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Review Article

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A REVIEW ON NANOPARTICULATE SYSTEM FOR NASAL DRUG DELIVERY

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ABSTRACT

Drug delivery through nasal route has attracted the interest of scientific community as it has been potentially explored as an alternative route for the administration of vaccines and biomolecules such as proteins, peptides and non-peptide drugs that are susceptible to enzymatic or acidic degradation and first-pass hepatic metabolism. In addition it minimizes the lag time associated with oral drug delivery and offers, self-medication, patient comfort and patient compliance. Particulate systems like nanoparticles are used as a physical approach to vary and enhance the pharmacokinetic and pharmacodynamic properties of varied sorts of drug molecules. Delivery of drugs to the target site is accomplished by a colloidal drug delivery system mainly by using nanoparticles. In this review we have discussed advantages, limitations, anatomy of nose, mechanism of action and factor affecting the permeability of drugs or biomolecule through nasal mucosa of nasal drug delivery system in local delivery, systemic delivery of the Drug. In conclusion, nanoparticles are one of the convenient drug delivery systems, which can be of potential use in controlling and targeting nasal drug delivery.

KEYWORDS: Intrasal drug delivery, advantages, limitations, nanoparticles preparation of nanoparticles etc.

INTRODUCTION

Conventionally the nasal cavity is used for the treatment of local diseases, such as rhinitis and nasal congestion. However, in the past decades nasal drug delivery has much more attention as a promising drug administration route for the systemic therapy. This is due to the anatomy and physiology of the nasal passage, It as the large surface area, highly vascularized epithelium, porous endothelial membrane, and the avoid first-pass metabolism. This is particularly important for the delivery of peptides and proteins that currently administered through intravenous route because of their susceptibility to the gastrointestinal proteases. Nasal drug delivery can also provide a route of entry to the brain that circumvents the blood–brain barrier because olfactory receptor cells are in direct contact with the central nervous system.[1] Intra-nasal drug delivery – which has been practiced for thousands of years, has been given a new lease of life. It is a useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability such as proteins and peptides. One of the reasons for the low degree of absorption of peptides and proteins via the nasal route is rapid movement away from the absorption site in the nasal cavity due to the Muco-ciliary Clearance mechanism. The nasal route is easily accessible and suitable for self-medication. The large surface area of the nasal mucosa affords a rapid onset of therapeutic effect, potential for direct-to-central nervous system delivery.[2] Nanoparticle (NP) therapeutics is an emerging modality for the treatment of Parkinson's disease (PD) as it offers targeted delivery and enhances the therapeutic efficacy and/or bioavailability of neurotherapeutics.[3]

Advantages of Nasal Drug Delivery Systems

a) Large nasal mucosal surface area for dose absorption
b) Rapid drug absorption via highly vascularized mucosa
c) Rapid onset of action
d) Ease of administration, noninvasive
e) By pass the BBB
f) Avoidance of the gastrointestinal tract and first pass metabolism
g) Improved bioavailability
h) Direct transport into systemic circulation and CNS is possible.
i) Lower dose/reduced side effects
j) Improved convenience and compliance
k) Self-administration

Limitations of Nasal Drug Delivery System

a) Volume that can be delivered into nasal cavity is restricted to 25-200 µl.
b) Not feasible for high molecular weight more than 1k Da
c) Adversely affected by pathological conditions
d) Drug permeability may alter due to ciliary

movement.

e) Drug permeability is limited due to enzymatic inhibition.
f) Nasal irritants drugs cannot be administered through this route.[4]

Nasal Anatomy and Physiology of the Nose

The nose is part of the respiratory system and is the organ through which our body communicates with the external environment. It is an organ of sense and one of its main functions is the perception of external smells. Moreover, its most important role is to let the air pass favoring the gaseous exchanges which take place at the alveolar level. The inhaled air comes into contact with a total surface which amounts to 160 cm^2, referring to the nasal cavity, and reaches up to 96 cm^2, considering the presence of the nasal epithelium microvilli.

The nasal cavities are divided in three different functional areas: the vestibular, the respiratory and the olfactory regions (Figure 1).[5]

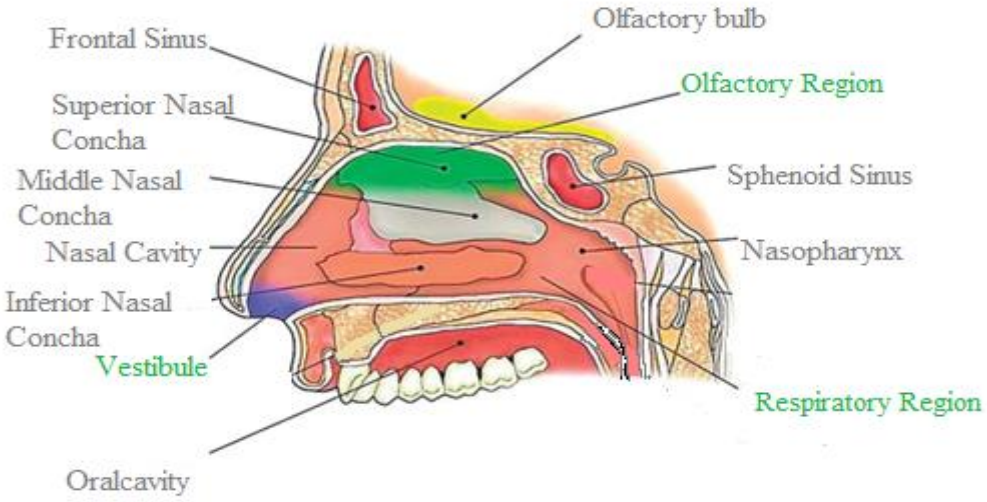

Figure 1: Anatomy of the nasal cavity.

1) The Respiratory Region

The respiratory region is the largest having the highest degree of vascularity and is mainly responsible for systemic drug absorption.

2) The Vestibular Region

It is located at the opening of nasal passage and is responsible for filtering out the air borne particles. It is considered to be the least important of the three regions with regards to drug absorption.

3) The Olfactory Region

It is of about 10cm^2 in surface area and it plays a vital role in transportation of drugs to the brain and the CSF. Human olfactory region comprises if thick connective tissue lamina propria, upon which rests the olfactory epithelium. Lamina propria has axons, Bowens bundle and blood vessels whereas epithelium consist of three different cells i.e. basal cells, supporting cells and olfactory receptor cells etc. Neurons are interspersed between supporting cells. The olfactory receptor cells are bipolar neurons with a single dendrite and extending from the cell body to the free apical surface where it ends in an olfactory knob carrying nonmotile cilia, which extend above the epithelium. The epithelium of the nasal passage is covered by a mucus layer, which entraps particles. The mucus layer is cleared from the nasal cavity by cilia and is renewed every 10-15 minutes the pH of the mucosal secretion's ranges from 5.5-6.5 in adults. Numerous enzymes for instance, Cytochrome P-450, Carboxylesterase and Glutathione S-transferase are present in nasal cavity.[6]

Mechanism of Drug Absorption

The first step in the absorption of drug from the nasal cavity is passage through the mucus. Small, unchanged particles easily pass through this layer. However, large or charged particles may find it more difficult to cross. Mucin, the principal protein in the mucus, has the potential to bind to solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes (i.e. pH, temperature, etc.).

- The first mechanism involves an aqueous route of transport, which is also known as the paracellular route. This route is slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. Poor bioavailability was observed for drugs with a molecular weight greater than 1000 Daltons.
- The second mechanism involves transport through a lipoidal route that is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show rate dependency on their lipophilicity. Drugs also cross cell membranes by an

active transport route via carrier-mediated means or transport through the opening of tight junctions. For example, Chitosan, a natural biopolymer from shell-fish, opens tight junctions between epithelial cells to facilitate drug transport.[7]

Factors Affecting the Permeability of Drugs through the Nasal Mucosa

Physiological factors

- Blood supply and neuronal regulation
- Nasal secretions
- pH of the nasal cavity
- Mucociliary clearance
- Pathological conditions

Physicochemical properties of drugs

- Molecular weight
- Particle Size
- Solubility& dissolution rate
- Lipophilicity
- pKa and partition coefficient

Physicochemical properties of formulation

- pH
- Osmolarity
- Viscosity
- Drug distribution
- Dosage form[8]

Physiological factors

- **Blood supply and neuronal regulation:** Nasal mucosa is highly permeable site. High blood supply due to parasympathetic stimulation gives congestion and low blood supply due to sympathetic stimulation gives relaxation, regulate the rise and fall in the amounts of drug permeated, respectively. Based on the above observations, we can conclude that increase in permeability of a compound is due to parasympathetic stimulation.
- **Nasal secretions:** Nasal secretions are produced by anterior serous and seromucous glands. Mucus production is approximately 1.5–2 l ml daily.
- **pH of nasal cavity:** Variation in ph is observed between 5.5–6.5 in adults and 5.0–7.0 in infants. Permeation of drug is greater if the nasal ph is lower than pka of drug because under such conditions the penetrant molecules exist as unionized species. Increase or decrease in the permeation of drug is observed because ionization is affected by change in ph of mucus, depending on the nature of the drug. Ph of formulation should be between 4.5 to 6.5 for better absorption and should also have good buffering capacity.
- **Mucociliary clearance (MCC):** Whenever a substance is nasally administered, it is cleared from the nasal cavity in ~21 min by MCC because mucociliary clearance is the normal defence mechanism of the nasal cavity which clears substances adhering to nasal mucosa and cleared in GIT by draining into nasopharynx. Drug permeation is enhanced by increasing contact time between drug and mucus membrane because reduced MMC; whereas, increased MCC decreases drug permeation.
- **Pathological conditions:** Mucociliary disfunctioning, hypo or hypersecretions, irritation of the nasal mucosa occurs due to diseases such as the common cold, rhinitis, atrophic-rhinitis and nasal polyposis, and drug permeation is affected by this.[9]

Physicochemical properties of drugs

- **Molecular weight:** A linear inverse correlation has been reported between the absorption of drugs and molecular weight up to 300 Da. Absorption decreases significantly if the molecular weight is greater than 1000 Da except with the use of absorption enhancers. Shape is also important. Linear molecules have lower absorption than cyclic - shaped molecules.
- **Particle Size:** It has been reported that particle sizes greater than 10μm are deposited in the nasal cavity.
- **Solubility & dissolution Rate:** Drug solubility and dissolution rates are important factors in determining nasal absorption from powders and suspensions. The particles deposited in the nasal cavity need to be dissolved prior to absorption. If a drug remains as particles or is cleared away, no absorption occurs.[10]
- **Lipophilicity**: Absorption of drug substance through biological Membrane may be dependent on hydrophilic lipophilic Balance of the compound. On increasing lipophilicity, the Nasal absorption of the compound normally increases.
- **Partition coefficient and pka:** According to the ph partition theory, unionized form of Drug are well absorbed compared with ionized form of Drug and the same theory is applicable in the case of nasal Drug absorption.
- **Chemical form:** The chemical form of a drug is important in determining Absorption. For example, conversion of the drug into a salt or ester form can alter its absorption. Reported that in-situ nasal absorption of carboxylic acid esters of L-tyrosine was significantly greater than that of unmodified L-tyrosine.

Physicochemical properties of formulation

pH of formulation: Both the pH of the nasal cavity and pKa of a particular drug need to be considered to rationalize systemic absorption. Nasal irritation is minimized when products are delivered with a pH ranging between 4.5 and 6.5.

The pH of a nasal formulation is important for the following reasons

- To avoid irritation of nasal mucosa
- To allow the drug to be available in unionized form for absorption
- To prevent growth of pathogenic bacteria in the nasal passage

- To maintain functionality of excipients such as preservatives
- To sustain normal physiological ciliary movement

Osmolarity: Drug absorption can be affected by tonicity of the Formulation. Hypertonic saline solutions are also known to inhibit or cease ciliary activity. Low pH has a similar effect on cells as hypertonic solutions.[11]

Nasal Drug Delivery System Dosage Forms

The selection of dosage form depends upon the drug being used, proposed indication, patient population and last but not least, marketing preferences. Four basic formulations must be considered, i.e. solution, suspension, emulsion and dry powder systems.

1. Liquid Nasal Formulations

Liquid preparations are the most widely used dosage forms for nasal administration of drugs. They are mainly based on aqueous state convenient and useful, since many allergic and chronic diseases are often connected with crusts and drying of mucous membranes. Microbiological stability, irritation and allergic rhinitis are the major drawbacks associated with the water-based dosage forms because the required preservatives impair mucociliary function and the reduced chemical stability of the dissolved drug substance and the short residence time of the formulation in the nasal cavity are major disadvantages of liquid formulations. The several types dosage forms available in liquid form are described below.

a) Instillation and Rhinyle Catheter: Catheters are used to deliver the drops to a specified region of nasal cavity easily. The formulation is placed in the tube. One end is positioned in the nose, and the solution is delivered into the nasal cavity by blowing through the other end by mouth.

b) Compressed Air Nebulizers: Nebulizer is a device used to administer medication in the form of a mist, inhaled into the lungs. The compressed air fills into the device, so it is called compressed air nebulizers. The common technical principle for all nebulizers is to use oxygen, compressed air or ultrasonic power, as means to break up medical solutions/ suspensions into small aerosol droplets, for direct inhalation from the mouthpiece of the device.

c) Squeezed bottle: Squeezed nasal bottles are mainly used as delivery devices for decongestants. They include a smooth plastic bottle with a simple jet outlet. While pressing the plastic bottle the air inside the container is pressed out of the small nozzle, thereby atomizing a certain volume. By releasing the pressure again air is drawn inside the bottle.

d) Metered-dose Pump Sprays: Most of the pharmaceutical nasal preparations in the market containing solutions, emulsions or suspensions are delivered by metered-dose pump sprays. Nasal sprays, or nasal mists, are used for the nasal delivery of a drug or drugs, either locally to generally alleviate cold or allergy symptoms such as nasal congestion or systemically. Although delivery methods vary, most nasal sprays function by instilling a fine mist into the nostril by the action of a hand-operated pump mechanism. The three main types available for local effect are antihistamines, corticosteroids, and topical decongestants. Metered- dose pump sprays include the container, the pump with the valve and the actuator. The dose accuracy of metered-dose pump sprays is dependent on the surface tension and viscosity of the formulation. For solutions with higher viscosity, special pump and valve combinations are available in the market.

2. Powder Dosage Forms

Dry powders are less frequently used in nasal drug delivery. Major advantages of this dosage form are the lack of preservatives and the improved stability of the formulation. Compared to solutions, the administration of powders could result in a prolonged contact with the nasal mucosa. The types of powder dosage forms are described below.

a) Insufflators: Insufflators are the devices to deliver the drug substance for inhalation. It can be constructed by using a straw or tube which contains the drug substance and sometimes it contains syringe also. The achieved particle size of these systems is often increased compared to the particle size of the powder particles due to insufficient disaggregation of the particles.

b) Dry Powder Inhaler: 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. Dry powder inhalers are bolus drug delivery devices that contain solid drug, suspended or dissolved in a non-polar volatile propellant or in dry powder inhaler that is fluidized when the patient inhales. These are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema and COPD and have also been used in the treatment of diabetes mellitus.

3. Pressurized MDI's

A metered-dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine that is inhaled by the patient. It is the most commonly used delivery system for treating asthma, chronic obstructive pulmonary disease (COPD) and other respiratory diseases. The advantages of MDIs are their portability and small size, availability over a wide dosage range per actuation, dose consistency, dose accuracy, protection of the contents and that they are quickly ready for use. To use the inhaler, the patient presses down on the top of the canister, with their thumb supporting the lower portion of the actuator. The propellant provides the force to generate the aerosol cloud and is also the medium in which the active component must be suspended or dissolved.

4. Nasal Gels

Nasal gels are high-viscosity thickened solutions or

suspensions. Until the recent development of precise dosing devices, there is not much interest in this system. The advantages of a nasal gel include reduction of post-nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients and target delivery to mucosa for better absorption. The deposition of the gel in the nasal cavity depends on the mode of administration. Due to its viscosity, the formulation has poor spreading abilities.[12]

Novel Intranasal Drug Delivery Systems to Target CNS

Over last few years novel drug delivery systems such as liposomes, micro and nano emulsions, microspheres, micro and nanoparticles have been used to improve nasal drug permeation.

1. Liposomes

Liposomes are non-toxic, biodegradable and biocompatible lipid carriers made up of animal lipid such as phospholipids and sphingolipids. These have the drawback of holding hydrophilic, lipophilic, and amphoteric product molecules stuck within or on their micellar surface. Often lipids used in liposomal drug distribution are phospholipids that shape self-sustaining bilayer structure to shape liposomes. This may be used to encapsulate the medication molecule directly into diseased tissues or organs.

2. Micro-emulsions

Micro-emulsions are clear, stable, isotropic mixtures of oil, water and surfactant, frequently in combination with a co surfactant. These systems are currently of interest to the pharmaceutical scientist because of their considerable potential to act as drug delivery vehicles by incorporating a wide range of drug molecules. They offer the advantage of spontaneous formation, ease of manufacturing and scale-up, thermodynamic stability, and improved drug solubilization and bioavailability.

3. Microsphere

Microsphere technology is one of the advanced systems that is becoming increasingly prevalent in the design of nasal products, offering long-term interaction with nasal mucosa and thereby improving absorption and bioavailability. During the midst of microspheres, nasal mucosa is dehydrated by microsphere moisture absorption. It results in a permanent shrinkage of the tissues, which creates a transient physical state. Separation of close (intercellular) junctions that improve drug absorption. Microsphere used in nasal drug distribution is water insoluble but draws water into the structure, resulting in the swelling of the spheres to form a gel.

4. Nanoparticles

Nanoparticles are colloidal structures with a compact arrangement where the therapeutic agent is either stuck within a colloidal matrix or deposited on a particle surface through conjugation or adsorption. Nanoparticles may have a continuous and regulated release of medications, often made up of polymer, lipid or a mixture of both. Nano systems used to build nano drug delivery mechanisms in the diagnosis of CNS diseases involves polymeric nanoparticles, nano-suspensions, nano-emulsions, nano-gels, nano-micelles and nanoliposomes, carbon nano-tubes, nano-fibers and nano-robots, strong lipid nanoparticles (SLNs), nano-structured lipid carriers (NLCs) and lipid conjugates (LDCs).[13]

Nanoparticulate System for Nasal Drug Delivery

Nanoparticles are defined as appropriate dispersions or solid particles with a size in the range of 10-1000nm. The drug is dissolved, entrapped, encapsulated, or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nano capsules can be acquired. The major intention in designing nanoparticles as a delivery system is to control particle size, surface properties, and release of pharmacologically active agents to accomplish the site-specific action of the drug at the therapeutically excellent rate and dose regimen.[14] Nanoparticles are not simple molecules as such and therefore composed of three layers i.e. (a) The surface layer, which may be functionalized with a variety of small molecules, metal ions, and polymers. (b) The shell layer, which is chemically distinct material from the core in all aspects, and (c) The core, which is essentially the central portion of the Nanoparticle and generally refers to the Nanoparticle itself.[15]

Preparation of nanoparticles

For the preparation of nanoparticles, the selection of the appropriate method is based on the drug to be loaded and the physicochemical properties of the polymer. The most Widley used methods are,

A. Emulsion-Solvent Evaporation Method
B. Solvent Displacement/Precipitation method
C. Polymerization method
D. Coacervation or ionic gelation method
E. Salting out method
F. Emulsions - Diffusion method

A. Emulsion-Solvent Evaporation Method: The nanoparticles are usually prepared by using this method. Two steps are mainly involved in this method shown in Fig 2. In an aqueous phase, emulsification of the polymer solution is required in the first step. While in the second step, evaporation of polymer Solution occurs and noospheres are formed by inducing the polymer precipitation. Collection of nanoparticles is done by ultracentrifugation and to eliminate free drug or residue, washed with distilled water and for storage these are lyophilized. This method is also known as the solvent evaporation method and high-pressure emulsification.

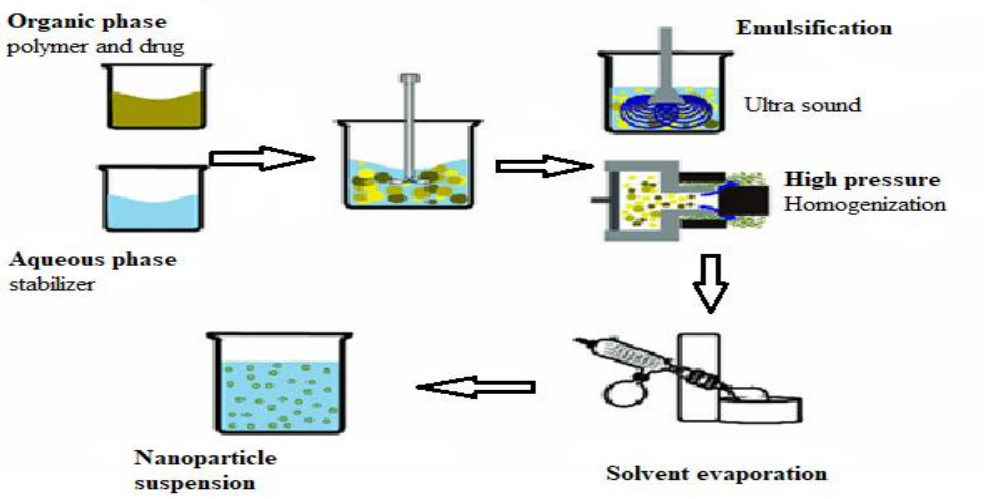

Fig. 2: Nanoparticle preparation using emulsion solvent evaporation methods.

B. Solvent Displacement/Precipitation Method: Solvent displacement involves from an organic solution, the precipitation of a preformed polymer, and in the aqueous medium the diffusion of the organic solvent in the presence or absence of surfactant. In semi-polar water-miscible solvents like acetone or ethanol, polymers, drug, and lipophilic surfactant are dissolved. Then the solution is injected using magnetic stirring, into a stabilizer containing an aqueous solution. By the rapid solvent diffusion, Nanoparticles are formed. Then under reduced pressure solvent is removed from the suspension. The particles size is also affected by the rate of addition of the organic phase into the aqueous phase. It was observed that by increasing the rate of mixing, both particles size and drug entrapment decrease. For most of the poorly soluble drugs, the nano precipitation method is well suited.[16]

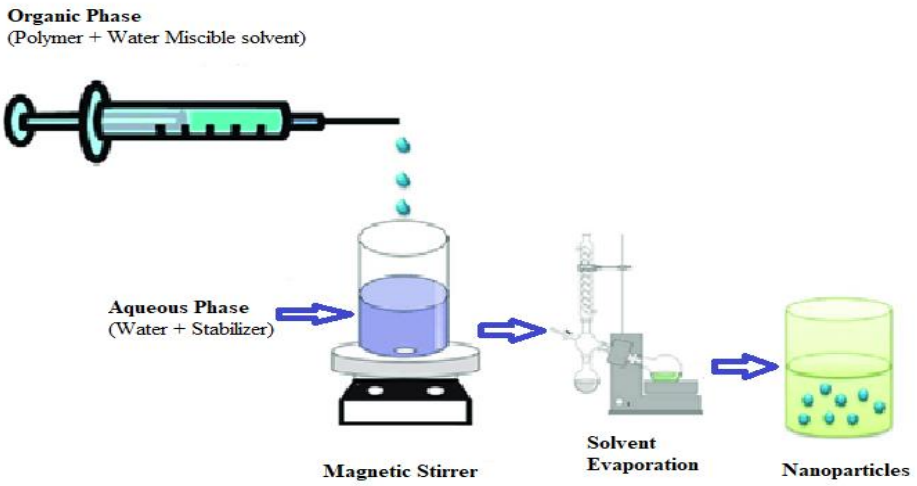

Fig. 3: Nanoparticle preparation using the solvent displacement method.

C. Polymerization Method: In this method, monomers are polymerized to form nanoparticles in an aqueous solution. The drug is included either by being liquefied in the polymerization medium or by adsorption onto the nanoparticles after polymerization is completed. The nanoparticle suspension is then filtered to eliminate various stabilizers and surfactants employed for polymerization by ultracentrifugation and re-suspending the particles in an isotonic surfactant-free medium. This technique has been described for making poly butyl cyanoacrylate or poly (alkyl cyanoacrylate) nanoparticles. Nano capsule development and their particle size depending on the concentration of the surfactants and stabilizers used.

D. Coacervation or Ionic Gelation Method: The preparation of nanoparticles utilizes biodegradable hydrophilic polymers such as chitosan, gelatine, and

sodium alginate. Calvo and co-workers developed a method for developing hydrophilic chitosan nanoparticles by ionic gelation. The method includes a mixture of two aqueous phases, of which one is the polymer chitosan, di-block copolymer ethylene oxide or propylene oxide (PEO-PPO) and the other is a polyanion sodium tripolyphosphate. In this method, positively charged chitosan links with negatively charged to form coacervates with a size in the range of nanometre. Coacervates are developed as a result of electrostatic interaction between two aqueous phases, whereas, ionic gelation includes the material undergoing a transition from liquid to gel due to ionic interaction due to ionic interaction conditions at room temperature.

E. Salting Out Method: This technique is based on the separation of water-miscible solvent from an aqueous solution by the salting-out effect. In this method, toxic solvents are not utilized. Polymer and drug dissolved in a solvent which emulsified into an aqueous solution containing salting-out agent but salting out can also be produced by saturation of the aqueous phase using colloidal stabilizer/ emulsion stabilizer/viscosity increasing agent such as polyvinyl pyrrolidine or hydroxyethyl cellulose, PVA, PLGA, and poly (tri methylene carbonate). After preparation of o/w emulsion diluted with the addition of sufficient water to allow the complete diffusion of acetone into the aqueous phase, thus inducing the formation of noospheres. This technique does not require an increase in temperature and stirring energy required for lower particle size. The disadvantage of this technique is its entire application to lipophilic drugs and the extensive nanoparticle washing steps. Solvent and salting-out agents are then eliminated by cross-flow filtration (Fig:4).

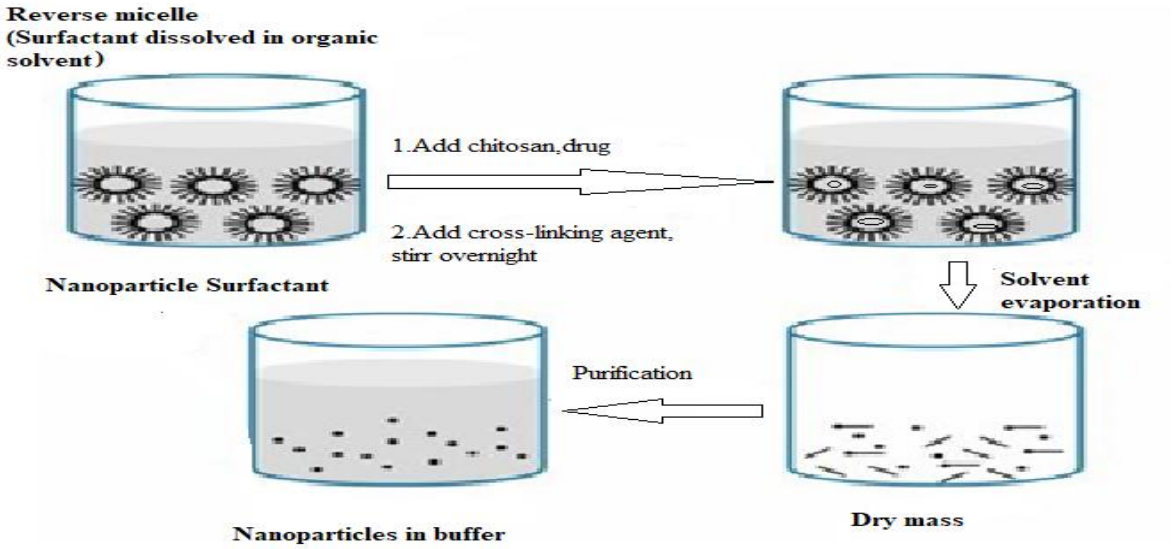

Fig. 4: Nanoparticle preparations using salting-out method.

Emulsion-Solvent Evaporation Method

The nanoparticles are mostly prepared by using this method. Two steps are mainly involved in this method. In an aqueous phase, emulsification of the polymer solution required in the first step. While in the second step, evaporation of polymer solutionoccurs and nanospheres are formed by inducing the polymer precipitation. Collection of nanoparticles is done by ultracentrifugation and to remove free drug or residue,washed with distilled water and for storage these are lyophilized.

This method is also known as solvent evaporation methodand highpressure emulsification. This technique involves homogenization under high pressure and overall stirring to remove organic solvent. By adjusting the stirring rate, viscosity of organic and aqueous phases, temperature, type and amount of dispersing agent the size can be controlled. However to lipid soluble drugs, this technique can be applied and by the scale up issues limitation are imposed. Polymers used are PLA, Poly (β-hydroxybutyrate) (PHB) Poly (caprolactone) (PCL) PLGA cellulose acetate phthalate and EC in this method.

F. Emulsions - Diffusion Method: In this method, the polymer is liquefied in water-miscible solvent and saturated with water. Polymer water-soaked solvent phase is emulsified in an aqueous solution containing a stabilizer. Then the solvent is eliminated by evaporation or filtration.[17]

Evaluations of Nasal Drug Formulation

- ***In Vitro* diffusion studies**

In vitro diffusion studies were performed using jacketed nasal diffusion cell sheep nasal mucosa. The receptor chamber was filled with 50ml distilled water (370 C± 20 C) and 0.2 ml test formulation was placed on the dorsal

mucosa. Sample (1ml) at predetermined interval were transferred to test tubes and analyzed spectrophotometrically at 276nm.[18]

- ***In Vitro* Release Studies**

In vitro release study of the formulated in situ gel was carried out in two chamber diffusion cells through dialysis membrane-70 with molecular weight cut off 1200-1400 KDa. Diffusion of diameter 1.5cm and 20 ml capacity consisted of upper cylindrical compartment open from above and diffusion membrane at its base. To prepare artificial membrane, pieces of dialysis membrane were soaked in PBS pH 7.4 for hrs before mounting on diffusion cell. Dialysis membrane was in a two chamber cells. In situ gels of poloxamer 407 loaded with drug were placed in the donor compartment. 20 ml of PBS 7.4 was placed in the receptor compartment. The temperature of receiver compartment was maintained at the 370 C ±1.00C during experimental and the content of the receiver compartment was stirred using magnetic stirrer. The position of the donor compartment was adjusted so that dialysis membrane just touches the diffusion medium. An aliquot of 1ml was withdrawn from receiver compartment initially after 15 and 30 min and then 1 hr interval and replaced with same amount of fresh medium. Withdrawn were diluted and analyzed using UV spectrophotometer at 276nm for drug. In vitro drug release was carried out for 8hrs.[19]

- ***In vitro* permeation study**

Fresh nasal tissues were carefully removed from the nasal cavity of goat obtained from the local slaughterhouse. Tissue sample were inserted in Franz diffusion cell displaying a permeation area of 1.76cm^2 7ml of 6.4 pH phosphate buffer saline was added to the acceptor chamber and agitated with magnetic stirrer at 340 C. After pre incubation time of 20 min, pure drug solution and formulation equivalent to 0.25%w/v of Salbutamol sulphate was placed in the donor chamber. From the acceptor compartment 0.2ml sample aliquots were withdrawn at predetermined time interval up to 6 hrs replacing the sample volume with 6.4 pH PBS after each sampling, filtered and analyzed by UV spectrometer at 276nm.[20]

CONCLUSION

The delivery of drug molecules across the nasal mucosa opens a new hope for the both local and systemic delivery of medicaments. Nasal drug delivery is a promising alternative route of drug administration for local, systemic and central nervous system action. It has advantages in terms of reduces systemic exposure and hence side effects and avoiding first-pass metabolism. The small and dynamic dimensions of the nasal cavity and the anterior anatomy are among the most important hurdles for more efficient nasal drug delivery. In future, the extensive research is necessary to make this route of delivery more efficient and popular.

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