CHAPTER - 3

REVIEW OF LITERATURE

This work involved preparation of nanoparticles (NPs) using poly (lactide-co-glycolide) [PLGA], the grade used Resomer RG 502 H® (RsG), encapsulating Sumatriptan Succinate (SS) for administration through intranasal route for migraine treatment. Therefore, literature review for this study included reports related to all the aspects which include nasal bioavailability of few compounds, nasal route of administration, NPs using PLGA and SS for migraine treatment.

There are numerous work executed, to study the intranasal (i.n), route of administration in humans and also in different animal models. The compilation of details of nasal drug delivery, from the history, factors affecting nasal absorption, absorption enhancement, methods to study nasal drug delivery were stated by Chang et al. This work also cited the non-peptide drugs which were being studied for nasal delivery. To name a few gentamycin, streptomycin, cephalosporins, tyrothricin, ergotamine tartrate, diergotamine, enviroxime, dobutamine, nicotine, ipratropium, nitroglycerin, verapamil, cocaine, lidocaine, diazepam, meclizine, colloidal inorganic compounds like gold, silver, estradiol, progesterone, vitamins.

The above mentioned list showed that different salts or derivatives of the same drug base have been evaluated for nasal delivery, with an aim to improve the bioavailability, for example ergotamine tartrate and diergotamine.

The administration of systemically acting products in the modern scientific system of medicine via nasal route began in the 1980 s. The peptide oxytocin, was one of the first nasally administered peptide hormones. The study took advantage of the reports which established the existence of nasal absorption for systemic effect, in particular the existence of transport form the nasal route through the olfactory region.
to the central nervous system (CNS) (mainly to the brain). The following Table - 4 gives a list of compounds which were evaluated for their potential to be delivered by i.n route. The relative bioavailability shown in the table.

**TABLE - 4**

**NASAL BIOAVAILABILITY AND T<sub>MAX</sub> OF FEW PHARMACEUTICALS**<sup>41</sup>

<table>
<thead>
<tr>
<th>Active Pharmaceutical Ingredient</th>
<th>Animal model</th>
<th>t&lt;sub&gt;max&lt;/sub&gt; (min)</th>
<th>Relative nasal bioavailability (%) <a href="a">reference route of administration</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>Rat</td>
<td>2 to 5</td>
<td>95 [ID]</td>
</tr>
<tr>
<td></td>
<td>Human</td>
<td>5</td>
<td>----</td>
</tr>
<tr>
<td>Clofilium tosylate</td>
<td>Rat</td>
<td>&lt;10</td>
<td>69.6 [PO]</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Human</td>
<td>58 (solution)</td>
<td>----</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35 (crystals)</td>
<td>----</td>
</tr>
<tr>
<td>Cromoglycate disodium</td>
<td>Rat</td>
<td>20</td>
<td>----</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Rhesus monkey</td>
<td>15</td>
<td>----</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Human</td>
<td>60</td>
<td>----</td>
</tr>
<tr>
<td>Ergotamine tartrate</td>
<td>Rat</td>
<td>20</td>
<td>62 [ID]</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Human</td>
<td>30</td>
<td>----</td>
</tr>
<tr>
<td>Hydralazine pH 3.0</td>
<td>Rat</td>
<td>30</td>
<td>----</td>
</tr>
<tr>
<td>pH 6.5</td>
<td></td>
<td>&lt;10</td>
<td>----</td>
</tr>
<tr>
<td>pH 3.0 {with penetration enhancer}</td>
<td></td>
<td>&lt;10</td>
<td>----</td>
</tr>
<tr>
<td>Naloxone</td>
<td>Rat</td>
<td>20</td>
<td>101 [ID]</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Human</td>
<td>1 to 2</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>Rat</td>
<td>6</td>
<td>100 [ID]</td>
</tr>
<tr>
<td>Prostaglandin</td>
<td>Rabbit</td>
<td>15</td>
<td>88 [PO]</td>
</tr>
<tr>
<td>Prostaglandin</td>
<td>Rabbit</td>
<td>5 (spray)</td>
<td>82.5 [ID]</td>
</tr>
<tr>
<td>Prostaglandin</td>
<td>Rhesus monkey</td>
<td>5.5</td>
<td>----</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Rat</td>
<td>5 to 6.3</td>
<td>100 [PO]</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Dog</td>
<td>5</td>
<td>103 [PO]</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Rat</td>
<td>&lt;2</td>
<td>90 to 99 [ID]</td>
</tr>
</tbody>
</table>

(a) Reference route of administration given in parenthesis;

PO – Per oral - ID – Intra duodenal
Apart from the above mentioned there are numerous proteins and peptide based drugs which have been investigated or are currently under investigation for nasal delivery and to improve the drug delivery when administered i.n.

Table 5 gives a comprehensive overview about the research executed on nasal route of administration for systemic effects. Studies related to the localized effects are not included.

### TABLE - 5

**RESULTS OF STUDIES ON NASAL ADMINISTRATION OF FEW COMPOUNDS**

<table>
<thead>
<tr>
<th>STUDY</th>
<th>DRUGS</th>
<th>RESULT AND INFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorptive capacity of the sinus membrane of dogs.(^ {42} )</td>
<td>Phenol red</td>
<td>The dye was excreted after approximately 2 h, thereby proving that sinus membrane was able to absorb water soluble substance.</td>
</tr>
<tr>
<td>Comparative studies of antihistamines in allergic rhinitis.(^ {43} )</td>
<td>Prophen pyridamine maleate Chlorphen pyridamine maleate</td>
<td>Combination was more effective. The results indicate presence of H(_1) and H(_2) receptors in nasal blood vessels.</td>
</tr>
<tr>
<td>Intranasal absorption.(^ {44} )</td>
<td>Scopolamine</td>
<td>i.n. and s.c. routes of administration superior to sublingual.</td>
</tr>
<tr>
<td>Evaluation of transport via olfactory region to the CSF.(^ {45} )</td>
<td>Radioactive colloidal gold</td>
<td>Radioactive colloidal gold penetrates the nasal mucosa from the olfactory region directly into the CSF of the anterior cranial fossa.</td>
</tr>
<tr>
<td>Comparison of oral and nasal absorption in Syrian hamsters.(^ {46} )</td>
<td>Inorganic radio labeled substances</td>
<td>More than 50% of the deposited radioactive substances were detected in circulation. Nasal bioavailability was equal or more than oral bioavailability</td>
</tr>
<tr>
<td>Nasal delivery for treatment of migraine in humans.(^ {47} )</td>
<td>Propranolol</td>
<td>Nasal administration was more effective and fast acting to avoid development of migraine.</td>
</tr>
<tr>
<td><strong>Systemic absorption.</strong> Evaluated the existence of pathway, from nose to CNS.</td>
<td><strong>Progesterone</strong> Norethisterone</td>
<td>Ovulation prevented in rhesus monkey after i.n. administration.</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Comparing oral and nasal administration.</td>
<td>Cocaine</td>
<td>Nasal offered detectable plasma concentration after 15 min but not so after oral administration.</td>
</tr>
<tr>
<td><strong>Comparison of absorption after i.n.,oral,i.m. administration.</strong></td>
<td>Sulbenicillin, Cephacetrile, Cefazoline</td>
<td>Intranasal was better than oral but less than that of i.m.</td>
</tr>
<tr>
<td><strong>Human nasal absorption studies – effect of adding surfactant.</strong></td>
<td>Gentamicin</td>
<td>Surfactant – glycocholate improves absorption to a significant level.</td>
</tr>
<tr>
<td><strong>Nasal absorption.</strong></td>
<td>Clofilium tosylate; Enkephalin analogs; Dobutamine hydrochloride</td>
<td>Compound with short biological half life mimics i.v. infusion.</td>
</tr>
<tr>
<td><strong>Microsphere for nasal delivery in rats and sheep.</strong></td>
<td>Gentamicin</td>
<td>50 % more gentamicin was absorbed when given as microsphere with lysolecithin when compared to that of simple nasal solution of the same.</td>
</tr>
<tr>
<td><strong>Improving nasal absorption in rats by using lysophosphatidylcholine.</strong></td>
<td>Insulin</td>
<td>Nasal penetration enhancers improve absorption and produced a 65 % decrease in blood glucose levels.</td>
</tr>
<tr>
<td><strong>Randomized, controlled clinical trial of bioavailability when given i.n.</strong></td>
<td>Salmon calcitonin</td>
<td>Counteracts early postmenopausal bone loss by inhibiting bone resorption.</td>
</tr>
<tr>
<td><strong>Nasal absorption in humans.</strong></td>
<td>Metoclopramide</td>
<td>Absorption was faster and increase in bioavailability was observed.</td>
</tr>
<tr>
<td><strong>Emulsions for i.n. administration.</strong></td>
<td>Testosterone</td>
<td>Charged nasal sprays showed better bioavailability than neutral sprays.</td>
</tr>
<tr>
<td><strong>Management of post operative pain.</strong></td>
<td>Fentanyl</td>
<td>Only 1.1 to 1.5 times higher doses were required when compared with the i.v. dose.</td>
</tr>
<tr>
<td><strong>In vitro</strong> absorption studies in rabbits after nasal administration.(^{59})</td>
<td>Apomorphine</td>
<td>Loading and maintenance dose may be achieved by formulation for nasal administration.</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Evaluation of nasal spray.(^{60})</td>
<td>Melatonin</td>
<td>A peak level of nasal melatonin was 50 times than that after oral administration.</td>
</tr>
<tr>
<td>Determination of possibility of olfactory pathway transport to the brain in mice.(^{61})</td>
<td>Dopamine</td>
<td>Proved the existence of olfactory transport to the olfactory bulb in the brain.</td>
</tr>
<tr>
<td>Bioavailability from starch microspheres in rabbits.(^{62})</td>
<td>Apomorphine</td>
<td>Lyophilized powder achieved sustained release but microspheres released the drug at faster rate like immediate release</td>
</tr>
<tr>
<td>Pharmacokinetics of nasal spray and nasal powder in rabbits.(^{63})</td>
<td>Ketorolac tromethamine</td>
<td>Spray showed absolute bioavailability of 91%</td>
</tr>
<tr>
<td>Bioavailability enhancement by microspheres.(^{64})</td>
<td>Gentamicin</td>
<td>Bioavailability of gentamicin was increased to about 42.9 % when administered as microspheres</td>
</tr>
<tr>
<td>Nasal absorption in humans.(^{65})</td>
<td>Glucagon</td>
<td>Spray produced irritation. Powder used along with microcrystalline cellulose did not produce any irritation</td>
</tr>
<tr>
<td>Transfer through olfactory pathway to CNS in rodents.(^{66})</td>
<td>Morphine</td>
<td>By autoradiography it was proved that morphine reached the ventricles via the olfactory bulb within 5 min, which was significantly faster than that after i.v. administration</td>
</tr>
</tbody>
</table>

In addition to the above mentioned list, about thirty five to forty substances, for example nerve growth factor, local anaesthetics, inorganic mercury, taurine, dihydroergotamine; carboxylic acids have been reported to reach the CNS after nasal administration.\(^{61}\)
From the review it is evident that as early as 1978, Kornhauser et al. \(^ {47}\) have demonstrated the fast and rapid relief from migraine headache when propranolol was administered i.n. This was the specific basis for the future research works which were executed.

A report by Hirai et al. \(^ {67}\) used surfactants to improve the nasal absorption of insulin preparations and reported that the nasal administration of insulin preparation to rats resulted in dose-dependent hypoglycemia. The report stated that among the non-ionic surfactants, the addition of an ether type having a HLB (hydrophile-lipophile balance) value from 8 to 14 was found to produce the highest promoting effect on the nasal absorption of insulin and the bioavailability of nasally administered insulin with the surfactant was estimated to be about 30% by comparing the hypoglycemic effect with that obtained after intravenous administration.

Scientific validation was provided by further evidence based on the result of work done by Westin et al. \(^ {66}\) whereby it was deduced that morphine reached olfactory bulb within five minutes of nasal administration which was significantly faster than the i.v route of administration. This work in rodents proved that nasal route may be exploited for conditions which require rapid action.

The relationship between lipophilicity and nasal absorption was demonstrated by Sakane et al. \(^ {68}\), after the study on sulfonamides and concluded that increasing lipophilicity enhanced direct uptake of sulfonamides from the nasal cavity in to cerebro spinal fluid (CSF), in rats.

A study by Gizurarson et al. \(^ {69}\), demonstrated the delivery of insulin into the brain when administration was done through i.n. route in animal models. The distribution of insulin between blood and brain was investigated in mice. The drug was administered subcutaneously and by instilling the drug to the olfactory region of
the nasal cavity. A significantly higher concentration of insulin was measured in the brain, following intraolfactory administration compared to s.c. injection. The absorption was also found to be very rapid. 10 min after the administration the concentration in the brain had reached to an extent of 47% higher than achieved after s.c injection. The results suggested that it may be possible to achieve absorption directly into the brain, by-passing the blood-brain barrier. The olfactory region may be the key for this absorption.

Specific reports on human studies have led credibility to the theory of nose-to-brain transports. The report of work executed by Pietrowski et al. demonstrated the brain evoked potential changes were greater with i.n. than the i.v. AVP19 which is the cholecystokinin analog CCK-8.

A review by Behl et al., extensively listed the factors affecting systemic nasal drug delivery. This report detailed the physicochemical properties, formulation properties, biological properties which affect nasal drug delivery.

A study by Perras et al., reported that intranasal growth hormone –releasing hormone (GHRH), increased rapid eye movement sleep and slow wave sleep in humans and decreased growth hormone, which is likely due to a CNS effect of the GHRH following direct delivery to the brain.

Analysis of report of Smolnik et al., concluded that the action of ACTH 4-10 on human event related brain potential and attention was due to direct delivery of the peptide form the nose to the brain and did not require prior resorption into the blood.

The direct transport of cocaine from the nasal cavity to the brain following intranasal cocaine administration in rats was demonstrated in a study executed by Chow et al.
Nasal formulations containing ketorolac were developed by Quadir et al\textsuperscript{75}. Powder and sprays were prepared and evaluated. The pharmacokinetics was evaluated using rabbits. It was reported that the spray showed highest bioavailability of 91\% and that the plasma concentration resembling i.v dose was reached within 30 min. But the powder formulations showed low bioavailability of 38\% and it was reasoned that they were cleared faster from the nasal epithelium.

Thorne et al (2000)\textsuperscript{76}, claimed in their report, that preliminary evidence was available to state that the trigeminal neural pathway also may be involved (apart from the olfactory pathways), in the rapid delivery of protein therapeutic agents, such as insulin-like growth factor I, to the brain and spinal cord following i.n. administration.

A new method was devised for drug transport studies on pig nasal mucosa using a horizontal Ussing chamber. This method was simple, fast and predicted \textit{in vivo} results. This work also stated that though studies have been performed using nasal mucosa of rabbit, sheep and ox, the pig (porcine) nasal mucosa appeared similar to that of humans. It was also stated that relatively large mucosa, which could be obtained intact and unstrained, may be obtained from slaughter house where it was a waste product.\textsuperscript{77}

A study reported the targeting of CNS by direct transport from the nose to the brain. The model drug used was lidocaine hydrochloride. Pharmacokinetic study was executed. A microdialysis method was standardized for quantification.\textsuperscript{78}

An overview about nasal drug delivery has been presented by Sarasija et al.\textsuperscript{79} The relevant details are: nasal route is important for drugs used for crisis management such as for pain and for CNS drugs where the direct pathway from the nose to the brain might provide a faster and more specific therapeutic effect. Lipophilic drug exhibit rapid and efficient absorption when given nasally. Nasal absorption of polar
drugs like sumatriptan is less than 10%. Formulation administered to the human respiratory epithelium has been found to be cleared from the nasal cavity with half life of clearance of about 15 min. Several enzymes were also present in the nasal mucosa. Addition of penetration enhancers and increasing the residence time in the nasal cavity were the commonly followed methods to improve nasal absorption. pH, particle size plays important role in absorption. The olfactory region was the only site in the human body where the nervous system was in direct contact with the surrounding environment. There were transcellular and paracellular pathways. This enabled the drug to reach CNS within min. In addition, intracellular axonal transport was also possible, but this was a slow pathway.

A stable dipyprone formulation was developed and studied for its antipyretic effect after i.n. administration in rabbits and rats. Administration methods were established. It was shown that the nasal volume of rabbits is large enough to hold 100 ml solution. After i.n. administration, improved pharmacodynamics was obtained with the newly developed dipyprone formulation compared to the normal dipyprone solution. Significant decrease of body temperature was observed 10 min after dosing. In conclusion, the dipyprone formulation is effective and safe for clinical medication.80

The effect of mucolytic agent (N-acetyl -1-cysteine), was evaluated by Matsuyama et al81 and a nonionic surfactant (lauryl ether (laureth-25)), for improving the nasal absorption of poorly absorbable hydrophilic compounds. Rat studies with fluorescent isothiocyanate-labeled dextran, as a model hydrophilic compound revealed dramatic enhancement of nasal absorption. Synergistic enhancement resulted from the mucolytic activity, which reduced mucous viscosity by which the accessibilities to the epithelial membrane increased. Further rat studies proved that this formulation increased nasal absorption of salmon calcitonin. The probability of
the formulation to cause tissue damage in terms of hemolytic activity and liberation of phospholipids from the nasal membranes was nil or slight.

The effect of bioadhesive formulations on the distribution of drugs to the systemic circulation and CNS was determined using an angiotensin antagonist as model drug. The nasal administration in rat model was followed and the following conclusions were stated. There was improved trans mucosal drug delivery. The method of administration and length of the cannula used to administer dosage form to the animals, affected the results. But there was no significant difference between the control and bioadhesive formulation.

From the analysis of the above mentioned reports, the following statements may be arrived at:

1] Faster absorption of drugs is possible when they are administered by the nasal route.
2] Lipophilic drugs are absorbed rapidly
3] pH affects the nasal absorption.
4] Penetration or absorption enhancers increase the nasal bioavailability.
5] The dosage form or delivery mechanism affects the nasal absorption.
6] Bioavailability may be increased when drugs are administered by nasal route depending on the dosage form.
7] The use of penetration enhancers, increasing the residence time in the nasal cavity, enhances nasal absorption.
Review for Nanoparticles:-

Strategy for miniaturized drug delivery systems were developed by Prof. Peter Paul Speiser and in the late 1960’s the first NPs for drug delivery purpose and vaccine preparations were reported. This marked the advent of the concept of NP for drug targeting. Succeeding years witnessed a variety of applications in pharmaceuticals using NPs.\textsuperscript{83}

Nanotechnology has the potential to produce low-cost, self-replicating systems that could revolutionize the scientific landscape.\textsuperscript{84} NP drug delivery, utilizing degradable and absorbable polymers, provides a more efficient, less risky solution to many drug delivery challenges.\textsuperscript{85}

Additionally, the use of absorbable or degradable polymers, such as polyesters, provides a high degree of biocompatibility for NPs delivery systems. Furthermore, the use of NPs allows for design of individual delivery systems for highly specific applications. Among the adaptations that can be made are surface modifications of the polymer, use of different fabrication methods, and selection of a variety of pre-existing polymers or copolymers, and formulation of novel polymeric materials.\textsuperscript{86}

The advent of NPs drug delivery may be traced back to 1972, when Scheffel \textit{et al}\textsuperscript{87} reported albumin nanospheres prepared by heat denaturation. The credit for preparing rapidly biodegradable acrylic NPs goes to Couvreur \textit{et al}.\textsuperscript{88}

Gurny \textit{et al} \textsuperscript{89}, successfully produced NPs with preformed polymer. PLA was used for delivering testosterone. The study detailed the physicochemical properties, stability, drug release, histopathology after i.m injection in rats. Different manufacturers adopted different methods for preparing PLA and PLGA polymers and
this resulted in numerous varieties available for many applications and made the polymer versatile. Deasy et al.\textsuperscript{90}, in their review, observed that depending on the composition and/or the molecular weight of these polymers, they slowly hydrate in the body and release the drug. The co-polymers of lactic and glycolic acids were of intermediate degradation rate between the two pure polymers. Increasing the molecular weight or changing the composition of the polymers also affects their rate of biodegradation.

The manufacturer Boehringer Ingelheim\textsuperscript{®}, Germany, have developed numerous grades of PLGA and a different series named H series. This series was developed with higher number of free carboxylic end groups, with an aim to increase the water uptake and the degradation of the polymer.

Conti et al.\textsuperscript{91}, stated that the polymers of lactic and glycolic acids and their copolymers are biocompatible and safe for parenteral administration, since the biodegradable polymers need not be removed from the body.

Ucida et al.\textsuperscript{92}, stated that these biodegradable PLA, PGA, PLGA have been widely used for the encapsulation of various drugs for different purposes. Commonly, these polymers were used for the encapsulation of peptides and proteins.

Corre et al.\textsuperscript{93} and Yang et al.\textsuperscript{94} reiterated that the important and widely studied application of these polymers was controlling the drug release.

Anderson et al.\textsuperscript{95}, in their review made the following observations. Among the numerous polymers available, PLGA provides excellent biodegradation and biocompatibility. The mechanism of degradation is considered to be hydrolysis. The rate of degradation is affected by many factors. To name a few, size of the colloidal particle, loading level of the drug, acidic or basic nature of the drug present with the
polymer. Fastest degradation amongst the PLGA was observed in 50:50, having a half life of just 15 days. The half life was only 7 days inside a macrophage. Biodegradation of PLGA 50: 50 has been studies in brain tissue and they proved to be safe without any immunological reactions. Basic compounds can catalyze ester linkage scission and this accelerated polymer degradation. A tertiary amino compound –thioridazone accelerated the degradation rate of PLGA microspheres.

Okada et al 96, stated that PLGA was the material of choice for many biodegradable drug delivery systems. The advantages were excellent biocompatibility, relatively inert composition, low production cost.

Julienne et al 97 incorporated amphotericin B into PLGA NPs, biodegradable drug carriers, for specific targeting inside the cell and reported that anti-leishmanial activity was observed with drug-free NPs. Trehalose, a cryoprotector of the freeze-dried NPs, altered parasite growth and activated macrophages.

Kreuter et al 98, demonstrated the passage of NPs across blood brain barrier.

Song et al 99, prepared various drug loaded PLGA, NPs for intravascular drug delivery. Emulsification followed by solvent evaporation method was followed for the preparation. The drug release kinetics from the NPs may be controlled by selecting the composition and the molecular weight of the polymer matrix. The ex vivo method for evaluating the NPs uptake by arterial perfusion was adopted.

Blanco et al 100, developed PLGA nanospheres using proteins. Effect of capped and uncapped (containing free carboxyl end group), PLGA, was studied. It was reported that hydrophilic substance loading was to an extent of 90 % and initial burst release was followed by controlled release. The method of preparation followed was multiple emulsion (w/o/w) followed by solvent evaporation.
Gaspar et al.\textsuperscript{101}, reported the preparation of L-asparaginase—a hydrophilic enzyme, entrapped in PLGA matrix as NPs by the w/o/w emulsion—solvent evaporation method. Effects of polymer on loading, release were studied. It was reported that PLGA containing free carboxyl groups, entrapped higher percentage of hydrophilic drug and also released them better when compared with end capped PLGA with esterified carboxyl groups.

Lamprecht et al.\textsuperscript{102}, prepared and evaluated PLGA and poly-\textepsilon\,caprolactone NPs as potential drug carriers for the proteins. The hydrophilic bovine serum albumin was used as model drug. Homogenization was used in the multiple emulsion solvent evaporation method and a very high entrapment efficiency of above 80\% was reported. Biphasic release pattern and almost 92\% of drug release was observed from PLGA NPs.

Jeon et al.\textsuperscript{103}, prepared PLGA NPs by dialysis method using norfloxacin as model drug. Large particles released drug slowly. It was reported that dialysis method may be followed when the final NPs must be free of surfactants.

Jung et al.\textsuperscript{104}, presented a review on biodegradable NPs for peptide delivery. In this work, the different methods to study NP absorption have been explained. The in vitro, in situ, ex-vivo, in-vivo methods have been described. The mouse, rat, guinea pig, rabbit, pig were reported to be the common animals models for evaluation.
Saez et al\textsuperscript{105}, presented a study on freeze drying of polycaprolactone and PLGA NPs, with and without cryoprotectants. Differential scanning calorimetry and freeze-thaw cycles were used to optimize the lyophilization process. There was slight particle size alteration when cryoprotectants were used. Therefore, the addition affects the final size.

Murakami et al\textsuperscript{106}, executed an extensive work on preparation methods for NPs, using different grades of PLGA and PLA. The modified spontaneous emulsification solvent diffusion method was evaluated. It was concluded that by varying the binary solvent mixture, NPs of uniform size may be produced by the procedure explained.

Betbeder et al\textsuperscript{107}, studied the anti nociceptive activity, blood and brain delivery of nasal morphine with or without Biovector\textsuperscript{TM} NPs in mice. It was reported that, NPs increased the antinociceptive activity of morphine after nasal administration. In the same study it was reported that nasal permeation enhancer was unable to improve nasal morphine activity.

Kompella et al\textsuperscript{108}, prepared and evaluated PLA NPs, containing budesonide, with an aim to sustain the release of the same. Solvent evaporation method was used to yield NPS which were characterized. Entrapment efficiency was as high as 70\% and the sustained release was observed for two weeks. Thermal analysis was also performed to determine drug interaction with the polymer.

Kreuter\textsuperscript{109}, had presented a review of NPs for brain targeting. In this report, the successful passage of NPs across BBB to reach the CNS was stated.
Jung et al. evaluated the potential of novel tetanus toxoid (TT) loaded NPs for eliciting an immune response in mice against TT. In this work, mice were immunized by oral (p.o.), nasal (i.n.) and intraperitoneal (i.p.) application of TT NP loaded by adsorption. As polymer a novel polyester, sulfobutylated poly (vinyl alcohol)-graft-poly (lactide-co-glycolide), SB (43)-PVAL-g-PLGA was used. Blood samples were collected 4 and 6 weeks after immunization and assayed for serum IgG- as well as IgA antibody titers by ELISA. NP formulations varying in size and loading were compared to alum adsorbates as well as to TT solutions. It was concluded that both, p.o. and i.n. administration of TT associated NP increased serum titers up to $3 \times 10^3$ (IgG) and $2 \times 10^3$ (IgA). While small NP induced significantly higher titers then larger ones after oral administration, intermediate NP induced antibodies after nasal application. Of the mucosal routes investigated, i.n. seems to be more promising compared to p.o. immunization. The conclusion was that antigen loaded NP prepared from surface modified polyesters combined with CT show considerable potential as a vaccine delivery system for mucosal immunization.

Konan et al. investigated the feasibility of producing sterile and freeze dried polyester NPs. PLGA, PLA were used. Salting-out procedure was followed for the preparation. Freeze drying was executed. Bacterial contamination was avoided by covering the vials with membrane filters ($0.22 \ \mu m$) before lyophilization.

Ahlin et al. designed and characterized PLGA and polymethylmethacrylate NPs containing enalaprilat for oral administration. Emulsification –diffusion method was followed for preparation. Characterization was by evaluating physicochemical parameters. This work again reported the biphasic pattern of release from PLGA NPs, where an initial burst phase was followed by slow release phase.
Sahoo et al.\textsuperscript{113}, studied the effect of residual poly vinyl alcohol (PVA), in the preparation of NPs with PLGA. Bovine serum albumin was used as model drug. It was concluded that residual PVA was an important formulation parameter that can be used to modulate the pharmaceutical properties of PLGA NPs.

Vandervoot et al.\textsuperscript{114}, studied the effect of PVA in PLGA NPs by applying the factorial design. It was concluded that PVA was essential for obtaining nanosized particles. Method of preparation was w/o/w solvent evaporation. If PVA was excluded, sizes of the particles obtained were high to a range above 1 \( \mu \)m.

Hans et al.\textsuperscript{115}, presented a widely researched review article with details of all published literature reports relating to biodegradable NPs for drug delivery and targeting. It has been reported that NPs using PLGA may be prepared by solvent diffusion, solvent displacement, nanoprecipitation, solvent evaporation, multiple emulsion, salting out, interfacial deposition, phase inversion nanoencapsulation. Commonly used solvent for PLGA was dichloromethane.

Vila et al.\textsuperscript{116}, prepared and evaluated poly (ethylene glycol) (PEG)-coated PLA - NPs, chitosan (CS)-coated PLGA- NPs and chitosan (CS) nanoparticles. These NPs have been tested for their ability to load proteins, to deliver them in an active form, and to transport them across the nasal and intestinal mucosa. The stability of some of these NPs in simulated physiological fluids was studied. Results showed that the PEG coating improves the stability of PLA -NPs in the gastrointestinal fluids and helps the transport of the encapsulated protein, tetanus toxoid, across the intestinal and nasal mucosae. Intranasal administration of these NPs provided high and long-lasting immune responses. The coating of PLGA -NPs with the mucoadhesive polymer CS improved the stability of the particles in the presence of lysozyme and enhanced the nasal transport of the encapsulated tetanus toxoid. NPs made solely of
CS were stable upon incubation with lysozyme. Also these particles were very efficient in improving the nasal absorption of insulin as well as the local and systemic immune responses to tetanus toxoid, following intranasal administration. They concluded that, rational modification in the composition and structure of the NPs, using safe materials, increased the prospects of their usefulness for mucosal protein delivery and transport.

Raghuvanshi *et al* \(^{117}\), prepared and evaluated, PLGA and PLA particles entrapping immunoreactive tetanus toxoid by solvent evaporation method. By the solvent evaporation method, entrapment efficiency was reported to be 72 % and NPs size 670 nm. It was concluded that selection of polymer, altering formulation variables affect the final result and activity of the drug entrapped.

Fonseca *et al* \(^{118}\), developed NPs of PLGA (RsG) entrapping paclitaxel for i.v administration. It has been reported that NPs prepared using PLGA of the RsG grade, exhibited biphasic release pattern of initial burst phase for first 24 h and later a slow, continuous release phase. *In vitro* anti tumoral activity results showed the enhanced cytotoxic effect of NPs when compared with free drug.

Koziara *et al* \(^{119}\), prepared two novel NPs and evaluated *in situ* transport across BBB. Radiolabelling method was followed. It was proved that NPs were detected in the CNS. In this work, it was stated that brain tissue was analyzed for NPs and also for quantitative determination of the drug. It was reported that olfactory transport of NPs depended on the lipophilicity and molecular weight of the drug. It was reported that endocytosis and /or transcytosis may explain the absorption.

Konan *et al* \(^{120}\), standardized the method of emulsification-diffusion followed by sterilization by filtration for PLGA NPs containing meso-tetra(4-hydroxyphenyl)porphyrin as model drug. The NPs were sub -200 nm size range and
high drug loading was obtained. Membrane filtration was an effective method for sterilization.

Panyam et al \textsuperscript{121}, reviewed the application of NPs for drug delivery. Specific emphasis was laid on the biodegradable NPs for drug and gene delivery to cells and tissues.

Panyam et al \textsuperscript{122}, studied the effect of particle size of PLGA NPs and micro particles on the release rate and degradation. W/O/W multiple emulsion method was followed using bovine serum albumin as model protein. The particles exhibited biphasic pattern of release irrespective of size. The nano range particle showed faster initial burst phase. This phenomenon was explained by the high surface volume ratio of the NPs.

Panyam et al \textsuperscript{123}, prepared NPs containing bovine serum albumin by the double emulsion solvent evaporation method to characterize the process of endocytosis, exocytosis and intracellular retention of PLGA NPs \textit{in vitro}, using human arterial vascular smooth muscle cells.

Pandey et al \textsuperscript{124}, prepared and evaluated PLGA NPs for treating tuberculosis by improving the bioavailability of antitubercular drugs (ATDs) and to assess the feasibility of administering ATDs via the respiratory route. Three ATDs, rifampicin, isoniazid and pyrazinamide were encapsulated in PLGA NPs for nebulization. On nebulization of NPs containing drugs to \textit{M. tuberculosis} infected guinea pigs at every 10\textsuperscript{th} day; no tubercle bacilli could be detected in the lung after five doses of treatment whereas 46 daily doses of orally administered drug were required to obtain an equivalent therapeutic benefit. Therefore it was concluded that nebulization of NPs-based ATDs improves drug bioavailability and reduces the dosing frequency for better management of pulmonary tuberculosis.
Bala et al.\textsuperscript{125}, presented a review about NPs and the following facts were stated. NPs represent drug delivery systems suitable for most administration routes. Over the years, a variety of natural and synthetic polymers have been explored for the preparation of NPs, of which PLA, PGA, and PLGA have been extensively investigated because of their biocompatibility and biodegradability. NPs act as potential carries for several classes of drugs such as anticancer agents, antihypertensive agents, immunomodulators, and hormones; and macromolecules such as nucleic acids, proteins, peptides, and antibodies. The options available for preparation have increased with advances in traditional methods, and many novel techniques for preparation of drug-loaded NPs are being developed and refined. NPs can be designed for the site-specific delivery of drugs. The targeting capability of NPs is influenced by particle size, surface charge, surface modification, and hydrophobicity. Finally, the performance of NPs \textit{in vivo} is influenced by morphological characteristics, surface chemistry, and molecular weight. Careful design of these delivery systems with respect to target and route of administration may solve some of the problems faced by new classes of active molecules.

Kumar et al.\textsuperscript{126}, executed work on PLGA, a biocompatible and biodegradable polyester co-polymer of PLA and PGA, for its ability to deliver genes. Surface modification of PLGA NPs was carried out, with cationic chitosan in an effort to improve their gene delivery capability. PLGA NPs were synthesized by emulsion-diffusion-evaporation technique using PVA-chitosan (PLGA1) or PVA-chitosan-PEG (PLGA2) blend as stabilizers. This method is reproducible and produced NPs with hydrodynamic diameter of less than 200 nm. The NPs were tested for their ability to transport across the nasal mucosa \textit{in vivo} in mice. The results show that both PLGA1 and PLGA2 facilitate gene delivery and expression \textit{in vivo} with increased efficiency and without causing inflammation. The results indicate that chitosan-modified PLGA NPs have greater potential as gene carriers.
Dillen et al \textsuperscript{127}, prepared ciprofloxacin containing PLGA NPs by multiple emulsion, solvent evaporation method, using PVA as stabilizer. The effect of variables on the parameters evaluated was studied by factorial design and was reported.

Yoo et al \textsuperscript{128}, prepared and evaluated PLGA NPs for oral delivery of Salmon calcitonin. The reason for selecting PLGA of 50:50 ratio of lactic acid and glycolic acid concentration was due to the fact that this particular ration leads to the fastest degradation rate among the different PLGA available.

Ravikumar et al \textsuperscript{129}, formulated PLA and PLGA NPs for gene delivery. PLGA NPs containing DNA were prepared by emulsion-solvent evaporation technique and PVA was used as a stabilizer. Surface properties of the nanospheres produced were evaluated. It was concluded that cationic PLGA nanospheres could serve as potential alternative of the existing negatively charges NPs.

Dillen et al \textsuperscript{130} evaluated the water-in-oil-water, multiple emulsion technique for the preparation of PLGA NPs using ciprofloxacin as model drug. A factorial design was developed and applied to arrive at the suitable combination.

Ubrich et al\textsuperscript{131}, evaluated the w/o/w method of preparation for NPs containing hydrophilic drug in different polymer matrices including PLGA. The drug used was propranolol hydrochloride. The highest entrapment efficiency reported was 83.3\% in PLGA. This report also stated the biphasic release pattern observed in PLGA NPs. It was concluded that NPs prepared by w/o/w emulsification followed by solvent evaporation may be suitable for NPs containing hydrophilic drugs.
Pamujula et al.\textsuperscript{132}, developed an orally active amifostine NPs using spray drying technique. Two different NPs formulations (Amifostine-PLGA (0.4:1.0 and 1.0:1.0)) were prepared using a Buchi B191 Mini Spray Dryer. A tissue distribution study in mice was conducted following oral administration of the formulation containing drug-polymer (0.4:1.0). The efficiency of encapsulation was 90\% and 100\%, respectively, for the two formulations while the median particle sizes were 257 and 240 nm. The tissue levels of WR-1065, the active metabolite, was detected in significant amounts in all tissues, including bone marrow, jejunum and the kidneys, and there was some degree of selectivity in its distribution in various tissues. This work demonstrated the feasibility of developing an orally effective formulation of amifostine that can be used clinically.

Shivakumar et al.\textsuperscript{133}, presented a review on NPs for targeting neurotherapeutic agents across blood brain barrier. In this review, it was stated that amitriptyline, dalagrin, kyotorphin, loperamide were few of the many drugs used for NPs preparation and were evaluated for analgesic activity by the hot plate test. All the formulations resulted in increasing the latency by approximately 50 \%. Numerous patents awarded for CND targeting using NPs were listed.

Bilati et al. (2005)\textsuperscript{134}, investigated formulation and process modifications to improve the versatility of the nanoprecipitation technique, particularly with respect to the encapsulation of hydrophilic drugs. Various grades of PLGA were used and solvent systems were standardized.

Bilati et al.\textsuperscript{135}, investigated the entrapment of 3 different model proteins (tetanus toxoid, lysozyme, and insulin) into PLA and PLGA NPs, prepared by modified nanoprecipitation and emulsion based method and evaluated process-related stability issues. The results obtained showed that tetanus toxoid and lysozyme were
incorporated to an extent of 98% by the double emulsion procedure. The nanoprecipitation method led NPs with some batches showing 90% drug release. In conclusion, both the double emulsion and nanoprecipitation methods allowed efficient protein encapsulation. Few relevant steps in the procedure from this report have been utilized in this current work.

Kim et al.\textsuperscript{136} studied the interaction of PLGA NPs with human blood constituents. PLGA NPs were prepared by nanoprecipitation method. But in this work, high polymer concentrations were utilized and only PLGA particles devoid of drugs were prepared. It was concluded that pegylated PLGA were safe when compared with PLGA NPs.

Blasi et al.\textsuperscript{137}, executed a study on the effect and nature of hydration on the glass transition temperature (Tg) of PLGA and investigated the physical state of water within the polymer during hygrothermal aging. The water content and the thermal behavior of PLGA-water system were assessed by Karl Fischer titration and modulated differential scanning calorimetry, respectively, the hygrothermal aging was monitored by gel permeation chromatography. Water depressed reversibly the Tg by about 15 °C regardless of the incubation conditions. It was concluded that the water responsible for plasticizing the polymer was non-freezable (bound) water and the small fraction of such water which was absorbed at high relative humidity caused polymer degradation in the same manner as bulk water.

Li et al.\textsuperscript{138}, in a study, incorporated α-cobrotoxin into the microspheres composed of PLGA and poly[1,3-bis( p-carboxy-phenoxy) propane-\textsuperscript{co– p- (carboxyethylformamido) benzoic anhydride}] (P(CPP:CEFB)) and intranasally delivered to model rats in order to improve its analgesic activity. The microspheres with high entrapment efficiency (>80%) and average diameter of about 25 m could
be prepared by a modified water-in-oil-in-oil (w/o/o) emulsion solvent evaporation method. A tail flick assay was used to evaluate the antinociceptive activity of the microspheres after nasal administration. Compared with the free α-cobrotoxin and PLGA microspheres, PLGA/P (CPP: CEFB) microspheres showed an apparent increase in the strength and duration of the antinociceptive effect at the same dose of α-cobrotoxin (80 g/kg body weight).

Vila et al. studied the PLA-PEG particles for nasal protein delivery. Nasal bioavailability of tetanus toxoid which was used as model drug was calculated. The results emphasize the utility of PLA–PEG NPs may be suitable for carriers for nasal administration of proteins.

Segundo et al. produced and characterized triclosan loaded PLGA (RsG) NPs, by emulsification-diffusion process. PVA was used as a stabilizer. It was concluded that a fast release was present. About 75% of drug from PLGA NPs released within 30 min from few formulations and to an extent of 90% drug was released within 30 min from NPs (mean size 354 nm). This was with RsG type PLGA.

Higaki et al., prepared PLGA NPs containing a hydrophilic drug, betamethasone sodium phosphate and evaluated its efficiency for treatment of experimental arthritis in rats. A single injection of NPs were significantly effective in controlling inflammation when compared to unencapsulated drug (a 30% decrease in paw inflammation was obtained in 1 day and maintained for 1 week with a single injection of 100 μg of PLGA-nanosteroid). This proved the effectiveness of encapsulated drug performing better than free drug.

Mainardes et al., studied the effect of formulation variables on size distribution of PLGA NPs containing praziquantel. It was reported that sonication time, PLGA concentration, drug concentration, PVA concentration, ratio between
aqueous and organic phases, method of solvent evaporation have significant influence on size distribution of the NPs.

Astete et al\textsuperscript{143} presented a review about the different preparation and characterization methods of NPs using PLGA. NPs of PLGA of different physical characteristics (size, size distribution, morphology, zeta potential) can be synthesized by controlling the parameters specific to the synthesis method employed. The aim of this review is to clearly, quantitatively and comprehensively describe the top–down synthesis techniques available for PLGA NPs formation, as well as the techniques commonly used for NPs characterization. Many examples have been discussed in detail to provide the reader with an extensive knowledge base on the important parameters specific to the synthesis method described and ways in which these parameters can be manipulated to control the NPs physical characteristics.

Reis et al\textsuperscript{144} stated in their review that lyophilization seems to be a highly stabilizing process and is applied to enhance the physicochemical stability of the NPs to achieve a pharmaceutically acceptable product, especially in cases in which the storage conditions are unfavorable. The freeze dried NPs are obtained in the form of a dry powder that is easy to handle and store. In most cases the freeze-dried particles are readily dispersible in aqueous medium. Finally, NPs can be stored in sealed vials at room temperature, or in laboratory desiccators, or even in the refrigerator, especially for temperature-sensitive drugs and hygroscopic excipients.

Nishivama et al\textsuperscript{145} presented a review on nanocarriers. Polymeric micelles, self-assemblies of block copolymers, are promising nanocarrier systems for drug and gene delivery. It was stated that polymeric micelles are nanotechnology-based carrier systems that might exert the activity of potent bioactive compounds in a site-directed manner, ensuring their effectiveness and safety in the clinical use.
Csaba et al.\textsuperscript{146} have reported the formation of a new type of NPs consisting of blends of PLGA and polyethylene oxide (PEO) derivatives, which exhibit the capacity to associate and release plasmid deoxy ribo nucleic acid (DNA) in a controlled manner and the ability of these NPs to overcome cellular and mucosal barriers (i.e. nasal mucosa) and thus, to work as gene delivery carriers. The results of the \textit{in vitro} cell culture studies showed the ability of these new NPs to enter the cells and transport the associated DNA molecule across the cell membrane. \textit{In vivo} administration of the fluorescent NPs evidenced their capability to overcome the nasal mucosal barrier. The results of the immunization studies showed that DNA-loaded NPs elicit a fast and strong response, significantly more pronounced than that corresponding to the naked plasmid DNA for up to 6 weeks. These results suggest that these new NPs have a potential as carriers for the delivery of DNA across the nasal mucosa.

Singh et al.\textsuperscript{147}, have reported the preparation and evaluation of poly-(\(\varepsilon\)-caprolactone) (PCL), PLGA-PCL blend and co-polymer NPs encapsulating diphtheria toxoid (DT) for their potential as a mucosal vaccine delivery system. The NPs, prepared using a water-in-oil-in-water (w/o/w) double emulsion solvent evaporation method, demonstrated release profiles which were dependent on the properties of the polymers. The highest uptake mediated by the most hydrophobic NPs using Caco-2 cells was mirrored in the \textit{in vivo} studies following nasal administration a significant positive correlation between hydrophobicity of the NPs and the immune response was observed following i.n. administration. The positive correlation between hydrophobicity of the NPs and serum DT specific IgG antibody response was also observed after i.n. administration of the NPs.

Choi \textit{et al.}\textsuperscript{148}, prepared PLGA NPs loaded with recombinant human granulocyte colony stimulating factor (rhG-CSF), by spontaneous emulsion/solvent
diffusion method. RsG was the polymer grade of PLGA used and the encapsulation efficiency was about 87.8% and biphasic release pattern was observed. It was concluded that polymer grade, method of preparation and size of the particle affects the release pattern.

*Torchilin*[^149^], presented a review on multifunctional nanocarriers. This report stated that currently used pharmaceutical nanocarriers, such as liposomes, micelles, nanoemulsions, polymeric NPs and many others demonstrated a broad variety of useful properties and suggested possible future directions in the emerging area of multifunctional nanocarriers with primary attention on the combination of such properties as longevity, targetability, intracellular penetration and contrast loading. It was also stated that the engineering of multifunctional pharmaceutical nanocarriers combining several useful properties in one particle can significantly enhance the efficacy of many therapeutic and diagnostic protocols.

Surti *et al*[^150^], prepared PLGA NPs and lectin (Wheat germ agglutinin) conjugated PLGA NPs of budesonide for intracellular drug delivery, and evaluated the *in-vitro* antiproliferative activity of NPs using A549 cell line. Budesonide encapsulated NPs were prepared using emulsion-solvent evaporation technique. Wheat germ agglutinin-conjugation was done by two-step carbodiimide method. NPs were characterized for particle size and zeta potential, entrapment efficiency and *in-vitro* drug release profile using HPLC assay. The *in-vitro* release profile of unconjugated showed burst release of the drug, but the conjugated showed sustained release.

**REVIEW FOR SUMATRIPTAN:**

The report of the international study group[^151^], listed that, Sumatriptan, a medication frequently prescribed by the general or family physician consulted for
migraine, has been shown in clinical trials to be effective in the treatment of migraine headache, clinical disability, and associated symptoms such as nausea, photophobia, and phonophobia. Headache was alleviated in approximately 80% of patients within 2 hours of s.c. dosing and in approximately 70% of patients within 4 h of oral dosing. These clinical results were substantiated and extended by data from studies documenting patients' perceptions of sumatriptan.\textsuperscript{152,153}

Dixon \textit{et al.}\textsuperscript{154}, described the disposition of SS in laboratory animals and humans after oral and parenteral administration. Oral absorption of sumatriptan was essentially complete in dogs and rabbits, but only approximately 50% in rat. In humans, at least 57% of an oral dose was absorbed. Bioavailability of oral dosage form were species dependent (14, 23, 37, and 58% in humans, rabbits, rats, and dogs) reflecting differing degrees of first-pass metabolism. Protein binding of sumatriptan was low in all species. Disposition half-lives of sumatriptan were approximately 1 h in rats and rabbits, and approximately 2 hr in dogs and humans. Interesting species differences were evident in the metabolism of sumatriptan. Thus, in humans, the indole acetic acid metabolite was excreted partly as a glucuronide, whereas in animals conjugation of this metabolite was not apparent. In addition, demethylation of the sulfonamide side chain of the drug was evident in rodent and lagomorph species only.

The results of survey of 648 patients who had received s.c. sumatriptan in a clinical trial, as reported by Luciani\textsuperscript{152}, stated the patients' overall satisfaction with sumatriptan therapy, and sumatriptan was rated more favorably than aspirin, acetaminophen, or patients' usual medications with respect to effectiveness, speed of relief, and number of doses required to achieve relief; but that s.c injection may not be the optimal dosage form for all patients.
One fifth of s.c sumatriptan users in the study of 351 migraineurs carried out by Dahlof\textsuperscript{153} using injectable or oral sumatriptan on an outpatient basis, cited syringe phobia as a reason for their hesitation to use it. Besides fear of injections, ease of use may be an impediment to the use of s.c sumatriptan among some patients: it was rated significantly less favorably than aspirin or acetaminophen on the dimension of ease of use.\textsuperscript{152}

Oral tablets might be a viable treatment option for patients with reservations about using injectable medication; however, some patients’ migraine-associated nausea and vomiting preclude the effective use of oral medication. The results of early European studies, reported by Salone\textsuperscript{155}, in which sumatriptan hemisulfate nasal spray (1, 5, 10, 20, or 40 mg) was administered for a single migraine attack demonstrate that sumatriptan hemisulfate nasal spray (10, 20, or 40 mg) is consistently more effective than placebo at alleviating headache and migraine-associated symptoms, including nausea, photophobia, and phonophobia, and at reducing clinical disability. The most frequently occurring adverse event in these studies was unpleasant taste, which was reported more often in the sumatriptan nasal spray groups compared with the placebo group. In addition, patients required second dose of the same approximately after 2 h for continuing the relief.

The report by Mitsikostas \textit{et al}\textsuperscript{156}, which present the effect of sumatriptan on brain monoamines in rats using different doses of 0.3 mg/kg, 0.6 mg/kg and 0.9 mg/kg, stated that changes related to the therapeutic action was found at the dose of 0.6 mg/kg and above. It was concluded that subcortical antidopaminergic and antiserotoninergic effect of sumatriptan may be involved in its antimigraine action. This was taken as a basis for fixing the dose for pharmacodynamic action.
Eliane et al \textsuperscript{157}, presented a review of i.n. sumatriptan. It was stated that substantial proportions of migraine patients have gastric stasis and suffer severe nausea and/or vomiting during their migraine attack. This may lead to erratic absorption from the gastrointestinal tract and make oral treatment unsatisfactory. For such patients, an i.n. formulation may be advantageous. After i.n. administration, sumatriptan was directly and rapidly absorbed, with 60\% of the maximum plasma concentration (C\textsubscript{max}) occurring at 30 min after administration of a single 20 mg dose. Following i.n. administration, approximately 10\% more sumatriptan was absorbed probably via the nasal mucosa when compared with oral administration. Mean C\textsubscript{max} after a 20 mg i.n. dose was approximately 13.1 to 14.4 \text{ng/ml}, with t\textsubscript{max} approximately between 1 to 1.75 h. The elimination phase half-life is approximately 2 h, consistent with administration by other routes. Single-dose pharmacokinetics in pediatric and adolescent patients following i.n. sumatriptan was studied to determine the effect of changes in nasal morphology during growth, and of body size, on pharmacokinetic parameters. The pharmacokinetic profile observed in adults was maintained in the adolescent population; generally, factors such as age, bodyweight or height did not significantly affect the pharmacokinetics. Clinical experience suggests that i.n. sumatriptan had some advantages over the tablet (more rapid onset of effect and use in patients with gastrointestinal complaints) or s.c (noninvasive and fewer adverse events) formulations.

Gayatri et al \textsuperscript{158}, prepared and evaluated niosomal SS for nasal administration. Niosomes of SS were prepared using lipid hydration method. The prepared niosomes were evaluated for entrapment efficiency, size analysis and \textit{in vitro} release studies. Further, the niosomes were evaluated for nasal absorption using an \textit{ex vivo} animal model. The entrapment efficiency was found to be 57.9 +/- 0.96 \%. The niosomes released 58.71 \% of SS over a period of 6 h and 78.1 \% of the drug was absorbed from the nasal mucosa \textit{ex vivo}. 

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Mahajan et al\textsuperscript{159} prepared and evaluated the pharmaceutical parameters of mouth dissolving tablets of SS.

Chavanpatil et al\textsuperscript{160}, studied the effect of bile salts to increase the nasal absorption of SS. A rat \textit{in situ} nasal perfusion technique was used to examine the rate and extent of absorption of SS. \textit{In vitro} enzymatic drug degradation studies were carried out with rat nasal washings. Various experimental conditions such as nasal perfusion rate, pH of the perfusion medium and concentrations of absorption enhancers such as sodium deoxycholate, sodium caprate, sodium tauroglycocholate and EDTA were optimized. \textit{In vivo} studies were carried out for the optimized formulation in rabbits and the pharmacokinetics parameters of nasal solution were compared with marketed nasal solutions. Nasal absorption of SS was pH dependent. It was found maximum at pH 5.5 and decreased at higher pH values. In \textit{in vitro} enzymatic degradation studies, no measurable degradation was observed during the first week. The extent of drug absorption was increased by absorption enhancers. Sodium deoxycholate appeared to be more effective for enhancing the nasal absorption of SS than the other absorption enhancers. The order of increasing absorption of SS caused by the enhancers was sodium deoxycholate > sodium caprate > sodium tauroglycocholate > EDTA.

Chaudhari \textit{et al}\textsuperscript{161}, executed preformulation study of SS nasal gel prepared using Pluronic F-127 as the gelling agent. The effect of formulation additives on gelation properties has been reported. But this report did not evaluate the SS release.

Majithiya \textit{et al}\textsuperscript{162}, applied the concept of thermoreversible mucoadhesive gel for nasal delivery of Sumatriptan. This study reported the preparation and evaluation of gel using Pluronic PF 127 and Carbopol 934 P. It was concluded that the absorption
of Sumatriptan may be improved by increasing the residence time of the formulation in the nasal region.

Vyas et al.\textsuperscript{163} utilized the microemulsion formulation for delivery of Sumatriptan through i.n. route. Characterization of the microemulsions was followed by evaluation in rat model by gamma scintigraphy. This report stated that microemulsions of the base sumatriptan resulted in rapid, large extent of transport to the brain, when compared with plain sumatriptan.

Redkar et al.\textsuperscript{164}, formulated stable onion phases of the biodegradable surfactant, PEG -8, Distearate (PEG8DS) and evaluated its application in encapsulating SS, a Biopharmaceutical Class System (BCS), class III, potent antimigraine drug. Drug loaded and placebo onion phases were prepared by shearing lyotropic lamellar phases of the surfactant. Effect of drug/surfactant ratio, shear rate and shear time on particle size, and encapsulation efficiency were studied. The onion phases were characterized by different methods. It was reported that SS was present in the aqueous phases of the multilamellar vesicles; high encapsulation efficiency (\textasciitilde 90\%) and rapid \textit{in vitro} drug release (>90\% in 10 min). Onion phases stored at 5°C \pm 3°C revealed no significant drug leakage at the end of 3 months suggesting adequate stability. SS loaded stable onion phases of PEG8DS with high entrapment efficiency and rapid drug release suggests potential application of the onion phases in drug delivery.