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A REVIEW ON MICROSPHERE AS A NASAL DRUG DELIVERY SYSTEM

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ABSTRACT

"The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body and then maintain the desired drug concentration. A well designed controlled drug delivery system can overcome some of problems of conventional therapy and enhance therapeutic efficacy of the given drug. There are various approaches in delivering therapeutic substance to the target site in sustained and controlled release fashion". 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. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective *in vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective *in vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body. Approaches are discussed here for increasing the residence time of drug formulations in the nasal cavity, resulting in improved nasal drug absorption. The article highlights the importance and advantages of the nasal drug delivery systems. mucoadhesive systems have been prepared for both oral and peroral administration in the

past. The nasal mucosa presents an ideal site for bioadhesive drug delivery systems. In this review we discuss the effects of microspheres and approaches also method of preparations with future opportunities of microsphere in nasal drug delivery system.

KEYWORDS: Nasal Drug Delivery System, polymers, absorption mechanism, method of preparation, future opportunities.

INTRODUCTION

"Nasal drug delivery has been recognized as a very promising route for delivery of therapeutic compounds including biopharmaceuticals. Nasal administration is a logical choice for topical nasal treatments such as antihistamines and corticosteroids. The nasal mucosa has also received attention as a viable means of systemic administration of analgesics, sedatives, hormones, cardiovascular drugs, and vaccines. Conventionally, the nasal route has been used for local delivery of drugs for treating nasal allergy, nasal congestion, or nasal infections. However systemic delivery through the nasal route has recently begun to explore possibilities for those requiring a rapid onset of action or necessitating avoidance of severe proteolysis involved in oral administration (e.g., most peptide and protein drugs).[1]

Successful attempts to deliver corticosteroid hormones through the nasal route for systemic absorption have triggered further studies in this area. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects.

However the primary function of the nose is olfaction, it heats and humidifies inspired air and also filters airborne particulates. Consequently, the nose functions as a protective system against foreign material. There are three distinct functional zones in the nasal cavity, namely: vestibular, olfactory, and respiratory areas. The vestibular area serves as a baffle system; it functions as a filter of airborne particles. The olfactory epithelium is capable of metabolizing drugs. The respiratory mucosa is the region where drug absorption is optimal.[2]

Nasal drug delivery – which has been practiced for thousands of years, has been given a new lease of life.[2]

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 mucociliary clearance mechanism. The nasal route circumvents hepatic first pass elimination associated with the oral delivery: it is easily accessible and suitable for self-medication. During the past several decades, the feasibility of drug delivery via the nasal route has received increasing attention from pharmaceutical scientists and clinicians. Drug candidates ranging from small metal ions to large macromolecular proteins have been tested in various animal models. It has been documented that nasal administration of certain- hormones and steroids have resulted in a more complete absorption This indicates the potential value of the nasal route for administration of systemic medications as well as utilizing this route for local effects.

This review article provides a brief overview of the advantages and limitations of nasal drug delivery system and anatomy of nasal cavity, microsphere as a novel drug delivery system, barriers to nasal absorption, strategies to improve nasal absorption, microsphere nasal drug delivery formulation and applications of nasal drug delivery systems with future opportunities of microsphere as a nasal drug delivery system.[3]

Advantages of nasal drug delivery system

1). Provide sustained therapeutic effect.

2). Reduces the frequency of drug administration and thus improve patient compliance.

3). Improve the bioavailability of drug by improving absorption.

4). As drug dose is reduced, the chance of adverse effects also decreased.

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

6) Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.[3,4]

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.[5]

Disadvantages of Nasal Drug Delivery System

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

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

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

4. Drug permeability is limited due to enzymatic inhibition.

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

6. Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.[5,6]

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

8. 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.[7]

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.[6,7]

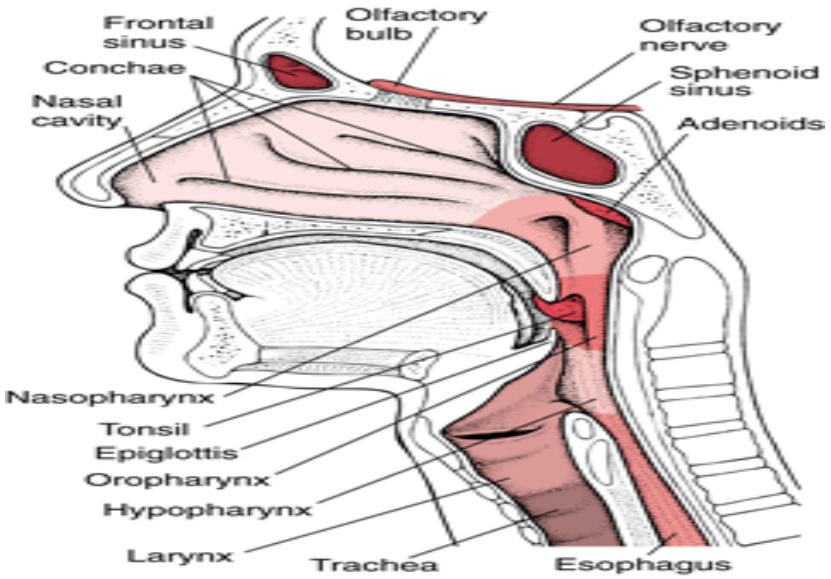

Figure1: Anatomy of Nose.

(http://maggiesfarm.anotherdotcom.com/archives/5767-A-hint-of-licorice-and-blackberry-The-Physiology-of-the-Wine-Critic.html).[8]

1. 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.[8]

2. The Olfactory Region

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.[8, 9]

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.[9]

MICROSPHERES AS NASAL DRUG DELIVERY SYSTEM

All types of microspheres that have been used as nasal drug delivery systems are water-insoluble but absorb water into the sphere's matrix, resulting in swelling of the spheres and the formation of a gel. The building materials in the microspheres have been starch, dextran, albumin and hyaluronic acid, and the bioavailability of several peptides and proteins has been improved in different the absorption of large hydrophilic drugs. Microspheres also exert a direct effect on the mucosa, resulting in the opening of tight junctions between the epithelial cells. The nasal route for systemic drug delivery has mainly been investigated with large hydrophilic peptides and proteins in mind, although other type of drugs has also been investigated. Different types of absorption enhancers have been used to avoid the problem of low absorption. Also, some low-molecular weight drugs have been successfully delivered in microsphere preparations. The residence time in the cavity is considerably increased for microspheres compared to solutions.[9,10]

On the basis absorptions two type of the polymers used in microspheres

1. Mucoadhesive
2. Bioadhesive

1. Mucoadhesion: Refers to adhesion of matter to a mucus layer for an extended period of time 6. A mucoadhesive agent is thus a substance that adheres to mucus. The term

bioadhesion is less specific and can be used to denote adhesion to any biological surface 6-7. The effect of water-insoluble, Mucoadhesive powder mixtures on the absorption of insulin who concluded that they had a positive effect on the nasal absorption in comparison with a solution and a water-soluble powder formulation. Many investigations have since shown positive results for nasal delivery by Mucoadhesive microparticles, *i.e.*, micron-sized particles of drug and excipients, in comparison with liquid formulations or the pure drug . Several mucoadhesive polymers, for example degradable starch microspheres, cellulose, carbomer, alginate and the popular, cationic polymer chitosan, have been investigated.[9,11]

2. Bioadhesion: The attachment of a synthetic or biological macromolecule to a biological tissue. An adhesive bond may form with epithelial cell layer, the continuous mucus layer or a combination of the two. The term "mucoadhesion" is used specifically when the bond involves mucous coating and an adhesive polymeric device. The use of dry-powder formulations containing bioadhesive polymers for nasal administration of peptides and proteins water- insoluble cellulose derivatives were mixed with insulin and the powder mixture was installed into the nasal cavity.. Microspheres of albumin, starch and DEAE-(Di-ethyl amino ethyl) dextran absorbed water and formed a gel-like layer which was cleared slowly from the nasal cavity. Three hours after administration, 50% of the de-livered amounts of albumin and starch microspheres and 60% of the DEAE-dextran microspheres were still present at the site of deposition. It was suggested that an increased contact time could increase the absorption efficiency of drugs.[10,11]

Material used in microsphere

Microspheres used usually polymers are classified into two types

1. Synthetic Polymers

Poly alkyl cyano acrylates is a potential drug carrier for parenteral as well as other ophthalmic, oral preparations.

Poly lactic acid is a suitable carrier for sustained release of narcotic antagonist, anti cancer agents such as cisplatin, cyclophosphamide, and doxorubicin.

Sustained release preparations for anti malarial drug as well as for many other drugs have been formulated by using of co-polymer of poly lactic acid and poly glycolic acid.

Poly anhydride microspheres (40µm) have been investigated to extend the precorneal residence time for ocular delivery.

Poly adipic anhydride is used to encapsulate timolol maleate for ocular delivery.

Poly acrolein microspheres are functional type of microspheres.

They do not require any activation step since the surfacial free CHO groups over the poly acrolein can react with NH2 group of protein to form Schiff's base.[11]

Synthetic polymers are divided into two types.
a. Non-biodegradable polymers
e.g. Poly methyl methacrylate (PMMA) Acrolein Glycidyl methacrylate Epoxy polymers
b. Biodegradable polymers
e.g. Lactides, Glycolides & their co polymers, Poly alkyl cyano acrylates, Poly anhydrides.[11]

2. Natural polymers

Albumin is a widely distributed natural protein .It is considered as a potential carrier of drug or protiens (for either their site specific localization or their local application into anatomical discrete sites).

It is being widely used for the targeted drug for the targeted drug delivery to the tumour cells. Gelatin microspheres can be used as efficient carrier system capable of delivering the drug or biological response modifiers such as interferon to phagocytes.[11,12]

Starch belongs to carbohydrate class. It consists of principle glucopyranose unit, which on hydrolysis yields D-glucose.

It being a poly saccharide consists of a large number of free OH groups. By means of these free OH groups a large number of active ingredients can be incorporated within as well as active on surface of microspheres.

Natural polymers are divided into different sources like proteins, carbohydrates and chemically modified Carbohydrates, Proteins: Albumin6, Gelatin7, and Collagen.

Carbohydrates: Agarose, Carrageenan, Chitosan, Starch.

Chemically modified carbohydrates: Poly dextran, Poly Starch.

In case of non-biodegradable drug carriers, when administered parenterally, the carrier remaining in the body after the drug is completely released poses possibility of carrier toxicity over a long period of time.[12]

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.

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.[12,13]

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 tumor's 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.[13]

Strategies of microsphere nasal drug delivery

Microspheres: Microsperes of different materials have been evaluated in vivo as nasal drug delivery systems. Microspheres of albumin, starch and Diethylamonoethyl (DEAE)-dextran absorb water and form a gel-like layer, which cleares slowly from the nasal cavity.[14]

1) Dextran microspheres

They were proven bioadhesive microspheres for prolonging the residence time in the nasal cavity. The slowest clearance was detected for DEAE-dextran, where 60% of the delivered dose was still present at the deposition site after 3 hours. However, these microspheres were not successful in promoting insulin absorption in rats. The insulin was too strongly bound to the DEAE groups to be released by a solution with an ionic strength corresponding to physiological conditions. Structural changes due to the lyophilization process were observed in spheres with insulin incorporated, which probably further decreased the release rate.[14,15]

2) Degradable starch microspheres (DSM)

DSM is the most frequently used microsphere system for nasal drug delivery and has been shown to improve the absorption of insulin, gentamicin, human growth hormone, metoclopramide and desmopressin. Insulin administered in DSM to rats resulted in a rapid dose-dependent decrease in blood glucose. DSM as a delivery system for insulin (2 $IU.kg^{-1}$) has also been tested in sheep. The absolute bioavailability was 4.5% and the time to reach maximum effect, i.e., a 50% decrease in plasma glucose, was 60 min.

Studies in rabbits have demonstrated that DSM does not induce serious hysto pathological changes to the nasal mucosa. Moreover, the DSM was well tolerated by 15 healthy volunteers and did not cause significant changes in mucociliary transport.

The effect of starch microspheres on the absorption enhancing efficiency of various enhancer systems with insulin after application in the nasal cavity of the sheep was investigated. The DSM was shown to synergistically increase the effect of the absorption enhancers on the transport of the insulin across the nasal membrane.[14,15,16]

BARRIERS USED IN NASAL DRUG DELIVERY SYSTEM

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.

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.

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.[17]

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.

The use of bioadhesive excipients in the formulations is an approach to overcome the rapid mucociliary clearance.[18]

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 diamino peptidases 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.[18,19]

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DIFFERENT TYPES OF METHODS FOR PREPARATION OF MICROSPHERES

The microspheres can be prepared by using any of the several techniques given below but choice of the technique mainly depends on the nature of the polymer used, the drug, the intended use and the duration of therapy.[21]

1) SINGLE EMULSION TECHNIQUE

The micro particulate carriers of natural polymers i.e., those of proteins and carbohydrates are prepared by Single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium e.g., oil.

The chemical cross linking agent used include gluteraldehyde, formaldehyde, terephthaloyl chloride, diacid chloride, etc.

Croslinking by heat is carried out by adding the dispersion, to previously heated oil. Heat denaturation is however, not suitable for the thermolabile drugs while the chemical cross-linking suffers disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation.

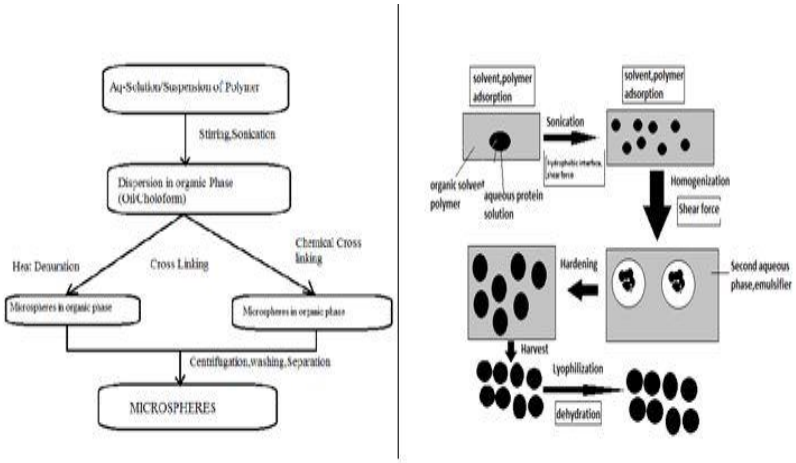

Figure. 2. A schematic diagram presentation of single emulsion technique.[21,22]

2) DOUBLE EMULSION TECHNIQUE

Involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to the water-soluble drugs, peptides, proteins and the vaccines.

This method can be used with both the natural as well as the synthetic polymers.

The aqueous protein solution is dispersed in a lipophilic organic continuous phase.

This protein solution may contain the active constituents.

The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase.

The primary emulsion is then subjected to the homogenization or the sonication before addition to the aqueous solution of the polyvinyl alcohol (PVA).

This results in the formation of the double emulsion.[22]

The emulsion is then subjected to the solvent removal either by solvent evaporation or by solvent extraction process.

The solvent evaporation is carried out by maintaining emulsion at reduced pressure or by stirring the emulsion so that the organic phase evaporates out. In the latter case, the emulsion is added to the large quantity of water (with or without surfactant) into which organic phase diffuses out.

The solid microspheres are subsequently obtained by filtration and washing.

A number of hydrophilic drugs like luteinizing hormone releasing hormone (LH-RH) agonist; vaccines, proteins and conventional molecule are successfully incorporated in to the microspheres using the method of double emulsion solvent evaporation/extraction.[22,23]

3) POLYMERIZATION TECHNIQUES

The polymerization techniques used for the preparation of the microspheres are mainly classified as

1. Normal polymerization
2. Interfacial polymerization

1) Bulk polymerization

A monomer or a mixture of monomer along with the initiator is usually heated to initiate the polymerization and carry out the process.

The catalyst or the initiator is added to the reaction mixture to facilitate or accelerate the rate of the reaction.

The polymer so obtained may be molded or fragmented as microspheres. For loading of drug, adsorptive drug loading or adding drug during the process of polymerization may be adopted.[23]

2) The suspension polymerization

It is carried out by heating the monomer or mixture of monomers with active principles (drugs) as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives.

3) The emulsion polymerization

The suspension polymerization as due to presence of the initiator in the aqueous phase, which later on diffuses to the surface of the micelles or the emulsion globules.[23,24]

4) PHASE SEPERATION AND COACERVATION

Phase separation method is specially designed for preparing the reservoir type of the system, i.e. to encapsulate water soluble drugs e.g. peptides, proteins, however, some of the preparations are of mat r i x type particularly, when the drug is hydrophobic in nature e.g. steroids.

In matrix type device, the drug or the protein is soluble in the polymer phase.

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.

The coacervation can be brought about by addition of the third component to the system which results in the formation of the two phases, one rich in the polymer, while the other one. In this technique, the polymer is first dissolved in a suitable solvent and then making its aqueous solution disperses drug.[24, 25]

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.

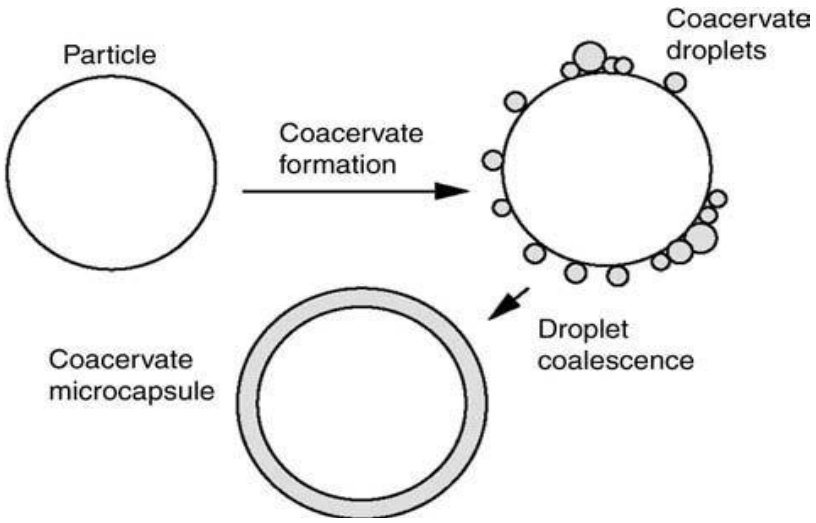

Figure 3: Schematic diagram of the formation of a coacervate around a core material.[24]

5. SPRAY DRYING AND CONGEALING

Spray drying and spray congealing methods are based on the drying of the mist of the polymer and drug in the air.

Depending upon the removal of the solvent or the cooling of the solution, the two processes are named spray drying and spray congealing respectively.

The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc.

The drug in the solid form is then dispersed in the polymer solution under high speed homogenization.

This dispersion is then atomized in a stream of hot air.

The atomization lead to the formation of small droplets or the fine mist from which the solvent evaporates leading to the formation of microspheres in a size range 1-100µm.

Microparticles are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying.[25]

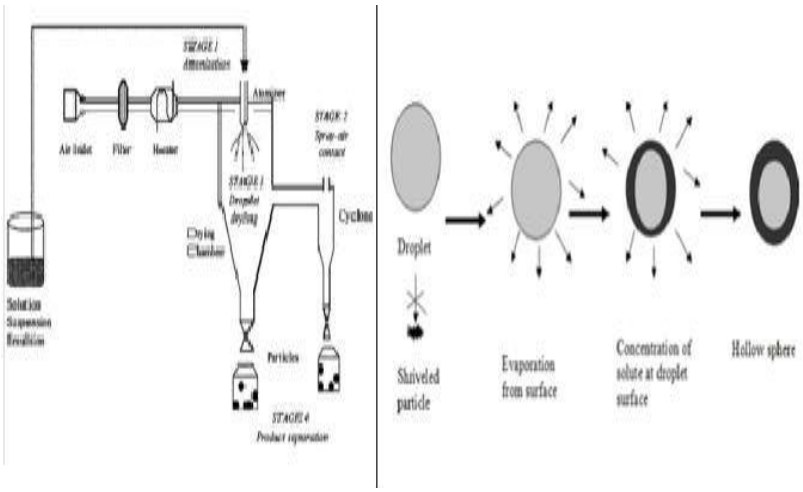

Figure4. Spray drying method for preparation of microspheres and diagrammatic presentation formation of product in spray drying.[25]

6) SOLVENT EVAPOARATION

This method is used for the preparation of micro particles, involves the removal of the organic phase by evapoarate of organic solvent.

The method involves water miscible organic solvent such as isopropanol; organic phase is removed by evaporate with water.

The process decreases the hardening time for the microspheres.

One variation of the process involves direct addition of the drug or protein to polymer organic solution.

The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer.[25,26]

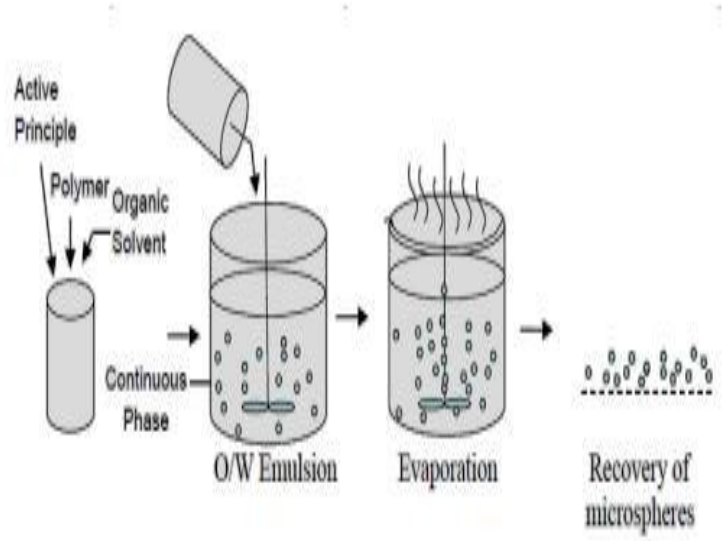

Figure 5. Emulsion Solvent evaporation method.[25]

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.

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.

Example: - Ibuprofen.[25,26]

8. HYDROXY 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.[26]

9. THERMAL CROSSLINKING METHOD

Reported CM preparation by the thermal crosslinking method using citric acid, which served as crosslinking agent.

Citric acid was 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 dropwise to 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.[27]

10. REVERSE 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.[27,28]

11. 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.[28]

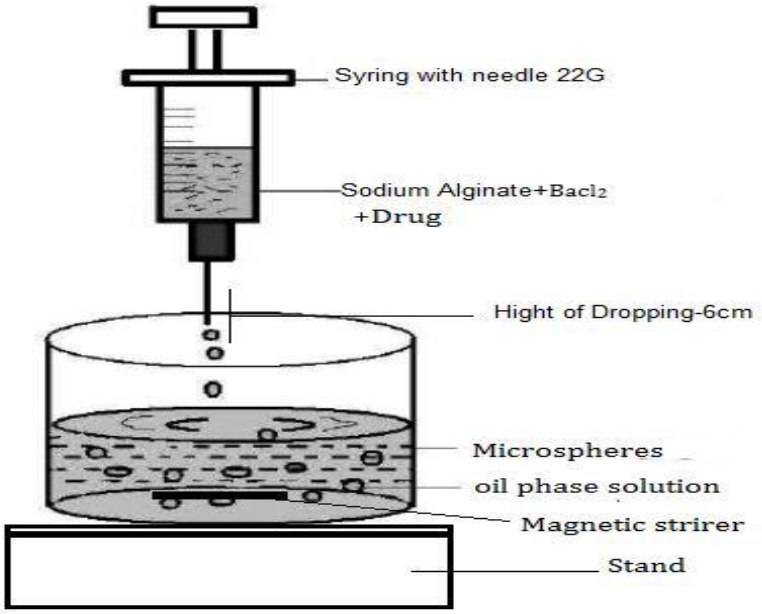

Figure 6. Method of preparation of Microspheres.[28]

MECHANISMS FOR IMPROVED DRUG ABSORPTION BY MICROSPHERES

The mechanism for the increased absorption of drugs administered with degradable starch microspheres (DSM) has been shown to be due to an effect on tight junctions between the epithelial cells. Mono layers of Caco-2 cells were investigated in a transmission electron microscope prior to, immediately after, 15 min after and 180 min after the administration of dry microspheres.

It was clearly shown that the tight junctions started to separate after only 3 min and that the separation continued for up to 15 min after administration.

Thus, when the microspheres absorb water from the mucus and swell, the epithelial cells are dehydrated and cause the tight junctions to separate.[28]

After 3 h, the tight junctions between the Caco-2 cells were comparable with the controls, indicating that the enhancing effect of DSM is rapid and reversible.

Since the process is reversible, an increase in absorption for drugs that are transported via the paracellular pathway will take place mainly during the short period when the tight junctions are separated.

These findings are in agreement with the rapid absorption of insulin and the normalization of glucose levels seen in animals when insulin was administered with DSM.

For an optimum effect, the drug has to be available for absorption, i.e. dissolved, when the spheres swell by taking water from the mucus layer and the underlying epithelial cells, resulting in the temporary widening of the tight junctions.

Additional evidence for the validity of this suggested mechanism of action is that the absorption-enhancing effect of DSM is lost when the microspheres are administered in a pre-swollen state, this mechanism cannot explain the results obtained for the same type of microspheres in an absorption study in rats by Pereswetoff-Morath and Edman.

Insulin administered with dextran microspheres induced a maximum decrease in plasma glucose after 30– 40 min. These findings are comparable to those published for insulin in degradable starch microspheres in rats.

The plasma peak concentration of insulin was reached about 10 min after administration, which would most likely also be the case for the dextran microspheres due to the similar plasma glucose concentration profile.[28,29]

If calcium binding had been crucial for the insulin absorption from dextran microspheres in this study, it would not have been possible to reach the peak concentration so soon after administration.

Oechslein estimated the pre-soaking time needed to achieve calcium binding to be at least 30 min, and this would result in a much later plasma concentration peak for insulin in the study by Pereswetoff-Morath and Edman.[29]

CHARACTERISATION AND EVALUATION OF MICROSPHERE

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. The average particle size was determined by using Edmundson's equation.

$$D \text{ mean} = \Sigma nd/\Sigma n$$

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.

$$\% \text{ Entrapment} = \text{Actual content/Theoretical content} \times 100.$$

Percentage yield: The yield was calculated for each batch. The percentage yield of microspheres was calculated as follows.

$$\{\% \text{ Yield} = \text{Weight of Microspheres /Theoretical weight of drug and polymer} \times 100\}$$

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. The swelling index of the microsphere was calculated by using the formula.

$$\text{Swelling index} = \text{Initial weight} - \text{Final weight/ Initial weight} \times 100$$

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.[28,29,30]

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.[30]

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 - 700C.[29]

UV-FTTR (Fourier transform infrared)

The drug polymer interaction and degradation of drug while processing for microencapsulation can be determined by FTIR.

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.[30]

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

About 3mm, the lid has three opening, each for sampling, thermometer, and a donor tube chamber.

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.[30,31]

Ex vivo permeation studies

Ex-*vivo* drug permeation study was performed using a glass fabricated nasal diffusion cell.

The water jacketed recipient chamber has a total capacity of 60 ml and flanged top of 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.[31,32]

Table 1: Application[33, 34, 35]

Type of microspheres	Applications
Bioadhesive microspheres	Buccal, oral, ocular, nasal, colonic drug delivery Nasal – Gentamicin, Insulin, GI – Glipizide. Colonic – Insulin, Ocular – Methyl prednisolone.
Magnetic microspheres	Used in DNA analysis, cell isolation, protein purification and 580argeting drugs to tumour sites(Doxorubicin)
Floating microspheres	Carriers for drugs like antiviral, antifungal and antibiotic agents(so called absorption windows), non-steroidal anti inflammatory drugs, Prednisolone, Lansoprazole

Radioactive microspheres	For diagnostic purpose – Diagnostic radioembolization: 99mTc-macroaggregated human serum albumin (MAA), Thrombus imaging in deep vein thrombosis: 99mTc-sulfur colloid For therapeutic purpose – Radioembolization of liver and spleen tumours: 90Ymicrospheres**,** Local radiotherapy: 212Pb-sulfur colloid.
Polymeric microspheres	Vaccine delivery: Hepatitis, Influenza , Pertussis, Diptheria toxoid, Oral drug delivery of easily degraded drugs: Gene therapy with DNA plasmids; delivery of insulin, LHRH Controlled drug delivery after local application: Release of proteins, hormones and peptides over extended times.

FUTUTRE OPPORTUNITIES OF NASAL MICROSPHERES NASAL VACCINATION

To create mass and rapid immunization, a nasally applicated aerosol vaccine has a great potential. Development of nasal immunity and generalized immunization in a whole population has been proven successfully in several pilot studies in Russia and South America.[36]

Table.2: Nasal Drug Products For Vacination Available In Market.[37, 38]

DRUG OR Vaccine NAME (Product name)	Dosage form	Status	Manufacturer
Human influenza vaccine(Nasalflu Berna)	Virosomes (Spray)	Marketed (withdrawn)	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
Human Streptococcus A vaccine (StrepAvax)	Proteosomes (nanoparticulate)	Phase 2	ID Biomedical

CONCLUSION

All types of microspheres that have been used as nasal drug delivery systems are water-insoluble but absorb water into the sphere's matrix, resulting in swelling of the spheres. The dextran microsphere system was as effective as an absorption enhancer for insulin as degradable starch microspheres (DSM). The maximum decrease in plasma glucose and the kinetics of the effect curve were similar for both systems. These systems also have a similar effect on mucosal integrity and lack a of adjuvant effect on the immune system after repeated nasal administration. It is therefore likely that the mode of action for improved absorption

found for starch microspheres is also applicable to dextran micro spheres, i.e. separation of the tight junctions during the swelling process of the microspheres. An important factor for the absorption of large hydrophilic molecules is probably the initial availability of the drug during the period when the tight junctions are separated. Microsphere is a short term but it is having wide applications in drug delivery systems. Most important are the targeted drug delivery (Bioadhesive microspheres-nasal, ocular, buccal, rectal etc., Magnetic microspheres and radioactive microspheres-For tumours), Controlled and sustained drug delivery (Polymeric microspheres, Floating microspheres). By combining various strategies, microspheres will find central place in novel drug delivery mainly particularly in cell sorting, diagnostics and Genetic engineering. From the study it is proved that Microspheres act as effective carriers for the novel drug delivery system.

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