou, M., Florea, B I, Langemeyer, M W, Verhoef, J C and Junginger, H E, 2000. N-trimethylated chitosan chloride (TMC) improves the intestinal permeation of the peptide drug buskerlin in vitro (Caco-2 cells) and in vivo (rats). *Pharm Res*, 17(1), 27-31.

Vyas, S.P. and Khar, R K., 2002. *Nasopulmonary Drug Delivery in Controlled Drug Delivery: concept and advances*. Vallabh prakashan, India. pp.341-342.

Wuthrich, P and Buri, P, 1987. Intranasal absorption of drugs with an in situ recirculation method in rats. In Aiche, J M, Hirtz, J (Eds.), *Proceedings of the Third European Congress of Biopharmaceutics* 1, 21-24.