

**BIODEGRADABLE MICROSPHERES: A REVIEW**

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**ABSTRACT**

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers having a particle size ranging from 1-1000  $\mu\text{m}$ . The range of techniques for the preparation of microspheres offers a variety of opportunities to control aspects of drug administration and enhance the therapeutic efficacy of a given drug. Of the many polymeric drug delivery systems, biodegradable polymers have been used widely as drug delivery systems because of their biocompatibility and biodegradability. The majority of biodegradable polymers have been used in the form of microparticles, from which the incorporated drug is released to the environment in a controlled manner. They can be employed to deliver medication in a rate-controlled and sometimes targeted manner. Medication is released from a microsphere by drug leaching from the polymer or by degradation of the polymer matrix. This review discusses characteristics and degradation behaviors of biodegradable polymers which are currently used in drug delivery.

**Keywords:** Microspheres, biodegradable polymer, novel drug delivery system.

**INTRODUCTION**

For the past few decades, biodegradable polymers have been applied as carriers for controlled delivery of low molecular weight drugs as well as bioactive proteins. Delivering drugs through biodegradable microspheres has numerous advantages compared to conventional delivery systems. While in conventional systems the drug is usually released shortly after delivery and stops working after a brief period of time, biodegradable polymer offer a way to provide sustained release over a longer time, thus eliminating the need for multiple doses and ensuring sustained and controlled drug delivery over weeks or months<sup>1-5</sup>. These, either synthetic or natural, are capable of being cleaved into biocompatible byproducts through chemical or enzyme-catalyzed hydrolysis. They prolongs the residence time when come in contact with mucous membrane due to it's high degree of swelling property with aqueous medium, results gel formation. The rate and extent of drug release is controlled by concentration of polymer<sup>6</sup> 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<sup>7</sup>. The release rates of the drugs from biodegradable polymers can be controlled by a number of factors, such as biodegradation kinetics of the polymers<sup>8-9</sup>, physicochemical properties of the polymers and drugs<sup>10-11</sup>, thermodynamic compatibility between the polymers and drugs<sup>12</sup>, and the shape of the devices<sup>13-16</sup>.

A few examples of biodegradable polymers used in microsphere preparation include

**Synthetic Polymers:**

Polyesters, Poly(ortho esters), Polyanhydrides, Polyphosphazenes.

**Natural Polymers:**

Drug delivery systems using natural polymers have been based on:

- Proteins (e.g., collagen, gelatin, and albumin)
- Polysaccharides (e.g., starch, dextran, hyaluronic acid, and chitosan).

**Classification of biodegradable polymers:**

Biodegradable polymers may be classified based on the mechanism of release of the drug entrapped in it as under:

- Slow dissolution and erosion by hydrolysis

- Water insoluble polymer undergoing hydrolysis, ionization or protonation of pendant group without undergoing backbone cleavage.
- Water insoluble polymer degrades to water soluble products by backbone cleavage.

**ADVANTAGES**

- Microspheres provide constant and prolonged therapeutic effect.
- Reliable means to deliver the drug to the target site with specificity.
- Reduces the dosing frequency and thereby improve the patient compliance.
- Solid biodegradable microspheres have the potential throughout the particle matrix for the controlled release of drug.
- Studies on the macrophage uptake of microspheres have demonstrated their potential in targeting drugs to pathogens residing intracellularly.
- Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
- The size, surface charge and surface hydrophilicity of microspheres have been found to be important in determining the fate of particles *in vivo*.
- Their morphology allows a controllable variability in degradation and drug release<sup>17</sup>.

**DISADVANTAGES**

Some of the disadvantages were found to be as follows

1. The modified release from the formulations.
2. The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
3. Differences in the release rate from one dose to another.
4. 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 potential toxicity.
5. Dosage forms of this kind should not be crushed or chewed<sup>17</sup>.

**APPLICATIONS**

Some of the applications of microencapsulation can be described in detail as given below

1. Prolonged release dosage forms. The microsphere drug can be administered, as microsphere is perhaps most useful for the preparation of tablets, capsules or parenteral dosage forms.
2. Microsphere can be used to prepare enteric-coated dosage forms, so that the medicament will be selectively absorbed in the intestine rather than the stomach.
3. From the mechanical point of view, microsphere has been used to aid in the addition of oily medicines to tableted dosage forms. This has been used to overcome problems inherent in producing tablets from otherwise tacky granulations. This was accomplished through improved flow properties. For example, the non-flowable multicomponent solid mixture of niacin, riboflavin, and thiamine hydrochloride and iron phosphate may be encapsulated and made directly into tablets. [18]
4. It has been used to protect drugs from environmental hazards such as humidity, light, oxygen or heat. Microsphere does not yet provide a perfect barrier for materials, which degrade in the presence of oxygen, moisture or heat, however a great degree of protection against these elements can be provided. For example, vitamin A and K have been shown to be protected from moisture and oxygen through microsphere.
5. It helps in the separations of incompatible substances, for example, pharmaceutical eutectics have been achieved by encapsulation. This is a case where direct contact of materials brings about liquid formation. The stability enhancement of incompatible aspirin-chlorpheniramine maleate mixture was accomplished by microencapsulating both of them before mixing.
6. They can be used to decrease the volatility. An encapsulated volatile substance can be stored for longer times without substantial evaporation<sup>19</sup>.

**Factors affecting the release from the particulate system:**  
**Table 1**

Drug	Microsphere	Environment
Position in microspheres	Type and amount of the matrix polymer	PH
Molecular weight	Size and density of the microspheres	Polarity
Physicochemical properties	Extent of cross linking	Presence of enzyme

**VARIABLES INFLUENCING DRUG RELEASE PATTERN OF MICROSPHERES:**

There are following factors which directly/indirectly affect the drug release characteristics of the microspheres

**A. Concentration of the polymer in dispersed phase:**

Polymer concentration in aqueous phase indirectly affects the time and drug release. As the polymer concentration in aqueous phase increases, size of microspheres is increased which results increase in time and slower drug release from microspheres<sup>20</sup>.

**B. Drug: Polymer Ratio (DPR):**

Drug release from microspheres is affected by the ratio of the drug to the polymer as increasing in the first causes faster drug release. By increasing the amount of drug loading, a point will be reached when the solid drug particles upon dissolution will begin to form continuous pores or channels within the matrix. Under these circumstances, the path of release for drug molecules will be diffusion within the channels formed from areas where drug has previously leached out from the matrix. In other words, as the amount of drug content is increased the matrix will become more porous as drug is leached out from the polymer and thus faster drug

release rate occurs. At lower drug-polymer ratios, the mean particle size of the micropellets was less than that at higher drug-polymer ratios. Therefore, the drug release from micropellets prepared at lower drug-polymer ratios was faster than that of micropellets prepared at higher drug-polymer ratios because of the small size of the micropellets, which provided a large surface area for faster drug release<sup>21</sup>.

**C. Selection of solvent system for the dispersed phase**

Selection of solvent system based on the volatility of solvent, solubility of polymer and type of method of preparation used for preparation of microspheres. Solvent should have high volatility and high polymer solubility.

**D. Effect of Temperature:**

Microspheres prepared at 60°C showed faster drug release than the microspheres prepared at 10°C. This can be attributed to the decrease in viscosity of the oily phase as the temperature increases, which in turn decrease the microspheres<sup>22</sup>.

**E. Effect of stirring speed:**

The drug release rate was increasing on increasing the stirring rate. Drug release was higher in the case of microspheres prepared at a higher stirring rate but at low stirring rate the release rate was slow. This can be attributing that smaller size microspheres have a larger surface area exposed to dissolution medium, giving rise to faster drug release<sup>23</sup>.

**PREPARATION METHOD OF MICROSPHERES**

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.
- Release of active reagent with a good control over a wide time scale.
- Biocompatibility with a controllable biodegradability<sup>24</sup>.

**Preparation of microspheres of can be done by suitable methods like:**

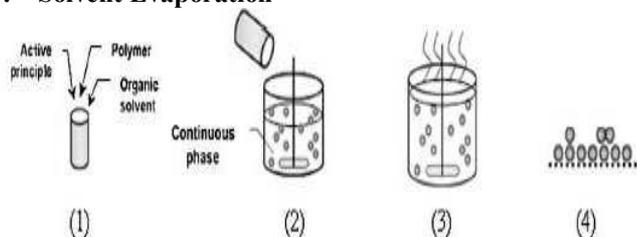
**1. Spray Drying**

In Spray Drying 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 evaporate instantaneously leading the formation of the microspheres in a size range 1-100µm. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of process is feasibility of operation under aseptic conditions this process is rapid and this leads to the formation of porous micro particles<sup>25</sup>.

**2. Spray congealing.**

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 cold 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<sup>26</sup>.

### 3. Solvent Evaporation

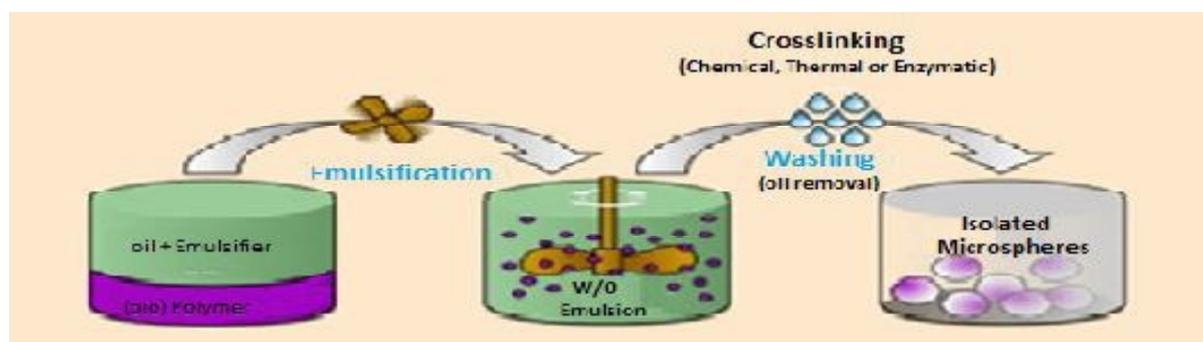


The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microsphere. The mixture is then heated if necessary to evaporate the solvent. The solvent Evaporation technique to

produce microspheres is applicable to wide variety of core materials fig1<sup>27</sup>.

### 4. Single emulsion technique

The microspheres can be prepared by using any of natural polymers, i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in the non aqueous medium e.g., oil. In the second step of preparation, cross linking of the dispersed globules carried out. The cross-linking agents can be achieved either by means of heat or by using cross-linking agents used include glutaraldehyde, formaldehyde, diacid chloride, etc. cross linking by heat is affected by adding the dispersion to previously heated oil. Heat denaturation is however, not suitable for the thermolabile drugs while the chemical cross-linking suffers disadvantage of excessive exposure of active ingredient to chemical cross-linking suffers disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation figure 2.



### 5. Double emulsion technique

Double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA). This results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction. a number of hydrophilic drugs like leutinizing hormone releasing hormone (LH-RH) agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation/ extraction<sup>28</sup>.

### 6. Polymerization techniques

The polymerization techniques conventionally used for the preparation of the microspheres are mainly classified as:

#### I. Normal polymerization

#### II. Interfacial polymerization.

Both are carried out in liquid phase.

#### I. Normal polymerization

It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. In bulk, a monomer or a mixture of monomers along with the initiator or catalyst is usually

heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done during the process of polymerization. Suspension polymerization also referred as bead or pearl polymerization. Here it is carried out by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives. Emulsion polymerization differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. Bulk polymerization has an advantage of formation of pure polymers.

#### II. 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<sup>27</sup>.

### 7. Phase separation coacervation technique

This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer. Poly lactic acid (PLA) microspheres have been prepared by this method by using butadiene as incompatible polymer. The process variables are very important since the rate of achieving the coacervates determines the distribution of the polymer film, them particle size and agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize

globules start to stick and form the agglomerates. Therefore the process variables are critical as they control the kinetic of the formed particles since there is no defined state of equilibrium attainment<sup>29</sup>.

#### Characterization and evaluation:

##### 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<sup>17</sup>. 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<sup>1</sup> 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.

##### 2. Electron spectroscopy for chemical analysis

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

##### 3. Attenuated total reflectance Fourier Transform-Infrared Spectroscopy

FT-IR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring attenuated 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 ATRFTIR provides information about the surface composition of the microspheres depending upon manufacturing procedures and conditions.

##### 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 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 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. Capture efficiency

The capture efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyse. The lysate is then subjected to the determination of active constituents as per monograph

requirement. The percent encapsulation efficiency is calculated using following equation:

$$\% \text{ Entrapment} = \text{Actual content} / \text{Theoretical content} \times 100$$

##### 7. 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 200C within a minute of deposition of microspheres.

##### 8. 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 physico 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.

##### 9. 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.

##### 10. Dissolution apparatus

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

##### 11. 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"<sup>1</sup>. Such correlations allow one to develop product specifications with bioavailability.

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