

SECTION I

Chapter 1 **Introduction**

1.1 INTRODUCTION

Headache- in particular migraine is one of the most common complaints encountered. Migraine is a chronic, incapacitating neurovascular disorder, characterized by attacks of severe headache, autonomic nervous system dysfunction, and in some patients, an aura involving neurologic symptoms. It affects a substantial fraction of world's population, with a higher prevalence in females (15-18%) than in males (6%) (Lipton et al, 2001) A recent survey by the World Health Organization (WHO) rates severe migraine, along with quadriplegia, psychosis and dementia, as one of the most disabling chronic disorders (Menken et al, 2000). At present, there are two theories for the existence of migraine headache: vascular theory and neuronal theory. The main goal of migraine therapy is to identify etiologic or exacerbating factors and eliminate them. In addition, prophylactic and abortive therapy may be employed to prevent, reduce duration and treat symptomalogies.

In the last two decades there has been tremendous progress in the acute therapy of migraine. The introduction of sumatriptan succinate belonging to a class of drugs know as 5HT_{1B/1D/1F} receptor agonists, for the treatment of migraine signaled the start of a new era in the management of this common disabling disorder (Vries et al, 1999). The 5-HT_{1B} receptor is located on intracranial blood vessels and CNS neurons. The 5-HT_{1D} receptor is located on CNS neurons and trigeminal nerve endings. 5-HT_{1F} receptors are located on trigeminal nerve endings. Sumatriptan is an agonist for a vascular 5- hydroxytryptamine (5-HT_{1D} /_{1B}) receptor subtype (a member of the 5-HT family), and has only weak affinity for 5-HT_{1F} receptors. It is effective in relieving the headache itself, as well as the debilitating associated symptoms such as photophobia and phonophobia. It constricts extracerebral intracranial vessels, inhibits trigeminal neurons and blocks transmission in the trigeminal nucleus. It minimally constricts human coronary arteries. It blocks plasma protein extravasation by activating prejunctional trigeminal 5-HT_{1D} and 5-HT_{1F} heteroreceptors, blocking neuropeptide release (Silberstein, 2004).

Sumatriptan is available in the oral dosage form and although oral administration of a drug is considered as most convenient, this route possesses particular problems when administering an anti-migraine drug to patients suffering from a migraine attack. Because of the episodic nature of migraine attacks, treatment options that rapidly and effectively minimize pain are needed, the problem encountered with this formulation is slow onset of

action (at least one hour). Oral route of administration is often impractical because of the high association of nausea and vomiting with migraine attacks. Up to 92 percent of patients have experienced nausea during a migraine attack, and 50 to 68 percent also have vomited (Silberstein et al, 1995). In addition, the absorption of oral medications may be delayed or diminished because of the high prevalence of gastro paresis during the attack (Tfelt et al, 1984).

Hence a means of directly inserting the drug into the bloodstream by parenteral route would be appropriate for the administration of an anti-migraine drug. However, the consequent pain, risk of infection, the complex procedures of self-administration and potential for low patient compliance make such parenteral administration undesirable. The intranasal route may be a viable alternative route of self administration whereby above limitations are overcome. Intranasal administration appears to be an attractive alternative because it avoids gastro-intestinal degradation, the hepatic first-pass effect, it allows for convenient and simple self-administration along, a direct route to the blood stream and proximity to the central nervous system (Chien et al, 1989). Following intranasal administration, transport of drugs to the brain circumventing blood-brain barrier (BBB) provides a unique feature and better option to target drugs to the brain (LeuBen et al, 1994). The nasal tissue being highly vascularized, nasal route has fairly rapid absorption and hence rapid onset of action can be achieved. However problem associated with nasal delivery of sumatriptan solution is lower retention time of solution in nasal cavity (<15 minutes) resulting in lower bioavailability as well as lower rate of transfer of the drug directly to the brain through olfactory pathway. After 15 minutes, sumatriptan is swallowed to GIT where remaining dose is absorbed. Although sumatriptan nasal spray provides faster onset of effect than the tablet but produces a similar headache response after about 2 hours (Lacey et al, 1995). Hence to overcome all the above drawbacks and facilitate efficient antimigraine therapy, there exists the need for the development of nasal drug delivery systems that would increase residence time in the nasal cavity associated with increased drug absorption. Very little research has been done on the development of intranasal formulation of antimigraine drugs, and hardly any report is available pertaining to research on increasing residence time of antimigraine drugs in nasal cavity and thereby enhancing its absorption into brain.

The major factor limiting the bioavailability of nasally administered polar drugs is poor ability to cross mucosal membranes and mucociliary clearance mechanism in the nasal cavity that rapidly removes non bioadhesive solutions and powders from the absorption site. To overcome these problems and to facilitate nasal absorption of polar molecules two main approaches have been used ; the modification of permeability of the nasal mucosal membrane by employment of absorption enhancers and use of bioadhesive systems, both liquid formulations and as powders, that decrease the mucociliary clearance of the drug formulation. Over the past few decades, the use of mucoadhesive polymers as a non-toxic alternative to enhancer systems has been investigated. Mucoadhesive drug delivery systems improve drug absorption by various mechanisms (Hochman et al, 1994). They first absorb water from their site of deposition, the mucus layer, leading to swelling and adhesion onto the mucus thereby slowing down the mucociliary clearance. Mucoadhesion also causes a transient widening of epithelial tight junctions (Hochman et al, 1994) and thus increases both the drug concentration gradient across the epithelium and its residence time within the nasal cavity; all these culminating in improved drug absorption.

Mucoadhesive polymers have been used to improve the bioavailability of several drugs. The cationic polymer, chitosan and polyacrylic acid polymers, carbomers and polycarbophil are very widely used in attempts to formulate mucoadhesive drug delivery systems for application to various mucosal sites. The compositions may adhere to the mucosa, at least to some extent, and this may facilitate retention of the composition of the mucosa and/or enhance the absorption of the active ingredient through the membrane and hence increases the bioavailability of the active drug as compared to when the drug delivery system is administered without said mucoadhesive material.

Microspheres, which are bioadhesive and which have desired release properties may also provide similar benefit as an absorption promoting agent. The ideal particulate size for nasal route of administration is 5-100 μm which promotes them to adhere to the nasal cavity wall, consequently increasing contact time.

Viscous solutions are also reported to increase residence time in the nasal cavity. However, application of the viscous solutions to the nasal cavity is unlikely. Therefore, application of in-situ gelling solutions of low molecular weight triblock copolymers of poly(ethylene oxide) and poly(propylene oxide) (Pluronic) exhibiting thermoreversible

properties have been proposed to lower the viscosity of the nasal formulations below the body temperature (Illum et al, 1999). By modulating the gelation temperature of different pluronic solutions, liquid bases for nasal use can be formulated which form a gel in the nasal cavity at body temperature with suitable gel strength resulting in enhancement of the residence time in the nasal cavity. They have been widely used for parenteral administration. Besides injectables, other administration routes such as rectal, vaginal, transdermal and ophthalmic have also been evaluated (Garipey et al, 2004). Pluronics are also reported to exhibit mucoadhesive potential. Furthermore, in order to fortify the adhesion of administered drugs onto the mucosal surfaces, mucoadhesive polymers such as polycarbophil, hydroxypropyl cellulose, polyvinylpyrrolidone have been added to the in situ-gelling liquids (Chu et al, 1991). However, there are very few reports on evaluating pluronics for intranasal drug delivery (Bromberg et al, 2001). Effect of addition of mucoadhesive polymer on rheological behavior, mucoadhesive strength and in vitro permeation across nasal mucosal membrane has never been studied. In the past no attempt has been ever done to study effect of pluronics or its combination with mucoadhesive polymer on permeation of drug across the mucosal membrane. Moreover, combination of non-ionic surfactant pluronic as thermoreversible polymer and cationic polymer chitosan glutamate as mucoadhesive polymer and absorption enhancing material has never been explored before as potential drug delivery system with number of advantages.

This thesis describes our attempt to develop and evaluate novel microparticulate system containing effective amount of sumatriptan as succinate salt and mucoadhesive polymer (chitosan glutamate and carbopol) which has the property of increasing the residence time in the nasal cavity and increasing absorption of sumatriptan across nasal membrane with delivery to intracranially located target sites. This local transfer of sumatriptan to target sites will not only result in rapid onset of action but also provides increased residence time for the formulation in the nasal cavity which results in highly effective antimigraine therapy. Although there are previous reports where carbopol microspheres are prepared by spray drying process, investigations have not been carried out on optimization of spray drying process parameters for the preparation and scaling of mucoadhesive microspheres of carbopol934P. Hence an attempt is also made to optimize spray drying process parameters using 2^3 factorial design to obtain uniform micronized products by reducing number of experiments. This thesis also describes our attempts to develop effective intranasal delivery systems of sumatriptan using thermoreversible polymer pluronic and

mucoadhesive polymer chitosan glutamate or carbopol 934P. The formulations were evaluated for rheological characteristics, mucoadhesive force and in vitro permeation across sheep nasal mucosa. As the receptors to sumatriptan are located intracranially, increased concentration of the drug in the brain would be highly beneficial. Hardly any research has been reported on exploring possibility of increasing brain concentration for effective treatment of migraine. Some reports are available on clinical studies pertaining to sumatriptan nasal spray for treatment of migraine, while no reports are available on the study of absorption of sumatriptan across the nasal cavity to brain and cerebro spinal fluid. Therefore in vivo pharmacokinetic studies of all the formulation was conducted in rat model after intranasal administration to rats. Drug levels were estimated in blood, brain and cerebro spinal fluid, using accepted technique to investigate transport of drug across the nasal membrane into the CNS using rat model (24). Cardiotoxicity of sumatriptan succinate incorporated in the formulations was evaluated using rat model. Further to evaluate antimigraine activity of the formulations and its effectiveness, pharmacodynamic study in rat migraine model was conducted.

1.2 OBJECTIVES OF THE WORK

1. Formulation, characterization and evaluation of chitosan glutamate and carbopol microspheres loaded with sumatriptan succinate.
2. Preparation and characterization of thermoreversible gel of pluronic loaded with sumatriptan succinate and drug loaded thermoreversible gel prepared by addition of mucoadhesive polymers chitosan glutamate and carbopol in addition to pluronic.
3. In vitro permeation study of drug and formulations.
4. Histopathological evaluation of nasal mucosa after permeation study to assess toxicological implications of the formulations on the nasal mucosa.
5. HPLC method development and validation for analysis of sumatriptan in plasma, brain tissue and cerebro spinal fluid.
6. In vivo pharmacokinetic study of different formulations after intranasal instillation in rat model.
7. To evaluate potential of formulations to increase transport of drug across nasal mucosa to important target sites located intracranially for improved antimigraine therapy.
8. To evaluate formulations for their cardiovascular toxicity on rat model.
9. To evaluate formulations for their antimigraine effect on rat model.

1.3 REFERENCES

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1.4 MATERIALS

Acetone - Qualigens, India

Acetonitrile - Qualigens, India

Ammonium phosphate monobasic – S.D Fine chemical Ltd., India

Benzylkonium chloride - S.D Fine chemical Ltd., India

Calcium chloride - S.D Fine chemical Ltd., India

Capsacain - Sigma Chemical, St. Louis, MO, U.S.A

Carbopol 934P – Himedia (India)

Chitosan glutamate – RITA Corporation, U.S.A

Di sodium hydrogen phosphate - S.D Fine chemical Ltd., India

EDTA (ethylene diamine tetra acetate) - Himedia, India

EGTA (ethylene glycol-bis(β -aminoethylether)- N,N,N',N' -tetraacetic acid) – Himedia, India

Ethyl acetate - Qualigens, India

Formaldehyde - S.D.Fine Chemical Ltd., India

Glucose - S.D.Fine Chemical Ltd., India

Glutaraldehyde - E.Merck India Limited, India

Heavy liquid paraffin - S.D.Fine Chemical Ltd., India

Hydrochloric acid - Qualigens, India

Hydroxylamine hydrochloride - S.D.Fine Chemical Ltd., India

Iso propyl alcohol - Qualigens, India

Light liquid paraffin - S.D.Fine Chemical Ltd., India

Magnesium sulphate - S.D.Fine Chemical Ltd., India

N-methyl D glucamine - Himedia, India

Ofloxacin – Alembic Chemicals Ltd., India

O-phosphoric acid - Qualigens, India

Petroleum ether, Qualigens, India

Pluronic F127 - Sigma Chemical, St. Louis, MO, U.S.A

Potassium chloride - S.D.Fine Chemical Ltd., India

Potassium dihydrogen phosphate - S.D.Fine Chemical Ltd., India

Propylene glycol - S.D.Fine Chemical Ltd., India

Rat CGRP Enzyme Immunoassay kit - SPIBIO, USA

Sodium bicarbonate - S.D.Fine Chemical Ltd., India

Sodium chloride - S.D.Fine Chemical Ltd., India

Sodium hydroxide - S.D.Fine Chemical Ltd., India

Soyabean oil- National chemicals, India

Span 85 - S.D.Fine Chemical Ltd., India

Sumatriptan succinate – Natco Pharmac Ltd. (India) and Cipla Ltd (India)

Trypan blue - Sigma Chemical, St. Louis, MO, U.S.A

Tween 80 - S.D.Fine Chemical Ltd., India

Urethane - Sigma Chemical, St. Louis, MO, U S.A