wjpmr, 2024, 10(6), 196-207

SJIF Impact Factor: 6.842

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Review Article

ISSN 2455-3301

WJPMR

NOSE TO BRAIN DRUG DELIVERY SYSTEM

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Article Received on 06/04/2024 **Article Revised on 27/04/2024** **Article Accepted on 17/05/2024**

1. ABSTRACT

Direct nose-to-brain drug delivery offers the opportunity to treat central nervous system disorders more effectively due to the possibility of drug molecules reaching the brain without passing through the blood–brain barrier. Such a delivery route allows the desired anatomic site to be reached while ensuring drug effectiveness, minimizing side effects, and limiting drug losses and degradation. Absorption of intranasally administered entities is a complex process that considerably depends on the interplay between the characteristics of the drug delivery systems and the nasal mucosa. The preclinical models (in silico, in vitro, ex vivo, and in vivo) are used to study the transport of drugs after intranasal administration. This article attempts to summarize the different computational and experimental models used so far to investigate the direct delivery of therapeutic agents or colloidal carriers from the nasal cavity to the brain tissue.it provides a critical evaluation of the data available from different studies and identifies the advantages and disadvantages of each model. In coming years, intranasal delivery of drugs will demand more complex and automated delivery devices to ensure accurate and repeatable dosing. Thus, new efforts are needed to make this non-invasive route of delivery more efficient and popular, and it is also predicted that in future a range of intranasal products will be used in diagnosis as well as treatment of CNS diseases. This review will embark the existing evidence of nose-to-brain transport. It also provides insights into the most relevant pre-clinical studies of direct nose–brain drug delivery system.

KEYWORD: Nose to Brain, Intranasal Drug delivery System, Blood Brain Barrier.

2. INTRODUCTION

- **DEFINATION OF NOSE TO BRAIN DRUG DELIVERY SYSTEM**
- Nose to brain drug delivery system is an interesting approach to deliver a drug directly in the brain through the nose. Intranasal drug delivery is very beneficial because it avoids first-pass metabolism and achieves a greater concentration of drugs in the central nervous system (CNS) at a low dose.
- Its therapy is chronic and usually consists in oral or intravenous administrations of antiepileptic drugs which present some limits, connected to problems of low-bioavailability, side-effects, first-pass metabolism. The nose-to-brain drug delivery can be, therefore, an important way to overcome these problems.
- Nasal Mucosa is considered as potential administration route to achieve rapid and higher level of drug absorption. Nasal cavity having a larger surface area, porous endothelial membrane, high total blood flow and avoidance of problem of first pass metabolism are these few reasons.

Researchers are interested in nasal route for the systemic delivery of medications due to their high degree of permeability of nasal mucosa. Delivery of drug to the brain is Major challenge due to Presence of two Physiological barriers that restrict the delivery of drug to the Central Nervous System (CNS), The Blood Brain Barrier (BBB) and Blood Cerebrospinal Fluid Barrier (BCSFB).

- **ANATOMY OF NASAL ROUTE**

The nose is responsible for olfaction and respiration. It is comprised of two symmetric cavities, divided by the septum which lies along the midsagittal plane. The cavities are lined with a layer of mucosa, and the total area of both cavities is ~150 cm2. These cavities can be further divided into three regions. The first is the vestibular region, which is the most anterior and lies immediately deep to the nostril openings. It is relatively small with a total surface area of 0.6 cm2 and contains the nasal hairs which serve to filter inhaled particles.

The primary cell type is squamous, with few if any ciliated cells. The small surface area of this region is the reason for minimal absorption of drugs in this region.

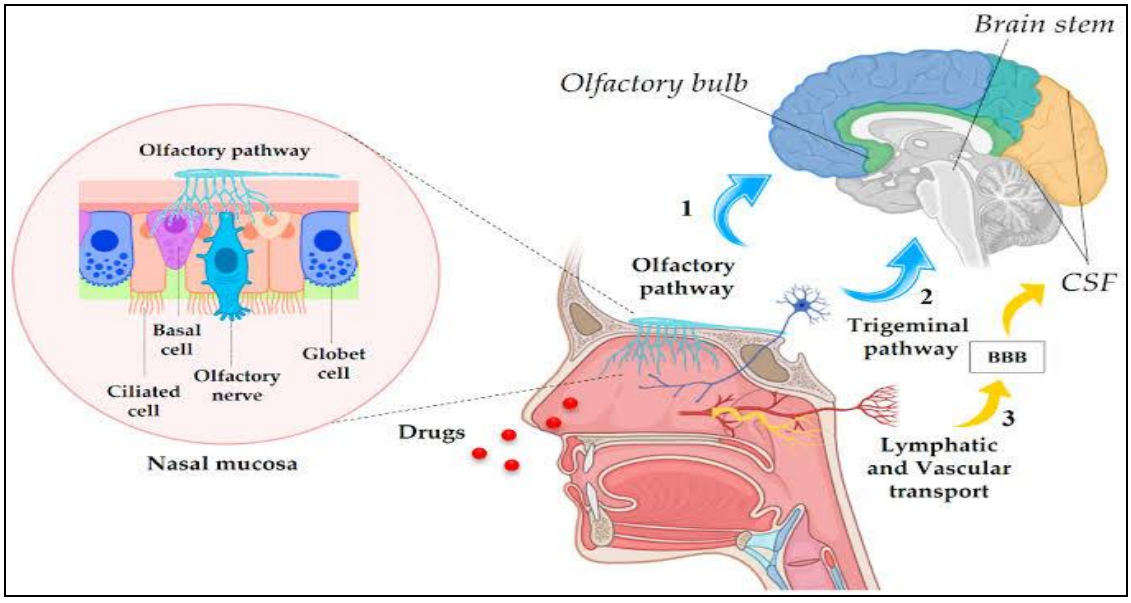


Fig 1: Nose to Brain Drug Delivery Pathway 1) Intracellular Pathway for Olfactory Nerve to the Olfactory Bulb with a focus on Nasal Mucosa, 2) Intra-cellular Pathway from trigeminal pathway nerve to brain stem, 3) Lymphatic and Vascular System route to Cerebrospinal fluid across BBB.

- **DRUG DISTRIBUTION OF INTRA-NASAL FORMULATION THROUGH DIFFERENT PATHWAY**

A) OLFACTORY REGION (MAJOR PATHWAY)

Olfactory neural pathways, drug material is travelled from the olfactory region in the nasal cavity to CSF or brain parenchyma, It is also transverse to the nasal olfactory epithelium. In this pathway, the arachnoid membrane surrounding the subarachnoid space having three different pathways across the olfactory epithelium, first is transcellular pathways especially across the Sustentacular cells were receptor mediated endocytosis, fluid phase endocytosis or the passive diffusion for the lipophilic drugs is mediated rapidly and at a high rate. This route is mainly responsible for the transport of lipophilic drug molecules and the transport rate is depended in their lipophilicity. Second is a paracellular pathway in which, the tight junctions between Sustentacular cells having the clefts between Sustentacular cells and olfactory neurons. Nasal absorption of hydrophilic drugs undergoes diffusion mechanism through aqueous channels or pores. This pathway is slow and it is responsible for the transport of hydrophilic drugs under rate dependency on the molecular mass of the drug material. Drugs with a molecular weight in the range between 300 - 1000 Dalton shows good bioavailability without absorption enhancer and the molecular weight of drugs up to 6000 Dalton with absorption enhancers. Third is olfactory nerve pathway in which, the drug is taken up to the neuronal cells by endocytosis or pinocytosis mechanism and transported by the intracellular axonal transport to the olfactory bulb. Thus, the different modes of drug transport across the nasal olfactory epithelium are the transcellular passive diffusion, Paracellular passive diffusion, efflux transport.

B) TRIGEMINAL PATHWAY (MINOR PATHWAY)

Trigeminal nerve pathways is the largest nerve pathway among all cranial nerve pathways in which, innervates the respiratory and olfactory epithelium of the nasal passages and enters the central nervous system (CNS). The small portion of the trigeminal nerve pathways is terminating the olfactory bulbs. The trigeminal nerve is communicating in sensory information from the nasal cavity, oral cavity, eyelids and the cornea to CNS via ocular, maxillary and the mandibular divisions of trigeminal nerves. The former two is sensory functions while later the both sensory and motor functions. The ocular and maxillary nerve is important for nose to brain delivery as neurons from these branches passed directly through the nasal mucosa. The unique feature of the trigeminal nerve is that enters the brain from the respiratory epithelium of the nasal passages at the two sites first through anterior lacerated foramen near the pons and second through cribriform plate near olfactory bulb is creating the entry points into the both caudal and rostral brain areas following the nose to brain administrations. Since the portion of the trigeminal nerve pathway enters the brain through the cribriform plate along the olfactory pathway, It is difficult to differentiate the nose to brain administered drugs reach the olfactory bulbs and other rostral brain areas (anterior olfactory nucleus and frontal cortex) via olfactory pathway, brainstem, spinal cord via trigeminal pathway and the both extracellular, intracellular pathways is involved for bypassing the BBB.

C) VASCULAR PATHWAY

Pharmaceutical or Therapeutic agents is transported in nose to brain through the blood vessels supplying the nasal cavity to systemic circulation following the nasal administration. Nose to brain route is utilized to deliver

drug to the systemic circulation through absorption into the capillary blood vessels underlying the nasal mucosa. The nasal mucosa is highly vascularised for receiving blood supply from branches of both the internal and external carotid artery, including the branches of the facial artery and maxillary artery. The olfactory mucosa was received blood from the anterior and posterior ethmoidal artery (smallest artery of ocular cavity), where the respiratory mucosa is received the blood from the sphenopalatine artery The relative density of the blood vessels is greater in the respiratory mucosa than the olfactory mucosa, making the former an ideal region for adsorption of drug into the systemic circulation.

D) LYMPHATIC PATHWAY

Lymphatic pathways The CSF production via choroid plexus and its absorption via arachnoid villi to the cerebral venous sinuses had remained widely accepted. The functional and anatomical connection between the extracranial lymphatics (nasal submucosa and cervical lymphatics) and subarachnoid spaces via the perineural spaces to the cribriform plate. Nasal submucosa is consisting of dense vascular network that leads to systemic circulation and dense network of lymphatics that communicates directly with the subarachnoid space. The nasal submucosal lymphatics leads directly to the subarachnoid space via a perineural route to the cribriform plate. Nasal lymphatics is offering a direct transport through the subarachnoid space and have been proposed as a potential pathway for the invasion of the pathogens such as S. pneumoniae, N. meningitis or H. influenza responsible for bacterial meninge.

ADVANTAGES OF NOSE TO BRAIN DRUG DELIVERY SYSTEM

1. It is a rapid, safe, non-invasive and convenient method of drug delivery.
2. It avoids drug degradation in gastrointestinal tract, particularly peptide drugs.
3. It avoids hepatic first-pass metabolism.
4. It bypasses BBB thereby providing CNS targeted drug delivery, thereby reducing systemic exposure of drugs and associated systemic side effects.
5. It is enhanced bioavailability.
6. Therapeutics agent does not require any modification for drug delivered via nose to brain drug delivery system.
7. Rapid drug absorption and quick onset of action highly vascularized and permeable structure of nasal mucosa.
8. Better patient compliance and self-medication.
9. It is alternative route for parenteral administration.

- **DISADVANTAGES OF NOSE TO BRAIN DRUG DELIVERY SYSTEM**

1. Rapid elimination of drug substances from nasal cavity due to mucociliary clearance absorption enhancer used in formulation may create mucociliary toxicity.
2. There is a great deal of variability in the concentration attainable in different regions of brain and spinal cord.
3. High molecular weight of drugs may result in decreased permeability across nasal mucosa.
4. Some therapeutics agents may cause irritation to nasal mucosa or enzymatic degradation and metabolism in the nasal mucosa surface.
5. Nasal congestion due to cold or allergic condition.

4. DRUG PARAMETRES AND EXCIPIENT

- **DRUG PARAMETRES CONSIDERED IN INTRA-NASAL FORMULATIONS.**

Sr.no	Drug Parameters	Values
1.	**Molecular weight**	Less than 600 Dalton
2.	**Lipophilicity**	On increasing lipophilicity of the compounds, the permeation of the compounds normally increases through nasal mucosa. The lipid domain plays an important role in the barrier function of these membranes.
3.	**Dissociation Constant**	The Nasal absorption is depending on the dissociation constant (pKa) of the drug and on the pH of the nasal absorption site (5.0-6.5). pKa is depends in degree of ionization and degree of non-ionization.

- **EXCIPIENTS USED IN NOSE TO BRAIN DRUG DELIVERY SYSTEM**

1.	**ENZYMATIC INHIBITORS**	• Bile Salt • Fusidic acid.
		• Disodium ethylenediamine-tetra acetic acid
2.	**CO-SOLVENT**	• Glycerol
		• Ethanol
		• Propylene Glycol
		• Ethylene Glycol
3.	**ABSORPTION ENHANCER**	• **Surfactant**: SLS, Poloxamer, tweens • **Bile Salts**: Sodium Glycodeoxycholate Sodium Tauro deoxycholate
		• **Fatty Acids**: Taurodihydrofusidate, oleic acid, ethyl oleate
		• **Chelators**: EDTA, citric acid
		• Peppermint oil
		• **Polymers:** cyclodextrins and Methylated

		• Cyclodextrins, chitosan, trimethyl chitosan, Carbopol, starch
4.	**LIPIDS**	• **Hard fat types:** Witepsol W, Stearic acid, Palmitic acid, Decanoic acid, Behenic acid etc. • **Waxes**: Cetyl palmitate, Carnauba wax, Beeswax etc. • **Triglycerides**: Tricaprin, Tri laurin, Trimyristin, Tripalmitin, Tristearin, Tribehenin etc. • **Diglycerides**: Glyceryl palmitostearate, Glyceryl Di behenate, Glyceryl palmitostearate. • **Monoglycerides:** Glyceryl
5.	**EMULSIFIER/CO-EMULSIFIER**	a) **Ionic surfactants:** Sodium cholate, Sodium glycocholate, Sodium taurocholate, Sodium Tauro deoxycholate etc. b) **Amphoteric surfactants**: Egg phosphatidylcholine, Soy phosphatidylcholine, Hydrogenated egg phosphatidylcholine, Hydrogenated soy phosphatidylcholine, Phospholipid 80 H. c) **Non-ionic surfactants**: Poloxamer, Tyloxapol, Polysorbate Span etc d) **Co- emulsifiers**: Butanol, Butyric acid, ethanol etc.

Table 1: List of preservatives used along with their concentration range.

Sr.	Preservatives	Concentration range (% w/w)
1.	**Benzoic acid (sodium benzoate)**	0.1–0.2
2.	**Benzalkonium chloride**	Up to 0.1
3.	**Thiomersal**	0.003-0.01
4	**Chlorobutanol**	0.5
5	**Chlorobutol**	0.25
6.	**Potassium sorbate**	0.1-0.2

5. FORMULATION METHODS OF NANOPARTICLES

- There are three kinds of approaches to produce nanoparticles. These methods are as follows:

1. **Physical Methods**
2. **Chemical Methods**
3. **Biological Methods**

1. Physical methods

I) Mechanical method

a) Ball milling

Ingenious approaches for the creation of nanoparticles. Forms of mills used are planetary, vibratory, rod, tumbler. The container contains hard balls made up of steel or carbide. Nanocrystalline Co, Cr, W, Ag-Fe, are synthesized using this method. The ratio of balls to materials is 2:1. The container is filled with inert gas or air and is rotated at high speed around the central axis. The materials are pressed between the walls of the container and balls. The speed and duration of milling play a significant role in synthesizing nanoparticles of optimum size.

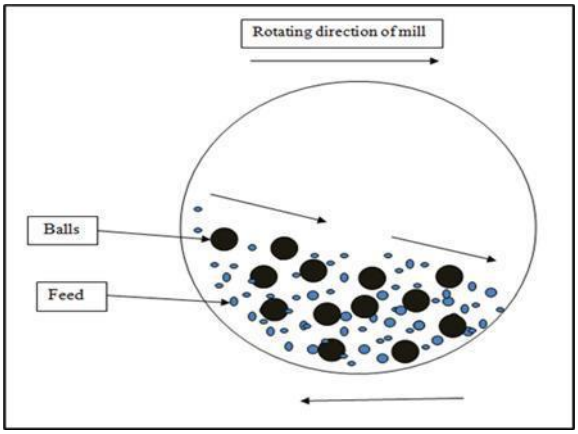


Fig. 3: Ball mill.

b) Melt mixing

Mixing molten streams of metals at high velocity with turbulence form nanoparticles. Nanoparticles get arrested in a glass. Glass–is an amorphous solid, deficient symmetric organization of atoms or molecules. Metals, when cooled at great cooling proportions, can form amorphous solids-metallic glasses. Ex: A melted stream of Cu-B and a heated stream of Ti forms nanoparticles of TiB_2.

2. Pulse Laser Ablation

The target sample is placed inside a vacuum chamber. The high-pulsed laser beam is focused on the sample and plasma is generated, which is formerly transformed into a colloidal solution of nanoparticles. The second-

harmonic group type laser is frequently used to formulate nanoparticles. Elements affecting the final creation are the type of laser, some pulses, type of solvent, pulsing time.

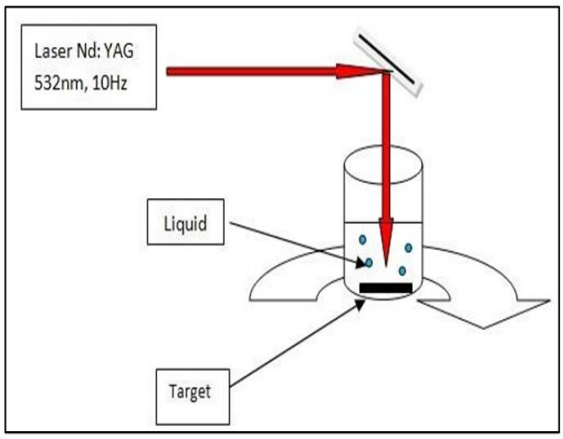


Fig. 4: Pulse laser ablation technique.

3. Pulsed wire discharge method

The physical technique to prepare nanoparticles. Most widely used method for synthesis of metal nanoparticles. A metal wire is vaporized by a pulsated current to yield a vapour, which is then cool by ambient gas to procedure nanoparticles. This scheme has possibly a high fabrication speed and high energy productivity. Ex. Nitride nanoparticles.

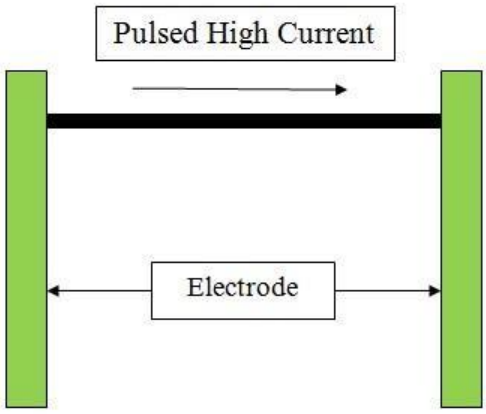


Fig. 5: Pulse wire discharge method.

4. Chemical vapor deposition

A thin film of gaseous reactant is deposited on the substrate at around 300-1200 °C. A chemical reaction occurs between heated substrate and combining gas as an outcome thin film of product formed on the surface of the substrate. The applied pressure varies in the range of 100-10^5Pa. There are many variants of CVD like Metallo Organic CVD, Atomic Layer Epitaxy, Vapor Phase Epitaxy, Plasma Enhanced CVD. The advantages of this technique are stiff, uniform, robust and highly pure nanoparticles are manufactured. The byproducts formed on the substrate must be conveyed back to the gaseous phase eliminating them from the substrate. Cold wall and hot wall are two techniques by which substrates are heated. In the hot wall arrangement, the deposition can take place even on reactor walls. This is evaded in cold wall strategy. Gas pressure and the substrate temperature ultimately affects the growth rate and quality of film.

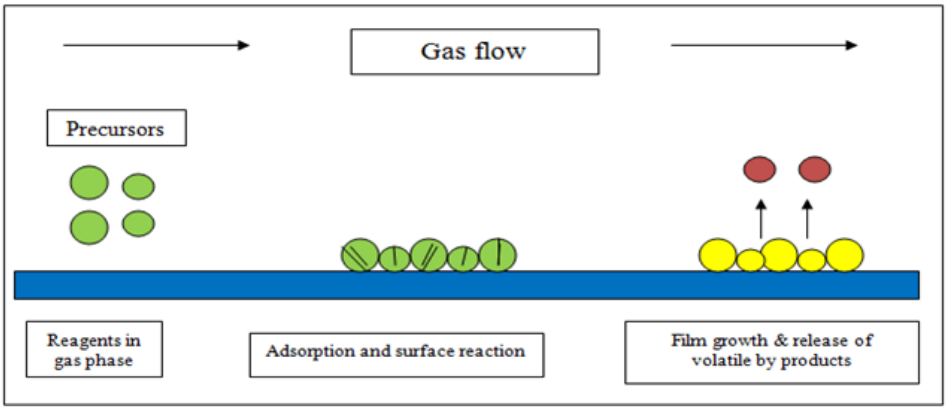


Fig. 6: Chemical vapour deposition.

5. Laser pyrolysis

The process of synthesis of nanoparticles by using a laser is known as laser pyrolysis. An intense laser beam is focused to decompose the mixture of reactant gases in the existence of some inactive gas like helium or argon. The gas pressure shows a significant part in determining the particle sizes and their distribution.

6. Ionised cluster beam deposition

The method was developed in 1985. The main aim of this method is to obtain high-quality single-crystalline thin films. The arrangement comprises a source of evaporation, a nozzle through which material can expand into the chamber, an electron beam to ionize the clusters, an arrangement to accelerate the clusters, and a substrate on which nanoparticle film can be deposited, all housed

in a suitable vacuum chamber. After impact with an electron beam, collections get ionized. Due to applied hastening voltage, the clusters are focused near the substrate. It is likely to control the energy with which the clusters hit the substrate by monitoring the accelerating voltage. Steady clusters of certain materials would need significant energy to break their bonds and would rather favour remaining as small as clusters of particles.

Hence the films of nanocrystalline material using an ionized cluster beam can be produced.

B. Chemical methods

I) Sol-gel method

It comprises the condensation, hydrolysis, and thermal decomposition of metal alkoxides or metal precursors in solution. A stable solution is formed, known as the sol. Upon hydrolysis or condensation, the gel is formed with increased viscosity. The particle size can be monitored by changing precursor concentration, temperature, and pH values. A mature step is mandatory to empower the development of solid mass it may take a few days in which the removal of the solvent, Ostwald ripening, and phase alteration could happen. The unstable reagents are detached to produce nanoparticles.

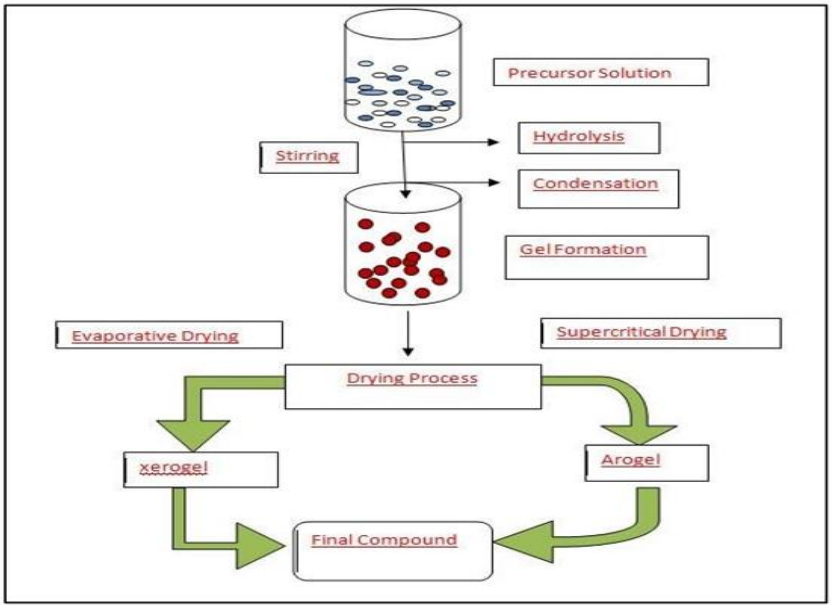


Fig. 7: Sol- gel method.

II) Sono chemical synthesis

Pd-CuO nanohybrids have been effectively invented by the Sono chemical fusion with copper salt in the existence of palladium and water. In the existence of palladium and water, switch metal salts could be altered into their oxides with the help of ultrasound energy. The palladium source is either pure metallic palladium Pd (0) or the palladium salts.

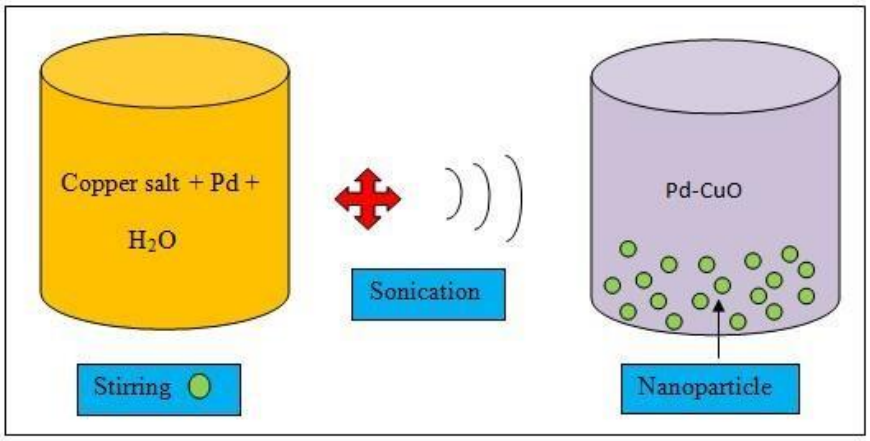


Fig. 8: Sono chemical synthesis.

III) Co-precipitation method

It is a wet chemical process, also called a solvent displacement method. Polymer phase can be synthetic or natural; polymer solvents are ethanol, acetone, hexane, and nonsolvent polymer. Nanoparticles are produced by rapid diffusion of polymer-solvent into a nonsolvent

polymer phase by mixing the polymer solution at last. Nanoparticles are produced by interfacial tension at two phases.

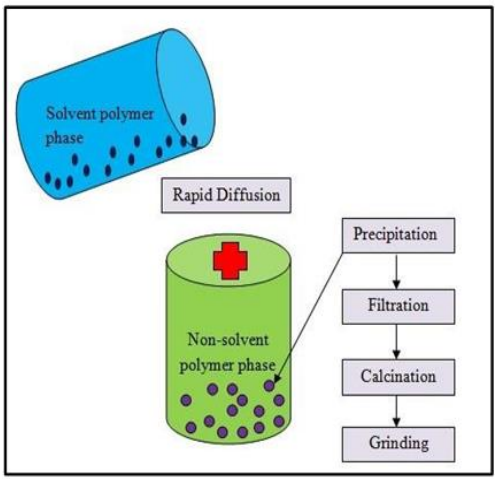


Fig. 9: Co-Precipitation Method.

IV) Inert gas condensation method

This process is broadly implemented for the creation of metal nanoparticles. The inactive gas compression technique, in which nanoparticles are produced via vanishing of metallic source in an inactive gas, had been widely used to yield fine nanoparticles. Metals are vaporized at a reasonable rate at an attainable temperature. Copper metal nanoparticles are synthesized by subjecting metal inside a chamber containing argon or helium or neon where the metal is vaporized. Once the atom is boil-off immediately loss its energy, by the cooling of the vaporized atom with inert gas. The gases cool by liquid nitrogen, to form nanoparticles in the series of 2-100 nm.

V) Hydrothermal synthesis

It is one of the most usually used methods for the preparation of nanoparticles. It is principally a chemical reaction-based approach. Hydrothermal synthesis involves a broad temperature range from room temperature to very high temperatures for the synthesis of nanoparticles. This method has a wide range of advantages over physical and biological methods. The nanomaterials generated through hydrothermal synthesis may be unstable at higher temperature ranges.

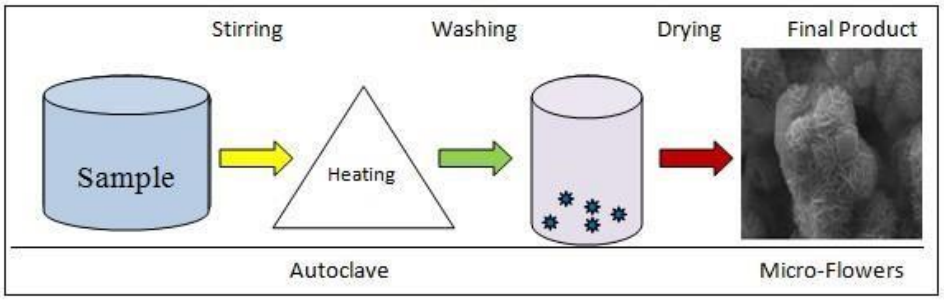


Fig. 10: Hydrothermal synthesis.

C. Biological methods

a) Synthesis using microorganisms

In recent years synthesis of nanoparticles using microorganisms have gained more attention due to cost-effectiveness and eco-friendliness. There are two techniques by which nanoparticles can be synthesized from a microorganism, one is extracellular biosynthesis and another is intracellular biosynthesis. Certain microbes are capable of separating metal ions. *Pseudomonas stuzeri* Ag295 is frequently found in silver mines, accomplished by collecting silver inside or outside the cell walls. Different types of reductase enzymes exist in microorganisms thus can store and detoxify heavy metals. *Klebsiella pneumonia* can be used to produce CdS nanoparticles.

b) Synthesis using plant extracts

Plant extracts show a vital character in the biosynthesis of nanoparticles. This process is also recognized as green synthesis or a green process of manufacture of nanoparticles. Leaves of the geranium herb (*Pelargonium graveolens*) have been used to manufacture gold nanoparticles. 1 ml of 1 mmol aqueous solution of silver nitrate is added to 5 ml of the plant extract to synthesize silver nanoparticles. The same procedure is followed for synthesis from alcoholic extract, The plant extract, along with silver nitrate, is kept in a shaker at 150 rpm in the dark.

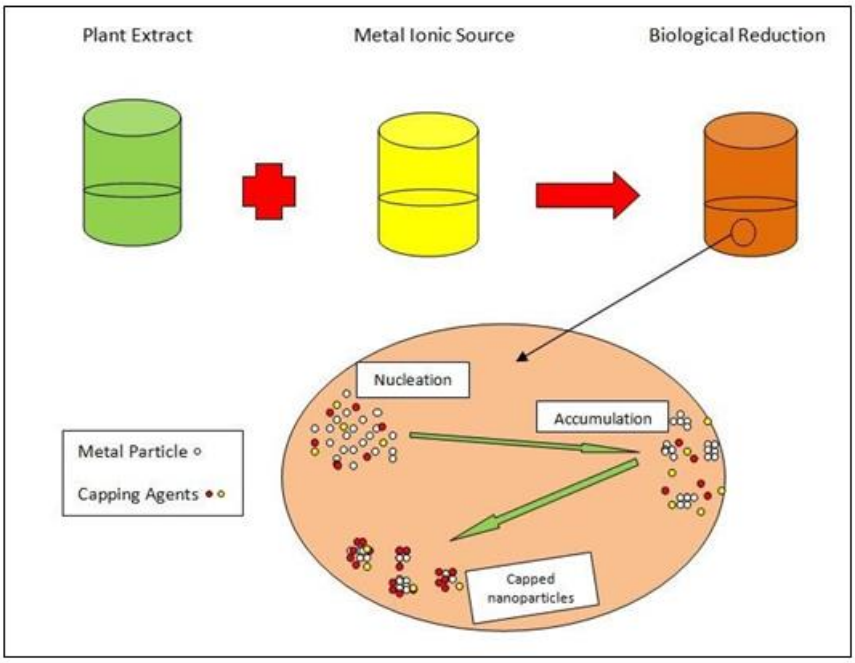


Fig. 11: Synthesis using plant extract.

C) Synthesis using algae

Preparation of algae extract in Aqueous Solvent or an organic solvent by heat or boiling it for a definite period. Preparation of molar solution of ionic metallic complex. Incubation of algae solution and molar solution of ionic metallic complexes followed whichever by nonstop stirring or without stirring for a definite period under controlled conditions. Nanoparticles synthesis is dose dependant process and depends on the type of algae used. The biomolecules peptides, pigments and polysaccharides are accountable for the reduction of metals. Nanoparticles synthesis using algae takes a shorter duration than other biosynthesizing methods. To synthesize AgNPs of varying sizes and shapes certain seaweeds (*Sargassumwightii* and *Fucusvesiculosus*) can be used.

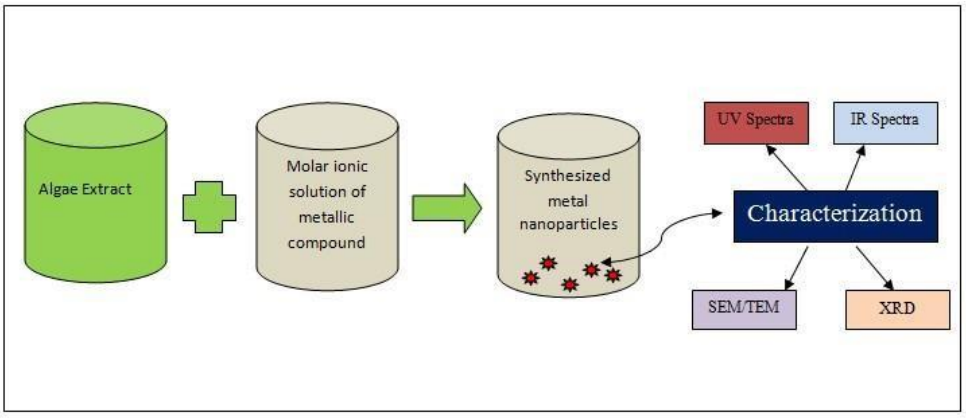


Fig. 12: Nanoparticles synthesis using algae.

6. FORMULATION TYPES OF INTRA-NASAL ROUTE

1. Solutions

Simply dissolving the drug molecule in an aqueous phase has been used to administer molecules via the nose to brain route. Most clinical studies, which report pharmacological effects, have involved a solution of the drug in aqueous media. One of the first reports on the delivery of peptides to the brain involved the intranasal delivery of insulin to the brain in an insulin solution. Pharmacological activity has been observed in clinical studies, yet preclinical studies reveal just how little of the applied dose is delivered to the brain. Thorne delivered a Cmax of 0.0064% of the dose of radiolabelled interferon-b1b to a monkey brain using an aqueous solution of the drug and speculated that delivery would be improved with the addition of absorption enhancers in the formulation. In all cases where the Cmax has been reported as a percentage of the total dose, brain weight was assumed to be 1% of the animal's average body weight Where a range of body weights are given, a midpoint is taken as the representative body weight.

Oxytocin has also been delivered to the brain via the nasal route using a solution with a Cmax of 0.003% of a 10-µg dose being found in the brain. A solution of the HIV replication inhibitor DB213 delivered the drug to the rat brain with a Cmax that was estimated at no more than 0.007% of the administered dose.

EXAMPLE

1. Nanoparticles

To address the very low drug transfer levels seen with conventional solution nasal formulations, drug delivery experiments have been conducted with nanoparticulate formulations (nano emulsions, lipids, or polymer particles). Essentially these formulations offer the possibility of penetration enhancement or a longer nasal cavity residence time, with good evidence that nanoparticulate result in improved delivery of the cargoes, but limited quantitative evidence of delivery of the actual nano systems. Others found that nano emulsion particles of 100 nm penetrated the olfactory bulb and could be found in the brain to a small extent while particles of 900 nm did not penetrate the brain at all. The nano emulsion cargo was distributed throughout the brain with the 100 nm emulsion droplets.

1.1. Lipid Nanoparticle

Lipid nanoparticles, also known as solid lipid nanoparticles, consist of a lipid core stabilized by a surfactant and they differ from oil in water emulsions in that the lipids are solids at room temperature and the formulation is prepared by melting the lipid, followed by a form of size reduction and then surfactant stabilization of the resulting particles in an aqueous disperse phase with hydrophobic drugs and on application via the nasal route have been shown to deliver drugs to the brain. Valproic acid lipid nanoparticles when administered intranasally delivered significantly more drug to the brain, when compared to the drug in solution and protected animals against seizures in a maximal electric shock seizure model; with the protection being to a similar extent to that seen on administration of intraperitoneal phenytoin.

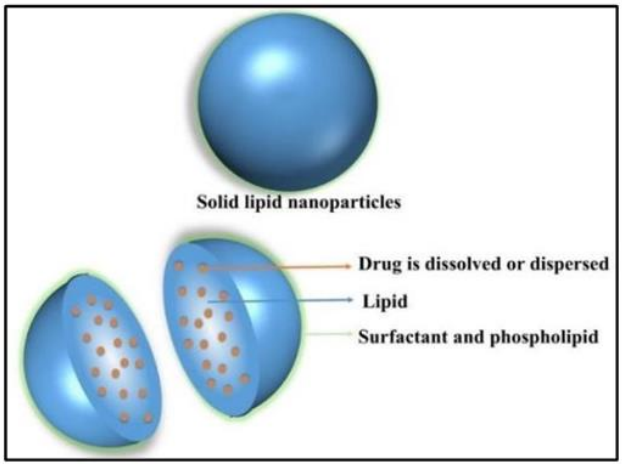


Fig: General structure of Solid Lipid Nanoparticle (SLN) loaded with drug.

1.2. Chitosan and Chitosan Derivative Nanoparticles

Chitosan has been incorporated into a number of nose to brain nano formulations as chitosan solution and chitosan nanoparticles (prepared by physical cross linking of chitosan with tripolyphosphate) have been shown to act as penetration enhancers, by temporarily opening intercellular tight junctions. However, while studies have shown superior nose to brain delivery using chitosan nanoparticles, the mechanism of brain delivery enhancement is not completely understood. The application of quetiapine chitosan nanoparticles, with the nanoparticles formed by chitosan tripolyphosphate, resulted in 34% more drug being delivered to the brain when compared to an intranasal solution of the drug.

1.3. Polynanoparticles

Poly(L-lactide-co-glycolide) is a polymer approved for human use in the world's largest markets. It is approved for use in drug delivery systems and this means that it is the polymer of choice for preparing medicinal product as it is biodegradable and demonstrates no toxicity concerns when used in humans. PLGA may be used to protect drugs from degradation in the nasal cavity and may be loaded with hydrophobic drugs. These properties have been exploited for nose to brain delivery. Olanzapine when loaded on to PLGA nanoparticles resulted in delivery to the brain which was ten times more efficient than nose to brain delivery with olanzapine solution, resulting in a Cmax of 0.049% of the dose and a Cmax of 0.0045% of the dose with the nanoparticle and solution formulations respectively. As well as pharmacokinetics evidence of nose to brain transport, pharmacodynamics evidence of nose to brain transport has been recorded in the form of a reduction in seizures in a rat seizure model, using PLGA nanoparticles.

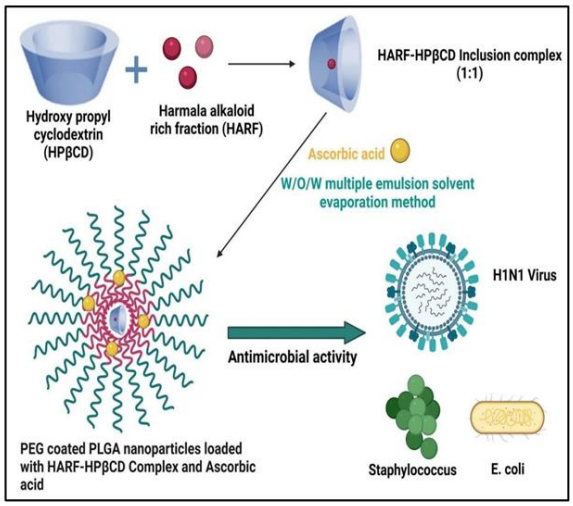


Fig: Poly-nanoparticles Loaded with Cyclodextrin-Peganum harmala Alkaloid Complex and Ascorbic Acid.

7. EVALUATION PARAMETERS OF INTRA-NASAL SOLUTIONS

Table 2: Evaluation Parameters Intra-Nasal Solutions.

Sr. No	Parameter	Instrument/Equipment
1.	Appearance, Colour, Clarity	Visual Detection
2.	In-vitro Diffusion Studies	Nasal Diffusion Cell,
3.	Drug Content	U.V. Spectrophotometer.
4.	In-Vivo Nasal Absorption Studies	Rat, Rabbit, Monkey & Dog Model
5.	Rheological Property	Brook-Field Viscometer
6.	Gelation Temperature	Thermometer
7.	Flammability and Combustibility a) Flash Point b) Flash Projection	a) Open cup tag apparatus b) Product Spray on flame
8.	Physiochemical Characteristics **a)** Vapour Pressure **b)** Density **c)** Moisture Content **d)** Identification of Propellent	a) Can Puncturing Device b) Hydro-meter, Pycometer c) Karl-Fisher Method, Gas d) Chromatography e) Gas Chromatography, IR Spectroscopy
9.	Performance **a)** Foam Stability **b)** Particle Size Determination	a) Visual Evaluation, Rotational Viscometer b) Cascade Impactor, Light Scattering decay
10.	Biological Testing a) Toxicity Studies	a) Irritation Effect

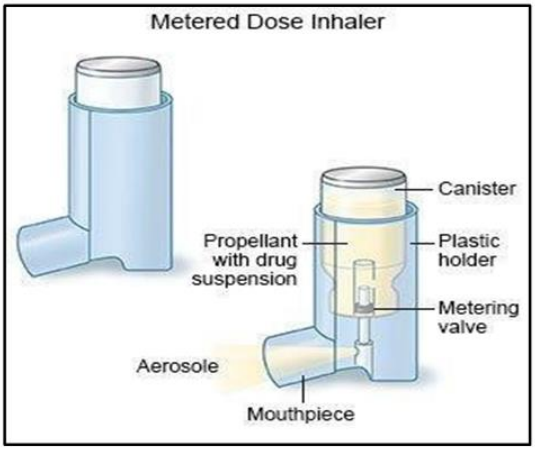
- **MARKETED FORMULATION OF NASAL DRUG**
- **Nasal Drug Delivery Devices: A) Dry Powder Inhalers**
  Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route.
- **Disease Condition:** asthma, bronchitis, emphysema, and COPD and have also been used in the treatment of diabetes mellitus.
- **Dosage Form Administered:** Capsules and Solid Dosage Form.

Single Dose Dry Powder Inhaler

Multiple Dose Dry Powder Inhaler

B) Metered-dose pump sprays

- Marketed nasal formulation such as suspension, emulsion, solution are directly delivered to intranasal pathway by using metered dose pump sprays
- **Disease Condition:** nasal hypersensitivity and other nasal disorders, topical decongestants, antihistamine.
- **Dosage Form Administered:** Suspension, Emulsion, Solutions.



Metered Dose Inhaler

C) Squeezed Bottle

They are smooth plastic bottles with simple jet outlet by pressing the bottle air passes in inside the container is pressed out of the small nozzle, having the optimum volume. **Disease Condition:** Nasal Decongestant.

8. CONCLUSION

This review has covered recent strategies to deliver drugs to the brain in the past five years. To design effective drug delivery systems for brain diseases, detailed understanding of disruption is necessary. With recent advances, research has not only demonstrated the permeable in brain injury, but also revealed the mechanisms of regulation. In addition to the common technologies including viral vectors and nanoparticles, novel non-invasive techniques such as MEUS and TMS have been studied to temporally open the enhance brain drug uptake. Innovative delivery systems should be expected to facilitate brain disease diagnostics. With understanding of the leaky barrier, previously developed nanoparticles that target tumours according to the EPR effect could be applied to brain diseases. Gliomas contain highly heterogeneous ranges in which permeability is normal in peripheral regions. Thus, a combination of strategies penetrating both permeable and normal might have to be considered. Additionally, further studies on the dynamics of disruption will come out, which will assist the design of sufficient delivery systems by taking advantages of it. Another important area that deserves further investigation is the influence of aging on Brain dysfunctions. Brain drug delivery systems that have considered the influence of aging and were tested in animals of different ages are rarely found in the literature. In summary, the complexity of the brain requires further detailed studies on delivery strategies, but on the other hand, it might offer unique opportunities to design efficient delivery systems to treat various brain diseases.

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