CHAPTER - 1

INTRODUCTION

Developing new drug delivery systems are the forte of a pharmaceutical formulator, who is a specialist in dosage form design. Several approaches are available for rectifying potential problems arising in pharmacokinetic aspect or pharmacodynamic action or for enhancing the performance, of a pharmaceutical active ingredient. Among the numerous approaches, designing a new drug delivery system is an option in the era of patenting and intellectual property rights. This work was started with an objective to design a new drug delivery system for rapid relief from acute migraine.

Headache is a common condition affecting practically every human. Headache may be of different varieties, each of which has its own unique pain characteristics. The types of headache include tension, sinus, cluster, rebound and migraine.

1.1 MIGRAINE

Migraine is a very common neurobiological disorder that is caused by the increased excitability of the central nervous system. It is a primary episodic headache disorder characterized by various combinations of neurological, gastrointestinal and autonomic changes.¹ The word migraine is derived from the Greek word hemi crania (Galen about 200 A.D).² It is an incapacitating headache disorder of moderate to severe intensity.³ Migraine attacks are commonly unilateral and are usually associated with anorexia, nausea and vomiting. A report by World Health Organization classifies severe migraine as one of the most disabling chronic conditions. The aggregate impact reflects not only its attack characteristics like pain severity, duration and associated symptoms but also its impact on psychological well-being, family
dynamics and occupational performance. It imposes a substantial burden on the individual patient, as well as his/her family, employer and society as a whole. Migraine is differentiated from other types of headaches by proper diagnosis, based on the characteristics and associated symptoms of the headache. Worldwide almost 20% of the population suffers from this illness and in India approximately 15-20% of people are affected. The female to male ratio is 2:1, with predominantly females suffering more when compared with males.

1.2 CHARACTERISTICS OF MIGRAINE:

Migraine sufferers sometimes get a warning signal before the onset of the headache phase of a migraine attack. The warning signals apparent to the migraineur are classified as aura. The period of aura is preceded by a period classified as prodromal or premonitory period. The periods of aura and premonitory are present before the headache. The International Headache Society (IHS) defines aura as neurological symptoms that usually develop over 5-20 min and last less than 60 min. Headache may occur directly or after an aura free interval of less than 60 min.

The migraine attack consists of the following phases:

- Premonitory
- Aura
- Headache
- Resolution

PREMONITORY PHASE: Prodrome or premonitory symptoms may have physical and mental components. Symptoms occur hours to days before the onset of headache. The symptoms have been classified by clinical presentation as excitatory and inhibitory symptoms. Excitatory symptoms include, but are not limited to,
irritability, euphoria (being `high`), physical hyperactivity, excessive yawning, excessive sleepiness, increased sensitivity to light and sound, and craving for foods. Inhibitory symptoms include, but are not limited to, depression, mental withdrawal, and behavior sluggishness, feeling tired, poor concentration, muscle weakness, anorexia and fluid retention. They can include psychological, neurological, constitutional or autonomic features such as depression, cognitive dysfunction and bouts of food craving. The most common symptoms are feeling weary and tired, difficulty in concentrating and stiff neck. Poor functioning commonly predicts headache.

AURA PHASE: The migraine aura consists of focal neurological symptoms that precede, accompany, or (rarely) follow an attack. Aura usually develops over 5 to 20 min, lasts for less than 60 min, can be visual, sensory, or motor, and can involve language or brain stem disturbances. Auras vary in complexity. Simple auras include scotomata, simple flashes, specks, geometric forms and shimmering in the visual field. More complicated visual aura includes teichopsia/fortification spectra, metamorphopsia, micropsia, macropsia, zoom vision and mosaic vision. Paraesthesias are often cheiroaural: numbness starts in the hand, migrate up to the arm, and jumps to involve the face, lips and tongue.

HEAD ACHE PHASE: The typical headache is unilateral, of gradual onset, throbbing, moderate to mark in severity and aggravated by movement. Pain lasts for about 4 to 72 h in adults and 1 to 72 h in children. Anorexia is common. Nausea occurs in almost 90 % of the patients while vomiting occurs in about a third.

RESOLUTION PHASE: Tired, irritable, listless, scalp tenderness, mood changes are the commonly observed features in the resolution phase.
The general somatic symptoms accompanying migraine, in the order of frequency are sensitivity to light, blurred vision, nausea, tenderness about the scalp, dizziness or lightheadedness, lethargy, vomiting, retention of fluid, photopia, vertigo, anxiety, parenthesis, diarrhea, fortification spectra, nasal stuffiness, mild aphasia, syncope or near syncope, severe confusion, seizures, fever, hemi paresis or hemiplegia, ataxia and/or dysarthria (brain stem dysfunction)$^5$.

1.3 PATHOPHYSIOLOGY OF MIGRAINE

There are few theories associated with the pathophysiology of migraine. However, two important theories namely the vascular and migraine threshold theories are briefly explained.

VASCULAR THEORY: The vascular theory of migraine suggested that the headache was caused by the dilatation of blood vessels while the aura of migraine resulted from vasoconstriction. This theory is no longer considered plausible in isolation. While vasodilatation undoubtedly plays an important role in the severe throbbing headache, it is itself probably an epiphenomenon, resulting from instability in the central neurovascular control mechanism.

The alternative and widely accepted theory is that “migraine is a group of familial disorders with a genetic component and it is primarily neuronal dysfunction.” It originates in the central nervous system (CNS), leads to a sequence of changes intracranial and extra cranially that account for the different stages of migraine.

MIGRAINE THRESHOLD THEORY: This theory proposes that individuals prone to attack have a genetic migraine threshold that renders them susceptible to an attack upon exposure to some or any of a range of patient-specific trigger factors. Hormonal influences, environmental and physiologic stressors, low blood sugar, and
fatigue are all thought to determine this threshold. Once the threshold is exceeded, trigeminovascular discharge is thought to be responsible for inducing a migraine.

The role of 5-hydroxytryptamine (5-HT) in migraine is well proven. Alterations in the 5-HT release, affects the self aborting mechanism observed in the population. P-type neuronal calcium channels mediate 5-HT and excitatory neurotransmitter release. Dysfunction of the P-type neuronal calcium channel can impair release of 5-HT and predispose patients to migraine attacks or impair their self-aborting mechanism. Voltage-gated P-Q-type calcium channels mediate glutamate release, are involved in cortical spreading depression, and might be integral in initiating the migraine aura. 6

On reaching the threshold, a wave of depolarization spreads across the cerebral cortex from occipital to frontal regions at a rate of about 2 to 3 mm/min, resulting in brain ion dysfunction and secondary vasoconstrictor vascular events. These changes account for the progression and variety of symptoms that occur during the prodromal and aural phases.

The headache phase is probably due to the results from activation of meningeal and blood vessel nociceptors combined with a change in central pain modulation. It may be related to trigeminovascular activation. This activation results in the release of inflammatory neuropeptides such as substance P, neurokinin A and calcitonin gene-related peptide in the trigeminal vascular system. Among these substances, the neuropeptides interact with the blood vessel wall, producing dilation, plasma protein extravasation, and platelet activation. Neurogenic inflammation can also occur along with central sensitization. This, in turn, results in vasodilatation. It is suggested that in addition to the vasodilatation component of the pain, there is direct stimulation (via the thalamus) of the cortical pain areas situated in higher centers of
the CNS which produce the pain of headache. The aura is not prerequisite for an attack. The direct effects and the secondary vasoactive responses account for the headache in patients who have an episode without the aura.

The pathophysiology of the postdrome is unknown, but may represent a gradual recovery phase from the extreme neurological disruption that occurs during migraine.

During an episode, calcitonin gene-related peptide and not substance P is raised in external jugular venous blood. Superior sagittal sinus stimulation results in release of calcitonin gene-related peptide, but not of substance P.

The above mentioned theories still does not explain all the observed characteristics but are commonly followed for explaining the pathophysiological aspect.

1.4 TREATMENT FOR MIGRAINE:

Over the period of years treatment varied from appeasing spirits, blood-letting thereby purging the offending substance to bizarre suggestion of treatment by centrifugation. Currently the physicians and the patients have a wide array of therapeutic options for abortive migraine therapy ranging from non specific to specific therapy. Therapy using paracetamol, acetylsalicylic acid, non-steroidal anti-inflammatory drugs, and products containing one or more of caffeine, isomethptene, butalbital, codeine and / or opiates are categorized under non specific therapy. Specific medications include ergotamine, dihydroergotamine mesylate and the triptans.
The benefit of ergot alkaloid was exploited in the treatment of migraine in the year 1925 when, ergotamine was subcutaneously administered successfully for intractable migraine.\textsuperscript{10}

The role of 5-HT was highlighted in the migraine threshold theory and advances in the receptor mechanism and agonists for 5-HT signaled the advent of the ‘triptans’ – which are migraine specific medications. A new class of acute migraine specific medications, the ‘triptans’ was created in 1980s.\textsuperscript{11} The acute abortive treatment of migraine was revolutionized by the development of sumatriptan which is a highly selective 5-HT receptor agonist.\textsuperscript{12}

SEROTONIN (5-HT) RECEPTORS:-There are seven classes of 5-HT receptors namely 5-HT\textsubscript{1}, 5-HT\textsubscript{2}, 5-HT\textsubscript{3}, 5-HT\textsubscript{4}, 5-HT\textsubscript{5}, 5-HT\textsubscript{6}, 5-HT\textsubscript{7}.\textsuperscript{13} In humans there are six subtypes: - 5-HT\textsubscript{1A}, 5-HT\textsubscript{1B}, 5-HT\textsubscript{1C}, 5-HT\textsubscript{1D}, 5-HT\textsubscript{1E}, 5-HT\textsubscript{1F}.

The 5-HT\textsubscript{1B} receptor is located on intracranial blood vessels and CNS neurons.

The 5-HT\textsubscript{1D} receptor is located on CNS neurons and trigeminal nerve endings.

The 5-HT\textsubscript{1F} receptors are located on trigeminal nerve endings.

Ergots and triptans act at the 5-HT\textsubscript{1B}, 5-HT\textsubscript{1D} and inpart, at the 5-HT\textsubscript{1F} receptors by constricting extracerebral intracranial vessels, inhibiting trigeminal neurons and blocking transmission in the trigeminal nucleus. They minimally constrict human coronary arteries and block plasma protein extravasation by activating prejunctional trigeminal, 5-HT\textsubscript{1D} and 5-HT\textsubscript{1F} heteroreceptors, leading to blockade of neuropeptide release. The caudal trigeminal nucleus is activated by stimulation of the sagittal sinus, and this activity is transmitted to the thalamus. Ergot and triptans suppress this activation. In addition, sumatriptan reduced high concentrations of calcitonin gene-related peptide in a migraine attack and in animals.
during trigeminal ganglion stimulation. \(^{14}\) Sumatriptan relieved the headache and associated symptoms but did not normalize the altered cortical blood flow in the brain stem.

A figurative representation of action of triptans on brain stem is given in figure 1.

![Figure 1: Action of triptans on brain stem.](image)

The drug moiety may be effective for treating a disease condition, but the time of administration and the rapidity of action are of paramount importance, particularly in acute conditions. This is exemplified by the following statement
Central sensitization might play a key part in maintaining the headache. Triptans administered early prevented central sensitization: late triptan intervention did not reverse central sensitization.

Trigeminal sensitization during migraine attacks leads to development of cutaneous allodynia. Triptans can prevent, but not reverse, cutaneous allodynia. Without allodynia, triptans completely relieved the headache and blocked development of allodynia. In 90% of the attacks, with established allodynia, triptans provided little or no headache relief and did not suppress alldynia. However, late triptan therapy eliminated peripheral sensitization (throbbing pain aggravated by movement) even when pain relief was incomplete and allodynia was not suppressed. Early intervention might work by preventing cutaneous alldynia and central sensitization.  

An important consideration in the treatment modality for acute migraine attack is that, it is necessary to treat migraine early in the attack before pain escalates.

Patients with episodic migraine are advised to administer their acute medication as soon as possible after the recognition of their characteristic migraine headache, preferably with in 20 min, and before pain become moderate or severe. Literature review shows that triptans can prevent but not reverse central sensitization, a phenomena which occurs in many patients with migraine during acute attacks. Central sensitization leading to the clinical consequence of producing cutaneous alldynia appears to be resistant to therapy in migraine patients when the sensitization is developed fully. Acute therapy with triptans is significantly more effective when given while pain is mild and early administration of triptans has been shown to improve a wide range of headache response outcome.
1.5 ROUTE OF ADMINISTRATION

The route of administration is the way by which any drug in a dosage form is administered to the patient. The route selected governs many factors, namely:

- Rate of absorption of the drug
- Rate of distribution of the drug
- Onset of action
- Design of the dosage form
- Dose of the drug
- Ease of administration
- Patient acceptability

Table 1 shows the different route of administration and dosage forms designed for therapy of acute migraine.
<table>
<thead>
<tr>
<th>ROUTE</th>
<th>SPECIFICITY</th>
<th>MEDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>Nonspecific</td>
<td>Opioids, NSAIDs.</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>Specific</td>
<td>Dihydroergotamine mesylate</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td></td>
<td>Sumatriptan</td>
</tr>
<tr>
<td>Oral Tablets</td>
<td>Nonspecific</td>
<td>Paracetamol, aspirin, NSAIDs.</td>
</tr>
<tr>
<td></td>
<td>Specific</td>
<td>Triptans-sumatriptan, rizatriptan.</td>
</tr>
<tr>
<td>Orally disintegrating</td>
<td>Nonspecific</td>
<td>Paracetamol and caffeine</td>
</tr>
<tr>
<td>Tablets</td>
<td>Specific</td>
<td>Rizatriptan,Zolmitriptan</td>
</tr>
<tr>
<td>Intranasal spray</td>
<td>Nonspecific</td>
<td>Butorphanol</td>
</tr>
<tr>
<td></td>
<td>Specific</td>
<td>Dihydroergotamine mesylate, sumatriptan, rizatriptan</td>
</tr>
<tr>
<td>Rectal suppository</td>
<td>Nonspecific</td>
<td>Paracetamol, aspirin, NSAIDs.</td>
</tr>
<tr>
<td></td>
<td>Specific</td>
<td>Ergotamine,sumatriptan</td>
</tr>
</tbody>
</table>

NSAIDs – Non steroidal anti inflammatory drugs.
The major factors influencing choice of the medication and formulation for migraine treatment are:

- Time of onset of action
- Efficacy evaluated by decreasing the intensity or eliminating the headache
- Consistency of response
- Prevention of recurrence
- Tolerability by the patient
- Convenience and ease of administration
- Personal ability to swallow Tablets during an acute migraine attack
- Idiosyncratic and dose related side effects
- Economics- cost factors.

All the available medications have their own advantages and disadvantages. Migraine specific therapy is provided by the triptans and the first among the group was Sumatriptan. It is available in different dosage forms to be administered via different route of administration. All the currently available dosage forms have their own limitations. Table 2, gives the comprehensive therapeutic parameters for the different dosage forms of sumatriptan.
### TABLE - 2

**COMPARISON OF THERAPEUTIC PARAMETERS FOR DIFFERENT DOSAGE FORMS OF SUMATRIPTAN**

<table>
<thead>
<tr>
<th>Dosage form (Sumatriptan dose in mg)</th>
<th>Headache Response</th>
<th>Therapeutic gain</th>
<th>Pain free frequency</th>
<th>Pain free therapeutic gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet (100 mg)</td>
<td>59 (57-61)</td>
<td>29 (25-33)</td>
<td>29 (27-31)</td>
<td>20 (18-22)</td>
</tr>
<tr>
<td>Intranasal (i.n) (20 mg)</td>
<td>61 (55-78)</td>
<td>31 (28-43)</td>
<td>32 (27-37)</td>
<td>19.5 (11-28)</td>
</tr>
<tr>
<td>Subcutaneous (s.c) (6 mg)</td>
<td>69 (70-88)</td>
<td>50 (38-77)</td>
<td>48.5 (48-49)</td>
<td>45 (43-46)</td>
</tr>
</tbody>
</table>

In addition to the detail given, subcutaneous injection (dose 6 mg) has rapid onset of action, and peak plasma concentration was seen within 12 min. Bioavailability is 97% for sumatriptan when given as s.c injection.\(^\text{20}\)

Bioavailability of sumatriptan succinate from the tablet dosage form is about 14.3%. Oral administration did not provide full pain relief to more than 50% of the patients. Headache recurrence was reported in 30% of patients. Oral dose produces adverse effects to patients with cardiovascular risks and this was observed in s.c injection also. In addition there was no complete response. A complete response is defined as 2 hour (h) headache response, with no recurrence and no need for rescue medication.\(^\text{20}\)

The bioavailability of sumatriptan when given as intranasal spray (where sumatriptan is converted to sumatriptan hemi sulphate *in situ*) is 15.8%.
Nasal spray is associated with disagreeable taste and variability in absorption due to administration techniques. The other disadvantages of nasal formulations are nasal irritation and the need to administer second dose after two hours of the first dose.

Other anti migraine drugs which are available as nasal formulations are - dihydro ergotamine mesylate, butorphanol and zolmitriptan.

Sumatriptan undergoes first pass hepatic metabolism when administered orally which may be the reason for high inter subject variation in bioavailability. Low bioavailability is also due to this reason – that is 14 % on average, when all dosage forms are compared. 20

Designing a different dosage form, which can be given by different routes of administration, may be an option to improve bioavailability.

1.6 ASSOCIATED SYMPTOMS OF MIGRAINE

Common symptoms which are significant and incapacitating during a migraine attack are gastrointestinal disturbances, notably nausea and vomiting. These affect the drug efficacy, dosage form preference and the route of administration. 21 Gastric emptying may be delayed and oral drug absorption impaired during a migraine attack. Nausea can interfere with the ability to take oral medications and vomiting may result in drug loss. 22 Therefore the common modality in treatment is to administer an anti emetic drug followed by other medications. Commonly used anti nauseants are listed in Table -3.
TABLE - 3

ANTI-NAUSEANT DRUGS FOR MIGRAINE TREATMENT

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE (mg/day)</th>
<th>ROUTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domperidone</td>
<td>10-80</td>
<td>Oral</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>5-10</td>
<td>Oral / i.v</td>
</tr>
<tr>
<td>Promethazine</td>
<td>50-125</td>
<td>Oral / i.m</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>10-25</td>
<td>Oral / i.v</td>
</tr>
</tbody>
</table>

The non oral routes (parenteral), like intra venous (i.v), intra muscular (i.m), and s.c, intranasal, rectal may be exploited for migraine treatment.

The quick pain relief was an important criterion for selecting the drug. This was exemplified by the study conducted by Loder et al 23 who reported after an open labeled two period crossover study comparing patient preferences for rizatriptan 10 mg oral disintegrating Tablet versus sumatriptan 50 mg oral Tablet. The important reason cited for selecting rizatriptan was faster pain relief.

In this present work, nasal route of administration has been selected because intranasal administration appears to be an ideal alternative for systemic drug delivery; therefore a brief overview about nose is given below.

Nasal drug delivery has received intensive interest since ancient times and intranasal administration has been an accepted form of treatment in the Ayurvedic system of Indian medicine. Psychotropic drugs have been used as snuffs by natives of South America. In the past two decades, many drugs have been shown to achieve better bioavailability by self –medication via the nasal route. The nasal absorption has
been improved by co administering absorption enhancers, enzyme inhibitors, microspheres and bioadhesive or mucoadhesive polymer containing dosage forms.

The nasal route of administration has been widely used for local effects like decongestant and for treating allergic rhinitis.

The use for systemic administration is also possible and few drugs are given by nasal route for systemic absorption. The presence of olfactory region which acts as direct pathway between external environment and the central nervous system, has led to research the possibility that the intranasal route might be useful for a variety of centrally acting drugs.

1.7 ANATOMY OF THE NOSE:

The nose is a complex organ from a kinetic point of view because three different processes: deposition, clearance or translocation and absorption of drugs, take place inside the nose. For effective administration of therapeutic drugs through the nasal route, its anatomy and related physiological features must be taken into consideration. Nasal anatomy is designed to provide sizable resistance to air flow and to control the temperature and humidity of inhaled air.

In an adult, the surface area is about 180 cm$^2$ and the nasal cavity extends 12-14 cm, from the nostrils to the nasopharynx (throat) and is divided in two, laterally, by the nasal septum. The septum consists mostly of cartilage and skin, and therefore, the penetration of drugs is low. The nasal vestibule has the smallest cross-sectional area in the respiratory tract (approximately 0.3 cm$^2$) and extends from the entrance of the nostrils, which are guarded by vibrissae (hairs), to the anterior ends of the inferior turbinate. The lining of the vestibule changes from skin at the entrance, to squamous epithelium and then to ciliated columnar secretory epithelium at the turbinate. The
olfactory region of the nose is located towards the roof of the nasal cavity and is lined with non-ciliated neuro-epithelium. The remainder of the main nasal passage is lined with pseudostratified columnar secretory epithelium consisting of basal cells, goblet cells and columnar cells which may be ciliated or unciliated. Below the epithelium is the lamina propria. The blood vessels, nerves, serous glands, and mucus secretory glands are present in this region. The lamina propria also houses a dense network of capillaries, many of which are very permeable for drug absorption. Microvilli are found on the columnar cells which increase the surface area available for absorption. The intercellular spaces are filled with homogenous muco-protein like substances. The olfactory region is a small patch of tissue containing the smell receptors. Approximately 20% of the air flowing through the nasal cavity is directed upwards to the olfactory region. The most efficient area for drug absorption is the highly vascularized lateral wall of the nasal cavity: the mucosa lined over the middle turbinate or conchae. Figure 2 shows the anatomy of the nose. The blood perfuses the nasal cavity with a flow of 40 μl/cm for each 100 g of tissue.

Figure 2: Anatomy of the nose
The cell bodies of the olfactory cells are typically located in the middle and deeper regions of the epithelium. The nuclei of the second major type of cell, the supporting cells, are organized in a single layer closer to the mucosal surface. These supporting cells enclose the olfactory cells throughout the entire depth of the epithelium; tight junctions join the supporting cells and also appear at the junction with the olfactory nerve cells. The single dendrites of the olfactory cells terminate in olfactory knobs (with a slightly larger diameter than the dendrites), which extend above the epithelial surface and exhibit about 10 to 25 immobile cilia each.

The olfactory axons are 0.1 to 0.7 µm in diameter and form the olfactory nerve bundles after passing into the lamina propria. The bundles are surrounded by Schwann cells and perineural cells. The extracellular space inside the perineural cells is believed to be continuous with the subarachnoid space, surrounding the brain. This comprises, along with axonal transport, the suggested pathway taken by compounds exhibiting direct nose-to-brain transfer. The lamina propria also contains Bowman’s glands, responsible for the mucus production in the olfactory mucosa. High activities of both phase I and phase II enzymes have been found in the olfactory mucosa. It has been suggested that the physiological functions of this high metabolizing capacity are to terminate the olfactory signals and act as a nose-brain barrier.

1.8 ADVANTAGES OF THE NASAL ROUTE:

- It is a non-invasive route.

- Nasal devices offers ease, convenience and simplicity of self administration.

- The nasal cavity offers a readily accessible surface for drug delivery.
• The nasal cavity offers a relatively large surface area (180 cm²) for drug absorption.

• It can be used for eliciting both local and systemic effects. There is rapid absorption leading to shorter time to onset of effect.

• The rate and extent of absorption and the plasma concentration versus time profiles are relatively comparable to that obtained by i.v. medications.

• The rich vasculature and highly permeable structure in the nasal mucosa is advantageous.

• The drugs are not subjected to first pass hepatic metabolism if administered through the nasal route. When compared with the gastrointestinal tract’s pre-systemic clearance, the nasal cavity has low metabolic activity. This leads to higher bioavailability.

• When other routes of administration are unfeasible, for example in patients with nausea, vomiting, and swallowing difficulty then the drugs may be formulated for nasal delivery.

• When compared with injectables, this method does not produce any biohazardous waste.

• Patent life of a product may be extended by developing an alternative dosage form.

• There is a possibility that the drug can transport directly from nasal cavity to the brain via the olfactory route.
• The nasal route is highly recommended for acute pain relief after caesarean sections or in children.

• In case of analgesics, patients can self administer at convenient times when appropriate.

• Nasal administration often requires smaller amount of drug when compared to the oral route; hence, there is reduction of side effects.

• Nasal route provides safety with efficacy along with the economic efficiency of the health care system combined with patience compliance.

1.9 DISADVANTAGES OF THE NASAL ROUTE:

• Mucociliary clearance reduces the retention time of the drug within the nasal cavity. This limits the absorption of slowly absorbed drugs.

• Mucus barrier may function as a physical barrier for few drugs preventing their absorption.

• Presence of few metabolic enzymes will affect the bioavailability of the drug.

• Drugs with high doses cannot be administered by this route.

• Physiology of the nose is altered in the population to a greater extent; this may interfere with the absorption. Therefore reproducibility is questionable under diseased conditions.

• Drugs which irritate or sensitize the nasal epithelia are not administered by this route.
• The efficacy is reduced if the person has nasal disease (e.g. rhinitis, polyps).

• Nasal septal deviations may cause obstructions resulting in less amount of the drug delivered to the site.

• Repeated use can cause irritation and chronic inflammation.

1.10 FACTORS AFFECTING NASAL BIOAVAILABILITY

1.10.1 PHYSIOLOGICAL FACTORS

• Area: Though the total surface area available is about 160 cm$^2$, the convolutions of the turbinates and the microvilli increases the area. However, the effective surface area available is influenced by the type of dosage form from which the drug is administered.

• Blood supply: The rich blood supply results in rapid onset of action, which can be utilized.

• Contact time and mucociliary clearance: Contact time will influence how much drug crosses the mucosa. Clearance depends on the site of deposition. The nasal passage epithelium is covered by a mucus layer that is renewed every 10 to 15 min. The pH of the mucosal secretions ranges from 5.5 to 6.5 in adults and 5.0 to 6.7 in children. The mucus layer entraps particles, which are then cleared from the nasal cavity by the cilia. The mucus moves through the nose at an approximate rate of 5 to 6 mm/min resulting in particle clearance within the nose every 20 min. Figure 3 give a representation of mucociliary clearance in the nose.
The absorption of drugs is influenced by the residence (contact) time between the drug and the epithelial tissue. The mucociliary clearance is inversely related to the residence time and therefore inversely proportional to the absorption of drugs administered. Nasal mucociliary clearance can also be stimulated or inhibited by drugs, excipients, preservatives and/or absorption enhancers and thus affect drug delivery to the absorption site.

- **Disease**: Pathophysiological conditions like rhinitis, common cold, hay fever, sinusitis, asthma, nasal polyposis, Sjogren’s and Kartagener’s syndromes affect the absorption.

- **Enzymatic activity**: The nasal mucosa and fluids are shown to have exopeptidases and endopeptidases, which may cause enzymatic degradation. The olfactory region has more cytochrome P450 activity than the liver, due to high NADPH-cytochrome P450 reductase content. Other enzymes detected in the human nose include carboxyesterases and glutathione S-transferases.

**Figure 3: Mucociliary clearance of the nose**
• Immunological clearance: The excipients used in the formulation may induce immunological changes.

• Mucus barrier: This may hinder drug absorption and may also bind to the drugs.

• Transport mechanism: Paracellular route, transcellular route, carrier-mediated processes and endocytic processes play important role in nasal drug absorption.

1.10.2 FORMULATION FACTORS:

Physicochemical factors associated with the drug.

• Faster rate of absorption is dependent on the lipophilicity of the drug. Slower rate is dependent on molecular weight.

• Concentration: Drugs absorbed by passive diffusion are affected by concentration in the dose administered.

Factors associated with the dosage form:

• Delivery system: Deposition of the formulation in the anterior portion of the nose provides a longer nasal residence time. However, the anterior portion of the nose is an area of low permeability. On the other hand, depositing a drug in the posterior portion of the nose, where the drug permeability is generally higher, provides shorter residence time. The method of administration and properties of the formulation determine the deposition site. Nasal sprays were deposited anteriorly, after which small portions were cleared slowly into nasal pharynx by mucociliary clearance. In contrast, drops were deposited mostly posteriorly and were removed rapidly in large portions into the nasal pharynx.
• Formulation pH: The pH of a nasal formulation is important for the following reasons:
  • To avoid irritation of nasal mucosa;
  • To allow the drug to be available in unionized form for absorption;
  • To prevent growth of pathogenic bacteria in the nasal passage;
  • To maintain functionality of excipients such as preservatives; and
  • To sustain normal physiological ciliary movement.

• Lysozyme is found in nasal secretions, which is responsible for destroying certain bacteria at acidic pH. Under alkaline conditions, lysozyme is inactivated and the nasal tissue is susceptible to microbial infection. The formulation at a pH of 4.5 to 6.5 is considered to be ideal.

• Buffer capacity: Nasal formulations are generally administered in small volumes ranging from 25 to 200 µL with 100 µL being the most common dose volume. Hence, nasal secretions may alter the pH of the administrated dose. This can affect the concentration of un-ionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in-situ.

• Osmolality: Drug absorption can be affected by tonicity of the formulation. Shrinkage of epithelial cells has been observed in the presence of hypertonic solutions. Hypertonic saline solutions also inhibit or cease ciliary activity. Low pH has a similar effect as that of a hypertonic solution.

• Additives: Solubilizers, preservatives, antioxidants, humectants, and absorption enhancers affect drug absorption besides playing role in irritation of the nasal mucosa.
1.11 MECHANISM OF DRUG ABSORPTION

Several mechanisms have been proposed but the following two mechanisms have been considered predominantly. Nasal mucosa is reported to be a leaky epithelium. Transport across the nasal mucosa appears to be by parallel lipoidal pathways with oil and water solubilities and molecular weight providing an estimate of permeation. The first mechanism involves an aqueous route of transport, which is also known as the para cellular route. This route is slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. Poor bioavailability was observed for drugs with a molecular weight greater than 1000 Daltons.

The second mechanism involves transport through a lipoidal route that is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions.

Another special feature of this route of administration is that the neural connections between the nasal mucosa and the brain provide a unique pathway for noninvasive delivery of therapeutic agents to the central nervous system (CNS). Pathogen and toxic metals could be transported from the nasal mucosa to the CNS along neural pathways (from olfactory epithelium to the olfactory cortex). The neural connection is made via the olfactory neural pathway. This pathway provides both intraneuronal and extraneuronal pathways in to the brain. It is hypothesized that the extra neuronal pathway probably relies on bulk flow transport through perineural channels which deliver drugs.
1.12 FORMULATION DESIGN

Physicochemical properties of drugs

- Chemical Form: The chemical form of a drug can be important in determining absorption.

- Polymorphism: Polymorphism is known to affect the dissolution rate and solubility of drugs and thus their absorption through biological membranes. It is therefore advisable to study the polymorphic stability and purity of drugs for nasal powders and/or suspensions.

- Molecular Weight: A linear inverse correlation has been reported between the absorption of drugs and molecular weight up to 300 Daltons. Absorption decreases significantly if the molecular weight is greater than 1000 Daltons except with the use of absorption enhancers.

- Particle Size: Particle sizes greater than 10 µm are deposited in the nasal cavity. Particles that are 2 to 10 µm can be retained in the lungs, and particles of less than 1 µm are exhaled. This is observed for insufflations.

- Solubility and dissolution Rate: Drug solubility and dissolution rates are important factors in determining nasal absorption from powders and suspensions. The particles deposited in the nasal cavity need to be dissolved prior to absorption. If a drug remains as particles or is cleared away, no absorption occurs.

- Delivery Systems: The selection of delivery system depends upon the drug being used, proposed indication, patient population and last but not least, marketing preferences.
Some of these delivery systems and their important features are summarized below:

- **Nasal drops:** Nasal drops are one of the most simple and convenient systems developed for nasal delivery. The main disadvantage of this system is the lack of dose precision and therefore nasal drops may not be suitable for prescription products. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.

- **Nasal sprays:** Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose from 25 to 200 µL. The particle size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly.

- **Nasal gels:** Nasal gels are high-viscosity thickened solutions or suspensions. These preparations have slightly longer residence time in nasal region when compared with drops or sprays.

- **Nasal powders:** This dosage form may be developed if solution and suspension dosage forms cannot be developed due to lack of drug stability. The advantages to the nasal powder dosage form are the absence of preservative and provide superior stability of the formulation. However, the suitability of the powder formulation is dependent on the solubility, particle size, aerodynamic properties and nasal irritancy of the active drug and/or excipients. Local application of drug is another advantage of this system but nasal
mucosa irritancy and metered dose delivery are some of the challenges for formulation scientists and device manufacturers.

Formulations incorporate absorption enhancers to increase absorption. Generally, they act via any one of the following mechanisms:

- Inhibit enzyme activity;
- Reduce mucous viscosity or elasticity;
- Decrease mucociliary clearance;
- Open tight junctions; and
- Solubilize or stabilize the drug.

Absorption enhancers are generally classified as physical and chemical enhancers. Chemical enhancers act by destructing the nasal mucosa very often in an irreversible way, whereas physical enhancers affect nasal clearance reversibly by forming a gel. The enhancing effect continues until the gel is swallowed. Osmolarity and pH may accelerate the enhancing effect.

If a nasal formulation is delivered to the target site of absorption (turbinates), benefits can be gained from increased absorption and/or decreased dosage requirements. There may also be a reduction of taste of the drug because of minimum or reduced swallowing of the administered drug. As the latest development, tip aperture design pumps are available to administer formulations in an upward direction. Because the turbinate are located at the sides of the nostrils, the entire dose volume cannot be administered to the target site of absorption. This also leads to swallowing of part of the dose. It may be possible to design a side aperture pump to direct the entire dose volume directly to the absorption site, the turbinate, for more efficient (target) nasal delivery.25,26
Other than the factors cited above, the most useful factor in the nasal anatomy is that the nerves coming from the olfactory bulb spread out in bundles close to the cribiform plate (the part of the ethmoid bone constituting the roof of the anterior cranial fossa). The bundles cross this bony wall and enter the nasal cavity, ending in many small protrusions on the mucosal surface. The presence of a particular transport mechanism from the olfactory mucosa to the brain may be utilized when CNS targeting is essential. The rapid onset of action is linked to high mucosa permeability and indicates using the nose for therapies requiring prompt response. To conclude, the nasal mucosa is suitable for administering many drugs, particularly for reaching CNS via the olfactory route.\textsuperscript{26}

1.13 DOSAGE FORM DESIGN

The route of administration plays an important role in finalizing the design of the dosage form and the drug delivery system. In this work, the colloidal particles are selected for administering via intranasal route. Therefore an overview of the colloidal particles particularly nanoparticles is given.

Colloidal particles are those particles whose size falls in the nano and micrometer scales and they possess specific properties named colloidal properties by the virtue of their size.

Nanoparticles (NPs) are solid or semi solid colloidal particles ranging in size from 10 to 1000 nm. They consist of macromolecular materials in which the active principle (drug or biologically active material) is dissolved, entrapped, encapsulated and/or to which the active principle is adsorbed or attached and can be used as drug carriers.\textsuperscript{27} Polymeric NPs is a collective name for nanospheres and nanocapsules. Nanospheres have matrix–type structure. The matrix may be constituted by natural,
semi synthetic or synthetic polymers. Nanocapsules have a polymeric shell and an inner liquid core.

When a dosage form is administered, the amount of drug reaching the site of action is often only a small fraction of the administered dose. Therefore conventionally, large doses are administered so as to provide sufficient active moiety at the site of action, to elicit the required response. This may lead to accumulation at non target sites, which causes adverse reactions and undesirable side effects. A way of modifying the original biodistribution is to entrap the active moieties in submicroscopic drug carriers. Liposomes, polymeric NPs, solid lipid NPs and pharmacosomes are few such carriers. In the pharmaceutical drug delivery systems, the liposomes and the nanoparticles are the major colloidal drug delivery systems investigated with different polymers and drugs with an aim to prolong or control or target the release. Nanospheres are widely prepared and evaluated due to the versatility offered.

Historically nanospheres were first attempted using monomers and polymerization step was introduced during preparation. With the advent of preformed polymers, modifications in the techniques of preparations were adapted.

There are different methods of preparation. The selection of the method depends on polymer selected, solubility of the drug to be encapsulated, final size required. NPs have been extensively investigated in biomedical and biotechnological areas and, especially, in drug delivery systems for drug targeting.

The advantages of targeted drug delivery to the specific site of body, paved the way for applying NPs to achieve this type of drug delivery. Much attention has been provided to non parenteral routes like oral, pulmonary, nasal, opthalmic delivery of the drugs.
It has been cited that production of NPs has been limited due to the difficulties and complexities of the preparation methods. Therefore novel preparation methods are needed for development of effective nanoparticulate drug delivery vehicles.

The commonly followed preparation methods are:

- *In situ* polymerization techniques or by dispersion of preformed polymers.


- Nanoprecipitation.

The preformed polymers have the advantage of being well characterized and biodegradable and they are already commercially used for microparticulate drug delivery systems.

1.13.1 **Advantages of Nanoparticles (NPs)**

- The submicron size creates particles with large surface area.

- Smaller size offers versatility.

- Water soluble drugs may be encapsulated for administration.

- As the biodistribution is altered due to the small size, bioavailability may increase, targeting of delivery sites is possible and long circulating particles may be prepared. Therefore, a variety of release may be obtained by NPs.

- Comparing with liposomes, NPs offer better stability.

- As it is a growing field, there is versatility in preparation methods, selecting polymers and drugs

- Surface modifications to suit the final requirements are possible in the NPs.
1.13.2 Limitations of Nanoparticles (NPs)

- Preclinical results are yet to reach the clinical trial stage.
- Selective accumulation of the particles in the reticulo endothelial system limits the application.
- They are widely reported for injectable preparations. Oral route of administration has been experimented. But application through other routes of administration is limited.

As the NPs are prepared with an aim to target the brain via the intranasal route, the requirements are:

A] They must be non toxic, biodegradable, biocompatible.

B] Physical stability coupled with minimal nanoparticles excipient–induced drug alteration (chemical degradation/alteration).

C] Modulation of drug release to suit the actual requirement.

D] Scalable and cost-effective manufacturing process.

1.14 Drug Profile: - Sumatriptan Succinate (SS)

Chemical name: 3-[2-(dimethylamino) ethyl]-N-methyl-indole-5-methanesulphonamide succinate (1:1)

Molecular formula: C₁₄H₂₁N₃O₂S C₄H₆O₄

Molecular mass: 413.51
Physicochemical Properties

Physical characteristics: White to off-white powder with a melting point between 164.6 and 165.5 °C. (May increase up to 171 °C).

Solubility: In water (4°C) = 54 mg/ml
In water (20°C) = 101 mg/ml
In saline (0.9% w/v, 4°C) = 62 mg/ml
In saline (0.9% w/v, 20°C) = 109 mg/ml

pH and pKa: The pH of a 1% w/v solution of sumatriptan succinate in water is approximately 4.9 [Range 4.5 to 5.3]

pKa1 (succinic acid) = 4.21, 5.67
pKa 2 (3° amine group) = 9.63
pKa 3 (sulphonamide group) >12

Partition coefficient (between n-octanol and water): log P = 1.07 at a pH of 10.7
MECHANISM OF ACTION:

This is a selective agonist of vascular serotonin (5-hydroxytryptamine; 5-HT) type 1-like receptors. The agonist activity at the 5-HT$_{1D}$ receptor subtype provides relief of acute headache. It is a highly selective agonist at this receptor subtype and has no significant activity at other 5-HT receptor subtypes or at adrenergic, dopaminergic, muscarinic, or benzodiazepine receptors. It has also been proposed that neurogenic inflammation in areas innervated by the trigeminal nerve may contribute to the development of migraine headaches and there is some evidence that serotonergic mechanisms may be involved. Sumatriptan may also relieve migraine by decreasing release of neuropeptides and other mediators of inflammation. The concentrations of calcitonin gene-related peptide, a substance that increases vascular permeability and promotes plasma protein extravasation, are elevated during migraine attack and return to normal as the headache is relieved by sumatriptan.

USES:

Vascular headaches: Sumatriptan is used orally, by s.c injection or intranasal for the acute management of attacks of migraine with aura (also called classical migraine) or migraine without aura (also called common migraine) and by s.c injection for the acute management of cluster headache episodes.

SS has been effective in 70% of the patients within 60 min and in 81% patients within 120 min, after s.c administration. About 12 to 20% patients may need additional analgesics, and 38 to 44% may have a recurrent headache within 24 h, presumed to be a result of the short half life. When given orally, 75% patients were relieved within 4 h, but recurrence rate was 44%. In patients with recurrence, 74% had relief with an additional treatment dose. Sumatriptan should be used only in patients in whom a clear diagnosis of migraine and cluster headache has been established.
PHARMACOKINETICS:32

- Absorption: SS is rapidly absorbed when given by s.c route absorption is rapid and bioavailability is approximately 97% of that achieved with an i.v injection. Nasal absorption is rapid but bioavailability is low (approximately 17%), primarily because of presystemic hepatic metabolism and incomplete absorption. Oral absorption occurs within 20 min dose administration but bioavailability is low (approximately 15% of a dose), primarily because of presystemic hepatic metabolism.33

- Distribution: SS is rapidly and extensively distributed to tissues but passage across the blood-brain barrier is limited. Protein binding is low in the plasma (14 to 21%).

- Biotransformation: Extensive metabolism occurs in the liver and about 80% of a dose is metabolized. The major metabolite is an inactive indole acetic acid derivative. In vitro studies with human hepatic microsomes indicate that sumatriptan is metabolized by monoamine oxidize (MAO).

Half-life (t_{1/2}): Distribution t_{1/2} for SS when administered via s.c route is about 15 min. Disposition phase t_{1/2} for SS, when given by s.c or oral route is around 2.5 h. After nasal spray administrations, the disposition t_{1/2} of SS is about 2 h. Onset of action: After nasal unidose spray onset is within 20 to 30 min. After oral tablet administration, it is within 30 min. After s.c injection, the relief of headache pain is within 10 min.

Time to peak serum concentration: For nasal route it is between 1 and 1.5 h. After oral administration, it is approximately 2 h (range 0.5 to 5 h). The wide interindividual variability found in pharmacokinetic studies may be related to
the appearance of multiple peaks in the concentration over time. After s.c administration, it is approximately 12 min (range 5 to 20 min).

Peak serum concentration: After nasal administration, it is approximately 5 ng /ml (0.012 μm/l) for 5 mg dose and 16 ng/ml (0.039 μm/l), for 20 mg dose. For oral, single 100 mg dose, it is approximately 54 ng /ml (0.13 μm/l) (range 26.7 to 137 ng/ml [0.06 to 0.33 μm/l]). After a 6 mg s.c dose, it is approximately 72 to 74 ng/ml (0.17 to 0.18 μm/l) (range, 54.9 to 108.4 ng/ml [0.13 to 0.26 μm/l]).

Time to peak effect: Relief of headache (moderate or severe pain being reduced to mild or no pain): After oral (single 100 mg dose), it is within 2 h in 50 to 75 %, and within 4 h in 15 to 25% of patients. After s.c (single 6 mg dose): it is within 1 h in 70% and within 2 h in an additional 12% of patients. Relief of associated symptoms (nausea, vomiting, photophobia, phonophobia): After oral (single 100 mg dose) is within 2 h. After s.c (single 6 mg dose): it is within 1 h in 68%, and within 2 h in an additional 13%, of patients.

Duration of action: Return of migraine headache occurs within 24 to 48 hours in approximately 40% of patients. Therefore the duration of action is between 24 and 48 h. But after nasal spray administration, about 44 % of patients required a second dose after 2 h.

• Elimination: Elimination takes place through renal route, via active renal tubular secretion, following hepatic metabolism. 80% of a dose is eliminated as metabolites. After nasal administration, 3% of the dose is eliminated as unchanged sumatriptan and 35% as the indole acetic acid metabolite. After oral administration, 57% of a dose is eliminated in the urine (3% of the dose as unchanged sumatriptan, 35% as the indole acetic acid metabolite, and 8% as
the glucuronide conjugate of the indole acetic acid metabolite) and another 38% of the dose is eliminated in the feces (9% as unchanged sumatriptan and 11% as the indole acetic acid metabolite). After s.c administration, 22% of a dose is eliminated in the urine as unchanged sumatriptan and another 38% as the indole acetic acid metabolite. Only 0.6% and 3.3% of a dose are eliminated in the feces as unchanged sumatriptan and the indole acetic acid metabolite, respectively.

SIDE EFFECTS34: Most of the adverse effects reported with sumatriptan are mild and transient (lasting less than 1 hour after s.c injection and 2 h or less after oral administration) and resolve without treatment. Although several deaths have been reported after administration of sumatriptan, a direct causal relationship could not be established in most cases. Most of the fatalities occurred 3 h or more after administration and probably were spontaneous events or were caused by underlying disease. Some of the deaths were attributed to strokes, cerebral hemorrhages, or other cerebrovascular events. However, migraineurs are known to be at increased risk of cerebrovascular accidents or transient ischemic attacks; in many of these cases a cerebrovascular event, rather than a migraine, may have been causing the symptoms that led to therapy with sumatriptan. Therefore it may not be conclusive to state that SS caused the fatalities.

Some of the adverse events reported after administration of sumatriptan (nausea, vomiting, malaise, fatigue, dizziness, vertigo, weakness, drowsiness, sedation) often occur during and/or following a migraine headache; whether sumatriptan contributes to their occurrence has not been established. Although a causal relationship to sumatriptan has not been established, the following adverse events have also been reported in open, uncontrolled studies (incidences < 1%) and/or post marketing: cardiac arrhythmias (atrial fibrillation, ventricular fibrillation,
ventricular tachycardia, sinus arrhythmia), other transient changes in the electrocardiogram (ST segment elevations, other ST or T-wave changes, prolongation of PR or QTc intervals, nonsustained ventricular premature beats, isolated junctional ectopic beats, atrial ectopic beats, delayed activation of the right ventricle), hypotension, bradycardia, syncope, Prinzmetal's angina, vasodilatation, Raynaud's disease, acute renal failure, seizures, cerebrovascular accident, dysphagia, subarachnoid hemorrhage, polydipsia, dehydration, gastrointestinal reflux, dyspnea, erythema, pruritus, skin rashes, peptic ulceration, gallstones, swelling of extremities, transient hemiplegia, hysteria, globus hystericus, intoxication, mental depression, myoclonia, monoplegia or diplegia, dystonia, dysuria, urinary frequency, renal calculus, photosensitivity, and exacerbation of sunburn. Irritation in the nose (burning; discharge; pain; or soreness), taste perversion (change in sense of taste) occurs with nasal spray only. Nausea and vomiting often occur in conjunction with migraine headaches. However, these effects occurred more frequently after oral than after s.c administration of SS in clinical trials, may be due to the unpleasant taste of the dispersible Tablet used in the studies.

Flushing and sensations of burning, warmth, or heat generally appear after s.c injection.

In the pharmaceutical formulation aspect, internal reaction after packing happens where in the sulphuric acid added in the nasal spray formulation, for adjusting pH, reacts with sumatriptan base forming the hemisulphate salt of sumatriptan in situ.

SS is official in British Pharmacopoeia and United States Pharmacopoeia.

Till date there are no published reports in peer reviewed journals for nanoparticles of SS for nasal administration.
The amount of drug reaching the site of action is often only a small fraction of the administered dose. Accumulation at non-target sites may lead to adverse reactions and undesirable side effects. A way of modifying the original biodistribution of substances is to entrap them in submicroscopic drug carriers. Among such particles, polymeric nanoparticles are receiving great attention in the present research.

The preformed polymers have the advantage of being well characterized and biodegradable, and they are commercially used for microparticulate drug delivery systems.

Research in nanoparticles started with the use of natural polymers but later due the limitations of these, synthetic polymers were exploited. Synthetic polymers and natural macromolecules have been extensively researched as colloidal materials for nanoparticle production designed for drug delivery. Synthetic polymers have the advantage of high purity and reproducibility over natural polymers. Among the synthetic polymers, the polyester family (i.e., poly (lactic acid) (PLA), poly (ε-caprolactone) (PCL), poly (glycolic acid) (PGA)) is of interest in the biomedical area because of their biocompatibility and biodegradability properties. In drug delivery applications, poly (d, l-lactide co-glycolide) (PLGA), is considered as the pharmaceutical polymer of the future. PLGA is water–insoluble polymer; strength, hydrophobicity and pliability are the significant advantages. As a polymeric vehicle, biocompatibility, biodegradability, predictability of degradation, ease of fabrication and regulatory approval features make PLGA desirable for medical applications. Apart from these facts, PLGA has been FDA approved for human therapy. PLGA polymers have been investigated extensively for drug delivery and have been proposed as the most suitable candidate for pharmaceutical purpose. These polymers undergo hydrolysis upon administration in to the body; forming biocompatible and metabolizable moieties (lactic acid, glycolic acid) that are eventually removed by the citric acid cycle. This endows the polymers with safety and tissue compatibility.
General reports state the complete biodegradation of PLGA (50:50), takes about two months. PLGA is produced from a mixture of D, L-lactide and glycolide. It is amorphous powder and shows a glass transition range between $40^\circ C$ and $60^\circ C$. It is soluble in dichloromethane, chloroform, acetone, ethyl acetate, benzyl alcohol, tetrahydrofuran, dimethylformamide, hexafluoro isopropanol.

Additionally there is a wide range of PLGA copolymers which afforded the versatility to entrap wide variety of drugs and manipulation to different size, drug loading and release capacitites. Research was executed mostly on parenteral nanoparticles administered as i.m, s.c, i.v. Then they were extended to oral administration. The pharmaceutical application of nano sized particles has been extended to the field of non parenteral deliveries of drugs via pulmonary, nasal or oral routes.\textsuperscript{38}

Polymers with free carboxyl end groups incorporate hydrophilic drug better than capped polymers where there are no free carboxyl groups. In addition, presence of free carboxyl group significantly increased the degradation of the polymer. These hydrophilic groups allow better penetration of water molecules into the polymer matrix enabling faster release of the incorporated drug. Hence, in this work, an uncapped polymer of PLGA with equal lactide and glycolide units was used.

Polymer for the matrix formation selected was a preformed copolymer of lactic acid and glycolic acid in the form of poly lactide-co-glycolide (50: 50 w/w).
1.15. **POLYMER PROFILE: - RESOMER® RG 502 H (RsG)**

Chemical name: Poly (D, L-lactide-co-glycolide)

CAS number : 26780-50-7

![Chemical structure of Resomer RG 502 H](image)

**Specification**

**Description** : White to off-white powder

**Odour** : Nearly odourless

**Polymer composition** : 48:52 to 52:48 molar ratios (D, L-lactide: glycolide)

**Inherent viscosity** : 0.16 - 0.24 dl/g 0.1 % in chloroform, 25 °C

**Residual monomer** : Maximum (max.) 0.5 % D, L-lactide monomer

max. 0.5 % glycolide monomer

**Residual solvent** : max. 0.1 % acetone

max. 890 parts per million (ppm) toluene

max. 0.1 % total solvent

**Water** : max. 0.5 %

**Tin** : max. 200 ppm

**Heavy metals** : max. 10 ppm

**Sulphated ash** : max. 0.1 %

**Acid number** : minimum- 6 mg potassium hydroxide/g
Copolymer from lactide /glycolide denoted with an additional “H” in the product name contains predominantly free carboxylic acid groups on one of the chain ends.

**Advantages of Resomer RG 502H (RsG)**

- Hydrophilic drugs are more adsorbed when free carboxyl end groups are present.
- Low molecular weight of RsG when compared with other higher molecular weight polymer of the same category facilitated higher loading of the drug.
- Low molecular weight RsG releases water soluble drug at a much faster rate when compared with higher molecular weight polymers.
- RsG was reported to show initial burst release followed by prolonged release. This was initially due to substantial water uptake followed by bulk erosion.\(^{39}\)

**Limitations of Resomer RG 502 H (RsG)**

- Chlorinated organic solvents may be required for dissolving RsG
- The microenvironment pH in the area where RsG is degraded is acidic and this must be considered in long term use in humans.

All the above mentioned factors were suitably utilized to meet the final requirements in this work.