Summary...
XL SUMMARY

As the field of drug delivery continues to advance, nasal drug delivery continues to grow and become a viable alternative to oral and injectable routes of administration for some compounds. Protein and peptide drugs stand to benefit from nasal delivery the most, as do drugs that require quick onset of action. Techniques employing bioadhesion and absorption enhancement remain at the forefront of systemic nasal drug delivery. Several formulation factors will influence the development of a drug with a nasal drug delivery system, including the physical and chemical characteristics of the drug molecule, the molecular weight and desired therapeutic action.

The aim of this work was to develop and characterize some in situ gelling bioadhesive nasal gel and a solid bioadhesive nasal patch for the prolonged systemic drug delivery via nasal route. The potential of thermoreversible gel formulation to prolong the residence time in the nasal cavity was evaluated. Taken together, four different drugs with different properties and pharmacological action but having ideal characteristic to be suitable candidate for nasal drug delivery were used as model drug for various gel bases. Thermoreversibal gel bases were optimized for different formulations.

Poloxamer gel base for tramadol hydrochloride was optimized with PEG 4000 and propylene glycol along with mucoadhesive agent (carbopol 934 P). The effect of drug, PEG-4000, propylene glycol and carbopol 934P on gelation temperature was determined. Depending on the effect shown by drug and additives the formulations were optimize to have a gelation temperature in the range of 34 °C - 37 °C. Further the formulations were evaluated for parameters like bioadhesion, gel strength, invitro diffusion, viscosity, stability, ease of administration, safety etc. In-vivo studies were performed in patients suffering from various pains and normal human volunteers using gamma sintegraphy. The results showed satisfactory drug release and sol-gel transition temperature of the optimized formulation. Moreover the results of gamma sintegraphy showed that the formulation retained in nasal cavity upto eight hours and also patient felt good pain relief by use of thermoreversible gel of tramadol hydrochloride.

Metoprolol tartrate thermoreversible gels with increase gel strength were formulated by using different mucoadhesive polymers (carbopol 934P, polycarbophil,
HEC, and PVP) to have an extended release nasal formulation. The formulations were evaluated for above-mentioned evaluation parameter. In vivo testing of optimized formulations in normal human volunteers was done using HPLC method. The results revealed that the blood levels of metoprolol tartrate thermoreversible gels were sustained by formulation containing 15%w/w: 15%w/w of poloxamer 407:polxamer188 and carbopol 934P (0.4%w/w) as compared to tablet dosage form. Carbopol 934P has shown a penetration enhancing effect. Thus an extended release nasal gel of metoprolol tartrate can be developed using a combination of P407, P188 and C934P.

A novel approach of dispersing liposomes of propranolol hydrochloride in thermoreversible gel to sustain the release of drug when given by nasal route was tried. Liposomes of propranolol hydrochloride were prepared by using $3^3$ factorial design by the method of reverse phase evaporation. Satisfactory percentage drug entrapment was achieved to disperse the liposomes in thermoreversible gel. All the gels were evaluated and optimized by the evaluation parameters mentioned above. It was observed that poloxamer 407 gels have potential to retain their thermoreversible property even after dispersion of liposomes of propranolol hydrochloride in the thermoreversible gel. Diffusion studies showed that polymer is the major rate-controlling factor for diffusion of drug. The formulation of liposomes of propranolol hydrochloride dispersed in thermoreversible gel showed a retarding effect on the diffusion of drug. Also the result of gamma scintigraphy shows that the formulation of thermoreversible gel in which liposomes of PH are dispersed remains in the nasal cavity for upto 8 hrs indicating significant bioadhesion.

Sumatriptan succinate thermoreversible nasal gel with penetration enhancers (EDTA, Sodium glycocholate and transcutol), pluronic lecithin organogel and nasal patches with different polymers (Pemulen and carbopol 934P) were formulated. All the gels were evaluated and optimized by the evaluation parameters mentioned above. Pluronic lecithin organogel and transcutol showed good release of sumatriptan succinate from the thermoreversible gel formulations. Pluronic lecithin organogel was optimized by using $3^3$ factorial design to have gelation temperature near $37^\circ C$. Nasal patch formulation of sumatriptan succinate showed a satisfactory in vitro performance. Pemulen was found to be a better polymer for preparing nasal patch as compared to carbopol 934P. Satisfactory reduction in headache was shown by sumatriptan succinate nasal gel when used in-patient suffering from migraine.
Attempt was made to prepare a water-soluble derivative of chitosan. The derivative formed was water-soluble but it had less bioadhesive force and also it showed less retarding effect on diffusion of drug as compared to chitosan. Structural changes were observed in the synthesized derivative of chitosan.

The present work shows that the gelation temperature of poloxamer depends on its concentration. PEG 4000 and propylene glycol can modify the gelation temperature and thus can be used to optimize the formulation. Studies also revealed that the above-mentioned drugs are compatible with polymers used. Drug also changes the gelation temperature. Moreover, no toxic effect was seen on nasal mucosa of sheep when histopathological test was performed in vitro. During in vivo studies the volunteers and patients did not feel any discomfort when the formulation was administered in the nasal cavity. This reflects the safety of the optimized formulations used.

In conclusion, this study performed with various in situ gelling formulations of PF127 reflects that these bases are suitable for delivery of drug for nasal route. With modification of polymer and excipients concentration the base can be used for number of drugs to have a sustained release effect as well as a formulation with penetration enhancing effect. Along with this system, extended release nasal insert drug delivery system can be formulated with carbopol 934P and pemulen.