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An updated review on microspheres: a suitable drug carrier in sustained release drug delivery

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Article Info :	Abstract
Article History Received on: 16-03-2022 Revised on : 26-03-2022 Accepted on : 17-04-2022	With advances in biotechnology, genomics, and combinatorial chemistry, a wide variety of new, more potent and specific therapeutics are being created. Because of common problems such as low solubility, high potency, and/or poor stability of many of these new drugs, the means of drug delivery can impact efficacy and potential for commercialization as much as the nature of the drug itself. Thus, there is a corresponding need for safer and more effective methods and devices for drug delivery. Microspheres having particle size in range between 0.1-200 μm , can be delivered by several routes like oral, parenteral, nasal, ophthalmic, transdermal, colonic etc. In future by combining various new strategies, microspheres will find a central place in novel drug delivery, particularly in diseased cell sorting, genetic materials, safe, targeting and effective drug delivery.
	Keywords: Drug release, shell thickness, drug release rate, microsphere, polymer, microsphere.

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Introduction

To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. The development of new delivery systems for the controlled release of drugs is one of the most interesting fields of research in pharmaceutical sciences [1, 2, 3].

A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects [4, 5].

There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. The process of targeting and site specific delivery with absolute accuracy can be achieved by attaching bioactive molecule to liposome, bioerodible polymer, implants, monoclonal antibodies and various particulate. One such approach is using microspheres as carriers for drugs. Microsphere can be used for the controlled release of drugs, vaccines, antibiotics, and hormones [6, 7].

The goal of this controlled drug delivery system is to provide a therapeutic amount of drug at the required site promptly and after achieving therapeutic level, to maintain the desired drug concentration at the site of action [8].

Oral route is the most convenient and commonly employed route for most of the drugs. Some Drugs that are easily absorbed by the G.I.T. and having short $t_{1/2}$ are eliminated quickly from the blood circulation. Controlled Drug delivery System can avoid the problems of conventional drug delivery system by releasing the drug slowly into the G.I.T. and maintain a constant drug concentration in the serum for longer period of time [9].

The number and chemical diversity of drugs has increased, new and updated strategies are required to be developed for orally active therapeutics. Thus, gastro retentive dosage forms, which prolong the residence time of the

drug in stomach and improve their bioavailability, have been developed [10, 11].

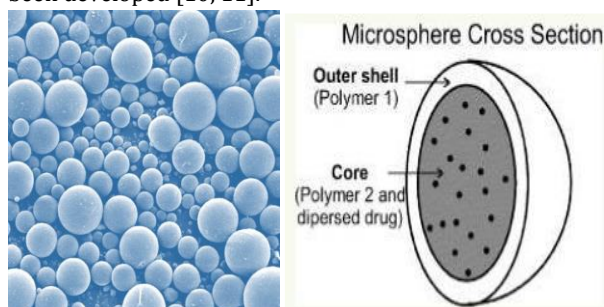


Figure 1: Microsphere

Limitations of microspheres [12,13,14]

- ★ Controlled release rate of microspheres may vary due to certain factors like intrinsic or extrinsic factors may be food, rate of transit through gut, mucin turnover rate etc.
- ★ There are differences in release from one to another dosage form.
- ★ Low drug loading is done in case of parenteral microspheres.
- ★ In case of parenteral application of microspheres it is difficult to remove carrier completely from the body.
- ★ Parental delivery of microspheres may interact or form complex with blood components.
- ★ The release of formulation can be modified.
- ★ Any loss of integrity in release pattern may cause potential toxicity.
- ★ Controlled release dosage form cannot be crushed

A number of different substances both Biodegradable and Non-biodegradable have been investigated for the preparation of microspheres. This includes polymer of Natural and Synthetic origin and also Semi synthetic polymers.

1. **Natural Polymer:** These polymers are obtained from different sources like Protein, Carbohydrate and chemically modified Carbohydrates [15].

Protein: Albumin, Gelatin, Collagen

Carbohydrate: Starch, Agarose, Carrageenans

Chemically Modified Carbohydrate: Poly acryl Dexron, Poly acryl Starch

2. **Synthetic Polymer:**

Biodegradable Polymers: Polyanhydride, Polyalkyl cyano acrylates, Lactides and Glycolides and copolymer [16].

Non-Biodegradable Polymers: Acrolein, Glycidyl Methacrylates, Epoxy Polymer etc.

Ideal characteristics of Carrier [17]

Carrier provides longer duration of action to drug molecule.

It provides stability to the drug molecule

It provides protection to drug.

It provides water solubility.

It provides sterilizability to drug.

Method of Preparation of microspheres [18]

The choice of method of preparation depends upon the nature of Drug, nature of Polymer and duration of therapy. There are several techniques to prepare microspheres:

1. Single Emulsion Technique

Heat Stabilization Method

Chemical Stabilization Method

Ionic Chelation Method

2. Double Emulsion Technique [19]

Polymerization Technique

Normal Phase (Bulk, Suspension, Emulsion)

Interfacial Phase

Spray Drying Technique

Solvent extraction Technique

Phase separation Co-Acervation Technique

Solvent Evaporation Technique

Criteria for Microsphere Preparation

Incorporation of solid, liquid or gases into one or more polymeric coatings can be done by micro encapsulation technique. The different methods used for various microspheres preparation depends on particle size, route of administration, duration of drug release and these above characters related to rpm, method of cross linking, drug of cross linking, evaporation time, coprecipitation etc [20].

Preparation of microspheres should satisfy certain criteria [21]

1. The ability to incorporate reasonably high concentrations of the drug.
2. Stability of the preparation after synthesis with a clinically acceptable shelf life.
3. Controlled particle size and dispersability in aqueous vehicles for injection.
4. Release of active reagent with a good control over a wide time scale.
5. Biocompatibility with a controllable biodegradability and
6. Susceptibility to chemical modification

Types of Microspheres

Bioadhesive microspheres

Microspheres loaded with drug adhering to the mucosal layer present in buccal, ocular, rectal, nasal, etc., using the adhering property of the water-soluble polymers are known as bioadhesion. These kinds of microspheres show properties such as close exposure to the absorption area. It also shows extended residence time at the targeted area and hence, produces a better therapeutic efficacy, for example, ophthalmic administration of Acyclovir, nasal administration of insulin, and buccal administration of nifedipine through bioadhesive microspheres [22].

Magnetic microspheres

This kind of delivery system is very much important which localizes the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller

amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. The different types are therapeutic magnetic microspheres and diagnostic microspheres [23].

Therapeutic magnetic microspheres

It is used to deliver chemotherapeutic agent to liver tumor. Drugs like proteins and peptides can also be targeted through this system [24].

Diagnostic microspheres

It can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming Nano size particles supramagnetic iron oxides [25].

Floating microspheres

In floating microspheres the bulk density is less than the gastric fluid therefore it remains buoyant in stomach without affecting on gastric emptying rate. Drug is released slowly at the desired rate of the site. It also reduces chances of striking and dose dumping Produces [26].

There are two types of floating microspheres:

1. Effervescent microspheres
2. Non-effervescent microspheres.

Radioactive microspheres

The size range of radioembolization therapy microspheres is 10–30 nm which is greater than the diameter of the capillaries and is trapped in the first capillary bed. These microspheres are injected in the arteries leading to the targeted tumor tissues [27].

So in all these situations radioactive microspheres without harming remaining tissues focus on a particular site and transport high radiation dose. The various types of radioactive microspheres are α emitters, β emitters, and γ emitters [28].

Polymeric microspheres

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and synthetic polymeric microspheres [29].

Biodegradable polymeric microspheres

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also Bio adhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium, results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is, in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release [30].

Synthetic polymeric microspheres

The interest of synthetic polymeric microspheres are widely used in clinical application, moreover that also

used as bulking agent, fillers, embolic particles, drug delivery vehicles etc. and proved to be safe and biocompatible. But the main disadvantage of these kind of microspheres, are tend to migrate away from injection site and lead to potential risk embolism and further organ damage [31].

Radioactive microspheres Radio embolization therapy microspheres sized 10-30 nm are of larger than capillaries and gets trapped in first capillary bed when they come across. They are injected to the arteries that lead to tumor of interest. So these radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are α emitters, β emitters, γ emitters [32].

Porous microspheres

Porous microspheres either have external surface pores or internal pores in the core where the active pharmaceutical ingredient can be dispersed or dissolved. The pores are formed by porogens which leach out completely later in process, for example, of porogen used is effervescent salts such as ammonium bicarbonate, hydrocarbon waxes, inorganic salts such as sodium chloride, carbohydrates, ice, linear polymers, gelatin, and sugar. The outer framework is fabricated with materials such as calcium carbonate (CaCO_3), mesoporous silica, hydroxyapatite, and biodegradable porous starch foam, for example, delivery of proteins and peptides [15, 16].

Mucoadhesive microspheres Mucoadhesive microspheres which are of 1-1000 μm in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it and coupling of mucoadhesive properties to microspheres has additional advantages, *e.g.* efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions and antibodies, etc. on the surface of the microspheres. Mucoadhesive microspheres can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs [19].

Limitation

The costs of the materials and processing of the controlled release preparation, are substantially higher than those of standard formulations. Controlled release rate of microspheres may vary due to certain factors like intrinsic or extrinsic factors may be food, rate of transit through gut, mucin turnover rate etc. The fate of polymer matrix and its effect on the environment. There are differences in release from one to another dosage form. Any loss of integrity in release pattern may cause potential toxicity.

The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers. Reproducibility is less. Low drug loading is done in case of parental microspheres. Process situations like change in temperature, pH, solvent addition, and evaporation/agitation may influence the stability of core particles to be encapsulated. Parental delivery of microspheres may interact or form complex with blood components. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents [18].

Ingredients of Microspheres

Polymers

In microsphere formulation, most commonly biodegradable and non-biodegradable variety of polymers are used by researchers. The polymers which are used in microspheres preparation are classified into different types as Natural and Synthetic. Before choosing the polymer for the microsphere formulation, we need to consider a few parameters such as nontoxicity, biocompatibility, biodegradability, and easy availability of polymers. It should be biocompatible, biodegradable, non-toxic, and easily available. These polymers which pass all parameters for their selection have many advantages like they increase the residence time of the drug in the body because of which we get better bioavailability of drug compared to conventional drug delivery system. Examples of natural polymers include Albumin, Collagen, and Gelatin which are proteins while Agarose, Carrageenan, Chitosan, and Starch are carbohydrates whereas 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) form the other class. Examples of synthetic polymers fall under three category where Lactides, Glycolides and their copolymers, polyanhydrides, poly alkyl cyanoacrylates are biodegradable in nature while Glycidyl methacrylate, Acrolein, Epoxy polymers, and polymethyl methacrylate are non-biodegradable and finally, polysebacic anhydrides, Poly Esters/Poly Lactides, poly orthoesters, polycarbonates, polylactic glycolic acid (PLGA), polycaprolactones, polyphosphazenes, ethylcellulose, Eudragit L100, Eudragit S100, HPMC, Eudragit RS100, and Eudragit RL100 form the other class [18-19].

Surfactant

In microsphere formation surfactant play an important role during emulsification and extrusion process. Surfactants play an important role by lowering the interfacial tension between hydrophilic and hydrophobic molecules, because of which stable emulsion is formed. Use of surfactant leads to the formation of discrete microspheres by preventing the emulsion droplets from coalescing. Hydrophilic-lipophilic balance (HLB) indicator is used for selection of proper emulsifier. Hydrophilic surfactants have HLB value in the range of 8-18 and are

used for oil in water emulsion while emulsifiers with HLB value in the range of 3.5-6 are known as lipophilic surfactants. The particle size of microspheres is decreased by increasing the concentration of surfactant because of which smaller size and size distribution of microspheres were formed. Examples are Sodium Laureth Sulfate, Sodium dodecyl sulfate as anionic surfactants and Polysorbate 80, Tween 40, Tween 20, Span 85, Span 80, Span 20, Poloxamer188, Brij58, Poly Glycerol Polyricinoleate, and Sorbitan as non-ionic surfactants [20-21].

Oil

Particle size, size distribution, and uniformity of microspheres are affected by the ratio of viscosity of the oil phase to the viscosity of the water phase, for example, It is reported that the particle size of microspheres are more which were prepared using olive oil compared to microspheres which were prepared using liquid paraffin as the viscosity of olive oil is higher compared to liquid paraffin oil. There are various types of oils which are used in the fabrication of microspheres during emulsification/gelation method. Examples are liquid paraffin, soya bean oil, olive oil, sunflower oil, castor oil, groundnut oil, rapeseed oil, and rapeseed methyl esters [22].

Crosslinkers

Most commonly used crosslinkers for microspheres preparation are Ca^{2+} , Sr^{2+} , and Ba^{2+} ions. However, Sr^{2+} and Ba^{2+} ions are mildly toxic and Ca^{2+} ions are non-toxic because of which Ca^{2+} ions are widely used crosslinkers for preparation of microspheres. At low concentration of Ca^{2+} ions agglomeration of microspheres takes place. By increasing Ca^{2+} ions concentration entrapment efficiency of microsphere slightly increases. However, after optimum concentration of cross-linker if more crosslinker is added the entrapment efficiency decreases due to overloading of crosslinker. Examples are glutaraldehyde, sulfuric acid, and calcium carbonate [23-24].

Solvent

Solvents mostly used when microspheres are prepared using a solvent evaporation method. Examples are Chloroform, Dichloromethane (DCM), Ethanol, Acetonitrile, Polyvinyl alcohol (PVA), Methylene chloride, and Methanol [25-26].

CRITERIA FOR MICROSPHERE PREPARATION

By micro encapsulation technique the Incorporation of liquid, solid or gases into one or more polymeric coatings can be done. The various methods that are used for the preparation of various microspheres depends on the route of administration, particle size, drug release duration & these above characters related to the rpm, the cross linking method, drug of cross linking, co precipitation, the evaporation time, etc. The preparation of microspheres should satisfy certain criteria:

- ✓ The release of active reagent with the good control over the wide time scale.

- ✓ It should have the ability to incorporate reasonably high concentrations of the drug.
- ✓ It should have the susceptibility to chemical modification.
- ✓ The stability of the preparation after synthesis with the clinically acceptable shelf life.
- ✓ The biocompatibility with the controllable biodegradability.
- ✓ The controlled particle size & dispersability in the aqueous vehicles for injection. [27,28,29]

Methods of Preparation

Spray drying

In this technique coating polymer is first to dissolve/dispersed in an organic solvent such as acetone and DCM the drug then incorporated into polymeric solution along with high-speed homogenization [40]. The resultant mixture then atomized in a stream of hot air. Atomization leads to the formation of fine mist or droplets from which organic solvent evaporates immediately which leads to the formation of microspheres in a size range of 10 µm–100 µm [30].

Simple Emulsion Technique

The microparticulate carriers of natural polymers, i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in the non-aqueous medium e.g., oil. In the second step of preparation, cross-linking can be achieved either by means of heat or by using the chemical cross linkers. The chemical cross-linking agents used include glutaraldehyde, formaldehyde, terephthaloyl chloride, diacid chloride, etc. Cross-linking by heat is affected by adding the dispersion to previously heated oil. Heat denaturation is however, not suitable for the thermolabile drugs while the chemical cross-linking suffers disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation.

Double emulsion technique

This technique involves the preparation of double emulsion either w/o/w or o/w/o type. The Aqueous solution contains the drug which is dispersed in the organic phase. The organic phase containing coating polymer encapsulates the drug present in the dispersed aqueous phase and leads to the formation of primary emulsion. Then, this primary emulsion undergoes homogenizing or sonicating before adding into an aqueous solution of PVA to form a secondary emulsion, and then prepared microspheres filtered and dried in desiccator [31].

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 [32].

Spray congealing

In this technique, the drug is dissolved/dispersed in polymeric solution, that is, lipophilic polymer like wax. The hot molten solution then sprayed to form fine droplets into a vessel that already kept in carbon dioxide ice bath [33].

Solvent extraction

This method involves the removal of the organic phase by extraction of the organic solvent through using hydrophilic organic solvents like iso-propyl-alcohol. Organic phase then extracted using water, this process leads to a decrease in the hardening time of microspheres [33].

Quassi emulsion solvent diffusion

Using this technique microsphere 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 microspheres then filtered, washed, and dried in a vacuum oven for 24 h [31].

Cross-linking agent method

In this method, cross-linking agent is used for fabrication of the microspheres. The first specific concentrated polymeric solution has been made in an aqueous medium then added in continuous phase containing oil and specific concentration of surfactant to form w/o emulsion, followed by drop by drop incorporation of an aqueous solution of cross-linker coupled with continuous agitation and then permitting for the stiffening of the surface of microspheres. Resultant microspheres then washed and dried [30].

Ionic gelation method

In this method, suspension of hydrophilic polymer along with drug is complexed with multivalent cation, that is, calcium chloride resulting in the formation of highly viscous gel spheres. An iridescent suspension is obtained. This suspension is centrifuged to get the uniform size of microspheres. Microspheres are then washed and dried at room temperature for 24 h [37, 38].

Evaluation Techniques

Physicochemical evaluation

Particle size and shape

Particle size can be determined by optical microscopy with the help of calibrated eyepiece micrometer. The size of around 100 microspheres is measured and their average particle size is calculated

$$D_{\text{mean}} = \frac{\sum n d}{\sum n}$$

Where,

n = number of microspheres checked;

d = Mean size

Density determination

The density of microspheres can be measured by using a multi volume pycnometer. Accurately weighed sample in a cup is placed into the multi volume pycnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume and hence the density of microsphere carriers is determined [21].

Isoelectric point

The isoelectric point can be measured by using micro electrophoresis apparatus by measuring electrophoretic mobility of microspheres. The mean velocity at different pH value from 3-10 is calculated by measuring the time of particle movement over a distance of 1 nm²⁸.

Angle of contact

The angle of repose θ of microspheres, which measures the resistance to particle flow is calculated as where, $2h/d$ is the surface area of free standing height of microspheres heap that is formed after making microspheres flow from the glass funnel³¹.

Electron spectroscopy for chemical analysis

The surface chemistry of microspheres can be determined by using electron spectroscopy for chemical analysis (ESCA). ESCA provides a means for the determination of atomic composition of the surface. The spectra obtained using ESCA can be used to determine the surface degradation of biodegradable microspheres²⁹.

Fourier transform infrared spectroscopy

Drug polymer interaction and degradation of microspheres can be assessed by FTIR.

Drug entrapment efficiency

Weighted amount of microsphere are taken and crushed. Then dissolved in buffer solution with the help of stirrer and filtered. The filtrate is assayed by UV spectrophotometer at particular wavelength by using calibration curve²⁵.

$$\text{Drug Entrapment efficiency} = \frac{\text{Actual weight of microspheres}}{\text{Theoretical weight of drug and polymer}} \times 100$$

Percentage yield

It is calculated as the weight of microspheres obtained from each batch divided by total weight of drug and polymer used to prepare that batch multiplied by 100.

Swelling index

It is determined by measuring the extent of swelling of microspheres in a particular solvent. The equilibrium swelling degree of microspheres is determined by swelling

of 5 mg of dried microspheres poured in 5 ml of buffer solution overnight in a measuring cylinder. It is calculated by given formula [28].

$$\text{Swelling index} = \frac{\text{Mass of swollen microsphere} - \text{Mass of dried microspheres}}{\text{Mass of dried microspheres}} \times 100$$

In vitro methods

This method allows the determination of release characteristics and permeability of a drug through membrane. *In vitro* method is employed as a quality control procedure in pharmaceutical production and in product development etc. Sensible and reproducible release data derived from physically, chemically and hydro dynamically defined conditions are necessary [23].

Beaker method

In this method Dosage form is made to adhere at the bottom of beaker containing the medium and stirred uniformly using overhead stirrer. Volume of the medium used in the literature for the studies varies from 50-500 ml and the stirrer speed from 60-300rpm [22].

Interface diffusion method

This method was developed by Dearden and Tomlinson. It consists of four compartments. Compartment A represents the oral cavity, and initially containing an appropriate concentration of drug in buffer. The compartment B representing the buccal membrane, containing 1-octanol, and compartment C representing body fluids, containing 0.2M HCl. The compartment D represents protein binding, also containing 1-octanol. Before use, the aqueous phase and 1-octanol are saturated with each other. Samples are withdrawn and returned to compartment A with a syringe²⁸.

Modified keshary chien cell method

It utilizes specialized laboratory designed apparatus. It comprises of a Keshary Chien cell containing distilled water (50 ml) at 37 °C as dissolution medium. TMDDS (Trans Membrane Drug Delivery System) is placed in a glass tube fitted with a 10# sieve at the bottom which reciprocates in the medium at 30 strokes per minute²¹.

Dissolution apparatus method

Standard USP or BP dissolution apparatus have been used to study *in vitro* release profiles using both rotating elements Paddle and basket. Dissolution medium used for the study varies from 100-500 ml and speed of rotation from 50-100rpm⁷.

In vivo method

Method for studying the permeability of intact mucosa comprises of technique that gives the biological response of the organism locally or systemically and those that involve direct local measurement of uptake or accumulation of penetrate at their surface. The most widely used methods of *in vivo* studies include using animal models, buccal absorption tests [8].

Animal models

It is used mainly for the screening of series of compounds, investigating the mechanisms and evaluating a set of formulations. Animal model such as dogs, rats, pigs and sheep etc. are reported. Generally the procedure involves anesthetizing the animal followed by administration of dosage form, withdrawing blood at different time intervals and analysing [11].

In vitro/in vivo correlation

Correlations between *in vitro* dissolution rates and the rate and extent of availability as determined by blood concentration and or urinary excretion of drug or metabolites are referred to as "*in vitro-in vivo* correlation". Such correlations allow one to develop product specifications with availability [14].

APPLICATIONS OF MICROSPHERES IN INDUSTRY [16, 21, 29]

New applications for microspheres are discovered every day, below are just a few:

Assay - Coated microspheres provide measuring tool in biology and drug research.

Buoyancy - Hollow microspheres are used to decrease material density in plastics (Glass and polymer).

Ceramics - Used to create porous ceramics used for filters (microspheres melt out during firing, Polyethylene Microspheres).

Cosmetics - Opaque microspheres used to hide wrinkles and give color, Clear microspheres provide "smooth ball bearing" texture during application (Polyethylene Microspheres).

Drug delivery - As miniature time release drug capsule made of, for example, polymers. A similar use is as outer shells of micro bubble contrast agents used in contrast-enhanced ultrasound.

Electronic paper - Dual Functional microspheres used in Gyricon electronic paper.

Personal Care - Added to Scrubs as an exfoliating agent (Polyethylene Microspheres).

Spacers - Used in LCD screens to provide a precision spacing between glass panels (glass).

Standards - monodisperse microspheres are used to calibrate particle sieves, and particle counting apparatus.

Retroreflective - added on top of paint used on roads and signs to increase night visibility of road stripes and signs (glass).

Thickening Agent - Added to paints and epoxies to modify viscosity and buoyancy.

Cancer research: One useful discovery made from the research of microspheres is a way to fight cancer on a molecular level. According to Wake Oncologists, "SIR-Spheres" microspheres are radioactive polymer spheres that emit beta radiation. Physicians insert a catheter through the groin into the hepatic artery and deliver millions of microspheres directly to the tumor site. The SIR Spheres microspheres target the liver tumors and spare healthy liver tissue. Cancer microsphere technology is the latest trend in cancer therapy. It helps the

pharmacist to formulate the product with maximum therapeutic value and minimum or negligible range side effects. A major disadvantage of anticancer drugs is their lack of selectivity for tumor tissue alone, which causes severe side effects and results in low cure rates. Thus, it is very difficult to target abnormal cells by the conventional method of the drug delivery system. Microsphere technology is probably the only method that can be used for site-specific action, without causing significant side effects on normal cells.

Recent Applications of Controlled Release Microspheres

Controlled-Release Vaccine

Vaccination has been highly successful for controlling or even eradicating many important types of infectious diseases, and new or improved vaccines are being heavily investigated for AIDS, hepatitis B, anthrax, and SARS. A frequent problem is the need for repeated administrations—usually KYE KYOON "KEVIN" KIM AND DANIEL W. PACK injections—to ensure long-lasting immunity. For example, the current anthrax vaccine requires a series of boosters at 2 and 4 weeks, and at 6, 12, and 18 months following the first inoculation; and the Recombivax H-B vaccine for hepatitis B—required for most healthcare workers in the U.S.—is administered in three injections at 0, 1, and 6 months. The need for multiple injections poses a serious problem for patients in developing countries with limited access to medical care, where awareness is lacking, or for transient populations [33].

Table 1: List of Marketed Microsphere Drug Products

Drug	Commercial Name	Company	Technology
Risperidone	RISPERDAL® CONSTA®	Janssen®/Alkermes, Inc.	Double emulsion (oil in water)
Naltrexone	Vivitrol®	Alkermes	Double emulsion (oil in water)
Leuproli de	Lupron Depot® Enantone Depot® Trenantone® Enantone Gyn	TAP Takeda Takeda	Double emulsion (water in oil in water)
Octreotide	Sandostatine® LAR	Novartis	Phase separation
Somatropin	Nutropin® Depot	Genentech/Alkermes	Alkermes ProLase® Technology (Cryogenic spray drying)

Triptorelin	Trelstar™ depot Decapeptyl® SR	Pfizer Ferring	Phase separation
Buserelin	Suprecur® MP	Sanofi-Aventis	N/A
Lanreotide Ipsen	Somatulin® LA	Ipsen-Beaumont	Phase separation
Minocycline	Arestin®	Orapharma	N/A

Conclusion

From this review, we could conclude that various types of preparation methods along with its pharmaceutical application are being used for Microspheres as a drug delivery system for delivering the definite amount of medications in a controlled manner. By developing newer delivery technologies, it can give much more therapeutic and commercial benefits by improving the safety and reducing the toxicity. Today, many pharmaceutical companies are introducing their newer products to the market which may give good therapeutic response when compared with conventional drug delivery. The development of upcoming drug delivery technologies can be applied for solving problems regarding pharmaceutical, biopharmaceutical and pharmacokinetic aspects thus, the delivery systems are growing and accepting worldwide for its better utilization.

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Conflict of Interest

The authors report no conflict of Interest.

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