Chapter 1
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Pain is a perception that signals the individual that tissue damage has occurred or may be occurring. It is subjective and very complex. The processes in the body that are involved in the perception of pain are called "nociception." Basic and clinical research during the past 50 years has confirmed that there are many mechanisms involved in nociception. Pain can be "acute" or "chronic." Acute pain lasts a short time, or is expected to be over soon. The time frame may be as brief as seconds or as long as weeks. Chronic pain may be defined as pain that lasts beyond the healing of an injury, continues for a period of several months or longer, or occurs frequently for at least months. One common classification based on mechanisms distinguishes pain into categories called "nociceptive," "neuropathic," and "psychogenic."

Nociceptive pain is believed to be caused by the ongoing activation of pain receptors in either the surface or deep tissues of the body. There are two types: somatic pain and visceral pain. Neuropathic pain is believed to be caused by changes in the nervous system that sustain pain even after an injury heals. In most cases, the injury that starts the pain involves the peripheral nerves or the central nervous system itself. It can be associated with trauma or with many different types of diseases, such as diabetes. Psychogenic pain is a simple label for all kinds of pain that can be best explained by psychological problems (Bonica et al., 1979).

Migraine headache is an episodic headache disorder. It is a common condition with a prevalence of 17.6% in females and 5.7% in males. An American Migraine Study estimated that 23 million persons older than 12 years of age have severe migraine headaches; however, this condition is under-treated and under-diagnosed worldwide. Not all headache sufferers seek medical attention, but those who do generally consult family practitioners, internists or paediatricians, ophthalmologists, and neurologists.

The treatment of migraine has not only medical but also serious economic and social implications (Capobianco et al., 1996).

While there are many variations, there are two main types of Migraines
• Migraine without aura (previously called common migraine). Almost 80 percent of migraine sufferers have this type of migraine.
• Migraine with aura (previously called classic migraine).

Hypotheses for the mechanisms of many aspects of migraine have been extensively studied (Welch et al., 1997). The aura symptoms are, most likely caused by a mechanism similar to spreading excitation and depression (Spierings et al., 1995).
Opioids remain the mainstay for the management of pain. Opioids are the first-line drugs for the treatment of moderate to severe pain but opioids must be administered with care. The effective dose required varies from individual to individual. As a result, the dose used must be titrated to avoid dose-related adverse side effects as well as inadequate analgesia. As with all analgesics, the effects of treatment must be constantly monitored, and changes in therapy should be made as indicated. Unfortunately, opioid-induced adverse side effects are common and can be serious. Common side effects of opioids include nausea, vomiting, sedation, and pruritus. Less common but more serious side effects include respiratory depression and sometimes cardiac arrest. Clearly, patient care includes appropriate monitoring and therapy for these events. In an effort to improve pain control and decrease the incidence and severity of drug-induced adverse side effects, many clinicians have introduced the use of non-opioids drugs like Tizanidine HCl and Cyclobenzaprine HCl for the management of pain (Ashburn et al., 1994).

The brain is a delicate organ, and evolution built very efficient ways to protect it. Unfortunately, the same mechanism protect it against intrusive chemicals can also frustrate therapeutic interventions. Despite enormous advances in brain research, brain and central nervous system disorders remain the world's leading cause of disability, and account for more hospitalizations and prolonged care than almost all other diseases combined. The major problem in drug delivery to brain is the presence of the Blood Brain Barrier (BBB). Drugs that are effective against diseases in the CNS and reach brain via the blood compartment must pass the BBB.

In recent years, the nasal mucosa has been considered as an administration route to achieve faster and higher level of drug absorption. The richly supplied vascular nature of the nasal mucosa coupled with its high drug permeation makes the nasal route of administration attractive for centrally acting drugs, which are not being effectively and efficiently delivered using conventional drug delivery approach to brain or central nervous system (CNS) due to its complexity. Intranasal drug delivery is one of the focused delivery options for brain targeting, as the brain and nose compartments are connected to each other via the olfactory route and via peripheral circulation. For some time the BBB has impeded the development of many potentially interesting CNS drug candidates due to their poor distribution into the CNS. Owing to the unique connection of the nose and the CNS, the intranasal route can deliver therapeutic agents to the brain bypassing the BBB. Absorption of drug across the
olfactory region of the nose provides a unique feature and superior option to target drugs to brain.

Scientists have also focused their research toward intranasal administration for drug delivery to the brain especially for the treatment of diseases, such as pain, epilepsy, migraine, emesis, depression and erectile dysfunction. The investigation till date has attracted researchers to place the intranasal drug delivery option under the microscope. Nevertheless, it is imperative to understand the uptake of drug across the nasal mucosa. From a kinetic point of view, nose is a complex organ since three different processes, such as disposition, clearance and absorption of drugs, simultaneously occur inside nasal cavity. For effective absorption of drugs across nasal mucosa, it is essential to comprehend the nasal anatomy and related physiological features of the nose (Lisbeth Illum et al., 2002). Intranasal mucoadhesive nanoparticulate systems improve mucosal absorption, because they strongly attach to the mucosa and increase the viscosity of mucin. Thereby they significantly decrease the nasal mucociliary clearance rate and thus increase the residence time of the formulation in the nasal cavity (Soane et al., 2001). Additionally, nanoparticles cross the mucosal epithelium better than microparticles do, since not only microfold (M) cells overlaying the mucosal associated lymphoid tissue (MALT) but also the epithelial cells are involved in the transport of NPs (Desai et al., 1996).

In recent years, the polysaccharide material, chitosan has attracted much interest as a nasal delivery system that is able to efficiently deliver polar drugs (including peptides) to the systemic circulation and provide therapeutically relevant bioavailability. Chitosan (poly [β -(1-4)-2-amino-2-deoxy-D-glucopyranose]) is a biodegradable cationic polysaccharide produced by partial deacetylation of chitin derived from naturally occurring crustacean shells. The polymer is comprised of copolymers of glucosamine and N-acetyl glucosamine. The term chitosan embraces a series of polymers that vary in molecular weight (from approximately 10,000 to 1 million Dalton) and degree of deacetylation (in the range of 50-95%). Since chitosan displays mucoadhesive properties, strong permeation enhancing capabilities for hydrophilic compounds and a safe toxicity profile (Singla et al., 2001), it has received considerable attention as a novel excipient in drug delivery system and has been included in the European Pharmacopoeia since 2002. Despite its biocompatibility, the uses of chitosan in biomedical fields are limited by its poor solubility in physiological
media. Chitosan has an apparent pKa value between 5.5 and 6.5 and upon dissolution in acid media the amino groups of the polymer are protonated rendering the molecule positively charged. At neutral and alkaline pH, most chitosan molecules lose their charge and precipitate from solution. To improve the poor water-solubility of chitosan at physiological pH, several derivatives have been studied, for example, the modification of chitosan by quarterization of the amino groups (Sieval et al., 1998, Le Dung et al., 1994), N-carboxymethylation (Muzzarelli et al., 1982) and PEGylation (Saito et al., 1997, Ohya et al., 2000) have been reported. Moreover, chitosan was used to modify the surface of poly (D, L-lactic acid) (PDLLA) in order to enhance its cell affinity (Cai et al., 2002).

Thiolation of chitosan provide much higher mucoadhesive properties than polymers and the enhancement of mucoadhesion can be explained by the formation of covalent bonds between the polymer and the mucus layer which are stronger than non-covalent bonds such as ionic interactions of chitosan with anionic substructures of the mucus layer. These thiolated polymers are also known as thiomers that interact with cysteine rich subdomains of mucus glycoproteins via disulfide exchange reactions (Snyder et al., 1983) or via simple oxidation process. These thiolated chitosans have several advantageous features in comparison to chitosan, such as significantly improved mucoadhesive and permeation enhancing properties. Moreover, solutions of thiolated chitosans display in situ gelling properties at physiological pH values (Sreenivas et al., 2008, Andreas et al., 2003) and the strong cohesive properties of thiolated chitosans make them highly suitable excipients for controlled drug release dosage forms.

Chitosan in its protonated form facilitates the paracellular transport of hydrophilic drugs by combination of bioadhesion and a transient widening of the tight junctions in the membrane. N-trimethyl chitosan (TMC), a partially quaternized chitosan derivative, shows good water solubility over a wide pH range. Hence, soluble TMC has mucoadhesive properties and excellent absorption enhancing effects even at neutral pH. The quaternization of amino group with simplest alkyl group i.e. methyl is the unambiguous step towards comprehending the hypothesis (Kotze et al., 1998, Kotze et al., 1997).

The absorption promoting effect of chitosan has been found to be a combination of mucoadhesion and a transient opening of the tight junctions in the mucosal cell membrane. Over the past 30 years, chitosan nanoparticles preparation technique has
been developed based on chitosan microparticles technology. There are at least four methods available: ionotropic gelation, microemulsion, emulsification solvent diffusion and polyelectrolyte complex. The most widely developed methods are ionotropic gelation and self assemble polyelectrolytes. These methods offer many advantages such as simple and mild preparation method without the use of organic solvent or high shear force. Thus, they would be applicable to a broad categories of drugs including macromolecules which notorious as labile drugs. In general, the factors found to affect nanoparticles formation including particle size and surface charge are molecular weight and degree of deacetylation of chitosan. The entrapment efficiency is found to be dependent on the pKa and solubility of entrapped drugs. The drug is mostly found to be associated with chitosan via electrostatic interaction, hydrogen bonding, and hydrophobic interaction.

Tizanidine HCl is a centrally acting skeletal muscle relaxant, used for the symptomatic treatment of painful muscle spasms and spasticity. Furthermore, tizanidine HCl has analgesic properties and is used for the treatment of chronic headache, back pain and post operative pain. The problem associated with oral dosage form is tizanidine HCl having oral bioavailability about 21% mainly due to extensive first-pass metabolism and its mean elimination half-life is approximately 3 h.

Cyclobenzaprine HCl is a muscle relaxant. It works by blocking nerve impulses (or pain sensations) that are sent to your brain. Cyclobenzaprine HCl is thought to act primarily at brain stem (and to a lesser extent at spinal cord level) to relieve skeletal muscle spasms of local origin without altering muscle function. Cyclobenzaprine HCl is used together with rest and physical therapy to treat skeletal muscle conditions such as pain or injury. It is not useful for spasticity due to neurologic conditions such as cerebral palsy. Although centrally acting muscle relaxants like cyclobenzaprine HCl are also helpful in aborting a migraine headache. Estimates of mean oral bioavailability of cyclobenzaprine HCl range from 33% to 55% and Cyclobenzaprine HCl is eliminated quite slowly, with an effective half-life of 18 hours by oral administration.

1.2. Research envisaged

Objectives of the work were to develop and characterize drug loaded chitosan and modified chitosan (thiolated and trimethylated) nanoparticles for intranasal administration and stabilize it by lyophilization and assess its performance in-vitro and in-vivo to justify its role in alleviation of pain and migraine. Centrally acting
drugs, tizanidine HCl and cyclobenzaprine HCl, having low dose but first pass effect and low bioavailability were selected for these investigation.

It is hypothesized that drug loaded nanoparticles prepared after modification of chitosan will provide high mucoadhesive property is due to the formation of covalent bonds between the thiol groups of thiolated chitosan and cysteine residue and the formation of ionic bond between positively charged trimethyl chitosan and negatively charged sialic groups on the mucus protein structure and mucoadhesion will dilate mucosal tight junction facilitating paracellular transport of hydrophilic drugs across mucosal barriers. These chemical modifications of chitosan will lead to enhance solubilities of derivatized chitosan and results into reversible disruption of mucosal barrier. Hence, improved mucoadhesion will results into enhanced permeation of drug and reduced mucosal toxicity.

The proposed plan of work may be divided into following specific aims:

I. Literature reviews covering mechanisms, barriers and various approaches to intranasal drug delivery.

II. Analytical method development for tizanidine HCl and cyclobenzaprine HCl for quantification of drug into nanoparticles formulations.

III. To prepare and characterize the thiolated chitosan and trimethyl chitosan.

IV. To prepare tizanidine HCl loaded/cyclobenzaprine HCl loaded chitosan/thiolated chitosan/trimethyl chitosan nanoparticles and to characterize them for particle size, zeta potential, entrapment efficiency, surface morphology and in-vitro drug release, nasal toxicity and mucoadhesive strength.

V. To study the stability of modified and unmodified chitosan nanoparticles with respect to appearance, particle size, zeta potential and drug content.

VI. To study the cell viability and cell permeation studies of modified chitosan, unmodified chitosan and its nanoparticles using RPMI 2650 cell line.

VII. To prepare and optimize the radiolabelled formulations in suitability for in vivo studies.

VIII. To study the pharmacokinetics and biodistribution of nanoparticles after intravenous, oral and intranasal administration in swiss albino mice.

IX. To study the gamma scintigraphy imaging in animals to ascertain nose to brain transport of drug.

X. To study the Pharmacodynamic effect of the drugs on suitable animal models.
1.3. References


