JOURNAL OF PHARMA INSIGHTS AND RESEARCH

REVIEW ARTICLE

Biodegradable polymers for microencapsulation systems

Amirtha Lakshmi. B*[1], Dhanusha K[1], Ayisha Siddiqkha .A[1], Vijayalakshmi M.K[2]
[1] *Final Year B. Pharmacy Student, Faculty of Pharmacy, Bharath Institute of Higher Education and Research, Selaiyur, Chennai, Tamil Nadu, India.*
[2] *Associate Professor, Faculty of Pharmacy, Bharath Institute of Higher Education and Research, Selaiyur, Chennai, Tamil Nadu, India.*

Publication history**:** Received on 21st October; Revised on 18th November; Accepted on 22nd November

Article DOI: 10.5281/zenodo.10232746

Abstract: As scientific research and industrial processes have advanced, there has been a growing demand for environmentally friendly alternatives. According to current trends, the most promising option for artificial microcapsule systems is biodegradable polymers. Among the qualities that biodegradable systems in microencapsulation can offer for a wide range of applications are safety, efficiency, biocompatibility, and biodegradability. Most biodegradable polymers have been employed as microparticles, which allow the integrated medication to be released into the environment in a regulated way. The physicochemical characteristics of drugs, the rate at which polymers degrade, and the shape and size of microparticles are the factors that regulate the rate at which drugs release their effects. For controlled, delayed, and sustained release, biodegradable polymeric matrices have been created. This article provides an overview of various polymers, specifically biodegradable polymers, that have the potential to be used in the synthesis of microcapsules. The first topic covered is natural polymers, which are broken down into two groups: protein polymers (gelatin) and polysaccharide-based polymers(cellulose, starch, chitosan, and alginate). The second section discusses synthetic polymers, with biodegradable polymers like polyesters and polyamides among others given as examples. This review provides an overview of each polymer's history, pertinent characteristics, uses, and examples from the literature pertaining to its application in biodegradable microencapsulation systems.
Keywords: Sustainable; Ecofriendly; Biocompatible; Degradation kinetics; Natural polymers; green microencapsulation.

1. Introduction

Microencapsulation is a technology that is developing quickly. It involves applying comparatively thin coatings to tiny solid particles, liquid droplets, and dispersions. Microencapsulation is a useful technique for controlling the release characteristics or availability of coated materials, protecting the environment, changing colloidal and surface properties, and turning liquids into solids. Fundamentally, developmentally, and commercially, microencapsulation is gaining a lot of attention. A spherical particle that ranges in size from 50 nm to 2 mm and contains a core substance is referred to as a microcapsule. Strictly speaking, microspheres are spherically shaped, empty particles[1]. Nonetheless, there is a common confusion between the term's microsphere and microcapsule. The microspheres are characterized by their free-flowing powder form and are made of synthetic polymers or proteins that are biodegradable, with a preferred particle size of less than 200µm. Drug release that is regulated may be possible with solid biodegradable microcapsules that contain a drug that has been dissolved or distributed throughout the particle matrix [2]. Their prolonged release and ability to direct the anticancer medication toward the tumor attracted a lot of attention. Pharmaceutical companies that produce microencapsulated drugs have obtained multiple patents during the past 25 years [3].

Monomers, which are repeating structural units, make up polymers, which are large molecules. These macromolecules are crucial in many different fields because they can have a broad variety of sizes, structures, and characteristics. Polymers have seen numerous advancements in both their biodegradability and synthesis over the years [4]. These materials have drawn interest from researchers all over the world conducting therapeutic administration research, specifically focusing on drug administration and biomedical field applications. Nevertheless, the non-biodegradability of certain polymers has led to numerous issues [5]. Some non-biodegradable polymers have a number of drawbacks, including their high toxicity. Biodegradable polymers have emerged as a result of numerous researchers trying to find a solution to this drawback [6]. There are biodegradable polymeric matrices available for controlled, delayed, and sustained release.

* Corresponding author: Amirtha Lakshmi. B

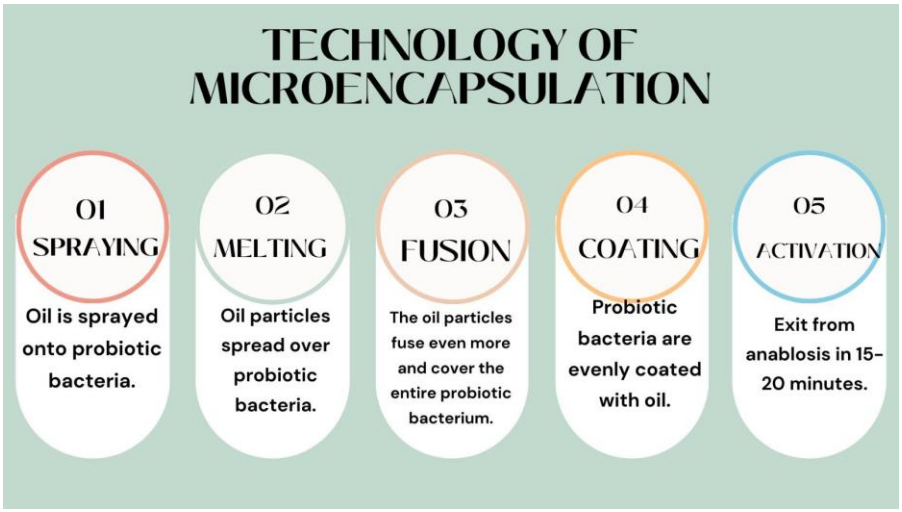

Figure 1 Types of technology of microencapsulation.

Microorganisms like bacteria, fungi, and enzymes naturally break down organic materials into simpler compounds, a process known as biodegradation. Reusing organic matter and preserving ecological balance are greatly aided by this process. Certain polymers are classified as biodegradable polymers because they are made to break down under the influence of microorganisms, forming simpler compounds like carbon dioxide, water, and biomass in the process. In addition to their advantages over conventional plastics for the environment, biodegradable polymers have a number of drawbacks that prevent their widespread use[7,8]. Degradation rate, limited end-of-life options, properties and performance, processing difficulties, cost considerations, infrastructure for recycling and composting, and research and innovation. In order to address these issues and develop a more efficient and sustainable system for the production, use, and disposal of biodegradable polymers, researchers, industry stakeholders, legislators, and consumers must work together[9,10].

Both natural and synthetic polymers are the two categories used in this review to report on the origins of biodegradable polymers. In addition to a review of the most pertinent scientific works regarding these materials' applicability in microencapsulation technology, a number of their characteristics and uses are discussed[11].

2. Biodegradable polymers

2.1. History

Microorganisms can break down biodegradable polymers into more easily absorbed molecules that are safe for the environment. When it comes to solving issues with plastic pollution and environmental sustainability, these polymers are crucial. The development of materials intended to address environmental issues related to conventional plastics is traced in the history of biodegradable polymers[12].

2.1.1. 1970s-1980s

Polyhydroxyalkanoates (PHAs) are a class of naturally occurring bio polymers that are produced by bacteria as a means of storing energy. They were discovered by researchers in the 1970s. Understanding PHAs was the primary focus of early research, and in the 1980s, ideas about their possible use in biodegradable plastics started to take shape [13].

2.1.2. 1990s

Polylactic Acid (PLA), which is made from sustainable materials like sugarcane or corn starch, has drawn interest. Early in the 1990s, PLA's development as a biodegradable polymer with commercial viability began. PLA was used to create packaging materials, throwaway silverware, and other one-time use products [14].

2.1.3. Early 2000s:

Polybutylene Succinate (PBS) and Polybutylene Adipate-Co-Terephthalate (PBAT**),** early in the new millennium, biodegradability was recognized for polybutylene succinate (PBS) and polybutylene adipate-co-terephthalate (PBAT). These polymers are utilized in compostable goods, mulch for agriculture, and packaging films [15].

2.1.4. Mid-2000s:

Biodegradable Mulch Films, biodegradable polymers gained popularity in agriculture, especially as mulch films that break down in the soil after use. After crop harvest, biodegradable mulch films eliminate the need for manual removal and have a lower environmental impact.

An ongoing search for environmentally friendly substitutes for conventional plastics is evident in the development of biodegradable polymers. The goal of ongoing research and technological developments is to increase the biodegradable polymer materials' effectiveness and adaptability even more [16,17].

2.2. BIODEGRADABLE POLYMERS USED IN MICROENCAPSULATION SYSTEM:

In the process of microencapsulation, which involves encasing active ingredients in polymeric shells to regulate their release, biodegradable polymers are essential.

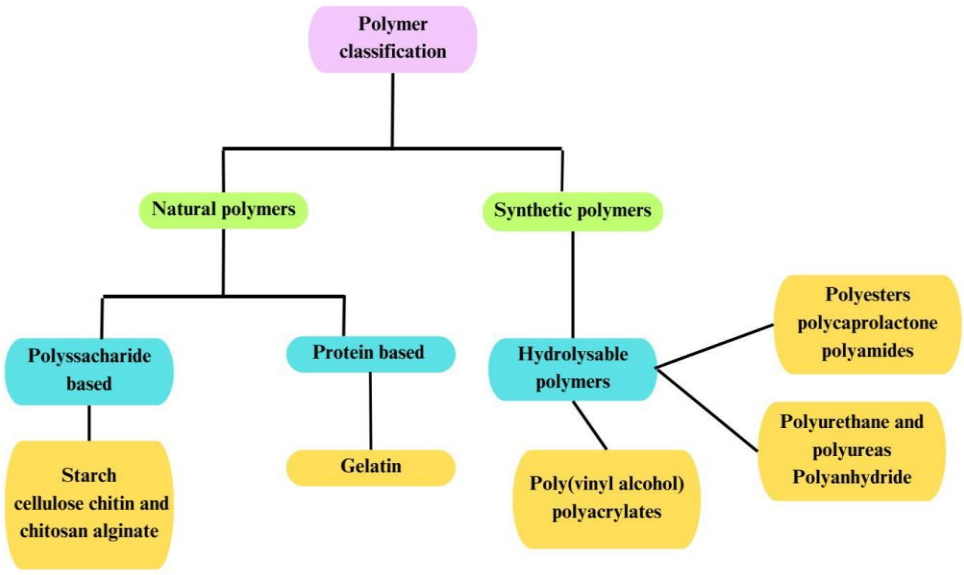

Figure 2 Classification of Polymers

2.2.1. Natural polymers

In the course of an organism's growth cycle, natural biodegradable polymers are created. These polymers are readily available, biocompatible, and biodegradable, among other benefits. The majority of natural polymers are derived from plants and animals and are soluble in water. Among their primary characteristics are their ability to stabilize complex formulas, emulsify oils, and extend the potency of active ingredients. For regulated medication delivery, gene delivery, regenerative medicine, and other biomedical applications, natural polymers are adaptable. When compared to synthetic polymers, natural polymers exhibit lower levels of toxicity [18, 19].

Polysaccharide-Based Polymers: Merely composed of monosaccharide units arranged in a backbone, polysaccharides are typically bound together by ether bond O-glycosidic bonds. They may be readily altered and are hydrophilic, biocompatible, biodegradable, and highly stable. Applying polysaccharides, the most popular ones are alginate and chitosan, which are used in the administration and targeting of pharmaceuticals [20, 21].

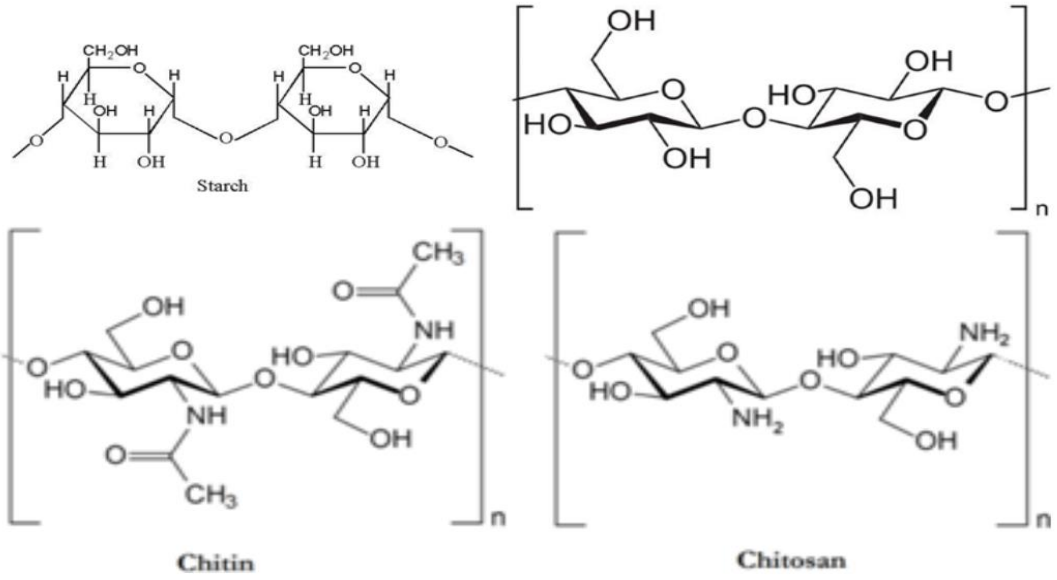

Figure 3 Structures of Starch, Cellulose, Chitin, Chitosan.

Protein-Based Polymers: Since most proteins are not soluble or bonded without breaking down, they are typically utilized in the environment in their natural state. Proteins are copolymers made up of various arrangements of amino acids, which makes the process of making them an intricate one involving a variety of enzymes. A reaction known as amide hydrolysis is used in the enzymatic breakdown of proteins by proteases [22,23].

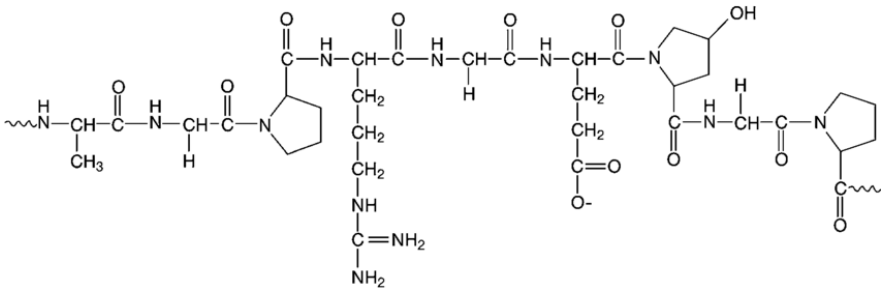

Figure 4 Structure of Gelatin

2.2.2. Synthetic Polymers:

Artificially produced synthetic polymers are made by humans using chemical reactions; they are frequently made from petrochemicals or other raw materials. Because of their adaptability, toughness, and specific qualities, these polymers have many uses. Because of these synthetic polymers' many uses and unique qualities, they are essential to contemporary industry and life. However, worries about how they affect the environment, particularly how long they persist in the environment, have raised awareness of recycling programs and sustainable alternatives [24,25].

Hydrolysable Polymers: Certain natural polymers are derived directly from nature, as was previously mentioned. However, there are also polymers that can be created by humans from natural sources but are not found in nature itself.

Chemical techniques are used to create a wide range of biocompatible and biodegradable polymers. The most prevalent compounds are esters, anhydrides, and amides; the primary source of biodegradability in synthetic biopolymers is the weak hydrolysable bonds that support them. Its monomer units can decompose chemically or enzymatically. For biomedical applications, hydrolysable polymers must be able to pass muster with the human body on a biological level [26,27,28].

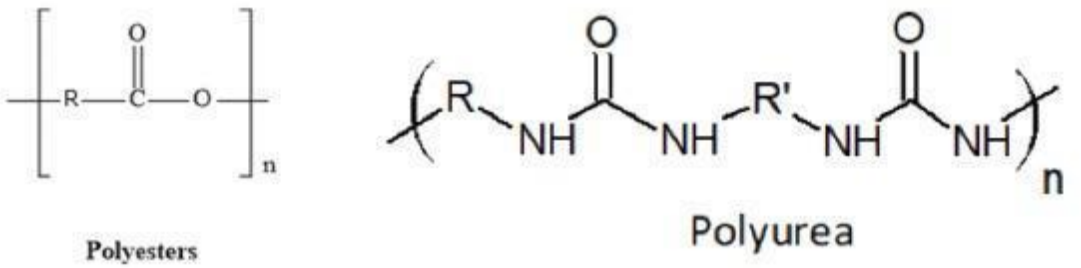

Figure 5 Structures of Polyesters and Polyurea.

2.3. Advantages and disadvantages of biodegradable polymers for microencapsulation:

2.3.1. Advantage:

For microencapsulation applications, biodegradable polymers have a number of benefits that make them sustainable and kind to the environment.

- Sustainability in the environment: Biodegradable polymers decompose into components that are safe for the environment, reducing their long-term effects and promoting sustainable practices.
- Waste Reduction: By using biodegradable polymers, the amount of non-biodegradable plastic waste that accumulates is decreased, addressing issues with plastic pollution.
- Greener End-of-Life: Compared to conventional polymers, biodegradable polymers naturally break down into simpler compounds through microbial activity, providing a greener end-of-life situation.
- Renewable Resources: Rather than relying solely on fossil fuels, many biodegradable polymers, including polylactic acid (PLA), are derived from renewable resources like corn starch or sugarcane.
- Controlled Release: The release kinetics of the substances encapsulated in biodegradable polymers can be precisely modulated by designing the polymers with controlled release properties.
- Biocompatibility: Chitosan is one of the naturally occurring biodegradable polymers that shows biocompatibility, which makes it appropriate for use in medical microencapsulation and pharmaceutical applications.
- Consumer and Regulatory Appeal: As environmental concerns have become more widely known, there has been a rise in the demand for sustainable and biodegradable products, which has increased the market appeal of biodegradable polymers[29,30,31].

2.3.2. Disadvantages

While biodegradable polymers offer many benefits, there are drawbacks as well, especially when it comes to microencapsulation.

- Differential Rates of Degradation: Biodegradable polymers can degrade at different rates depending on the surrounding environment, which makes it difficult to control and predict when encapsulated substances will release.
- Limited Mechanical Strength: When compared to non-biodegradable alternatives, biodegradable polymers may have a lower mechanical strength. The stability and longevity of the microcapsules may be impacted by this restriction.
- Difficulties in Processing: Certain conditions for processing some biodegradable polymers may differ from those for conventional polymers. Costs may rise and manufacturing procedures may become more difficult as a result.
- End-of-Life Considerations: Although biodegradable polymers are intended to decompose, appropriate conditions for this process may not exist in some disposal sites, such as landfills.
- Possibility of Contamination: If biodegradable polymers and conventional plastics are not appropriately separated, recycling facilities may face difficulties and possible contamination[32,33,34].

3. Techniques for microparticles preparation

Microparticles can be prepared using a variety of methods, each of which is appropriate for a given application and the desired properties. The emulsion-solvent evaporation/extraction process, spray drying, phase separation-coacervation, interfacial deposition, and in situ polymerization are a few of the methods available for microencapsulating pharmaceuticals. Every technique has pros and cons of its own. A specific technique's selection is influenced by the drugs and polymer's properties, the drug's site of action, and the length of the therapy.[35]

3.1. Emulsion - Solvent Evaporation Method

An approach that is frequently utilized in the creation of microparticles is emulsion solvent evaporation. For encapsulating medications, proteins, or other bioactive materials within the microparticles, this approach has advantages. Variations in surfactant content and polymer concentration can regulate the microparticles size and drug release kinetics[36].

3.1.1. Single Emulsion Method

An effective way to prepare microparticles is the single-emulsion method. A volatile organic solvent, like dichloromethane, is used to dissolve the polymer, and the medication is either suspended or dissolved in the polymer solution. With an emulsifier present, the resultant mixture is emulsified in a significant amount of water. The emulsion's solvent is extracted by a large-scale water extraction process or by evaporating at high temperatures, which forms compact microparticles. The ultimate morphology of microparticles is said to be influenced by the rate at which the solvent is removed. The temperature of the medium, the solvent employed, and the polymer's solubility properties all affect the pace at which the solvent is removed [37].

Unfortunately, the hydrophilic pharmaceuticals may diffuse out or partition from the dispersed oil phase into the aqueous phase, resulting in poor encapsulation efficiencies. For this reason, this approach is only applicable to hydrophobic medications. The oil-in-oil (o/o) emulsification process has garnered significant attention recently as a means of encapsulating hydrophilic medicines. In this technique, the medication and polymer are dissolved using water-miscible organic solvents, whereas the o/o emulsion's continuous phase is made of hydrophobic oils[38,39].

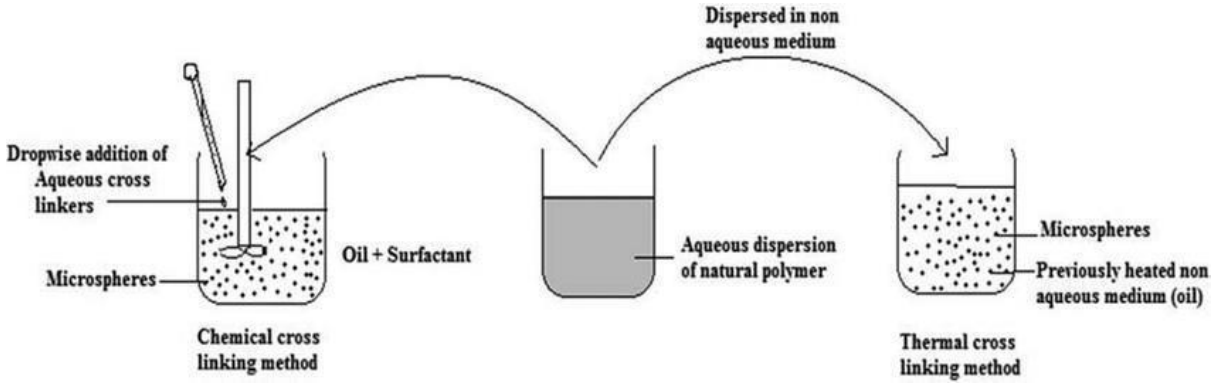

Figure 6 Single Emulsion Technique

3.1.2. Double Emulsion Method

Although the first paper on double emulsion was published 89 years ago (Seifriz, 1924), thorough research on the topic wasn't initiated until the end of the 1970s. Multiple emulsion reviews are available, mostly from three research groups: Matsumoto et al. (1980), Frenkel et al. (1983), Florence and Whitehill, 1981, and Florence and Whitehill, 1982. Preparing microparticles using the double emulsion method is useful, especially when it comes to encapsulating and delivering drugs. A double emulsion, also called a water-in-oil-in-water (W/O/W) emulsion, is made using this technique. First, an organic phase is used to emulsify an aqueous phase containing the material to be encapsulated. This primary emulsion is then reconstituted in a second aqueous phase [40].

Most drugs that are soluble in water have been encapsulated using water-in-oil-in-water techniques. To create the water-in-oil emulsion, the polymer-dissolved organic solution is emulsified with the water-soluble drug's aqueous solution. Sonicators or high-speed homogenizers are used to carry out the emulsification. To create a w/o/w emulsion, this primary emulsion is subsequently vigorously stirred into an excess of water containing an emulsifier. Evaporation or extraction are the methods used in the next step to remove the solvent. This technique has the benefit of encapsulating hydrophilic medications with a high encapsulation efficiency

in an aqueous phase. The development of protein delivery systems has thus made extensive use of the w/o/w emulsion system [41,42,43].

Temperature, the type and concentration of the emulsifier, the ratio of polymer to drug, the stirring/agitation speed during the emulsification process, and the properties of the polymer all affect the properties of the microspheres made using the double emulsion method [44].

3.2. Phase separation

A critical step in the microparticle preparation process during microencapsulation is phase separation. The process entails the dispersion of the active ingredient-containing dispersed phase and an immiscible phase, usually a polymer solution. Methods such as coacervation or solvent evaporation cause phase separation, which creates solid microparticles that contain the target material. In a variety of applications, like pharmaceuticals or food industry encapsulation, this process improves stability and aids in controlling drug release[45].

By gradually extracting the polymer solvent and creating soft coacervate droplets containing the drug, an organic non solvent is added to this mixture solution while being continuously stirred. The rate at which the nonsolvent is added influences the drug's encapsulation efficiency, size of microparticles, and solvent extraction rate. The nonsolvent that are frequently used are low-molecular-weight polybutadiene, vegetable oil, silicone oil, and light liquid paraffin. The coacervate phase is subsequently made harder by subjecting it to an excess of a different nonsolvent, such as diethyl ether, hexane, or heptane. Molecular weight of the polymer, non-solvent viscosity, and polymer concentration all affect the final microspheres' properties. The likelihood of creating large aggregates is this method's primary drawback. This method's primary drawback is its propensity to produce large aggregates. Before they fully phase separate, very sticky coacervate droplets usually stick to one another [46,47].

The preparation of protein-loaded microcapsules using this method appears promising. Traditional techniques for creating microparticles, for instance, require exposing proteins to large amounts of the hydrophobic polymer matrix, the interface between aqueous and organic phases, and acidic/basic microenvironments that arise from the polymer's breakdown. It has been reported that these adverse interactions cause conformational changes in proteins. Conversely, it has been demonstrated that the interfacial phase separation method reduces these sources of protein inactivation [48,49,50].

3.3. Spray drying

Making microparticles is often accomplished by spray drying. In order to create solid particles, a liquid solution or suspension is atomized into tiny droplets and rapidly dried. For the purpose of creating powders with regulated particle sizes, this method is extensively employed across numerous industries. Capturing active ingredients and achieving consistent powder formulations are effectively achieved with its help [51].

It is preferred to use volatile solvents when dispersing or dissolving the drug in the polymer solution. To create microparticles, a stream of heated air is used to spray the resultant solution or suspension. The parameters of atomization influence the size of the microparticles[52]. Due mainly to the microparticles' adherence to the spray-drier's inner wall, this technique's primary drawback is a sizable amount of product loss. Because the microparticles are extremely sticky before the solvent is completely removed, large aggregates are also commonly obtained [53]. Mannitol can be simultaneously sprayed on the surface of the microparticles and coated with polymer/drug solution through the use of a single nozzle for simultaneous spraying of aqueous maltosol solution [54]. The findings showed that applying mannitol to the microsphere increases product yield while reducing the degree of aggregation. To create protein-loaded microparticles, a non-aqueous, cryogenic method was employed [55]. Under this method, the polymer/drug solution is created as liquid droplets through a spraying nozzle, collected in liquid nitrogen that contains frozen ethanol, and then hardened by cooling the droplets to -80 ℃, which is the temperature at which solvent extraction takes place [56].

It has been demonstrated that using this technique, proteins can be encapsulated into microparticles without seriously sacrificing their biological activity [57].

3.4. Application of biodegradable polymers used for microencapsulation:

Applications for the biodegradable polymers used in microencapsulation include the following,

- Managed drug release to enhance patient compliance, minimize adverse effects, and provide longer-lasting therapeutic effects.
- Managed pesticide and fertilizer application, improving effectiveness and lessening environmental effect.
- For longer shelf life, taste masking, and controlled release, flavors, nutrients, or delicate ingredients can be encapsulated.

- The gradual release of active ingredients in skincare products, which improves the performance of the product and offers long-term benefits.
- Integration of functional additives, such as fragrances or antimicrobial agents, into textiles for regulated release.
- The application of microbes or enzymes to particular locations in order to carry out focused remediation operations.
- Encapsulation for applications in tissue engineering and regenerative medicine that require controlled release of biomolecules, proteins, or cells.
- Adding corrosion inhibitors, antimicrobials, or other functionalities to coatings for controlled release.
- Improving the active ingredients' stability and controlled release in cosmetics like sunscreens, lotions, and shampoos.
- Microencapsulating therapeutic agents to create materials with the ability to mend themselves[58,59,60].

4. Conclusion

The development of novel microencapsulation systems that possess both biodegradability and biocompatibility is facilitated by the use of biodegradable polymers. Unlike non-biodegradable polymers, it can be easily expelled from the body or released into the environment because it erodes in small residues. These polymers are good candidates because of their minimal cytotoxicity, biocompatibility, and mechanical properties. Though it takes time to manipulate the degradation pattern of polymers so that they do not produce any toxic products, there is still room for exploration in the field of biodegradable polymers. By carefully selecting and combining the right medications and polymers, biodegradable microparticles enable precise drug release for the treatment of a given ailment. The synthesis of microcapsules using biodegradable polymers has been a topic of exploration and ongoing innovation, as evidenced by the facts mentioned above. Yet there is still room for advancement in the form of novel applications, improved microencapsulation systems, and microencapsulation technologies.

References

1. Achinna, Poshadri & Kuna, A. . Microencapsulation technology: A review. J Res Angrau. 2010 Jan; 38(1)86-102.
2. S. S. Bansode, S. K. Banarjee, D. D. Gaikwad, S. L. Jadhav, R. M. Thorat. microencapsulation : a review Volume 1, Issue 2, March – April 2010; Article 008
3. Park JH, Ye M, Park K. Biodegradable polymers for microencapsulation of drugs. Molecules. 2005 Jan ;10(1):146-61.
4. Pekarek KJ, Jacob JS, Mathiowitz E. Double-walled polymer microspheres for controlled drug release. Nature. 1994 Jan ;367(6460):258-60.
5. Jeong B, Bae YH, Lee DS, Kim SW. Biodegradable block copolymers as injectable drug-delivery systems. Nature. 1997 Aug ;388(6645):860-2.
6. Ulbrich K, Pechar M, Strohalm J, Subr V, Ríhová B. Synthesis of biodegradable polymers for controlled drug release. Ann N Y Acad Sci. 1997 Dec ;831:47-56.
7. Hejazi R, Amiji M. Chitosan-based gastrointestinal delivery systems. J Control Release. 2003 Apr;89(2):151-65.
8. Zhao Z, Wang J, Mao HQ, Leong KW. Polyphosphoesters in drug and gene delivery. Adv Drug Deliv Rev. 2003 Apr;55(4):483-99.
9. Mi FL, Lin YM, Wu YB, Shyu SS, Tsai YH. Chitin/PLGA blend microspheres as a biodegradable drug-delivery system: phase-separation, degradation and release behavior. Biomaterials. 2002 Aug;23(15):3257-67.
10. Zhang Y, Chu CC. In vitro release behavior of insulin from biodegradable hybrid hydrogel networks of polysaccharide and synthetic biodegradable polyester. J Biomater Appl. 2002 Apr;16(4):305-25.
11. Abraham GA, Gallardo A, San Román J, Fernández-Mayoralas A, Zurita M, Vaquero J. Polymeric matrices based on graft copolymers of PCL onto acrylic backbones for releasing antitumoral drugs. J Biomed Mater Res A. 2003 Mar;64(4):638-4
12. Calandrelli L, De Rosa G, Errico ME, La Rotonda MI, Laurienzo P, Malinconico M, Oliva A, Quaglia F. Novel graft PLLA-based copolymers: potential of their application to particle technology. J Biomed Mater Res. 2002 Nov;62(2):244-53
13. Chen BH, Lee DJ. Slow release of drug through deformed coating film: effects of morphology and drug diffusivity in the coating film. J Pharm Sci. 2001 Oct;90(10):1478-96.
14. Tunón A, Gråsjö J, Alderborn G. Effect of intragranular porosity on compression behaviour of and drug release from reservoir pellets. Eur J Pharm Sci. 2003 Aug;19(5):333-44
15. Fulzele SV, Satturwar PM, Kasliwal RH, Dorle AK. Preparation and evaluation of microcapsules using polymerized rosin as a novel wall forming material. J Microencapsul. 2004 Feb;21(1):83-9
16. Felder ChB, Blanco-Príeto MJ, Heizmann J, Merkle HP, Gander B. Ultrasonic atomization and subsequent polymer desolvation for peptide and protein microencapsulation into biodegradable polyesters. J Microencapsul. 2003 Sep-Oct;20(5):553-67.

17. Kiyoyama S, Shiomori K, Kawano Y, Hatate Y. Preparation of microcapsules and control of their morphology. J Microencapsul. 2003 Jul-Aug;20(4):497-508
18. Sinha VR, Trehan A. Biodegradable microspheres for protein delivery. J Control Release. 2003 Jul;90(3):261-80
19. Sinha VR, Goyal V, Bhinge JR, Mittal BR, Trehan A. Diagnostic microspheres: an overview. Crit Rev Ther Drug Carrier Syst. 2003;20(6):431-60
20. Kissel T, Li Y, Unger F. ABA-triblock copolymers from biodegradable polyester A-blocks and hydrophilic poly(ethylene oxide) B-blocks as a candidate for in situ forming hydrogel delivery systems for proteins. Adv Drug Deliv Rev. 2002 Jan;54(1):99-134.
21. Tabata Y, Gutta S, Langer R. Controlled delivery systems for proteins using polyanhydride microspheres. Pharm Res. 1993 Apr;10(4):487-96
22. Kipper MJ, Shen E, Determan A, Narasimhan B. Design of an injectable system based on bioerodible polyanhydride microspheres for sustained drug delivery. Biomaterials. 2002 Nov;23(22):4405-12
23. Lin YH, Vasavada RC. Studies on microencapsulation of 5-fluorouracil with poly(ortho ester) polymers. J Microencapsul. 2000 Jan-Feb;17(1):1-11.
24. Deng JS, Li L, Tian Y, Ginsburg E, Widman M, Myers A. In vitro characterization of polyorthoester microparticles containing bupivacaine. Pharm Dev Technol. 2003;8(1):31-8
25. Wang C, Ge Q, Ting D, Nguyen D, Shen HR, Chen J, Eisen HN, Heller J, Langer R, Putnam D. Molecularly engineered poly(ortho ester) microspheres for enhanced delivery of DNA vaccines. Nat Mater. 2004 Mar;3(3):190-6.
26. Felt O, Buri P, Gurny R. Chitosan: a unique polysaccharide for drug delivery. Drug Dev Ind Pharm. 1998 Nov;24(11):979-93
27. S. Bhatia, Natural polymer drug delivery systems: Nanoparticles, plants, and algae, Springer, 2016.
28. Huh MS, Lee EJ, Koo H, Yhee JY, Oh KS, Son S, Lee S, Kim SH, Kwon IC, Kim K. Polysaccharide-based Nanoparticles for Gene Delivery. Top Curr Chem (Cham). 2017 Apr;375(2):31
29. Jain A, Gulbake A, Shilpi S, Jain A, Hurkat P, Jain SK. A new horizon in modifications of chitosan: syntheses and applications. Crit Rev Ther Drug Carrier Syst. 2013;30(2):91-181
30. Vilivalam VD, Illum I, Iqbal I. Starch capsules: an alternative system for oral drug delivery. Pharm Sci Technol Today. 2000 Feb;3(2):64-69
31. Pérez-Masiá R, López-Nicolás R, Periago MJ, Ros G, Lagaron JM, López-Rubio A. Encapsulation of folic acid in food hydrocolloids through nanospray drying and electrospraying for nutraceutical applications. Food Chem. 2015 Feb;168:124-33.
32. Tabata Y, Ikada Y. Macrophage activation through phagocytosis of muramyl dipeptide encapsulated in gelatin microspheres. J Pharm Pharmacol. 1987 Sep;39(9):698-704.
33. Tabata Y, Ikada Y. Synthesis of gelatin microspheres containing interferon. Pharm Res. 1989 May;6(5):422-7
34. Tabata Y, Uno K, Muramatsu S, Ikada Y. In vivo effects of recombinant interferon alpha A/D incorporated in gelatin microspheres on murine tumor cell growth. Jpn J Cancer Res. 1989 Apr;80(4):387-93.
35. Shinde BG, Nithianandam VS, Kaleem K, Erhan S. Flexibilized gelatin film-based artificial skin model: I. Preparation and properties of the films. Biomed Mater Eng. 1992 Fall;2(3):123-6.
36. PIEZ KA, GROSS J. The amino acid composition of some fish collagens: the relation between composition and structure. J Biol Chem. 1960 Apr;235:995-8
37. de Araújo JSF, de Souza EL, Oliveira JR, Gomes ACA, Kotzebue LRV, da Silva Agostini DL, de Oliveira DLV, Mazzetto SE, da Silva AL, Cavalcanti MT. Microencapsulation of sweet orange essential oil (Citrus aurantium var. dulcis) by liophylization using maltodextrin and maltodextrin/gelatin mixtures: Preparation, characterization, antimicrobial and antioxidant activities. Int J Biol Macromol. 2020 Jan;143:991-999.
38. Kumar N, Langer RS, Domb AJ. Polyanhydrides: an overview. Adv Drug Deliv Rev. 2002 Oct;54(7):889-910..
39. Leong KW, Kost J, Mathiowitz E, Langer R. Polyanhydrides for controlled release of bioactive agents. Biomaterials. 1986 Sep;7(5):364-71.
40. Tamada J, Langer R. The development of polyanhydrides for drug delivery applications. J Biomater Sci Polym Ed. 1992;3(4):315-53
41. Hombreiro Pérez M, Zinutti C, Lamprecht A, Ubrich N, Astier A, Hoffman M, Bodmeier R, Maincent P. The preparation and evaluation of poly(epsilon-caprolactone) microparticles containing both a lipophilic and a hydrophilic drug. J Control Release. 2000 Apr 3;65(3):429-38.
42. Passerini N, Craig DQ. Characterization of ciclosporin A loaded poly (D,L lactide-co-glycolide) microspheres using modulated temperature differential scanning calorimetry. J Pharm Pharmacol. 2002 Jul;54(7):913-9
43. Carrasquillo KG, Stanley AM, Aponte-Carro JC, De Jésus P, Costantino HR, Bosques CJ, Griebenow K. Non-aqueous encapsulation of excipient-stabilized spray-freeze dried BSA into poly(lactide-co-glycolide) microspheres results in release of native protein. J Control Release. 2001 Oct;76(3):199-208

44. Jiang W, Schwendeman SP. Stabilization of a model formalinized protein antigen encapsulated in poly(lactide-co-glycolide)-based microspheres. J Pharm Sci. 2001 Oct;90(10):1558-69.
45. Jiang, W.; Schwendeman, S. P. Stabilization and controlled release of bovine serum albumin encapsulated in poly(D, L-lactide) and poly(ethylene glycol) microsphere blends. Pharm Res 2001,18, 878-885.
46. Sinha VR, Trehan A. Biodegradable microspheres for protein delivery. J Control Release. 2003 Jul;90(3):261-80.
47. Crotts G, Park TG. Protein delivery from poly(lactic-co-glycolic acid) biodegradable microspheres: release kinetics and stability issues. J Microencapsul. 1998 Nov-Dec;15(6):699-713
48. Okochi H, Nakano M. Preparation and evaluation of w/o/w type emulsions containing vancomycin. Adv Drug Deliv Rev. 2000 Dec;45(1):5-26.
49. Mallardé D, Boutignon F, Moine F, Barré E, David S, Touchet H, Ferruti P, Deghenghi R. PLGA-PEG microspheres of teverelix: influence of polymer type on microsphere characteristics and on teverelix in vitro release. Int J Pharm. 2003 Aug;261(1-2):69-80.
50. Johansen P, Moon L, Tamber H, Merkle HP, Gander B, Sesardic D. Immunogenicity of single-dose diphtheria vaccines based on PLA/PLGA microspheres in guinea pigs. Vaccine. 1999 Sep;18(3-4):209-15.
51. Ruiz JM, Busnel JP, Benoît JP. Influence of average molecular weights of poly(DL-lactic acid-co-glycolic acid) copolymers 50/50 on phase separation and in vitro drug release from microspheres. Pharm Res. 1990 Sep;7(9):928-34.
52. Sarella PN, Thammana PK. Potential applications of Folate-conjugated Chitosan Nanoparticles for Targeted delivery of Anticancer drugs. Research Journal of Pharmaceutical Dosage Forms and Technology. 2023 Nov 9;15(4):281-8.
53. Yeo Y, Chen AU, Basaran OA, Park K. Solvent exchange method: a novel microencapsulation technique using dual microdispensers. Pharm Res. 2004 Aug;21(8):1419-27.
54. Sah H. Protein behavior at the water/methylene chloride interface. J Pharm Sci. 1999 Dec;88(12):1320-5.
55. Kim HK, Park TG. Microencapsulation of human growth hormone within biodegradable polyester microspheres: protein aggregation stability and incomplete release mechanism. Biotechnol Bioeng. 1999 Dec;65(6):659-67.
56. Takada S, Uda Y, Toguchi H, Ogawa Y. Application of a spray drying technique in the production of TRH-containing injectable sustained-release microparticles of biodegradable polymers. PDA J Pharm Sci Technol. 1995 Jul-Aug;49(4):180-4.
57. Johnson OL, Jaworowicz W, Cleland JL, Bailey L, Charnis M, Duenas E, Wu C, Shepard D, Magil S, Last T, Jones AJ, Putney SD. The stabilization and encapsulation of human growth hormone into biodegradable microspheres. Pharm Res. 1997 Jun;14(6):730-5.
58. Johnson OL, Cleland JL, Lee HJ, Charnis M, Duenas E, Jaworowicz W, Shepard D, Shahzamani A, Jones AJ, Putney SD. A month-long effect from a single injection of microencapsulated human growth hormone. Nat Med. 1996 Jul;2(7):795-9.
59. Bittner B, Morlock M, Koll H, Winter G, Kissel T. Recombinant human erythropoietin (rhEPO) loaded poly(lactide-co-glycolide) microspheres: influence of the encapsulation technique and polymer purity on microsphere characteristics. Eur J Pharm Biopharm. 1998 May;45(3):295-305.
60. Morlock M, Kissel T, Li YX, Koll H, Winter G. Erythropoietin loaded microspheres prepared from biodegradable LPLG-PEO-LPLG triblock copolymers: protein stabilization and in-vitro release properties. J Control Release. 1998 Dec;56(1-3):105-15.

Author's short biography

Vijayalakshmi M.K.:

Vijayalakshmi M.K. is working as an Associate Professor in department of Pharmaceutical Chemistry /Analysis at Faculty of Pharmacy, Bharath Institute of Higher Education and Research. She has completed her post-graduation in Pharmaceutical Chemistry in Madaras Medical College, Chennai. She has vast experience in Research and Development in various industries and Organisation. Her present interest on research in Computer Aided Drug Design with strong background in various pharmaceutical field as Quality Control Chemist, Senior Research Scientist and Academic Field. She has published many number of research article in peer reviewed national and international journals and many number of book chapters and also she edited many books.

Amirtha Lakshmi B:

Amirtha Lakshmi. B, B.Pharm Final year student at Faculty of Pharmacy, Bharath Institute of Higher Education and Research.

Dhanusha K:

K . Dhanusha ,B.Pharm Final year student at Faculty of Pharmacy, Bharath Institute of Higher Education and Research

Ayisha Siddiqkha:

Ayisha Siddiqkha .A, B.Pharm Final year student at Faculty of Pharmacy, Bharath Institute of Higher Education and Research