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Promising: Role of Steroids in Nasal Drug Delivery System

Ruchi Bansal[1], Dinesh Kaushik[2], Saroj Jain[3], Bharat Bhushan[4]

Department of Pharmaceutics, Hindu College of Pharmacy, Sonipat, Haryana, India

Abstract: ***Since their discovery about 80 years ago, steroids have been extensively used in the treatment of wide range of disease states, namely asthma, rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, and many others. Steroids are powerful anti - inflammatory and have immune modulating characteristics which play significant role in many clinical applications. Systemic steroids are an effective treatment for many skin disorders. Mucoadhesive microspheres serve as a way to enhance drug delivery by prolonging the duration of drug at the application or absorption site and facilitating close contact with underlying absorption surface. This helps to enhance and/or increase the therapeutic performance of drug. The process by which artificial and organic polymers attach to mucosal surfaces in the body is known as mucoadhesion. Drug absorption by mucosal cells may, in general, have the potency to be used for controlled and targeted release drug delivery if these materials are embedded into pharmaceutical formulations. However, coupling of mucoadhesive properties to microspheres has significant benefits like much more intimate contact with mucous layer, efficient absorption, and increased bioavailability of drugs due to high surface to volume ratio.***

Keywords: Steroids, Mucoadhesive microsphere, Mucoadhesion, anti - inflammatory, Absorption

1. Introduction

With regard to immunological, pulmonary, oncological, inflammatory, and dermatological illnesses, steroids like corticosteroids and androgenic steroids have wide variety of applications. Traditional wisdom advises against using corticosteroids during acute infectious episodes out of concern for impairing the immune response [1].

Numerous molecules with a variety of physiological actions can be referred as steroids [2]. In the field of respiratory medicine, corticosteroids are used to treat uncontrolled asthma attacks as well as acute COPD exacerbations. Additionally, they are utilised to treat immune - mediated vasculitis and hypersensitive pneumonitis [3].

Athletes and bodybuilders utilise anabolic steroids to improve their performance. The history of anabolic steroids dates back to the 1930s, long before the word "steroid" was even used. A male hormone called testosterone was synthesised in the 1930s by a team of scientists to help treat men who lacked sufficient levels of hormones for healthy growth, development, and sexual activity [4].

Anabolic steroids were first used only by bodybuilders, but because of their beneficial benefits, they were also frequently utilised in other sports, including cycling, football, hockey, swimming, volleyball, wrestling, and soccer [5]. When Russian weightlifters were given testosterone at the 1954 Olympics, professional athletes began abusing anabolic steroids [6]. The metabolic (glucocorticoid) and electrolyte - regulating (mineralocorticoid) functions of corticosteroids and their biologically active synthetic alternatives are different. Corticosteroids have grown to be one of the most popular and efficient treatments for a variety of inflammatory and autoimmune illnesses since their discovery in the 1940s. They are utilised as replacement treatment in the care of numerous dermatologic, ophthalmologic, rheumatologic, pulmonary, hematologic, and gastrointestinal (GI) problems as well as in supraphysiological doses for adrenal insufficiency. Systemic corticosteroids are utilised in the field of respirology to treat inflammatory parenchymal lung illnesses like hypersensitivity pneumonitis and immune - mediated vasculitis as well as acute exacerbations of COPD and chronic, uncontrolled asthma [7].

Corticosteroid misuse may result in over - or under - treatment [8,] worsening of symptoms, or ultimately therapeutic failure. Due to their proven, unfavourable side effects (osteoporosis, weight gain, etc.), corticosteroids may be avoided by patients [9]. The American College such as hyperglycaemia of Clinical Pharmacy states that the clinical pharmacist is crucial to patient education and adherence promotion [10]. Therefore, the clinical pharmacist's expertise in patient care helps to diagnose and manage chronic diseases. This review focuses on the categorization, applications, and dangers of steroids as well as their augmentation in chronic conditions.

Classification of Steroids

The body contains two different kinds of steroids. Corticosteroids from non adrenal cortex make up the first group, whereas androgenic/anabolic steroids make up the second [11].

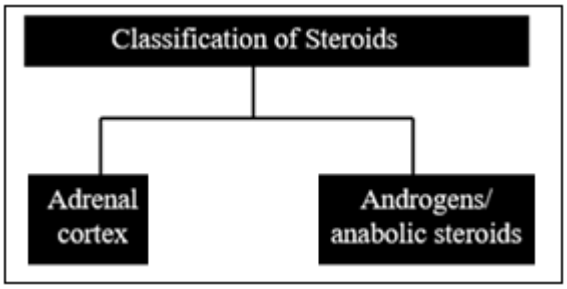

Figure 1: Classification of Steroids

1) Adrenal cortex

The adrenal cortex makes three types of hormones. In the gonads and adrenal glands, these hormones are made from

cholesterol. Corticosteroids, also known as adrenocorticoids, include the hormones glucocorticoids, mineralocorticoids, and androgens (sex hormones) [12].

a) Glucocorticoids

According to duration of action; glucocorticoids are further divided into the following categories:

- Glucocorticoids with short or intermediate half - lives
- Long - lasting corticosteroids

Glucocorticoids are released when the anterior pituitary is stimulated to release adrenocorticotropic hormone under stress. Cortisol and corticosterone are the two primary glucocorticoids. In the reticularis and zona fasciculata of the adrenal cortex, Cortisol is produced from cholesterol [12]. Numerous metabolic activities, including the synthesis of glucose from amino acids and fatty acids and the deposition of liver glycogen, are regulated by cortisol [13].

Following are some of glucocorticoids' functions:

- Promotion of gluconeogenesis
- Falling levels of protein synthesis
- Enhanced lipolysis in adipose tissue
- Increased salt and water reabsorption from the renal tubules [12].

Due to their ability to reduce inflammation and inhibit immune system, glucocorticoids are frequently recommended [11].

b) Mineralocorticoids

Kidney is the primary target of mineralocorticoids' actions, which result in salt and water retention as well as active excretion of protons and potassium. Aldosterone is the main mineralocorticoid, while progesterone and deoxycorticosterone are also endogenous hormones with mineralocorticoid activity. Only the zona glomerulosa area of adrenal cortex can manufacture aldosterone. The amount of salt in the blood affects aldosterone synthesis and its functions are: -

c) Control sodium reabsorption by the renal tubules is one of the primary functions.
d) Excretion of potassium [12]

2) Androgens/anabolic steroids

Anabolic steroids are synthetic or man - made versions of testosterone, a male sex hormone. Anabolic/androgenic steroids are the name given to this class of compounds. Male sex features are referred to as "androgenic, "and muscle growth is referred as "anabolic" The administration of anabolic androgenic steroids (AASs) can take variety of forms, including oral, intramuscular injection, parenteral, and transdermal [14]. There are two different forms of anabolic steroids: 17 alpha alkyl derivatives (such as oxandrolone, oxymetholone, and fluoxymesterone) and 17 beta ester derivatives (e. g., testosterone cypionate, testosterone enanthate, and nandrolone decanoate). The use of nandrolone phenpropionate by professional athletes as doping agent dates back to 1960 [15–17].

The primary functions are as follows:

- Growth and development of male sex organs
- Endogenous androgen is essential for secondary sex characteristics [18, 19].

Mechanism of action of Corticosteroids

After entering the cell, corticosteroids bind to cytosolic receptors, which are in charge of carrying hormones into the nucleus. The steroid receptor complex modifies gene expression by attaching to glucocorticoid response elements or mineralocorticoid - specific elements [20].

Glucocorticoids

The anti - inflammatory and immunosuppressive properties of glucocorticoids are demonstrated. Its process involves a loss in antibody synthesis as well as drop in the number of lymphocytes, basophils, and eosinophils in the blood, which in turn lowers the amount of T lymphocytes. As a result, lymphoid tissue gradually degrades, which inhibits a healthy immune response. Glucocorticoids primary immunosuppressive action appears to be regulation of cytokine production through suppression of nuclear factor B expression and nuclear translocation. Immunocompetent cells, which mediate both acute and chronic aspects of inflammation, emit cytokines that later play role in regulating the immune response. Additionally, glucocorticoids exhibit anti - allergic effects [21].

Mineralocorticoids

When there is a decrease in renal blood flow, kidney cells secrete the enzyme renin. As a result, the liver's angiotensinogen is transformed into angiotensin, which increases the adrenal cortex's synthesis of aldosterone. Aldosterone also causes the kidneys to excrete potassium and to reabsorb salt and water. As a result, blood volume and blood flow via the kidneys increase, which reduces renin synthesis and aldosterone secretion [12].

Androgens

A particular nuclear receptor in a target cell is where androgens attach. While testosterone serves as an active ligand in the muscle and liver, it must be converted to dihydrotestosterone (DHT) derivatives in order to function in other tissues. After entering the cells of the seminal vesicles, prostate, epididymis, and skin, testosterone is transformed to DHT by the enzyme 5 - alpha - reductase. It then attaches to the receptor. In the brain, testosterone is biotransformed into estradiol. The hormone/receptor combination that binds to DNA stimulates the creation of particular ribonucleic acids (RNAs) and proteins. [22]

Nasal Drug Delivery System

Drugs are typically administered via the nasal route to treat local disorders such as allergies, congestion, and infections of nose. [23, 24] But in recent years, this route has drawn considerable attention as a feasible and dependable strategy for the systemic distribution of medications, especially those that are inefficient when taken orally due to gastrointestinal tract or first - pass affect and must be injected [25]. The nasal route of administration, among many other promising non - parenteral methods, may completely meet the requirements for non - oral, non - parenteral systemic medicinal purposes [26]. The nasal cavity offers some benefits, including a basement membrane, a highly vascularized epithelial layer, improved blood flow, and easy accessibility for the systemic absorption of drugs [27, 28]. The poor contact time of the formulation with nasal mucosa,

however, is one of the fundamental drawbacks of nasal route of administration [29].

One of the most significant barriers to nasal medication administration is nasal mucociliary clearance. It efficiently prevents continuous nasal medication administration and substantially restricts the amount of time that can pass before drug absorption can take place. Mucoadhesive formulations, on the other hand, have been created to increase dosage form's contact time with mucosal layers of nasal cavities, resulting in improved drug absorption [30, 31, 32].

The Mucoadhesive Microspheres Drug Delivery System is an attractive prospect among the different methods accessible to improve transnasal drug delivery since it has the capacity to manage rate of drug clearance from nasal cavity as well as to safeguard the drug from enzymatic degradation [33]. The microspheres create a gel - like coating in the nasal cavity that clears rather slowly, prolonging the time the drug formulation spends there and raising the systemic bioavailability of medication. [34]

Anatomy and Physiology Of Nose

The main way for air to enter the respiratory system and be used by the body for breathing is through the nose [35]. The nasal cavity is separated into two by a cartilaginous wall known as the nasal septum and is 120–140 mm deep, extending from the nasal vestibule to the nasopharynx. The nose has a total volume of 16–19 ml and a surface area of about 160 cm^2 [36]. Warm, humid air is transported into the lungs through the nose. As it brings the inspired air into contact with the mucous - coated membrane, it functions as the principal organ for removing particles from the inspired air and as the first line of immunologic defence.

The vestibular, turbinate, and olfactory areas are the three primary parts of the nose. The nasal cavity'ssmallest portion is located in the vestibular region, which is located on the front of the nose. Most of this area is covered by vibrissae, making it possible to filter out airborne particles larger than 10 m in aer - odynamic particle size. At the beginning of the passage in the vestibular region, the surface lining transforms from skin to a stratified squamous epithelium [37, 38].

There are superior, middle, and inferior parts of the turbinate area, which is a substantial vascular portion of the nose. A pseudostratified columnar epithelium lines the inside. It is made up of basal, ciliated, non - ciliated, and mucus - secreting cells. The non - motile microvilli that cover both ciliated and non - ciliated cells increase the surface area of the cells, making this the area with the best medication absorption.

Mucociliary clearance is predominant because ciliated cells have an average of 100 motile cilia which are responsible for transporting mucus. Drugs, whether in the form of particles or solutions, will be removed from the nasal cavity and then have only a limited amount of access to the absorption site [39–41].

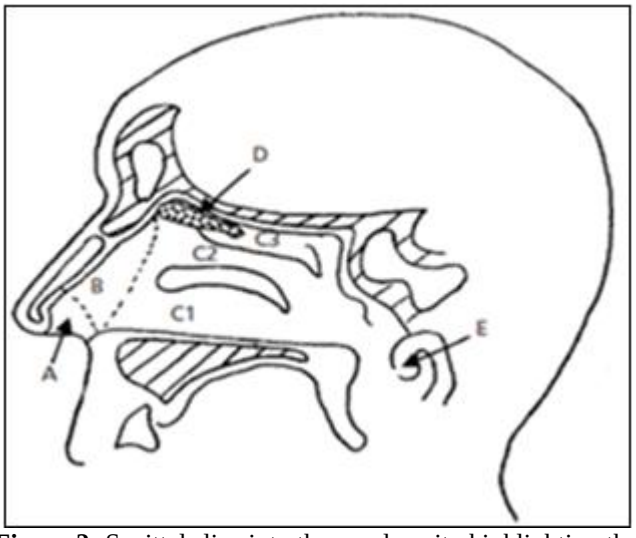

Figure 2: Sagittal slice into the nasal cavity highlighting the nasal vestibule (A), atrium (B), respiratory area inferior turbinate (C1), middle turbinate (C2), and superior turbinate (C3), as well as the olfactory region (D) and nasopharynx (E). [42]

The olfactory region is a nonciliated, pseudostratified columnar epithelium that makes up around 8% of the nasal epithelium's overall surface area. Drug delivery to the brain and cerebrospinal fluid depends on it (CSF). The epithelial cells are covered in a layer of mucus that is 5 m thick and catches foreign objects. Mucin, water, salts, proteins such albumin, immunoglobulin, lysozyme, and lactoferrin, and lipids make up the mucous discharge [43]. The nasal secretions have a pH that ranges from 5.0 to 6.5 [36]

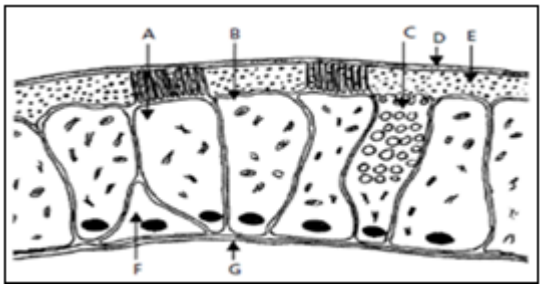

Figure 3: illustrates the many types of nasal epithelial cells, including ciliated and non - ciliated cells [A, B] goblet cells [C], mucous gel layer [D], sol layer [E], basal cells [F], and basement membrane (G). [42]

Various Formulation Administered by Nasal Route

Nasal sprays

Nasal sprays are manufactured from a mixture of solution and suspension. A nasal spray may provide a precise dose between 25 and 200 m due to the availability of metered dose pumps and actuators. The selection of the pump and actuator assembly is based on the morphology of the drug's particles (for suspensions) and formulation's viscosity [44, 45, 46, 47].

Nasal drops

They are the most efficient and easiest nasal medication delivery method yet created. You can administer nose drops using a pipette or a squeezy. These pharmaceutical preparations are frequently advised for the treatment of local

illnesses, including those that present difficulties such microbial growth, mucosal dysfunction, and non - specific loss of the nose or lower back [44–49]. Due to this system's prominent drawback—a lack of dose precision—nasal drops may not be appropriate for prescription medications. Human serum albumin is said to be deposited in the nostrils more effectively by nasal drops than by nasal sprays.

Dry powder inhaler

A dry powder formulation of an active medicine is given by means of dry powder inhalers (DPIs) for local or systemic impact via the pulmonary route. Dry powder inhalers are bolus drug delivery systems that fluidize when the patient inhales solid medicine that is suspended or dissolved in a non - polar volatile propellant or in a dry powder inhaler [50]. These have also been used to treat diabetes mellitus. They are frequently used to treat respiratory illnesses such asthma, bronchitis, emphysema, and COPD. Commonly, the drug is kept inside the inhaler in a unique form or in a capsule for manual loading. The user inserts the inhaler's mouthpiece into their mouth after it has been loaded or activated, inhales deeply, and holds their breath for 5–10 seconds. These devices come in a variety. Since larger powder doses may provoke coughing, the maximum quantity that can be administered in a single breath is normally less than a few tens of milligrammes [51].

Compressed air nebulizers

A nebulizer is a tool for delivering medication as a mist that is inhaled into the lungs. Nebulizers that use compressed air are those that fill with compressed air. The basic working principle of all nebulizers is to employ oxygen, compressed air, or ultrasonic energy to disperse medicinal solutions or suspensions into tiny aerosol droplets that can be inhaled directly through the device's mouthpiece. [52]

Squeezed bottle

Decongestants are often delivered by squeezed nasal bottles. They come with a smooth plastic container and a straightforward jet outlet. A particular amount of the air inside the plastic bottle is atomized when it is squeezed. This happens through the little nozzle. Air is drawn into the bottle by once more releasing the pressure. This process frequently causes nasal secretions to be sucked within and the fluids to become contaminated by bacteria. [53]

Nasal gels

There was not much interest in this method prior to the recent development of a precise dosage device. Nasal gels are thickened suspensions or solutions with a high viscosity. The advantages of a nasal gel include the reduction of post - nasal drip because of its high viscosity, the reduction of flavour effect because of less swallowing, the reduction of anterior formulation leaks, the reduction of discomfort because it targets the mucosa for more absorption. [54, 55]

Microspheres

The microsphere plays a significant part in nasal medication administration by improving absorption, sustaining release, and protecting the drug from enzymatic destruction [56].

Microspheres as Nasal Drug Delivery System

A mucin surface and a synthetic or natural polymer interact to form mucoadhesion [57]. The use of mucoadhesive hydrophilic polymers in pharmaceutical formulations like "microspheres" combined with active pharmaceutical ingredient have been widely advocated as a means of obtaining site - specific drug delivery (API). It is a dependable method for maintaining optimum concentration at the point of interest while delivering drug to target site with specificity, if altered [58]. Microspheres attracted a lot of interest for their sustained release as well as their ability to direct anti - cancer medications to the tumor. Microspheres will eventually take the lead in novel drug delivery by combining a number of other techniques, especially in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted, and efficient *in vivo* delivery, and supplements as miniature replicas of diseased organ and tissues in the body [59].

Mechnism of Mucoadhesion

It is still unclear exactly how some macromolecules adhere to the surface of mucous tissue. To begin close contact and increase surface contact, the mucoadhesive must spread throughout the substrate. This will encourage the dispersion of its chains within the mucus. There are forces of attraction and repulsion, and for a mucoadhesive to work, the attraction forces must prevail. The nature of the dosage form and method of administration can facilitate each phase. For instance, the attraction of surface water can induce a partially hydrated polymer to be absorbed by the substrate [60]. The contact stage and consolidation stage are the two stages that make up mucoadhesion mechanism. The mucoadhesive initial contact with mucous membrane, along with the formulation subsequent swelling and spreading, marks the beginning of its deep involvement with the mucous layer [61].

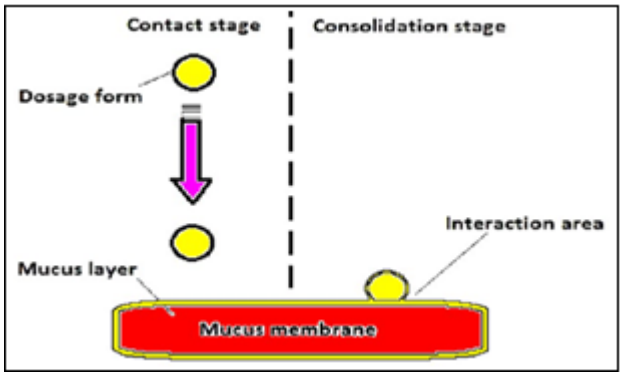

Figure 4: Mechanism of Mucoadhesion

Mucoadhesive Microspheres

Recent developments in drug carrier technologies and polymer science have laid down the way for the creation of innovative drug carriers such as mucoadhesive microspheres, which have increased the use of bioadhesion in drug delivery [62]. Microparticles and microcapsules with a diameter of 1 to 1000 µm that are either totally made of mucoadhesive polymer or have an exterior coating with adhesive properties are known as mucoadhesive microspheres [63]. Drug distribution that is both controlled and spatial may be accomplished using microspheres. Mucoadhesivenes added to microspheres result in effective

medication absorption and improved bioavailability. Utilizing homing agents (ligands) such plant lactin, bacterial adhesion, etc. on the surface of the microspheres allows for precise drug targeting to the absorption site. Mucoadhesive microspheres can be made to stick to the mucosal linings of the GIT, providing the possibility of regulated local and systemic medication absorption [64, 65].

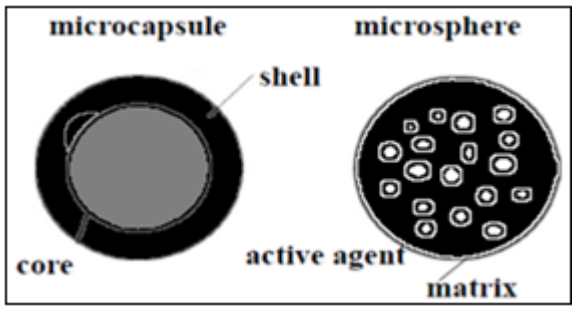

Figure 5: Diagram of Microsphere

Advantages of Mucoadhesive microspheres

When compared to traditional dose forms, mucoadhesive systems have following key advantages.

- Easily localized in the area and used to increase and improve drug absorption. For instance, gentamycin, insulin, dopamine, vasopressin, testosterone and its esters, etc.
- Promote close contact between the formulation and subsurface of absorption. This enables alteration of the tissue's permeability for macromolecule absorption such as proteins and peptides.
- Extend the dosage form's residence time at the application and absorption sites to enable once - or twice - daily dosing [66].
- Provides a great route for the systemic administration of medications with high first - pass metabolism, increasing bioavailability [67].
- Owing to API localization at the disease site, additional significant cost savings may be realized as well as a decrease in dose - related adverse effects [68].

Disadvantages of Mucoadhesive microspheres

- The formulations release may be altered.
- A number of variables, including food intake, intestinal transit times, mucin turnover rates, etc., may affect the release rate.
- There are variations in the release rate from one dose to the next.
- Potential toxicity may result from any degradation of the dosage form's release pattern.
- Crushing or chewing these dosage forms is not permitted.

Types of Mucoadhesive polymers

First generation mucoadhesive polymers

Anionic polymers, Cationic polymers, and non - ionic polymers are the three primary sub - categories of first generation mucoadhesive polymers. The strongest mucoadhesive properties of these anionic and cationic polymers have been observed [69].

- **Anionic polymers**

Due to their strong mucoadhesive functionality and low toxicity, anionic polymers are the most often used mucoadhesive polymers in pharmaceutical formulation. These include sodium carboxymethylcellulose, Carrageenan, poly (- acrylic acid) (PAA), and its weakly cross - linked derivatives (NaCMC). Due to the establishment of potent hydrogen bonding interactions with mucin, PAA and NaCMC exhibit good mucoadhesive properties [70]. Numerous studies have been conducted on polycarbophil and carbomer (Carbopol, PAA derivatives) as mucoadhesive platforms for GI tract medication administration. [71, 72].

While polycarbophil polymers are cross - linked with divinyl glycol, carbomers are cross - linked with allyl sucrose or allylpentaerythritol. While the cross - link density of the two compounds differs but frequently modified to suit pharmacological or cosmetic performance, both have the same acrylic backbone.

- **Cationic polymers**

The most prevalent polysaccharide in the world after cellulose is chitosan, a cationic polysaccharide [73]. Due to its excellent biocompatibility, biodegradability, and favourable toxicological properties, chitosan, one of the most researched mucoadhesive polymers, is gaining relevance [74]. Chitosan molecules are linear, which guarantee adequate chain flexibility for interpenetration [75]. Chitosan has been demonstrated to boost drug absorption via the paracellular route by neutralising fixed anionic sites within the tight junctions between mucosal cells [76, 77]. Chitosan may improve drug delivery via mucoadhesive mechanism.

Novel second - generation Mucoadhesive polymers

Lectins and thiolated polymers are included in the second generation.

- **Lectins**

These are usually understood to be non - immune proteins or glycoprotein complexes that have the ability to bind sugars selectively and non - covalently [78]. Lectins have been thoroughly investigated, particularly for drug - targeting applications [79, 80], and they have the ability to bind to carbohydrates on the mucus or epithelial cell surface. These second - generation bioadhesives enable subsequent endo - and transcytosis in addition to cellular binding.

- **Thiolated polymers**

These hydrophilic macromolecules, commonly known as thiomers, have free thiol groups on the polymeric backbone. These functional groups significantly improved a number of characteristics of polyacrylates and cellulose derivatives [81]. Thiol groups present in the polymer enable stable covalent connections to form with cysteine - rich subdomains of mucus glycoproteins, extending residence time and enhancing bioavailability [82]. Improved tensile strength, quick swelling, and water uptake behaviour are further benefits of thiolated polymers, which include, for example, chitosan - thioglycolic acid, chitosan - thioethylamidine, and alginate - cysteine.

Methods of preparation of Mucoadhesive microspheres

1) Emulsion cross - linking method

This method includes the polymer reactive functional group to crosslink with the cross - linking agent's aldehyde group. This technique involved emulsifying the polymer's aqueous solution in the oily phase to create a water - In - oil (w/o) emulsion. An appropriate surfactant, such as span 80 or dioctyl sodium sulphosuccinate, was used to stabilise aqueous droplets. A suitable cross - linker, such as glutaraldehyde, was used to cross - link the stable emulsion and harden the droplets. To get rid of any remaining oil residue, microspheres were filtered and repeatedly washed with petroleum ether or hexane. Finally, cross linkers were removed by washing them in water, and they dried for 24 hours at room temperature [83].

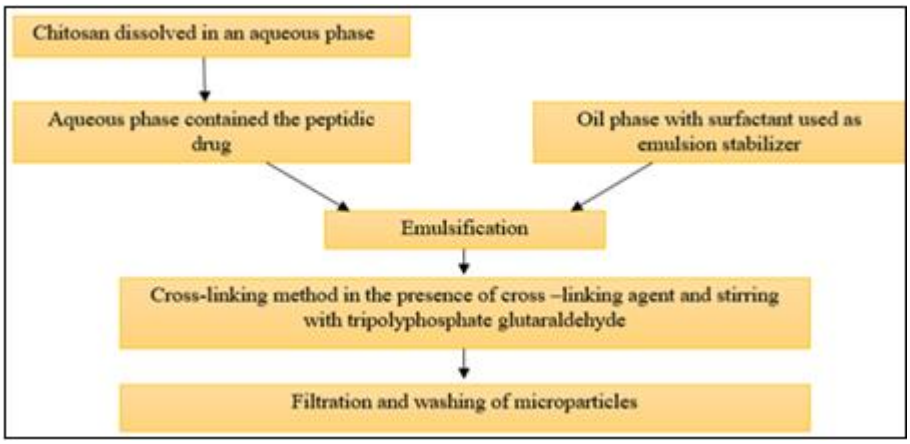

Figure 6: Flow chart of Emulsion cross - linking method

2) Single Emulsion Solvent Evaporation Technique

This technique involves the emulsification of an aqueous environment including the emulsifying agent, followed by the polymer dissolution in an organic solvent. The resulting emulsion is cleansed, rinsed, and dried in desiccators after being agitated for a number of hours in air conditions to allow the solvent to evaporate created and produced polymer - coated drug microspheres using the diffusion - evaporation process and an emulsion solvent. [84]

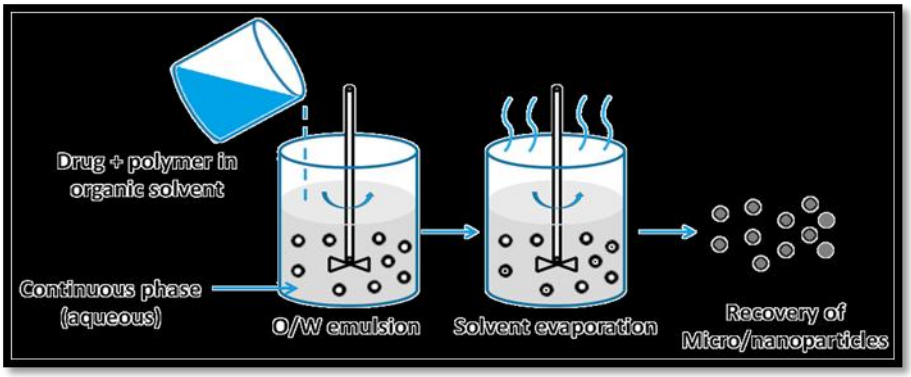

Figure 7: Preparation of microsphere by single emulsion solvent evaporation technique

3) Ionotropic Gelation method

Using this approach Gel - type polymers such as alginate, are dissolved in an aqueous solution, and then the active ingredient is suspended in the mixture and extruded through a needle to create micro droplets that fall into a calcium chloride - containing hardening solution while being stirred slowly. This process results in microspheres. The hardening solution's divalent calcium ions cause the polymer to crosslink, resulting in the formation of gelled microspheres [85].

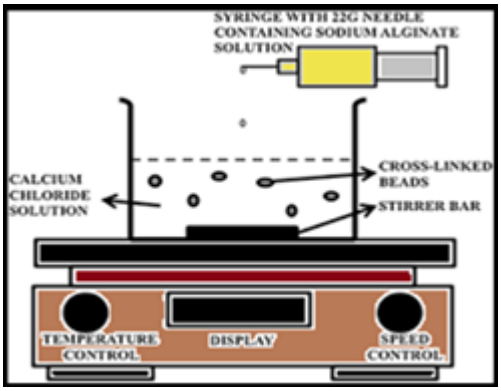

Figure 8: Ionotropic Gelation method

4) Phase Inversion Method

The procedure is mixing the medication with a weak non - solvent polymeric solution in methylene chloride, and then pouring the resulting combination in a 1: 100 ratio into a petroleum ether bath that has not been agitated. The resulting microspheres are then cleared, cleaned with petroleum ether, and allowed to air dry [86].

5) Spray drying technique

This was done to make polymer microspheres that were drug - charged. In order to achieve this, the raw material must be mixed with a liquefied coating liquid before being sprayed into the air where it will quickly solidify on the surface and evaporate the solvent. Microspheres containing drugs are created by mixing an organic solvent with a polymer solution in different weight ratios and spraying the mixture under certain laboratory conditions. Although quick, the crystalinity may be lost because to the quick drying. [87, 88]

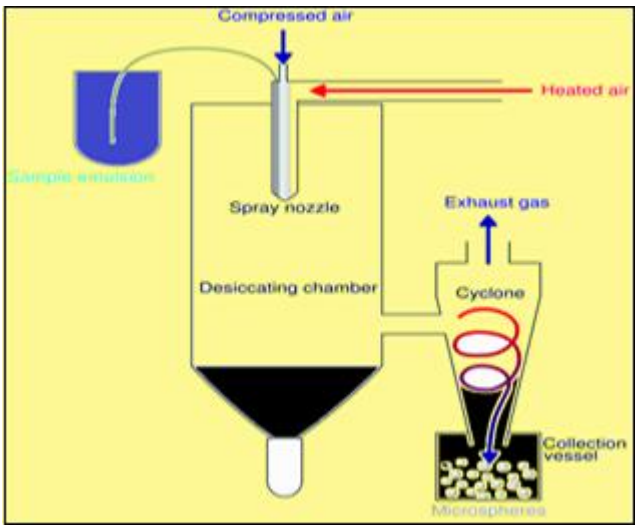

Figure 9: Spray drying technique

6) Wax coating and hot melt method

By dissolving or scattering the substance in melted wax, wax was utilised to encapsulate the major components. High - intensity mixing with cold water releases the waxy paste or combination, such as frozen liquid paraffin. At least an hour is spent warming the water. At least one hour is kept stirring the material. The microspheres are then submerged in a non - miscible solvent and dried with dry air after the exterior layer (liquid paraffin) has been decanted. Beeswax and carnauba wax are both acceptable components for the surface coating, and both should be mixed to get the desired effects. [89]

7) Solvent removal method

It is a non - aqueous technique for microencapsulation that works well with polymers that are sensitive to water, including polyanhydrides. This technique was employed by Carino and colleagues to create microspheres. By using a solution of the chosen polymer in a volatile organic solvent, such as methylene chloride, the medication was disseminated or dissolved in this approach. Following that, this mixture was suspended in silicone oil that also contained Span 85 and methylene chloride. Petroleum ether was added and agitated until solvent was extracted into the polymer solution in silicone oil after the polymer solution had been poured into the oil. After that, the resultant microspheres were vacuum - dried [90]

Applications of Microspheres [91]

- One potential method for extending GRT is the mucoadhesive microsphere. In order to achieve better therapeutic performance of drugs, mucoadhesive microspheres participate with the mucous of the GIT and are thought to be localised or stuck at the adhesive site by holding a dosage form at the site of action, or systemic delivery by holding a formulation in close contact with the absorption site. This may lead to a sustained gastric residence time as well as a betterment in the closeness of interaction with the inherent absorptive membrane.
- The delivery of vaccines for the treatment of illnesses such as hepatitis, influenza, pertussis, ricin toxoid, diphtheria, and birth control. A specific benefit of using microspheres in vaccine delivery is increased antigenicity through adjuvant action, regulation of antigen release, and stability of antigen.
- Mucoadhesive microspheres, a new drug delivery technology that can be used for local or systemic effects via buccal, oral, nasal, ophthalmic, vaginal, and rectal modes of administration.
- For the treatment of several disorders, mucoadhesive microspheres are employed as a targeted medication delivery device. The use of mucoadhesive microspheres is prevalent in both clinical and pharmacological settings.

2. Literature Review on Mucoadhesive microspheres

S. No.	Drug Used	Indication	Polymer used	Result	Ref
1.	Glipizide	Anti - diabetic	Sodium alginate	By using sodium alginate mucoadhesive microspheres of Glipizide should increase the length of stay of glipizide for the treatment of Diabetes.	92
2.	Ramipril	Hypertension Myocardial - Infraction	Chitosan, Ethyl cellulose	Mucoadhesive microspheric preparation of Ramipril prolonged the Gastrointestinal residence time and slow release of drug.	93
3.	Cephalexin	Treatment of respiratory tract infection	Sodium alginate, Guargum	Improved bioavailability of cephalexin and decrease the frequency of dosage form administration.	94
4.	Repaglinide	Anti - diabetic	Eudragit RS100 Chitosan	It has been concluded that drug loaded mucoadhesive microspheres are suitable delivery systems for Repaglinide.	95
5.	Nifidipine	Antihypertensive	HPMC, Carbapol	Mucoadhesive microspheres of Nifidipine showed good controlled release properties and polymer used showed good entrapment efficiency.	96

Evaluation of Mucoadhesive microspheres
The following factors are assessed for the microspheres

1) Particle Size and Shape Light microscopy
The size, shape, and external structure of microspheres can all be determined using either lightmicroscopy (LM) or scanning electron microscopy (SEM). [97]

2) Surface Characterization of The Mucoadhesive Microspheres
Data from electron, scanning tunnelling, and scanning electron microscopy can be used to understand the surface morphology of microspheres and the morphological changes brought on by polymer degradation. Microspheres can be incubated in phosphate buffered saline for varying lengths of time to observe changes in surface morphology brought on by polymer degradation [98]. It has been discovered that microspheres with a rougher surface have stronger mechanical contacts, which promote adherence, whereas microspheres with a smooth surface have weaker mucoadhesive characteristics [66, 99].

3) Surface Charge Study
From photon correlation spectroscopy data the surface charge (zeta potential) of the mucoadhesive microspheres can be determined. The surface charge can be determined by relating measured electrophoretic mobility into zeta potential with in - built software based on the Helmholtz–Smoluchowski equation [100]. Zeta potential is an indicator of particle surface charge, which can be used to predict and control the adhesive strength, stability, and the mechanisms of mucoadhesion. Process of mucoadhesion involves interactions between the mucus and mucoadhesive polymers, and is influenced by their structure including their charge. Measurement of zeta potential of microspheres and mucus helps to predict electrostatic interactions during mucoadhesion. [101]

4) Entrapment Efficiency
By retaining the microspheres in the buffer solution and permitting lysing, the microspheres' entrapment efficiency or percent entrapment can be calculated. The lysate is then filtered or centrifuged, and the active components are subsequently determined in accordance with the requirements of the monograph. The following calculation is used to compute the percent entrapment efficiency. [97]

% Entrapment = Actual content / Theoretical content x 100

5) Swelling Index
The ability of the mucoadhesive microspheres to swell at the absorbing surface by absorbing fluids present at the site of absorption is demonstrated by the swelling index, which is a crucial prerequisite for the beginning of mucoadhesion. [102]

The percent swelling value can be determined using following equation.
Percent swelling = DT - D0 / D0 × 100

Where, D0 = weight of dried microspheres
DT = weight of swelled microspheres

6) *In - Vitro* Release Study
Rotating basket or paddle type dissolving apparatus is used to analyse the *in - vitro* release profile in the dissolution media that is similar to the fluid present at the absorption site in accordance with the monograph. [103]

7) *Ex - Vivo* Mucoadhesion Study
According to the monograph, phosphate buffer is used to test the microspheres' mucoadhesive properties on the intestinal mucosa of goats. Weighed microspheres are applied to moist, rinsed tissue samples, and then the slides are immediately suspended from the arm of a USP pill dissolving test apparatus at 370°C with the necessary support. The weight of the microspheres that are leached out at various times is calculated. The following equation calculates the percentage mucoadhesion. [104]

Percentage mucoadhesion = $W_a - W_1 / W_a$ x 100
Where, Wa is the weight of microspheres applied
W_1 is the weight of microspheres leached out

Recent advancement in Microspheres [105]

1) Increase Stability of Drug
When a medicine is complexed with chitosan and made into a slurry and dough mass, kneading for 45 minutes, chitosan polymer is employed to boost the stability of the drug. This dough mass is sent through filter number 16 to create granules that are utterly stable under various conditions.

2) Orthopaedic Patients
In order to increase the osteo integration of orthopaedic and craniofacial implant devices, chitosan, a biopolymer, is attractive for use as a bioactive covering. It also exhibits osteoconductive, improved wound healing, and antibacterial properties. It has been shown to be effective in accelerating bone regeneration, increasing tissue growth during tissue repair, and wound healing.

3) Enhanced Bone Formation by transforming growth factor (TGF - pl)
In order to achieve high bone - forming efficacy, chitosan composite microgranules were created as bone substitutes. By dumping a mixed solution into a NaOH/ethanol solution, the chitosan microgranules were created. The chitosan microgranules were soaked in a TGF - pl solution to load them with TGF - pl.

4) Wound Healing Properties
Chitosan effectiveness in promoting wound healing was initially noted in 1978. Chitosan acetate films, which were strong and protective, had the benefit of having a high water absorption rate and good oxygen permeability.

5) Dental Medicine
Chitosan has been shown to hasten wound healing, achieve an aesthetically pleasing skin surface, and avoid the production of excessive scar tissue. Chitosan is also used in dental medicine as a tampon after radical therapy for maxillary sinusitis and as a bandage for oral mucosal wounds. It is also being looked into as a potential absorbent membrane for periodontal surgery. Chitosan is promoted as a nutritious meal that can treat or improve a variety of

diseases, including diabetes, cancer, hepatitis, and arthritis. It has a wide range of biological activity.

6) Cosmetics industry

The disclosure of cosmetic formulations for the treatment of hair or skin that contain brand - new quaternary chitosan derivatives of the formula. The chitosan derivatives exhibit qualities that strengthen and condition hair, especially with regard to the keratin in hair. Examples include gel - form, skin cream, hair treatment composition, oxidation hair - coloring composition, and hair toning composition.

7) Chitosan as Permeation Enhancer

According to certain reports, chitosan can open tight connections in a cell membrane because of its cationic character. This characteristic has prompted several research to examine the potential of chitosan as a permeation enhancer for hydrophilic medicines, such as peptides, which may otherwise have poor oral bioavailability. The phenomenon is pH and concentration dependent because the absorption amplification results from interactions between the cell membrane and positive charges on the polymer. Additionally, a polymer with a higher charge density would have a higher permeability.

8) Chitosan as Mucoadhesive Excipient

Bioadhesivity is frequently employed as a strategy to lengthen a drug's duration in the GI system, hence enhancing the oral bioavailability. Chitosan has a higher bioadhesivity than other frequently used polymeric excipients such cellulose, xanthan gum, and starch, according to a comparison with these substances.

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