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Review on Microsphere

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ABSTRACT

Novel drug delivery systems have several advantages over conventional multi dose therapy. Recent trends indicate that micro particulate drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. The release of drug from micro particles depends on a variety of factors including the carrier used to form the micro particles and the amount of drug contained in them. Consequently, micro particulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations, thus extending the frontier of future pharmaceutical development. One such approach is using microspheres as carriers for drugs. A well-designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a particular drug. It is the reliable mean to deliver the drug to the target site with specificity, if modified and to maintain the desired concentration at the site of interest without untoward effects. Microspheres received much attention not only for prolonged release but also for targeting of anticancer drugs to the tumor.

Key words: Microspheres, preparations, evaluation, applications, polymers, drug release kinetics

INTRODUCTION

Novel drug delivery system aims to deliver the drug at a rate directed by the needs of the body during the period of treatment and channel the active entity to the site of action. At present, no available drug delivery system behaves ideally achieving all the lofty goals but sincere attempts have been made to achieve them through novel approaches in drug delivery. A number of novel drug delivery systems have emerged encompassing various routes of administration to achieve controlled and targeted drug delivery (Li et al., 1987). Microsphere based drug delivery system has received considerable attention in recent years (Guiot and Couvreur, 1986). Microspheres of biodegradable and nonbiodegradable polymers have been investigated for sustained or controlled release depending upon the final application. The most important characteristic of microspheres is the microphase separation morphology which endows it with a controlled variability in degradation rate and also drug release.

Micro particulate delivery systems: Bakan (1987) stated that generally, the micro particulate delivery systems are intended for oral and topical use. The microparticles can be embedded within
Fig. 1: Classification of microparticle

a polymeric or proteinic matrix network in either as solid aggregated state or a molecular dispersion, resulting in the formulation of microspheres. Alternatively, the particles can be coated by a solidified polymeric or proteinic envelope, leading to the formation of microcapsules (Fig. 1).

The ultimate objective of micro particulate-delivery systems is to control and extend the release of the active ingredient from the coated particle without attempting to modify the normal bio fate of the active molecules in the body after administration and absorption. The organ distribution and elimination of these molecules will not be modified and will depend only on their physicochemical properties. Thus, the principle of drug targeting is to reduce the total amount of drug administered and the cost of therapy while optimizing its activity.

MICROSHERES

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers (Fig. 2) which are biodegradable in nature and ideally having a particle size less than 200 μm (Vyas and Khar, 1990) and can be injected by 18 or 20 number needle (Brahmankar and Jaiswal, 2009). Drug absorption and side effects due to irritating drugs against the gastrointestinal mucosa is improved because microsphere are made up of small particle size less than 200 μm which are widely distributed throughout the gastrointestinal tract (Prasanth et al., 2011).

Properties of an Ideal microsphere: Sahil et al. (2011), described that the preparation of microspheres should satisfy certain criteria:

- The ability to incorporate reasonably high concentrations of the drug
- Stability of the preparation after synthesis with a clinically acceptable shelf life
- Controlled particle size and dispersability in aqueous vehicles for injection
- Biocompatibility with a controlled biodegradability
- Susceptibility to chemical modification
- Control of content release
- Increase therapeutic efficiency
- Reduction of toxicity
- Sterilizability
- Bioreabsorbability

Advantages: Meena et al. (2011) and Urs et al. (2010), reported many advantages of microsphere such as:

- Masking of odor or bitter taste
- Improve physical stability and gastric enzyme stability
Fig. 2: Structure of microsphere

- Better process ability (improved flow ability, dispersability)
- Reduced dose size
- Reduced dosing frequency therefore, improves patient compliance
- Reduced toxicity
- High absorption window with respect to characteristics of drug in GIT
- Reduced gastric irritation
- Reduced first pass metabolism
- Enhanced biological half-life
- Improve bioavailability
- Increased therapeutic efficacy and prolonged duration of action
- Facilitated, controlled, sustained and targeted drug delivery
- Simply injected into body because of small size and spherical shape

Disadvantage: Bansal et al. (2011) and Thanou et al. (2001), reported some disadvantages of microsphere:

- The modified release from the formulation may be due to variety of factors like intrinsic and extrinsic factors, food and the rate of transit through gut
- Differences in the release rate from one dose to another
- Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to dumping of dose, result in failure of therapy and produce potential toxicity
- Dosage forms of this kind should not be crushed or chewed
- Low drug loading (maximum of 50%) for controlled release parental
- Once injected it is difficult to remove the carrier completely from the body in case of toxic effect or adverse effect
- Parental delivery of microsphere may interact or form complexes with the blood component

Types of microspheres: Microspheres are generally classified into following types (Fig. 3).

Bioadhesive 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 bioadhesion. The
term “bioadhesion” describes materials that bind to biological substrates, such as mucosal membranes. Adhesion of bioadhesive 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. Bioadhesive microspheres can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary, colon and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs (Patel et al., 2010; Vasir et al., 2003; Senthil et al., 2011a; Hafeli, 2004).

**Magnetic microspheres:** This kind of delivery system is very much important which localizes the drug to the disease site (Fig. 4). In magnetic targeting, a drug or therapeutic radioisotope is bound
to a magnetic compound, injected into a patient’s blood stream and then stopped with a powerful magnetic field in the target area (Widder et al., 1979). In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug to locally diseased sites, reaching effectively up to several fold increased localized drug levels (Gupta and Hung, 1989; Maestrelli et al., 2008). Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. (Chein, 1992). Depending on the type of drug, it is then slowly released from the magnetic microspheres.

The different types of magnetic microspheres are:

- **Therapeutic magnetic microspheres**: It used to deliver therapeutic radioisotopes and chemotherapeutic agent to liver tumors. The advantage of this method over external beam therapy is that the dose can be increased, resulting in improved tumour cell eradication, without harm to nearby normal tissues (Saini et al., 1987)

- **Diagnostic microspheres**: It acts as contrast agents for magnetic resonance imaging. Smaller supra magnetic iron oxides have been developed into unimodular manometer sizes and have since 1994 been approved and used for the imaging of liver metastases or to distinguish loops of the bowel from other abdominal structures (Najmuddin et al., 2010)

The aim of the specific targeting is to enhance the efficiency of drug delivery and to reduce the toxicity and its side effects. Magnetic drug transport technique is based on the fact that the drug can be either encapsulated into a magnetic microsphere or conjugated on the surface of the microsphere. When the magnetic carrier is intravenously administered, the accumulation takes place within area to which the magnetic field is applied and often augmented by magnetic agglomeration. The accumulation of the carrier at the target site allows them to deliver the drug locally. Efficiency of accumulation of magnetic carrier on physiological carrier depends on physiological parameters e.g., particle size, surface characteristic, field strength and blood flow rate etc. The magnetic field helps to extravasate the magnetic carrier into the targeted area. Very high concentration of chemotherapeutic agents can be achieved near the target site without any toxic effect to normal surrounding tissue or to whole body. It is possible to replace large amounts of drug targeted magnetically to localized disease site, reaching effective and up to several fold increased drug levels. This technique which requires only a simple injection is far less invasive than surgical methods of targeted drug delivery. Another advantage is that particles in the magnetic fluid, interact strongly with each other which facilitates the delivery of high concentrations of drug to targeted areas.

Magnetic microspheres can be filled with drugs or radioactive materials to treat a variety of illnesses. Magnets applied outside the body attract the spheres to the disease site where they deliver therapeutics in a targeted way. The magnets attract the microspheres to the immediate area of the wound site and stop them there. The spheres gradually break down and release growth factors over a period of weeks, allowing blood vessels and damaged tissues to regrow and repair.

**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, if the system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of striking and dose dumping. One another way, it produces prolonged therapeutic effect and therefore reduces dosing frequencies (Lachman et al., 1991):
Effervescent type: Nasa et al. (2010) stated that swellable polymers e.g., methylcellulose, chitosan and various effervescent compound e.g., sodium bicarbonate, citric acid and tartaric acid are used for the preparation of effervescent dosage. Floating microsphere of effervescent type liberates carbon dioxide gas due to which the density of the system is reduced and remains in floating condition in stomach for a prolonged period of time, this result in release of drug slowly at a desired rate

Non-effervescent type: Highly swellable cellulose type hydrocolloids, polysaccharide and matrix forming polymer such as polycarbonate, polyacrylate are used to form non effervescent system. This is prepared by thoroughly mixing the drug and gel forming hydrocolloids. When administered, it swells up when comes in contact with gastric fluid and attain a bulk density i.e., less than 1 g/44 mL

Radioactive microspheres: Radio emobilization therapy microspheres sized 10-30 nm is of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumor of interest. So, all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues (Amsden and Goosen, 1997). It differs from drug delivery system, as radioactivity is not released from microspheres but acts from a radioisotope within a typical distance and the different kinds of radioactive microspheres are α, β and γ emitters (Yadav and Mote, 2007). It offers new solutions for patients, who need drugs delivered directly to tumors, diabetic ulcers and other disease sites.

Diagnostic uses of radioactive microspheres: Heymann et al. (1977), described some diagnostic uses of radioactive microspheres such as:

- Gated blood pool study
- Thrombus imaging in deep vein thrombosis
- Blood flow measurements
- Investigation of biodistribution and fate of (drug-loaded) microspheres
- Lung scintigraphy
- Diagnostic radio emobilization
- Liver and spleen imaging
- Bone marrow imaging
- Infection localization
- Tumor imaging
- Gastrointestinal transit studies
- Local restenosis prevention in coronary arteries

Mucoadhesive microspheres: Mucoadhesive microspheres which are of 1-1000 mm in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it, respectively. Microspheres, in general, have the potential to be used for targeted and controlled release drug delivery but 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.

**Micellanious**

**Glass microspheres:** Glass microspheres are primarily used as filler for weight reduction, retro-reflector for highway safety, additive for cosmetics and adhesives, with limited applications in medical technology.

**Types of glass microspheres**

**Hollow glass microsphere:** Hollow microspheres vary widely in density and, therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material.

**Solid glass microsphere:** Solid microspheres vary widely in density and, therefore, are used for different applications. Solid microspheres have numerous applications depending on what material they are constructed of and what size they have.

**TYPES OF POLYMERS USED FOR THE PREPARATIONS OF MICROSPHERES**

Patel et al. (2011) and Alagusundaram et al. (2009) stated that a number of different substances both biodegradable and non-biodegradable have been investigated for the preparations of microspheres. These materials include the polymers of natural and synthetic origin and also modified natural substances (Fig. 5).

**METHODS OF PREPARATION OF MICROSPHERES**

There are different methods for the preparation of microspheres as shown in Fig. 6.

![Diagram of polymers used for the preparations of microspheres](image-url)
**Solvent evaporation method:**

- **Single emulsion technique:** The micro particulate carriers of natural polymers which are proteins and carbohydrates are prepared by single emulsion technique (Fig. 7). The natural polymers are dissolved/dispersed in aqueous medium followed by dispersion in the non-aqueous medium e.g., oil. In the next step, cross linking of the dispersed globule is carried out either by means of heat or by using chemical cross linkers. The chemical cross linking agents used gluteraldehyde, formaldehyde, terephthalate chloride, diacidchloride (Vyas and Khar, 2010; Trivedi et al., 2008). Crosslinking by heat is affected by adding the dispersion to previously heated oil. Heat denaturation is not suitable for the thermo labile drugs while the chemical cross-linking suffers disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing and separation (Schugens et al., 1994)
- **Double emulsion technique:** This process consumes formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to the water soluble drugs, peptides,
proteins and the vaccines (Fig. 8). The aqueous protein solution is dispersed in a lipophilic organic continuous phase which is generally consisted of polymer solution that eventually encapsulates protein contained in dispersed aqueous phase. The primary emulsion is then subjected to the homogenization before addition to aqueous solution of PVA. This results in formation of double emulsion which is then subjected to solvent removal by solvent evaporation maintaining the emulsion at reduced pressure or by stirring so that organic phase evaporates out. Examples are hydrophilic drugs like LHRH agonist, vaccines and proteins

- **Coacervation phase separation method:** This method is used preparing the reservoir type of the system to encapsulate water soluble drugs like peptides, proteins, matrix type particularly. When the drug is hydrophobic in nature e.g., steroids. In matrix type device, the drug or the protein is soluble in the polymer phase. The process is based on the principle of decreasing the solubility of the polymer in the organic phase to affect the formation of the polymer rich phase called the coacervates. The coacervation can be brought about by addition of the third component to the system which results in the formation of the two phases, one i.e., supernatant, depleted of the polymer. In this technique, the polymer is first dissolved in a suitable solvent and then drug is dispersed by making its aqueous solution, if hydrophilic or dissolved in the polymer solution itself, if hydrophobic. Phase separation is then accomplished by changing the solution conditions (Fig. 9)

- **Spray drying and spray congealing:** These methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or cooling of the solution, two processes are named spray drying and spray congealing, respectively (Fig. 10). The 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. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100 μm. Micro particles are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying. One of the major advantages of the process is feasibility
of operation under aseptic conditions. The spray drying process is used to encapsulate various penicillins. Thiamine mono nitrate and sulphadiazine are encapsulated in the mixture of mono and diglycerides of stearic acid and palmitic acid using spray congealing. Very rapid solvent evaporation, however, leads to the formation of porous microparticles

**Polymerization method:**

- **Normal polymerization:** It proceeds, using techniques like bulk, suspension precipitation, emulsion micellar polymerization processes. In bulk polymerization, a monomer with initiator is heated to start polymerization. Initiator is added to accelerate the rate of reaction. Drug is added during process of polymerization. The polymer so obtained is fragmented to microspheres (Fig. 11)
- **Suspension polymerization:** Suspension polymerization is carried out by heating the monomer or mixture of monomers with active principles (drug) as droplets dispersion in a
continuous phase. The droplets may also contain an initiator and other additives. The emulsion polymerization differs from the suspension polymerization as due to presence of initiator in the aqueous phase which later on diffuses to the surface of the micelles or the emulsion globules. The suspension and emulsion polymerization can be carried out at lower temperature, since continuous external phase is normally water through which heat can easily dissipate.

- **Interfacial polymerization:** It involves reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelopes the dispersed phase. In this, two reacting monomers are employed one of which is dissolved in the continuous phase while the other being dispersed in the continuous phase. Monomer present in either phase which diffuse or polymerize rapidly at the interface. If the polymer is soluble in the droplet, it will lead to the formation of monolithic type of the carrier on the other hand if polymer is insoluble in the monomer droplet, the formed carrier is of capsular (reservoir) type. The degree of polymerization can be controlled by the reactivity of monomer chosen, their concentration and the composition of the vehicle of either phases and by the temperature of the system. The particle size can be controlled by controlling the droplets or globule size of the disperse phase. The polymerization reaction can be controlled by maintaining the concentration of the monomers which can be achieved by the addition of an excess of the continuous phase.

**Coacervation method:**

- **Coacervation thermal change:** Performed by weighed amount of ethyl cellulose was dissolved in cyclohexane with vigorous stirring at 80°C by heating. Then the drug was finely pulverized and added with vigorous stirring on the above solution and phase separation was done by reducing temperature and using ice bath. Then above product was washed twice with cyclohexane and air dried then passed through sieve (sieve No. 40) to obtain individual microcapsule
- **Coacervation non solvent addition:** Developed by weighed amount of ethyl cellulose was dissolved in toluene containing propylisobutylene in closed beaker with magnetic stirring for
Fig. 12: Solvent evaporation

6 h at 500 rpm and the drug is dispersed in it and stirring is continued for 15 min. Then phase separation is done by petroleum benzoin, 14 times with continuous stirring. After that the microcapsules were washed with n-hexane and air dried for 2 h and then in oven at 50°C for 4 h

Solvent evaporation: The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be micro encapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer of the core material is disperse in the polymer solution, polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix type microcapsules are formed. The core materials may be either water soluble or water insoluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous (Fig. 12).

Solvent extraction: Solvent evaporation method is used for the preparation of micro particles, involves removal of the organic phase by extraction of the organic solvent. The method involves water miscible organic solvents such as isopropanol. Organic phase is removed by extraction with water. This process decreases the hardening time for the microspheres. One variation of the process involves direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer (Fig. 13).

Emulsion solvent diffusion technique: In order to improve the residence time in colon floating micro particles of ketoprofen were prepared using emulsion solvent diffusion technique. The drug polymer mixture was dissolved in a mixture of ethanol and dichloromethane (1:1) and then the mixture was added drop wise to Sodium Lauryl Sulphate (SLS) solution. The solution was stirred
with propeller type agitator at room temperature at 150 rpm for 1 h. Thus the formed floating microspheres were washed and dried in desicator at room temperature. The following micro particles were sieved and collected.

**Multiple emulsion method:** Oral controlled release drug delivery of indomethacin was prepared by this technique. In the beginning powder drug was dispersed in solution (methyl cellulose) followed by emulsification in ethyl cellulose solution in ethyl acetate. The primary emulsion was then re-emulsified in aqueous medium. Under optimized condition discrete microspheres were formed during this phase.

**Ionic gelation method:** Alginate/chitosan particulate system for diclofenac sodium release was prepared using this technique. The 25% (w/v) of diclofenac sodium was added to 1.2% (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added drop wise to a solution containing Ca²⁺/Al³⁺ and chitosan solution in acetic acid. Microspheres which were formed were kept in original solution for 24 h for internal gellification followed by filtration for separation. The complete release was obtained at pH 6.4-7.2 but the drug did not release in acidic pH.

**LOADING OF DRUG**

The active components are loaded over the microsphere principally using two methods i.e., during the preparation of the microsphere or after the formation of the microspheres by incubating them with the drug/protein. The active component can be loaded by means of physical entrapment, chemical linkage and surface adsorption. The entrapment largely depends on the method of preparation and nature of the drug or polymer (monomer, if used). Maximum loading can be achieved by incorporating the drug during the time of preparation but it may get affected by many other process variables such as method of preparation, presence of additives (e.g., cross-linking agent, surfactant stabilizers, etc.) heat of polymerization, agitation intensity, etc.

Percent incorporation in preformed microsphere is relatively less but the major advantage of the loading method being there no effect of process variables. The loading is carried out in

![Fig. 13: Solvent extraction](image-url)
preformed microsphere is by incubating them with high concentration of a drug in suitable solvent. The drug in this microsphere is loaded via., penetration or diffusion of the drug through the pores in the microsphere as well as adsorption on their surface. The solvent is then removed, leaving drug loaded microsphere. The drugs and protein can also be incorporated by physical or chemical linkage. The adsorption of the drugs by proteins depends on the nature of the polymers (Kipling, 1965). The Freundlich model is applied to determine the adsorption of the drugs. The Freundlich equation is:

\[ X = KM^{1/p} \]

where, \( K \) constant related to the capacity of the adsorbent for the adsorbate and \( P \) constant related to the affinity of the adsorbent for the adsorbate.

Although, this equation was first employed empirically, it can be derived with the assumption of a continuously varying heat of adsorption. The Freundlich model unfortunately predicts both infinite adsorptions at infinite concentration and an infinite heat of adsorption at zero coverage.

**DRUG RELEASE KINETICS**

Release of the active constituent is an important consideration in case of microspheres. Many theoretically possible mechanisms may be considered for the release of the drug from the microparticulates:

- Liberation due to polymer erosion or degradation
- Self-diffusion through the pore
- Release from the surface of the polymer
- Pulse delivery initiated by the application of an oscillating or sonic field

In most of the cases, a combination of more than one mechanism for drug of release may operate so, the distinction among the mechanism is not always trivial. The release profile from the microsphere depends on the nature of the polymer used in the preparation as well as the nature of the active drug. The release of the drug from biodegradable as well as non-biodegradable microsphere(s) is influenced by the structure or micro-morphology of the carrier and the properties of the polymer itself. The drug could be released through the microsphere by any of the three methods:

- The osmotically driven burst mechanism
- Pore diffusion mechanism
- Erosion or the degradation of the polymer

In osmotically driven burst mechanism water diffuses into the core through the biodegradable or non-biodegradable coating, creating sufficient pressure that ruptures the membrane. The burst effect is mainly controlled by the three factors:

- The macro molecule/polymer ratio
- Particle size of the dispersed macromolecule
- The particle size of the microspheres
The pore diffusion method is named so because as penetrating water front continue to diffuse towards the core. The dispersed protein/drug dissolve creating a water filled pore network through which the active principle diffuses out in a controlled manner.

In case of biodegradable polymers, the release is controlled by both the erosion as well as diffusion process. The polymer erosion i.e., loss of polymer is accompanied by accumulation of the monomer in the release medium. The erosion of the polymer begins with the changes in the microstructure of the carrier as water penetrates within it leading to the plasticization of the matrix. This plasticization of the matrix finally leads to the cleavage of the hydrolytic bonds. The cleavage of the bond is also facilitated by the presence of the enzymes (lysozymes) in the surroundings. The erosion of the polymer may be either surficial or it may be bulk leading to the rapid release of the drug/active components. The rate and extent of water uptake therefore determines the release profile of the system and depends on type of the polymer, porosity of the polymer matrix, protein drug loading etc.

Factors affecting the release of the drug from the particulate system in relation to drug, microspheres and bioenvironment (Tomlinson, 1983):

**Drug:**

- Position in microspheres
- Molecular weight
- Physicochemical properties
- Concentration
- Interaction with matrix

**Microspheres:**

- Type and amount of the matrix polymer
- Size and density of the microspheres
- Extent of cross linking, denaturation or polymerization
- Adjuvants

**Environment:**

- pH
- Polarity
- Presence of enzyme

Drug release from the non-biodegradable type of polymer can be understood by considering the geometry of the carrier. The geometry of the carrier i.e., whether it is reservoir type where the drug is present as a core or matrix type in which drug is dispersed throughout the carrier, governs overall release profile of the drug or active ingredients.

**Reservoir type system:** Release from the reservoir type system with rate controlling membrane proceeds by first penetration of the water through the membrane followed by dissolution of the
drug in the penetrating dissolution fluid. The dissolved drug after partitioning through the membrane diffuses across the stagnant diffusion layer. The release is essentially governed by the Fick’s first law of diffusion as:

\[ J = -D \frac{dc}{dx} \]

where, \( J \) is flux per unit area, \( D \) is diffusion coefficient and \( dc/dx \) is concentration gradient.

Diffusion across the membrane determines the effectiveness of the carrier system. The cumulative amount of drug that is released through the unit area \( Q \) at any time is given by the equation:

\[ Q_t = \frac{C_s KD_m D_t}{KD_m L_m + D_s L_s} \]

where, \( C_s \) represents saturation solubility of drug in dispersion medium, \( L_w \), \( D_s \) is diffusion coefficient of drug in static diffusion layer of thickness, \( L_s \), \( K \) is partition coefficient of drug between membrane and reservoir compartments.

The release rate from the carriers can be modified by changing both the composition and the thickness of the polymeric membrane.

**Matrix type system:** Release profile of the drug from the matrix type of the device critically depends on the state of drug whether it is dissolved or dispersed in the polymer matrix. In the case of the drug dissolved in the polymeric matrix, amount of drug and the nature of the polymer (whether hydrophobic or hydrophilic) affect the release profile.

In the case of drug dissolved in the polymeric matrix, the amount of the drug appearing in the receptor phase at time \( t \) is approximated by two separate equations. The first equation determines the initial 60% of the drug release while the second shows the release profile at later stage:

\[ \frac{dM_t}{dt} = 2Mx \left( \frac{D}{nL^2} \right) \]

\[ \frac{dM_t}{dt} = \frac{5DMx}{1'} \exp \left( -\frac{nDx}{L^2} \right) \]

where, \( L \) is thickness of polymer slab, \( D \) is diffusion coefficient, \( Mx \) is the total amount of the drug present in the matrix and \( Mt \) is the amount of the drug released in time \( t \). When the drug is dispersed throughout the polymer matrix then the release profile follows Higuchi’s equation:

\[ \frac{dM_t}{dt} = \frac{A_A (2DC_s C_o) \frac{L}{2}}{t} \]

where, \( A \) is area of matrix, \( C_s \) is solubility of the drug in the matrix and \( C_o \) represents total concentration in the matrix.
Taking porosity (ε) and tortuosity (τ) of the matrix into the consideration the above equation can be rewritten as:

$$\frac{dN}{dt} = \frac{ε}{\tau} \left( \frac{D_a (2C_0 - εC_c) C_c}{1} \right)^{1/2}$$

FATE OF MICROSPHERE IN THE BODY

Micro particulate carrier systems can be administered through routes such as intravenous, ocular, intramuscular, intraarterial, oral etc. Each route has its own biological significance, limitation and pharmaceutical feasibility. The micro particles are intended to be administered through different routes to achieve desired activity of either sustained action or targeting or both. Through different routes different mechanisms of uptake, transport and fate of trans located particles have been proposed (Table 1).

Biodegradable microparticulate carriers are of interest for oral delivery of drugs to improve the bioavailability (Maincent et al., 1988) to enhance drug absorption (Couvreur et al., 1979; Illum et al., 1983, 1987; Kreuter et al., 1983), to target particular organ with reduced toxicity (Kramer and Burnstein, 1976; Marty et al., 1978), to improve gastric tolerance of gastric irritant to the stomach and as a carrier for antigen. The polystyrene microspheres administered orally are reported to be taken up by Peyer’s Patch. They are subsequently translocated to discrete anatomical compartments such as mesenteric lymph vessels, lymph nodes and to a lesser extent in liver and spleen (Sanders and Ashworth, 1961; Jani et al., 1990). The particulate matters gain entry into follicle associated epithelium through Peyer’s Patches.

After the uptake of the particulate carrier via different mechanism their fate becomes important (Oh and Ritschel, 1999).

Some uptake mechanisms avoid the lysosomal system of the enterocytes. The particles following uptake by enterocytes are transported to the mesenteric lymph, followed by the systemic circulation and are subsequently phagocytosed by the Kupffer cells of liver. However, after uptake by enterocytes, some particulate carriers may be taken up into vacuoles and discharged back into gut lumen (Alpar et al., 1989).

Microspheres can also be designed for the controlled release to the gastrointestinal tract. The release of the drug content depends on the size of microparticles and the drug content within microspheres. The release of the drug could be regulated by selecting an appropriate hydrophilic/lipophilic balance of the matrix such as in the case of matrix of polyglycerol esters of fatty acid (Ebel, 1990). Microparticles of mucoadhesive polymers get attached to the mucous layer

<table>
<thead>
<tr>
<th>Site</th>
<th>Size range</th>
<th>Fate</th>
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<tbody>
<tr>
<td>Enterocyte/endocyte</td>
<td>&lt;220 nm</td>
<td>RES uptake</td>
</tr>
<tr>
<td>Paracellular uptake</td>
<td>100-200 nm</td>
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<td>Percorption</td>
<td>5-150 μm</td>
<td>Blood and excretory fluids</td>
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<td>Peyer’s Patches</td>
<td>20 nm-10 μm</td>
<td>PF and MLN</td>
</tr>
<tr>
<td>Follicle associated epithelium</td>
<td>&lt;750 nm</td>
<td>MLN</td>
</tr>
</tbody>
</table>
in GIT and hence prolong the gastric residence time and functionally offer a sustained drug release. The microspheres of particle size less than 0.87 \( \mu m \) are taken to the general circulation. The fluid environment of the GIT can affect the number and rate of particles translocation.

Microspheres given by the parenteral route (intravenous) distribute themselves according to their size range. The micro particulate carriers are rapidly cleared from the circulation mainly by means of reticulo endothelial system (Fig. 14).

After intravenous administration the particulate carriers distribute themselves passively or if suitably designed then actively. This distribution is referred to as passive mode of the site specific delivery of the microparticulates.

**PHYSICO-CHEMICAL CHARACTERIZATION**

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 (Barkai et al., 1997).

**Particle size and shape:** The most widely used procedures to visualize microspheres are conventional Light Microscopy (LM) and Scanning Electron Microscopy (SEM). Both can be used to determine the shape and outer structure of microspheres. Light Microscopy (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 (Jain, 2004). Scanning Electron Microscopy (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 (Bodmeier and Chen, 1989). 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.

**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 constant pressure 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 microspheres carrier is determined (Sinha et al., 2005).

**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 behavior or ion absorption nature of the microspheres.

**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 mounted above objective of inverted microscope. Contact angle is measured at 20°C within a minute of deposition of microspheres (Kawashima et al., 1991).

**Electron spectroscopy for chemical analysis:** The surface chemistry of the microspherees can be determined using the Electron Spectroscopy for Chemical Analysis (ESCA). Electron Spectroscopy for Chemical Analysis (ESCA) provides a means for the determination of the atomic composition of the surface. The spectra obtained using ECSA can be used to determine the surfacial degradation of the biodegradable microspheres.

**Fourier transform-infrared spectroscopy:** The FT-IR 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 through the 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 and conditions (Tanaka et al., 1977).

**Entrapment efficiency:** The capture efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lysate. The lysate is then subjected to the determination of active constituents as per monograph requirement. The percent encapsulation efficiency is calculated using following equation:

\[
\text{Entrapment (\%)} = \frac{\text{Actual content}}{\text{Theoretical content}} \times 100
\]

**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 physiochemically 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.

**Beaker method:** Ishida et al. (1983) and Collins and Deasy (1990) reported that 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 from 60-300 rpm.

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

**Modified Keshary Chien cell:** Save and Venkitachalam (1994) developed a specialized apparatus in the laboratory. It comprised of a Keshary Chien cell containing distilled water (50 mL) at 37°C as dissolution medium. Trans Membrane Drug Delivery System (TMDDS) was placed in a glass tube fitted with a 10 No. sieve at the bottom which reciprocated in the medium at 30 strokes per minute.

**Dissolution apparatus:** Standard USP or BP dissolution apparatus have been used to study in vitro release profiles using rotating elements, paddle (Parodi et al., 1996) and basket (Cassidy et al., 1993). Dissolution medium used for the study varied from 100-500 mL and speed of rotation from 50-100 rpm.

**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.

**Animal models:** Animal models are used mainly for the screening of the series of compounds, investigating the mechanisms and usefulness of permeation enhancers or evaluating a set of formulations. A number of animal models have been reported in the literature, very few in vivo animal models are the dogs (Rathbone et al., 1996), rats, rabbits (Hussain et al., 1987), cats (Oh and Ritschel, 1999), hamsters (Kellaway and Warren, 1991), pigs and sheep (Hoogstraate et al., 1996) etc. In general, the procedure involves anesthetizing the animal followed
by administration of the dosage form. In case of rats, the esophagus is ligated to prevent absorption pathways other than oral mucosa. At different time intervals, the blood is withdrawn and analyzed.

**Buccal absorption test:** The buccal absorption test was developed by Beckett and Trigg's (1967). It is a simple and reliable method for measuring the extent of drug loss of the human oral cavity for single and multi-component mixtures of drugs. The test has been successfully used to investigate the relative importance of drug structure, contact time, initial drug concentration and pH of the solution while the drug is held in the oral cavity.

**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.

**APPLICATIONS**

**Applications of types of microspheres:** New applications for microspheres are discovered every day few are given in Table 2 and 3. Some formulations are also presented in Fig. 15.

<table>
<thead>
<tr>
<th>Types of microsphere</th>
<th>Applications</th>
</tr>
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<tbody>
<tr>
<td>Radioactive</td>
<td>Radioembolization of liver and spleen tumors, local radiotherapy, local restenosis prevention in coronary arteries</td>
</tr>
<tr>
<td>Fluorescent</td>
<td>Blood flow determination, tracing, <em>in vivo</em> imaging and calibration of imaging</td>
</tr>
<tr>
<td>Hollow</td>
<td>Used to decrease material density</td>
</tr>
<tr>
<td>Monodisperse</td>
<td>Calibrate particle sieves and particle counting apparatus</td>
</tr>
<tr>
<td>Ceramics</td>
<td>Paints and powder coatings</td>
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<tr>
<td>Magnetic</td>
<td>Used for drug targeting, magnetic fluid hyperthermia, improvement in drug release</td>
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</tbody>
</table>

**Fig. 15:** Marketed formulations
<table>
<thead>
<tr>
<th>Target site</th>
<th>Drug use</th>
<th>Method of formulation</th>
<th>Applications</th>
<th>Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ophthalmic</strong></td>
<td></td>
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</tr>
<tr>
<td>Sahil et al. (2011),</td>
<td>Cyclosporine,</td>
<td>Cross linking and</td>
<td>Polymer hydrogels offer better acceptability. Increase precorneal drug residence time. Increase duration of efficacy of drug by using higher molecular weight polymer</td>
<td>Chitosan, Alginate and Gelatin</td>
</tr>
<tr>
<td>Bansal et al. (2011) and</td>
<td>Acyclovir,</td>
<td>coacervation phase separation</td>
<td></td>
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<tr>
<td><strong>Nasal</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Prasanth et al. (2011),</td>
<td>Beclomethasone,</td>
<td>Single emulsion, double emulsion</td>
<td>Brain achieved light concentration of drug, improve nasal absorption, increase bioavailability of drug</td>
<td>Starch, Dextran, Albumin,</td>
</tr>
<tr>
<td>Sahil et al. (2011),</td>
<td>Dipropionate monohydrate and Oxymetazoline</td>
<td>method and phase separation method</td>
<td></td>
<td>Chitosan+Gelatin, Carbopol BSA and Gelatin</td>
</tr>
<tr>
<td>Pereswetoff-Morath (1998) and Rathananand et al. (2007)</td>
<td>hydrochloride</td>
<td></td>
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<td><strong>Gastrointestinal drug delivery</strong></td>
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<tr>
<td>Sahil et al. (2011), Bansal et al. (2011), Singh and Chaudhary (2011) and Jyotsna et al. (2010)</td>
<td>Ranitidine hydrochloride, Melatonin, Aceclofenac, Fluoxetine, Amoxicillin, Prednisolone, Metoclopramide, Olipizid</td>
<td>Solvent evaporation and by dissolving drug in polymer cross linking separation method</td>
<td>Floating and hollow microsphere can be used in drug delivery, controlled drug release system, decrease fluctuation in plasma drug concentration and retention of microsphere in stomach for more than 10 h</td>
<td>Ethylcellulose+ Carbopol BSA and Gelatin</td>
</tr>
<tr>
<td><strong>Buccal</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Sahil et al. (2011) and</td>
<td>Chlorhexide, Nefidine and Propanol hydrochloride</td>
<td>Encapsulation and coacervation phase separation</td>
<td>Prolonged release of drug in buccal cavity, improve antimicrobial activity, decrease in toxicity and increase in patient compliance</td>
<td>Chitosan, Sodium alginate and Gellan gum</td>
</tr>
<tr>
<td>Bansal et al. (2011)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Oral</strong></td>
<td></td>
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</tr>
<tr>
<td>Sahil et al. (2011) and</td>
<td>Diabepam and Insulin</td>
<td>Cross linking method and solvent evaporation method</td>
<td>Increase patient compliance, multiple unit system can be produced, avoid the exposure of high concentration of drug to mucosa and faster drug release</td>
<td>Chitosan and Gelatin</td>
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<tr>
<td>Senthil et al. (2011b)</td>
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<tr>
<td><strong>Intra tumoral</strong></td>
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<tr>
<td>Sahil et al. (2011) and</td>
<td>Fluorouracil, Cisplatin, Methotrexate and Olantrafol</td>
<td>Dry in oil, w/o in admixture system and combined emulsion</td>
<td>Delivery of therapeutically relevant concentration of drug at tumour site, increase concentration of drug at tumour site, decrease in side effect and toxicity of anticancer drugs, enhance drug concentration in brain and Maximize therapeutic efficacy.</td>
<td>Gelatin, PLGA, Chitosan and PCL</td>
</tr>
<tr>
<td>Bansal et al. (2011)</td>
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<tr>
<td><strong>Vaginal</strong></td>
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<tr>
<td>Sahil et al. (2011) and</td>
<td>Metronidazole, Acriflamine, Methotrexate</td>
<td>Solvent evaporation and by dissolving drug in polymer cross linking</td>
<td>Treatment of mycotic infection of genitourinary tract, Increase residence time of vaginal mucosa tissue and Adequate release and good adhesion property</td>
<td>Chitosan, Gelatin and PLGA</td>
</tr>
<tr>
<td>Bansal et al. (2011)</td>
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</table>

<table>
<thead>
<tr>
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<th>Drug use</th>
<th>Method of formulation</th>
<th>Applications</th>
<th>Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transdermal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bansal et al. (2011)</td>
<td>Prednisolone, Lidocaine hydrochloride and Local anesthetics</td>
<td>Solvent extraction method, spray drying and spray concealing method</td>
<td>Relevant packaging sustained release action improving therapeutic efficacy biocompatible and biodegradable polymer system can be used</td>
<td>Chitosan alginate, Chitosan gelantine and PLGA</td>
</tr>
<tr>
<td><strong>Gene delivery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sahil et al. (2011)</td>
<td>Genes</td>
<td>Cross-linking method, polymerization method</td>
<td>Highly efficient and have wide range of cell targeting, it also causes immune responses and oncogenic effects and use as a carrier of DNA for gene delivery applications</td>
<td>Chitosan and Gelatin</td>
</tr>
<tr>
<td><strong>Monoclonal antibodies</strong></td>
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<tr>
<td>Vyas and Khar (1990) and Bansal et al. (2011)</td>
<td>Amoxicillin, Ampicillin, Tetracycline, Sulfadiazine and Griseofulvire</td>
<td>Solvent evaporation method, spray drying and coacervation method</td>
<td>Extremely specific site targeting, maximum stability of deliver antigen and prolonged antigen release and lasting immunity</td>
<td>Chitosan, Alginate and PLGA</td>
</tr>
</tbody>
</table>
CONCLUSION

It has been observed that microspheres are better choice of drug delivery system than many other types of drug delivery system because to it is having the advantage of target specificity and better patient compliance. It is concluded from above that microsphere is the promising candidate for sustained and as a targeted drug delivery in GIT, liver, colon, nasal, pulmonary system and ocular drug delivery etc. Its applications are enormous as they are not only used for delivering drugs but also for imaging tumours, detecting bio molecular interaction used as diagnostic agent and for treatment of cancer too, etc. Hence, in future microspheres will have an important role in the advancement of medicinal field.

REFERENCES


