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ALGINATE MUCOADHESIVE MICROSPHERES: A REVIEW

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ABSTRACT

The purpose of present work was to develop mucoadhesive microspheres of Simvastatin for nasal delivery with the aim to avoid hepatic first-pass metabolism. The microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature, and ideally having a particle size less than 200µm. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particles matrix have the potential for the controlled release of drug. The nasal mucosa has also received attention as a viable means of systemic administration of analgesics, sedatives, hormones, cardiovascular drugs, and vaccines.

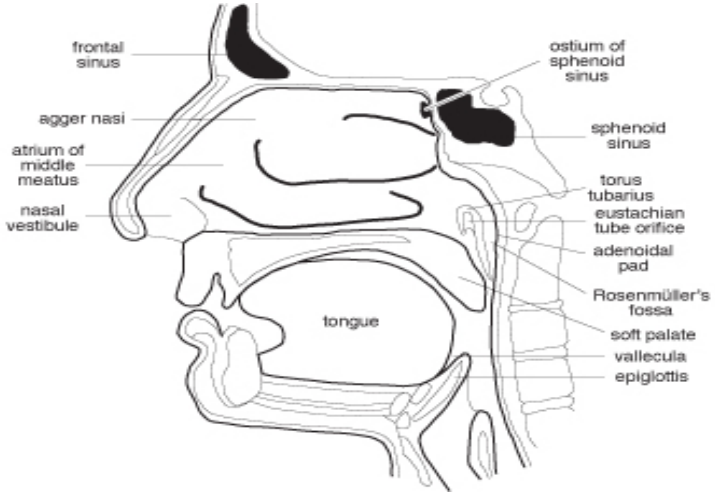
INTRODUCTION

The most desirable and convenient method of drug administration is the oral route. However, in many instances, oral administration is unsuitable when the drug undergoes significant degradation in the gastrointestinal tract or is metabolized to a high degree via the firstpass effect in the liver. Hence, an alternative route of administration would be preferred. Nasal administration has attracted much attention of many researchers within the last few decades because of its great potential utility for drug delivery (Hussain et al. 1980, Bechgaard et al. 1997). The nasal cavity possesses many advantages as a site for drug delivery such as a large surface area for absorption with a sub-epithelial layer that is highly vascularized, ease of administration and applicability for long-term treatments. In addition, blood is drained directly from the nose into the systemic circulation, thereby avoiding first pass metabolism by the liver. The range of compounds investigated for possible nasal application varies greatly from very lipophilic drugs to polar, hydrophilic molecules including peptides and proteins (Illum 2003). The nasal dosage forms involved include solutions (Chavanpatil and Vavia 2004, Harris et al. 2006), sprays (Daley-Yates and Baker 2001, Al- Ghananeem et al. 2008), gels (Pisal et al. 2004, Varshosaz et al. 2006), liposomes (Vyas et al. 1995, Muramatsu et al. 1999) and microspheres (Illum et al. 1987, Rajanikanth et al. 2003, Mao et al. 2004, Patil and Murthy 2006). Nasal mucociliary clearance is one of the most important limiting factors for nasal drug delivery. It severely limits the time allowed for drug absorption to occur. However, mucoadhesive preparations have been developed to increase the contact time between the dosage form and mucosal layers of nasal cavities, thus enhancing drug absorption. Mucoadhesion requires a highly expanded and hydrated polymer network, which could promote an intimate contact between microspheres and the mucus layer (Fundueanu et al. 2004). Thus, mucoadhesive microspheres have been developed to decrease the effect of mucociliary clearance (Illum et al. 1987).

ANATOMY AND PHYSIOLOGY OF NOSE

The human nose is divided by the median septum, a central partition of bone and cartilage; each symmetrical half opens at the face via the nostrils and connects with the mouth at the nasopharynx. The nasal vestibule, the respiratory region and the olfactory region are the three main regions of the nasal cavity. The lateral walls of the sub mucosal zone of the nasal passage is extremely vascular and this network of veins drains blood from the nasal mucosa directly to the

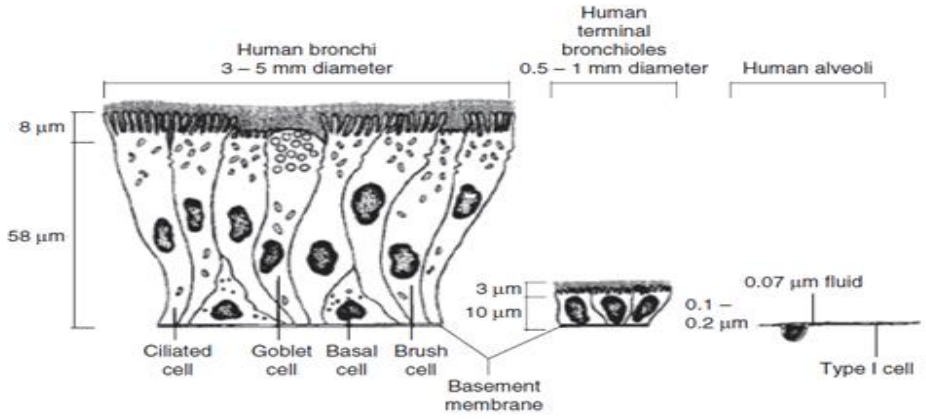
systemic circulation, thus avoiding first-pass metabolism the nasal cavity is covered with a mucous membrane which can be divided into non-olfactory and olfactory epithelium areas. The non olfactory area includes the nasal vestibule, which is lined with skinlike cells and respiratory region.



Anatomy of the nose (To the right is a cross-section of the nose)

- ***The Respiratory Region***
- ***The Olfactory Region***
- **The Respiratory Region**

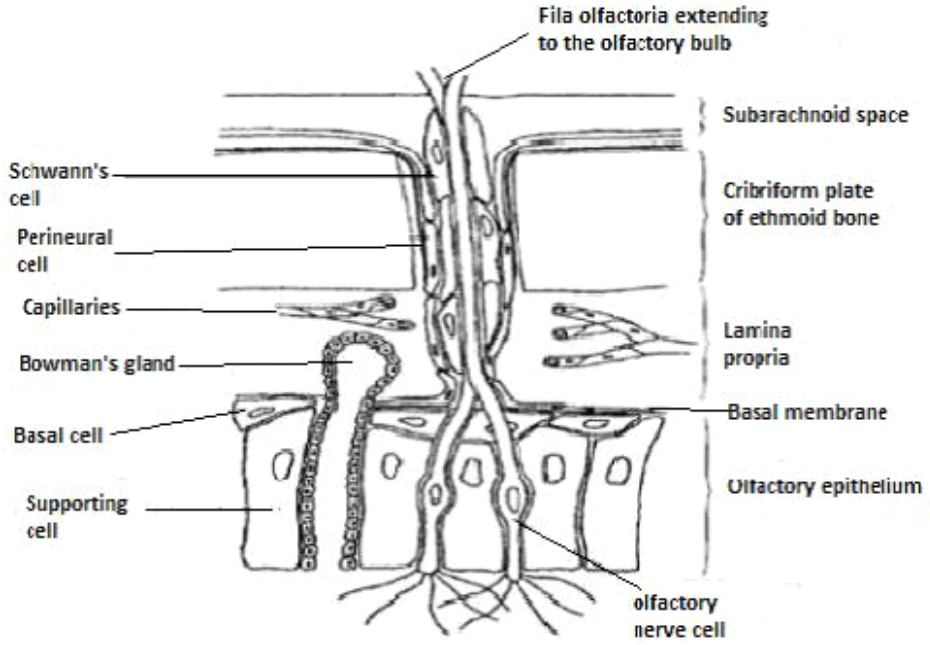
The respiratory epithelium is composed of four types of cells, namely, non-ciliated and ciliated columnar cells, basal cells and goblet cells. These cells facilitate active transport processes such as the exchange of water and ions between cells and motility of cilia (where applicable)



Respiratory epithelium of the nasal cavity, showing the four main types of cells.

The Olfactory Region

Thorne et al [6] have reported that the trigeminal neural pathway may also be involved in rapidly delivering protein therapeutic agents, such as insulin like growth factor-1 to brain and spinal cord following intranasal administration [2-5]**.** The transport of drugs across the nasal membrane and into the bloodstream may involve either passive diffusion of drug molecules through the pores in nasal mucosa, Including blood supply, nerve supply or some form of non passive transport.



Anatomical connections between the olfactory mucosa in the nose and the CSF in the subarachnoid space outside the olfactory bulb

BARRIERS FOR NASAL DRUG DELIVERY

1. **Low bioavailability:** Bioavailability of polar drugs is generally low, about 10% for low molecular weight drugs and not above 1% for peptides such as calcitonin and insulin [7]. The most important factor limiting the nasal absorption of polar drugs and especially large molecular weight polar drugs such as peptides and proteins are the low membrane permeability. Drugs can cross the epithelial cell membrane either by the transcellular route exploiting simple concentration gradients by the receptor mediated or vesicular transport mechanisms or by the paracellular route through the tight junctions between the cells. Polar drugs with molecular weights below 1000 Da will generally pass the membrane using the latter route [8].Although tight junctions are dynamic structures and can open and close to a certain degree when needed,

the mean size of these channels is of the order of less than 10 Å and the transport of larger molecules is considerably more limited. Larger peptides and proteins are able to pass the nasal membrane using an endocytotic transport process but only in low amounts [9,11].

2. **Mucociliary clearance:** This is especially the case when the drug is not absorbed rapidly enough across the nasal mucosa. It has been shown that for both liquid and powder formulations, which are not bioadhesive, the half life for clearance is of the order of 15 – 30 min.[12,13] The use of bioadhesive excipients in the formulations is an approach to overcome the rapid mucociliary clearance [14].

3. **Enzymatic Degradation:** Another contributing, but often less considered factor to the low bioavailability of peptides and proteins across the nasal mucosa is the possibility of an enzymatic degradation of the molecule in the lumen of the nasal cavity or during passage through the epithelial barrier. These sites both contain exo-peptidases such as mono and diaminopeptidases that can cleave peptides at their N and C terminals and endo-peptidases such as serine and cysteine, which can attack internal peptide bonds. The use of enzyme inhibitor may be approaches to overcome this barrier [15]. These challenges can be faced by various approaches, such as use of bio-adhesive systems and absorption enhancers.

Therapeutic Considerations

1. **Local delivery** [16]: Histamine H1-antagonist levocabastine [17], anti-cholinergic agent ipratropium bromide [18] and steroidal anti-inflammatory agents such as budesonide[19] (Stanaland, B.E. 2004), mometasone furoate [20].
2. **Systemic delivery:** Positive attributes of Intra Nasal systemic delivery include a relatively large surface area for drug absorption, rapid drug onset, no first-pass metabolism, and noninvasiveness to maximize patient comfort and compliance [21].

3. **Chronic versus acute therapeutic use:** When deciding on a delivery route, it is important to consider the dosing regimen for the drug [22].

1. **Vaccine delivery:** The nasal mucosa has received some attention as a vaccination route. Presentation of a suitable antigen with an appropriate adjuvant to the nasal-associated lymphoid tissue (NALT) has the potential to induce humoral and cellular immune responses [23,24]. An example of an Intra Nasal vaccine is FluMist®, a coldadapted live influenza virus [25].

NASAL FORMULATIONS

Different dosage forms and their application to deliver the drugs to the central nervous system following intranasal drug delivery are discussed in this section.

1. **Liquid Dosages Forms:** Liquid dosage forms either in form of soluble, suspended or colloidal systems are normally used for formulating nasal delivery systems.

2. **Nasal drops:** Nasal drops are one of the most simple and convenient delivery systems among all formulations. The main disadvantage of this system is the lack of dose precision [32]. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.

3. **Nasal sprays:** Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose anywhere from 25 to 200 μL. The particle size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly. Solution and suspension sprays are preferred over powder sprays because powder results in mucosal irritation [33].

4. **Nasal emulsions, microemulsions and nanoparticles:** Nasal emulsions offer the advantages for local application mainly due to the viscosity. One of the major disadvantages is poor patient acceptability. The physical stabilityof emulsion formulations and precise delivery are some of the main formulation issues.

SEMI-SOLID DOSAGE FORMS

1. **Nasal gels:** Nasal gels are thickened solutions or suspensions, of high-viscosity. Vitamin B12 and apomorphine gel have been successfully employed to achieve desired therapeutic concentrations following nasal administration.

SOLID DOSAGE FORMS: Solid dosage forms are also becoming popular for intranasal drug delivery, although these formulations are more suitable for pulmonary drug delivery and similar applications, since it can cover the vasculature within the epithelium of nasal mucosa.

i. **Nasal powders:** The advantages of a nasal powder dosage form are the absence of preservative and superior stability of the drug in the formulation. An additional advantage of this system is local application of drug, but nasal mucosa irritancy and metered dose delivery are some of the challenges for formulation scientists and device manufacturers who are interested in powder dosage forms [34].

Advantages

1.Drug degradation that is observed in the gastrointestinal tract is absent.

2.Hepatic first pass metabolism is avoided.

3. Rapid drug absorption and quick onset of action can be achieved.

4. The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.

5. The nasal bioavailability for smaller drug molecules is good.

6. Drugs that orally not absorbed can be delivered to systemic circulation by nasal drug Delivery

7. Studies so far carried out indicate that the nasal route is an alternate to parenteral route especially, for protein and peptide drugs

8. Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.

9 Drugs possessing poor stability in g.i.t. fluids are given by nasal route.

10. Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery.

Limitations of Nasal Drug Delivery System

i. The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established. Adversely affected by pathological conditions.

ii. Not feasible for high molecular weight more than 1000 Dalton.

iii. Volume that can be delivered into nasal cavity is restricted to 25-200 µl.

iv. Drug permeability is limited due to enzymatic inhibition.

v. Nasal irritants drugs cannot be administered through this route.

vi. Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.

vii. Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high concentration.

viii. There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.

Types of microspheres

A. **Bio adhesive microspheres:** Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc, can be termed as bio adhesion [35].

B. **Magnetic microspheres:** Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials magnetic microspheres: Are used to deliver chemotherapeutic agent to liver tumour.

C. **Floating microspheres:** In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach. The drug is released slowly at the desired rate Moreover it also reduces chances of striking and dose dumping.

D. **Biodegradable polymeric microspheres:** Natural polymers prolongs the residence time when contact with aqueous medium, results gel formation. The rate and extent of drug release is controlled by concentration of polymer.

E. **Radioactive microspheres:** They are injected to the arteries that lead to tumours' of interest. In these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. The different kinds of radioactive microspheres are α emitters, β emitters, γ emitters [36].

Methods of preparation

1. **Emulsion Solvent Evaporation Technique:**

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 was agitated at 500 rpm then the drug and polymer was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24 hrs [37]. Aceclofenac microsphere were prepared by this technique [38]. As shown in figure 5.

Figure 5. Emulsion Solvent evaporation method.

2. **Emulsion cross linking method:** In this method drug was dissolved in aqueous gelatine solution which was previously heated for 1 hr at 400C. The solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 350C, results in w/o emulsion then further stirring is done for 10 min at 150C. Thus the produced microspheres were washed respectively three times with isopropyl alcohol which then air dried and dispersed in 5mL of aqueous gluteraldehyde [39].Example for this technique is Gelatin microspheres.

3. **Phase separation and coacervation: -**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 coacervates. 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, As shown in figure

6. The process is carried out under continuous stirring to control the size of the microparticles [40]. As figure shows the steps of phases.

4. **Single emulsion Technique:** There are several Proteins and carbohydrates, which are prepared by this technique [41]. As shown in figure 6. 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, glutaraldehyde 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. Chitosan solution (in acetic acid) by adding to Liquid paraffin containing a surfactant resulting formation of w/o emulsion. Metformin hydrochloride microsphere are prepare by using gluteraldehyde 25% solution as a cross linking agent.

5. **Double emulsion technique :**A double emulsion is usually prepared in two main modes [42,43].

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 reemulsified byaqueous solution with a high HLB surfactant to produce a W/O/W double emulsion

[44].

6. **Multiple emulsion method:** In this method, a primary emulsion (oil-in-water) is first formed (nonaqueous 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 glutaraldehyde (as a crosslinking agent) or the evaporation of an organic solvent [45].

7. **Precipitation or coacervation method:** In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer.Sodium sulfate was also used to prepare CMs using this precipitation technique. Example of Recombinant humaninterleukin-2-loaded CMs were prepared by a dropwise addition of sodium sulfate-containing recombinant human interleukin-2 solution in acidic chitosan solution [46].

8. Polymerization techniques Mainly two techniques are using for the preparation of microsphere are classified as:

i. **Normal polymerization:** It is a pure polymer formation technique but it is very difficult to dissipate the heat of reaction which affects the thermo labile active ingredients. Suspension polymerization is carried out of lower temperature and also refer to as pearl polymerization in which heating the monomer mixture with active drug as droplets dispersion in continuous aqueous phase. Microsphere size obtained by suspension techniques is less the 100 μm.

ii. **Interfacial polymerization:** In this technique two reacting monomers are employed; one is dissolve in continuous phase while other is disperse in continuous phase (aqueous in nature) throughout which the second monomer is emulsified.

9. **Solvent extraction:** 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 [47].

10. 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. Microsponges 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 can be filtered to separate the microsponges. The product is then washed and dried by vacuum oven at 40ºC for 24hours [48]. Example: - Ibuprofen.

11. Spray drying and congealing technique Spray drying is one of the most widely investigated methods of preparing CMs in which chitosan solution is sprayed and then air-dried followed by the addition of a crosslinking agent. He et al prepared CMs by spray drying multiple emulsions (oil-in-water-in-oil or water-in-oil-inwater) to entrap cimetidine and famotidine into microspheres. The drug was released in a sustained and controlled fashion compared to the other microspheres prepared by traditional spray drying or the oil-in-water emulsion method as shown in figure 8. 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.

12. **Hydroxyl appetite (HAP) microspheres in sphere morphology**

This was used to prepare microspheres with peculiar spheres At first o/w emulsion was prepared by dispersing the organic phase (Diclofenac sodium containing 5% w/w of EVA and appropriate amount of HAP) in aqueous phase of surfactant. The organic phase was dispersed in the form of tiny droplets which were surrounded by surfactant molecules this prevented the droplets from co solvencing and helped them to stay individual droplets .While stirring the DCM was slowly evaporated and the droplets solidify individual to become microspheres [49].

13. **Thermal crosslinking method**

Orienti et al [50] reported CM preparation by the thermal crosslinking method using citric acid, which served as crosslinking agent. Citric acidwas added to chitosan solution in acetic acid (2.5% weight/volume) and then cooled to 0°C before adding to corn oil. After stirring for 2 minutes, the emulsion was then added dropwiseto corn oil by maintaining the temperature at

120°C. Then, the crosslinking was performed under vigorous stirring (1000 rpm) for 40 minutes and the microspheres obtained were filtered, washed, dried, and sieved.

14. **Reversed micellar method**

Reverse micellar is the stable liquid mixture of oil, water, and surfactants dissolved in organic solvents. To this mixture, an aqueous solution of chitosan and the target molecule are added before the addition of a crosslinking agent such as glutaraldehyde. Mitra et al [51] described the preparation of doxorubicin–dextran conjugateencapsulated chitosan nanoparticles [52].

15. Ionotropic external gelation technique

The alginate microspheres were prepared by ionotropic external gelation technique. In this method, weighed quantity of the drug Glipizide was 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 was 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 was filtered by using Whatman filter paper no-1. The

microspheres were allowed to dry at about 30- 40°C and stored in well closed container for further use. Process Variables: - The following process variables were 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 were analyzed for size, shape, drug content and drug release [53]. As shown in figure 9.

Characterization/ Evaluation of Microspheres Particle size determination:

Particle size was determined by optical microscopy with the help of calibrated eyepiece micrometer. The size of around 100 microspheres was measured and their average particle size determined [54,55]. The average particle size was determined by using Edmundson's equation. D mean = $\Sigma nd/\Sigma n$ Where, n = Number of microspheres checked; d = Mean size.

Median size of the microspheres formulations ranged from 15 to 40 um were considered to be suitable for nasal administration.

Drug entrapment efficiency:

Microspheres containing of drug (5mg) were crushed and then these microspheres 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. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content [56]. % Entrapment = Actual content/Theoretical content x 100

Percentage yield: The yield was calculated for each batch. The percentage yield of microspheres was calculated as follows. {% Yield= Weight of Microspheres /Theoretical weight of drug and polymer x100}

Equilibrium swelling degree: The equilibrium swelling degree (ESD) of microspheres was determined by swelling 5gms of dried microspheres in 5 ml of phosphate buffer pH 6.8 overnight in a measuring cylinder [57]. The swelling index of the microsphere was calculated by using the formula. Swelling index=.100

Density determination: The density of the microspheres can be measured by using a multi volume pychnometer. Accurately weighed sample in a cup is placed into the multi volume pychnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the density of the microsphere carrier is determined.

Viscometric determination: The absolute viscosity, kinematic viscosity, and the intrinsic viscosity of the polymer solutions in different solvents can be measured by a u-tube viscometer (viscometer constant at 400c is 0.0038 Mm2/s /s) at 25 ± 0.1 0c in a thermostatic bath. The polymer solutions are allowed to stand for 24 h prior to measurement to ensure complete polymer dissolution [58].

Surface Topography: The samples for the scanning electron microscope (SEM) analysis were prepared by sprinkling the microspheres on one side of an adhesive stub. Then the microspheres were coated with gold before microscopy [59].

Attenuated total reflectance Fourier Transform-

Infrared Spectroscopy: The ATR-FTIR provides information about the surface composition of the microspheres depending upon manufacturing conditions and procedures. FT-IR is mainly used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated and measuring alternated total reflectance (ATR).

X-ray diffraction: X-ray diffraction is mainly used to determine the Change in crystalline of drug.

Microparticles and its individual components were analysed by the help of an x-ray diffractometer (Bruker, Germany).Scanning range angle between 80C - 70 0C [60].

UV-FTTR (Fourier transform infrared): The drug polymer interaction and degradation of drug while processing for microencapsulation can be determined by FTIR [61].

Measurement of the *in vitro* release: A modification of the USP-III (reciprocating cylinder type) apparatus was used. The media used in this method was phosphate buffer of pH 6.4 and the volume of media taken was 25 ml that will just touch the surface of the reciprocating cylinder's mesh # 400. The temperature of the media was maintained at 37±0.5°C [62].

Kinetic Model Fitting: The in vitro drug release data were fitted to following model to evaluate the mechanism of drug release [63].

Model Equation Graph

Zero Order Q0 - Qt = K0t Cumulative amount of drug Released *vs* time

Higuchi ft = Q = {A√D(2C-Cs)Cs t} ½ Cumulative percentage drug release versus square root of

Korsmeyer-

Peppas

Mt / M∞ = Ktn Log cumulative percentage Drug release versus log time.

Baker-Lonsdale *f* 1 = 3/2 {1 –(1- Mt /M∞)2/3}

Mt/M∞ = *kt*

[d (*Mt /M*∞)] / dt

with respect to the root of Time inverse.

Ex vivo permeation studies: Ex-*vivo* drug permeation study was performed using a glass fabricated nasal diffusion cell [Figure 10]. 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 [64]. The 10 cm long donor chamber tube has an internal diameter of 1.13 cm. The nasal mucosa of sheep was separated from sub layer bony tissue and was stored in distilled water containing few drops of gentamycin sulphate injection. After the complete removal of blood from mucosal surface, it was attached to donor chamber tube. The donor chamber tube was placed in such a way that nasal mucosa just touches the diffusion medium (phosphate buffer of pH 6.8) in recipient chamber [65].

PHARMACEUTICAL APPLICATIONS

1. **Targeting using micro particulate carriers:**

The concept of targeting, i.e. site specific drug delivery is a well-established dogma, which is gaining full attention. The therapeutic efficacy of the drug relies on its access and specific interaction with its candidate receptors [30].

2. **Surface modified microspheres:** Different approaches have been utilized to change the surface properties of carriers to protect them against phagocytic clearance and to alter their body distribution patterns. Protein microspheres covalently modified by PEG derivatives show decreased immunogenicity and clearance.

3. **Chemoembolization:** Chemoembolization is an endovascular therapy, which involves the selective arterial embolizationof a tumor together with simultaneous or subsequent local delivery the chemotherapeutic agent.

4. **Imaging:** The microspheres have been extensively studied and used for the targeting purposes. Various cells, tissues and organs can be imaged using radio labelled microspheres.

5. **Monoclonal antibodies mediated microspheres:** Monoclonal antibodies targeting microspheres are immunomicrospheres. This targeting is a method used to achieve selective targeting to the specific sites.

NASAL DRUG PRODUCTS FOR VACCINATION AVAILABLE IN MARKET

Some available products for vaccination

DRUG OR Vaccine NAME (Product name)	Dosage form	Status	Manufacturer
Human influenza vaccine (Nasalflu Berna)	Virosomes (Spray)	Marketed	Berna Biotech
Equine influenza vaccine (Flu Avert)	Drops	Marketed	Heska
Porcine Bordetella bronchiseptica vaccine\(Maxi/ Guard Nasal Vac)	Drops	Marketed	Addison Biological Laboratory
Feline Bordetella bronchiseptica vaccine (Nobivac Bp)	Suspension drops	Marketed	Intervet
HumanStreptococcus A vaccine (StrepAvax	Proteosomes (nanoparticulate	Marketed	ID Biomedical

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