

DRUG MICRO-CARRIERS BASED ON POLYMERS AND THEIR STERILIZATION

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Abstract. This paper presents the main aspects regarding the production of biodegradable microspheres, the optimization of parameters in the drug encapsulation process, the techniques available for polymeric systems sterilization and the effects of γ -irradiation on microparticles.

Keywords: poly(butylene succinate), drug delivery systems, microparticles, sterilization, chemical modification.

1. Introduction

In conventional drug delivery system (DDS), the drug release kinetics is adjusted, aiming at the rapid release of the active species into the bloodstream. The therapeutic concentration of the drug must be maintained with subsequent administrations. In this context, the use of controlled release systems allows the reduction of administrations, avoiding fluctuations in the drug concentration [1-3]. These systems are often used when the drugs present low solubility in water, increasing bioavailability and reducing side effects [4-10].

Drugs can be carried by polymers through physical adsorption, by chemical bonding or by entrapping the drug in a polymeric structure in the form of a sphere [11-16] or capsule [17-22]. Encapsulation hinders the modification of the drug or active species, contributing to its protection. Furthermore, due to the small particle size (up to 500 μm) the encapsulation improves drug absorption [23-27]. Therefore, some of these systems are used in direct contact with body fluids, such as sublingual administration, *via* the gastrointestinal tract (oral), vagina and nasal cavity, and all non-parenteral drug delivery routes [28-39]. Thus, they must comply with the

requirements of the pharmacopeia for sterility [40-44]. However, some proposed sterilization methods, such as chemical sterilization with ethylene oxide, are not suitable for biodegradable aliphatic polyesters [45-48].

In turn, sterilization by gamma irradiation is the most frequently used technique in thermosensitive medical devices and can be successfully applied to biodegradable polymers and pharmaceutical substances. The advantages of this technique include the high penetrating power, low chemical reactivity and low measurable residues, necessary due to the safety involved in this method of sterilization and the relatively low cost [40, 49-54]. In this method, a minimum dose of 25 kGy is considered suitable for the sterilization of pharmaceuticals, being able to achieve the necessary level of sterility with confidence [41, 55-57].

2. Controlled Drug Release

Recent studies on the development of drugs that ensure more effective delivery and reduce side effects are focused mainly on controlled release systems. The drugs are entrapped within a suitable polymeric carrier, which allows a sustained delivery over days, weeks, months and even years [58-62]. A selection of suitable biocompatible and biodegradable carrier allows the drug to reach the target of interest, controlling the kinetics of drug release with the use of gastro-resistant polymers and achieving spatial control through incorporation of magnetic particles into the carrier matrix [63-70].

The primary objective of spatial controlled release systems is to deliver the drug directly to the diseased tissues or organs with the following advantages over the traditional route of administration:

- (i) a higher drug concentration at the target [71-73];
- (ii) protection of the drug until it reaches the desired destination, thereby increasing the possibility of using drugs that have a short half-life in the body [74-77];
- (iii) improved pharmacokinetics in the drug release, maintaining the active concentration within the therapeutic window [78, 79];

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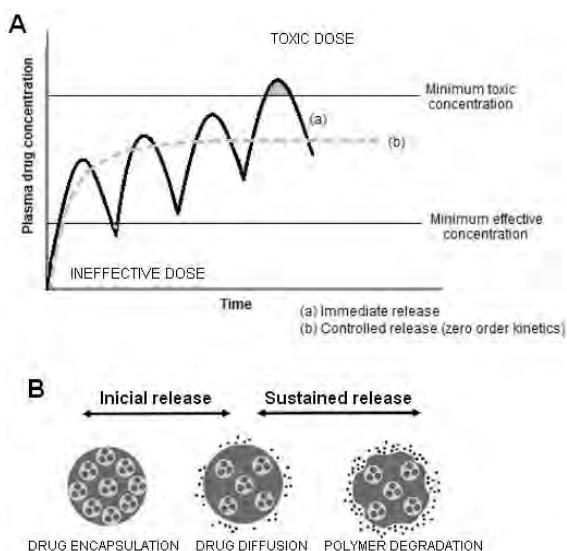


Fig. 1. Comparison between the conventional multidose system and a controlled release system (A) and drug release from sustainable release systems (B)

(iv) subsequent reduction of side effects [80-83]; and
 (v) reduction of subsequent administrations. This control allows a greater effectiveness of treatment, prolonging the action and increasing the drug bioavailability [84-87].

3. Polyesters Useful in Drug Delivery Systems

The use of aliphatic polymers as matrices of DDSs is one of the available strategies currently studied [88-90]. These polymer systems present a diversity of amphiphilic character, degradation rate, and physical characteristics. Also, they are easily prepared, allowing achievement of the desired requirements for a prolonged therapeutic effect of the drug, increasing the effectiveness of the treatment [91].

Among the polymers used for the preparation of these delivery systems, a special group, comprising aliphatic biodegradable polyesters, such as poly(ϵ -caprolactone) (PCL), poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and their copolymers, polyhydroxyalkanoates and polybutylene succinate have been drawing the attention of researchers [78, 92-95]. The bibliometry of the use of aliphatic polymers in delivery systems in recent years is presented in Fig. 2.

The use of PGA and PLA in academic studies has been widely discussed [96, 97], and their use for medical purposes has been approved by the Food and Drug Administration (FDA) since 1969 and 1971, respectively. Polyesters containing caprolactone have also been approved for clinical use by the FDA since 1997 [98-101].

Poly(hydroxy alkanooates) (PHAs) belong to the class of polyesters produced by bacteria. These bacteria produce a variety of PHAs, and, among them, poly(3-hydroxybutyrate) (PHB) is one of the best known. These polymers are carbon and energy reserves for bacteria and are deposited as insoluble inclusions in the cytoplasm of cells [102-107].

Among the aliphatic polyesters, poly(butylene succinate) (PBS) is noteworthy, because, in addition to its biodegradability, this material attracts the attention of many researchers due to its biomedical applications [108-112]. Besides, PBS presents good biocompatibility and excellent processability, and its degradation products are non-toxic, since PBS degrades into 1,4-butanediol and succinic acid, an intermediate in the tricarboxylic acid cycle, and then to dioxide carbon and water [113].

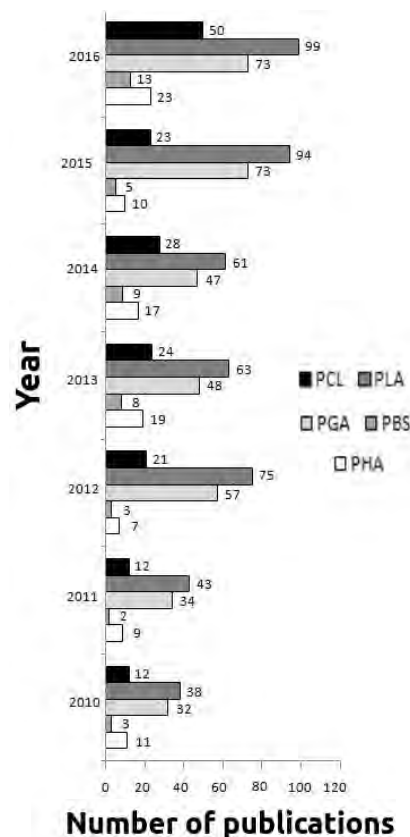


Fig. 2. Use of aliphatic biodegradable polyesters in delivery systems. Data was retrieved from Science Direct, accessed in February, 2017.

The key used was “delivery systems + specific polymer”

PBS has been commercially available since 1993 from Showa-Den, under the name of BionolleTM and by Mitsubishi Chemical Corporation, known commercially as GS PlaTM. The synthesis of PBS consists of two main steps. The first is the esterification of succinic acid and 1,4-butanediol, to eliminate water. The second phase is

the polycondensation of oligomers at high temperatures [98]. The use of elevated temperatures facilitates the removal of butanediol, leading to the formation of a high molar mass polymer [114]. The catalyst often used is titanium tetra-butoxide [115]. The polymerization scheme is shown in Fig. 3.

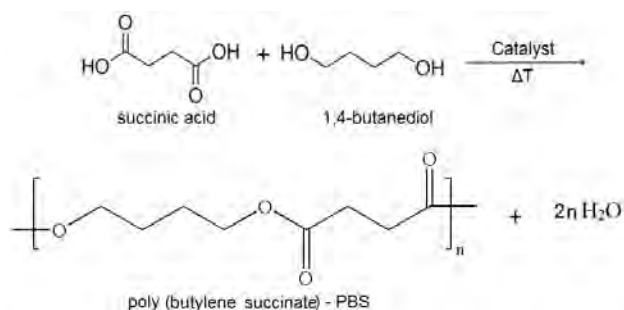


Fig. 3. Synthesis of PBS

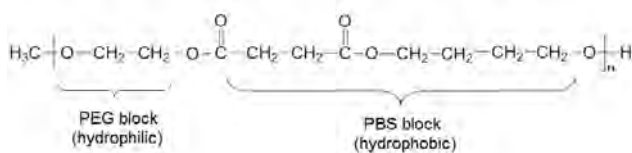


Fig. 4. PBS-PEG copolymer

Regarding its properties, PBS has a crystallization capacity between 35 and 45 %, melting temperature (T_m) in the range of 384–388 K, and glass transition temperature (T_g) below room temperature (236–255 K), being readily processed [114].

The biodegradation rate of a polymer chain is dependent on the hydrophilicity, polymer crystallinity, resultant porosity in the preparation of materials and on the molar mass of the matrix components [113, 116]. Cho *et al.* [116] investigated the effect of hydrolytic degradation of crystalline microstructure samples of PBS obtained by melting the samples and subsequently submitting some to quenching and others to isothermic crystallization at 333 K. As suggested by the authors, the first sample showed a greater crystallinity and slower degradation rate, indicating that hydrolytic degradation occurs preferentially in the amorphous region of PBS, while the sample crystallized isothermally presented spherulitic structure with less bundled fibrils, facilitating the penetration of water and increasing the degradation rate [116].

Gualandi *et al.* [117] reported the effects of hydrophobicity on the hydrolytic degradation of PBS, observing very slow degradation rates at *in vitro* simulated physiological conditions (pH 7.4 and 310 K), where the molecular weight remained relatively constant for weeks [117]. Because degradation can be controlled by the hydrophilic/hydrophobic balance of the material, the

addition of hydrophilic polymer structures in PBS chain can alter the polymer degradation rate. This is what Wang *et al.* [118] proposed when they added poly(ethylene glycol) (PEG) into the PBS chain, increasing the copolymer degradation rate due to a higher water absorption capacity of the hydrophilic segment of PEG. The scheme of the diblock copolymer of PBS-PEG is shown in Fig. 4.

Several studies have addressed the evaluation of the cytotoxicity of PBS, both in cells and in animals, which is key in their application in tissue replacement or as drug carriers [119-122]. Some authors have studied the cytotoxicity of PBS scaffolds in osteoblasts, fibroblasts and femoral bone of white rabbits, demonstrating the potential of PBS in tissue engineering applications [123-125].

4. Microparticles

Microparticles are commonly used for the delivery of long-term proteins, peptides, and small molecules, and are typically administered intramuscularly or subcutaneously [126-131]. Suitable DDSs depend on the type of carrier, the therapeutic agent used and the characteristics of administration [132-134]. The search for improvement of these delivery systems is widespread, and for that, the carrier matrix should be chosen appropriately. Furthermore, modifications of the material surface, such as PEGylation, are useful in making it more invisible to the immune system [135-141]. Another strategy is related to the binding of appropriate receptors that can be used as key-lock systems, such as albumin and folate [142-149].

Depending on the hydrophobicity of the polymer and its active characteristics, different structures may be formed. Hydrophilic components may be encapsulated into the aqueous core and hydrophilic drugs entrapped into the shell, forming capsules [150-155]. The generic diagram of the structure of a carrier with different components can be seen in Fig. 5.

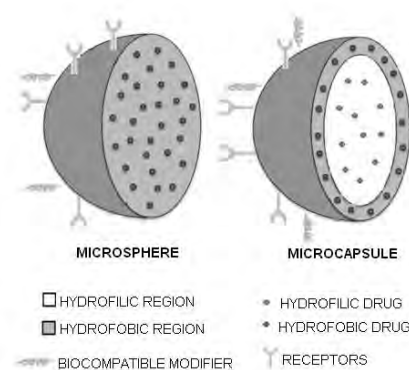


Fig. 5. Structure of a microparticle containing different components

4.1. Preparation of Polymer Microspheres

The chemical and structural properties of the microspheres are closely related to the drug release, biocompatibility, and encapsulation [156-160].

Mitragotri *et al.* [161] studied the main parameters of microparticles that affect drug release. The evaluated parameters are related to the porosity of microspheres, particle size and polydispersity, surface modifications and shape of materials. The porosity of the polymer matrix affects diffusion of the drug, which is facilitated when a larger number of pores presents in the matrix structure. Furthermore, the increase of porosity allows water penetration, facilitating its degradation and subsequent the drug release [94, 162-165].

The size of the spheres and polydispersity also make a significant contribution to drug delivery because the larger the particle size, the lower is the surface/volume ratio, which prolongs the release of the drug. Furthermore, polydispersity can cause variability in release rates, due to size distribution of the microspheres produced [166-169].

The surface characteristics of microspheres affect the interaction with the environment at the tumor site, especially the immune cells. Surface modification with polymers such as PEG is used to reduce the interactions of the microsphere with cells of the immune system [170-173]. Another important parameter in the microspheres project is the shape of the particles, which affects interactions with macrophages; since elongated particles, unlike the spherical ones, possess the internalization dependent on the macrophages guidance [161, 174-177].

Mohanraj *et al.* [78] developed PBS microcapsules loaded with Levodopa, a drug used for Parkinson's disease. The authors found that the microspheres with a smoother surface exhibited a higher encapsulation efficiency compared to the ones with the more porous surface. Moreover, the drug release was higher using a simulated cerebrospinal fluid than in a phosphate buffer, which shows that the release medium composition is an major factor in affecting drug release [78]. The influence of the dissolution parameters was also studied by Tomic *et al.* [178], verifying that a change in the medium may affect the rate of release during the erosion phase due to the different hydrolysis rates of ester bonds in alkali or acid media.

4.2. Techniques Used to Obtain Microparticles

Microencapsulation technique is a method in which the polymer acts as an external component, to form a barrier that surrounds and protects the drug [179-184]. Among the techniques for microencapsulation, emulsi-

fication followed by a solvent evaporation is frequently used [185-190]. Another route is electrospraying. The methods used for the preparation of microencapsulated systems may be affected by the hydrophilic-hydrophobic characteristic of the drug [191-198].

4.2.1. Electrospraying

The electrospraying technique is based on loading a syringe with a solution containing the polymer and the drug and, with the aid of a syringe pump, the content is injected at a constant rate into a collector through a capillary output. The voltage applied, typically around 30 kV, and the distance between the capillary and the collector can be controlled [199]. The main advantage of this technique is the production of microspheres with a small size distribution, facilitating their clinical use [200]. The relevant processing parameters, which change the shape and structure of the microspheres produced, are the solvent type, polymer concentration, applied voltage and distance between capillary and collector [108].

Some papers have been published evaluating the effects of flow rate and conductivity on the size and morphology of PLGA microspheres [199, 201]. As the polymer of interest, Murase *et al.* [108] studied the electrospraying parameters on the preparation of PBS microspheres, with several indole (a natural product) derivatives, through PBS pre-solubilization in chloroform and formic acid, aiming to increase the ionic conductivity. The authors observed that the type of substituent and the active position also resulted in changes in the hydrophobicity and porosity of the prepared microspheres. The particles presented diameters around 10 μm and with a smoother surface when 2-phenyl indole was used instead of 1-methyl indole.

4.2.2. Emulsification and solvent evaporation

The emulsification and solvent evaporation technique consists of four main steps. First is the dissolution or dispersion of a hydrophobic drug in a suitable organic solvent, containing the previously dissolved polymer. Then this organic phase, called the dispersed phase, is slowly poured into an aqueous phase (continuous phase) containing a surfactant, forming micro-droplets. Stirring is kept, the solvent is evaporated and the solid particles formed are recovered and dried to remove the residual solvent and form solid microspheres [202-207]. This emulsification method is often used for hydrophobic drugs and is not suitable for hydrophilic drugs, since they tend to migrate to the polar solvent, decreasing the drug encapsulation efficiency [185, 208-212].

For hydrophilic drugs, a double emulsion method is required, which is similar to the single emulsion technique, but with the addition of a second emulsification step containing another aqueous phase with the surfactant.

The use of a high-pressure homogenizer or a sonicator reduces the droplet size [213-216]. Fig. 6 shows the difference between two emulsion methods.

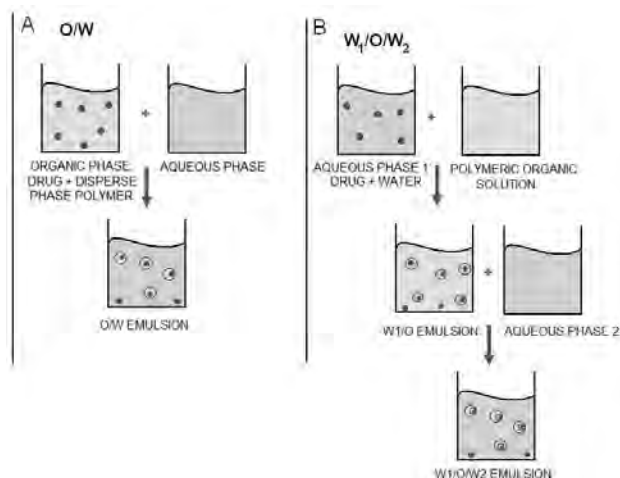


Fig. 6. Preparation of microspheres from O/W or W/O/W emulsions

The proper dispersion of nanometric droplets into the continuous aqueous medium is a fundamental requisite to the formation of particles with good morphological features. As a matter of fact, a very stable colloidal dispersion is generally obtained through ultrasonication or high shear devices that might be combined with a surfactant and a hydrophobic agent, which acts as a co-stabilizer in order to lead to the formation of droplets lying in the interval from 50 to 500 nm, exhibiting very narrow particle size distributions. Generally, high-pressure homogenizers or sonicators are necessary when the formation of nanometric droplets requires a large amount of energy, which results from the application of high shear rates on the oil-in-water medium, leading efficiently to the breakage of the larger droplets to produce small droplets [217-223].

Some emulsification conditions also influence the size and morphology of the microspheres. The choice of suitable parameters increases the drug encapsulation too [224]. It is agreed that the drug release rate is strongly dependent on variables such as average particle diameter and particle size distribution, average molar mass of the polymers and its molar mass distribution, system crystallinity polymer matrix porosity, pH and temperature sensibilities, among others. In this scenario, one should keep in mind that the particle size should be regarded as a very representative variable for practical reasons. It is well known that small particles can be responsible for poor incorporation of the drug whereas big particles are not easily transported through a syringe needle or a catheter, potentially causing its occlusion during the surgical procedure. Additionally, the release rate also exhibited

dependence on the particle size. For this reason, the main parameters of the emulsification stage must be optimized to guarantee the polymer carriers with suitable morphological features [217, 219, 225].

4.2.3.1. Optimization of the emulsification parameters

Although the process of emulsification and solvent evaporation has been widely discussed because of its ease, certain factors are important for the morphology of microspheres and drug encapsulation efficiency [226, 227]. For instance, the concentration and polymer molecular weight influence the viscosity of the organic phase, which modifies the drug diffusion constant [228]. A high organic phase viscosity, resulting from the use of high molecular weight polymers or polymers in high concentrations, results in high encapsulation efficiency [229, 230]. The concentration, as reported by Brunner *et al.* [179], changes both the morphology and the size of the particles. According to the authors, PBS microspheres prepared by double emulsion, with polymer concentrations in dichloromethane of 1 %, 3 %, and 5 %, generate particles with spherical morphology at lower concentrations of PBS. Also, the average diameter of the particles increased with the increase in PBS concentration. This change in the morphology of the microspheres illustrates the influence of porosity on the drug release. The drug release was slower from microspheres prepared with higher polymer concentration. This behavior was attributed to the formation of a dense polymer matrix, resulting in smaller pores [179].

Porosity can also be dependent on the composition of the microspheres. Park *et al.* [231] synthesized PBS/PCL microcapsules containing indomethacin to evaluate the effect of PCL on morphology and the drug release profile. The authors concluded that the indomethacin release rate was lower with the smaller pore size of the resultant microcapsules, which occurred when the incorporation of PCL was increased from 10 to 20 %.

In the study of Crucho and Barros [232], polymeric nanoparticles were synthesized by nanoprecipitation using different experimental parameters (choice of organic solvent and evaporation rate) to verify their influence on the average size of the particles obtained. In the case of the solvent, the miscibility of the organic solvent and water can influence the particle size, since the difference between the solubility parameters of the solvent and water is minimized by increasing the miscibility. According to the authors, the smallest particle size values were obtained using acetone and the largest size using tetrahydrofuran (THF). The polydispersity also exhibited a similar result; a narrower particle size distribution for acetone and broader distribution for THF. This effect is a consequence of the lower miscibility of THF, and higher miscibility of acetone, in water. With an increase in miscibility between

the organic and aqueous phase, the diffusion of the solvent into the water increases, producing a faster dispersion of the polymer into the water, resulting in the formation of smaller and more homogeneous droplets [232]. The second experimental factor studied by the authors was the solvent evaporation rate. The average size of the nanoparticles obtained using reduced pressure (300 mm Hg) was 96 nm. On the other hand, the largest size, 132 nm, was observed when the same particles were evaporated at atmospheric pressure. The analysis suggests that as the evaporation rate increases, the probability of coalescence between the prepared particles reduces [232-234].

Several studies have also been performed aiming to investigate the efflux of amphiphilic drugs into the aqueous phase of an emulsion, reducing the encapsulation efficiency [224, 235-237]. The addition of many salts (NaCl, NaBr, NaSCN, NaClO₄, and Na₂SO₄) to the outer layer has been one of the solutions used by some authors to minimize the effects of drug migration. Moreover, the appropriate choice of surfactants has also an influence, increasing the encapsulation efficiency of hydrophilic drugs [202, 238-241].

In the double emulsion method, the emulsification stability of the first step is essential for achieving high efficiency of encapsulation. Stability can be improved by the addition of poly(vinyl alcohol) (PVA) as a protective colloid (stabilizer) or an ionic surfactant with concentration below the critical micelle concentration (CMC) to prevent drug migration and/or the formation of micellar structures, which leads to a poor encapsulation efficiency as previously reported [242].

Brunner *et al.* [179] studied the effect of PVA on the morphology of PBS microspheres. The synthesis of PBS was by double emulsion technique and the PVA variation, in the second aqueous phase, was 0.5, 1, 2, 4 and 6%. For PBS microspheres at 0.5% PVA concentration, spherical and rough wall microcapsules were observed. At 1% and higher concentrations of PVA, on the other hand, smaller-walled and smooth microspheres were obtained [179]. Mohanraj *et al.* [78] also developed PBS microspheres by double emulsion technique, using chloroform and dichloromethane as organic solvents and ionic surfactants such as sodium dodecyl sulfate (SDS, an anionic surfactant), cetyltrimethylammonium bromide (CTAB, a cationic surfactant) and poly(vinyl alcohol) (PVA, a non-ionic stabilizer). They observed that the microspheres exhibited an external surface with high porosity when dichloromethane was used as the solvent, while with chloroform the microspheres were rougher. In addition, the PVA as the surfactant increased the surface irregularity of the particles.

In other study performed by Zhang *et al.* [243], PLGA microspheres were prepared by the single emulsion method, varying the surfactants. The authors showed the effects of surfactant on morphology and on *in vitro*

release. When hydrophilic surfactants were used, microspheres presented some pores on their surfaces, which could be attributed to the phase separation of the surfactant and PLGA during solvent evaporation. A high porosity will allow the release medium to penetrate the particles more easily, favoring faster drug release by pore diffusion.

Jagdale and Pawar [244] have evaluated the effect of the concentration oils (oleic acid, vegetable oil, light liquid paraffin, olive oil, castor oil and linseed oil), surfactants (span 80, tween 80, span 20 and tween 20) and co-surfactants (propylene glycol, propylene glycol 400) on the formation of emulsion based on ofloxacin intended for transdermal drug delivery system. According to the authors, transdermal emulgel delivery for ofloxacin can successfully be developed by adjusting the concentration of the emulsion components associated with a gelling agent such as HPMC K100M and Carbopol 940. It was also observed that the emulgel exhibited good *in vitro* and *ex vivo* and viscosity, behaving as a reservoir for the drug, which is properly released at the targeted site exhibiting good antimicrobial property.

Haider *et al.* [245] have studied the synthesis of salbutamol sulfate loaded poly(vinyl alcohol) (PVA)/sodium alginate (Na-Alg) blend microspheres through the water-in-oil (W/O) emulsion crosslinked technique in order to produce a sustained drug delivery system. The influence of different PVA/Na-Alg ratios on drug loading and release has been investigated, showing that the drug can be properly delivered up to 12 h, which indicates that PVA/Na-Alg polymer matrix can be regarded as useful support for sustained drug delivery.

Calderó *et al.* [246] have evaluated the formation of ethylcellulose nanoparticles in oil-in-water (O/W) nanoemulsions through low-energy emulsification technique. As stated by the authors, ethylcellulose system enhanced the self-aggregation of the surfactant due to its ability to make it more hydrophilic whereas the release time of the encapsulated dexamethasone (DXM) was increased. It was also observed the high capacity of incorporation of DXM into the nanoparticles above 90%, and comparatively, the drug release from the nanoparticle dispersions was slower than the one observed in an aqueous solution.

Marto and coworkers [247] also employed a Pickering emulsion technique to stabilize the system by employing solid particles instead of surfactants and/or protective colloids. They have investigated the formation of starch-based Pickering emulsions intended for topical drug delivery applications in pharmaceutical and cosmetic fields. According to the experimental protocol, the starch-stabilized emulsions were prepared by employing aluminum starch octenyl-succinate (ASt) as the stabilizer in oil-in-water emulsions consisting of liquid paraffin and caprylic/capric acid triglyceride mixture. Emulsions were

formulated based on different operating conditions of time and stirring speed, indicating that the emulsion systems were non-irritant with self-preserving properties and that they can be used as a template for the production of pharmaceutical and cosmetics vehicles intended for topical administration purposes [247].

E. Bulut [248] has also employed an emulsion crosslinking technique to obtain microspheres based on chitosan-graft-polyacrylamide (CS-g-PAAm) using glutaraldehyde (GA) and as a crosslinker to be used as drug delivery matrices. Paracetamol loading into the microspheres was observed in the range of 32–73 %, and the drug release CS-g-PAAm in acidic and phosphate buffer solutions (pH 1.2–7.4) was strongly dependent on the concentration of CS-g-PAAm and crosslinker, and the paracetamol/polymer ratio.

Recently, Yi *et al.* [249] have developed a new drug nanocrystal self-stabilized Pickering emulsion of silybin nanocrystal suspension (SN-NCS) by using a high-pressure homogenizer at different homogenization pressures and drug contents. The system consisting of an oil-in-water (O/W) Pickering emulsion of silybin was stabilized by silybin nanocrystals in the absence of ionic surfactants or protective colloids (polymer stabilizers). According to the authors, silybin nanocrystal self-stabilized Pickering emulsion (SN-SSPE) presented a core-shell structure and good physical stability, which might enhance the dissolution rate and oral bioavailability of silybin, when oral drug delivery system for poorly water-soluble drugs are considered [249].

5. Sterilization of the Polymer Materials

The material sterilization process is intended to remove or destroy all forms of life, macroscopic or microscopic, from the product of interest, ensuring that the inactivation of cellular enzymes and toxins occurs. According to the sterility assurance requirements described in pharmacopoeias, a sterility assurance level (SAL) of 10^{-6} (statistical probability of finding one contaminated unit is equal to 1:1000000) is accepted for sterilization procedures of materials and pharmaceutical products [55, 250-252].

The sterilization method should be carefully selected, since it can result in changes in physical and mechanical properties of the materials during the process [253].

5.1. Sterilization Techniques

5.1.1. Chemical methods

Sterilization using chemical methods can be used with a suitable gas, usually ethylene oxide [56, 254].

Although this method has disadvantages such as the degradation of the polymer chain, it can be applied to materials that cannot withstand high temperatures. The main disadvantages are the high flammability, mutagenic properties, the possibility of forming toxic residues in the treated materials and limited penetration capability in the polymer [255-258].

5.1.2. Physical methods

5.1.2.1. Heating

Among physical methods for sterilization, heating is very simple. Here, the sterilizing agent is moist or dry heat [259-262]. In spite of the sterilization by heat being inexpensive and safe, it presents disadvantages regarding the degradation of polymeric biomaterials, since the technique often uses temperatures that exceed the glass transition temperature (T_g) and melting temperature (T_m) of the material [263-265]. Sterilization by moist heat is performed in an autoclave using saturated steam under pressure and is dependent on the time of exposure to heat and temperature. As a reference, the temperature used is at least 393 K for 15 min [266]. Sterilization by dry heat is performed in an oven with forced air circulation, to promote homogeneous distribution of heat. The standard temperature used is 433 K for 2 h and a sterility assurance level of 10^{-12} can be reached [41, 55, 267, 268].

5.1.2.2. Size exclusion

The other physical method for sterilization is based on size exclusion, by filtration on a porous matrix [269]. The efficiency of filtration depends on the pore size and the sorption of micro-organisms within the filter matrix [270, 271]. For sterilization purposes, the filtration is performed using membranes with pore size of 0.2 μm or lower, under a minimum pressure of 30 psi [41, 55, 271, 272].

5.1.2.3. Ionizing radiation

The use of ionizing radiation from various sources, such as α , β , γ , and X-rays, fits very well the purpose of sterilization. Among these, the electron beam from electron guns (not the same of β -rays from radioactive decay), X-rays from accelerators, and gamma radiation are the most widely used [40, 273-277]. The irradiation process consists in subjecting the material to a dose of radiation that is sufficient to reduce the level of contaminants to an acceptable value. With the interaction of radiation with matter, the energy transferred by the radiation removes electrons from the molecules producing ruptures in the bonds and with that change in the properties of the materials. When these alterations occur in live organisms, the interaction usually occurs with the DNA of the microorganisms causing damages that prevent their reproduction, thus reducing the number of viable individuals. The irradiation technique is widely

used to sterilize medical products such as surgical sutures, implants and other metallic materials. In the case of polymeric materials, irradiation has the potential to penetrate the polymer chain and leave no toxic residues [278-280]. However, it can cause undesirable changes in the structure of some polymers, such as degradation or crosslinking [109, 281]. Irradiation is especially useful for sterilizing heat-sensitive materials. In this case, the controlling factor is the absorbed radiation dose. Normally, the reference dose is 25 kGy but this may be changed to achieve a certain level of lethality and reproducibility depending on material bioburden [282].

Effects of γ -irradiation in polymeric systems

γ -Irradiation is one of the most widely used techniques in the biomedical field; however, it induces fragmentation of covalent bonds and the production of free radicals in the irradiated material. Due to this, many researchers have been interested in the influence of γ -rays in polymeric systems, which can result in physical changes such as stiffening, softening, discoloration, odor generation, and changes of average molar mass [106, 116, 266, 267].

In this sterilization process, two types of ionizing radiation can be used: gamma rays emitted by artificial ^{60}Co and ^{137}Cs radioactive isotopes, and electron beams, obtained from electron accelerators [285]. The interaction mechanism, for both radiation sources, involves atomic ionization and subsequent ejection of a high energy electron. This electron continues to produce numerous electronic excitations and ionizations along the path taken [286]. The difference between the sources is the energy range supplied and degree of penetration in the material. The dose rate for a ^{60}Co source is KGy/h while the mean dose rate for electron beam is 10,000 times larger. The difference between the dose rates is 4–5 orders of magnitude. Moreover, the electron beam emissions have a moderate degree of penetration, while the gamma rays have high penetrating power in the material. At high residence times, changes in the properties of the polymers due to gamma rays are intensified, due to the greater diffusion of oxygen in the material [285-287].

If water is present in these materials, as in the irradiation of aqueous solutions, a diffusion of oxidant (hydroxyl radical OH) and reducer (hydrated electron) generated by the radiolysis of water takes place [288]. The high-dose irradiation by an electron beam system in a polymer matrix produces a high concentration of free radicals in the steady state, increasing the probability of reactions between the radicals located on the same macromolecule (intramolecular crosslinking) compared to the effect on the system by gamma radiation, where priority is given to intermolecular crosslinking at a low irradiation dose [286, 288, 289]. One option that is gaining market is the conversion of electrons into X-rays. Although the conversion efficiency is low, only about 7.6% of the energy is harnessed, the gain with X-ray

penetration in the material can be an advantage in the processes of commercial irradiation [290].

Reports in the literature demonstrate that radiation treatment for polymers is employed to induce crosslinking of polymer chains, improving mechanical properties, or for the sterilization of medical devices [291-295]. The effects of radiation on polymers depend on the polymer chain and the energy absorbed after irradiation. The controlled exposure to gammas rays can modify the physical properties of polymers, through a chain scission and crosslinking (see Fig. 7). Although both processes co-occur, if cleavage dominates over cross-linking, the molecular weight decreases; the process is called degradation. However, if the irradiation increases molecular weight, the process involves crosslinking [296-301].

In the case of biodegradable aliphatic polyesters, the physical changes depend on the presence or absence of methyl side group [296]. In polyesters such as PCL and PBS, which have no methyl group, the biomaterials are cross-linkable by radiation [281, 302-307]. Nugroho *et al.* [109] proposed a blend of PCL and PBS (30/70) by melting the polymers in the extruder. The pellets were irradiated by γ -rays from a ^{60}Co source, in order to improve the stability of the PCL during processing. The authors found that an increase in irradiation dosage increases the molar mass of the material and the polydispersity. As for the polymers with methyl groups, the predominant consequence of irradiation is the chain scission, such as is observed in PHB, PLLA and PLGA [296, 308-315].

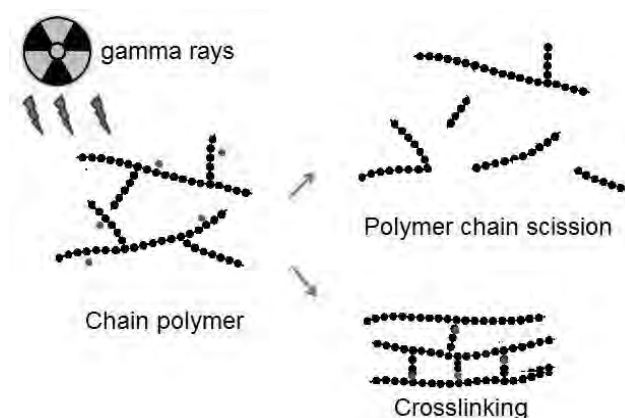


Fig. 7. Scheme of changes in the polymer chain after irradiation

Effect of γ -irradiation on microparticulates systems

As mentioned earlier, the application of γ -irradiation to polymers can generate the polymer chain scission or crosslink. These effects produce different changes in morphology and size distribution of microparticles as well as in the drug release rate [40, 309, 316-318]. Moreover, the results are dependent on the

chemical structure of the active species (drug), presenting particularities on expected changes and the encapsulation efficiency of the drug. The determination of the powerful effect depends on the irradiation conditions, the structure of the macromolecule and the presence of air or additives [213, 319-325].

Lee *et al.* [213] studied the effects of irradiation on thermal diffusivity of the drug etanidazole, inserted into double-walled microspheres formed of PLLA and PLGA. The authors found a slow diffusion of the drug for about three weeks from unirradiated microspheres; however, when the microparticles were irradiated the slow drug release phase decreased to one week.

Bozdag and Su [319] encapsulated diclofenac, an anti-inflammatory drug, in PLGA microspheres and submitted these systems to irradiation at different dosages: 5, 15 and 20 kGy. The authors realized that there was an increase in the average diameter of the prepared microspheres, suggesting that it is possible to control the release characteristics of the drug with the appropriate irradiation dosage. In more recent studies, Checa-Casalengua *et al.* [326] prepared PLGA microspheres by emulsion-solvent evaporation methods and irradiated them at 25 kGy using the ^{60}Co equipment. The morphology of microspheres was unmodified by the sterilization method. However, the molecular weight decreased from $35.076.8 \pm 292.4$ g/mol to $28.441.0 \pm 279.3$ g/mol after sterilization.

Erdemli *et al.* [327] synthesized PCL microspheres with different surfactants, to increase the stability of the prepared microparticles. Samples were subjected to 25 kGy γ -irradiation and the average size measured by Scanning electron microscopy (SEM). The size distribution between non-irradiated and irradiated microspheres was not statistically significant, indicating stability of the systems prepared [327, 328].

In another study, the effect of irradiation of PLGA microspheres containing ovalbumin (OVA) on the immunological properties of mice was tested. The microspheres were characterized by Mastersizer and the microbial load. None of these properties changed significantly after irradiation. However, the irradiation of free OVA strongly influenced the antigen presentation, while encapsulated OVA was not affected by irradiation. This fact demonstrates that encapsulation of antigen into PLGA microspheres protects the drug from the potential detrimental effect of irradiation, which would lead to inactivation or altered immunogenicity [324].

Bilensoy and Hincal [266] produced injecting particles of β -cyclodextrin for cancer treatment and compared the effects of sterilization by γ -irradiation (25 kGy) and heat. The authors observed a significant change in zeta potential of the irradiated materials, suggesting that with the irradiation fragmentation and partial break of the covalent bonds in the chain occurred.

This hypothesis was confirmed by *in vitro* study of the prepared materials.

Another point of interest in systems submitted to sterilization by gamma rays is the encapsulation efficiency. This entrapment ability is dependent on the chemical structure of the drug, which may be changed after the sterilization process, depending on its chemical structure [329]. Selmin *et al.* [330] prepared PLGA microspheres grafted with caffeic acid to micro-encapsulate ovalbumin (OVA). OVA is used in vaccine development and is sensitive to γ -radiation. The authors reported that 25 kGy irradiation of microspheres caused a variation of less than 1 % of the weight average molecular weight (M_w) when compared to non-irradiated microspheres. Furthermore, the degradation patterns of the non-irradiated and irradiated microspheres were superimposed, indicating that the irradiation did not affect the physical properties of PLGA-caffeic acid microspheres [330].

Rajawat *et al.* [331] produced chitosan microspheres containing acyclovir (ACV) and investigated the effect of irradiation on the microparticles. The rate of release of ACV from irradiated chitosan microspheres was higher than that of non-irradiated microspheres during the 12 h dissolution study. The effect of γ -irradiation on polymer microspheres has been explained by the theory of free diffusion volume. After exposure to gamma rays, the average molecular weight of the polymer decreases, decreasing the extent of entanglement of the polymer chain and increasing the mobility of the polymer. Consequently, the free volume available for diffusion of the drug molecule increases.

6. Conclusions

The kinetic control of drug release needs the optimization of several parameters, such as the biopolymer used and its characteristics, the form of the barrier responsible for the encapsulation of the drug, the morphology and size of the microparticles obtained, and the sterilizing method used on the final product, which can alter the physical and morphological properties of the macromolecular material. Many biopolymers are used to control the release of drugs. As demonstrated here, poly(butylene succinate) is increasingly studied, aiming at the preparation of drug delivery systems, due to its desirable properties, such as biodegradability, biocompatibility, melt processability, and both thermal and chemical resistance. Whatever the polymer used, sterilization is a subject frequently addressed. In particular, γ -irradiation sterilization is extremely advantageous since this technique can be used for thermosensitive polymers. However, γ -irradiation may result in changes in the polymer chain, such as degradation or crosslinking, which

will impact the kinetics of the drug release. Although several publications have presented the use of biodegradable polyesters as drug delivery systems, the knowledge about these systems based on PBS, mainly after irradiation, should be closely studied.

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МІКРО-НОСІЇ ЛІКАРСЬКИХ ЗАСОБІВ НА ОСНОВІ ПОЛІМЕРІВ ТА ЇХ СТЕРІЛІЗАЦІЯ

Анотація. Розглянуто основні аспекти виробництва біодеградуючих мікросфер, оптимізація параметрів процесу інкапсуляції лікарських засобів, методи стерилізації полімерних систем та вплив γ -опромінення на мікрочастинки.

Ключові слова: полі(бутилен сукцинат), системи доставки лікарських засобів, мікрочастинки, стерилізація, хімічне модифікування.