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# NASAL MICROSPHERES AS A NOVEL DRUG DELIVERY SYSTEM

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**Keywords:**

Nasal microspheres, Controlled release, Bioavailability, Rapid onset of action

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## ABSTRACT

Nasal drug delivery systems are those which provide intimate contact of the drug with the nasal mucosa for an extended period of time. They improve the bioavailability of the drug and hence improve its therapeutic effect and decreases the undesired side effects. Nasal route can be exploited for the controlled release of drugs such as small molecular weight polar drugs, peptides and proteins that are not easily administered via other routes than by injection, or where a rapid onset of action is required. It delivers the drug accurately and safely at the precise time period to gain the maximum therapeutic effect. Nasal microspheres are biodegradable in nature, and ideally have a particle size of about 10-50µm. Various methods are used for the preparation of nasal microspheres, such as emulsion solvent evaporation, phase separation and co-acervation, single emulsion technique, double emulsion technique, multiple emulsion method, solvent extraction method, Quasi-emulsion solvent diffusion method, Ionotropic external gelation technique, spray drying methods. The evaluation of nasal microspheres includes Particle size determination, Percentage yield, UV-FTTR (Fourier transform infrared), X-ray diffraction, Drug entrapment efficiency, Surface Topography, *In-vitro* drug release , *Ex-vivo* studies.

## INTRODUCTION

Inhalation therapy is widely employed to deliver drugs to the respiratory epithelium, predominately for the treatment of local disorders such as asthma and COPD, although there is increasing interest in using pulmonary delivery for the administration of systemically-acting macromolecules, exemplified most notably by the recent launch of the inhaled insulin product, Exubera.[1] Systemic delivery of drugs via the nasal route is associated with several positive factors such as the relatively large surface area available for absorption, the highly vascularized epithelial layer, lower enzyme levels compared to gastrointestinal tract and liver, high total blood flow per cm3, direct drug transport to the systemic circulation, thereby avoiding first-pass hepatic metabolism, and its ready accessibility. But rapid mucociliary clearance and low permeability of the nasal mucosa to drugs tends to affect these positive release of the drug to some extent. [2 ] The most important factor limiting the chronic application and nasal absorption of polar drugs and especially large molecular weight polar drugs such as proteins and peptides is the low membrane permeability. Several attempts have been made to overcome these limitations by incorporating either a penetration enhancer or some form of mucoadhesive material into the formulation to facilitate drug transport through the mucosal membrane or to increase the retention time in the nasal cavity. [3] Nasal route is non-invasive, therefore, reduced risk of infection, ease of convenience and self-medication resulting in improved patient compliance.[4] Powder-based formulations are more preferable for nasal administration due of their good physical stability, ease and size of packaging and ease of handling as compared to liquid formulations.[5] Also, there is an evidence that the powders are cleared more slowly than liquids from the nose in human volunteers.[6] Dry powder inhalers have edge over the existing liquid inhaler systems like Metered dose inhalers (MDIs), Nebulizer and Aerosol Sprays etc. A dry powder inhaler (DPI) offers better patient compliance as well as overcomes the instability. They provides reduction in side effects, no first pass metabolism, maintenance of effective plasma concentration and reduces dosing frequency. A wide range of nasal products is in development, mostly in correlation with the rapid onset of action of nasal route, for example, for the treatment of pain (nasal morphine and ketamine) and for the treatment of erectile dysfunction (nasal apomorphine).[7] Mucoadhesive materials can increase the time available for drug absorption. Starch microspheres were the first mucoadhesive microparticulate nasal delivery system.[8] Possible pathways for a drug to permeate across the nasal mucosa are passive transportation, carrier mediated, trans-cytosis and transport through intercellular tight junctions.[9] Mucoadhesive

polymers have been introduced to construct microparticle type formulations which could overcome problems of poor bioavailability by increasing the residence time in the applied site. Mucoadhesive polymers that have been used for drug delivery include polyacrylic acids, cellulose derivatives, chitosan, gelatin and hyaluronic acid. [10] Recently, microsphere technology has been applied in designing formulations for nasal drug delivery. The primary rationale behind selection of microspheres is to provide a better chance for the drug to be absorbed by allowing a more intimate and prolonged contact between the drug and the mucosal membrane. [11] Microspheres swell in contact with nasal mucosa and form a gel which controls the rate of clearance from the nasal cavity. In the presence of microspheres, the nasal mucosa is dehydrated due to moisture uptake by the microspheres. This results in reversible shrinkage of the cells, providing a temporary physical separation of the tight (intercellular) junction, which increase the absorption of the drug. [12] Hence, a formulation that would increase residence time in the nasal cavity and at the same time increased absorption of drug would be highly beneficial in all respects. The systemic absorption of conventional drugs as well as polypeptides across nasal mucosa has been considerably enhanced by mucoadhesive microspheres without the use of absorption enhancers which are known to have an irritating effect on nasal mucosa. [13] When formulating a dry powder for inhalation, micronisation is usually employed to reduce the particle size of the drug powder to less than 5 µm. However, powders in this size range exhibit strong interparticulate cohesion, leading to poor powder flow properties. [14, 15] Furthermore, factors known to influence the aerosolisation properties of dry powders (e.g. particle morphology, density and surface composition) cannot be controlled effectively during the micronisation process. Researchers in the field have investigated a number of approaches to improve powder aerosolisation, such as mixing the micronised drug with inert carrier particles or modification of particle morphology, particle surface roughness, particle porosity or powder density. [16-24]An alternative approach to the generation of dry powders for pulmonary drug delivery is offered by spray-drying technology. Whereas micronisation is a destructive technique, spray drying is a one-step constructive process that provides greater control over particle size, particle morphology and powder density. Indeed, dry powders generated by spray-drying have been investigated by a number of researchers for suitability as dry powder inhaler (DPI) formulations.[23,25-30] In nasal drug delivery, coupling of bioadhesive properties to microspheres is of great importance because of additional advantages: efficient absorption and enhanced bioavailability of the drug, a much more intimate contact with the mucus layer

and reduction in frequency of drug administration due to the reduction in mucociliary clearance of drug delivery system adhering to nasal mucosa. [31] The nasal drug delivery finds the alternative way of targeting the drug to central nervous system (CNS) with the advantage of its high vascularization and faster onset of action. Intranasal Therapy has been an accepted form of treatment in the ayurvedic system of Indian Medicine. Intranasal drug delivery offers a promising alternative route for administration of such drugs. Nasal drug delivery system is also suitable for restricting and obstacles blood brain barrier so that drug can be delivered in the bio phase of CNS. It is also considered for the administration of vaccines. The most commonly used excipients are Solubilizers, buffer components, antioxidants, preservatives, humectants, and gelling/viscosifying agents. [32, 33]

**Mechanism of drug absorption:**

In the nasal drug delivery, absorption includes firstly by passing of drug through the nasal mucosa. Uncharged as well as small particles easily pass through mucous. However, charged as well as large particles may find it more difficult to cross. Then it follows the 2 main mechanisms. They are:

1. The first mechanism of drug absorption involves an aqueous route of transport (Paracellular route). Paracellular route is slow and passive. Here, there is an inverse log-log correlation between the molecular weight of water-soluble compounds and intranasal absorption. Drugs with a molecular weight greater than 1000 Daltons shows poor bioavailability.
2. The second mechanism includes transport of drug through a lipoidal route (transcellular process). Transcellular route is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Cell membranes may be crossed by drugs by an active transport route *via* carrier mediated means or transport through the opening of tight junctions.

   Example: Chitosan opens tight junctions between epithelial cells and hence facilitate drug transport. [32, 34-36]

**Factors affecting nasal drug absorption:**

There are 3 main factors that affects the normal drug absorption. They are as follow:

- **Nasal physiological factors:**

**Blood flow:** Rich supply of blood and a large surface area gives an optimal location for drug absorption. It is influenced by blood flow rate, as it increases the amount of drug that passes through the membrane and hence reaching the general circulation. Several studies were made

to evaluate this influence. For example, Kao et al. stated that nasal absorption of dopamine was relatively slow and incomplete probably due to its own vasoconstrictor effect. From above observations, it was concluded that vasoconstriction decreases nasal drug absorption by diminishing the blood flow. [37]

**Enzymatic degradation:** Internasally administration of drugs avoids gastrointestinal and hepatic first-pass effect. Drugs may be metabolized in lumen of nasal cavity due to the presence of a broad range of metabolic enzymes in nasal tissues. Some examples of enzyme which may play role in enzymatic degradation of drugs are carboxyl esterase, aldehyde dehydrogenases, epoxide-hydrolases, glutathione S-transferases and Cytochrome P450 isoenzymes have been found in nasal epithelial cells. The proteolytic enzymes (amino peptidases and proteases) were also found and they play an important role in degradation of calcitonin, insulin. The pharmacokinetic and pharmacodynamic profile of drugs administered through nasal route may be affected by xenobiotic metabolizing enzymes. [38-41]

**Mucociliary clearance (MCC):** It is the self-clearing mechanism of the bronchi. Also known as Mucociliary apparatus. Nasal mucus layer defend the respiratory tract by preventing the lungs from foreign substances, pathogens and particles carried by inhaled air. These agents adhere to the mucus layer and transported to the gastrointestinal tract. Above elimination is designated MCC and it influences significantly the nasal drug absorption. The MCC system has been described as a ‘‘conveyer belt’’ wherein cilia provide the driving force whereas mucus acts as a sticky fluid that collects and disposes foreign particles. Hence MCC efficiency depends on the length, density and beat frequency of cilia as well as the amount and viscoelastic properties of mucus. MCC may increased by all factors that increase mucus production, decrease mucus viscosity or increased ciliary beat frequency. In physiological conditions, mucus is transported at a rate of 5 mm/min and its transit time in human nasal cavity is reported to be 15-20 min. The values which are not within the range these references are abnormal and suggestive of impaired MCC. From the above discussion we can say that the residence time of the drugs in nasal mucosa increased and hence permeation may be enhanced when MCC decreases. When MCC increases permeation rate of drug is decreased. MCC does not work properly in the following pathological conditions. [42-45]

**Transporters and efflux systems:** The absorption of drugs into systemic circulation and CNS through nasal route is of great interest. Multidrug resistance transporters have been identified which may be involved in the transportation of hydrophobic and amphiphilic drugs. The apical area of ciliated epithelial cells and sub mucosal vessels of the human olfactory

region contain P-gp is an efflux transporter which plays an important role in avoiding the influx of drugs from nasal membrane. [46-48]

- **Physicochemical properties of drugs:**

**Molecular weight, lipophilicity and pKa:** Lipophilic drugs such as propranolol, progesterone and fentanyl are well absorbed from the nasal cavity, exihibiting pharmacokinetic profiles similar to those obtained after intravenous administration. These drugs are absorbed quickly and efficiently across the nasal membrane via transcellular mechanisms. This observation is true for lipophilic compounds having molecular weight lower than 1 kDa. The extend of nasal absorption of lipophilic drugs bigger than 1 kDa is significantly reduced. On the other hand, the rate and degree of nasal absorption of polar drugs is low and highly dependent of the molecular weight. Drug absorption is expected to be diminished with decrease lipophilicity because the nasal membrane is lipophilic. Thus we can say that polar drugs may not easily transport across nasal membrane. Whenever lipophilicity is too high, the drug permeation through the wall may be reduced because drug does not dissolve easily in the aqueous environment of nasal cavity. [49-51]

**Solubility:** For drug absorption, drug dissolution is a pre-requisite because molecularly disperse form of a drug may cross the bio-membranes. Therefore the drug must be dissolved in the nasal cavity fluid before absorption. Drug allowed enough contact with the nasal mucosa which may show slow absorption. Drugs with poorly soluble in water may require high doses hence can cause a problem. The problem can be overcome by enhancing drug solubility using various techniques. [46, 52]

**Stability:** Biological, chemical and physical drug stability studies are a major consideration in all process during the development of new drug formulations. The biological stability of nasally administered drugs may reduce due to the metabolism of drugs by defensive enzymatic mechanisms by nasal cavity. To overcome this difficulty a variety of strategies may be followed, mainly through the use of prodrugs and enzymatic inhibitors. [46, 53]

- **Effect of drug formulation:**

**Viscosity:** Formulation with higher viscosity has a better contact time thus increases the absorption. At the same time, high viscosity enhanced the permeability of drugs. This has been observed during nasal delivery of insulin, acyclovir and metoprolol. Zaki et al. observed that the residence time enhanced as viscosity increased but drug absorption diminished. [54]

**pH:** The pKa of drug and pH at the absorption site plays important role in absorption of drug through nasal route. Thus the stability can achieve by proper selection of pH of formulation.

However, the pH of formulation should be near on human nasal mucosa (5.0-6.5) to prevent the sneezing. [55]

**Pharmaceutical form:** Nasal drops are the simplest and the most convenient nasal pharmaceutical dosage form, but the exact amount of drug delivered is not easily quantified and often results in overdose. Moreover, rapid nasal drainage can occur when using this dosage form. Instead of powder sprays solution and suspension sprays are preferred because powder spray may cause nasal mucosa irritation. Nowadays nasal gel has been developed for accurate drug delivery. This increases the nasal absorption by enhancing the drug residence time and diminishing MCC. [32, 33]

**Pharmaceutical excipients:** In nasal formulations pharmaceutical excipients are selected accordingly to their functions. The most commonly used excipients are solubilizers, buffer components, antioxidants, preservatives, humectants, and gelling/viscosifying agents. [32, 33]

**Mechanism of drug Permeation:**

A drug administered through the nasal cavity can permeate either passively by the paracellular pathway or both passively and actively via the transcellular pathway. This basically depends on the lipophilicity of the compound. Apart from the passive transport pathways, carrier mediated transport, transcytosis and transport through intercellular tight junctions are other possible pathways for a drug to permeate across the nasal mucosa. Lang *et al.* mathematically expressed the effective permeability coefficient Peff under steady state conditions across excised mucosa. [56]

$$Peff = (dc/dt)ss\ V/ (A\ CD) \quad \text{..... Equation 1}$$

Where

(dc/dt) ss is the time-dependent change of concentration in the steady state,

A is permeation area,

V is the volume of the receiver compartment

CD is the initial concentration in donor compartment

Fluorophore labeled markers and drugs, in combination with sophisticated microscopy techniques such as confocal laser scanning microscopy have been used in visualizing the permeation pathways.

**Permeability issues:**

The enhanced permeability from nasal mucosa was demonstrated by Hussain *et al.* when they achieved plasma concentrations of propanolol comparable with those of intravenous concentrations. [57] Various factors that synergistically enhance the permeation of nasally

administered drugs are: the relatively large surface area because of the presence of a large number of microvilli, a porous endothelial membrane and a highly vascularized epithelium. [58] The main barriers for drug permeation are the enzymes present in nasal cavity and the nasal mucosal lining. Nasal vasculature is richly supplied with blood to fulfil the basic functions of the nasal cavity such as heating and humidification, olfaction, mucociliary clearance and immunological functions. The cavity has a relatively large surface area (approximately~150–160 cm2) because of the presence of ~400 microvilli per cell and the total volume of nasal secretions is ~15 ml per day under normal physiological conditions. Together all of these factors account for the large and rapid permeability of drugs through the nasal mucosa.

**METHODS OF PREPARATION**

**1. Emulsion Solvent Evaporation Technique:**

In this method, the drug is dissolved in polymer which was previously dissolved in volatile organic solvent and the resulting solution is added to aqueous phase containing emulsifying agent. The above mixture is agitated at 500 rpm then the drug and polymer is transformed into fine droplet which solidifies into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24 hrs. [59, 60]

Example: Aceclofenac microsphere.

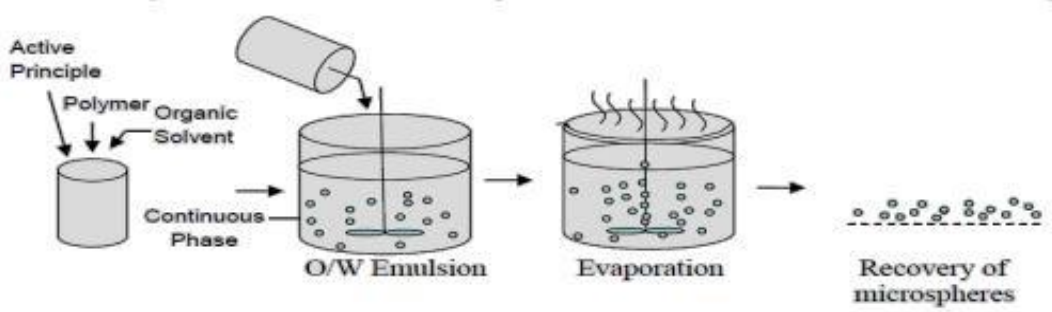


**Figure 1. Emulsion Solvent evaporation method.**

**2. Phase separation and co-acervation:**

The process is based on the principle of decreasing the solubility of the polymer in the organic phase to affect the formation of the polymer rich phase called the co-acervates. In this technique, the polymer is first dissolved in a suitable solvent and then making its aqueous solution disperses drug. Phase separation is then accomplished by changing the solution conditions by using any of the method mentioned above. The process is carried out under continuous stirring to control the size of the microparticles. [61]

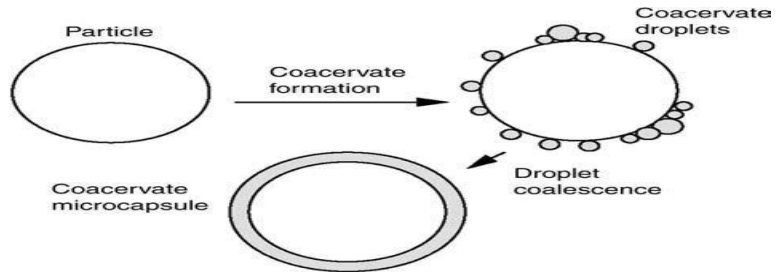


**Figure 2. Schematic diagram of the formation of a Co-acervate around a core material.**

**3. Single emulsion Technique:**

There are several Proteins and carbohydrates, which are prepared by this technique. [62]

**a. Cross linking by heat: -** By adding the dispersion into heated oil, but it is unsuitable for the thermolabile drugs.

**b. Chemical cross linking agents: -** By using agents i.e. formaldehyde, gluteraldehyde etc. but it is having a disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing and separation. Eg. Metformin hydrochloride microsphere are prepare by using gluteraldehyde 25% solution as a cross linking agent.

**4. Double emulsion technique:**

A double emulsion is usually prepared in two main modes: [63, 64]

**Mode 1: One-step emulsification**

**Mode 2: Two-step emulsification**

- In one step emulsification mode a strong mechanical agitation is used for the water phase containing a hydrophilic surfactant and an oil phase containing large amounts of hydrophobic surfactant. Due to this a W/O emulsion is formed which quickly inverts to form a W/O/W double emulsion.
- A two-step procedure is reported where the primary emulsion can be formed as a simple W/O emulsion which emulsion can be formed as a simple W/O emulsion which is prepared using water and oil solution with a low HLB (hydrophilic-lipophilic balance) surfactant. In the second step, the primary emulsion (W/O) is re-emulsified by aqueous solution with a high HLB surfactant to produce a W/O/W double emulsion.

**5. Multiple emulsion method:**

In this method, a primary emulsion (oil-in-water) is first formed (non-aqueous solution containing the target molecule in chitosan solution). This primary emulsion is then added to an external oil phase to form multiple emulsions (oil-in-water-in-oil) followed by either the addition of gluteraldehyde (as a crosslinking agent) or evaporation of an organic solvent. [65]

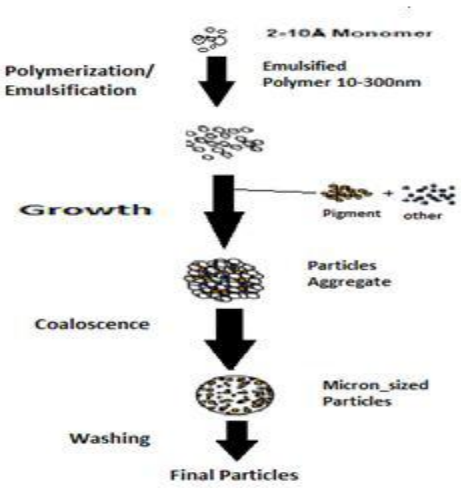


**Figure 3. A Schematic Diagram of multiple emulsions.**

**6. Solvent extraction:**

In this method, the contaminants are separated from the solvent either by changing the pressure and temperature, by using a second solvent to pull the first solvent out of the solvent/contaminant mixture, or by other physical separation processes. [66]

**7. Quasi-emulsion solvent diffusion method:**

A novel quasi-emulsion solvent diffusion method to prepare the controlled release microspheres of drugs with acrylic polymers has been reported in the literature. Micro-sponges can be prepared by a quasi-emulsion solvent diffusion method using an external phase containing distilled water and polyvinyl alcohol (PVA). The internal phase is consisting of drug, ethyl alcohol and polymer is added at an amount of 20% of the polymer in order to facilitate the plasticity. At first, the internal phase is prepared at 60ºC and added to the external phase at room temperature. After emulsification, the mixture is continuously stirred for 2 hours. Then the mixture is filtered to separate the micro-sponges. The product is then washed and dried by vacuum oven at 40ºC for 24hours. [67]

Example: Ibuprofen.

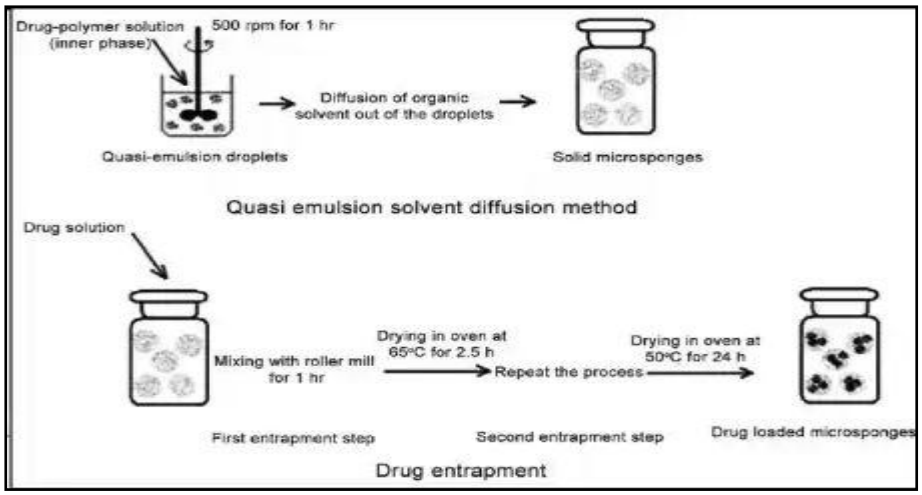


**Figure 4. Quasi-emulsion solvent diffusion method**

**8. Ionotropic external gelation technique:**

In this method, weighed quantity of the drug is added to 50 ml of phosphate buffer solution (pH-7.4) containing the sodium alginate and thoroughly mixed with a stirrer at 400 rpm. For the formation of microspheres, 50 ml of this solution is extruded drop wise from a needle of 22 G in diameter from a height of about 6 cm into 100 ml aqueous calcium chloride solution and stirred at 100 rpm. Then the solution containing the gel formed microspheres is filtered by using Whatman filter paper no-1. The microspheres are allowed to dry at about 30- 40°C and stored in well closed container for further use.

**Process Variables:** - The following process variables are investigated (Bore diameter of the needle; concentration of calcium chloride and sodium alginate; height of dropping; crosslinking time; drying time and temperature) and the different batches thus produced are analyzed for size, shape, drug content and drug release. [68]

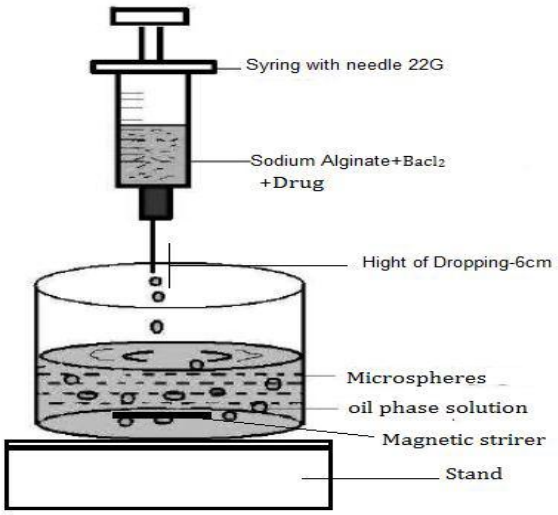


**Figure 5. Ionotropic external gelation technique**

**9. Spray drying and congealing technique:**

Spray drying is one of the most widely investigated methods of preparing microspheres in which drug-polymer solution is sprayed and then air-dried followed by the addition of a crosslinking agent.

Three steps involved in spray drying.

a. Atomization: - Atomization of a liquid feed change into fine droplets.

b. Mixing: - it involves the passing of hot gas stream through spray droplets which result in evaporation of liquids and leaving behind dried particles.

c. Dry: - Dried powder is separated from the gas stream and collected.

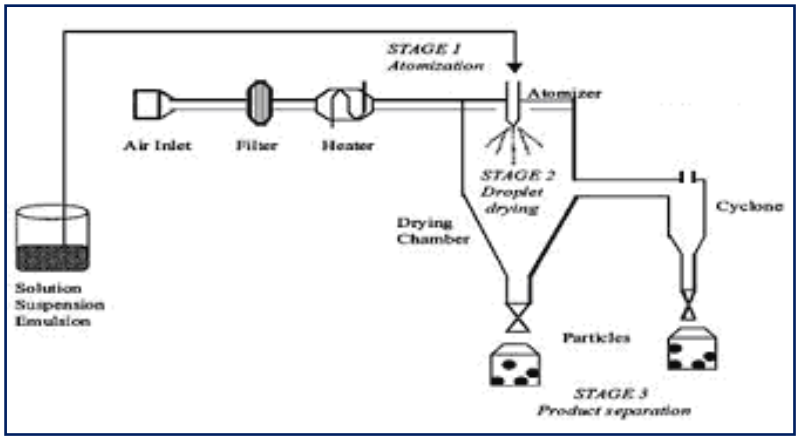


**Figure 6. Spray drying method**

**Evaluation of the microspheres:**

**Particle size determination:** Particle size is determined by optical microscopy with the help of calibrated eyepiece micrometer. The size of around 100 microspheres is measured and their average particle size is determined by using Edmundson's equation. [69].

D mean = Σnd/Σn

Where, n = Number of microspheres checked; d = Mean size.

**Percentage yield:** The percentage yield of microspheres is calculated as follows.

% Yield = Weight of Microspheres /Theoretical weight of drug and polymer x100

**UV-FTTR (Fourier transform infrared):** The drug polymer interaction and degradation of drug while processing for microencapsulation can be determined by FTIR [70]

**X-ray diffraction:** X-ray diffraction is mainly used to determine the change in crystallinity of the drug. Microparticles and its individual components are analysed by the help of an x-ray diffractometer (Bruker, Germany).Scanning range angle between 80C - 70 °C [71]

**Drug entrapment efficiency:** Microspheres containing of drug (5mg) are crushed and then these microspheres are dissolved in distilled water with the help of ultrasonic stirrer for 3 hr,

and then filtered and assayed by uv-visible spectroscopy and then entrapment efficiency is calculated. [72]

Entrapment efficiency = actual drug content /theoretical drug content

**Surface Topography:** The samples for the scanning electron microscope (SEM) analysis are prepared by sprinkling the microspheres on one side of an adhesive stub. Then the microspheres are coated with gold before microscopy. [73]

***In-vitro* release study:** Dissolution test is performed on a USP Type II tablet dissolution test apparatus (VEEGO) at a stirring speed of 150 rpm. Here, a dialysis membrane (Himedia, LA 401) is cut into equal pieces of about 5 cm x 3 cm and pre-treated. Microspheres (50 mg) are accurately weighed out on the pre-treated dialysis membrane and sealed with clips. The pouch thus formed are attached to the paddles of the apparatus using cotton threads over the clips. 900 ml of Phosphate buffer at pH of 7.4 is used as a dissolution medium to ensure sink conditions. Samples are withdrawn for analysis at specified time points, and assessed for Isoniazid content by UV spectroscopy (Shimazdu UV-1700, Japan) at the suitable wavelength. Each dissolution experiment is performed in triplicate. [74]

***Ex-vivo* permeation studies:**

Ex-vivo drug permeation study can be performed using a glass fabricated nasal diffusion cell. The water jacketed recipient chamber has a total capacity of 60 ml and flanged top of about 3mm, the lid has three opening, each for sampling, thermometer, and a donor tube chamber. [75] The 10 cm long donor chamber tube has an internal diameter of 1.13 cm. The nasal mucosa of sheep is separated from sub layer bony tissue and is stored in distilled water containing few drops of gentamycin sulphate injection. After the complete removal of blood from mucosal surface, it is attached to donor chamber tube. The donor chamber tube is placed in such a way that nasal mucosa just touches the diffusion medium (phosphate buffer of pH 6.8) in recipient chamber. [76] The membrane is equilibrated before carefully dispersing the microspheres or solution equivalent to 10 mg of drug onto the donor side. Samples are periodically withdrawn from the receptor compartment, replaced with the same amount of fresh buffer solution of same temperature and assayed spectrophotometerically (UV- 1700 Shimadzu, Japan) at the suitable wavelength. [77]

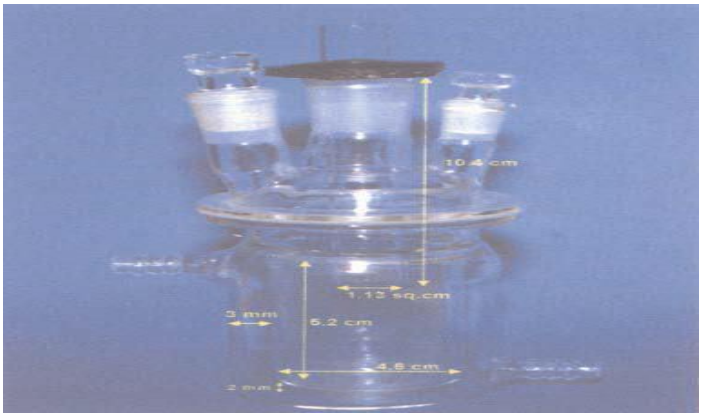


**Figure. 7 Assembly of Nasal Diffusion Cell.**

**Stability study:** It includes subjecting the optimized batch to short-term stability studies of 3 months. The vials filled with microspheres are sealed with rubber caps and are kept under ambient temperature and moisture conditions (40_C and 75% RH) for a period of 3 months in a stability chamber (CHM-10S$^{R}$, Remi Instruments, Mumbai, India). The samples are evaluated for drug content and particle size analysis at 1-month interval. [78]

**ABBREVIATION:**

| Sr.no | Units | Abbreviation |
|---|---|---|
| 1 | Degree Celsius | °C |
| 2 | Micrometer | µm |
| 3 | Revolutions per minute | rpm |
| 4 | Centimeter | Cm |
| 5 | Milliliter | mL |
| 6 | Number | no |
| 7 | Percent | % |
| 8 | Potential of Hydrogen | pH |
| 9 | That is | i.e |
| 10 | Approximately | ~ |
| 11 | Less than | < |
| 12 | Minute | min |
| 13 | kilo Daltons | kDa |
| 14 | Cubic Centimeter | $Cm^3$ |
| 15 | Through | via |

**TABLE NO. 1**

## CONCLUSION

The intranasal route is an accessible alternative route for drug administration. This route provides future potential for several drugs through the development of safe and efficacious formulations for simple, painless and long-term therapy. From this route drugs can be directly target to the brain in order to attain a good therapeutic effect in CNS with reduced systemic side effects. Nasal product will include drugs for acute and long term diseases and also vaccines with better local or systemic protection against infections. These products will, in the first instance, most probably comprise products for crisis treatments, such as erectile dysfunction, sleep induction, acute pain (migraine), panic attacks, nausea, heart attacks and Parkinson's disease because of the ability to provide rapid absorption of drug from the nasal cavity into the systemic circulation. On a longer term, novel nasal products for treatment of long-term illnesses, such as diabetes, growth deficiency, osteoporosis, fertility treatment and endometriosis, will also be marketed.

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