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Review Article

Gastro Retentive Microspheres-Drugs for Parkinson's Disease

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Abstract

Microspheres are small micron size particles ranging from 1 micron to 1000 microns and are free flowing particles. These are prepared to acquire prolonged and controlled drug delivery to enhance the bioavailability, stability, and target specific sites. These are made up of natural or synthetic polymers and these are of various types. In this review majorly three types of microspheres are discussed namely mucoadhesive or buccoadhesive microspheres, magnetic microspheres, and floating microspheres. General methods of preparation techniques like single emulsion, double emulsion, polymerization, solvent extraction, phase separation or coacervation, spray dryings or pray concealing, orifice ionic gelation method. Microspheres evaluation methods include flow properties, Swelling index, isoelectric point, *in vitro* dissolution test, ATR FTIR. Advantages, disadvantages, and their applications are discussed in detail. A note on Parkinsonism is added to the review. The scope to develop microspheres of MAO-B inhibitors and other agents in the treatment of Parkinson's disease is discussed.

Keywords: Controlled release; Mucoadhessive; Floating; Microspheres; MAO-B inhibitors; Parkinson's disease

Introduction

A drug is defined as the active pharmaceutical ingredient that upon formulation into dosage form using excipients is used to deliver drugs into the body to exhibit a therapeutic effect. Drug administration to show the therapeutic effect in the body is known as drug delivery. Various conventional dosage forms are developed that can be classified as oral, buccal, nasal, rectal, sublingual, intramuscular, intravenous, and subcutaneous based on their mode of administration into the body. Each has its advantages and disadvantages. A multidisciplinary approach including polymer science, pharmaceutics, bio-conjugation, and molecular biology to deliver and target the drug in a specific tissue is gaining enormous significance. Many new technologies are under development to overcome issues faced using conventional dosage forms like drug degradation, harmful side effects, bioavailability problems, and problems related to the delivery of the drug to the target site [1].

By using novel advanced technologies and new dosage forms, a Novel drug delivery system (NDDS) has been developed. These are acquiring more importance as the potency of the drug is enhanced and the action of the drug is specific and localized. Major advantages of NDDS are, when the conventional dosage forms are administered the concentration of the drug content levels in the body fluctuates and are not maintained in the therapeutic ranges whereas the novel drug delivery systems once administered, it maintains drug level within the effective therapeutic ranges and utilizes the maximum drug induced into the body, preventing fluctuations and toxicity. Novel drug delivery systems can release the drug in a controlled manner for a specified period and in specific locations, for expensive drugs, these formulations can make the best use of the drug and decrease the production cost [2].

NDDS are classified into different modes based on their technologies used as follows [3].

Targeted drug delivery system

These systems target the specific site in the body and release the drug in a controlled manner for a period so that drug fluctuations are minimized. These systems are exclusively suitable for cancerous tissues in the body that can target the specific tumor tissue and release the drug at the targeted area. The drug becomes active only at the targeted site; hence, the tissues in the other body parts are not affected by the drug, this minimizes side effects and toxicity.

Controlled drug delivery system

These dosage forms are modified in such a way that the drug is released over a long time, maintaining the drug in the effective therapeutic region for prolonged periods. The dosage forms are modified in such a way that the release of the drug can be sustained and maintained for a specific period for slow and controlled release. They can be modified

into delayed release forms from which the drug is released after a lag time and show its action.

Modulated drug delivery system

These are novel drug delivery systems utilizing devices for drug delivery for example inhalers, nebulizers etc. NDDS based on drug delivery systems is classified as

Carrier based drug delivery system

Drug is loaded onto carriers and delivered into the body. Various carriers include nanoparticles, Niosomes, Liposomes, Microspheres, Monoclonal antibodies, and Resealed erythrocytes.

Transdermal Drug Delivery System (TDDS)

These are an integral part of NDDS which are applied on intact skin and are self-sustained, discrete dosage forms that deliver the drug to the systemic circulation through the skin. Various types of TDDS include Sonophorosis, and Osmotic pump drug delivery, and Micro-encapsulation.

This review is focused on one of the novel drug delivery carrier microspheres, its advantages and disadvantages, preparation methods, characterization, and recent advances. Microspheres are freely flowing powders that are small size spherical particles of micron size, ranging from 1 micron to 1000 microns, and are prepared for sustained release formulations. These are biodegradable and are prepared from polymeric or protein matrix and NA these dosage forms have 200 micron size microspheres. These NA is solid or dispersed in the embedded protein or polymeric matrix and releases the drug is aimed to be in a controlled fashion [4,5].

Materials Used For the Preparation of Microspheres

Materials used in the preparation of microspheres are natural and synthetic polymers. Synthetic polymers are used for bio-degradable and non-biodegradable polymers [6–8]. Few examples under polymers are as follows:

Natural polymers

These are obtained from natural sources of carbohydrates such as chitosan, starch, agarose, carrageenan, sources of proteins such as collagen, gelatine, and albumin, and sources of chemically modified carbohydrates such as poly starch and poly dextran [9,10].

Synthetic non-biodegradable polymers

Acrolein, epoxy polymers, polymethyl methacrylate, glycidyl methacrylate [11].

Synthetic biodegradable polymers

Glycosides and lactides and their copolymers, poly anhydrides, poly alkyl cyanoacrylates [12].

Types of Microspheres

The three major types of Gastro retentive microspheres are

Bioadhesive or Mucoadhesive microspheres

In these mucoadhesive polymers like cellulose derivatives, pectin, chitosan, alginate, hyaluronic acids exhibiting adhesive properties are used in preparation. Hence, the microspheres exhibit adhesion properties, when coming in contact with the mucous layer, they get adhere to the mucosal linings in the oral, nasal, ocular, rectal and vaginal mucosa. Thus offering localized drug delivery with enhanced absorption and increases bioavailability due to increased intimate contact with the mucosa, hence having a high surface to volume ratio [13–18].

Magnetic microspheres

Magnetic carriers like chitosan; dextran is incorporated into the formulation of microspheres. The drug can be encapsulated or conjugated onto these microspheres; the magnetic carriers can be localized in the targeted region using a powerful magnetic field outside the body and deliver the drug at the targeted site. This will localize the maximum amount of the drug was injected into the body at the site of action, thus less dose of the drug can be injected to show maximum therapeutic effect [19-23].

Floating microspheres

In this technique, the drug loaded microspheres float on the gastric fluid and remain buoyant for a prolonged period by slowly releasing the drug. These formulations have less bulk density than the gastric fluid hence they float. The microspheres may be the effervescent type that contains swellable polymers like chitosan incorporated with effervescence releasing compounds like sodium bicarbonate and citric acid and thereby upon contact with the gastric fluid releases carbon dioxide, become less dense and float. Non-effervescent floating microspheres have highly swellable hydrocolloids mixed with polymers which swell rapidly when comes in contact with the gastric fluid and become less dense and hence float [23–26].

General methods of preparation of microspheres

- Single emulsion method
- Double emulsion method
- Polymerization
- Solvent extraction
- Phase separation/coacervation
- Spray drying and spray concealing
- The orifice ionic gelation technique

Single emulsion technique

Natural polymers are dissolved or dispersed in an aqueous solution and the dispersed droplets are then mixed with a non-aqueous medium. The obtained emulsion is then cross linked using chemical cross linkers such as glutaraldehyde, formaldehyde, or subjected to heating. Then, this is subjected to centrifugation for isolation of the microspheres. The microspheres thus obtained after centrifugation are subjected to washing and followed by filtration [27].

Double emulsion technique

In this method, initial water in oil (w/o) emulsion is prepared and then this prepared emulsion is dispersed in water continuous phase to get w/o/w emulsion which is suited for water soluble drugs? The aqueous polymer protein solution is dispersed in the chosen lipophilic organic continuous phase. This is subjected to homogenization for emulsion formation. To this primary emulsion, an aqueous solution of Polyvinyl Alcohol (PVA) is added from that w/o/w multiple emulsion is formed. This mixture is subjected to solvent extraction or solvent evaporation, then filtered to obtain microspheres. These prepared microspheres are subjected to washing using an organic solvent to remove traces amounts of oil. The active ingredient can be added to the aqueous protein solution that is encapsulated by the lipophilic continuous phase [28,29].

Polymerization technique

In this method, the Active Pharmaceutical Ingredient (API) is mixed with an aqueous solution of sodium hydroxide using a surfactant. The above mixture is subjected to heating, which results in polymerization. After polymerization, the mixture is kept aside for settling from this mixture microsphere is obtained [30].

Phase separation/Coacervation technique

In this method, the first polymer solution is prepared, so that the drug is added to make it an aqueous solution. Then, to this aqueous solution, phase separation is induced by the addition of co-solvents, salts, or changes the pH of the solution, or adding incompatible polymer. This results in the formation of polymer rich globules that on hardening the process to obtain microspheres [30].

Spray drying/Spray congealing

In this method, the volatile polymer solution is prepared using organic solvents like acetone. The drug is dissolved in the polymer solution and subjected to high speed homogenization for uniform mixing. This solution is then subjected to spray drying in which the drug solution is sprayed like a stream into hot air results in atomization. From a fine mist of spray, the solvent gets evaporated simultaneously leaving the dry particles in the air; the dry particles thus obtained are small spherical microspheres [31].

Solvent extraction technique

In this method, the organic solvent is extracted using a water solution, hence water soluble organic solvents like Isopropyl Alcohol (IPA) are used for the preparation of the polymer solution. Then, the organic phase is removed by extraction of the organic solvent. As the organic solvent used in this method is water soluble, water is used for organic phase extraction and the microspheres thus obtained are filtered and washed. In this method, the hardening time in the formation of microspheres is reduced [32].

The orifice ionic gelation technique

In this method, a homogenous polymer solution is prepared by dissolving a mixture of sodium alginate and Mucoadhesive polymers like pectin, chitosan into the purified water. To this solution, the active ingredient is added and stirred continuously until a viscous dispersion is obtained. A 10% calcium chloride solution is prepared and to this solution, the viscous solution of the drug dispersion is added manually dropwise using 18 size syringe needle gauge. The added droplets are left in the calcium chloride solution for 20 mins to complete the curing process and thereby producing spherical and rigid microspheres. Then, is solution is filtered to obtain microspheres and dried at 45°C for 12 hours [33,34].

Loading of drug

The Active Pharmaceutical Ingredient (API) is loaded onto microspheres by physical entrapment, chemical linkage and surface adsorption in two ways

1. During the preparation of microspheres
2. After the formation of the microspheres.

Evaluation of microspheres

The percentage yield of microspheres. The obtained microspheres are dried thoroughly and accurately weighed and calculated as follows

%Yield=(mass of microsphere obtained/total weight of drug and polymer) × 100

Particle size analysis

Particle size analysis is done using the sieving method, particle size distribution; particle size determination is simultaneously calculated and represented graphically. Based on particle size, the drug release rate can be determined.

Angle of repose

This is done by a conventional fixed funnel method [35]. The free flowing powder is poured from the funnel onto the paper; the funnel is adjusted in such a way that the heap of the poured powder touches the funnel tip. The area of the powder that is fallen on the paper is circled and its diameter is noted and the angle of repose is calculated as follows

The angle of repose (θ)=Tan¯1 h/r

Where,

θ=angle of repose in degrees

h=height of the pile

r=radius of the base

Carr's compressibility index

It is the measurement of flow property and is obtained from the bulk volume and tapped volume.

Carr's compressibility index=(Vb-Vt)/Vb × 100

Where

Vb=bulk volume

Vt=tapped volume

Determination of the drug content, entrapment efficiency

The required amount of the prepared microspheres is weighed accurately and crushed into powder using a mortar and pestle. This is dissolved in 100 ml of water and kept aside for 12 hours. The next day supernatant is collected and filtered and analysed for drug content using a UV spectrophotometer. The drug content and entrapment efficiency can be calculated as the ratio of the actual drug content to the theoretical drug content [36]. Percentage entrapment efficiency=(Actual Drug Content/Theoretical Drug Content) × 100

Swelling index

Accurately weighed amount equivalent to 50 mg of the drug (microspheres) is added to different solvents (100 ml) like distilled water and buffer solutions of pH 1.2, 4.5, and 7.4, kept in an orbital shaker which is maintained at 37°C and shaken occasionally. The weight of swollen microspheres was noted. This is done until equilibrium is attained and no more swelling is seen thereafter. The Swelling Index (SI) is calculated as follows.

SI=We-Wo/Wo

Where,

We=Initial weight of microspheres

Wo=Weight of microspheres at equilibrium swelling in the media

Isoelectric point

The isoelectric point can be determined using a micro-electrophoresis apparatus in which electrophoretic mobility of microspheres can be determined. The mean velocity of particles at different pH values ranging from 3-10 is calculated by measuring the time of particle movement over a distance of 1 mm. The electric mobility of the particle can be determined using the above obtained data [37].

***In vitro* dissolution testing**

In this method, dissolution apparatus USP XXIII is used with the basket at 37°C ± 0.5°C with varying volumes of dissolution media as required from 100 ml–500 ml of varying speed of 50 rpm-100 rpm is set. A sample equivalent to 100 mg microspheres is loaded into the dissolution apparatus and aliquots of samples were periodically withdrawn at regular time intervals and replace with fresh dissolution media is added to maintain sink conditions. The samples collected were analysed at an appropriate wavelength using a UV spectrophotometer [38].

Attenuated Total Reflectance-Fourier Transforms Infrared Spectroscopy (ATR-FTIR)

The ATR-FTIR provides information on the surface composition of the microspheres. It is used for the determination of the degradation of the polymeric matrix of the carrier system and the surface of the microspheres is investigated by measuring ATR [39].

Advantages

- Controlled, sustained, and targeted release from the formulation.
- Avoid gastric irritation and the first pass effect.
- Increased bioavailability because of the small size.
- Dosing frequency or reduction in overall dose in a day.
- Enhanced flow properties and dispersibility.
- Enhanced drug solubility
- Protection of unstable and sensitive drugs.
- Anticancer drugs to the tumour site can be targeted.
- Enhancement of shelf life by preventing degradative reactions.
- Improved patient compliance.

Disadvantages

A common problem with the controlled release dosage form is dose dumping. This is the main disadvantage as the drug quantity in the formulation is high for controlled release, once if the formulation loses its integrity there is a high dose release in the body at once, which leads to toxicity.

These dosage forms have a caution that cannot be crushed or broke or chewed as these are modified release dosage forms.

Sometimes at the injection site embolism can be seen leading to potential toxicity

The reproducibility is less during the formulation process the production costs is also high.

Applications

Oral drug delivery

The film forming nature of the polymers and the pH sensitivity coupled with the reactivity of primary amine groups make microspheres very unique for the formulation of a novel approach for enhanced bioavailability of the drug through oral delivery.

Nasal delivery

As the microsphere formulation has polymers with bioadhesive properties, the formulation when comes in contact with the mucosal linings gets swell easily, increasing the residence time in the nasal mucosa that enhancing the bioavailability of the drug.

Buccal delivery

The polymer's mucoadhesive property acts as an excellent absorption enhancer in the buccal cavity.

Gastrointestinal drug delivery

The polymers like Eudragits having internal cavities used in the preparation of microspheres exhibit floating properties and remain buoyant when coming in contact with the GI fluids and release the drug in a controlled fashion.

Blood flow determination

Here fluorescent microspheres were prepared using polystyrene, polyvinyl toluene. The fluorescent dye enters the swollen microspheres and enters the pores of microspheres. Upon swelling of these microspheres entrap the fluorescent dye and when injected locally get lodged in the capillaries. The fluorescent dye is extracted from the tissue sample is quantified using a spectrofluorometer.

Microspheres in chemotherapy

Microspheres act as carriers in many anticancer treatments, passive targeting through Enhanced Permeability and Retention (EPR) effect and active targeting through ligand coupling receptor [40].

Parkinsonism

Parkinson's disease (PD) is a progressive neurodegenerative disorder in which dopaminergic neurons in the substantia nigra slowly degenerate. Hence, the decrease in dopamine levels occurs, which leads to Parkinson's disease. Motor and non-motor functions both are affected by Parkinson's disease. The support of treatment is Levodopa (LD) but in later stages, stress induced dyskinesia is seen as a side effect. Hence alternative treatments with other drugs are prescribed along with LD. Symptoms of Parkinsonism include involuntary movements, bradykinesia, impaired balance, coordination, tremors, and rigidity. Non-motor symptoms include mood disorders, cognitive impairment, sleep alterations, and hallucinations. Parkinsonism is most commonly seen in people above 60 years of age, and in few members below 20 years of age which is called juvenile Parkinsonism. The chances of occurrence of PD are more in males than females [41]. Causes of Parkinson's disease are age factors, genetic, environmental factors, and sometimes head injuries. Patients whose family members have a history of PD or persons when exposed to chemical toxins such as carbon monoxide, organic solvents such as manganese, and certain pesticides are most likely to have Parkinsonism [42].

In the treatment of PD many medications are available and in severe conditions, sometimes surgery is advised. Medication includes carbidopa levodopa antagonists, monoamine oxidase–B inhibitors (MAO-B inhibitors), Catechol-O-methyl Transferase (COMT) inhibitors, anticholinergic drugs, and amantadine. This review focused on MAO-B inhibitors, which inhibit the breakdown of dopamine in the brain. MAO-B is an enzyme in the brain responsible for dopamine breakdown, thus by inhibiting this enzyme action dopamine in the brain is not metabolized. Examples of MAO-B inhibitors are Selegiline and Rasagiline [43].

Tables 1-3 gives the information regarding microsphere formulations approved, under approval and approval formulation with polymer and their category [44–48].

Table 1: List of microsphere formulations with drug, commercial name and technology employed in the preparation

Drug	Commercial name	Technology
Risperidone	RISPERDOL, CONSTA	Double Emulsion (Oil In Water)
Naltrexone	VIVITROL, LUPRON DEPOT	Double Emulsion (Oil In Water)
Leuprolide	TRENANTONE	Multiple Emulsion
Octreotide	SANDOSTAIN LAR	Phase Separation
Somatropin	NUTROPIN	Cryogenic Spray Drying
Triptorelin	TRELSTAR DEPOT	Phase Separation
Buserelin	SUPRECUR MP	Dispersion method
Lanreotide	SOMATULINE LA	Phase Separation
Bromocriptine	PARLODEL LAR	Spray Drying

Table 2: List of microsphere formulation under approval

Patent Number	Drug Used
CN201110142359	Ketoprofen
CN201110313846	Paclitaxel
CN201210025085	5-Flurouracil
US08455091	Ganciclovir
EPI9980924438	Cimetidine
EP20070808011	Risperidone
CA2217462	Cyclosporine
CA2579533	Irinotecan
DE1999609777	Levenorgesterol
DE1994632867	Doxorubicin

Table 3: List of microsphere formulations approved with polymer and their category

Drug	Polymer	Category
Metformin Hcl	Sodium Alginate	Anti-diabetic
Amoxicillin Trihydrate	Ethyl Cellulose	Antibiotic
Ibuprofen	Sodium alginate	Analgesic
Pioglitazone Hcl	Carbopol934	Anti-diabetic
Captopril	Sodium Alginate, Home, Chitosan, Pectin	ACE Inhibitor
Ketoprofen	Xanthan Gum, Pectin, Sodium alginate	Analgesics
Rasagiline	HPMC	MAO-B Inhibitor
Famotidine	Carbopol, HPMC	Antiulcer
Ketorolac	Eudragit Rs100, Eudragit Rl100	Anti-inflammatory
Selegiline	Sodium alginate	MAO-B Inhibitor

Discussion

As there is no permanent remedy for Parkinson's disease, treatment must be continued. The patient if fails to continue the treatment it leads to death. Hence formulation with controlled, sustained release helps the patient to reduce the dosing frequency and enhance the bioavailability of the drug. Microspheres are one of the best formulation choices, suitable for drugs having controlled and sustained release

properties.

Conclusion

This review article shows that there is a high scope for developing microsphere formulations using novel technologies and combining various strategies used in cell sorting, gene delivery, targeted, effective drug delivery to small tissues and organs in the body. The main scope of microsphere formulations is they can be modified, released at desired rate and site. These formulations can be used in controlled and sustained release rates of the drugs. Furthermore, it shows enhancing bioavailability and protecting the drug from chemical, enzymatic degradation, and preventing the first pass metabolism. Therefore, all these mucoadhesive/buccoadhesive, magnetic and floating microspheres make one of the best choices for developing novel drug delivery systems.

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Compliance with Ethical Standards

This article does not contain any studies with human participants or animals conducted by any author.

Conflict of Interest

The authors declared that they have no conflict of interest.

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