4. Summary

The nasal route of administration for systemic drug delivery offers a number of advantages compared to conventional routes, especially for peptide and protein drugs. Numerous nasal dosage forms have been developed but, except for nasal solutions, none of them have yet entered the market. Nasal solutions, however, have a limited ability for extended drug delivery, which would be advantageous when chronic treatment is required.

In situ gelling nasal inserts. The aim of this work was the development and characterization of in situ gelling nasal inserts: a new, bioadhesive, solid dosage form for the prolonged systemic drug delivery via the nasal route. The principle of the dosage form is to imbibe nasal fluid from the mucosa after administration and to form a gel in the nasal cavity to avoid foreign body sensation. This gel adheres to the nasal mucosa due to its bioadhesive properties. In addition, it acts as release controlling matrix, thus allowing sustained drug delivery. Due to dissolution of the gel and / or mucociliary removal towards the nasopharynx, there is no need to remove the insert mechanically after it is depleted of drug.

The sponge-like structure of the nasal inserts is an important parameter to ensure rapid hydration and gelation at the nasal mucosa resulting in high water uptake by capillary forces and thus to reduce the foreign body sensation. The in situ gelling nasal inserts were therefore prepared by lyophilisation of aqueous solutions of drug, polymer as carrier and other excipients if required.

Initial studies were conducted to investigate the potential of polymeric excipients to form the sponge-structure and thus to allow rapid fluid uptake due to capillary forces as hypothesized. Next, the effect of the polymer type on the properties of nasal inserts, methods to control the drug release from inserts, and the influence of the drug species as well as the release medium composition on the release behavior were investigated. Low molecular weight model drugs were used for these in vitro studies. Further on, the application range of in situ gelling nasal inserts was broadened to low solubility drugs and protein antigens for nasal vaccination.

Effect of the polymer type. In situ gelling inserts can be prepared from various water-soluble polymers. The sponge-like structure of nasal inserts was formed by amorphous, but not by crystalline polymers during the freeze-drying process. The selected polymer dictated principal insert properties like water uptake behavior, bioadhesion potential, mechanical properties, and drug release profile. The bioadhesion potential was governed by the water uptake and dissolution of the polymer gel as well as by the ability of the polymer to interact with mucin / agar. Hydration of inserts made from low viscosity polymers resulted in polymer dissolution and consequent fast drug release (HPMC E5, Na-alginate, PVP 90). Water uptake and drug release of inserts from high viscosity polymers extended over more than 8 h (carrageenan, Carbopol®, NaCMC, xanthan gum, HPMC K15M). Taken together, the release of oxymetazoline HCl from nasal inserts prepared from different polymers was a complex phenomenon composed of multiple single processes such as drug-polymer interactions, water uptake and polymer mass loss during hydration, as well as the viscosity of the hydrated inserts. The hardness of different dry PVP inserts was successfully correlated with the glass transition temperature of the polymers. The elasticity of nasal inserts depended on the structure of the inserts formed during freeze-drying. Among the polymeric carriers tested, carrageenan and xanthan gum had the most promising in vitro properties with respect to bioadhesion, water uptake and polymer dissolution, drug release profile, and mechanical properties of in situ gelling nasal inserts.

Drug release rate control. Further studies have concentrated on the manipulation of the drug release rate from inserts while maintaining the other insert properties, e.g. mechanical properties and bioadhesion potential, within acceptable ranges. An important prerequisite was to maintain fast water uptake for rapid gel formation, high bioadhesion potential to allow long nasal retention times, and sufficient mechanical properties for patient handling. Four different approaches were investigated: variation of the polymer content, addition of freely water-soluble additives, variation of the polymer molecular weight, and the use of polymer blends.

The drug release rate increased with decreasing polymer content of the nasal inserts as expected. Accelerating the drug release by reducing the polymer content was limited by the decreased mechanical stability of the inserts and possibly reduced bioadhesive properties. The upper limit in the solution concentration is determined by the processability of the polymer solutions, e.g. during polymer dissolution or the lyophilisation process, which primarily depends on the solution viscosity.

The incorporation of freely water-soluble additives, like mannitol, sorbitol and xylitol, did not enhance the water uptake of in situ gelling nasal inserts. Also no effect on the drug release was observed. The additives influenced the inserts' mechanical properties depending on their hygroscopicity (increased brittleness with the non-hygroscopic mannitol, strongly reduced hardness with the hygroscopic sorbitol). This limited the amount of additives in the inserts. Taken together, addition of freely water soluble additives was no feasible approach to control the drug release rates of nasal inserts.

Inserts prepared from polymers of lower molecular weight released drugs more rapidly, as demonstrated for diprophyllin from Na-alginate and carrageenan inserts. However, polymer dissolution and polymer / drug interactions have to be considered when using this approach to control the drug release from nasal inserts. Thus, carrageenan inserts, which did not disintegrate during the study and showed electrostatic interaction with oxymetazoline HCl, released this drug independent of the polymer molecular weight. For Na-alginate inserts a negative effect of polymer molecular weight reduction on the bioadhesion as well as on the mechanical properties was demonstrated. This led to the conclusion that polymer molecular weight variation is a possible but less desirable way to control the drug release from in situ gelling nasal inserts.

The use of polymer blends (carrageenan and Na-alginate) to prepare in situ gelling nasal inserts allows a broad control of the drug release rate from nasal inserts with the possibility of exact rate adjustment by choosing the appropriate polymer blend ratio. The blend ratio determined the effect of these blends on other inserts properties, e.g. polymer solution viscosity, water uptake, and mechanical properties. The bioadhesion potential deteriorated above a threshold blend ratio of 1:19 and correlated with the mass loss. The blend of carrageenan with Na-alginate had a superior bioadhesion potential compared to Carbopol® or xanthan gum blends with Na-alginate, while the Na-alginate was exchangeable, e.g. by PVP 90 or HPMC E5. Acceptable mechanical properties were obtained with inserts prepared from all blend ratios. Overall, these findings render the use of polymer blends as drug release control tool for in situ gelling nasal inserts superior to variation of the polymer content, addition of freely water-soluble additives, and polymer molecular weight reduction.

Effect of the drug. The effect of the physico-chemical drug characteristics on the release properties of in situ gelling nasal inserts were investigate to understand the underlying mechanism. The release of different low molecular weight drugs (diprophyllin, oxymetazoline

HCl, APAP) from in situ gelling nasal inserts was compared. Drug-polymer interactions resulted in the slower release of oxymetazoline HCl from carrageenan inserts as compared to HPMC K15M inserts. The latter showed no dose effect. Diprophyllin loading did not influence the relative release rate from HPMC K15M and carrageenan inserts. Low drug solubility in case of APAP in hydrating HPMC K15M inserts resulted in reduced relative release rates with higher loadings. Results from film casting, differential scanning calorimetry, and scanning electron microscopy studies were used to explain the release data. In conclusion, the results showed that the main physico-chemical drug properties involved in the drug release process are (i) solubility, when its is locally exceeded, (ii) the physical state in the solid inserts, and (iii) electrostatic interactions between drug and polymer.

Effect of the release medium. In addition to the effect of the drug, the in vivo performance of in situ gelling nasal inserts can also be influenced by the conditions of the nasal fluid which may change under pathological conditions. Therefore, drug release and water uptake of in situ gelling nasal inserts in varying release media with respect to pH, osmolality, and ion content have been examined. Due to the neutral character of HPMC K15M and the absence of electrostatic interactions between HPMC K15M and the model drug oxymetazoline HCl, water uptake and release were not influenced by pH, sodium ion content and osmolality of the medium. Water uptake and oxymetazoline HCl release of carrageenan inserts were also independent of the osmolality. Effects of the sodium ion content on water uptake and release of oxymetazoline HCL from carrageenan inserts were attributed to the swelling behavior of carrageenan and ion exchange phenomena. Water uptake and drug release of carrageenan inserts were also susceptible to pH changes of the medium. This was associated with neutralization of charges at extreme pH-values and corresponding lower interaction. Overall, changes in the composition of the medium for water uptake and drug release can vary the behavior of nasal inserts with a possible impact on the in vivo performance.

Estradiol containing nasal inserts. The practically water-insoluble drug estradiol was chosen for further studies in order to extent the applicability of in situ gelling nasal inserts to a broad spectrum of drugs. The drug solubility was significantly increased by incorporation of estradiol into water soluble methylated β-cyclodextrin (MβCD). This solubilization of the poorly water-soluble drug estradiol by inclusion into MβCD allowed the incorporation of estradiol into in situ gelling nasal inserts. The cyclodextrin additive increased the viscosity of carrageenan solutions, reduced the bioadhesion potential of HPMC K15M nasal inserts, increased the moisture sorption of inserts and affected the mechanical properties of dry nasal inserts. The estradiol release was independent of the dose but partially influenced by the estradiol:MβCD ratio. In in vivo studies in situ gelling nasal inserts were compared with microparticles prepared by film grinding and a commercially available aqueous solution (Aerodiol®). In vivo estradiol levels after nasal application of Aerodiol® and microparticles resulted in rapid and high serum peaks. Nasal inserts led to a more gradual absorption of estradiol with lower peak serum levels and low serum level fluctuations. Gelled carrageenan inserts were still present in the nasal cavity 6 h post administration. Thus, in vivo studies showed the potential of nasal inserts based on carrageenan to deliver estradiol over a period of at least 6 h without initial high estradiol serum peaks.

Influenza vaccine containing inserts. Influenza split vaccine was successfully incorporated into nasal inserts without loss of the hemagglutinin-specific activity. The in vitro protein release from polymer solutions and inserts containing vaccine was incomplete, likely due to electrostatic binding of fractions of the vaccine proteins (hemagglutinin positively charged, nucleoprotein negatively charged) to the gelled polymer. In vivo with vaccine in polymeric solution studies revealed seric and local mucosal immune response in mice. Xanthan gum had immune response enhancing properties. Out of the adjuvants tested, DC-cholesterol and poly-L-arginine had the highest potential. Further in vivo immunization studies showed that also vaccine-loaded nasal inserts provoked an immune response. Nasal inserts have therefore also a potential as nasal vaccine delivery system although more investigations are necessary to elucidate the different performance of various polymers and enhancers and to further optimize the choice of materials.

In conclusion, in situ gelling nasal inserts are a promising alternative to current nasal drug delivery systems. They can incorporate and deliver a wide variety of drugs and can be adapted to different therapeutic requirements such as immediate or prolonged drug delivery.