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# TECHNOLOGY OF PREPARATION OF MICROENCAPSULATED FORMS FOR SUSTAINED RELEASE USING BIODEGRADABLE POLY LACTIC-CO-GLYCOLIC ACID (PLGA) POLYMER– REVIEW

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**ABSTRACT**

Sustained-release drug-loaded microspheres provide a prolonged and precise delivery of medications combined with other advantageous effects. These microspheres are available in several varieties and may be synthesized using numerous techniques, which are reasonably straightforward to execute. Consequently, they have garnered considerable interest and are widely employed in tissue engineering and other associated disciplines. The aim of this review article is to offer a thorough and up-to-date examination of the essential understanding and present state of PLGA biodegradable microspheres. This work contains a discussion of the properties, pharmacokinetics and pharmacodynamics of the PLGA matrix material. In addition, the report outlines the several techniques used to prepare PLGA microspheres, including emulsification, microfluidic technology, electrospray, and spray drying.

**KEYWORDS:** Poly lactic-co-glycolic acid (PLGA), sustained release drugs, microencapsulation, emulsification, microfluidics, spray drying, electrospraying.

## 1. INTRODUCTION

Microencapsulation is the technique employed to produce particles within the range of microns in size. These particles consist of one or more central components and are enveloped by one or more outer shell elements. Microencapsulation, a method that entails encapsulating minute particles or droplets within a shielding layer, has been in use since the 1930s. Microencapsulation technology was utilized to create carbonless copy paper, which became the inaugural commercially accessible product in its category.[1] Following then, this technology has experienced significant progress, leading to a wide variety of products in industries such as pharmaceuticals, medicine, agriculture, food, manufacturing, and cosmetics. The pharmaceutical sector frequently employs microencapsulation techniques to produce medication delivery systems.

A microsphere is a spherical object that has a diameter of one micron or less. The system is comprised of a homogeneous phase consisting of one or more polymers that are blended and dissolved together. In this matrix,

medicines and other components are distributed or dissolved.[2] Microspheres may be classified into four categories: solid, double-layer, hollow, and porous microspheres.[3,4,5] A solid microsphere has a uniform and substantial density over its whole volume. Although solid microspheres have the capacity to provide extended drug release, they are impeded by challenges such as excessive initial concentration bursts, prolonged drug release durations and restricted encapsulation efficacy. Therefore, solid microspheres are currently not widely used.[6,7] In order to tackle the problems related to solid microspheres, a potential solution is to enhance them by employing polymers as a protective layer. The purpose of this coating is to reduce the initial amount of the microspheres materials released in a burst. The microsphere are commonly known as double-layer microspheres or double-walled microspheres. Using polymers as coatings for microspheres can improve their drug delivery capabilities while also reducing the initial release of the medicament.[8] Hollow microspheres possess a hollow center and a uniform exterior shell, enabling them to enclose medications and other minuscule molecular substances. Studies have shown that hollow adhesive microspheres with optimal characteristics have both buoyancy and sustained-release capabilities due to their hollow interiors.[9] The fabrication of empty microspheres using the self-loading method was shown by Li et al. The microspheres demonstrated improved encapsulation efficiency, larger diameter, higher conductivity, and greater drug uptake in organisms.[10] Porous microspheres possess several voids on the surface of their shell. Porous microspheres are formed by incorporating a pore-generating material into solid microspheres. The microspheres exhibit numerous noteworthy characteristics, including a significant specific surface area, low density, and modifiable porosity.[11] Porous microspheres are created using three main types of pore-forming agents: permeable, gas-forming, and extractable agents. Wang et al. conducted an in vitro investigation to investigate the drug release characteristics of porous microspheres, solid microspheres, and hollow microspheres. It was found that the porous microspheres had a superior rate of encapsulation and a bigger cumulative release of drugs in comparison to the other two types of microspheres. These findings indicate that porous microspheres have great potential for application in sustained-release systems.[12]

Microspheres are predominantly administered by oral, intravenous, or subcutaneous implantation methods, as well as via intraperitoneal injection, among other means. Studies have demonstrated that microspheres significantly improve patient adherence in comparison to traditional medicines.[13] The pharmaceutical industry can employ microencapsulation for several goals, including representation, application, and potential benefits. These include the reduction of adverse effects and the enhancement of therapeutic efficacy by targeting the intended site of action. Additionally, microencapsulation allows for the controlled release of drugs from the encapsulated microparticles, ensuring optimal drug delivery. Furthermore, it enhances the stability of drugs by creating a protective barrier between the drug and its surrounding environment. Microencapsulation also aids in improving the solubility of poorly soluble drugs through particle size reduction. Lastly, it can effectively mask the taste and odor of certain drugs, improving patient acceptance and adherence to medication regimens.[14]

Microspheres have a uniform shape and size, as well as unique properties that allow them to absorb or spread ions, extracellular chemicals, and drugs throughout the regeneration process. Furthermore, microspheres have the capability to act as reservoirs for medications and act as carriers for bioactive compounds.[15]

Microencapsulated particles are increasingly vital in systems that regulate the release of drugs. Biocompatible microparticles that have been modified to have different drug release profiles offer significant benefits for the

development of injectable formulations, particularly for achieving sustained release, responsive release to specific signals, and pulsatile release.[16]

Sustained release involves encapsulating medicines within one or more shell materials to control the rate of diffusion of drugs from the microparticle into the surrounding environment. In addition, certain microparticles demonstrate drug release by an erosion mechanism, where the rate and extent of drug release are directly linked to the speed and quantity of degradation of the shell material. Consequently, the microparticles gradually and continuously release medications over a prolonged period of time. The duration of drug release may be controlled by defining a set of microencapsulation process parameters. A significant advantage of this approach is its ability to maintain drug levels in the bloodstream within the therapeutic range for an extended period of time. This has substantial implications for improving patient adherence, since it frequently results in a reduced frequency of necessary administrations.[16]

Signal-responsive release involves the deliberate and regulated release of medicines from microparticles in reaction to either internal or external stimuli. This technology enables the alteration of the release patterns of conventional medication formulations in a sophisticated manner. In this situation, microparticles demonstrate low or insignificant drug release until a signal is detected that modifies the rate of release. Significant obstacles have emerged in attempts to link the administration of medications to internal stimuli, such as distinct chemical signals or biological needs. However, much research has been conducted on the effects of external stimuli, such as a magnetic field, on release, and the results have been promising. Moreover, the magnetic field possesses the capacity to accurately direct the concentrated accumulation of microparticles. Utilizing signal-triggered release offers the capacity to reduce detrimental side effects associated with the extensive utilization of injectable formulations.[16]

Pulsatile Release: Pulsed systems include the precise and controlled release of drugs in one or many discrete pulses over a defined period of time. Usually, these systems are formed by deliberately adding one or more time delays in the process of microparticle degradation. The concept of pulsatile delivery is now in its initial phases but shows considerable promise, especially for the delivery of many challenging antigens and peptide hormones. Administering antibiotics in a discontinuous manner hinders the growth of antibiotic-resistant bacterial strains. To improve patient compliance, the need for additional booster injections following the initial injection can be eliminated. The medication delivery impact of the method can be replicated by constructing pulsatile devices.[17]

**2. Biodegradable Polymers**

Biodegradable materials, irrespective of their source, undergo destruction within living organisms by enzymatic or non-enzymatic mechanisms, or a combination of both. The deterioration results in the creation of by-products that are both biocompatible and non-toxic. Afterwards, the body's intrinsic metabolic pathways remove these remaining chemicals. In the last ten years, there has been a significant rise in the quantity of substances employed in controlled medication delivery, either as primary constituents or as supplementary compounds. The biomaterials employed in drug delivery may be classified into two main categories: synthetic biodegradable polymers and naturally generated polymers. Some examples of synthetic biodegradable polymers include hydrophobic compounds like α-hydroxy acids (e.g., poly lactic-co-glycolic acid, PLGA), polyanhydrides, and several others. Hyaluronan and chitosan are examples of complex polysaccharides found in nature, while hydroxyapatite is an inorganic material.[18,19,20] The diverse selection of materials utilized in drug administration is a result of the wide array of illnesses, dose quantities, and specific requirements that may be encountered. Biocompatibility is a crucial factor to consider, but it is essential to

acknowledge that it is not an inherent characteristic of a material. However, the outcome is contingent upon the biological milieu and the level of tolerance for certain interactions between drugs, polymers, and tissues. [20]

### 2.1. Poly Lactic-co-Glycolic Acid (PLGA)

Poly Lactic-co-Glycolic Acid (PLGA) is a polyester copolymer synthesized by combining poly lactic acid (PLA) and poly glycolic acid (PGA). At now, it is the biomaterial that has been most accurately described in terms of its design and performance for delivering drugs. Poly lactic acid possesses an asymmetrical α-carbon, commonly referred to as either the D or L form in traditional stereochemical nomenclature, or occasionally as the R or S form, respectively. PLA, a polymer, exists in two enantiomeric forms: poly D-lactic acid (PDLA) and poly L-lactic acid (PLLA). PLGA is an abbreviation for poly D,L-lactic-co-glycolic acid, which is a chemical made up of equal quantities of D- and L-lactic acid.[21]

#### *2.1.1. Physico-Chemical Properties*

A comprehensive study of the physical, chemical, and biological aspects of PLGA is crucial for improving the controlled release of pharmaceuticals. The physicochemical properties of both optically active PDLA and PLLA are almost identical. PLA, a kind of polymer, may often be found in two unique forms: extremely crystalline, known as PLLA, or entirely amorphous, referred to as PDLA. The differentiation between the two states, amorphous and crystalline, is determined by the organization of polymer chains, where the amorphous state is defined by a lack of order or chaos. The PGA molecule lacks any methyl side groups and possesses a highly crystalline structure, as seen in Figure 1, in contrast to PLA. PLGA possesses remarkable processability, allowing it to be transformed into various shapes and sizes. Furthermore, it has the ability to enclose molecules of almost any size. The material has a high solubility in commonly used solvents such as chlorinated solvents, tetrahydrofuran, acetone, and ethyl acetate.[22,23] PLGA undergoes degradation in water by the hydrolysis of its ester bonds (Figure 2). The hydrophobicity of PLA is increased compared to PGA by including methyl side groups. As a result, PLGA copolymers with a high lactide content exhibit lower hydrophilicity, less water absorption, and thus, slower degradation. The process of hydrolysis of PLGA can cause time-dependent alterations in properties that are commonly thought to be constant in a solid formulation, including the glass transition temperature (Tg), moisture content, and molecular weight. The influence of these polymer properties on the speed of drug release from biodegradable polymeric matrices has been thoroughly examined. The alteration of PLGA characteristics during polymer biodegradation affects the rates of drug molecule release and degradation. The physical characteristics of PLGA are influenced by several parameters, including as the initial molecular weight, the lactide to glycolide ratio, the size of the device, water exposure (surface shape), and storage temperature.[24]

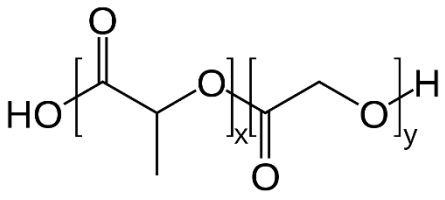


**Figure 1: Structure of poly lactic-co-glycolic acid (x is the number of lactic acid units and y is number of glycolic acid units).**

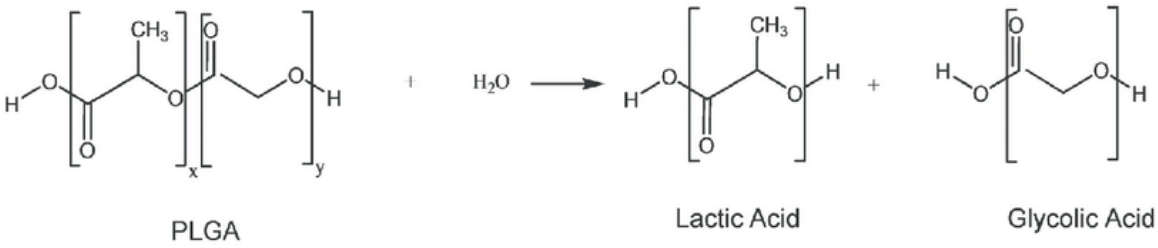


**Figure 2: Hydrolysis of poly lactic-co-glycolic acid.**

The mechanical resilience of PLGA is influenced by physical characteristics such as the molecular weight and polydispersity index. Moreover, these attributes exert an impact on the capacity to be utilized as a vehicle for medication administration and can regulate the pace of device deterioration and hydrolysis. The rate at which a medication is released is regulated by its exact makeup, as indicated by a recent study.[25] The crystallinity level of the PLGA has a direct influence on the mechanical strength, swelling behavior, hydrolysis capacity, and rate of biodegradation of the polymer. The degree of crystallinity is also affected by the particular kind and molar ratio of the different monomer components found in the copolymer chain. The addition of PGA to PLA during polymerization decreases the crystalline nature of PLGA, leading to a faster rate of hydration and hydrolysis. In general, an increased concentration of PGA results in faster deterioration, unless there is an equivalent 50:50 ratio of PLA and PGA. Under these circumstances, the degradation rate reaches its peak, and as the PGA content rises, the period of deterioration below 50% is prolonged. The molecular weight of a polymer has a direct correlation with both its degree of crystallinity and melting point. The PLGA copolymers have a known glass transition temperature (Tg) that is higher than the usual physiological temperature of 37 °C. As a result, they have a glass-like quality and consist of a rather inflexible chain arrangement. According to reports, the glass transition temperature (Tg) of PLGAs decreases when there is a decrease in the amount of lactide and the molecular weight in the copolymer composition.[26] PLGA polymers that are commercially accessible are typically evaluated based on their inherent viscosity, which is strongly associated with their molecular weights.

### *2.1.2. Pharmacokinectics and Pharmacodynamics*

To achieve the desired therapeutic outcome, the drug delivery vehicle, known as PLGA, must possess the ability to transport its cargo with the required duration, biodistribution, and concentration. Hence, the design should include protocols that facilitate the decomposition and eradication of both the vehicle and the active pharmaceutical ingredients (API). These aspects encompass the content, shape, and location. The distribution and processing of PLGA in the body exhibit a non-linear and dose-dependent relationship.[27] Furthermore, prior research indicates that the number and type of PLGA carrier systems may impact the evacuation of blood and its absorption by the mononuclear phagocyte system (MPS).[28] Moreover, findings derived from whole-body autoradiography and quantitative distribution studies suggest that certain forms of PLGA, namely nanoparticles, exhibit fast aggregation in the liver, bone marrow, lymph nodes, spleen, and peritoneal macrophages. During the early phase, around 30% of the overall deterioration of the PLGA carriers takes place rapidly. Subsequently, the rate of breakdown decelerates until it is entirely eliminated by inhalation in the lung.[29] In order to overcome these restrictions, researchers have examined the consequences of modifying the surface. Research has shown that the use of surface modifying chemicals can greatly extend the length of time that blood circulates in the body.[30]

### 2.2. Copolymers of PLGA

The demand for improved delivery formulations, including a diverse range of medications and administration techniques, has led to the creation of several block copolymers consisting of polyesters and polyethylene glycol (PEG). PLGA/PEG block copolymers have been synthesized as diblock (PLGA-PEG),[31,32] ABA triblock (PLGA-PEG-PLGA) [33], and BAB triblock (PEG-PLGA-PEG)[34] structures. The PEG chains in diblock topologies align towards the outer aqueous phase within micelles, effectively enveloping the contained contents. The addition of this polyethylene glycol (PEG) layer serves as a protective measure, minimizing interaction with external substances by steric and hydrated repulsion, hence prolonging the shelf life of the product.[35] Nevertheless, the inclusion of PEG in the system leads to a decrease in the effectiveness of enclosing medicines and proteins, even when utilizing the most suitable manufacturing methods. The decrease in drug incorporation can be attributed to the steric barrier caused by the interaction between the drug/protein and the PEG chains. The specific mechanism accountable for this impact remains undisclosed. Diblock copolymer compositions have exhibited superior release kinetics compared to PLGA alone. Scientific literature has documented several methods for precise drug delivery employing diblock nanoparticles.[31,35,36] Triblock copolymers can function as thermogels, exhibiting both ABA and BAB configurations, in which an A-block is covalently bonded to a B-block by an ester linkage. The copolymer typically exhibits a liquid state at low temperatures and can undergo a phase transition to produce a very viscous gel at physiological temperature. The temperature-responsive copolymers, PLGA-PEG-PLGA or PEG-PLGA-PEG, consist of hydrophobic PLGA segments and hydrophilic PEG segments arranged in blocks. The PLGA segments, possessing hydrophobic properties, establish intermolecular linkages, whilst the PEG segments, possessing hydrophilic properties, enable the copolymer molecules to remain in a dissolved state. At lower temperatures, the main interaction in the liquid solution is the creation of hydrogen bonds between hydrophilic PEG segments and water molecules, leading to the ability of PEG to dissolve in water. With rising temperature, the strength of hydrogen bonding decreases, while the hydrophobic forces between the PLGA segments strengthen, causing a transition from a liquid state to a gel state. The appealing characteristics of these thermoresponsive polymers lie in their easy manipulation during the stages of manufacture, formulation, filtering, and filling. The controlled release of medications and proteins from ABA and BAB copolymers is governed by two primary mechanisms: (i) the drug diffuses out of the hydrogel during the first release phase, and (ii) the drug is released when the hydrogel matrix gradually erodes in the subsequent phase. The degradation of PEG-PLGA-PEG gel results in the targeted removal of PEG-rich constituents. Consequently, the gel that remains becomes more resistant to water in a damp environment, leading to a decrease in its water content.[33,37,38,39,40] This pattern may be extended to incorporate more combinations of co-polymers, such as different copolymers of PLGA and polycaprolactone.[41,42]

## 3. Methods of manufacturing

Controlled or targeted release is employed in the pharmaceutical business to enhance specificity, reduce toxicity, and mitigate treatment-related risks. This approach is particularly useful for drugs and proteins. The scarcity of marketable pharmaceuticals can be ascribed to the stability and delivery difficulties connected with these molecules. To enhance the longevity of peptide and protein therapies, it is often crucial to employ solid-state formulation to restrict hydrolytic breakdown processes.[43] When administering peptides and proteins through medicine, it may be important to use parenteral formulations to prevent degradation in the digestive system and metabolism during the first pass. Moreover, the limited duration of peptides and proteins emphasizes the need for parenteral formulations that can decrease the frequency of administration. To circumvent the arduous and unpleasant surgical intervention of implanting sizable prosthetics, an alternative approach involves using injectable PLGA particles that possess the properties of being both

biodegradable and biocompatible. These particles, such as microspheres, microcapsules, nanocapsules, and nanospheres, are employed for the controlled release administration of pharmaceuticals. The release of medicinal chemicals from these polymeric devices occurs by a combination of diffusion over the polymer barrier, erosion of the polymer material, or a combination of both diffusion and erosion processes. PLGA exhibits biocompatibility, compatibility with pharmaceuticals, appropriate rates of biodegradation, and advantageous mechanical qualities. Furthermore, it may be readily processed and fabricated into many shapes and sizes. This section outlines several manufacturing procedures employed in the production of PLGA controlled drug delivery systems.[20]

### 3.1 Emulsifcation method

The emulsification-evaporation method is a direct process used to synthesize PLGA polymeric microparticles (MPs). The procedure entails generating one or more emulsions and subsequently vaporizing the organic solvent.[44] The execution of this process can be performed in a batch manner. Alternatively, one can employ advanced techniques such as the membrane emulsification approach[45] or the microfluidic system.[46;47] This part will present a concise elucidation of the fundamental concept and the latest advancements of this technique, including the utilization of both single and double emulsion ways in the batch operation, along with the use of microfluidics technology. In this instance, the single emulsion approach is utilized.

#### *3.1.1 Single emulsion technique*

The single emulsion approach is frequently used to encapsulate lipophilic compounds, such as steroids (e.g. Budenoside [48] and Leuprolide[49,50]), nutraceuticals (such curcumin)[51], and medicines (e.g. Donepezil[52] and Ketoprofen[53]). This method entails creating an emulsion of oil in water (O/W),[51] where both the polymer and drug are dissolved in a suitable solvent. Currently, the recommended solvents include of halogenated solvents that have a low boiling point, such as dichloromethane, chloroform, hexafluoro-isopropanol, as well as non-halogenated solvents including ethyl acetate, isopropanol, methyl ethyl ketone, acetone, and benzyl alcohol. Occasionally, a mixture of solvents is employed when necessary.[54] The oil phase (O) is mixed with the water phase, consisting of water and a surfactant or emulsifying agent such as polyvinyl alcohol (PVA), polyethylene glycol sorbitan monolaurate, sorbitan monooleate or sodium dodecyl sulfate, through the process of sonication or homogenization. The ultimate emulsion is produced as a consequence of this method (Figure 3a).

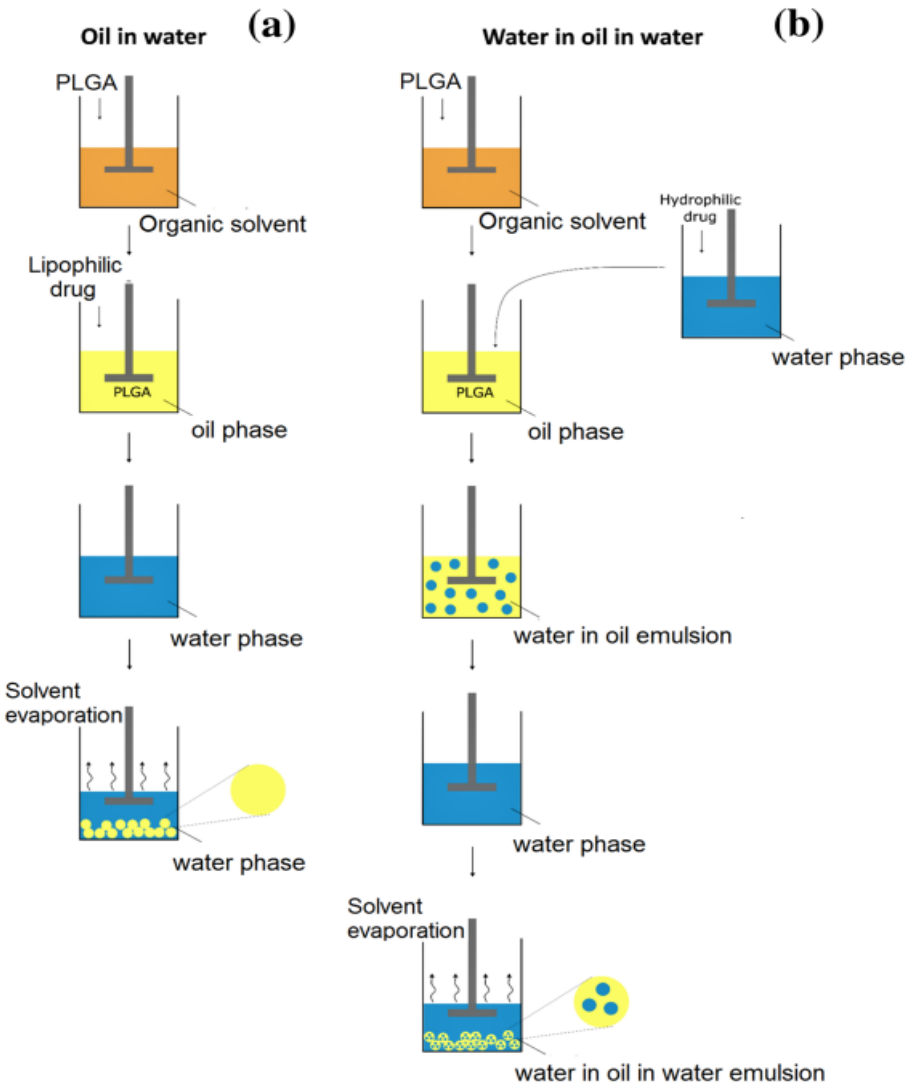


**Figure 3: Schematic representation of emulsion techniques: O/W single emulsion method (a) and W/O/W double emulsion (b).[55]**

The maturation of MPs is accomplished by the evaporation of the solvent, which may be expedited by either continuous stirring or by utilizing a solvent draw system at reduced pressure.[56] This methodology[57] has demonstrated significant efficacy in the management of neurological diseases. In Parkinson's disease (PD), neuronal death occurs due to oxidative stress, which is marked by an elevated generation of reactive oxygen species (ROS) and a decline in the activity of ROS-sensitive enzymes that help prevent the accumulation of neurotoxic substances in the brain, such as lecithin-cholesterol acyltransferase (LCAT).[58] Fernandez et al. administered rasagiline mesylate (RM), a very effective antioxidant compound, encapsulated in PLGA microspheres, to rats with an experimental model of Parkinson's disease (PD). Although there were no statistically significant differences observed between administering RM in solution or encapsulated inside microparticles, the ability to regulate the release of RM every 2 weeks makes this novel therapeutic technique a tempting option for managing PD.[59]

In recent years, authors have been progressively employing non-toxic solvents, such as dimethyl sulfoxide (DMSO), glycofurol, liquid PEG, propylene carbonate, ethyl propionate, dimethyl carbonate, and ethyl formate. The preference arises from the necessity to utilize safer methods of preparation and adhere to the regulations set out by the

International Conference on Harmonization (ICH) on residual solvents (Q3C(R4)). The ICH standards classify solvents into three separate categories: class I, which must be entirely avoided; class II, which should be limited; and class III, which provide a minimal risk of toxicity. Furthermore, the ICH standards establish the acceptable daily intake (ADI), the maximum allowable concentration for each solvent, and the recommended analytical technique for measuring the quantity of solvent residue.[60] By utilizing a non-toxic solvent, it is feasible to surmount these obstacles and get a more secure end product for the pharmaceutical sector.[61]

PLGA MPs can be readily altered by including excipients into the water or oil phase to enhance porosity,[62] enhance encapsulation efficiency,[63] and regulate drug release and stability.[64] To enhance porosity, one can utilize porous agents such as pluronics,[65] homogenized gelatin,[66] and cyclodextrins. Porogens may be categorized into three groups based on the mechanism of pore creation: osmosis-inducing agents, extractable porogens, and gas-foaming agents. Osmogens, which are substances that stimulate osmosis, lead to the creation of openings as a result of variations in osmotic pressure between the internal and exterior phases.[62] Pore structures are created by the use of extractable porogens, which take advantage of the time delay between the solidification of PLGA and the removal of porogens from the oil phase to the water phase.[66] In contrast, the formation of holes with gas-foaming agents is accomplished by the generation of gas bubbles (such as carbon dioxide, $CO_2$) induced by either an acidic solution or high temperature.[67] Alternatively, solid microparticles can be subjected to treatment with supercritical carbon dioxide to augment the creation of pores. Supercritical $CO_2$ has the ability to penetrate the PLGA matrix and expand, resulting in the creation of pores when the pressure is reduced while keeping the temperature constant.[68,69,70]

The regulation of drug release kinetics relies on the crucial aspect of adjusting the porosity of the microparticles, as mentioned before. This issue will be further scrutinized in the next part. The single emulsion process is a straightforward approach for producing PLGA MPs. However, this process does have certain drawbacks, such as a restricted capacity to properly encapsulate hydrophilic compounds. The encapsulation of these chemicals can be enhanced by employing a double or multiple emulsion approach.

### *3.1.2 Double emulsion technique*

The primary approach employed for encapsulating water-soluble pharmaceuticals, such as proteins, peptides, and vaccines, is the double emulsion technique. This technology is used because it has a straightforward operation, uses cost-effective equipment, and allows for precise control of process parameters.[71] Contrary to the single emulsion approach, this technique entails the creation of a multiple emulsion known as water in oil in water (W/O/W). The dispersive system has three distinct stages. An initial water-in-oil (W/O) emulsion is generated by combining an aqueous solution of hydrophilic medicines with a polymer solution, which is then emulsified using either a sonicator or a high-speed homogenizer. The emulsion in issue is generally known as the "primary emulsion". The first emulsion is then coupled with a considerable amount of continuous water phase, along with the introduction of an emulsifying agent (PVA), resulting to the development of the final W/O/W double emulsion, also known as the "secondary emulsion". The penultimate stage in obtaining the solidification of micro- and nanoparticles includes either evaporating or extracting the solvent, which is analogous to the single emulsion process (Figure 3b). Usually, this approach is employed to contain antiviral medications, proteins,[72,73] and nucleic acids,[74] which, unhappily, display great instability. In order to minimize the clumping and unfolding of proteins during the process of emulsification, sugars like trehalose and sorbitol are utilized in the internal water phase solution as stabilizing interface-active additives.[75,76]

Azizi et al. recently performed this technology to create W/O/W PLGA nanoparticles that encapsulate chondroitinase ABC (ChABC), a bacterial enzyme used to breakdown chondroitin sulfate proteoglycans (CSPGs) for the treatment of spinal cord injuries (SCI).[77] The solvent evaporation strategy employed both single and double emulsion procedures, creating micro- and nanoparticles with irregular form, high polydispersity, and low drug content. These constraints can be circumvented by adopting advanced technologies such as membrane emulsification or microfluidic devices, which alleviate the fundamental issues associated with the solvent evaporation approach, such as mechanical stirring and longer solvent evaporation time.

### *3.2 Microfluidics*

The traditional techniques of solvent evaporation, including the single and double emulsion processes, are widely used for synthesizing PLGA MPs because they are cost-effective and have simple procedures. Nevertheless, these techniques exhibit restricted ability to be replicated, a wide spectrum of particle dimensions, reduced ability to manipulate structure, and inadequate effectiveness in enclosing substances. In response to these considerations, different methodologies have been recently adopted to produce MPs with desired characteristics in a controlled way.[78] The utilization of microfluidic technology is the most effective method for generating MPs in this particular situation.

Microfluidic devices are comprised of microchannels made from various materials, such as polymers like poly-dimethyl siloxane (PDMS), poly-(methyl methacrylate) (PMMA), polycarbonate (PC), and polyimide, as well as metal (aluminum), phenol formaldehyde resin-based materials, and glass capillaries made of quartz, fused silica, and borosilicate. In this situation, a microchannel system is used to propel the internal phase into the continuous phase, resulting in a monodispersed emulsion. This process is similar to creating an O/W emulsion or multiple W/O/W emulsions, as shown in Figure 4a and Figure 4b respectively.[79]

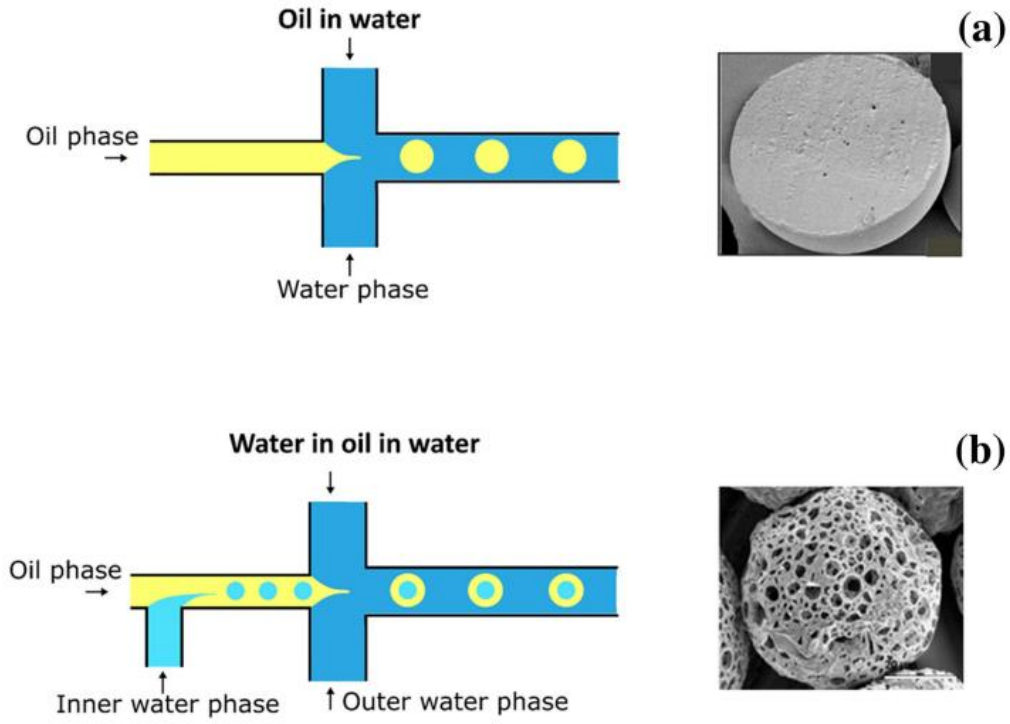


**Figure 4: Schematic representations of microfuidics devices for preparation of PLGA MPs by O/W emulsion (a) and W/O/W emulsion (b) techniques.[55]**

The use of targeted surface treatment to microchannels is commonly necessary to produce a wide range of emulsions. Currently, a range of techniques are used to alter PDMS surfaces, including covalent modification, glass coating, treatment with ionic wetting agents, oxidation, chemical vapor deposition, oxidation of the PDMS surface, and layer-by-layer (LbL) deposition of positively and negatively charged substances onto the surface. Montazeri et al. developed a method for producing a microfluidic device that had both hydrophilic and hydrophobic characteristics. This was achieved by adding a surfactant to PDMS solutions before they were cured.[79,80] Specifically, they added Silwet L-77®, a biodegradable nonionic surfactant known for its outstanding spreading characteristics, into PDMS. This additive improves the capacity of PDMS to spread over hydrophobic solid surfaces by increasing its wettability. The researchers successfully employed microfluidic chips to produce PLGA MPs containing several medicines.[81] The MPs successfully included both hydrophilic and lipophilic compounds using the double emulsion approach.[82] These devices may be classified into two types: droplet-based (segmented) and continuous microfluidic devices. Droplet-based devices are the preferred technique for generating microparticles, whereas continuous devices are commonly employed for manufacturing nanoparticles.[81] The droplet-based system may be defined by the process of droplet breakdown, which encompasses cross-flow, coflow, and flow focussing.[81,83] The main differentiation among these three devices is in the morphology of the channels, which affects the viscous shear force that causes droplet fragmentation and effects the final characteristics of the microparticles. The two stages of cross-flow devices engage at intersections with varying angles, such as T-junctions, Y-junctions, double T-junctions, V-junctions, and K-junctions.[79] The T-junction is the most common form of junction. The co-flow or coaxial junction is formed by two channels that are concentric, with the dispersed phase flowing in parallel into the continuous phase channel. Flow focusing has resemblances to co-flow geometry, however the droplet size is determined by both the capillary number and the ratio of the dispersed phase to continuous phase flow rate. Microfluidic devices typically comprise a combination of microchannels. A curcumin-loaded PLGA MPs have been generated utilizing a liquid-driven co-flow focusing (LDCF) technology. The chip comprises three injection pumps, a central device including a coaxial needle and a pressure chamber, a collector, a safety waste system, and a monitoring system. This microchip fabricates curcumin-loaded microparticles with a precise and homogeneous size distribution, while simultaneously attaining great efficiency in encapsulating the drug and a quick loading rate. Furthermore, it enables the medicine to be released in a regulated manner based on a pre-established pattern.[84] Microfluidics facilitates the generation of microparticles with a limited size range, precise control over droplet size, and correct morphology.[85] The drug release mechanism is governed by these characteristics; the homogeneity of the particles enables precise control of the release rate and encapsulation efficiency. Particles of a narrow size dissolve at a faster rate compared to larger particles. As a result, a high polydispersity index (PDI) is associated with an initial rapid release and uncontrolled release of drugs due to the presence of MPs of varying sizes.[78] Microfluidic devices provide precise regulation of the whole preparation and manipulation procedures. They allow for the adjustment of flow rate, pressure, and viscosity, enabling precise control of these parameters. The level of control achieved ensures the prevention of mistakes and allows for the implementation of a process waste solution with an almost negligible amount of waste (Anon n.d.). An further advantage is the uniform blending of the liquids and the ability to operate with very small volumes, ranging from microliters to picoliters.[84] Nevertheless, microfluidic technology has notable constraints, particularly regarding the compatibility of the polymers used to create microchannels with various organic solvents. PDMS and PMMA, often employed materials in the production of microfluidic devices, exhibit a tendency to undergo swelling upon exposure to

strong solvents such as acetone. The expansion of microfluidic channels impacts the flow of fluids, resulting in the creation of unregulated micro-particles of varying sizes and shapes.

### 3.3 Electrospray

Electrospray typically consists of a high-voltage power source, syringe pump, metallic nozzle, and collecting substrate[86,87] (Figure 5). A syringe pump is utilized for the purpose of introducing the polymer solution into the capillary nozzle. Presently, an electric current is applied between the nozzle and the collecting substrate in order to create a significant difference in pressure.[88] The fluid that has been released forms a distinct 'Taylor cone' shape at the nozzle, leading to the formation of droplets that eventually break apart into particles. Afterward, these particles are transported to the collecting substrate, which possesses an opposing charge.[89,87] The particles generated typically range in size from tens of nanometers to hundreds of microns and exhibit a restricted range of particle sizes.[86,87] Several commonly used electrospinning (ES) systems consist of mono-Coaxial ES (MES), coaxial ES (CES), and multiplexed ES (MCES). CES employs an injection pump to convey the carrier solution (outer layer) and pharmaceutical solution (inner layer) into a single nozzle through two separate feeding channels. The outer layer solution can generate particles with a core-shell configuration by enveloping the inner layer solution.[75] The MCES architecture has several parallel capillary tubes, resulting in enhanced microsphere production and enabling efficient large-scale manufacturing.[90;87] The electrospray method enables the production of microspheres with diverse sizes and shapes by altering several experimental parameters, such as voltage and velocity.[91;92;93] The electrospray method enables the efficient encapsulation of chemicals into microspheres in a single operation.[94] The entire procedure is uncomplicated and does not result in substantial losses. Furthermore, it is possible to enclose delicate things such as proteins and cells.[75,86]

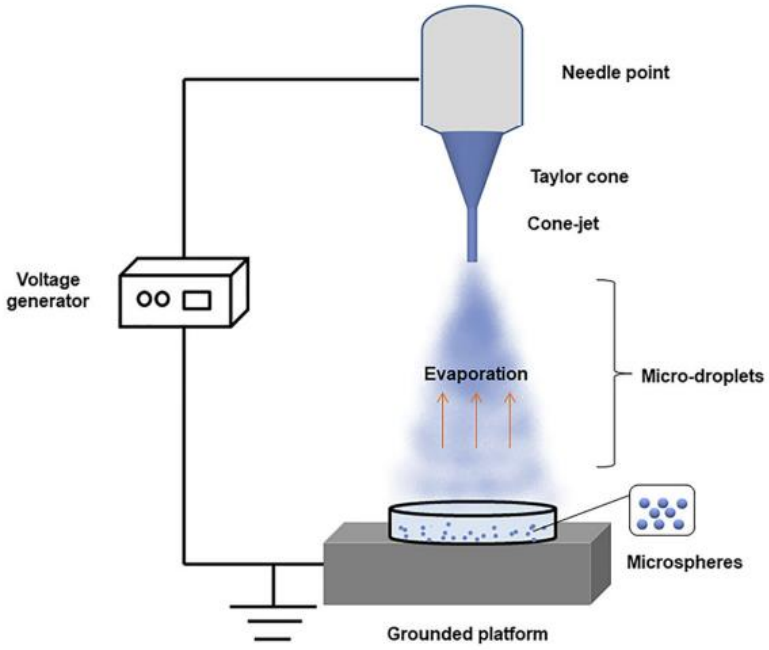


**Figure 5. Schematic of the electrospray process.[95]**

### *3.4 Spray drying*

Spray drying is a method that involves disintegrating pharmaceuticals and polymer solutions, suspensions, or emulsions into minuscule droplets using a nozzle, and subsequently exposing them to hot air [96] (Figure 6). The atomized droplets

undergo fast solidification when the solvent evaporates rapidly.[97,98] The spray drying process typically consists of four distinct stages: atomization, mixing of droplets with dry gas, evaporation of the solvent, and separation of the final product. The atomization process, which encompasses the selection of the atomizer, management of the nozzle pressure, and regulation of the feed or air flow rate, significantly influences the distribution of droplet sizes.[99,100,101,102,103,97] The spray drying method enables the efficient and continuous production of particles in a single step, removing the requirement for a separate drying procedure in other preparation methods.[104,105,106] The whole preparation process is fully automated, resulting in a considerably high rate of encapsulation.[107] This characteristic makes it very appropriate for encapsulating proteins or peptides,[108,97] plasmid DNA,[109,110,111] and small molecule drugs.[112] This method is applicable to a wide range of medicinal compounds, regardless of their water-philic or water-repelling properties, as it does not necessitate the use of an additional solvent phase.[113]

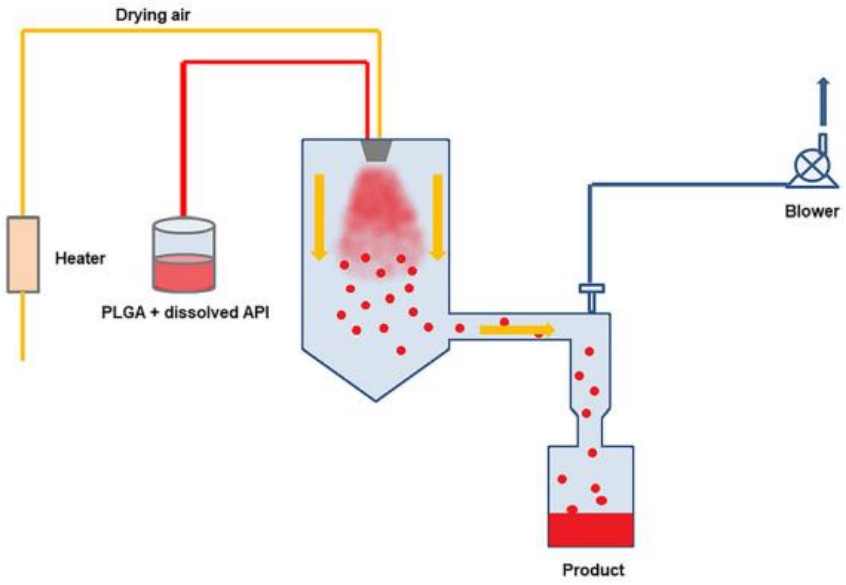


**Figure 6: Schematic of the spray drying process.[95]**

## 4. CONCLUSION

This article is a comprehensive summary of the latest scientific advancements in the area of sustained release pharmaceutical microspheres. Initially, we presented the objectives and categorizations of drug delivery systems, with particular emphasis on the fundamental principles of sustained-release drug carriers and microspheres. Microspheres can exhibit various microstructures, which are determined by the properties of the medication and the carrier material. Consequently, this results in diverse utilization and implementations. Furthermore, we have thoroughly evaluated the choice of carrier materials, specifically focusing on PLGA. The composition, molecular weight, and concentration of PLGA have an impact on the size, ability to carry drugs, and release properties of PLGA microspheres. When choosing materials, researchers should take into account the physicochemical qualities of medications and the features of PLGA. Selecting the appropriate PLGA carrier material is beneficial in achieving the desired structure and functionality of PLGA microspheres. The primary benefits of PLGA-based biodegradable microspheres are in their biocompatibility, enduring stability, and inherent biodegradability. They have the ability to store different kinds of medications and transport them to certain locations in the correct manner. Subsequently, we provided a concise overview of the techniques utilized in the production of microspheres to fulfill diverse requirements and purposes, elucidating the range of procedures employed in the fabrication and management of microspheres. To summarize, sustained-release drug

microspheres, which act as a type of sustained-release drug carrier, show great potential for further progress. Nevertheless, there exist several constraining elements that impede the advancement of sustained release medication microspheres. Future research still need to address several intricate technological challenges. These duties involve the complex process of encapsulating certain therapeutic properties and producing microspheres, as well as the challenge of effectively translating research findings into actual clinical applications. Given the ongoing advancements in biodegradable microsphere research and the growing demand, it is anticipated that PLGA-based biodegradable microspheres will remain a favoured method for drug administration in the future. These microspheres are expected to be more and more used in the treatment of many illnesses in both clinical and practical settings.

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