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Review on Microspheres as Drug Carriers for Controlled Drug Delivery

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Abstract

Microspheres are organic or inorganic spherical particles with a diameter of 1–1000 µm. These materials can encapsulate drugs or bioactive molecules and release them in a controlled way. Biodegradable polymers are frequently used for the development of microsphere matrixes such as polylactic acid and copolymer of lactic acid and glycolic acid. Apart from them, there is an extensive range of microspheres prepared from albumin, albumin dextran sulfate, and fibrinogen. Administration of medication via micro particulate systems is advantageous because microspheres can be ingested or injected; they can be tailored for desired release profiles and used for site-specific delivery of drugs and in some cases can even provide organ-targeted release. Microspheres in drug delivery are used for targeted as well as prolonged drug release in the diseased area. It also protects the unstable or pH-sensitive drugs before and after the administration. In this review we have discussed about advantages, disadvantages, methods of preparations and evaluation and types of microspheres.

Keywords: Microsphere, Biodegradable polymers, Polymer Microsphere, Drug Release

Introduction

Microspheres can be characterized as solid, approximately spherical particles with a diameterhaving between 1–1000µm, including dispersed drugs in certain solution or microcrystalline shape. Both the terms microcapsules and microspheres are often used as synonyms.[1-2] Medication That is simply transmitted in from gastrointestinal tract (GIT) and also has a short half-life is immediately destroyed from circulatory system in the blood. The oral sustained or controlled release (CR) have also been developed to avoid this problem, as that will Slowly discharge the substance into the GIT and retain a steady medication intensity in the plasma for a prolonged time period. A suitable dosage formulation is one that reaches the required plasma therapeutic Drug concentration and remains constant throughout the treatment period. This can be achieved by delivering a traditional dosage type in a fixed dose and at a specific frequency.[3] A benefit they are not microcarriers over nanoparticles migrate across the range of 100 nm carried by the lymph into the interstitial, and therefore function locally. Probably toxic chemicals can be transported Encapsulated, and in place of liquid the dried microparticles may be known as solids. The intake dose is delivered in several tiny different for multiarticulate particles, which hold and discharge a part of the dosage; therefore, the breakdown of a specific subunit does not affect the whole dosage failure.[4-5] Microparticles used in skin applications required to benefit the release of the medication into the skin ensure that now the drug remains localized at the application site and does not enter the systemic circulation unnecessarily. They act as a reservoir which releases an active ingredient over a longer period of time to maintain effective concentration of drug products in the skin while decreasing undesired side effects.[6-7] Consequently, cycles of over- and under-medication are reduced. It is especially relevant for the reduction of antimicrobial resistance in the management of infectious diseases. These distribution mechanisms can also boost product safety or integration into appropriate vehicles.[8]

Advantages of Microspheres [9-11]

A. Decrease of the size contributes to an increasing the surface area and can increase the potency of the poorly soluble material.

B. Providing a steady quantity of medications in the body that can improve patient compliance;

C. Dose and risk reduced.

D. Drug packaging with polymers prevents the drug avoid enzymatic cleavage while making it suitable for drug method delivery system.

E. Less duration of dosing contributes to higher patient compliance.

F. Effective usage of medications can enhance bioavailability, and decrease harmful effects occurrence or severity.

G. Helps protect the GIT from opioid irritants.

H. Transform liquid into solid shape and block the unpleasant taste.

I. Reliable means, if changed, to transmit the medication to the target location with precision and to sustain the targeted concentrations at the targeted site and with no undue impact.

J. Reduce central reactivity related to the external world.

K. Degradable microspheres get the benefit over large polymer implants through that they just do not really necessarily involve medical treatments for implantation and reduction.

L. Controlled release delivery degradable microspheres are being used to regulate release of drug prices while also reducing toxicity and reducing the discomfort of repeated injection.

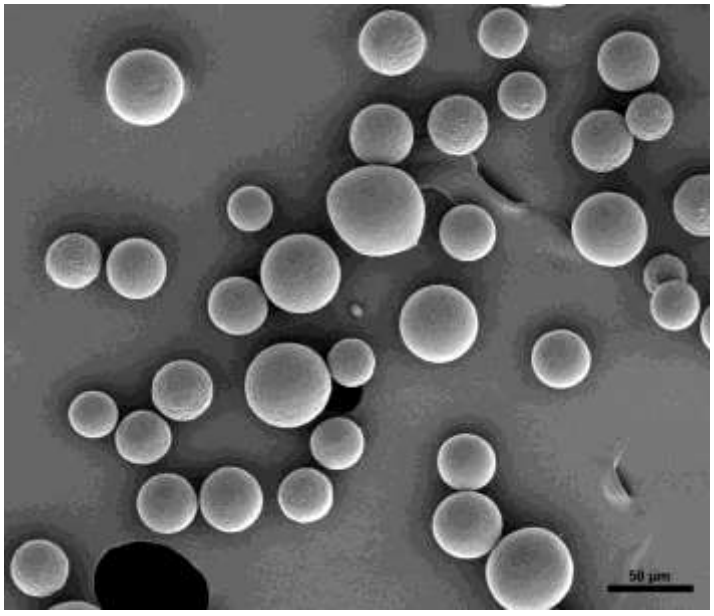

Figure: 1 Microsphere

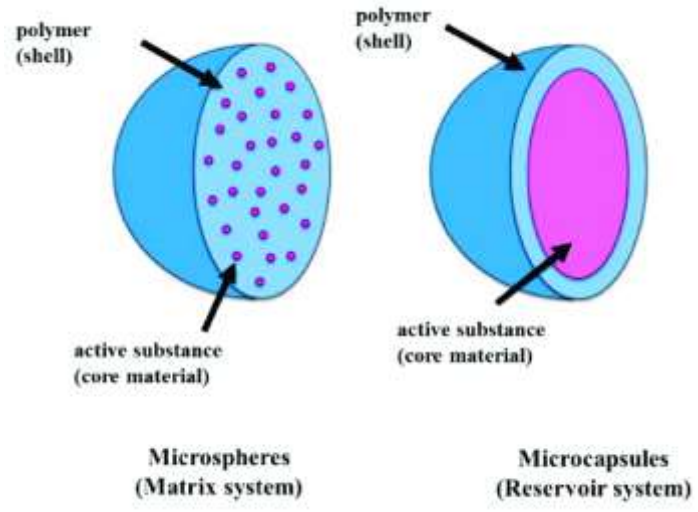

Figure: 2 Microsphere cross section

Disadvantages of Microspheres[12-13]

A. The changed releases from the formulations.

B. The release rate of the regulated dose process of release which differ from a number of Factorslike diet and transfer levels through gut.

C. Variations in rate of discharge from one dosage to the next.

D. Controlled release formulations typically have a higher dose load and so any lack of quality of the release properties of the drug substance can contribute to

E. Potentially dangerous.

F. These dosing types must not be broken or chewed.

Tretinoin microsphere formulation

Microsphere delivery formulations of tretinoin reached the market more than a decade ago with a significantly improved tolerability profile relative to standard formulations. In a study comparing the efficacy and tolerability of tretinoin 0.1% microsphere cream to that of adapalene 0.1% gel, tretinoinhad increased dryness and peeling, but the incidence of erythema, burning/stinging, and itching wassimilar in both groups. With a newer tretinoin 0.04% microsphere formulation, data show that cumulative irritancy was either similar to or lower than that associated with adapalene.[14-16] Compared to tretinoin microsphere gel 0.1%, tretinoin microsphere gel 0.04% was associated with fewer patient reports of dryness during the early phase of treatment, while overall tolerability, as measured by incidence of peeling, burning/stinging, and itching, was similar between the two groups; the incidence of erythema was reduced in the tretinoin group. Another study compared tretinoin microsphere gel 0.04% to tretinoin 0.025% cream in subjects with healthy skin. Subjects in the investigator-blind, evaluator-blind, randomized trial applied the topical medications in a split-face fashion for two weeks. There was no significant difference in tolerability between the two arms despitethe fact that microsphere formulation had the higher tretinoin concentration, as indicated by measures of erythema, skin dryness, itching, and stinging.[17-19] In addition to enhanced tolerability, microsphere formulations provide the benefit of improved drug stability. Tretinoin has been shown to degrade significantly upon exposure to ultraviolet (UV) radiation as well as when combined with BPO. However, when microsphere-encapsulated tretinoin was exposed to UV and BPO, it was only minimally degraded. At two and six hours after exposure to UV radiation, 89and 81 percent of the initial tretinoin remained stable, respectively. At two and six hours after being combined with clindamycin/BPO, 86 and 80 percent of the tretinoin remained stable, respectively. By contrast, for the tretinoin not in microspheres, just 19 and 10 percent of the UV-exposed tretinoin remained unchanged and 7 and 0 percent of the BPO-exposed tretinoin, remained, respectively, at two and six hours.) These findings have been confirmed *in vivo.* A recent study shows that patients who cleansed the face with a BPO 5% wash each morning followed by topical tretinoin gel microsphere 0.04% had a response similar to that seen in individuals who used the same wash each morning and tretinoin microsphere gel together each evening. Patients (n=247) 12 years of age or older participated in the 12-week study. These findings suggest that tretinoin was not degraded by BPO. The once-daily regimen was well tolerated and may be associated with better adherence than the two-times-a-dayregimen.[17,20-22]

Objectives and need of microsphere in formulations

Oral drug delivery is the most desirable and preferred method of administering therapeutic agent for their systematic effect

such as patient acceptance, convenience in administration and cost effective manufacturing process. Thus, wide variety of approaches of drug delivery system has been investigated for oral application. However, development process is precluded by several physiological difficulties, such as inability to restrain & localize drug delivery system within desired region of GIT tract and highly variable nature of gastric emptying process.[23] For example, relatively brief gastric emptying time can result in incomplete drug release from drug delivery devices leading to diminished efficacy of administered dose. Floating drug delivery system is noted orally applicable drug delivery system for prolongation of gastric emptying time. The bulk densityof floating drug delivery system is lower than that of gastric fluid and thus it remains buoyant on stomach content for long time in the drug releasing process. Hence it is useful for obtaining sufficient bioavailability for long time and effective plasma level. Microspheres provide a constant & prolonged therapeutic effect which will reduce dosing frequency.[24-26] it was reported that microspheres prepared with proton pump inhibitor effective in reducing gastric acid level and allowing acid related disease to heal. Lansoprazole (benzimidazole derivative) is important proton pump inhibitor. Whose mechanism action is to reduce the increased gastric acid level by acting on H+ K+ ATP'ase an enzyme presents in the gastric parietal cell. This drug is effective in treatment of gastric and duodenal ulcer, in treatment of heartburn disease and other symptoms associated with gastroesophageal reflux disease and its plasma elimination half-life is 1 to1.5 hours.[27]

Methods of microsphere preparation

The choice of technique depends upon the nature of polymer as well nature of drug and the duration of therapy. The most important physical chemical factors that may be controlled in microsphere manufacture are,[28-32]

- The particle size requirement
- Molecular weight of polymer
- Polymer to drug ratio
- No stability problem
- Final product should be non-toxic.
- Total mass of drug and polymer
- Reproducibility
- Controlled particle size and dispersibility in aqueous vehicles for injection

Following techniques are used in the manufacturing of microspheres

1. ***Single emulsion techniques***
2. ***Double emulsion techniques***
3. ***Polymerization***

a. Normal polymerization

- Bulk
- Suspension
- Emulsion

b. Inter-facial polymerization

4. ***Phase separation coacervation technique***
5. ***Spray drying***
6. ***Solvent extraction***
7. ***Solution-enhancement dispersion method***
8. ***Wax coating Hot-melt method***

1. *Single emulsion technique*

There are several Proteins and carbohydrates, which are prepared by this technique. In which the natural polymers are dissolved in aqueous medium and the followed by dispersion in oil phase i.e.,non-aqueous medium. That is the first step in Next step cross linking is carried out by two methods

(1) Cross linking by heat: by adding the dispersion into heated oil, but it is unsuitable for theThermolabile drugs.

(2) Chemical cross-linking agents: - by using agents i.e., formaldehyde, di acid chloride, glutaraldehyde etc. but it is having a disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing and separation. Chitosan solution (in acetic acid) by adding to Liquid paraffin containing a surfactant resulting formation of w/o emulsion5. Metformin hydrochloride microsphere are prepared by using glutaraldehyde 25% solution as a cross linking agent.

2. *Double emulsion technique*

It is formation of multiple emulsions i.e., W/O/W is preparing by pouring the primary w/o emulsion into aqueous solution of poly vinyl alcohol. This w/o/w emulsion put a t constant stirring for 30 min. Slowly add some water to the emulsion over a period of 30 min. collect Microcapsules by filtration and dry under [vacuum. It is best suited to water soluble drugs, peptides, proteins and the vaccines. Natural as well as synthetic polymer can use for this method. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. Disperse in oil/organic phase homogenization/vigorous i.e., formation of first emulsion then addition to aqueous solution of PVA (Poly Vinyl Alcohol) i.e., multiple emulsion formed now by addition to large aqueous phase denaturation/hardening after this separation, washings' and dryingand collection of microspheres1 genistein chitosan microsphere were prepared by the o/w/o multiple emulsion method by Wu and Li.

3. *Polymerization techniques*

Mainly two techniques are using for the preparation of microsphereare classified as:

(a) Normal polymerization

In bulk polymerization, a monomer or a mixture of number of monomers along with the initiator orcatalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done by adding the drug during the process of polymerization. It is a pure polymer formation technique but it is very difficult to dissipate the heat of reaction which affects the thermos labile active ingredients. Suspension polymerization is carried out of lower temperature and also refer to as pearl polymerization in which heating the monomer mixture with active drug as droplets dispersion in continuous aqueous phase. Microsphere size obtained by suspension techniques is less the 100 µm. Emulsion polymerization is differed from the suspension as due presence of initiator in aqueous phase but is also carried out at low temperature as suspension external phase normally water in last two techniques so through which heat can easily dissipate.

formation of higher polymer at faster rate is possible by these techniques but association of polymer with the un reacted monomer and other additives can occur.

(b) Interfacial polymerization

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase. In this technique two reacting monomers are employed; one is dissolved in continuous phase while other is disperse in continuous phase (aqueous in nature) throughout which the second monomer is emulsified. Two conditions arise because of solubility of formed polymer in the emulsion droplet. That is formation is monolithic type of carrier if the polymer is soluble in droplet. Capsular type formed if the polymer is insoluble in droplet.

4. Spray drying and spray congealing

Concept of spray drying technique depending upon the removal of solvent or the cooling of solution the two processes are spray drying & spray congealing. Evaporation is the basic mechanism in spray drying, whereas in spray congealing it is that of a phase inversion from a liquid to a solid.

Both processes are similar, except for energy flow. Spray drying is the most widely used industrial process involving particle formation and drying. Therefore, spray drying is an ideal process wherethe end product must comply with precise quality standards regarding particle size distribution, residual moisture content, bulk density, and particle shape.

Three steps involved in spray drying

a.) Atomization: of a liquid feed change into fine droplets.

b.) Mixing: it involves the passing of hot gas stream through spray droplets which result in evaporation of liquids and leaving behind dried particles.

c.) Dry: Dried powder is separated from the gas stream and collected.

In this technique polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air, this form small droplets or the fine mist, from which the solvent evaporates instantaneously leading.

The size range is 1-100 µm. By using hot air separate of Microparticle by means of the cyclone separator while the traces of solvent are removed by vacuum drying. Advantages of the process are feasibility of operation. This technique is very useful to encapsulate various penicillins. Thiamine mononitrate and sulpha ethylthiadizole are encapsulated in a mixture of mono- and diglycerides of stearic acid and palmitic acid using spray congealing.

The prepared solution was sprayed through a nozzle in a spray-drier under different experimental conditions. Solid microspheres were collected into final bottom vessel spray-drier.Very rapid solvent evaporation, however leads to the formation of porous microparticles. The sprays are produces by either rotary (wheel) or nozzle atomizers. Evaporation of moisture from the droplets and formation of dry particles proceed under controlled temperature and airflow conditions. The microsphere size is controlled by the rate of spraying, nozzle size, temperature (in drying and collecting chambers.) and the feed rate ofpolymer drug solution.

The quality of product is improved by addition plasticizer spray flow rate should kept constant around 6ml/min. Spray drying technique is also useful for preparing chitosan microsphere. In 1999 He et.al. used formaldehyde as a crosslinking and also reported a novel method in which cimetidine and famotidine were entrapped in microspheres prepared by spray drying of multiple emulsion (o/w/o or w/o/w). They found that the release of the drugs from microspheres by this novel method was significantly sustained as compared to those prepared by conventional spray drying or o/w emulsion method. In 1994 Gunched et al. was used spray drying used for the preparation of PCL microspheres of ketoprofen. He used the organic solution of the drug and two polymers, cellulose acetate butyrate and PCL was made in a mixture of dichloromethane and chloroform. The prepared solution was sprayed through a nozzle in a spray-drier under different experimental conditions. Solid microspheres were collected into final bottom vessel spray-drier.

Ideal characteristics of microspheres

1. Microsphere size may be critical to the proper function of an assay, or it may be secondary to other characteristics. Considering traditional diagnostic methods, the test or assay format commonly dictates particle size, such as the use of very small spheres (~0.1- 0.4µm) to ensure satisfactory wicking in lateral flow tests, or the use of larger, cell-sized spheres (~4-10µm) for bead-based flow cytometric assays.[33-34]

2. Common microsphere compositions include polystyrene (PS), poly-methyl methacrylate (PMMA), and silica. These materials possess different physical and optical properties, which may present advantages or limitations for different applications. Polymer beads are generally hydrophobic, and as such, have high protein binding abilities. However, they often require the use of some surfactant (e.g. 0.01-0.1% Tween® 20 or SDS) in the storage buffer to ensure ease of handling. During synthesis, functional monomers may be co-polymerized with styrene or methyl methacrylate to develop beads withsurface reactive groups. Functional groups may be used in covalent binding reactions, and also aid in stabilizing the suspension. Silica microspheres are inherently hydrophilic and negatively charged. Consequently, aqueous silica suspensions rarely require use of surfactants or other stabilizers. Carboxyl and amine functionalized silica spheres are available for use in common covalent coating protocols, and plain silica microspheres may be modified using a variety of silanes to generate functional groups or altersurface properties.[35-36]

3. Microspheres may be coated with capture molecules, such as antibodies, oligonucleotides, peptides, etc. for use in diagnostic or separation applications. Microsphere coatings are typically optimized to achieve desired specific activity, while minimizing nonspecific interactions. Consideration should also be given to the required stability, development time frame and budget, and the specific biomolecule to be coated. These factors will aid in determining the most fitting coating strategy for bothshort and long-term objectives. Standard microsphere products support three basic coating strategies: adsorption, covalent coupling, and affinity binding.[37]

4. Many applications in the life sciences demand added properties, such as fluorescence or a visible colour, or iron oxide inclusions for magnetic separations. Polymer spheres (and polymer based magnetic spheres) are often internally dyed via organic solvent swelling, and many standard products are available. Dye concentrations can be adjusted to produce beads with different intensities to meet special needs, such as Quantum Plex™ for multiplexed flow cytometric assays, or our Dragon Green or Flash Red Intensity Standards, which support imaging applications and associated instrument QC. Many surface or internally

labelled fluorescent beads are also available as specialized flow cytometry standards.[38-40]

Types of microspheres

1. *Bio adhesive microspheres*

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bio adhesion. The term "bio adhesion" describes materials that bind to biological substrates', such as mucosal members. Adhesion of bio adhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of administration. This prolonged residence time can result in enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanospheres, liposomes, nanoparticles, etc., which modulates the release and absorption of the drug. Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity.[41-43]

2. *Magnetic microspheres*

This kind of delivery system is very much important which localises 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. Therapeutic magnetic microspheres are used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targetedthrough this system.[44]

3. *Floating microspheres*

In floating types, the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, and the system is found to be floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover, it also reduces chances of dose dumping. It produces prolonged therapeutic effect and therefore reduces dosing frequencies. Drug (ketoprofen) is given in the form of floating microspheres.[45-46]

4. *Radioactive microspheres*

Radio embolization therapy microspheres sized 10-30 nm are of larger than the diameter of the capillaries and gets tapped in first capillary bed when they come across. They are injected in the arteries that leads them to tumour of interest so all these conditions 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.[47]

5. *Polymeric microsphere*

The different types of polymeric microspheres can be classified as:

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 prolong 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.[48]

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 andbiocompatible. 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.[49]

Evaluation parameters of microspheres

The characterization of the micro particulate carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. These microspheres have different microstructures. These microstructures determine the release and the stability of the carrier.

1. *Particle size and shape*

The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine the shape and outer structure of microparticles. LM provides a control over coating parameters in case of double walled microspheres. The microspheres structures can be visualized before and after coating and the change can be measured microscopically. SEM provides higher resolution in contrast to the LM. SEM allows investigations of the microspheres surfaces and after particles are cross-sectioned, it can also be used for the investigation of double walled systems. Confocal fluorescence microscopy is used for the structure characterization of multiple walled microspheres. Laser light scattering and multi size coulter counter other than instrumental methods, which can be used for the characterization of size, shape and morphology of the microspheres.[50]

2. *Electron spectroscopy for chemical analysis*

The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA). ESCA is used for the determination of the atomic composition of the surface. The spectra obtained using ECSA can be used to determine the surficial degradation of the biodegradable microspheres.

3. *Attenuated total reflectance-fourier transform*

Fourier Transform-Infrared (FTIR) spectroscopy is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring alternated total reflectance (ATR). The IR beam passing throughthe ATR cell reflected many times through the sample to provide IR spectra mainly of surface material. The ATR-FTIR provides information about the surface composition of the microspheres depending upon manufacturing procedures.

4. *Density determination*

The density of the 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 constantpressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of reduction in

pressure at different initial pressure are noted. From two pressure readings the volume and hence the density of the microsphere carrier is determined.

5. Isoelectric point

The micro electrophoresis is an apparatus used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined. The mean velocity at different pH values ranging from 3-10 is calculated by measuring the time of particle movement over a distance of 1 mm. By using this data the electrical mobility of the particle can be determined. The electrophoretic mobility can be related to surface contained charge, ionisable behaviour or ion absorption nature of the microspheres.

6. Angle of contact

The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. This thermodynamic property is specific to solid and affected by the presence of the adsorbed component. The angle of contact is measured at the solid/ air/ water interface. The advancing and receding angle of contact are measured by placing a droplet in a circular cell mount above objective of inverted microscope. Contact angle is measured at 200 °C within a minute of deposition of microspheres.[47]

7. In-vitro methods

There is a need for experimental methods which allow the release characteristics and permeability of a drug through membrane to be determined. For this purpose, a number of *in-vitro* and *in-vivo* techniques have been reported. *In-vitro* drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc. Sensitive and reproducible release data derived from physic chemically and hydro dynamically defined conditions are necessary. The influence of technologically defined conditions and difficulty in simulating *in-vivo* conditions has led to development of a number of *in-vitro* release methods for buccal formulations; however, no standard *in-vitro* method has yet been developed. Different workers have used apparatus of varying designs and under varying conditions, depending on the shape and application of the dosage form developed. The dosage form in this method is made to adhere at the bottom of the 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 form 60-300 rpm. Standard USP or BP dissolution apparatus have been used to study *in-vitro* release profiles using rotating elements, paddle and basket. Dissolution medium used for the study varied from 100-500 ml and speed of rotation from 50-100 rpm.[42-43]

8. In-vivo methods

Methods for studying the permeability of intact mucosa comprise of techniques that exploit the biological response of the organism locally or systemically and those that involve direct local measurement of uptake or accumulation of penetrants at the surface. Some of the earliest and simple studies of mucosal permeability utilized the systemic pharmacological effects produced by drugs after application to the oral mucosa. However, the most widely used methods include *in-vivo* studies using animal models, buccal absorption tests, and perfusion chambers for studying drug permeability.

9. In-vitro/In-vivo correlations

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* correlations. Such correlations allow one to develop product specifications with bioavailability.

Percent of drug dissolved in-vitro Vs peak plasma concentration:

One of the ways of checking the *in-vitro* and *in-vivo* correlation is to measure the percent of the drug released from different dosage forms and also to estimate the peak plasma concentrations achieved by them and then to check the correlation between them. It is expected that a poorly formulated dosage form releases amount of drug than a well formulated dosage form, and, hence the amount of drug available for absorption is less for poorly formulated dosage form than from a well formulated dosage form.

Percent of drug dissolved Vs percent of drug absorbed:

If the dissolution rate is the limiting step in the absorption of the drug, and is absorbed completely after dissolution, a linear correlation may be obtained by comparing the percent of the drug absorbed to the percent of the drug dissolved. If the rate limiting step in the bioavailability of the drug is the rate of absorption of the drug, a change in the dissolution rate may not be reflected in a change in the rate and the extent of drug absorption from the dosage form.

Dissolution rate Vs absorption rate:

The absorption rate is usually more difficult to determine than the absorption time. Since the absorption rate and absorption time of a drug are inversely correlated, the absorption time may be used in correlating the dissolution data to the absorption data. In the analysis of *in-vitro* and *in-vivo* drug correlation, rapid drug absorption may be distinguished from the slower drug absorption by observation of the absorption time for the dosage form. The quicker the absorption of the drug the less is the absorption time required for the absorption of the certain amount of the drug. The time required for the absorption of the same amount of drug from the dosage form is correlated.

10. Swelling index

Swelling index was determined by measuring the extent of swelling of microspheres in the given buffer. To ensure the complete equilibrium, exactly weighed amount of microspheres were allowed to swell in given buffer. The excess surface adhered liquid drops were removed by blotting and the swollen microspheres were weighed by using microbalance. The hydrogel microspheres then dried in an oven at 60° C for 5 h until there was no change in the dried mass of sample. The swelling index of the microspherewas calculated by using the formula;

Swelling index = (mass of swollen microspheres – mass of dry microspheres/mass of dried microspheres)x 100.20

Application of microspheres in pharmaceutical industry

Microspheres in vaccine delivery

An ideal vaccine must fulfil the requirement of efficacy, safety, convenience in application and cost. Biodegradable delivery systems for vaccines that are given by parenteral route may overcome the shortcoming of the conventional vaccines. The interest in parenteral (subcutaneous, intramuscular, intradermal) carrier lies since they offer specific advantages including Improved antigenicity by adjuvant action, modulation of antigen release, stabilization of antigen.

Targeting using micro particulate carriers

The concept of targeting, i.e. site specific drug delivery is a well-established dogma, which is gaining full attention. The

therapeutic efficacy of the drug relies on its access and specific interaction with its candidate receptors. The ability to leave the pool in reproducible, efficient and specific manner is centre to drug action mediated by use of a carrier system.

Monoclonal antibodies mediated microspheres targeting

Monoclonal antibodies targeting microspheres are immune microspheres. This targeting is method used to achieve selective targeting to the specific sites. Monoclonal antibodies are extremely specific molecules. They can be directly attached to the microspheres by means of covalent coupling.

Chemoembolization

Chemoembolization is an endovascular therapy, which involves the selective arterial embolization of a tumour together with simultaneous or subsequent local delivery the chemotherapeutic agent.

Imaging

The particle size range of microspheres is an important factor in determining the imaging of particular sites using radio labelled microspheres. The particles injected intravenously apart from the portal vein will become entrapped in the capillary bed of the lungs. This phenomenon is exploited for the scintigraphy imaging of the tumour masses in lungs using labelled human serum albumin microspheres.

Topical porous microspheres

Micro sponges are porous microspheres having myriad of interconnected voids of particle size range 5- 300 µm. These micro sponges having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils etc., are used as the topical carries system.

Medical application

They releases proteins, hormones and peptides over extended period of time. They helps in Gene therapy with DNA plasmids and also delivery of insulin. There is a vital role in vaccine delivery for treatment of diseases like hepatitis, influenza, pertussis, and ricin. They involves in passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intra-arterial/ intravenous application as well as Tumour targeting with doxorubicin. Microspheres helps in the treatments of leishmaniasis. Magnetic microspheres can be used for stem cell extraction and bone marrow purging. Microspheres also used in isolation of antibodies, cell separation and toxin extraction by affinity chromatography. Various diagnostic tests for infectious diseases like bacterial, viral, and fungal can be done by using microspheres.[51]

Radioactive microsphere's application

Microspheres can be used for radio embolization of liver and spleen tumors. They also used for radio synovectomy of arthritis joint, local radiotherapy, interactivity treatment. Imaging of liver, spleen, bone marrow, lung and even imaging of thrombus in deep vein thrombosis can be done by using them.

Additionally, some marketed formulations offering MDDS are mentioned in Table 1.

S. No	Brand Name	API	Manufacturer/Company
1.	Brexin L. A	Chlorpheniramine Pseudoephedrine	Savage Laboratories, Bangalore
2.	Fastin	Phentermine	Berlex Laboratories, USA
3.	Coreg CR	Carvedilol phosphate	GSK
4.	Dillard XL 180	Diltiazem hydrochloride	Smith Kline & French, Mumbai
5.	Bontril SR	Phendimetrazine Tartrate	Car nick laboratories, Inc
6.	InnoPran XL	Propranolol Hydrochloride	GSK
7	Inderal	Propranolol Hydrochloride	Astrazeneca US Ltd.
8.	Compazine	Prochlorperazine	Smith & French, Mumbai
9.	Focalin XR	Dexmethylphenidate	Novartis
10	Spansule	d-amphetamine sulfate	GSK
11.	Ibugesic SR 300	Ibuprofen	CIPLA Ltd, Ahmadabad
12	Cymbalta	Duloxetine Hydrochloride	Eli Lilly and Company, USA
13	Nicobid T. S	Niacin	U.S Vitamin, USA

Other applications

Applications of microencapsulation in other industries are numerous. The best-known microencapsulated products are carbonless copying paper, photosensitive paper, microencapsulated fragrances, such as ''scent- strips'' (also known as ''snap-n-burst''), and microencapsulated aromas ''scratch-n-sniff''. All of these products are usually prepared by gelatine–acacia complex coacervation. Scratch-n-sniff has been used in children's books and food and cosmetic aroma advertising. Microcapsules are also extensively used as diagnostics, for example, temperature-sensitive microcapsules for thermos graphic detection of tumours. In the biotechnology industry microencapsulated microbial cells are being used for the production of recombinant proteins and peptides. The retention of the product within the microcapsule can be beneficial in the collection and isolation of the product. Encapsulation of microbial cells can also increase the cell loading capacity and the rate of production in bioreactors. Smaller microcapsules are better for these purposes; they have a larger surface area that is importantfor the exchange of gases across the microcapsule membrane.

Conclusion

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Microspheres by ionotropic gelation technique promises to be potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body The present review article that is microspheres are better of drug delivery system than other type of drug delivery system. In upcoming days this microsphere novel drug delivery system which shows more effective in cancer therapy or in any other disease treatment like a pulmonary related, cardiac related, nervous system related this microsphere formulation shows more potency this having more effective in in-vivo delivery system. Mainly this formulation gives safety to the active pharmaceutical ingredient and also other excipients used in formulation.

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