Chapter 2
Literature Review

2.1. MIGRAINE

Migraine is a common, chronic, incapacitating neurovascular disorder, characterized by attacks of severe headache, autonomic nervous system dysfunction, and in some patients, an aura involving neurologic symptoms (Goadsby et al, 2002). Migraine is characterized by episodes of head pain that is often throbbing and frequently unilateral and may be severe. It occurs in 6% of males and 15-18% of females, with the highest prevalence between the ages of 25 and 55 years. Attacks consist of moderate or severe headache, associated with nausea, vomiting, photo- and phonophobia. The headache lasts 4 to 72 hours and increases with physical activity. In about 15% of patients (*migraine with aura*), an aura may precede the migraine headache within about one hour The aura usually consists of visual symptoms such as fortifications, scotoma or hemianopsia, but may also be sensory (paresthesia), motor- (weakness, paresis) or speech-related (dysarthria, aphasia). 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. This ranking suggests that in the judgment of the WHO, a day with severe migraine is as disabling as a day with quadriplegia (Goadsby et al, 2002).

2.1.1 Migraine pathophysiology

Migraine is best understood as a primary disorder of the brain (Goadsby et al, 2001). It is a form of neurovascular headache: a disorder in which neural events result in the dilation of blood vessels, which, in turn, results in pain and further nerve activation (May and Goadsby, 1999). Migraine is not caused by a primary vascular event. Migraine attacks are episodic and vary within and among patients. We may best explain this variability by considering the basic biologic problem in migraine to be the dysfunction of an ion channel in the aminergic brain-stem nuclei that normally modulates sensory input and exerts neural influences on cranial vessels. Other factors such as hormonal changes and relaxation after stress (e.g. migraine attacks during the weekend) may also contribute. Although the initiation of migraine attacks has extensively been studied, the exact mechanism has not yet been identified. Recently, it was demonstrated with positron emission tomography that the brain stem is activated during migraine attacks, and that this activation persists even after amelioration of the headache by sumatriptan (Diener et al, 1997 and Weiller et al, 1995). This finding suggests that there may be a 'migraine generator', possibly located in the brain stem.
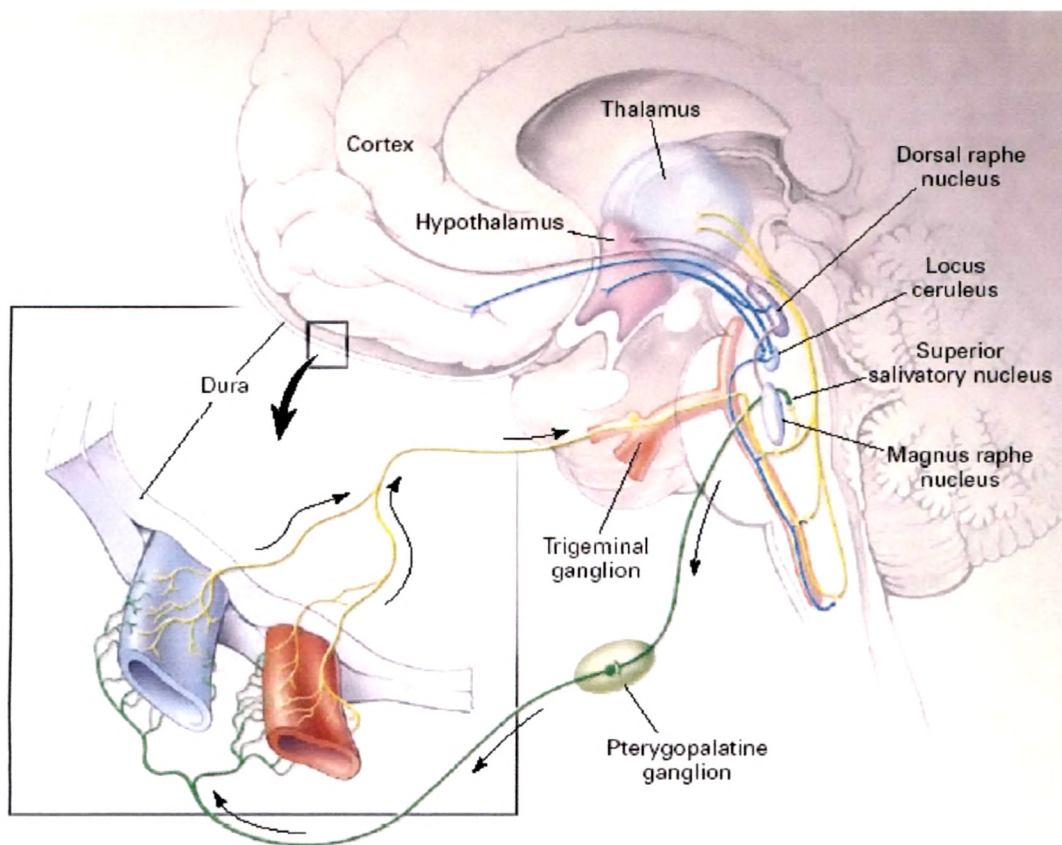
Figure 2.1. Pathophysiology of Migraine.

Migraine involves dysfunction of brain-stem pathways that normally modulate sensory input. The key pathways for the pain are the trigeminovascular input from the meningeal vessels, which passes through the trigeminal ganglion and synapses on secondorder neurons in the trigeminocervical complex. These neurons, in turn, project through the quintothalamic tract, and form synapse with neurons in the thalamus. There is a reflex connection between neurons in the pons in the superior salivatory nucleus, which results in a cranial parasympathetic outflow that is mediated through the pterygopalatine, otic, and carotid ganglia. This trigeminal–autonomic reflex is present in normal persons (Burstein et al, 2000) and is expressed most strongly in patients with trigeminal–autonomic cephalgias, such as cluster headache and paroxysmal hemicrania; it may be active in migraine. Brain imaging studies suggest that important modulation of the trigeminovascular nociceptive input comes from the dorsal raphe nucleus, locus ceruleus, and nucleus raphe magnus. (Goadsby et al, 2002)

Migraine aura

As mentioned above, the migraine aura is experienced by about 15% of migraine patients. The aura usually consists of visual symptoms (fortifications, scotoma, hemianopsia), but may also be sensory (paresthesia), motor- (weakness, paresis) or speech-related (dysarthria, aphasia). The aura may be caused by 'cortical spreading depression', a short-lasting depolarisation wave starting in the occipital cortex and moving across the cortex at a speed of 3-5 mm/min, followed by a depression of neuronal activity which induces a regional reduction in cerebral blood flow.

Headache phase

The reduced cerebral blood flow in the aura phase is followed by the headache phase, which is characterized by a vasodilatation of cranial extracerebral large arteries and arteriovenous anastomoses (e.g. in the dura mater, base of the skull and scalp). This vasodilatation probably may be assigned to increased neuronal innervation of the blood vessels Vasodilator peptides that may be involved include neurokinin A, substance P, calcitonin gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP). In addition, nitric oxide (NO) may be involved in the vasodilatation during a migraine attack. Dilated blood vessels may well be responsible for the pulsating headache during a migraine attack The cranial vasodilatation activates perivascular afferent terminals of the trigeminal sensory nerve that may then also release neuropeptides, continuing or intensifying the attack. Axonal conduction transmits nociceptive information towards the trigeminal nucleus caudalis and higher brain centres such as thalamus and hypothalamus for the registration of pain, photophobia, phonophobia and nausea (Figure 2.2).
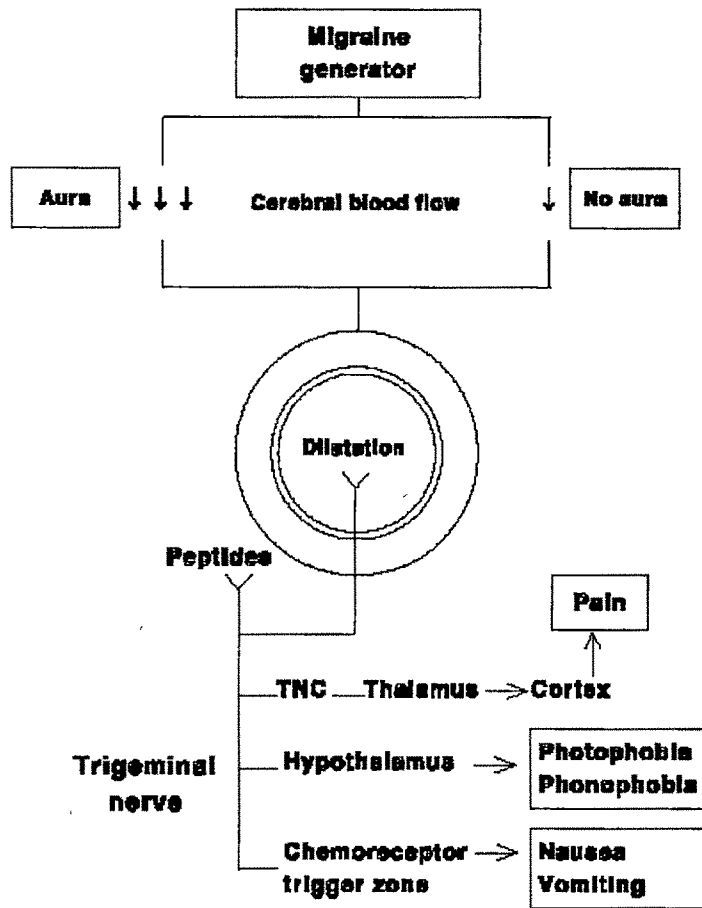
Migraine
generator

Aura ↓ ↓ ↓ Cerebral blood flow ↓ No aura

Dilatation

Peptides

Pain

TNC —Thalamus —>Cortex

Trigeminal
nerve

Hypothalamus —> Photophobia
Phonophobia

Chemoreceptor —> Nausea
trigger zone Vomiting

Figure 2.2 Diagram showing putative changes in migraine. (De Vries et al, 1999)

2.1.2. Serotonin (5-HT) receptors and migraine treatment

There are seven classes of 5-HT receptors: 5-HT1, 5-HT2, 5-HT3, 5-HT4, 5-HT5, 5-HT6, and 5-HT7 (Hoyer et al, 1994). In humanbeings, there are five 5-HT1 receptor subtypes: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F} (Hartig et al, 1996). 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 (Longmore et al, 1997). Ergots and triptans act at the 5-HT_{1B}, 5-HT_{1D}, and, in part, at the 5-HT_{1F} receptors. They constrict extracerebral intracranial vessels, inhibit trigeminal neurons, and block transmission in the trigeminal nucleus. They minimally constrict human coronary arteries. They block plasma protein extravasation (Markowitz et al, 1988) by activating prejunctional trigeminal 5-HT_{1D} and 5-HT_{1F} heteroreceptors, blocking neuropeptide release. Plasma protein extravasation can also be blocked by non-

steroidal anti-inflammatory drugs(Buzzi et al,1989), aminobutyric acid agonists (Lee et al, 1995), neurosteroids (Limmroth et al,1996), substance P antagonists (Lee et al,1994), and the endothelin antagonist, bosentan (May et al, 1996) Dihydroergotamine and the centrally penetrant triptans label nuclei in the brainstem and spinal cord involved in pain transmission and modulation (Goadsby et al and Gundlach et al, 1991). The caudal trigeminal nucleus is activated by stimulation of the sagittal sinus, and this activity is transmitted to the thalamus. Ergots and triptans suppress this activation.

2.1.3. Drugs for the acute treatment of migraine

Mild to moderate migraine attacks may be treated by non-specific drugs such as analgesics and rapidly absorbable NSAIDs such as aspirin, ibuprofen and paracetamol. Antiemetic compounds such as metoclopramide and domperidone are able to speed up gastric emptying and may thus, when taken early during a migraine attack, improve the absorption of other drugs. The combination of aspirin and metoclopramide has proven to be highly effective in the treatment of migraine. The specific drugs include the ergot alkaloids ergotamine and dihydroergotamine and 5-HT1B/1D receptor agonists (triptans), from which sumatriptan has been extensively studied. Some new triptans (zolmitriptan, naratriptan and rizatriptan) have been recently marketed and some others (eletriptan, almotriptan and frovatriptan) are expected to be marketed in near future.

Ergot alkaloids

For decades, ergot alkaloids have been the only specific drugs for the acute treatment of migraine. Although these drugs are widely used, their efficacy has been poorly demonstrated by controlled clinical trials. Ergotamine and dihydroergotamine are vasoconstrictors, but they also inhibit perivascular inflammation in animals. Ergotamine and, to a lesser extent, dihydroergotamine, may induce many side effects such as nausea, vomiting, vertigo, gastric symptoms, dry mouth, restlessness and, chest symptoms. In addition, incidental overdose or chronic overuse may induce ergotism, a rare but severe generalized vasospasm causing cyanosis, necrosis and infarctions of the heart and brain (Tfelt et al, 1999). More frequent are ergot-dependent headaches, which may occur when the ergots are taken more often than once per day per week (Ferrari et al 1998). The high occurrence of side effects is probably due to the fact that ergotamine and dihydroergotamine display affinity for a large number of receptors, among which α-

adrenoceptors, dopamine receptors and 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1F}$ and 5-HT2 receptors (Tfelt et al, 1999). Ergots have a low oral and rectal bioavailability and the clinical response is not related to the plasma concentration of the drug (Martin et al, 1995), which is due to the slow washout of these compounds from their receptor biophase (Martin et al, 1995).

The Triptans

In comparison with the ergot derivatives, the have distinct advantages -notably, selective pharmacology, simple and consistent pharmacokinetics, evidence-based prescription instructions, established efficacy based on well-designed controlled trials, moderate side effects, and a well established safety record (Welch et al,2001). The most important disadvantages of the triptans are their higher cost and the restrictions on their use in the presence of cardiovascular disease.

2.1.4. Pharmacology and Mechanisms of Action of triptans

The triptans are serotonin 5-HT$_{1B/1D}$–receptor agonists. The triptans all activate the 5-HT$_{1B/1D}$ receptor and, to a lesser extent, the 5-HT$_{1A}$ or 5-HT$_{1F}$ receptor. It is likely that the 5-HT$_{1B/1D}$–agonist activity is the primary mechanism of the therapeutic effects of these drugs, although a therapeutic action at the 5-HT$_{1F}$ receptor has not been excluded. We define a triptan as a 5-HT$_{1B/1D}$–receptor agonist (Goadsby et al, 2000). Triptans have three potential mechanisms of action: cranial vasoconstriction, peripheral neuronal inhibition, and inhibition of transmission through second-order neurons of the trigeminocervical complex (Goadsby et al, 2002).

Sumatriptan was designed to act selectively as a vasoconstrictor at 5-HT1 receptors in cranial blood vessels, but the drug also acts on 5-HT1 receptors located in peripheral human blood vessels Sumatriptan has affinity for the 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1F}$ and, although less, for the 5-HT$_{1A}$ receptors. The discovery of the relatively selective 5-HT1 receptor agonist sumatriptan was a major improvement in the acute treatment of migraine. The drug is highly effective and is generally well tolerated. However, sumatriptan also has some shortcomings such as low oral bioavailability (14%) and recurrence of the headache within 24 hours after initial headache relief in up to 40% of patients with initial good response (Visser et al, 1996). Furthermore, the drug is contraindicated in patients with coronary artery disease because of its potential to constrict coronary arteries.

Currently, six triptans are marketed (zolmitriptan, naratriptan, rizatriptan) or are expected to be launched in near future (eletriptan, almotriptan, frovatriptan). The triptans are all indole derivatives with chemical structures similar to sumatriptan. Standardised data on clinical efficacy are still limited. The second-generation triptans display slightly higher affinities at the 5-HT_{1B} and 5-HT_{1D} receptors than sumatriptan. In summary, all second-generation triptans seem to display pharmacodynamic properties not substantially different from sumatriptan. Most probably, the main differences between these compounds will be determined by their different pharmacokinetics. Since all triptans induce blood vessel contraction, it is to be expected that their ability to contract coronary arteries, eventually leading to myocardial ischemia, will be similar.
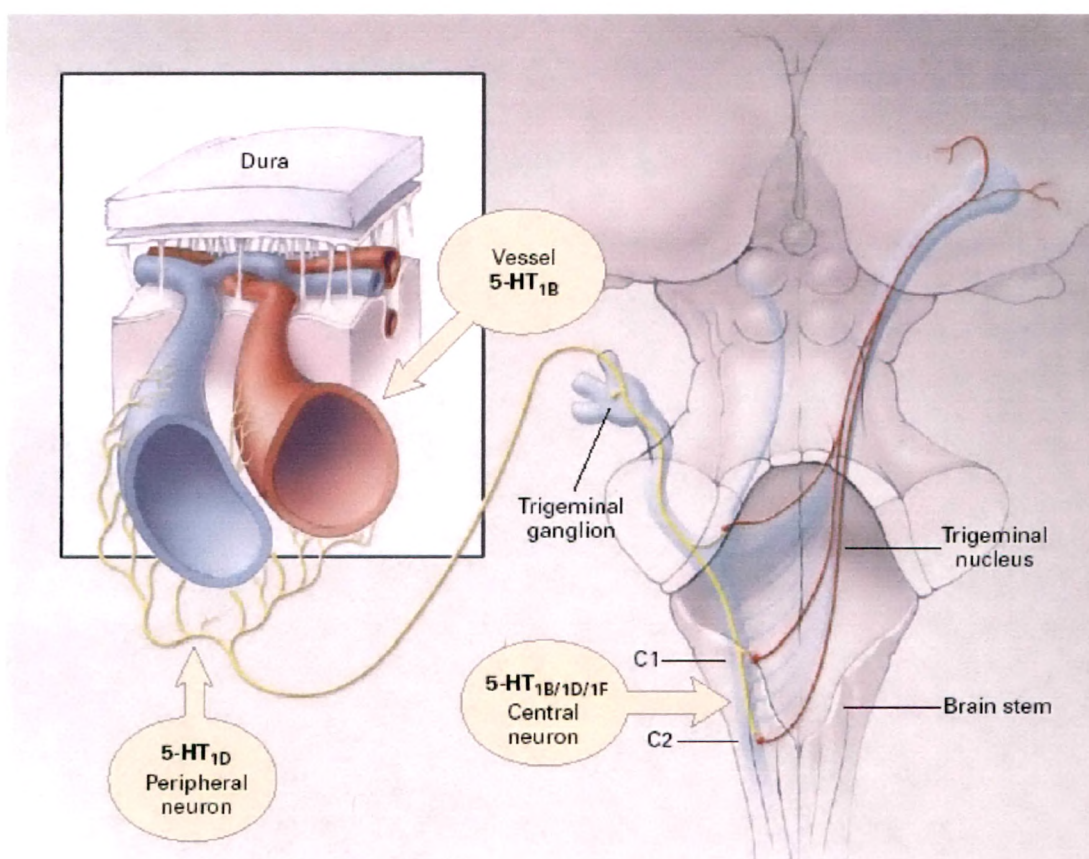

Figure 2.3 Possible Sites of Action of Triptans in the Trigeminovascular System.

2.1.5. Side effects of Triptans

The most frequent side effects are tingling, paresthesias, and sensations of warmth in the head, neck, chest, and limbs; less frequent are dizziness, flushing, and neck pain or stiffness. Triptans can constrict coronary arteries and may cause chest symptoms, sometimes closely mimicking angina pectoris. Such symptoms may cause alarm, so the cardiovascular issues warrant discussion. In rare instances, however, triptan therapy has been associated with myocardial infarction (Welch et al, 2001). There has thus been general concern about the safety of triptans. This concern is supported by in vitro pharmacologic studies that demonstrate the potential of the triptans to constrict the coronary vessels of humans, although ergotamine and dihydroergotamine have a more potent and longer-lasting effect than the triptans. It is clear from anatomical studies using antibodies selective for human $5\text{-}HT_{1B}$ or $5\text{-}HT_{1D}$ receptors that $5\text{-}HT_{1B}$ receptors are located primarily in the cranial circulation but are also found in the coronary circulation (Longmore et al, 1997). There have been relatively few reports of clinically important myocardial ischemia or infarction. However, all triptans are $5\text{-}HT_{1B}$ agonists, and thus the sensible contraindications of ischemic heart disease, uncontrolled hypertension, and cerebrovascular disease apply to the entire class.

2.1.6. Need for mucoadhesive nasal drug delivery system for sumatriptan

Although the triptans represent an important advance, they are ineffective in some patients. A crucial improvement would be a treatment for acute attacks that had lesser vascular effects — in other words, an antimigraine treatment with increased neural action. In addition, rapid onset of action and enhanced absorption to the cranially active target sites would be required for effective therapy. Nasal drug delivery systems that can enhance the residence time of sumatriptan in the nasal cavity and enhance the permeability across the olfactory epithelium to cranially located target sites would be highly beneficial as it would not only result in quicker onset of action but also result in reduced prevalence of recurrent headache at 2 hours, moreover targeted action to brain will result in dose reduction further reducing cardiac side effects.

2.2.NASAL DELIVERY SYSTEM

2.2.1 Introduction

Recently widespread interest has been generated among scientific community in use of nasal cavity as an alternative route of drug delivery for drugs susceptible to acidic or enzymatic degradation and hepatic metabolism High permeability of nasal mucosa in addition to richly supplied vasculature makes nasal route of administration attractive for many drugs, also it aids in avoiding aforementioned degradation (Chang and Chien, 1984). Furthermore large surface area of nasal cavity and relatively high blood flow promotes rapid drug absorption, another attractive feature of nasal drug delivery is patient compliance as self medication is easy and convenient compared to other more invasive alternatives The enhanced permeability of nasal mucosa for propanolol has been reported where concentration time profile similar to intravenous route of administration was obtained resulting in rapid onset of pharmacological activity.(Hussain et al,1980). Currently increasing number of systematically acting drugs is being delivered as nasal formulations ranging from protein to vaccines. Wide ranges of nasal formulations include amtimigraine drugs like sumatriptan, zolmitriptan, rizatriptan, ergotamine, butorphanol, where rapid onset of action is highly beneficial. Some of the peptides that have been successfully administered through the nasal route include buserelin, desmopressin, calcitonin, insulin, leuprolide, parathyroid hormone, interferon, oxytocin, leutinizing hormone releasing hormone, growth hormone , adrenocorticotrophic hormone,α-human atrial natriuretic peptide and heparin,which are normally administered by injection due to low membrane permeability and susceptibility to enzymatic degradation. Furthermore administration via nasal cavity has shown considerable systematic effects for various analgesics [buprenorphine, oxymorphone, butorphanol], steroids [testosterone, progesterone, estradiol, corticosteroids] and antihypertensives [hydrazaline, propranolol, nitroglycerine]. Nasal route apart from being explored for systemic delivery, is also been used for vaccination Reason for this is possibility of obtaining not only systemic immune response by nasal route of delivery but also achieving local immune response which will provide higher level of protection. Nasal route of administrating vaccines against plague, diphtheria, tetanus, influenza, cholera, pertussis and HIV has been proved to induce systemic as well as local immune response against the antigen (Majithiya and Murthy, 2004).

Recent developments have highlighted the possibility of exploiting the nasal route for direct transport of drugs from nose to brain in man. Targeting the brain via nasal administration of drugs offers potential due to presence of olfactory receptor cells in the nasal cavity which are in direct contact with the brain Absence of strict nose to brain barrier allows drugs to be delivered directly in the CNS. Drug will have to cross the olfactory membrane and also the arachnoid membrane surrounding the arachnoid space containing the CSF(depending on the pathway used) in order to reach the CNS from the nasal cavity.

Presence of olfactory pathway was first demonstrated in 1937 by Faber (Faber et al, 1937) who observed Prussian blue dye in perineural space of the olfactory nerve and subarachnoid space in the brain after administration of the dye in the nasal cavity of the rabbit. Existence of the pathway from the nose to brain has been confirmed by various studies in animal and in man, the concentration of cocaine in the brain was higher after nasal administration than after intravenous injection (Illum et al, 2000). It was shown recently that (^{3}H)-dopamine reached the olfactory lobe after nasal administration and 27 times higher concentration was achieved in the lobe compared to intravenous injection after 4 hours administration in the mouse model (Dahlin et al, 2001).

2.2.2 Nasal cavity:

Prime functions of nasal cavity are breathing and olfaction Physiologically, structure and function of the cavity are related to other important tasks like filtration, warming and humidification the inhaled air before it reaches lungs, this conditioning of the inhaled air is facilitated by the fluid secreted by the mucosa and high blood supply in the nasal epithelium (Chein et al, 1987). Moreover inhaled particles and microorganisms are trapped by the hairs covering the nasal vestibule or by the mucus layer; these particles are carried to the throat and further to oesophagus and finally gastro intestinal tract by mucocilliary mechanism which clears the mucus layer. The nasal cavity is divided into two non-connected halves by central septum of bone and cartilage. Each cavity consists of three regions, firstly the nasal vestibule, is region just inside the nostrils with an area of about 0.6cm^2 and is lined by skin like stratified squamous epithelium cells. Secondly, olfactory region, located on the roof of the nasal cavity in humans and forms about 10% of total area of nasal cavity and thirdly respiratory region consisting of the remaining area. The respiratory region is considered as major site of drug absorption into the systemic

circulation and it contains the three nasal turbinates, the superior, the middle and the inferior which are attached to the lateral wall of the nasal cavity. Respiratory epithelium is covered by pseudo stratified columnar epithelium, these cells are covered by microvilli and the major part of these cells is also covered with cilia. Large number of microvilli results in increased surface area responsible for relatively high absorptive capacity of nasal cavity whereas ciliated cells propel the mucus layer in a direction from the anterior towards the posterior part of the nasal cavity. Cilia beat with a frequency of 1000 strokes per min and the mucus layer is transported at the rate of 5mm per minute. The mucus layer is renewed every 15–20 min (Illum et al, 2003) and hence the formulations applied to human nasal cavity are cleared with clearance half life of 15 minutes (Soane et al, 1999).

The olfactory epithelium consists of pseudo stratified columnar cells of three types: olfactory receptor cells, supporting cells and basal cells, olfactory neurons are interspersed between the supporting cells. Olfactory receptor cells are specialized for detection of odorants. The olfactory region is unique in the CNS in that it is in direct contact with the environment. The route by which nasally delivered drugs can reach the cerebro-spinal fluid (which surrounds the brain and the actual brain tissue) is depicted in Figure 2.4. However of all other routes depicted, route of special interest is the transport of drug across the olfactory region in the nasal cavity directly into the brain tissue (e.g. olfactory bulb) or the CSF (cerebro spinal fluid).
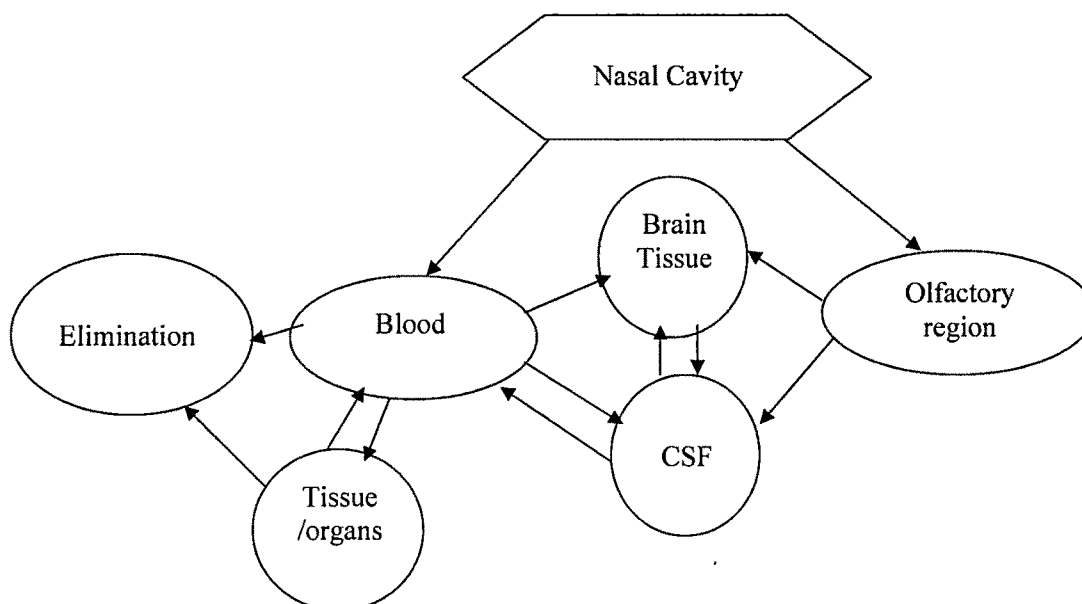
Figure 2.4 Possible route of transport of drug administered nasally

2.2.3 Factors influencing absorption of drugs across nasal epithelium

Factors influencing absorption are related to nasal physiology, physicochemical characteristics of drugs and formulation aspects.

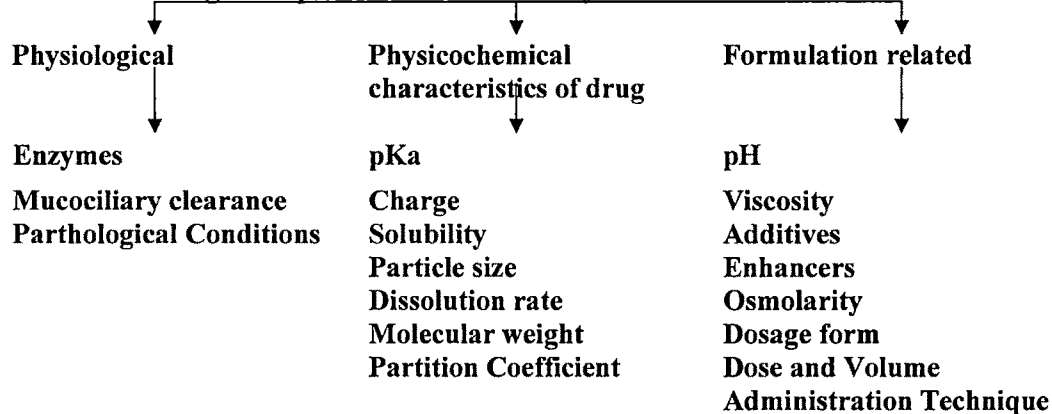**Factors affecting absorption across nasal cavity**

Physiological	Physicochemical characteristics of drug	Formulation related
Enzymes	pKa	pH
Mucociliary clearance	Charge	Viscosity
Parthological Conditions	Solubility	Additives
	Particle size	Enhancers
	Dissolution rate	Osmolarity
	Molecular weight	Dosage form
	Partition Coefficient	Dose and Volume
		Administration Technique

Figure 2.5 Schematic representation of factors affecting absorption across nasal mucosa

2.2.4 Olfactory region

Human olfactory region comprises of thick connective tissue lamina propria, upon which rests the olfactory epithelium. The olfactory epithelium is situated between the transnasal septum and the lateral wall of each side of the two nasal cavities and just below the cribriform plate of the ethmoid bone separating the nasal cavity from the cranial cavity Lamina propria has axons, bowmans bundle and blood vessels whereas epithelium consists of three different cells i.e. basal cells, supporting cells and olfactory receptor cells. Neurons are interspersed between supporting cells. The olfactory receptor cells are bipolar neurons with a single dendritic end extending from the cell body to the free apical surface where it ends in an olfactory knob carrying non-motile cilia, which extend above the epithelium. Neurons are 5-6 cells thick and at the basal end neuron tapers into slender non-myelated axon that joins with other axons into a bundle to form glomeruli (fillia olfactoria) in lamina propria region, surrounded by glial cells (and CSF) and penetrates into the cranial cavity through small holes in the cribriform plate. Nuclei are concentrated in middle third of epithelium (Uraih et al, 1990)
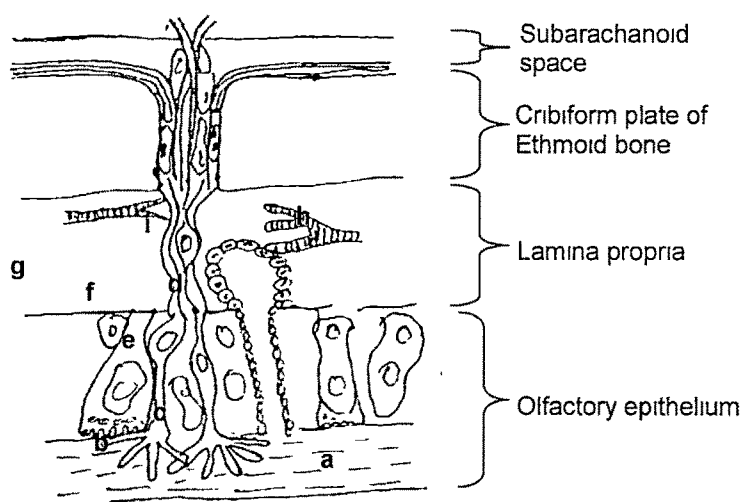
a-Mucus,b-Dendritic cells,c-Olfactory knob,d-Olfactory nucleus,e-Suppoting cells,f-Basal cells,g-Basal membrane,h-Bowman'sbundle,i-Filia olifactoria,j-Perineural space.

Figure 2.6. The olfactory epithelium of the nasal cavity and anatomical connection between nasal mucosa and CSF in the subarachnoid space outside the olfactory bulb(Modified from Mathison(Mathison et al,1998).

2.2.5 Transport Mechanisms along olfactory pathway

Olfactory pathway have been extensively reviewed by several authors, however Mathison et al(Mathison et al,1998) have broadly classified transport pathway from olfactory mucosa in the nasal cavity to CNS along olfactory neurons into two main pathway i.e axonal transport(olfactory nerve pathway) and olfactory epithelial pathway. For utilization of olfactory epithelial pathway, substance must be able to cross olfactory epithelium. The pathways across olfactory epithelium are similar to that with other epithelium. Substance can cross epithelial barrier wither by passive diffusion through supporting cell or Bowman's bundle or by paracellular route through tight junctions between supporting cells After entering lamina propria substances are transported through perineural space to the CNS, this pathway is depended on connection between nasal mucosa and subarachnoid space. The perineural space around olfactory neurons is extension of subarachnoid space and fluid in perineural space is in direct contact with CSF (Mathison et al, 1998). Thus transport via olfactory epithelium is more rapid compared to axonal transport. It has been shown that NGF was transported to CNS within 20 minutes after nasal administration to rat; this indicated that it was more likely that transport would have taken place through extracellular transport to CNS rather than axonal transport along olfactory neurons (Frey et al, 1997) Olfactory nerve pathway is useful for the agents that are able to enter olfactory receptor cells by endocytotic or pinocytotic mechanisms, which are further transported to olfactory bulb by intracellular axonal transport. Axonal transport to the brain is reported for hepatitis and vesicular stomatitis viruses (Huneycutt et al, 1994).

2.2.6 Factors affecting transport across olfactory epithelium

Factors affecting transport across olfactory epithelium are similar to that discussed above

2.2.7 Approaches to enhance nasal drug absorption

Intranasally delivered drugs show a rapid rise in peak blood concentrations, and several studies conducted in animal as well as human models have shown that peptide and protein drugs are absorbed across nasal epithelium within 5–15 min. However, contact time between drug and epithelial tissue in the nasal cavity plays important role in absorption of intranasally administered drug The nasal drug absorption is explained by two factors; the permeability of the nasal epithelium and the nasal mucociliary clearance. The first one is the relatively high permeability of the nasal respiratory epithelium for large molecules,

whereas diffusion path length across the nasal mucosal epithelium is short, consisting of only two cell layer. The second factor, nasal mucociliary clearance limits the residence time of drugs administered into the nasal cavity, decreasing the time available for the drug to be absorbed. Nasal bioavailability of drugs that are poorly absorbed from the nasal mucosa can be increased by increasing the nasal membrane permeability, or increasing the contact time for absorption by decreasing the mucociliary clearance rate. In order to increase contact time of formulation with the site of absorption in nasal mucosa polymer gels can be added to the formulation which will increase the viscosity of the formulation and hence reduce the nasal clearance rate Another way of increasing contact time of formulation with the nasal mucosa is by incorporating some mucoadhesive material in the formulation which will in turn provide increase absorption of the drug be adhering to the nasal mucosa and hence combating the problem caused due to mucociliary clearance mechanism. The three major approaches that have been attempted for enhancing absorption of drug across nasal cavity are the use of chemical enhancers to improve absorption, incorporation of enzyme inhibitors and increasing drug local residence time using mucoadhesive polymers (Illum et al, 2002).

2.2.8 Transport of agents from nose to brain

Euphoria derived from sniffing of cocaine in human subjects occurred rapidly within 3-5 min (Illum et al, 2002). This could be attributed to presence of direct pathway from nasal cavity to the CNS and capacity of drug to concentrate in specific regions of the brain, along with rapid absorption. Olfactory epithelium may serve as portal for entry into the brain It has been demonstrated in 1937 that bacteria's pneumococcus and S enteralis entered CNS via olfactory mucosa and perineural space after nasal administration to mice

By the study conducted by Sakane et al (Sakane et al, 1991), water soluble antibiotic cephalexin preferentially entered CSF after nasal administration as compared to i v. and intraduodenal administration in rats The levels in CSF were 166-fold higher 15 min after nasal administration than those of the other two routes. It was postulated that cephalexin was transported from the nasal cavity to CSF by passive diffusion, i.e. via the olfactory epithelium pathway. Wang et al (Wang et al, 1998) concluded that ^{3}H-Dihydroergotamine was able to enter the brain directly from the nasal cavity, with the olfactory bulb being a part of the direct passage from nasal cavity to brain.

The results of this various studies conducted in animal models using drugs like dopamine, methotrexate, zidovudine, progesterone, benzodiazepines etc showed significantly higher amounts of unchanged drug in brain tissue samples / CSF after nasal administration than after intravenous administration, indicating a direct pathway for this drug from the nasal cavity along the olfactory neurons into the brain.(Dahlin et al,2001)

It was reported that nasal administration of arginine-vasopressin (Pietrowsky et al, 1996), cholecystokinin-8 (CCK)(59), insulin (Kern et al,1999), an active fragment of adrenocorticotrophin (Smolnik et al,1999) and a corticotrophin releasing hormone(Kern et al,1996) etc in human models resulted in effects that are not seen after intravenous administration assuming a direct delivery of the compounds into the CNS

It is evident that in situations where it is necessary to target receptors in the brain, as for example for Parkinson's disease, treatment of Alzheimer's disease or the treatment of pain, a specific delivery to the CNS would be beneficial In such situations efforts should be given to the development of delivery systems capable of increasing the fraction of the drug that reaches the CNS after nasal delivery (Illum et al,2003).

2 .3 MUCOADHESIVE DELIVERY SYTEMS

2.3.1 Introduction

An alternative approach to improve nasal drug absorption is to increase the duration of formulation residence within the nasal cavity. This is achieved by the use of bioadhesive polymers. Bioadhesion is the ability of a synthetic or natural material to adhere to a biological tissue for a prolonged period of time (Longer & Robinson, 1986) Mucoadhesion means specially that the adhesive (mucoadhesive) interacts with the mucus covering of a biological tissue in such a way that the local residence time is prolonged. It involves interaction between mucin and a synthetic or natural polymer leading to a net attraction (Leung & Robinson, 1990). The use of mucoadhesives can solve a number of problems encountered in controlled drug delivery. It localizes the formulation at a particular region in the body, thereby improving the bioavailability of drugs with low bioavailability. The increased contact time and localization of the drug due to the strong interaction between the polymer and mucus is essential for the modification of tissue permeability. Furthermore, enzymatic activity can be locally inhibited to improve the bioavailability of drugs that are subject to enzymatic degradation.

This has been demonstrated for some mucoadhesive polymers such as Carbopol 934P and polycarbophil that inhibit the proteolytic enzyme trypsin, which can thus increase the stability of coadministered peptides (Leuben et al, 1994). Some studies have also demonstrated that mucoadhesive polymers can also directly interact with the epithelial tight junctions by increasing their permeability to administered drug molecules (Leuben et al, 1994) Nasally administered substances are rapidly cleared by MCC. Nasal mucoadhesive drug delivery has been under active investigation due to the peculiar advantages of the nasal cavity, in particular the opportunity to formulate controlled-release dosage forms (Ugwoke et al, 1999; Ugwoke et al, 1999a, b). The types of polymers used to improve the nasal bioavailability of several drugs and the levels of improved bioavailability obtained have been comprehensively reviewed (Kamath & Park, 1994; Dondeti et al, 1996).

Several theories have been put forward to explain the mechanism of polymer and mucus interactions that lead to mucoadhesion. The sequential events that occur during bioadhesion include an intimate contact between the bioadhesive polymer and the

biological tissue due to proper wetting of the bioadhesive surface and swelling of the bioadhesive. Following this is the penetration of the bioadhesive into the tissue crevices, interpenetration between the mucoadhesive polymer chains and those of the mucus. Subsequently low chemical bonds can become operative (Duchene et al, 1988).

Using a mathematical model that describes the rate processes involved in nasal drug delivery, the effect of bioadhesive carrier systems on the reduction of the mucociliary clearance rate constant can be simulated (Gonda et al, 1990). The simulations predict that bioadhesion may improve systemic bioavailability, and reduce the variability in nasal drug absorption caused by a variable pattern of drug deposition. The clearance of nasal preparation from the nasal cavity may also be influenced by the viscosity of the preparation. The rheological characteristics of the polymers determine their ability to reduce the mucus transport rates.

2.3.2 Nasal mucoadhesive drug delivery system

A number of mucoadhesive delivery systems have been investigated for intranasal drug administration. Spray preparations containing 0.25% methylcellulose have been reported to exhibit decreased mucociliary clearance (Harris et al,1988), resulting in a delayed absorption of nasally administered desmopressin, without affecting the bioavailability of desmopressin (Harris et al,1989). The clearance half-time of nasal spray solutions containing hydroxypropyl methylcellulose tended to increase with increasing concentration, but the differences between the concentrations were not significant (Pennington et al,1988). Studies on the nasal delivery of beclomethasone, formulated in a powder mixture with hydroxypropylcellulose as a bioadhesive, have shown that the formulation remains in the nasal cavity for as long as 6 h after application, with apparently no damage to the nasal mucosa (Nagai and Machida, 1990). Freeze-dried formulations of insulin and neutralized polyacrylic acid increased the nasal absorption of insulin in dogs, and the absorption was sustained with maximal plasma insulin levels 90 min (T max) after administration (Nagai et al, 1984). Hyaluronan and its autostrated cross-linked esters showed good adhesion in vitro, comparable with that of polyacrylic acid. Although the formulation of hyaluronan into microspheres tended to reduce its adhesive properties, the microspheres displayed significantly decreased mucociliary clearance on the frog palate (Pritchard et al, 1996). Chitosans have been proposed as novel nasal drug delivery systems because of their bioadhesive properties. In sheep, the

nasal absorption of insulin was increased after the administration of chitosan, and the Tmax was delayed from 20 min for a solution of insulin, to 75 min for a solution of 0.5% chitosan with insulin (Illum et al, 1994). The morphology of the nasal mucosa of rats was not changed after application of a chitosan solution for 60 min (Illum et al, 1994). Frog palate mucus clearance was transiently decreased by chitosan (Aspden et al, 1995). In rats, only a small amount of a 3% chitosan gel was cleared from the nasal cavity within 2 h (Zhou et al, 1996).

It was observed that the total clearance of a polymer gel formulation was not dependent on its initial clearance. Very viscous or fluid formulations demonstrated rapid initial bulk clearance, but if they were bioadhesive, their total clearance from the nasal cavity was limited (Zhou et al, 1996) In order to reduce nasal clearance and thereby increase nasal drug absorption, microspheres have been studied as nasal dosage forms (Illum et al, 1987).

2.3.3. Chitosan as a mucoadhesive material

Partial deacetylation of chitin results in the production of chitosan, which is a polysaccharide comprising copolymers of glucosamine and *N*-acetylglucosamine Chemically chitosan is Poly-β-(1,4)-2-Amino-2-deoxy-D-glucose Chitosan is the term applied to deacetylated chitins in various stages of deacetylation and depolymerization and it is therefore not easily defined in terms of its exact chemical composition (Zikakis, 1974). The degree of deacetylation necessary to obtain a soluble product must be greater than 80–85%. Chitosan is commercially available in several types and grades that vary in molecular weight between 10000 and 1000000, and vary in degree of deacetylation and viscosity.

Chitosan is a cationic polyamine with a high charge density at pH <6 5 (and so adheres to negatively charged surfaces and chelates metal ions). It is a linear polyelectrolyte with reactive hydroxyl and amino groups (available for chemical reaction and salt formation) (Singla et al, 2001) The properties of chitosan relate to its polyelectrolyte and polymeric carbohydrate character. The presence of a number of amino groups allows chitosan to react chemically with anionic systems, which results in alteration of physicochemical characteristics of such combinations. The nitrogen in chitosan is mostly in the form of primary aliphatic amino groups Chitosan therefore undergoes reactions typical of amines:

for example, N-acylation and Schiff reactions (Kumar, 2000) Chitosan dissolves readily in dilute and concentrated solutions of most organic acids and to some extent in mineral inorganic acids (except phosphoric and sulfuric acids). Upon dissolution, amine groups of the polymer become protonated, resulting in a positively charged polysaccharide (RNH^{+3}) and chitosan salts (chloride, glutamate, etc.) that are soluble in water; the solubility is affected by the degree of deacetylation A pharmaceutically acceptable chitosan salt (GMP grade) for nasal drug delivery is chitosan glutamate. Chitosan glutamate is preferred for nasal drug delivery system from the view point of tolerability. Chitosan is generally regarded as a nontoxic and nonirritant material It is biocompatible with both healthy and infected skin. Chitosan has been shown to be biodegradable.
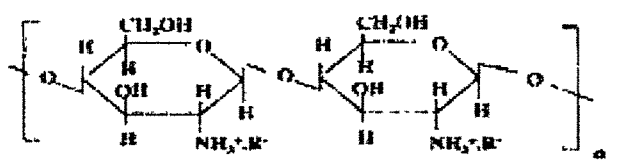
R= -OOCCH,CH,CHNHCOOH for chitosan glutamte

Chitosan is reported to be mucoadhesive material as well as it is also a preferred absorption enhancer It enhances drug absorption across mucosal membranes. The mechanism of action was suggested to be a combination of bioadhesion and a transient widening of the tight junctions in the nasal membrane. The viscoelastic properties of the mucus-chitosan complex render cilia unable to transport the particles over the surface of the infiltrated protective mucus blanket. The complex formed is believed to be the result of an interaction between the negatively charged sialic acid residues of the mucus and the cationic chitosan molecules. 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 material.

2.3.3a Applications in Pharmaceutical Industry

Chitosan is used in a number of pharmaceutical formulations. The suitability and performance of chitosan as a component of pharmaceutical formulations for drug delivery

applications has been investigated in numerous studies (Kumar, 2000). These include controlled drug delivery applications (Kubota et al, 1991), use as a component of mucoadhesive dosage forms (He et al,1999), rapid release dosage forms (Shirashi et al, 1990), improved peptide delivery (Leussen et al, 1994), colonic drug delivery systems (Leussen et al, 1997), and use for gene delivery (Leong et al, 1998). Chitosan has been processed into several pharmaceutical forms including gels (Kristl et al, 1993), films (Senel et al, 2000), beads (Sezer et al, 1999) microspheres (Ganza-Gonzalez et al, 1999), tablets (Sabnis et al, 1997) and coatings for liposomes (Takeuchi et al, 1996).

2.3.4 Carbopol as a mucoadhesive material

Carbopol polymers are synthetic high-molecular-weight polymers of acrylic acid that are crosslinked with either allylsucrose or allyl ethers of pentaerythritol. They contain between 56% and 68% of carboxylic acid (COOH) groups calculated on the dry basis. The molecular weight of carbomer resins is theoretically estimated at 7×10^5 to 4×10^9.
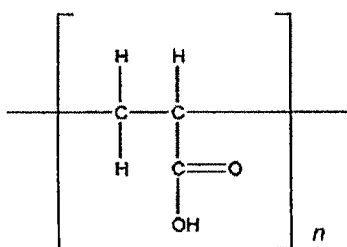
Acrylic acid monomer unit in carbomer resins

Carbopol polymers are formed from repeating units of acrylic acid. The monomer unit is shown above. The polymer chains are crosslinked with allyl sucrose or allylpentaerythritol.

Carbopol are used extensively in nonparenteral products, particularly topical liquid and semisolid preparations. They may also be used in oral formulations. Acute oral toxicity studies in animals indicate that carbopol 934P has a low oral toxicity, with doses up to 8g/kg being administered to dogs without fatalities occurring. Carbopol are generally regarded as essentially nontoxic and nonirritant materials; there is no evidence in humans of hypersensitivity reactions to carbopols used topically.

Carboxylic groups of carbopol gradually undergo hydrogen bonding with sugar residues in oligosaccharide chains in the mucus membrane resulting in formation of strengthened network between polymer and mucus membrane Thus carbopol having high density of available hydrogen bonding groups would be able to interact more strongly with mucin glycoproteins. In addition, carbopol may also adopt more favorable macromolecular conformation with increased accessibility of its functional groups for hydrogen bonding. It is speculated that the higher mucoadhesive strength of delivery system may lead to the prolonged retention and increased absorption across mucosal tissues (Luessen et al, 1995). Carbopol is also reported to demonstrate permeation enhancing properties. These

polymers were shown to express a high Ca^{2+} binding ability, which will result in altering integrity of tight junctions.

2.3.4a Applications in Pharmaceutical Industry

Carbopols are mainly used in liquid or semisolid pharmaceutical formulations as suspending or viscosity-increasing agents. Formulations include creams, gels, and ointments for use in ophthalmic (Amin et al, 1996), rectal (Morimoto et al 1987), and topical preparations (Tamburic et al, 1995) Carbopol have also been investigated in the preparation of sustained-release matrix beads (Neau et al,1996), as enzyme inhibitors of intestinal proteases in peptide-containing dosage forms (Luessen et al, 1996), as a bioadhesive (Woolfson et al, 1995) and for intranasally administered microspheres (Vidgren et al, 1992),and in magnetic granules for site-specific drug delivery to the esophagus (Ito et al, 1990)

2.4 MUCOADHESIVE MICROSPHERES

Mucoadhesive microspheres include microparticles and microcapsules (having a core of the drug) of 1–1000μm in diameter and consisting either entirely of a bioadhesive polymer or having an outer coating of it, respectively (Mathiowitz et al., 2001). Microspheres, in general, have the potential to be used for targeted and controlled release drug delivery, but coupling of bioadhesive properties to microspheres has additional advantages, e g efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, specific targeting of drugs to the absorption site. Prolonged release of drugs and a reduction in frequency of drug administration can highly improve the patient compliance for the drugs administered intranasally due to the reduction in mucociliary clearance of drugs adhering to nasal mucosa.

Use of mucoadhesive delivery systems increases the residence time of formulations in nasal cavity thereby improving absorption of drugs. It has been shown (Illum et al , 1987) by gamma scintigraphy study that radiolabelled microspheres made from diethyl amino ethyl dextran (DEAE–dextran), starch and albumin is cleared significantly more slowly than solutions after nasal administration in human volunteers. Hence, it was suggested by Illum et al that the intranasal application of bioadhesive microspheres (in powder form) causes them to swell on coming in contact with the nasal mucosa to form a gel and decrease their rate of clearance from the nasal cavity, thereby providing poorly absorbed drugs a longer time for absorption. The excellent absorption enhancing properties of mucoadhesive microspheres are now being used extensively for both low molecular weight as well as macromolecular drugs like proteins.

The concept of using a bioadhesive delivery system in the form of degradable starch microspheres (DSM) for nasal delivery of drugs was introduced in 1988. DSM system when combined with absorption enhancers, such as lysophosphatidylcholine (LPC), successfully improved the nasal absorption of gentamicin (Illum et al., 1988). The bioavailability of gentamicin was increased to 10% with the use of bioadhesive microspheres and was further increased to 57% by the addition of LPC to microsphere formulation.

The DSM/LPC system has also been proposed as an efficient method for delivery of insulin into the systemic circulation via nasal route (Farraj et al , 1990). A rapid and much higher absorption of the human growth hormone (hGH) has been observed when hGH was administered in the form of DSM/LPC system of microspheres (Illum et al., 1990).

Critchley et al. (1994) evaluated bioadhesive starch microspheres as a nasal delivery system for desmopressin, and observed significant improvement in the absorption of drug, both in terms of peak plasma levels and bioavailability A five-fold increase in maximum plasma concentration (Cmax) and a doubling of bioavailability was observed on addition of LPC in a concentration of 0.2% to the starch microspheres

Other bioadhesive microspheres used for nasal administration of peptides and proteins include the cross-linked dextran microspheres, which are water insoluble and water absorbable. Sephadex and DEAE–Sephadex were found to improve the nasal absorption of insulin, but to a lesser extent than the starch microspheres (Edman et al., 1992).

Hyaluronic acid ester microspheres were used for the nasal delivery of insulin in sheep and the increase in nasal absorption was found to be independent of the dose of microspheres in the range of 0.5–2 0 mg/kg (Illum et al., 1994).

Gelatin microspheres were evaluated for intranasal delivery of salmon calcitonin(sCT) in rat model. The AAC values after nasal administration of sCT in gelatin microspheres were significantly higher than that of sCT in PBS, indicating that the gelatin microspheres enhanced the nasal absorption of sCT compared to sCT solution (Morimoto et al, 2001). Nasal delivery of insulin using chitosan microspheres was found to reduce blood glucose level in diabetic rats to 67% of iv route and has an absolute bioavailability of 44% which seems promising (Varshosaz et al,2004)

The in vivo performance of mucoadhesive microspheres of salbutamol sulphate prepared using chitosan showed prolonged and controlled release of salbutamol as compared with oral administration of conventional dosage form (Jain et al, 2004).

Bioadhesive sodium alginate microspheres of Metoprolol tartrate (MT) for intranasal systemic delivery were prepared as an alternative therapy to injection, and to obtain

improved therapeutic efficacy in the treatment of hypertension and angina pectoris. In vivo studies indicated significantly high bioavailability for microspheres. The results thus indicate that all the microspheres were not only able to improve the bioavailability of drug by the intranasal route due to avoidance of first-pass effect, but also were able to provide sustained and controlled inhibition of isoprenaline-induced tachycardia as compared with nasal, oral, and I.V. routes (Rajnikant et al, 2003).

Lim et al evaluated biodegradable microparticles prepared using chitosan glutamate (CH), hyaluronic acid (HA) and a combination of both polymers for nasal administration of gentamicin .The bioavailability of gentamicin was poor when administered as a nasal solution (1.1%) and dry powder (2.1%) when compared with IV. However, the microparticulate systems composed of CH and HA/CH considerably enhanced the bioavailability of gentamicin (31.4 and 42.9%, respectively,) with HA microparticles inducing a less significant enhancement (23.3%).This study demonstrated that when HA and CH were combined in the HA/CH formulation, the polymers appeared to improve the absorption of incorporated gentamicin synergistically in comparison to the individual polymers, suggesting a promising nasal delivery system(Lim et al, 2002).

2.5 THERMOREVERSIBLE GELS

The nasal bioadhesive gels might be used to provide an enhanced bioavailability compared with oral delivery (D'Souza et al, 2005). A very good example for such a system is EnerB (Nature's Bounty Inc, NY), a vitamin B-12 supplement available in gel form. Aqueous solutions of some polymers undergo sol-to gel transition in response to temperature changes. Therapeutic agents such as drugs, cells or proteins might be mixed in a sol state and administered using a simple device. Viscous solutions are 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 triblock copolymers of poly (ethylene oxide) and poly(propylene oxide) (Pluronics) exhibiting thermoreversible properties have been proposed to lower the viscosity of the nasal formulations below the body temperature .

The Pluronics consist of more than 30 different non-ionic surface-active agents. These polymers are ABA-type triblock copolymers composed of PEO (A) and PPO units (B). The pluronic series covers a range of liquids, pastes, and solids, with molecular weights and ethylene oxide-propylene oxide weight ratios varying from 1100 to 14,000 and 1:9 to 8:2, respectively. Concentrated aqueous solutions of pluronics form thermoreversible gels. The gelation mechanism of poloxamer solutions has been investigated extensively, but is still being debated. Micellar mode of association has been indicated for its gelation behaviour. Micelle formation occurs at the critical micellization temperature as a result of PPO block dehydration (Zhou et al, 1988 and Bohorquez et al, 1999). With increasing temperature, micellization becomes more important, and at a definite point, micelles come into contact and no longer move. Also, packing of micelles and micelle entanglements may be possible mechanisms of pluronic solution gelation with increase of temperature (Cabana et al, 1997).

Pluronic PF 127 or polaxomer 407 is a ABA type block copolymer containing 70% of polyoxyethylene (PEO) fraction with a molecular weight of 12,500, and a structural formula

$$HO-[CH_2CH_2O]_x-[CH_2CHO]_y-[CH_2CH_2O]_x-H$$
$$\quad\quad\quad\quad\quad\quad\quad\quad\quad CH_3$$

EO   PO   EO
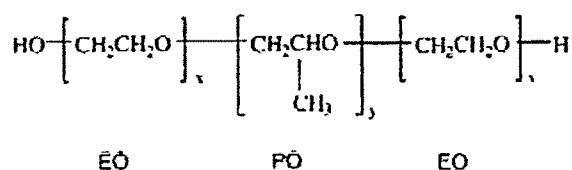
The reverse thermal gelation, high solubilizing capacity and non-toxic properties of PF 127 make it suitable for drug delivery compared to other pluronics. Pluronic PF 127 is more soluble in cold water than hot water. The cold solution process has been attributed to excessive hydrogen bonding between water molecule and ethereal oxygen of the polymer. The concentrated solutions are transformed from low viscosity transparent solutions at 5° C to solid gels on heating to body temperatures and the gelation achieved at elevated temperature is reversible upon cooling. Preliminary toxicity data indicate that this copolymer is well tolerated (Schmolka et al, 1972). Taken together, these results have prompted the use of pluronicF127 in the design of medical and pharmaceutical systems. Early studies evaluated pluronic F127 thermosensitive solutions for the treatment of burns (Schmolka et al, 1972), topical administration of anticancer agents (Miyazaki et al, 1984), and sustained delivery of drugs after extravascular parenteral injection (Johnston et al, 1989). Besides injectables, other administration routes have been evaluated, such as rectal(Choi et al,1998 and Ryu et al,1999), vaginal(Chang et al,2002 and Chang et al,2002), transdermal(Shin et al,2000 and Liaw et al,2000)and ophthalmic(Kamel et al,2002 and Wei et al,2002). Recently the development of thermoreversible nasal gels of Vitamin B12 using pluronic PF 127 which was aimed to improve systemic absorption and ease of administration was extensively studied by Pisal et al (Pisal et al, 2004) Aqueous PF127 gels show temperature-dependent gelation. Pluronic formulations generally increased drug residence time at application sites, resulting in improved bioavailability and efficacy. Some recent applications are reported in Table 2.1.

Table 2.2 Applications of pluronic F-127 in drug delivery

| Drug	Objective of the study	Reference
Recombinant human growth hormone	Controlled release of human growth hormone following intramuscular or subcutaneous administration.	Katakam et al, 1997
Insulin	Subcutaneous delivery of peptides and proteins having short half-lives.	Barichello et al, 1999
Vancomycin	Prolonged residence time of vancomycin in a body site with a high infection risk.	Veyries et al, 1999
Ibuprofen	Controlled release of ibuprofen for epidural analgesia.	Paavola et al, 2000
Paclitaxel	Intratumoral administration of paclitaxel.	Amiji et, 2002
Deslorelin or GnRH	Intramuscular sustained release of deslorelin and GnRH to induce the release of luteinizing hormone and formation of luteal tissue in cattle.	Wenzel et al,2002
Ceftiofur	Sustained release gel formulation of ceftiofur for treating foot infections in cattle.	Zhang et al, 2002
Acetaminophen	Increased bioavailability using an in situ gelling and mucoadhesive liquid suppository	Choi et al,1998
Propranolol	Increased bioavailability using an in situ gelling and mucoadhesive liquid suppository.	Ryu et al, 1999
Clotrimazole	Prolonged antifungal effects using an in situ gelling and mucoadhesive vaginal gel.	Chang et al,2002
Timolol maleate	Enhanced ocular bioavailability of timolol maleate.	Kamel et al, 2002
Piroxicam	Enhanced efficacy of piroxicam following percutaneous absorption.	Liaw et al,2000
Fentanyl	Poloxamer gels as release vehicles for percutaneous administration of fentanyl.	Shin et al, 2000
Interleukin-2	For intraperitoneal delivery	Johnston et al, 1992
Diclofenac and hydrocortisone	Topical gels	Tomida et al, 1987
Pilocarpine	Controlled occular delivery	Desai et al, 1998

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2.6 SUMATRIPTAN SUCCINATE

2.6.1 INTRODUCTION

Sumatriptan succinate has been shown to be effective in relieving migraine headache. Sumatriptan is an agonist for a vascular 5- hydroxytryptamine$_{1D}$ (5-HT$_{1D}$) receptor subtype (a member of the 5-HT$_{1A}$ family).

2.6.2 DESCRIPTION

2.6.2.1 Chemical Name. 3-[2-(dimethyl amino) ethyl]-N-methyl-- indole-5-methane sulphonamide, succinate (1.1)

2.6.2.2 Structural Formula:
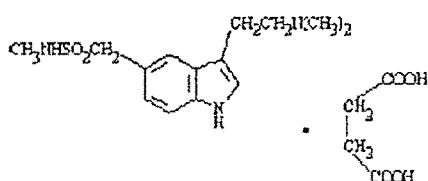
2.6.2.3 Molecular formula: C14 H21 N3 O2 S. C4 H6 O4

2.6.2.4 Molecular Weight: 413.5

2.6.2.5 Appearance and colour: White to off-white powder

2.6.3 PHYSICOCHEMICAL PROPERTIES

2.6.3.1 Solubility Freely soluble in water and in saline, sparingly soluble in methanol, practically insoluble in methylene chloride

2.6.3.2 Melting point 164.6°C-165.5°C

2.6.3.3. pH 4.5 to 5.3

2.6.3.4. Partition Coefficient (between n-octanol and water): log P = 1 07

2.6.3.5 Ultraviolet and visible spectrum. Ultraviolet and visible spectrum of sumatriptan succinate in water shows peak at 440nm and 282nm.

2.6.4 MECHANISM OF ACTION

Although sumatriptan's mechanism of action has not been established, suppression of migraine headaches may result from sumatriptan-induced decreases in the firing of serotonergic (5-hydroxytryptaminergic, 5-HT) neurons. Specifically, it is thought that agonist activity at the 5-HT $_{1D}$ receptor subtype provides relief of acute headache. Sumatriptan is a highly selective agonist at this receptor subtype; it has no significant

activity at other 5-HT receptor subtypes or at adrenergic, dopaminergic, muscarinic, or benzodiazepine receptors It has been proposed that constriction of cerebral blood vessels resulting from 5-HT $_{1D}$ receptor stimulation reduces the pulsation that may be responsible for the pain of vascular headaches. Studies in humans have shown that blood flow velocity in the middle cerebral arteries is significantly reduced during a migraine on the side of the headache, that relief of the headache by sumatriptan is accompanied by return of the blood flow velocity in these vessels to normal, and that sumatriptan treatment does not induce other changes in cerebral hemispheric blood flow. However, other studies have not consistently shown a significant correlation between dilatation of cerebral blood vessels and pain or other symptoms of migraine headaches, or between medication-induced vasoconstriction and relief of these headaches. Sumatriptan may also relieve migraines by decreasing release of neuropeptides and other mediators of inflammation and by reducing extravasation of plasma proteins. A study in humans has demonstrated that concentrations of calcitonin gene-related peptide, a substance that increases vascular permeability and promotes plasma protein extravasation, are elevated during a migraine and return to normal as the headache is relieved by sumatriptan (Dechant et al,1992).

2.6.5 PHARMACOKINETICS

Sumatriptan is rapidly absorbed after oral, subcutaneous and intranasal administration. The low oral (14%) and intranasal bioavailability (16%) is primarily due to metabolism (hepatic and presystemic) and partly due to incomplete absorption. Bioavailablity after subcutaneous administration is 97% compared to intravenous administration. It is rapidly and extensively distributed to tissues but passage across the blood-brain barrier is limited. It is less bound to plasma proteins (14-21%).The plasma half life is 2 to 2.5 hours. The volume of Distribution 170 lit. Significant relief begins about 10-15 minutes following subcutaneous injection, 15 minutes following intranasal administration and 30 minutes following oral administration (Product monograph-Imitrex).

2.6.6. METABOLISM

Elimination is Renal, via active renal tubular secretion, following hepatic metabolism. Sumatriptan is metabolized by monoamine oxidase (MAO), predominantly the A isoenzyme. In studies conducted in a limited number of patients, MAO inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure Non-renal clearance of sumatriptan accounts for about 80% of the total clearance. The major metabolite, the

indole acetic acid analogue of sumatriptan is mainly excreted in the urine where it is present as a free acid (35%) and the glucuronide conjugate (11%) (Product monograph-Imitrex)

2.6.7. TOXICOLOGY

No evidence of tumorigenicity and mutagenicity were found. Clinical signs observed following oral administration were generally minor and transient in nature and occurred predominantly at 500 mg/kg/day. These signs included post-dosing erythema, mydriasis, ataxia, salivation, subdued temperament, postural changes and moist eyes. The dogs also developed tachycardia lasting for several hours, often followed by bradycardia Sumatriptan-induced coronary artery vasospasm resulting in symptomatic myocardial ischemia and myocardial infarction has been documented in a few patients, primarily patients with a history of coronary artery disease or susceptibility to coronary artery vasospasm. Other less frequent side effects includes vomiting, nausea, discomfort in jaw, mouth, throat, tongue, nasal cavity, or sinuses, dizziness ,drowsiness, flushing , lightheadedness, muscle aches, cramps, or stiffness. In inhalation toxicity studies (dog, monkey), no irritants of the nasal passages or respiratory tract tissues was identified after intranasal administration of sumatriptan (Product monograph-Imitrex)

2.6.8. INDICATIONS

Sumatriptan succinate is indicated for the acute treatment of migraine attacks with or without aura (Product monograph-Imitrex)..

2.6.9 CONTRAINDICATIONS

Sumatriptan succinate is contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias (especially tachycardias). In addition, patients with other significant underlying cardiovascular diseases (e.g , atherosclerotic disease, congenital heart disease) should not receive sumatriptan succinate. As it may increase blood pressure it is contraindicated in patients with uncontrolled or severe hypertension. Concurrent administration of MAO inhibitors or use within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated. The use of sumatriptan succinate within 24 hours before or after treatment with other 5-HT receptor agonists, or ergotamine-containing

drugs or their derivatives is contraindicated. Sumatriptan succinate should not be administered to patients with severe hepatic impairment and hemiplegic, basilar, or ophthalmoplegic migraine. Sumatriptan injection should not be given intravenously because of its potential to cause coronary vasospasm (Product monograph-Imitrex)..

2.6.10. DOSAGE AND ADMINISTRATION

Oral- 25, 50 or 100 mg as a single dose. If necessary, additional doses up to 100 mg may be taken at intervals of at least two hours, up to a maximum of 200 mg a day.

Intranasal - 5 mg or 10 mg (1 or 2 sprays) in each nostril, respectively, or 20 mg (1 spray) into one nostril as a single dose.

Subcutaneous- 6 mg .An additional 6-mg dose may be administered, at least one hour after the first dose, if headache pain returns or increases in severity.

2.6.11. ANALYTICAL PROFILE

Various analytical techniques such as derivative spectrometry, ratio derivative spectrometry, TLC densitometry, high performance liquid chromatography (HPLC), LC-MS/MS are reported for the estimation of sumatriptan succinate in biological samples and pharmaceutical preparations

2.6.11.1 Spectrophotometry

Bebawy et al (Bebawy et al, 2003) reported first-derivative spectrophotometry and second-derivative spectrophotometry at 234 and 238 nm, respectively. These methods determine the drug in the concentration range 1.25- 10 µg/ml with mean percentage recovery 99.91% and 99 96% respectively. Bebawy et al (Bebawy et al ,2003) et al also reported ratio derivative spectrophotometric technique. The amplitude in the first derivative of the ratio spectra at 235 nm was selected to determine the sumatriptan succinate in the presence of its degradation products. Calibration graph is linear in the concentration range 1.25- 10 µg/ml with mean percentage recovery 100.19%. These methods for the determination of sumatriptan succinate in presence of its degradation products and in commercial formulations without interference from tablets excipients were successfully applied for determining sumatriptan succinate in bulk powder, laboratory-prepared mixtures and pharmaceutical dosage forms with good accuracy and precision.

2.6.11.2 Densiometric method

Bebawy et al (Bebawy et al, 2003) reported TLC-densiometric method where densitometric evaluation of thin-layer chromatography of sumatriptan succinate in the presence of its degradation products without any interference was done. Cyclohexane-dichloromethane-diethylamine (50:40:10 v/v/v) was used as a mobile phase and the diethylamine (50:40:10 v/v/v). The plate was removed, air dried and the spots were visualized under UV lamp at 254 nm. The chromatogram was scanned with spectrodensitometer at 228 nm. This method determines sumatriptan succinate in the concentration range 1- 8 µg per spot with mean percentage recovery 100.52%. The suggested methods can be used as stability indicating method for the determination of sumatriptan succinate in presence of its degradation products and in commercial formulations without interference from tablets excipients

2.6.11.3 Colorimetric method

Avadhanaulu et al (Avadhanaulu et al, 1996) adopted Salkowaski reaction for the determination of sumatriptan succinate which is generally applied for the colorimetric estimation of compounds which contain indole ring Reagent comprised of ferric chloride (1.5M) in 100 ml water and 60 ml of concentrated sulphuric acid Purple colour formed was estimated by spectrophotometer at 550nm after 30 minutes reaction time. Beer's law was obeyed in the range of 5-25µg/ml. The recovery obtained was 98-101%. This method can be applied for routine analysis of drug in its pure form and pharmaceutical preparations

2.6.11.4. LC-MS/MS

LC-MS-MS with atmospheric pressure chemical ionization has been reported by McLaughlin et al for quantitation of sumatriptan in human plasma. Sumatriptan were extracted using an automated solid-phase extraction technique on a C_2 Varian Bond-Elut cartridge The analytes were chromatographed using reversed-phase (nitrile) columns coupled via a heated nebulizer interface to an atmospheric pressure chemical ionization source. The chromatographic run times were less than 7 min. Both methods were precise, accurate and selective down to plasma concentrations of 0.5ng/ml (McLaughlin et al, 1996).

Dulry et al (Dulry et al, 1997) reported liquid chromatographic-electrospray-mass spectrometric assay for the determination of sumatriptan. The concentration of sumatriptan succinate was determined using a solid-phase extraction method and LC-ESI-MS analysis demonstrating the high sensitivity and specificity of the methods down to 0.5 ng/ml levels in rabbit plasma samples. The ion source was operated in the electrospray (ESI) mode and in the positive ion mode. A potential of 4.8 kV was applied to the needle electrode, producing charged liquid droplets at atmospheric pressure in a nitrogen sheath gas set at a pressure of 40 psi. The auxilliary gas was set at 15 ml min-I. A potential of + 5.8 V was applied to the capillary and + 44.6 V to the tube lens. The temperature of the heated capillary was set at 230°C

A liquid chromatographic tandem mass spectrometric method for the quantitative determination of sumatriptan in human plasma and urine has been developed and validated over the concentration range 0.2–20 ng/ml. Sumatriptan was extracted from human matrices using C_2 solid phase cartridges. The extracts were chromatographed on a C_{18} column, ionised using a heated nebuliser(500°C) assisted atmospheric pressure ionisation (API) interface and detected by MS:MS in the multiple reaction monitoring mode The corona discharge current was typically 4 mA and the orifice voltage was set at 40 V. The ions monitored were m/z 296→58 (Chenga et al, 1998).

Oxford et al (Oxford et al, 1989) reported liquid chromatographic mass spectrometric assay for the determination of sumatriptan in plasma using thermospray and interface tip of 148-152° with ion source at 250° and m/z 296 Separation was done on AASP C2 SPE cartridge and sample was chromatographed on Spherisorb ODS-2 column. This method had quantification limit of 2 ng/ml.

2.6.11.5. Voltametry

A voltammetric study of the oxidation of sumatriptan succinate (1:1) has been carried out at the glassy carbon electrode by Sagar et al (1992). This compound exhibited a single wave in Britton-Robinson buffer solutions of pH 2-11, with a maximum current at pH 5 0. The mechanism of oxidation was shown to be due to oxidation of the N-H group in the indole ring. Based on this study, a simple, rapid and sensitive voltammetric method was developed for the determination of the drug in a tablet dosage form

2.6.11.5. High performance liquid chromatography

S No	Mobile phase	Column	Type of sample	Determination at	Detection limit	Reference
1	Phosphate buffer (0.075 M,pH 7.0) methanol (35:65, v/v)	Spherisorb ODS-1 (5μm)	Human serum	Electrochemical detection at +0.55V	1 ng/ml	Dunne and Andrew (1996)
2	acetonitrile 25 mM, pH 7.5 sodium phosphate monobasic, (60 40, v/v).	C_{18} Column	Human plasma	Flourimetric detection at excitation of 225 nm and an emission wavelength of 350 nm.	1 ng/ml	Ge et al (2004)
3	ammonium phosphate monobasic (0.05 M)–acetonitrile (84.16, v/v)	C_{18} LUNA	residues on surfaces in the manufacture of pharmaceuticals	228 nm	9 ng/ml	Nozal et al(2002)
4	Phosphate buffer. acetonitrile(80:20,v/v), pH 6	Hypersil C_{18}	Pharmaceutical preparations	227nm	2 µg/ml	Shirsat et al (1998)
5	Phosphate buffer:methanol (40.60,v/v)	Shim Pak Phenyl	Pure drug form	230nm	0 5 µg/ml	Avadhanulu et al(1996 a)
6	0.0025M orthophosphoric acid : acetonitrile (95:5,v/v)	C_{18}	Pharmaceutical preparations	223 nm	200 ng/ml	Singh and Jain (1997)
7	Methanol . Buffer (60:40,v/v)	Spherisorb ODS-1	Blood and urine	Electrochemical detection at +0.8V	1ng/ml(blood) , 200 ng/ml (urine)	Andrew et al (1993)

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