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Solid Lipid Nanoparticles Acting on CNS through Nasal Drug Delivery System

[1]Priti P. Giradkar, [2]Rani S. Julme, [3]Pankaj M. Pimpalshende, [4]Satish B. Kosalge

Department of Pharmaceutics, Hi-Tech College of Pharmacy, Chandrapur, Maharashtra, India.

Department of Pharmacognosy, Hi-Tech College of Pharmacy, Chandrapur, Maharashtra, India.

Adstract

The development of solid lipid nanoparticles (SLN) as a next-generation drug delivery technology has opened up new opportunities for the pharmaceutical industry, cosmetics, research, clinical medicine, and other related fields of study. These SLN are receiving more and more interest as colloidal drug carriers for integrating hydrophilic or lipophilic medicines recently. Nasal medication delivery has drawn a lot of interest as a practical, dependable, and promising approach to systemic drug delivery. The present review is an attempt to provide some information concerning SLN acting on CNS through nasal drug delivery system such as lipid based nanoparticle, benefits, limitations, advantages, nasal anatomy, Preparation of SLN, factors affecting of nose to brain delivery.

Keywords: Solid lipid nanoparticle, Nasal drug delivery, Central Nervous System, Nose to brain, Preparation of SLN.

Introduction

The drug's stability, release, rate of dissolution, and systemic absorption are controlled by the drug delivery mechanism. A medicine must be administered in the correct dosage form in order to have the best possible pharmacological impact. The dosage form should be able to make unstable medications more stable, work specifically at a certain place, reduce toxicity, and be cost-effective (D. Ram et al., 2012). With the profound understanding acquired in the diverse domains of biotechnology, biomedical engineering, and nanotechnology, the field of novel drug delivery system is developing at an exponential rate. Numerous current formulation methods prepare API-containing nanoscale structures using nanotechnology (N. Yadav et al., 2013).

As a potential colloidal drug carrier for intravenous applications, nanoparticles consisting of solid lipids are gaining significant attention. They have been offered as an alternative particulate carrier system (M. Hanumanaik et al., 2013).

Traditional colloidal carriers were replaced by solid lipid nanoparticles (SLN) for the first time in December1991. These particles are spherical stable lipid cells with diameters in the nanometer range that are frequently dispersed in fluid surfactant arrangements or in water (A. Alssad et al., 2020).

In comparison to conventional dosage forms, nanoparticulate drug delivery systems may have several number of benefits, including better, reduced toxicity, enhanced biodistribution, treatment of chronic human diseases, and

improved patient compliance. Nanoparticles are colloidal particles with a size between 10 and 1000 nm. They are made from synthetic or natural polymers and are solid polymeric and submicronic colloidal systems that are good for medication administration and low toxicity. The widespread use of nanoparticles in clinical treatment has been constrained by the lack of safe polymers with regulatory permission and their expensive cost. Lipids have been proposed as an alternate carrier to circumvent these polymeric nanoparticle drawbacks, notably for lipophilic medicines. Solid lipid nanoparticles is the name given to these lipid nanoparticles. (SLNs) (D. Ram et al., 2012).

Lipid-based Nanoparticles

Lipid-based nanocarriers are drug delivery systems made of lipid and an aqueous phase, stabilised by surfactants. These biocompatible and biodegradable technologies offer excellent controlled release, drug protection, drug loading, stability, and surface adaptability. Because of their ability to pass through biological membranes and to encourage the partitioning of nanosized droplets in the nasal mucosa, lipid-based nanocarriers have a high potential to improve brain drug delivery after their IN administration. This is because they increase the residence time of the drug in the brain (M. Formica et al., 2022). The utilisation of solid lipids to create lipid nanoparticles has become a groundbreaking strategy since the early 1990s in the era of nanoparticulate controlled and site specific drug delivery systems (S. Patel et al., 2012). Based on the generations of lipid nanoparticles evolved, they are categorized in following types:

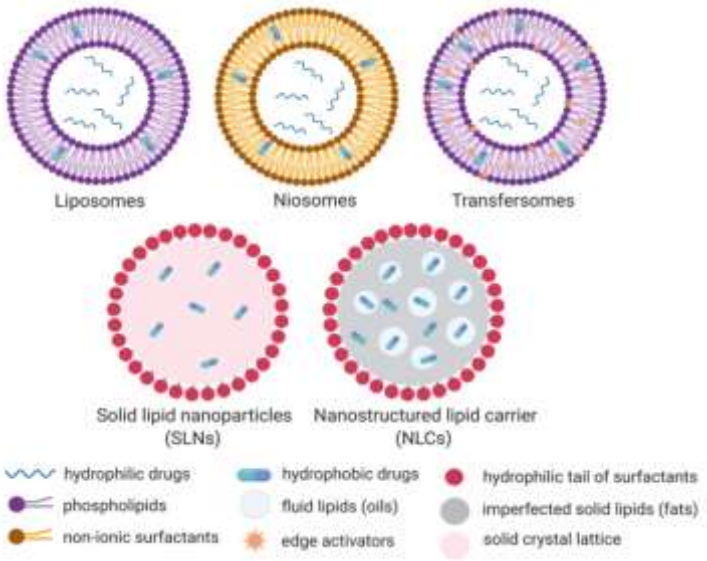

Fig. no. 1:- Lipid Based Nanoparticle (T. Thi et al., 2021)

Properties of SLN

- Small size
- Large surface area
- High drug loading
- Their potential to enhance pharmacological performance

Benefits of SLN

- Good biocompatible
- More appropriate for greater drug loading
- Increase the bioactive chemicals' stability
- Increase entrapped medicines' bioavailability
- Chemical defences for bioactive substances
- Simple to scale up and sterilise (S. Raziyabegum et al., 2013)

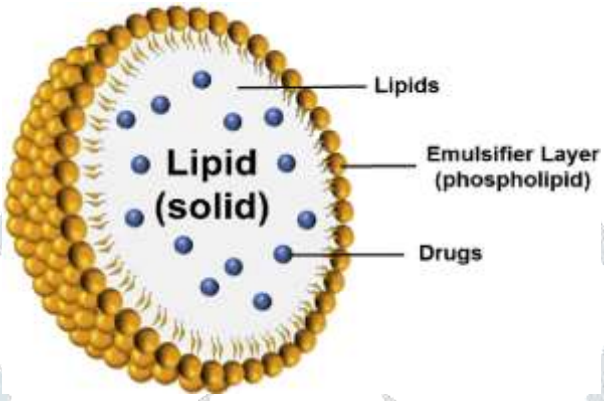

Fig.no. 2:- Solid Lipid Nanoparticle (SLN) (A. Ahmed et al., 2020).

Nasal Drug Delivery System

Nasal drug delivery has a long history that begins with earlier uses of medications meant for local effects. Nasal therapy, also known as "Nasya karma," is a recognised kind of treatment in the Indian medical system of Ayurveda (S. Pagar et al., 2013)

Nasal medication administration has been used for a long time to achieve both topical and systemic effects. Topical application has led to the development of a wide range of various drugs, including corticoids, antihistamines, anticholinergics, and vasoconstrictors, for the treatment of congestion, rhinitis, sinusitis, and related allergy or chronic disorders. Recent years have seen an increase in research on the nasal route, particularly on nasal application for systemic medication administration. Only a few nasal delivery methods, such as pressurised MDIs, dry powder inhalers, aqueous nasal sprays, nasal gel pumps, and multiple- or single-dose nasal drops, are now available on the market to deliver medicines into the nasal cavities. Currently, intranasal administration is used to treat conditions such as osteoporosis, nocturnal enuresis, migraine, smoking cessation, acute pain alleviation, and vitamin B12 deficiency. Cancer treatment, epilepsy, anti-emetics, rheumatoid arthritis, and insulin-dependent diabetes are some more examples of therapeutic areas in development or with potential for nasal delivery (M. Alagusundaram et al., 2010)

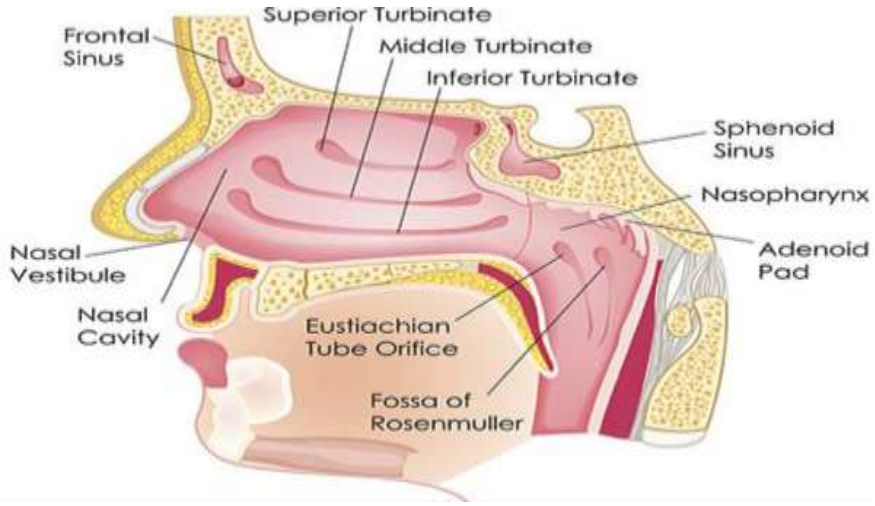

Fig. no. 3: Schematic of a saggital section of nasal cavity (S. Moinuddin et al., 2019)

Possibilities for the use of the nasal cavity for drug delivery (S. Alnasser, 2019)

The nose is a potential medication delivery organ due to its accessibility and surface area. The development of pharmaceutical products is a crucial task that is directly related to their therapeutic goals. The aspects to be considered for product development depend on whether it is intended for :

a) Local delivery

b) Systemic delivery

c) Single or repetitive administration.

Local delivery

In contrast to oral administration, nasal delivery offers the least risk of systemic side effects, making it the appropriate delivery method for local (or topical) treatment. As a result, relatively low doses are efficacious when taken via the nose route with fewer systemic harmful effects. Decongestants for the symptoms of a cold or sinus congestion and antihistamines and corticosteroids for allergic rhinitis are two prominent therapeutic types of medications administered.

Systemic delivery

Compared to oral and intravascular modes of administration, the intranasal delivery of medications is a useful method for increasing the systemic availability of pharmaceuticals. Compared to oral and parenteral delivery, it offered faster and longer drug absorption. Analgesics (exmorphine), cardiovascular medications like propranolol and carvedilol, hormones like levonorgestrel, progesterone, and insulin, anti-inflammatory medications like indomethacin and ketorolac, and antiviral medications are among the therapeutic classes of medications administered (acyclovir). For treating migraines and cluster headaches, two examples that are offered on the market are zolmitriptan and sumatriptan.

Nasal vaccines

Nasal mucosa is the initial site of contact with inhaled antigens during inhalation, hence its use for immunisation, particularly against respiratory illnesses, has undergone substantial research. Because nasal vaccination can raise systemic levels of both nasal secretory immunoglobulin A and specific immunoglobulin G, it is a prospective alternative to the traditional parenteral method. Intranasal vaccines against influenza A and B virus, proteosoma

influenza, adenovirus-vectored influenza, native Group B meningococcal infection, attenuated respiratory syncytial virus, and parainfluenza 3 virus are some examples of those with human efficacy.

Central Nervous System (CNS) Delivery through Nasal Route

The intranasal method has shown promise for delivering medications to the brain. Olfactory neuroepithelium may be involved in the nasal transport of medicines to the central nervous system. For the treatment of Alzheimer's disease, brain tumors, epilepsy, pain, and sleep disturbances, nasal drug administration into the CNS has been documented.

Advantages of nasal drug delivery system (S. Pagar et al., 2013; M. Alagusundaram et al., 2010)

- Rapid medication absorption occurs through highly vascularized mucosa.
- It is possible to achieve rapid medication absorption and activity.
- Nasal drug delivery is a method for delivering medications to the systemic circulation that are not orally digested.
- Drug degradation that has been seen in the GIT is avoided.
- Substitute for parenteral administration, particularly for proteins and peptides.
- A convenient approach for patients receiving long-term medication.
- Improved absorption.
- Less side effects from low dose.
- Improved patient comfort and compliance.
- It is possible to self-administrate.
- Direct transfer into the CNS and systemic circulation is possible.
- Reduces the risk of overdosing.

Limitations of nasal drug delivery system

- The delivery volume within the nasal cavity is limited to 25–200 L.
- Compounds with high molecular weights cannot be given in this way. (mass cut off ~1 kDa).
- The absorption enhancers utilised in the nasal drug delivery system's histological toxicity is not yet well-established.
- In comparison to the GIT, the nasal cavity has a lesser surface area for absorption.
- Comparatively less convenient for patients than oral delivery methods due to the potential for nasal discomfort.
- The permeability of a medication is affected by natural defensive mechanisms such as mucociliary clearance and ciliary beating.
- Nasal mucosa irritation caused by medications like Budesonide and Azilactine.

Delivery to the Central Nervous System (CNS) through the Nasal Route (S. Verma et al., 2021; B. Kalita et al., 2016)

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Table no. 1:- Structural features of various regions and their impact on the permeability of nasal cavity

Region	Structural Features	Permeability
Nasal vestibule	Nasal hairs (vibrissae)Epithelial cells are stratified, squamous and keratinized sebaceous glands present	Last permeable because of the presence of Keratinized cells
Atrium	Transepithelial region stratified squamous cells present anteriorly and pseudo stratified cells with microvilli present posteriorly	Less permeable as it has small surface area and stratified cells are present
Respiratory region	Pseudostratified ciliated columnar cells with microvilli (300per cell), large surface area Receives maximum nasal secretion because of the presence of seromucus gland, nasolacrimal duct and goblet cells	Most permeable region because of large surface area and rich vasculature
Olfactory region	Specialized ciliated olfactory nerve cells for smell perception Receives ophthalmic and maxillary division of trigeminal nerve Direct access to cerebrospinal fluid	Direct access to cerebrospinal fluid
Nasopharynx	Upper part contains ciliated cells and lower part contains squamous epithelium	Receives nasal cavity drainage

Nasal Anatomy

The nose controls the temperature and humidity of the air that is inhaled as well as the elimination of foreign pathogens. It also regulates olfaction. The nasal cavity is one of the tiniest organs in the human body, with a total surface area of around 160 cm2, a capacity of 13.0 mL, and a length of 12–14 cm from the nostrils to the nasopharynx. (C. Costaa et al., 2021).

The intranasal method has shown promise for delivering medications to the brain. Olfactory neuroepithelium may be involved in the nasal transport of medicines to the central nervous system. For the treatment of Alzheimer's disease, brain tumors, epilepsy, pain, and sleep disturbances, nasal drug administration into the CNS has been documented. (S. Alnasser et al., 2019).

Nose-to-Brain Delivery Pathway :- There has been substantial research on and reporting on nose-to-brain delivery channels. As shown in Figure 3, When a drug is administered intravenously, its molecules or drug-loaded particles go directly from the nose to the brain via the trigeminal and olfactory neurons and then indirectly into the bloodstream before crossing the blood-brain barrier to do so.

Medication is delivered to the respiratory and olfactory systems when it reaches the nasal cavity. Olfactory nerves in the nasal cavity start in the olfactory epithelia and end at the olfactory bulb. Four different pathways exist for drugs in the olfactory region to reach the brain: (1) an extraneuronal pathway along olfactory neurons; (2) an intraneuronal pathway by olfactory neuron endocytosis; (3) a pathway through supporting cells by endocytosis; and (4) a pathway through the intercellular space by passing tight junctions.

The main direct route for medication delivery from the nose to the brain, which can take up to 30 minutes, is extraneuronal. The intraneuronal route involves olfactory neurons endocytosing the medication, releasing it in the olfactory bulb, and then dispersing it to various brain regions. This procedure could take several hours or even days. Less significant is the drug's transit via or along supporting cells. In certain research, the olfactory route has been mentioned. For example, the olfactory bulb, cerebellum, and striatum all clearly displayed fluorescence responses to IN given Cyanine7 NHS ester-loaded SLNs (Cys7-SLNs). Also, although the trigeminal nerve pathway is less significant than the olfactory pathway, a fraction of medications that enter the respiratory region can travel directly to the brain through extraneuronal or intraneuronal routes (T. Nguyen et al., 2022).

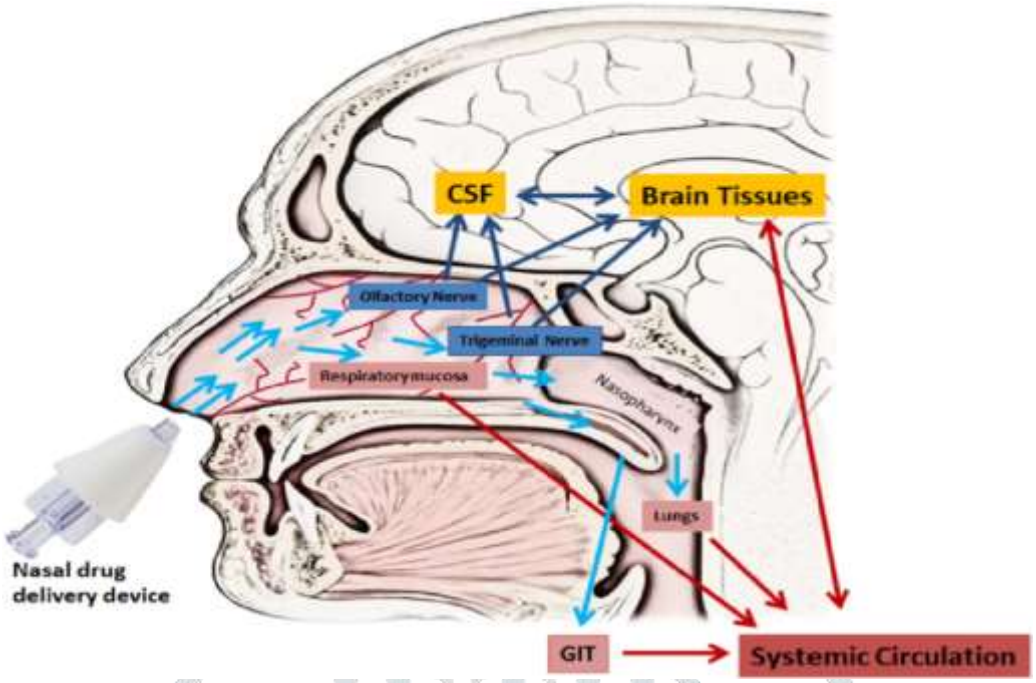

Fig. no. 4: Nasal drug delivery pathways. Nasally administered drug (light blue) can enter directly into the brain via the olfactory and/trigeminal neuronal pathways (dark blue), or indirectly following absorption into the systemic circulation (red). GIT is the gastrointestinal tract, CSF is cerebrospinal fluid. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article (M. Kapoor et al., 2016).

Main features of intranasal SLNs :- According to their characteristics, SLNs have a strong chance of enhancing drug delivery from the nose to the brain. Due to the presence of emulsifiers and their small sizes, respectively, these systems have a high degree of stability and the capacity to cross biological membranes. They also offer sustained drug release, improved bioavailability, and protection from chemical and/or enzymatic degradation. To extend the residence time of SLNs within the nasal mucosa and, consequently, the drug transport through the olfactory neurons, as well as modulators to open the tight junctions between the nasal cells, improving drug passage, it is possible to add bioadhesive excipients to the formulations of SLNs. These include gelling agents and viscosity enhancers. The development of a strong control system is crucial to ensuring the quality of the finished pharmaceutical products that contain SLNs. The formulation's critical quality attributes (CQAs), such as particle/droplet size, polydispersity index (PDI), zeta potential (ZP), and encapsulation efficiency, must be assessed in order to achieve this (EE) (C. Costaa et al., 2021).

Structure and Position of the Nose (Mohd Yasir et al., 2016)

The respiratory system's nasal cavity is its first component. As they relate to the nasal cavity, the following bones:

1) Roof: Consists of the ethmoid bone, sphenoid bone, frontal bone and nasal bone.

2) Floor: The roof of the mouth, with the soft palate (formed of the palatine bone) behind and the hard palate (made of the maxilla bone) in front, forms the floor of the nasal cavity.

3) Medial wall: The septum creates this wall.

4) Lateral walls: The ethmoid bone, maxilla, and inferior conchae make up the lateral walls.

5) Posterior wall: This structure is created by the pharynx's posterior wall. The septum separated the nasal cavity into two equal air entry routes. Each channel has a surface area of around 75 cm^2 and a volume of about 7.5 ml. The nasal cavity is externally opened by the anterior nares, while the pharynx is externally opened by the posterior nares.

There are four distinct functional regions in the nasal cavity based on morphological and histological characteristics, including

(i) Vestibule (ii) Atrium (iii) Respiratory region (iv) Olfactory region

Vestibule:-

The vestibule is a representation of the nasal cavity's frontal region. The stratified keratinized squamous epithelium with many sebaceous glands makes up this layer. The vestibule has a surface area of about 0.6 cm2. Due to its limited relative surface area and low permeability, this region is of little consequence for drug delivery applications.

Atrium:-

The atrium is situated between the nasal vestibule and the respiratory area. The front part of the atrium is covered in stratified squamous epithelium, and the posterior part is made up of pseudo-stratified columnar epithelial cells with microvilli on their surfaces. Due to its poor permeability and vasculature, the atrium is of minor value for drug delivery applications like the vestibule.

Respiratory region:-

Conchae or the respiratory region plays a vital part in the systemic administration of drugs. The superior, middle, and inferior turbinates are the three divisions. Basement membrane, lamina propria, and epithelium are all components of the respiratory area. The nasal cavity's highly vascularized epithelium is composed of ciliated columnar cells with many mucus-secreting goblets cells. The respiratory epithelium's cilia aid in moving mucus to the pharynx, while microvilli broaden the surface area for absorption.

Olfactory region:-

In humans, the olfactory region is located on the roof of the nasal cavity and has a surface area of between 10 and 20 cm2. In comparison to rats, who have olfactory areas that make up around 50% of their nasal cavities, humans have olfactory regions that make up roughly 8% of the entire nasal cavity. Direct communication between this region and the outside world is provided by the olfactory neurons. The serous glands in this region secrete a unique class of compounds that serve as an odorous solvent. The primary component of the olfactory epithelium, which connects the nose and brain, is the olfactory bulb.

Table no. 2:- Ingredients used in SLNs-based formulations (V. Mishra et al., 2018)

Ingredients	Examples
Lipid component	Beeswax, Stearic acid, Cholesterol, Caprylic/capric triglyceride, Cetylpalmitate, Glyceryl stearate (-mono, and -tri), Glyceryl trilaurate, Glyceryl trimyristate, Glyceryl behenate (Compritol), Glyceryl tripalmitate, Hardened fat (Witepsol E85, H5 and W35), Monostearate monocitrate, Solid paraffin, Behenic acid
Surfactant/Emulsifiers	Phosphatidyl choline, Soy and Egg lecithin, Poloxamer, Poloxamine, Polysorbate 80
Co-surfactant	Sodium dodecyl sulphate, Tyloxopol, Sodium oleate, Taurocholate sodium salt, Sodium glycocholate, Butanol
Preservative	Thiomersal
Cryoprotectant	Gelatin, Glucose, Mannose, Maltose, Lactose, Sorbitol, Mannitol, Glycine, Polyvinyl alcohol, Polyvinyl pyrrolidone
Charge modifiers	Dipalmitoyl phosphatidyl choline, Stearylamine, Dicetylphosphate, Dimyristoyl phophatidyl glycerol

Preparation of solid lipid nanoparticles

The many techniques used to create SLNs from lipid, emulsifier, and water/solvent are mentioned below.

1. High pressure homogenization

a. Hot homogenization

b. Cold homogenization

2. Ultrasonication/high speed homogenization

a.Probe ultrasonication

b.Bath ultrasonication

3. Solvent evaporation method
4. Solvent emulsification-diffusion method
5. Supercritical fluid method
6. Microemulsion based method
7. Spray drying method
8. Double emulsion method
9. Precipitation technique
10. Film-ultrasound dispersion
11. Solvent Injection Technique
12. Membrane contractor method

High Pressure Homoginization

For the fabrication of SLN, NLC, and LDC, HPH is an appropriate approach. It can be carried out at increased temperatures (hot HPH technique) or below room temperature (cold HPH technique). Turbulence and cavitation both reduce particle size. Lipids are forced through a small gap of a few micrometer ranges using high pressure (100-200 bars) in the high pressure homogenization procedure. Hence, the factors that result in the disruption of particles down to the submicron range are shear stress and cavitation (caused by a sudden fall in pressure). The lipid contents typically vary from 5 to 10%. The homogenizer is not affected by it at this concentration. The scaling up of high pressure homogenization does not exhibit any issues. There are basically two methods for producing SLN by high pressure homogenization: cold and hot homogenization procedures (D. Ram et al., 2012).

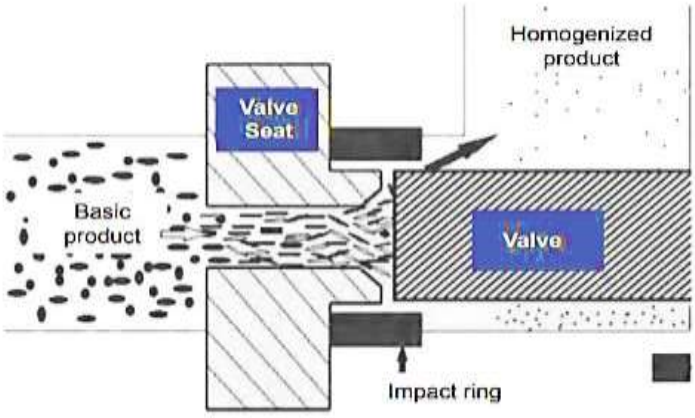

Fig. no. 5: Hot Pressure Homoginization (D. Ram et al., 2012).

a. Hot Homoginization

Hot homogenization, which is performed at temperatures over the lipid's melting point, can be viewed as the homogenization of an emulsion. The drug-loaded lipid melt and the aqueous emulsifier phase are mixed vigorously to create a pre-emulsion at the same temperature. At temperatures above the lipid's melting point, HPH of the pre-emulsion is conducted. Due to the inner phase's reduced viscosity, higher temperatures typically result in smaller particle sizes. High temperatures, however, speed up the medicine and carrier's decomposition. Because the particles have a high kinetic energy, increasing the homogenization pressure or the number of cycles frequently leads in an increase in particle size (P. Ekambaram et al., 2012)

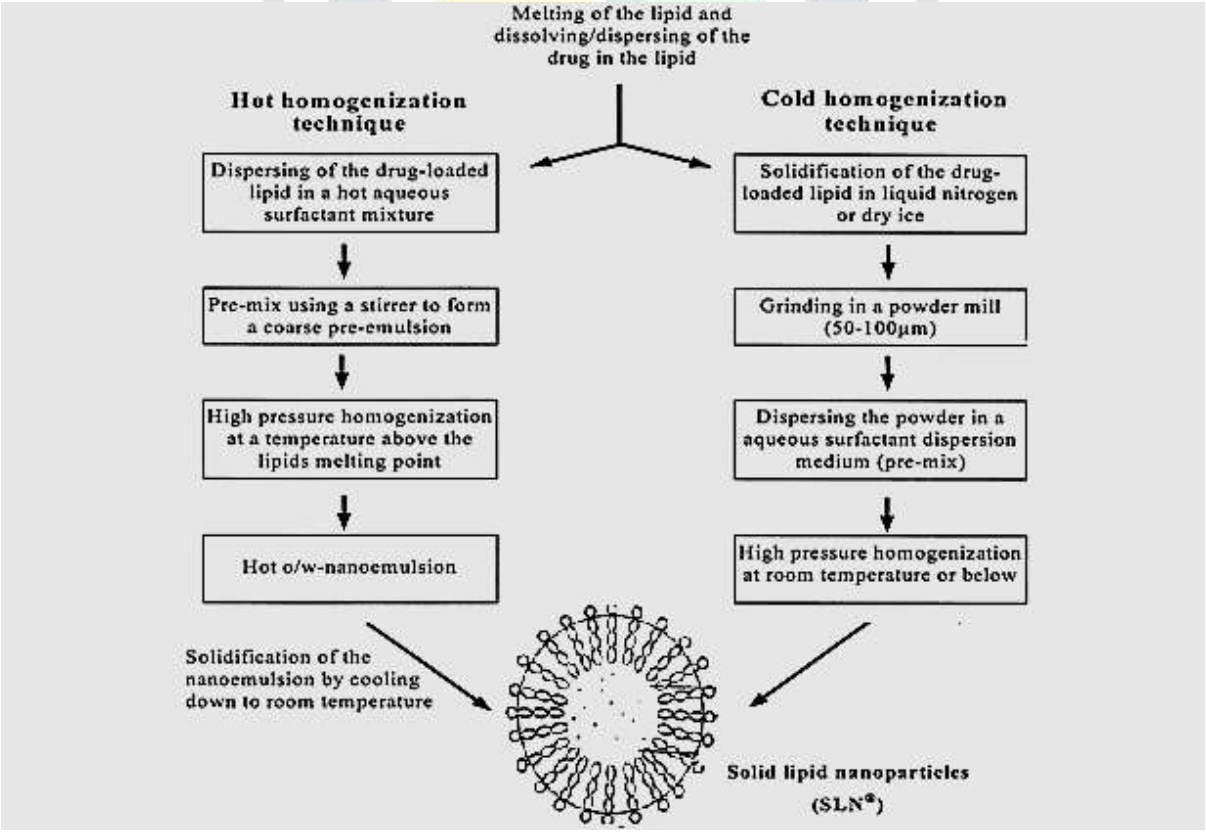

Fig. no. 6: Solid lipid nanoparticles preparation by hot homogenization process and cold homogenization process (R. Kabra et al., 2014).

b. Cold Homoginization

Cold homogenization has been developed to address severalnumber of issues with hot homogenization, including temperature-induced drug degradation, drug distribution into the aqueous phase during homogenization, and complexity of the nanoemulsion's crystallization step, which can result in multiple modifications and/or super cooled melts. In this method, the drug-containing lipid melt is cooled, the solid lipid is ground into lipid microparticles, and these lipid microparticles are dispersed in a cold surfactant solution to produce a pre-suspension. When this pre-suspension is homogenized at or below room temperature, the gravitational force is sufficient to shatter the lipid microparticles into solid lipid nanoparticles

Advantages

- Low capital expenditure.
- Seen in a laboratory setting.

Disadvantages

- An energy-intensive process.
- Displayed in a lab setting harm to biomolecules.
- Multidimensional distributions.
- Insufficient scalability (P. Ekambaram et al., 2012).

Ultrasonication/high speed homogenization

An additional technique for making SLNs is ultrasonication or high-speed homogenization. This method has the benefit of using equipment that is frequently found at lab scale. However, this approach has drawbacks like a wider size dispersion that goes into the micrometer range. Further downsides of this method include potential metal contaminations and physical instability, such as particle development upon storage (A. Garud et al., 2012).

Solvent evaporation method

With this method, a particle with an average diameter of 30 to 100 nm can be produced. The main benefit of this method is the absence of heat during preparation. In this method, the lipids are typically dissolved in an organic phase in a water bath at 50°C while using an acidic aqueous phase to alter the zeta potential and create SLN conservation. Centrifugation is then used to easily separate the lipids. The SLN suspension was created swiftly. The complete system that has been redistributed can then be centrifuged and suspended once again in distilled water (P. Mahajan et al., 2015).

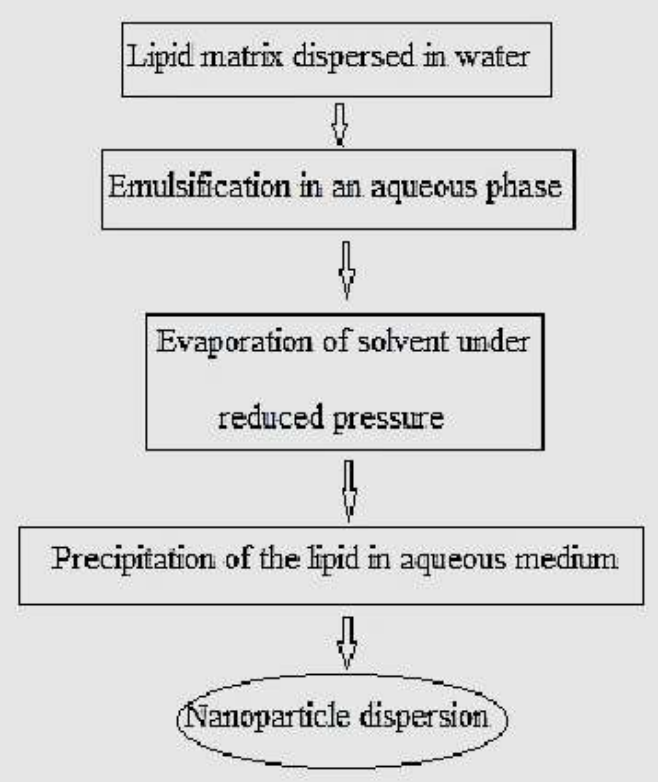

Fig. no. 7: Solid lipid nanoparticles preparation by Solvent evaporation process (P. Ekambaram et al., 2012).

Solvent emulsification-diffusion method

The technique of solvent emulsification and diffusion can also be used to create SLNs. The amount of lipid present in the organic phase and the type of emulsifier employed both affect the mean particle size. By using this method, particles with typical sizes of 30-100 nm can be produced. The main benefit of this method is that heat is avoided during preparation. Here, the lipid matrix is dissolved in an organic solvent that is inimical to water before being emulsified in an aqueous phase. As a result of the solvent's reduced pressure evaporation, the lipid precipitates as nanoparticles in an aqueous media (R. Kesharwani et al., 2013; A. Garud et al., 2012).

Supercritical fluid method

A benefit of the solventless procedure is that this is a new method.

Supercritical carbon dioxide solutions (99.99%) may be rapidly expanded to produce SLNs (S. Raziyabegum et al., 2013).

Advantages:-

- Avoid the use of solvents.
- ™Particles are obtained as a dry powder, instead of suspensions.
- ™Mild pressure and temperature conditions.
- Carbon dioxide solution is the good choice as a solvent for this method (P. Ekambaram et al., 2012).

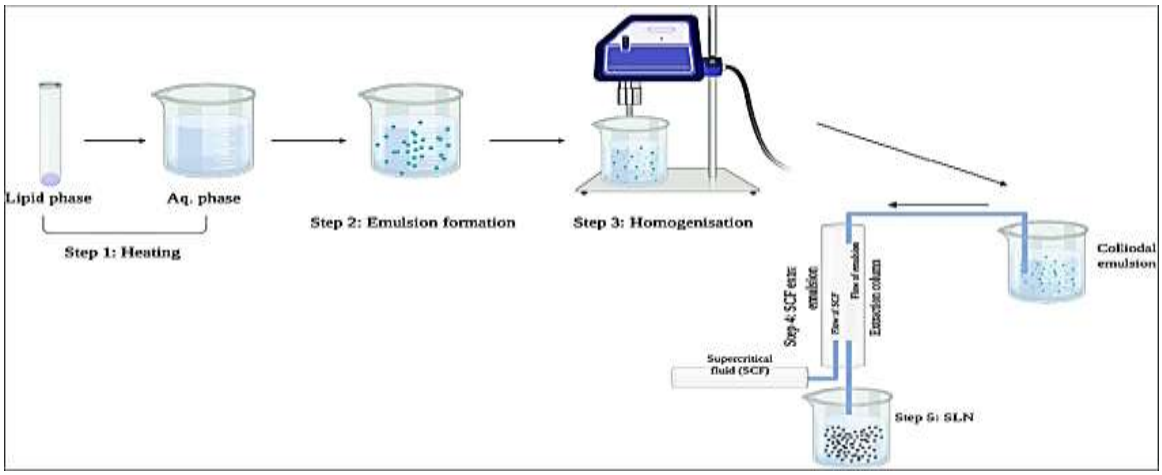

Fig. no. 8: Solid lipid nanoparticles preparation by Supercritical fluid method (K. Sastri et al., 2020).

Microemulsion based method

Techniques for SLN preparation that Gasco and colleagues created are based on diluting microemulsions. A low melting fatty acid (stearic acid), an emulsifier (polysorbate 20, polysorbate 60, soy phosphatidylcholine, and sodium taurodeoxycholate), co-emulsifiers (sodium monooctylphosphate), and water are generally used to create an optically transparent combination. Under stirring, the hot microemulsion is disseminated in cold water (2–3°C). The ratio of the hot microemulsion to the cold water is typically between 1:2 and 1:50. The makeup of the microemulsion has a significant impact on the dilution process. As the microemulsion already contains the droplet structure, no energy is needed to produce particles with submicron diameters.

By diluting polymer solutions with water, Fessi created polymer particles. The speed of the dispersion processes has a key role in determining particle size. Only acetone, a solvent that diffuses into the aqueous phase relatively quickly, may form nanoparticles; more lipophilic solvents provide larger particle sizes. Similar to how acetone forms polymer nanoparticles, the hydrophilic co-solvents of the microemulsion aid in the production of lipid nanoparticles (N. Yadav et al., 2013).

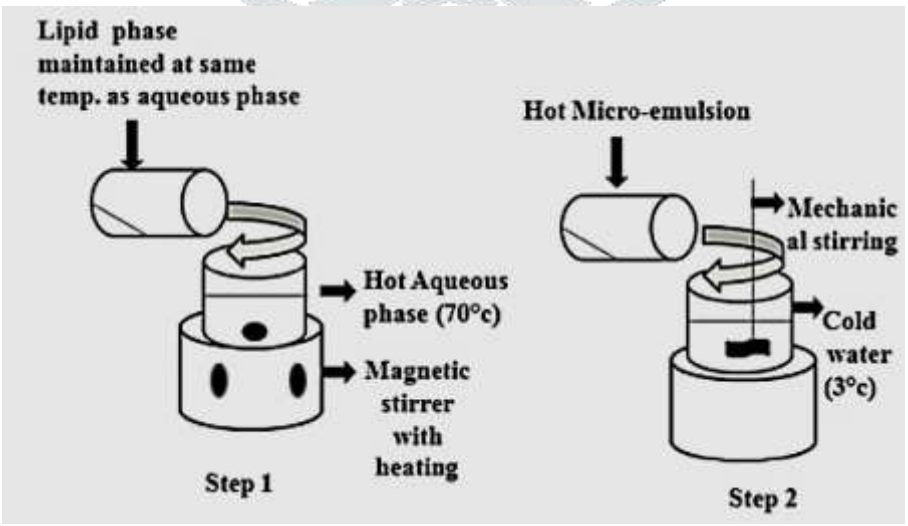

Fig. no. 9: Solid lipid nanoparticles preparation by Microemulsion based method (S. Bhatt et al., 2018)

Advantages:-

- A minimal input of mechanical energy.
- Stability of the theory.

Disadvantages:-

- Formulating requires a lot of work.
- Low levels of nanoparticles.
- Very sensitive to change (P. Ekambaram et al., 2012).

Spray drying method

This is an additional technique for turning SLN's liquid formulation into a dried medicinal product. This method, which is more profitable than lyophilization, makes more use of solid lipids with melting points over 70. Due to high heating, shear pressures, and partial melting of the nanoparticles, this approach causes aggregation of the particles (P. Shinde et al., 2019; A. Garud et al., 2012).

Double emulsion method

The medicine (often a hydrophilic agent) was first dissolved in an aqueous solution before being emulsified in melting lipids in the double emulsion process. Stabilizer was added to this basic emulsion (for example, gelatin or poloxamer-407) to make it more stable. Then, a hydrophilic emulsifier was used to disperse this stabilized primary emulsion in an aqueous phase (e.g. PVA). The double emulsion was then separated by filtration after being agitated. The creation of lipid nanoparticles containing peptides can be done without melting the lipid by using the double emulsion approach, and the surface of the nanoparticles can be changed by adding a lipid/-PEG derivative to sterically stabilize them. In the gastrointestinal fluids, sterical stabilization considerably increased these colloidal systems' resistance (S. Rewar et al., 2014).

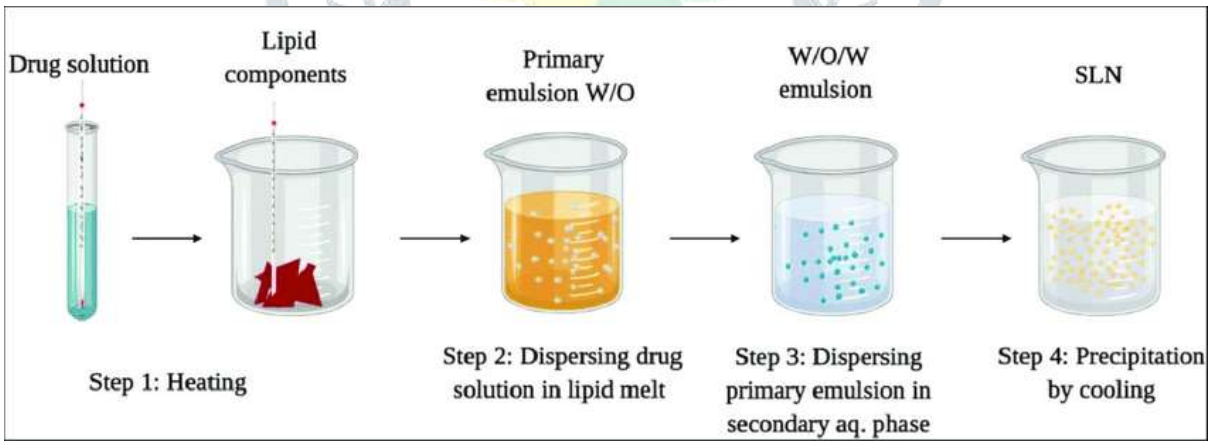

Fig. no. 10: Solid lipid nanoparticles preparation by double emulsion process (K. Sastri et al., 2020).

Precipitation technique

An organic solvent (like chloroform) is used to dissolve the glycerides, and the resulting solution is then emulsified in an aqueous phase. The lipid will precipitate and form nanoparticles following the organic solvent's evaporation. Using an organic solvent is necessary, which is the biggest drawback (S. Raziyabegum et al., 2013).

Film-ultrasound dispersion

The drug and lipid were combined with the appropriate organic solutions, and after the organic solutions were rotated, decompressed, and evaporated, a lipid film was created. Next, the emulsion-containing aqueous solution was added. SLN with small and homogeneous particle size is created by using ultrasound with the diffuser as the final step (P. Ekambaram et al., 2012).

Solvent Injection Technique

In this method, a water miscible solvent (such as ethanol, acetone, or isopropanol) or a water miscible solvent mixture was used to dissolve the solid lipid. Thereafter, a gradual injection of this organic solvent mixture with or without a surfactant was made into the agitated aqueous phase using an injection needle. After that, a filter paper was used to remove any extra lipid from the dispersion. By lowering the surface tension, surfactant in the aqueous phase aids in the production of lipid droplets at the injection site and stabilizes the generated SLNs until solvent diffusion is complete. Cinnarizine SLNs, a lipophilic medication, was created using the solvent injection lyophilization procedure (U. Bagul et al., 2018).

Membrane contractor method

The goal of the current work is to investigate a novel method for producing SLN on a wide scale by using a membrane contractor. At a temperature over the lipid's melting point, the lipid phase is compressed, and once the liquid has passed through the membrane pores, tiny droplets are created. Inside the membrane module, the aqueous phase is circulated before the droplets that develop at the pore exits are removed. The preparation is subsequently cooled to room temperature to create SLN. The effect of process variables on SLN size and lipid phase flux is examined. These parameters include aqueous phase and lipid phase temperature, aqueous phase cross-flow velocity and pressure, and membrane pore size. Moreover, SLN which has been loaded with vitamin E is synthesized, and their stability is shown (P. Mahajan et al., 2015).

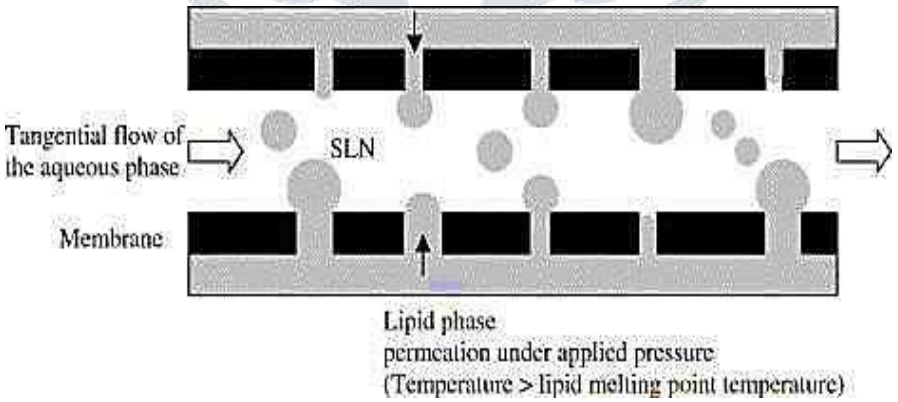

Fig. no. 11: Solid lipid nanoparticles preparation by Membrane contractor method (R. Parhi et al., 2010)

Factors Affecting Nose to Brain Drug Delivery

The physical and chemical qualities of the drug material, the environment around the nose, and the parameters of the dose form all have an impact on drug absorption when administered intravenously. Through intranasal medication

delivery, these characteristics significantly contribute to the drug's penetration and ability to reach the desired plasma concentration (D. Bhowmik et al., 2010; S. Majgainya et al., 2015).

Physiochemical Properties

Molecular weight:

The penetration and availability of the drug in the system through the nasal cavity are significantly influenced by the molecular weight of the drug. The nasal mucosa is easily pierced by drugs with molecular weights under 300 Daltons. Lipophilic medicines, such as proteins and peptides, exhibit high absorption through nasal mucosa when their molecular weight is more than 1 K Dalton. For example, the bioavailability of proteins and peptides typically varies from 0.5% to 5% when their molecular weight is about 1 K Dalton (S. Kushwaha et al., 2011; S. Singh et al., 2012).

Solubility:

Drug absorption is improved with the use of water-soluble medications. Before drug absorption, it should dissolve through the nasal membrane in the aqueous fluids of the nasal cavity. Because the nasal cavity is smaller than the oral cavity and hence has less fluid available for drug dissolution, it is necessary to use water-soluble medications for improved nasal absorption (M. Kamble et al., 2013). The drug's distributed particles may pass through the bio membranes at the absorption site after disintegration. Because the nasal cavity is so small, less medication is needed to administer drugs via the nasal route. If particles collect in the nasal cavity or are removed from it, drug absorption might not be seen. The ability of the formulator to create a product is limited if the medicine is not sufficiently soluble in the selected vehicle. From a mechanistic and thermodynamic perspective, it is important to understand the relationship between the drug's solubility, absorption, and saturation. The solubility of the medicine, as widely known, especially with the GIT and the skin, affects the absorption (S. Jyothi et al., 2017).

Lipophilic and hydrophilic balance:

Lipophilicity and hydrophilicity should be balanced in the medicine for improved nasal absorption because the nasal cavity membrane has a lipophilic character. Lipophilic medicines therefore absorb well and have nearly 100% bioavailability through this route. Polar medicines are more difficult to pass the nasal membrane than lipophilic medications (P. Sharma et al., 2011). When delivered through the nasal membrane, several lipophilic medications, including naloxone, buprenorphine, testosterone, and estradiol, are entirely absorbed (K. Jadhav et al., 2007).

Pka and partition coefficient:

Ionized molecules are less readily absorbed than unionized molecules when administered via the intranasal route, according to the pH partition theory. As the drug's lipid solubility grows, so does its concentration in biological tissues. Typically, nasal mucosa promotes lipophilic drug absorption. Hydrophilic medications, like peptides, have high molecular weight because they are easily permeated through the nasal membrane, but lipophilic drugs, with lower molecular weight, are more effectively absorbed through the nasal membrane. This improves mucociliary

clearance. The partition coefficient and nasal absorption have a continuous quantitative connection. Similar to how non-ionized classes of medications do, 10% of benzoic acid's drug is absorbed at pH 7 when administered orally. Drug passing across the biomembrane is often influenced by lipophilicity and hydrophilicity as well as the quantity of uncharged class of pharmaceuticals. This led to the conclusion that partition coefficient, for polar pharmaceuticals, is the main factor influencing drug transport through the nasal mucosa (S. Jyothi et al., 2017).

Osmolarity:

Absorption through the nasal mucosa is considerably impacted by generally isotonic formulation (J. Paun et al., 2010). It has been noted that. When hypertonic fluids are present, epithelial cells shrink. Hypertonic liquids reduce ciliary function. The low pH is balanced by the hypertonic solution. The drug's ability to be absorbed by animals through nasal discharge is influenced by the osmolarity factor (S. Dey et al., 2011). The preparation's sodium chloride content, which can exceed 0.45 M, has an impact on the absorption rate. The nasal epithelial toxicity is caused by the enhanced bioavailability of the salt solution (R. Dhakar et al., 2011).

Nasal Environmental Factors Blood Flow:

A considerable surface area is present for medication absorption in the nasal mucosa, which is provided by extensive vascularization. By maintaining the concentration gradient across the membrane, it is possible to control the blood flow rate, which in turn controls the rate at which drugs are absorbed through diffusion. Vasoconstrictor medication absorption lowers the rate of drug flow and significantly lowers absorption. Drugs are far more likely to pass through nasal tissue and come into touch with blood circulation when the blood flow rate increases. Blood vessels in the nasal mucosa are constrained by adrenergic neurons that function as alpha adreno receptors. Stimulation of these receptors reduces blood flow and blood content in the nasal membrane in both humans and animals. Ambient temperature, the presence of vasoactive medications, humidity, inflammation, and trauma are a few extrinsic factors that can impact nasal blood flow. This demonstrates that nasal flow is extremely susceptible to drugs with local or systemic action (P. Arora et al., 2002; S. Jyothi et al., 2017).

Nasal enzymes causing degradation of drugs:

The nasal cavity has a limited bioavailability for peptides and proteins. Therefore, the drug molecule in these medications may be degraded by an enzyme in the nasal cavity lumen or while passing through the epithelial barrier. Exo-peptidases and endo-peptidases can be found in these locations. Both mono-aminopeptidases and diaminopeptidases are exo-peptidases ((S. Jyothi et al., 2017).

Table no. 3:- Some important patent on SLN

Sr. no.	Patents name	Patents Number	Patentee	Reference
1	Drug-entrapping solid lipid nanoparticles that are hydrophilic or amphiphilic, as well as a method for making them.	WO 2013105101 A1	Indu Pal Kaur, Rouit Bhandari	(I. Kaur et al., 2013)
2	SLN is used in the formulation of UV absorbers.	US 7147841 B2	Bernd Herzog	(B. Herzog. 2003)
3	aqueous suspension with minoxidil-encapsulating solid lipid nanoparticle.	EP 2413918 A1	Karine Padois, Fabrice Pirot, Françoise Falson	(F. Falson et al., 2012)
4	Therapeutic proteins and peptides can be delivered via oral or mucosal distribution of polymerized solid lipid nanoparticles.	US 20080311214A1	Kollipara Koteswara Rao	(K. Rao. 2006)
5	Utilisation of SLN containing cholesteryl propionate and butyrate.	WO 2006128888 A1	Maria Rosa Gasco	(M. Gasco. 2006)
6	Lipid nanoparticle capsules	EP 2549977 A2	Josep L. Luis Viladot Petit, Raquel Delgado Gonzalez, Alfonso Fernández Botello	(J. Viladot et al., 2013)

Conclusion

SLNs have attracted the attention of numerous researchers due to their exceptional qualities and advantages over other conventional dosage forms. Other colloidal counterparts of SLNs have also emerged as a significant nanotechnology discovery due to their efficient performance and as a secure method of pharmaceutical drug delivery.

When compared to parenteral drug administration, the nasal drug delivery system is a viable alternative mode of administration for a number of systemically acting medicines with low bioavailability. It also has advantages in terms of enhanced patient acceptability and compliance. Because it involves quick and/or precise medication delivery to the brain and is an effective way to elicit an immune response against a variety of diseases like anthrax, influenza, etc., this delivery technique is advantageous in disorders like Parkinson's disease, Alzheimer's disease, or pain. A new hope for both local and systemic medication administration has been created through the delivery of drug molecules via the nasal mucosa. Drug delivery via the nasal mucosa is a possible alternate route for drugs with local, systemic, and CNS effects. Recent advances in polymer-based drug delivery technologies have significantly improved drug delivery directly to the brain interstitium. However, meaningful progress will only be made if the active hunt for more efficient means of delivering these medications to their CNS targets is matched by ongoing, intense research efforts to create more therapeutic and less toxic pharmacological molecules.

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