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Review Article

Microsphere-Based Drug Delivery Systems: An Overview

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ABSTRACT

Microspheres are widely studied drug delivery carriers developed to enhance the therapeutic effectiveness of drugs by enabling controlled and targeted release. They are small, spherical, free-flowing particles with sizes typically ranging from 1 µm to 1000 µm and are usually formulated using natural or synthetic polymers. These systems are capable of encapsulating active pharmaceutical ingredients and releasing them in a regulated manner, which helps to improve bioavailability, decrease dosing frequency, and reduce unwanted side effects. Various forms of microspheres, including bioadhesive, magnetic, floating, radioactive, polymeric, porous, and glass microspheres, have been explored for different pharmaceutical and biomedical purposes. Several manufacturing techniques such as spray drying, solvent evaporation, ionic gelation, phase separation coacervation, and solvent extraction are commonly employed for their preparation. Microspheres are characterized using different evaluation parameters like particle size, surface morphology, encapsulation efficiency, density, and both in vitro and in vivo drug release studies. These systems provide several benefits such as enhanced patient compliance, sustained drug release, and site-specific drug delivery. However, certain drawbacks including high manufacturing costs and issues related to reproducibility are still associated with their development. This review presents a detailed overview of microspheres, covering their classification, preparation techniques, formulation components, evaluation methods, advantages, limitations, and pharmaceutical applications.

INTRODUCTION

More than 90% of currently available therapeutic agents are administered through the oral route, as it is considered the most convenient and widely accepted method of drug administration. When a new chemical entity is discovered, one of the primary challenges faced by pharmaceutical

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scientists is to design a suitable dosage form that can be effectively delivered through the oral route. However, conventional oral drug delivery systems often show limitations such as reduced therapeutic effectiveness due to the need for frequent dosing in order to maintain consistent plasma drug concentrations, which may also lead to poor patient compliance. These pharmacokinetic limitations can be addressed by developing advanced dosage forms capable of releasing the drug in a slow and controlled manner over an extended period. One such promising approach is the use of microspheres, also referred to as microparticles.[1]

Microspheres are defined as spherical, microparticulate, free-flowing powders that are primarily composed of biodegradable polymers. They typically possess a particle size ranging from 1 µm to 1000 µm. These carriers can encapsulate therapeutic agents and are widely used for targeted drug delivery. Since the drug is incorporated within polymeric microspheres, it can be delivered directly to the specific target site, producing therapeutic action mainly at the desired tissue. Microspheres are therefore designed to improve the therapeutic efficiency of drugs by enhancing bioavailability while reducing toxicity and minimizing adverse side effects. [2]

Microspheres are mainly classified into two categories: reservoir-type microspheres and matrix-type microspheres.

Reservoir-type microspheres

In reservoir-type microspheres, the drug is enclosed within a core that is surrounded by a water-insoluble polymeric membrane, which regulates the rate of drug release. The polymer coating acts as a barrier and controls the diffusion of the drug from the core. Commonly used polymers in this system include ethylcellulose and polyvinyl acetate. These microspheres are also referred to as microcapsules.

Matrix-type microspheres

In matrix-type microspheres, the drug is uniformly dispersed throughout the polymeric matrix. The release of the drug occurs as it diffuses through the polymer network or as the polymer gradually degrades. Polymers such as sodium alginate and hydroxypropyl methylcellulose (HPMC) are frequently used in this system. These are also known as micromatrices.[3]

Mechanisms of drug release from microspheres

Drug release from microspheres generally occurs through two main mechanisms:

- **Dissolution:** In this mechanism, the rate of drug release is controlled by the dissolution of the drug or the polymer. The polymer may reduce the wettability of the drug or dissolve slowly in gastrointestinal fluids, thereby controlling the dissolution rate.

- **Diffusion:** In this process, the drug moves from an area of higher concentration within the microsphere to an area of lower concentration in the surrounding medium until equilibrium is reached.[4]

ADVANTAGES

- **Improved patient compliance:** Because microspheres deliver a steady release of medicine over an extended period of time, dose frequency is reduced, which is beneficial for patient compliance, particularly in pediatrics, geriatrics, and psychiatric patients**.**

- **Enhance bioavailability:** Microspheres are micron in size, which means that smaller sizes provide greater surface area to boost the

solubility of poorly soluble medications, hence enhancing systemic bioavailability of the pharmaceuticals.

- **Maintains constant drug plasma concentration:** Microspheres exhibit regulated drug release over a lengthy period of time; as a consequence, drug concentration in systemic circulation does not fluctuate, and a constant C max is established.

- **Reduced harmful effects:** Biodegradable polymeric microspheres are biocompatible with the bodily environment and do not need to be surgically removed. The systemic toxicity of the medicine is lowered as a result of its regulated release.

- **Enhance stability:** Liquid medications can be transformed into solid microspheres to boost their stability and clinical shelf life.

- **Parenteral formulation:** Microspheres are spherical in form, allowing a large dosage of the medicine to be administered as a parental depot.

Microspheres are utilized to target disease locations, especially tumor tissues, while the concentration stays low in other normal tissues**.** [5,6]

DISADVANTAGES

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- Microspheres are utilized to target disease locations, especially tumor tissues, while the concentration stays low in other normal tissues.

- Microspheres meant for oral administration should be swallowed, not chewed or crushed, to prolong drug release.

- **Keeping conditions consistent** pH, temperature, agitation, solvent evaporation, and heating can all affect the stability of the medicine to be encapsulated.

LIMITATION:

Some of the drawbacks were discovered to be as follows.

- The prices of ingredients and processing for the controlled release preparation are significantly greater than those for ordinary formulations.

- The destiny of polymer matrix and its impact on the environment.

- The destiny of polymer additives, including plasticizers, stabilizers, antioxidants, and fillers.
  Reproducibility is lower.

- Process factors such as temperature, pH, solvent addition, and evaporation/agitation may affect the stability of the core particles to be encapsulated.

- The environmental effect of polymer matrix breakdown products generated in reaction to

heat, hydrolysis, oxidation, solar radiation, or biological factors. [7]

CRITERIA FOR MICROSPHERE PREPARATION:

The microencapsulation technology allows for the incorporation of solid, liquid, or gas into one or more polymeric coverings[8].The diverse techniques used for various microspheres manufacture relies on particle size, route of administration, length of drug release, and these above features are connected to rpm, method of cross linking, drug of cross linking, evaporation time, co precipitation, etc [9] The preparation of microspheres should meet specific requirements [10].

- Ability to assimilate high drug concentrations.
- The preparation is stable after synthesis and has a therapeutically acceptable shelf life.
- Controlled particle size and dispersion in aqueous vehicles for injection.
- Successfully controlled the release of an active reagent over an extended period of time.
- High biocompatibility and controlled biodegradability.
- Susceptibility to chemical alteration. [11]

TYPES OF MICROSPHERES

Bioadhesive microspheres

Bioadhesion refers to microspheres loaded with drugs that adhere to the mucosal layer found in buccal, ophthalmic, rectal, nasal, and other areas employing the adhering property of water-soluble polymers. These types of microspheres exhibit traits such as close proximity to the absorption region. It also displays increased residence duration at the targeted location and so creates a superior therapeutic effectiveness, such as ocular administration of Acyclovir, nasal administration of insulin, and buccal administration of nifedipine using bioadhesive microspheres. [12,13]

Magnetic microspheres

This sort of microsphere has an important attribute for usage as a conveyance system: it confines the medicine to the illness location. The fundamental goal of these microspheres is to replace a large amount of freely spreading medicine with a smaller amount of magnetically focused drug. Magnetic microspheres are small (<4 μm) and circulate through blood capillaries without occlusion. They are targeted to disease sites using an external magnetic field of 0.5-0.8 tesla. For example, monoclonal antibodies conjugated to magnetic microspheres can be used to remove neuroblastoma cells from bone marrow.[14, 15]

Magnetic microspheres are of two types:

Therapeutic magnetic microsphere

The primary goal of this type of microsphere is to target liver tumors by delivering a chemotherapeutic drug to the disease location. These microspheres are often filled with proteins or peptide medicines for targeting.

Diagnostic magnetic microsphere

These microspheres were designed primarily for the imaging of liver metastases. It may also be used to create nanoparticles such as supramagnetic iron oxides, which are utilized to distinguish bowel loops from other abdominal structures.

Floating microspheres

The floating microspheres have a lower bulk density than gastric fluid, therefore they keep floating in the stomach without impacting gastric emptying rate. In this case, the medication is released gradually at the prescribed pace; these microspheres are buoyant on stomach content, increasing gastric residence length and resulting in a consistent level of drug plasma concentration. This type of microsphere minimizes the frequency of dose while simultaneously producing a sustained therapeutic impact, such as Ketoprofen floating microspheres and Felodipine floating microspheres. [16, 17]

There are two kinds of floating microspheres:

1. Effervescent microspheres.
2. Non-effervescent microspheres.

Radioactive microspheres

Radioembolization treatment microspheres have a size range of 10-30 nm, which is larger than the diameter of the capillaries and are tapped into the first capillary bed. These microspheres are injected into the arteries that supply the targeted tumor areas.

In all of these cases, radioactive microspheres focus on a specific region and carry a high radiation dosage while causing no injury to other organs. There are three types of radioactive microspheres: α, β, and γ emitters.[18]

Polymeric microspheres

The various types of polymeric microspheres can be classified as follows.

Biodegradable polymeric microspheres

Microsphere formulation uses starch, a natural polymer that is biodegradable, biocompatible, and bioadhesive. These biodegradable polymers have a longer residence time when exposed to mucous membranes due to their swelling properties caused by interaction with an aqueous media, which eventually results in gel formation. The rate and amount of medication released from the microsphere are completely dependent on the polymer concentration and release pattern. This release pattern occurs in a consistent manner. The primary drawback of biodegradable microspheres is their drug loading efficiency and release. However, they provide a wide range of applications in microsphere-based therapy, such as polylactic acid microspheres loaded with 5-fluorouracil.

Synthetic polymeric microsphere

These types of microspheres are widely employed in clinical utilization; additionally, they are useful as a bulking agent, fillers, embolic particles, drug delivery medium, etc., and have been demonstrated to be safe and biocompatible; however, the main drawback of these types of microspheres is that they shift away from the injection site, posing a risk of embolism and further organ damage. For example, Phenobarbitone microspheres using polymer Eudragit RL [19]

Porous microspheres

Porous microspheres feature either exterior surface pores or interior pores in the core via which the active medicinal ingredient can be disseminated or dissolved, as seen in Figure 1. Porogens generate the pores and then drain out fully later in the process. Examples of porogens include effervescent salts like ammonium bicarbonate, hydrocarbon waxes, inorganic salts like sodium chloride, carbohydrates, ice, linear polymers, gelatin, and sugar. The exterior structure is made of elements including calcium

carbonate (CaCO3), mesoporous silica, hydroxyapatite, and biodegradable porous starch foam. [20,21]

Glass microspheres

Hollow glass microspheres are a new type of glass with a diameter of 10 µm to 100 µm and a hollow central cavity surrounded by a 1 µm thick silica shell. They can be used as nanocarriers for oligonucleotides and proteins in tissue engineering applications. However, drug delivery applications need either an organic copolymer or the inclusion of elements (such as metal ions) into the glass matrix. [22, 23]

METHODS OF PREPARATION

Spray drying

In this process, the coated polymer is first dissolved/dispersed in an organic solvent such as acetone or DCM, and the medication is then integrated into the polymeric solution using high-speed homogenization [40]. The resulting mixture was subsequently atomized in a hot jet of air. Atomization produces fine mist or droplets from which the organic solvent evaporates rapidly, resulting in the creation of microspheres ranging in size from 10 um to 100 um. [24]

Solvent evaporation

This approach uses organic phase as a production vehicle; the process is divided into two stages. The first phase is aqueous, in which the medication is introduced with or without a stabilizing agent. Furthermore, the other phase is the organic phase, which is made up of polymer solution in an organic volatile solvent such as acetone or DCM. The aqueous and organic phases should be mixed with high-speed homogenization to form a w/o emulsion, which is then added to the large aqueous phase to form a w/o/w emulsion if necessary. The resulting mixture is heated with constant stirring, causing the organic phase to evaporate, shrinking the coated polymer across the core material and forming microspheres. [25]

Single emulsion technique

In this process, microspheres are created via an emulsification technique; the coated polymer is dissolved in an organic volatile solvent, resulting in the production of a polymeric solution. The resulting polymeric solution, when mixed with an aqueous phase containing an emulsifying agent, forms an o/w emulsion. This emulsion is then agitated for many hours under continuous environmental conditions, filtered, and dried in a desiccator. [26]

This approach includes creating a double emulsion, either w/o/w or o/w/o. The medication is present in the aqueous solution and is spread throughout the organic phase. The organic phase containing coated polymer encapsulates the medication in the dispersed aqueous phase, resulting in the development of a primary emulsion. The initial emulsion is then homogenized or sonicated before being added to an aqueous solution of PVA to generate a secondary emulsion, after which the resulting microspheres are filtered and dried in a desiccator. [27]

Phase separation coacervation technique

This method is generally used for fabrication of reservoir type of microspheres. Mostly this method used to encapsulate the hydrophilic drugs; in this method, coating polymer is dissolved in an organic volatile solvent and then an aqueous solution of the drug is added to allow the polymer to coat drug, then phase separation will be initiated by changing the ambient conditions such as

changing temperature, changing pH, and the addition of salt. [28]

Spray congealing

In this procedure, the medication is dissolved or disseminated in a polymeric solution, which is a lipophilic polymer similar to wax. The hot molten solution was then sprayed to produce small droplets into a vessel previously immersed in a carbon dioxide ice bath. [29]

Solvent extraction

This approach includes removing the organic phase by extracting the organic solvent using hydrophilic organic solvents such as isopropyl-alcohol. The organic phase is subsequently removed using water, which results in a reduction in the hardening time of microspheres.. [30]

Quassi emulsion solvent diffusion

Using this technique microsponge could be prepared. It involves two phases one is internal and the other is external. The external phase consists of PVA and distilled water and internal phase consist of polymer, drug, and ethanol. Internal phase is heated up to 60°C and then added to the external phase main. It is then maintained at room temperature. Resultant emulsion is then homogenized up to 2 h and fabricated into microsponges then filtered, washed, and dried in a vacuum oven for 24 h. [31]

Cross-linking agent method

For the manufacture of microspheres, a cross-linking agent is utilized. The first specific concentrated polymeric solution was made in an aqueous medium, then added in a continuous phase containing oil and a specific concentration of surfactant to form a w/o emulsion, followed by drop-by-drop incorporation of an aqueous solution of cross-linker coupled with continuous agitation, allowing for stiffening of the surface of microspheres. The resulting microspheres were then cleaned and dried. [32]

Hot melt microencapsulation

In this technique, the coating polymer is melted and then homogenized with the drug. The resultant mixture is then suspended in a lipophilic solvent such as silicon oil along with continuous agitation/stirring and heating the solution at 5°C up to the melting point of the polymer. After the emulsion stabilizes, it is cooled to solidify the polymeric microspheres. [33]

Ionic gelation method

In this technique, the coating polymer is melted and then homogenized with the drug. The resultant mixture is then suspended in a lipophilic solvent such as silicon oil along with continuous agitation/stirring and heating the solution at 5°C up to the melting point of the polymer. After the emulsion stabilizes, it is cooled to solidify the polymeric microspheres. [34, 35]

Hydroxyl appetite (HAP) microspheres in sphere morphology

Microspheres were created by creating an o/w emulsion and then evaporating the organic solvent. The first organic phase (a medication comprising 5% w/w EVA and an appropriate amount of HAP) is distributed in the surfactant's aqueous phase to generate an o/w type emulsion. The organic phase is disseminated in tiny droplets surrounded by surfactant moieties that prevent the droplets from combining and assist them to stay distinct droplet, while later the DCM began draining slowly, leaving behind the droplets of microspheres. [36]

INGREDIENTS OF MICROSPHERES [37-39]

Polymers

Researchers routinely employ biodegradable and non-biodegradable polymers in microsphere formulations. The polymers utilized in microsphere production are divided into two types: natural and synthetic. Before selecting a polymer for the microsphere formulation, we must evaluate several factors, including nontoxicity, biocompatibility, biodegradability, and polymer availability. It should be biocompatible, biodegradable, nontoxic, and conveniently accessible. These polymers, which pass all selection characteristics, offer several advantages, such as increasing the medication's residence duration in the body, resulting in higher bioavailability of the drug as compared to traditional drug delivery systems.

Natural polymers include Albumin, Collagen, and Gelatin, which are proteins; Agarose, Carrageenan, Chitosan, and Starch are carbohydrates; Poly (acryl) Dextran, Poly Starch, and DEAE Cellulose are chemically modified carbohydrates; and Sodium Alginate, cellulose ether, xanthan gum, Scheroglucan, Gum Arabica, Tamarind seed polysaccharide, Beeswax, carnauba wax, Chitin, and Corn protein (Zien) are the other class. Lactides, Glycolides and their copolymers, polyanhydrides, and poly alkyl cyanoacrylates are biodegradable in nature, while Glycidyl methacrylate, Acrolein, Epoxy polymers, and polymethyl methacrylate are non-biodegradable. Finally, polysebacic anhydrides, Poly Esters/Poly Lactides, poly orthoesters, polycarbonates, polylactic glycolic acid (PLGA), polycaprolactones, polyphosphazenes, ethylcellulose, Eudragit L

Surfactant

Surfactants play a key role in microsphere formation by emulsifying and extruding. Surfactants are significant because they reduce the interfacial tension between hydrophilic and hydrophobic molecules, resulting in a stable emulsion. Surfactants prevent emulsion droplets from consolidating, resulting in the creation of distinct microspheres. The hydrophilic-lipophilic balance (HLB) indicator is used to identify an appropriate emulsifier. Hydrophilic surfactants have an HLB value between 8 and 18 and are utilized in oil-in-water emulsions, whereas lipophilic surfactants have an HLB value between 3.5 and 6.

By raising the quantity of surfactant, the particle size of microspheres decreases, resulting in smaller sizes and size distributions. Anionic surfactants include sodium laureth sulfate and sodium dodecyl sulfate, whereas non-ionic surfactants include polysorbate 80, tween 40, tween 20, Span 85, Span 80, Span 20, Poloxamer188, Brij58, polyglycerol polayricinoleate, and sorbitan.

Oil

The ratio of the viscosity of the oil phase to the viscosity of the water phase affects particle size, size distribution, and homogeneity of microspheres. It has been observed that microspheres generated using olive oil have larger particle sizes than microspheres prepared with liquid paraffin because olive oil has a higher viscosity than liquid paraffin oil. Various oils are utilized in the manufacture of microspheres using the emulsification/gelation technique. Examples include liquid paraffin, soya bean oil, olive oil, sunflower oil, castor oil, groundnut oil, rapeseed oil, and rapeseed methyl esters.

Crosslinkers

The most frequent crosslinkers for microsphere preparation are Ca2+, Sr2+, and Ba2+ ions.

However, Sr2+ and Ba2+ ions are somewhat poisonous, but Ca2+ ions are non-toxic, hence Ca2+ ions are often utilized crosslinkers in the creation of microspheres. Agglomeration of microspheres occurs at low Ca2+ ion concentrations. The microsphere's entrapment effectiveness improves marginally as the concentration of Ca2+ ions increases. However, after reaching the optimal concentration of crosslinker, adding more crosslinker reduces entrapment efficiency owing to crosslinker overload. Examples include glutaraldehyde, sulfuric acid, and calcium carbonate.

Solvent

Solvents are most commonly employed while producing microspheres by solvent evaporation. Examples include chloroform, dichloromethane (DCM), ethanol, acetonitrile, polyvinyl alcohol (PVA), methylene chloride, and methanol.

EVALUATION TECHNIQUES

Characteristics

Characterizing these microparticulate carriers is an essential phenomena since it helps build a long-lasting and acceptable carrier for protein, medication, or antigen delivery. Each microsphere has a unique microstructure. These microstructures determine the carrier's release and stability.

Particle size and shape

The most popular techniques for photographing microspheres are conventional light microscopy (LM), confocal fluorescence microscopy, and scanning electron microscopy (SEM). These methods can be used to identify the shape and exterior structure of microspheres. Conventional LM allows for control over coating settings in the case of double-walled microspheres. The microsphere's architecture may be seen before and after coating, and the difference can be assessed microscopically. In contrast to LM, SEM gives better resolution. SEM: SEM enables for research of microsphere surfaces and, when particles have been cross-sectioned, it may also be utilized to investigate double-walled systems. [40] Confocal Fluorescence Microscopy: Confocal fluorescence microscopy is used to study the structure of many walled microspheres. In addition to experimental approaches, laser light scattering and multi-size Coulter counters can be used to characterize the size, shape, and morphology of microspheres. [41]

Angle of contact

The angle of contact influences microspheres' wetting properties in terms of hydrophobicity and hydrophilicity. This thermodynamic feature is specific to a solid material and is influenced by the existence of an absorbed component. The angle of contact is measured at the solid-air-water interface. To quantify the growing and decreasing angle of contact, a droplet is placed in a circular cell put above the objective of an inverted microscope. The contact angle is measured at 200°C within a minute after the deposition of microspheres. [42]

Attenuated total reflectance Fourier transform infrared (FT-IR) spectroscopy

FT-IR measures the degradation of the carrier system's polymeric matrix, and the alternating total reflectance (ATR) of the microspheres is calculated. A beam of infrared light is delivered through the ATR crystal in such a way that it reflects several times through the sample, yielding IR spectra mostly of surface material. Together, ATR-FTIR offers information regarding the surface composition of the sample microspheres.

Density determination

The multi-volume pycnometer is used to measure the density of microspheres. A cup contains an accurately weighed sample of microspheres, which is subsequently placed in a multi-volume pycnometer. At constant pressure, helium gas is put into the chamber and allowed to expand. Expansion of the helium gas lowers the pressure within the chamber, and two successive observations of pressure reduction at different beginning pressures are recorded. The sample microsphere's volume and density are calculated using these two pressure values.

Electron spectroscopy for chemical analysis (ESCA)

ESCA determines the surface chemistry of microspheres. ESCA also determines the atomic composition of the microsphere's surface and the surficial breakdown of biodegradable microspheres by producing spectra using electron spectroscopy. It is also known as X-ray photoelectron spectroscopy.

Surface carboxylic acid residue

Radioactive glycine is used to detect surface carboxylic acid residues. Radioactive glycine conjugates are created by a chemical reaction between c14 - glycine ethyl ester hydrochloride and sample microspheres. The glycine residue is coupled with the water-soluble condensing 1-ethyl-3 (3-dimethyl aminopropyl) carbodiimide (EDAC). The radioactivity of the conjugate is then determined using a liquid scintillation counter method. Thus, the carboxylic acid residue may be compared to the standard and conclusions formed appropriately. The free carboxylic acid residue can be utilized to determine if the microspheres are hydrophobic, hydrophilic, or any other form of derivative.

Isoelectric point

To estimate the isoelectric point, an equipment called as micro electrophoresis is employed, which examines the electrophoretic mobility of microspheres. The mean velocity for each pH value ranging from 3 to 10 is computed by monitoring the duration of particle movement across a 1-mm distance. This data may be used to assess the particle's electrical mobility. The electrophoretic mobility can be attributed to these three parameters: surface contained charge, ionizable behavior, or ion absorption nature of the microspheres.

Surface amino acid residue

The radioactive c14-acetic acid conjugate is utilized to determine surface-associated amino acid residues. The amino acid residue is measured indirectly by first measuring the carboxylic acid residue using a liquid scintillation counter. EDAC is utilized to condense the amino group and the c14-acetic acid carboxylic acid residue. The indirect estimate approach is used to quantify the free amino or carboxylic acid residues by detecting the radioactivity of c14 glycine ethyl ester hydrochloride, which contains acetic acid or glycine conjugates.

Capture efficiency

The capture effectiveness of the microspheres is measured by letting washed microspheres into the lysate. The lysate is then examined as indicated in the monograph to determine the active components in the formulation. The percentage encapsulation efficiency is obtained using the following equation:

% Entrapment=Actual content/Theoretical content×100.

In vivo methods

In vivo techniques are used to examine the permeability of intact mucosa. These strategies take use of the organism's biological reaction on a local or system level. Some of the first and most basic investigations of mucosal layer permeability were based on the systemic pharmacological effects of medicines following ingestion or absorption into the oral mucosa. However, animal models, buccal absorption assays, and corneal perfusion chambers are now the most often used approaches for evaluating drug permeability.

Animal models

A range of substances are tested in animal models to research the mechanisms and utility of permeation enhancers or to evaluate a set of formulations. Several animal models have been identified, including dogs, rats, rabbits, cats, hamsters, pigs, and sheep. The technique entails anaesthetizing the animal and administering the dose form for which the investigation is to be conducted. Rats' esophagus is ligated to limit absorption channels other than the oral mucosal layer. The absorption rate is calculated by removing and testing blood at various time intervals.

Buccal absorption test

It is well-known for its simplicity and dependability in assessing drug loss in the oral cavity using single and multi-component medication combinations. This test technique determines the structure, contact time, PH, and initial drug concentration of the solution when the drug is held in the oral cavity. [43]

Corneal perfusion chambers

The corneal perfusion chamber method is regarded as extremely effective in the development and testing of ophthalmic medicines. The purpose of this project is to construct and test a modified perfusion chamber that is suited for topical delivery of medicines extracted from corneoscleral preparations while also allowing continuous monitoring of endothelial cell activity. This approach uses a perfusion chamber made of polycarbonate and stainless steel to clamp corneas in a horizontal plane, making it appropriate for topical medication administration. Ultrasonic pachymetry and specular microscopy were used to measure endothelial cell activity during this perfusion. Fluorescein penetration was used to measure epithelial barrier function. Leakage was determined by measuring the penetration of a big protein. By traditional histology, tissue architecture following perfusion was investigated. [44]

In vitro methods

Beaker method

In this procedure, the dosage form is adhered to the bottom of the beaker holding the medium and evenly agitated with an overhead stirrer. The amount of media used varies from 50 to 500 ml, and the stirrer speed ranges from 60 to 300 rpm. A sample is extracted at regular intervals and the amount of drug dissolved in the medium is determined.[45]

Interface diffusion system

Dearden and Tomlinson created the interface diffusion system approach. It contains four sections. Compartment A depicts the oral cavity with a suitable concentration of medication in a buffer. Compartment B represents the buccal membrane and contains 1-octanol, whereas compartment C represents bodily fluids and includes 0.2 M HCl. The compartment D represents protein binding and includes 1-octanol. Before usage, the aqueous phase and 1-octanol

were saturated with one another. Samples were drawn and returned to compartment A using a syringe. As a result, medication concentrations in various cavities of the human body are evaluated by examining samples from all four compartments.

Modified keshary chien cell

A customized equipment was created in the laboratory. It was made out of a Keshary Chien cell with distilled water (50 ml) as the dissolving medium and heated to 370°C. Most Trans Membrane Drug Delivery Systems are stored in a glass tube with a 10# sieve at the bottom, which is then reciprocated in the dissolution fluid at a rate of 30 strokes per minute, measuring the rate of dissolution of the drug delivery system.

Dissolution apparatus

To analyze in vitro drug release patterns, a standard USP or BP dissolving equipment is employed, which includes both spinning parts (paddle 41, 42, 43 and basket 44, 45). The dissolution media employed in the study ranges from 100 to 500 cc, with rotation speeds ranging from 50 to 100 rpm.

Other methods

A few alternative approaches, such as plexiglass sample blocks put in flasks 46 and the agar gel method, have also been described. Although numerous ways have been documented, the optimum approach is one in which the sink state is maintained and the dissolution period in vitro mimics the dissolution time in vivo.

CONCLUSION

Microspheres have developed as a valuable medication delivery technology for controlling and directing drug release. They provide various benefits, including greater bioavailability, lower dose frequency, increased patient compliance, and less systemic adverse effects. Microspheres may be made from natural and synthetic polymers utilizing a variety of processes, including solvent evaporation, spray drying, ionic gelation, and phase separation.

Microspheres' flexibility makes them suitable for a wide range of pharmaceutical applications, including oral, parenteral, ophthalmic, nasal, and targeted drug delivery systems. Various types of microspheres, including bioadhesive, magnetic, floating, radioactive, and polymeric microspheres, have demonstrated promise therapeutic effectiveness. Despite their numerous advantages, microspheres have certain drawbacks, including high production costs, repeatability challenges, and potential toxicity from polymer breakdown products. However, ongoing research and developments in polymer science and formulation processes are expected to overcome these constraints. As a result, microspheres are a viable and successful strategy for developing innovative drug delivery systems, with important implications for future pharmaceutical and biological applications.

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