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“A Systematic Review On Biodegradable Polymer For Drug Delivery”

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ABSTRACT

Biodegradable polymers are a special class of polymers that breaks down after its intended purpose by bacterial decomposition process to result in natural byproducts such as gases, water, biomass, and inorganic salts. The interest in producing biodegradable polymers by chemical treatment, microorganisms and enzymes has increased to make it easier to dispose after the end of their use without harming the environment. Biodegradable polymers reported a set of issues on their way to becoming effective materials. In this article, biodegradable polymers, treatment, composites, blending, and modeling are studied. The environmental fate and assessment of biodegradable polymers are discussed in detail. The forensic engineering of biodegradable polymers and understanding of the relationships between their structure, properties, and behavior before, during, and after practical applications are investigated. This review article also examines the wide range of Synthetic biodegradable polymers and focuses on their application, characteristics, mechanisms, preparation methods, and properties. A thorough examination of the condition of biodegradable polymers as of today is summarized in this article.

Keywords: *Biodegradable, Nanoparticle, Polymer, Nanocarriers, Biodegradation Pathways*

INTRODUCTION

Biodegradable polymers are made to provide temporary support and break down within a short amount of time after being ingested by the body. With an estimated 68 million kg consumed annually in 2001^[1] biodegradable polymers are frequently employed in tissue engineering applications and as biomedical devices. There are two types of biodegradable polymers: natural and artificial. Synthetic polymers provide a number of benefits over naturally occurring materials. First, it is possible to synthesize synthetic polymers using a repeatable procedure that will always generate the same polymer with the same composition. They can be manufactured with an infinite variety of physical, chemical, and mechanical properties that can be altered according to the application. The principal drawback of the widely utilised biodegradable polymers, including polydioxanones and α -hydroxy acid, is that they are too rigid and inflexible to undergo reversible deformation. Moreover, they bear no resemblance to the physical characteristics of human soft tissue. As a result, the device may not integrate into the body as intended due to irritation, inflammation, and the production of scar tissue from their use. As a result, their effectiveness in tissue engineering applications is restricted.^[2]

In the case of traditional petroleum-derived plastics, the same durability qualities that make plastics ideal for many applications, such as in packaging, building materials and commodities, as well as in hygiene products, can also cause waste-disposal problems because these materials are not readily biodegradable and because of their resistance to microbial degradation, they accumulate in the environment. Additionally, there has been a significant rise in oil prices recently. The interest in biodegradable polymers, and specifically biodegradable biopolymers, has been sparked by these facts. In the 1980s, the first biodegradable plastics and polymers were introduced. Biodegradable plastics can be made from a variety of materials, including synthetic and natural polymers. While synthetic polymers are made from non-renewable petroleum resources, natural polymers can be found in enormous amounts from renewable sources.^[3] Over the past 20 years, there has been an increase in interest in polymers and other innovative materials in biological and biomedical research and development due to impressive advancements in biotechnology, bioengineering, and biomaterials with distinctive features. Despite the significant impact biomaterials have already had on biomedical research and clinical practise, more needs to be understood about the surface and interfacial chemistry of biomedical materials and tissue (or cells).^[4] Compared to other materials, biodegradable polymers have a number of benefits. The flexibility to customise the mechanical qualities, the rates of degradation, and the capacity to take on different forms are all significant benefits. The primary benefit of biodegradable polymers is that they may be removed surgically less often, which saves time and money. On the other hand, the generation of degradation products may also provide issues.^[5]

Table No. 1: Abbreviations of Some Important Biodegradable Polymers ^[6]

Abbreviation	Full Name
PLA	poly(lactide), poly(lactic acid)
PLLA	poly(L-lactide), poly(L-lactic acid)
PGA	poly(glycolide), poly(glycolic acid)
PDLLA	poly(DL-lactide)
PLGA	poly(DL-lactide-co-glycolide) poly(DL-lactic-co-glycolic acid) poly(L-lactide-co-glycolide) poly(L-lactic-co-glycolic acid)
PCL	poly(-caprolactone)

1.1 Classification of Biodegradable Polymer: ^[7]

1] Natural Biodegradable Polymer:

- a) Protein-based polymer: Collagen, Albumin, Gelatin
- b) Polysaccharides: Alginate, Cyclodextrin, Chitosan, Dextran, Agarose, Hyaluronic acid, Starch, Cellulose

2] Synthetic Biodegradable Polymers:

- a) Polyester: Poly lactic acid, Poly glycolic acid, Poly hydroxyl butyrate, Polyester, Polycaprolactone, Poly lactide-co-glycolide (PLGA), Poly diaxone
- b) Polyamide: Poly adipic acid, Poly sebacic acid, Poly terephthalic acid,
- c) Polyamides: Poly amino acid, Poly imino carbonate

2. SYNTHETIC BIODEGRADABLE POLYMER

Numerous artificial biodegradable polymers are presently being researched for use as scaffolds in tissue engineering or as drug delivery systems.^[8] To deliver effective therapy, each of these applications requires materials with certain chemical, biological, mechanical, and physical qualities. As a result, numerous degradable polymers—both synthetic and natural—have been researched for these uses. Nonetheless, the composition of natural polymers varies depending on the source.^[9]

Advantages of biodegradable polymer as a drug carrier:

The main benefits of using biodegradable polymers as drug carriers are as follows: ^[10]

- 1) The drug is delivered locally.
- 2) It is sustained.
- 3) It is stabilized.
- 4) Its release rate is less affected by the drug's characteristics.
- 5) Its release rate is constant over time.

3. COMMONLY USED BIODEGRADABLE POLYMERS IN DRUG DELIVERY SYSTEM

3.1 Biodegradable polymeric nanoparticles based drug delivery systems:

In addition to enhancing the therapeutic effect of several therapeutic treatments in a synergistic or additive manner, nanocarriers can also be used to overcome acquired resistance to individual chemotherapeutic medications. Chemo-resistant tumours can arise from a variety of sources, such as absorption mechanism downregulation or drug efflux rate elevation.^[10] Due to their small size, high surface area-to-volume ratio, advantageous drug release profiles, and targeting characteristics that may encourage their preferred accumulation in tumour tissues, nanocarriers are unique in the drug delivery industry.^[11] Nanoparticles have grown incredibly appealing for use in biology and medicine throughout the past ten years.^[12] They may alter entrapped medicines' biologic characteristics, pharmacokinetics, and therapeutic effectiveness.^[13] Synthetic polymers including poly(D,L-lactide) (PLA), poly(D,L-glycolide) (PLG), co-polymer poly(lactide-co-glycolide) (PLGA), polyalkylcyanoacrylates, and poly-ε-caprolactone are examples of biodegradable polymers. They are deemed safe, and the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have authorised a small number of biodegradable polymer products for use in pharmaceutical applications.^[14]

METHODS OF PREPARATION FOR POLYMERIC NANOPARTICLES:

The purpose of PNs is to encapsulate hydrophobic and hydrophilic materials, including proteins, salts, high-molecular-weight DNA, and antisense nucleic acids.^[15,16] The growth of PNs is influenced by a number of factors, including the molecular weight of the polymers, the presence of stabilising agents and cryoprotectants, etc.^[17,18]

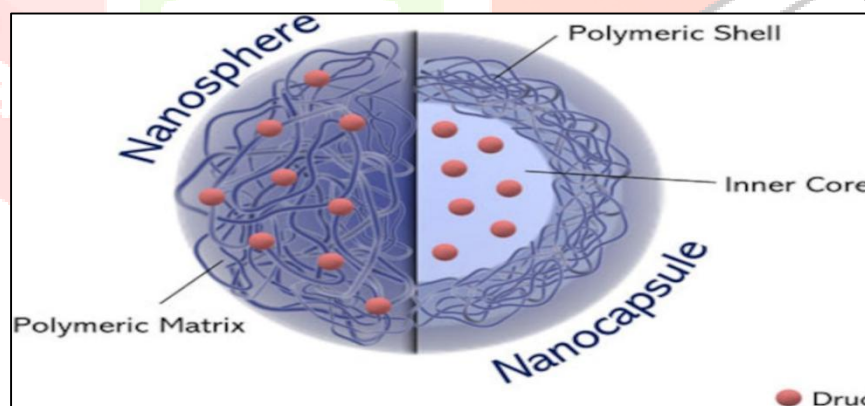


Fig. No.1: Diagrammatic depiction of the morphology-dependent properties of polymeric nanoparticles.^[19]

Polymeric nanoparticles can be either nanospheres or nanocapsules, depending on the methods utilised to create them (Figure 1). While the medication is contained within the aqueous or oily core of nanocapsules, which are encased in a polymeric shell, nanospheres are matrix systems where the drug is disseminated throughout the structure or adsorbed onto the surface.^[20] The behaviour of nanoparticles in intricate biological settings can be influenced by their physico-chemical characteristics, which include stability, drug-release profiles, size, shape, and surface features. The dispersion medium's pH and ionic strength can also affect the entrapped drug(s)' safety, pharmacological effectiveness, and biodistribution.^[21] Interaction with a biomaterial may promote the creation of aggregates or particles with varying mean sizes, which could have important implications for cell uptake and distribution, toxicity, and intracellular fate. Any size modification will also affect the nanoparticles' pharmacokinetic profile, modify where they are located inside tissue compartments, and cause unintentional

interactions with other biological substrates and receptors. For example, it has been shown that the particle size affects renal filtration and the MPS's nonspecific absorption.^[22]

3.2 Biodegradable Polymers used in Controlled Drug Delivery System:

The technique of delivering a pharmaceutical substance to produce a therapeutic effect in either humans or animals is known as drug delivery.^[23,24] Chemical engineers and chemists are making significant contributions to human health care through one of the scientific fields that is developing the fastest right now: controlled medication delivery technology. Comparing such delivery systems to traditional dose forms reveals many benefits, such as increased convenience and patient compliance, as well as decreased toxicity and increased efficacy. These systems frequently employ artificial polymers to transport the medications.^[25]

CDDS: A variety of prolonged action formulations that offer continuous release of their active components at a predetermined rate and for a predetermined amount of time fall under the category of controlled release dosage forms. Most of these formulations are meant to be taken orally, although more recently, parenteral administration, ocular insertion, and transdermal application have also been made possible with these devices. Ensuring higher patient compliance by providing an extended duration of action is the primary goal behind the creation of this technology.^[26]

As will be covered below, controlled drug delivery systems have a number of advantages over traditional medication delivery.^[26]

- 1) A decrease in the frequency and severity of harmful effects and toxicity.
- 2) Improved medication use and fewer dosage intervals.
- 3) Regulated release site and rate.
- 4) A more consistent medication concentration throughout the body.
- 5) A rise in patient adherence.

Examples of biodegradable polymers which are used in controlled drug delivery system^[6]

- a) Poly lactic and poly glycolic acid in polyester
Polyester, polycaprolactone, and polyhydroxyl butyrate
Poly diaxonone and Poly lactide-co-glycolide (PLGA)
- b) Polyanhydride, which includes polyadepic acid and polysebacic acid
- c) Polyamides: Poly amino acid, Poly imino carbonate, and Poly terphthalic acid

Drug release mechanisms for Controlled drug delivery

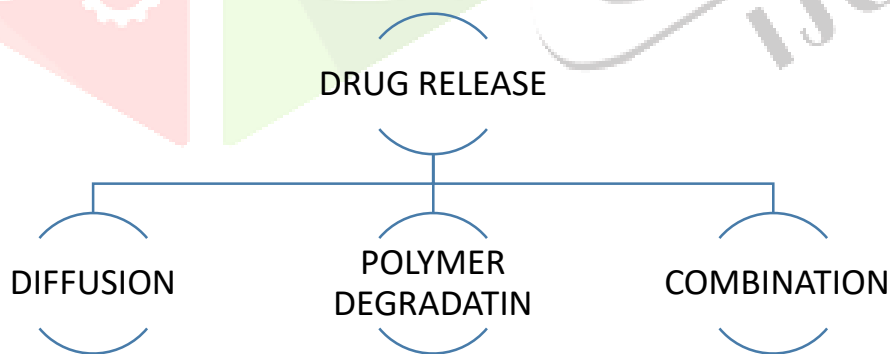


Fig No. 2: Possible drug release mechanism for controlled drug delivery^[27]

Polymer degradation includes:

- i. Enzymatic Degradation
- ii. Hydrolysis:
 - a) Bulk Erosion,
 - b) Surface Erosion
- iii. Combinational

Mechanism that regulates the release of the drug's active ingredient from the delivery system by osmosis, polymer erosion, or diffusion. In certain instances, the phrase "biodegradation" is restricted to the description of chemical processes, but the term "bio erosion" may be used to describe physical processes that cause a polymer device to

lose weight^[28]. The main mechanism of degradation is chain cleavage, which lowers the molecular weight. Conversely, erosion refers to any of the processes that cause the mass of the polymer matrix to be lost.^[29,30]

4. DIFFERENT DRUG DELIVERY APPLICATIONS OF BIODEGRADABLE POLYMERS

4.1 Biodegradable Polymers as Drug Delivery Systems for Bone Regeneration:

It is challenging to accomplish tissue regeneration with just cells; instead, a combination of cells, scaffolds, and signalling molecules must perform their corresponding functions.^[31] Autologous bone grafting, allogenic bone grafting, synthetic bone grafting, prosthetic joint replacement, and the induced membrane technique are among the methods available for treating bone deficiencies.^[32] Large bone defects that are too big to be repaired with bone tissue could need to be replaced with prosthetics made of titanium or cobalt-chromium alloy. As opposed to older individuals undergoing traditional artificial joint replacement surgery.^[32,33] For the restoration of bone abnormalities resulting from severe trauma or tumour removal, metallic megaprotheses have been employed. Compared to traditional arthroplasty, using megaprotheses has a greater rate of complications and increases the risk of revision surgery because of wear, loosening, and infection.^[34] Allogenic or autologous bone transplants are further treatments for bone abnormalities. Autologous bone harvesting from fibular or iliac donor sites damages healthy tissues; hence, the additional surgery may result in postoperative pain at the donor site, gait difficulties, and challenges with scarce graft availability.^[35-38]

By inserting a cement spacer into the bone defect, the induced membrane technique causes a biological membrane to form around the cement. After six to eight weeks, the cement spacer is taken out, and to encourage bone regrowth, a mixture of autologous bone and granular bone substitute is inserted into the cavity of the induced membrane. Compared to traditional autologous bone grafts, relatively big bone defects can be treated with less autologous bone because of the membrane that resembles the periosteum surrounding the lesion. Nevertheless, the induced membrane approach necessitates a two-step process, and the amount of bone defect amenable to regeneration is still restricted.^[39]

Scaffolds for bone tissue engineering are made of polymers.^[32]

Collagen, gelatin, cellulose, chitosan, and hyaluronic acid are natural polymers.

Polymers Synthetic: PCL, PEG, PLLA, PLGA, PVA

Properties of biodegradable scaffolds should be as bellow: ^[40]

1. Surface Properties

- Large & Open pores
- Mimics Extracellular matrix

2. Geometry

- Porous Template
- Interconnectivity

3. Mechanical Strength

- Tensile Strength
- Elastic Modulus
- Toughness
- Bio Stability

4. Biocompatible

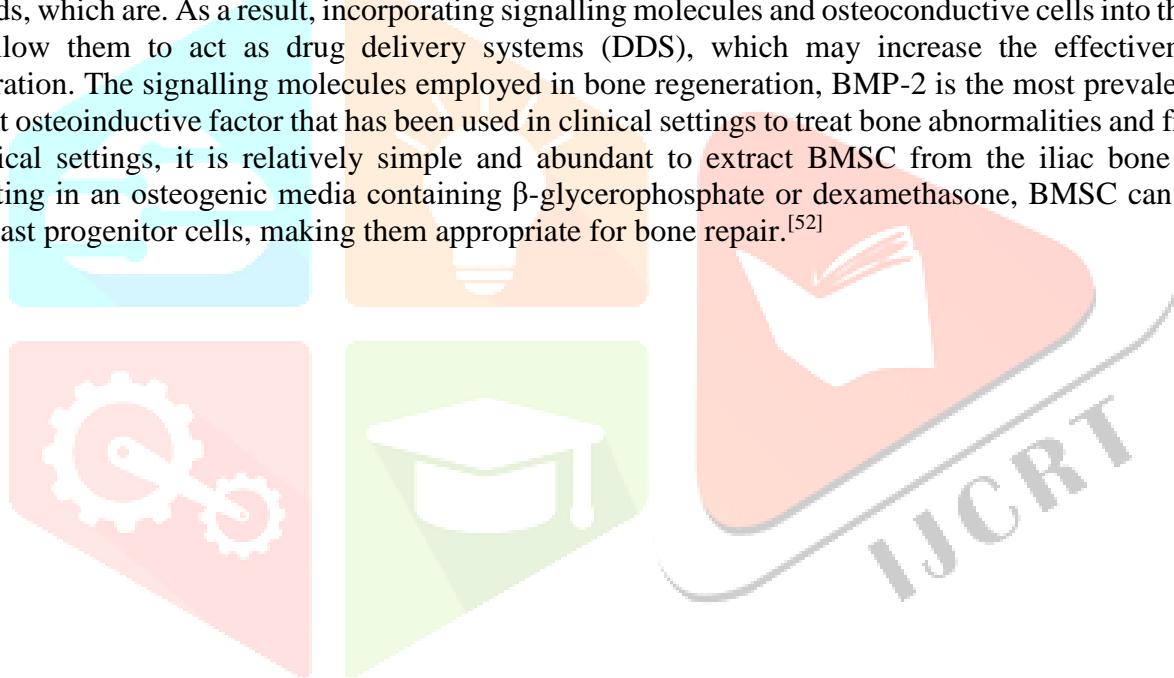
- Non Toxic
- Increase Biocompatibility

In-vivo, collagen is frequently seen as a component of bone, cartilage, and fibrous tissue. Collagen makes up about 90% of the proteins in the bone matrix in an organism. Osteoblasts produce type I collagen, the primary collagen found in bone. Procollagen's N- and C-termini, which are the cell's precursors for collagen, are released outside the cell where they are then broken down by protease to produce collagen molecules. Collagen fibrils are created when the molecules of collagen self-associate into aggregates and make cross-linking bonds with one another to create cross-linked collagen fibrils.^[41] Collagen has been extensively studied in regenerative medicine for its potential use as a scaffold and in the regeneration of the bladder and heart since it is a crucial component

of the hard and fibrous tissues of in vivo models.^[43] While hyaluronic acid, cellulose, and chitosan are the most popular naturally-derived scaffold materials, collagen is still one of the most widely utilised types. Other polymers are also being investigated as possible scaffolds. Although cellulose is a polymer made of glycosidic linkages and is a major component of plant fibres, it is also used as a raw ingredient for paper. Excellent biocompatibility is another property of cellulose, and the cellulose/hyaluronic acid complex has been used in clinical settings as a barrier to reduce postoperative adhesion.^[44,45] The structural component chitosan is produced through the deacetylation of chitin, a polysaccharide present in the exoskeleton of crustaceans like prawns and crabs. Chitin can be deacetylated by at least 75% by submerging and boiling it in an aqueous sodium hydroxide solution at a concentration higher than 40%. The degree of chitosan deacetylation can be increased by raising the temperature and alkali concentration, however this technique cannot completely deacetylate the material. The partially deacetylated chitosan is filtered out of the aqueous sodium hydroxide solution, completely rinsed with water to get rid of the sodium hydroxide, and then dried to get 100% deacetylated chitosan. Biomaterials made from chitosan have been investigated as skin and nerve regeneration scaffolds.^[46,47,48]

4.2 Biodegradable Scaffolds for Drug Delivery system:

There exists a limit to the size of the bone defect that can be treated with calcium phosphate-based artificial bones (TCP, HA), despite their osteoconductive qualities and relative effectiveness in mending tiny lesions on their own.^[49] Both natural and synthetic polymers are typically not osteoconductive, in contrast to calcium phosphate scaffolds, which are. As a result, incorporating signalling molecules and osteoconductive cells into these scaffolds may allow them to act as drug delivery systems (DDS), which may increase the effectiveness of bone regeneration. The signalling molecules employed in bone regeneration, BMP-2 is the most prevalent. BMP-2 is a potent osteoinductive factor that has been used in clinical settings to treat bone abnormalities and fractures.^[50,51] In clinical settings, it is relatively simple and abundant to extract BMSC from the iliac bone marrow. By cultivating in an osteogenic media containing β -glycerophosphate or dexamethasone, BMSC can develop into osteoblast progenitor cells, making them appropriate for bone repair.^[52]



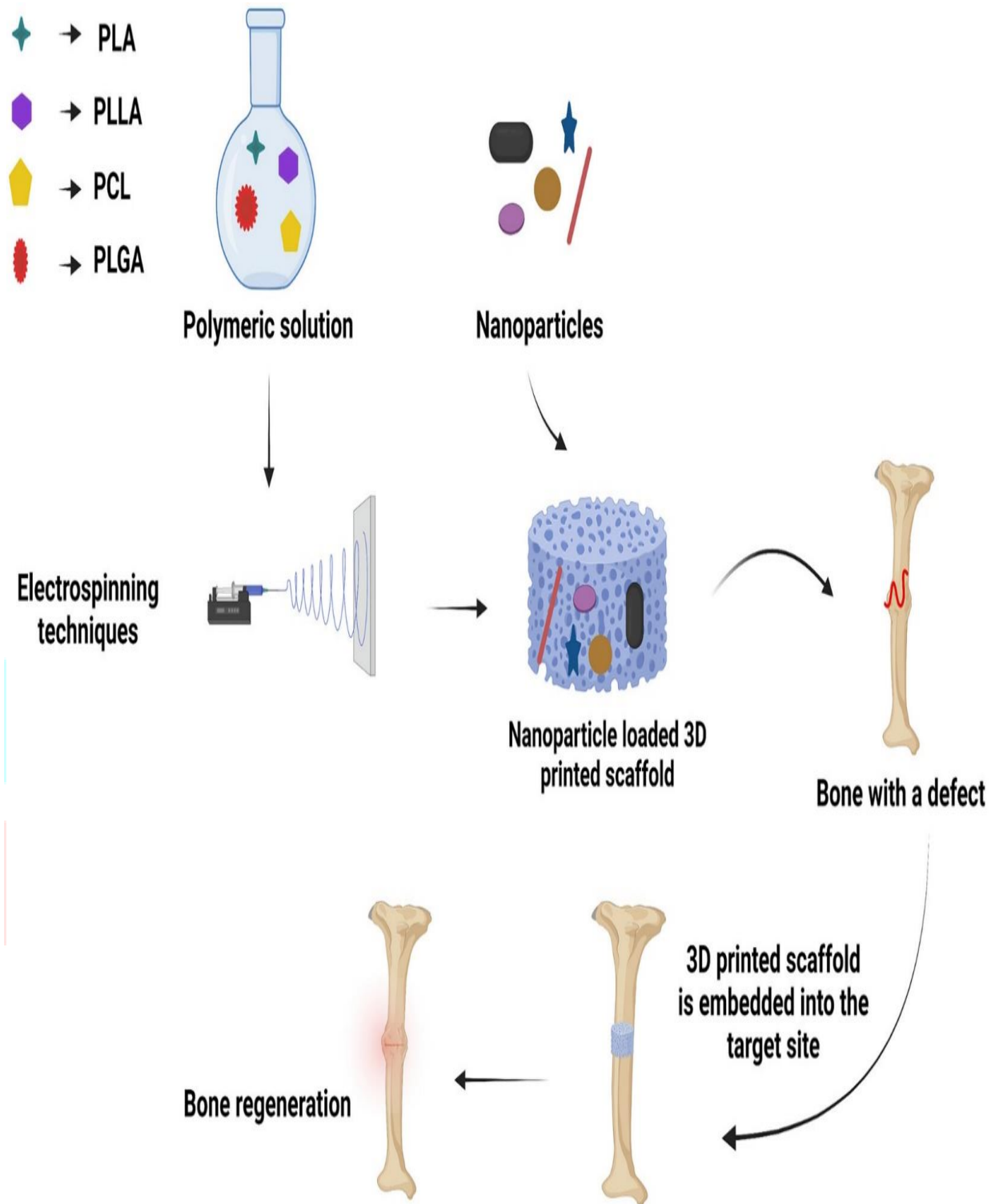


Fig No.3: Artificial polymers as scaffolds for bone engineering^[42]

5. APPLICATIONS OF BIODEGRADABLE POLYMERS:

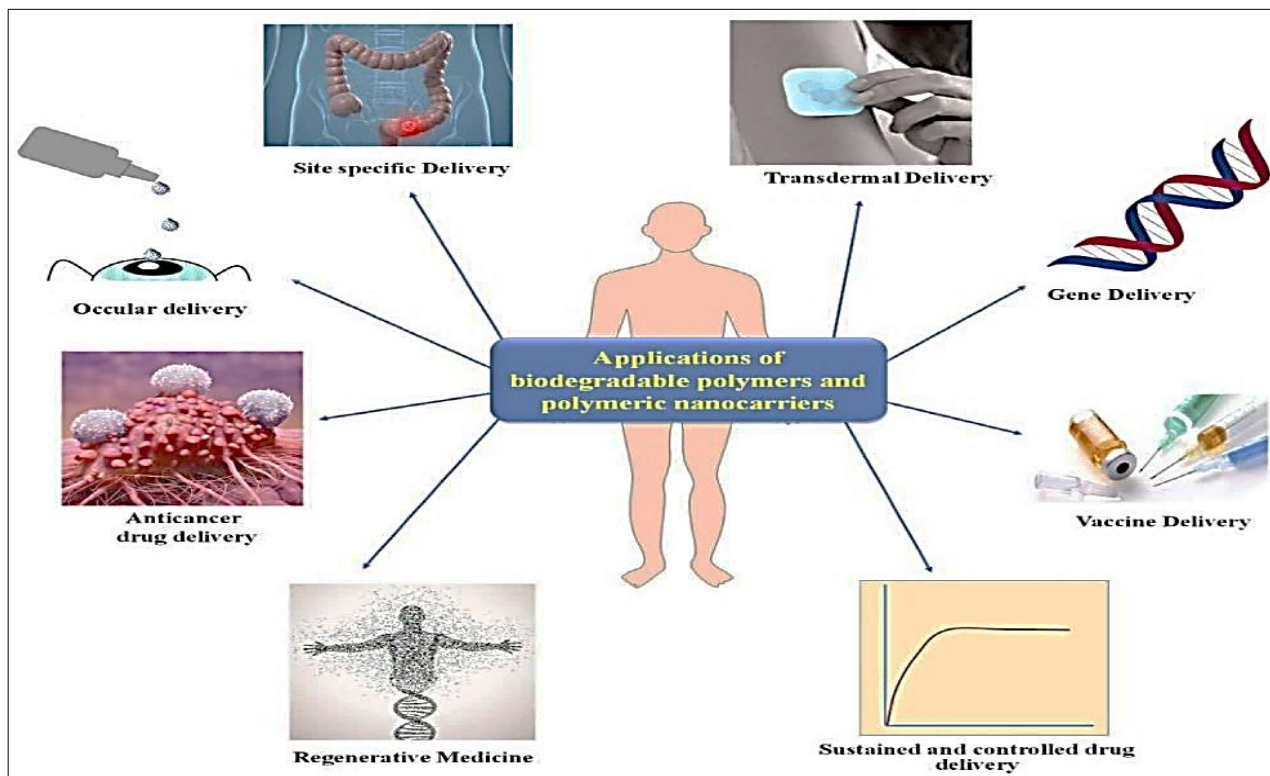


Fig No.4: Recent advances in biodegradable polymer. ^[56]

1. Site specific delivery: Drug delivery that is site-specific aims to deliver a medication straight to a particular biological site. Targeted drug delivery refers to the localization of a medication at therapeutic concentrations into a target site while limiting access to non-target regions in a selective and efficient manner. ^[53]

2. Transdermal delivery: Drugs are delivered directly via the skin in a process known as transdermal delivery. The most often used method involves the use of hypodermic needles, which can cause pain, needle anxiety, and even the spread of infectious diseases to patients. ^[54,55]

3. Gene delivery: Targetron-like systems—genes inserted into the intron's domain IV and the intron-encoded protein (RT) moved to a different location inside the same vector or onto a new vector altogether—are being developed as gene delivery platforms. ^[57]

4. Sustained and controlled drug delivery: medication delivery systems with sustained release allow for gradual medication release over a longer period of time following the administration of a single dose. And the controlled drug delivery means the medication delivery system that keeps drug levels in blood and tissue steady for a long time. ^[58, 59]

5. Anticancer drug delivery: The importance of biodegradable polymers in cancer therapy is demonstrated by the variety of biodegradable polymeric drug delivery systems that have reached the clinical stage of research. These systems are intended for the localised and systemic administration of therapeutic drugs as well as tumor-targeting macromolecules. ^[60]

6. Ocular delivery: Because of their capacity to degrade, biodegradable polymers have become attractive options for ocular drug-delivery systems (DDSs). This allows for the precise and continuous release of pharmaceuticals at the intended location. ^[61]

7. Site specific delivery: Drug delivery that is site-specific aims to deliver a medication straight to a particular biological site. Targeted drug delivery refers to the localization of a medication at therapeutic concentrations into a target site while limiting access to non-target regions in a selective and efficient manner. ^[62]

Table No.2: Advantages, Disadvantages and Applications of biodegradable polymers ^[68]

Polymer	Applications	Advantages	Disadvantages
Polyphosphazenes	Vaccination; Tissue Engineering Complementary	Artificial Flexibility Manageable Mechanical Characteristics	Complex Synthesis
Polyanhydrides	Drug Delivery; Tissue Engineering	Significant Monomer Flexibility; Controllable Degradation Rates	Low-molecular Weights; Weak Mechanical Properties
Polyacetals	Drug Delivery	Mild pH Degradation Products; pH Sensitive Degradation	Low Molecular Weights; Complex Synthesis
Poly(ortho esters)	Drug Delivery	Controllable Degradation Rates; pH Sensitive Degradation	Weak Mechanical Properties; Complex Synthesis
Polyphosphoesters	Drug Delivery; Tissue Engineering	Biomolecule Compatibility; Highly Biocompatible Degradation Products	Complex Synthesis
Polycaprolactone	Tissue Engineering	Highly Processable; Many Commercial Vendors Available	Limited Degradation
Polyurethanes	Prostheses; Tissue Engineering	Mechanically Strong; Handle Physical Stresses Well	Limited Degradation; Require Copolymerization with Other Polymers
Poly lactide	Tissue Engineering; Drug Delivery	Highly Processable; Many Commercial Vendors Available	Limited Degradation; Highly Acidic Degradation Products
Polycarbonates	Drug Delivery; Tissue Engineering; Fixators	Chemistry-Dependent Mechanical Properties; Surface Eroding	Limited Degradation; Require Copolymerization with Other Polymers

Nowadays, there is a lot of interest in the development of biopolymeric drug delivery systems, particularly in controlled delivery. More significantly, biodegradable capsules allow for controlled drug administration within people.^[63] Biodegradable polymers are specifically utilised to create innovative formulations, and the buccal mucosa's high permeability makes it a suitable target for medication administration.^[64] Notably, because of their bioactive properties that promote cell growth and regeneration potential, provide antibacterial conditions, and modulate immunological responses, biodegradable polymers are regarded as an outstanding candidate for wound healing.^[65] Furthermore, because biodegradable polymers can absorb large amounts of water, they are likely candidates for wound care. These polymers have recently been shown to have the ability to release medications at the site of injury, making them suitable for use in medicinal applications.^[66]

Numerous biopolymers exhibit favourable film-forming characteristics, rendering them suitable for use in traditional commodity applications.^[66] Furthermore, farming, filtration, hygiene, and protective clothing can all benefit from the usage of biodegradable polymers in non-woven form.^[67]

6. Recent advances of biodegradable polymers:

One of the frontiers of research is the search for novel approaches and modes of action for medication delivery systems. These use interdisciplinary scientific methods to produce significant improvements in therapeutic index and bioavailability at the point of drug delivery.^[69,70] Drug delivery systems combine engineered technology with one or more conventional drug delivery techniques. The systems enable precise targeting of the amount of a medicine released into the body and/or the rate at which it is released. Numerous innovative medication delivery techniques are made possible by the use of biodegradable and bioabsorbable polymers. The delivery component of the systems has been created using bio-absorbable polymers, such as hydrogels made of poly (lactic acid) and poly (glycolic acid), as well as their copolymers.^[71,72] The biodegradable and bio-absorbable polymers offer a secure framework for administering medication without endangering the body, regardless of

whether the drug delivery system depends on a biodegradable implant to deliver medication subcutaneously or deeply within the body. A formulation or a device that facilitates the entrance of a medicinal substance into the body is known as a polymeric drug delivery system. It enhances safety and effectiveness by regulating the pace, location, and duration of medication release throughout the body. Although drug delivery has advanced significantly over the past 20 years, controlling drug access into bodily organs like the brain is still a challenging task. But new research on the carrier-mediated passage of nanodrug delivery systems across the blood-brain barrier is starting to offer a logical foundation for managing drug delivery to the brain. The uptake transporters for natural nutrients such as amino acids, peptides, hexose, monocarboxylate, and stem cells are the transport mechanisms at the blood-brain barrier.^[73-75]

6.1 Artificial polymers for medication delivery systems

1] *Methacrylate poly(2-hydroxyethyl):*

2-hydroxyethyl methacrylate polymer (poly (HEMA)) is a polymer that reacts with water to generate an aqueous solution, or hydrogel.^[76] Through solution polymerization, 2-hydroxyethyl methacrylate (HEMA) was used as the raw material, azobisisobutyronitrile (AIBN) as the catalyst, ammonium persulfate or sodium pyrosulfite (APS/SMBS) as the hydrogel, and ethyleneglycoldimethacrylate (EGDMA) or triethyleneglycoldimethacrylate (TEGDMA) as the cross-linking additive to create the poly (PHEMA) hydrogel for intraocular lens material.^[77] In order to study a wide range of TPGDA concentrations for drug delivery systems, equilibrium swelling, structural characterisation, and solute transports in swollen poly (HEMA) gels cross-linked with TPGDA were examined.^[78] Hydrogels made of poly (HEMA) are frequently utilised in biomedical implants. Because poly (HEMA) is so highly hydrophilic, it resists protein fouling, which makes it a great option for coating ventricular catheters.^[79]

2] *Poly (ethylenimines):*

Linear poly (ethylenimine) (PEI) dissolves in ethanol, chloroform, hot water, and low pH. In acetone, benzene, ethyl ether, and cold water, they are insoluble. Arimidine ring-opening polymerization is the process used to create branched PEI. Poly (2-oxazolines) and N-substituted polyaziridines are two examples of polymers that can be post-modified to produce linear PEI.^[80]

3] *Dendritic polymers:*

High branching polymers with a dendritic structure controllable constructions with a substantial populace of terminal functional groups, low solution or melt viscosity, and good solubility. They are modifiable in terms of size, degree of branching, and functionality. through the synthetic methods. Dendrimer research has focused more on creating biocompatible dendrimers and using them to a variety of applications, biological sciences, such as immunology, medication administration, and the creation of vaccines, antibiotics, and antivirals^[81,82]

4] *Biodegradable and bio-absorbable polymer:*

When using drug carriers, bio-absorbable drug delivery systems are a preferable option because they only require the implant to be present temporarily.^[83] The most often utilised and employed polymers for drug delivery systems are aliphatic polyesters, which include poly (glycolic acid), poly (lactic acid), poly (caprolactone), and polydioxanone. These polymers are both synthetic and biodegradable. Numerous polymer classes, including biodegradable polycarbonates, poly (ortho esters), polyanhydrides, and poly (esters), have also been proposed as possible implant materials for medication administration.^[84-86] In addition to numerous other types of degradable polymers, typically used biodegradable polymers include α -hydroxy acids, polyanhydrides, poly (amides), poly (ester amides), poly (phosphoesters), poly (alkyl cyanoacrylates), poly (hyaluronic acids), and natural sugars like chitosan. In contrast to biodegradable polymers derived from natural polymers, synthetic biodegradable polymers are preferred in drug delivery systems because to their immunogenicity.^[87-89]

5] *Drug-free macromolecular therapeutics:*

Through the crosslinking of surface non-internalizing receptors, drugless macromolecular therapies cause cancerous cells to undergo apoptosis. The bio-recognition of high-fidelity natural binding motifs has mediated the receptor crosslinking. These have been linked to targeting moieties against cell receptors or grafted to the side chains of polymers. The lack of low-molecular-weight cytotoxic substances is a characteristic of this method. Molecular treatments, also known as polymeric nanomedicines, comprise a broad category of pharmaceuticals distinguished by their high molecular weight (MW). These drugs include polymeric micelles, polymeric drug conjugates, and polymeric-modified liposomes.^[90-92]

6] *Polymers that are bioinspired and biomimetic:*

When it comes to drug delivery, biomimetic and bioinspired systems enhance biocompatibility. A medication delivery system's effectiveness is contingent upon various factors, including form, feel, movement, texture, and techniques of preparation. Because of their significant interaction, high biocompatibility, low toxicity, and other qualities, the systems have a significant impact on biological systems.^[90-94]

7] *Using viral vectors to transfer polymeric genes:*

Not only can viral vectors efficiently infect cells, but they can also transmit DNA to the host without inciting an immunological reaction. Because they are unable to replicate, viral vectors are made to be safe. Because viral vector-transferred genes are more effective than physicochemical techniques, they have dominated clinical trials in gene therapy.^[95] Integrating and non-integrating viral vectors are the two categories of viral vectors. Retroviral and adeno-associated virus vectors, as well as other integrated and non-integrating viral vectors like adenoviral vectors, have been integrated into the human genome. Having not incorporated into the chromosomal DNA and RNA, they stay in the nucleus. Treating diseases resulting from genetic abnormalities, cancer, and other infections is made possible by gene delivery technologies. Reviewing both viral and non-viral delivery technologies, the latest advancements in gene delivery technology.^[96]

7. FUTURE PROSPECT & CONCLUSION

To sum up, this review article has given a thorough introduction to biodegradable polymers, examining their various uses and effects on the environment. These polymers' adaptability to a wide range of applications, from packaging to medical devices, emphasises their potential to solve sustainability issues. The use of biodegradable polymers presents a viable way to lessen the environmental impact of conventional non-biodegradable plastics as we move towards a more environmentally conscious future. The outlook for biodegradable polymers is promising going forward. Polymer science is a field that is always evolving, and this holds the prospect of producing novel formulations with improved qualities and customised functionality. The use of biodegradable polymers into conventional businesses has the potential to significantly decrease plastic pollution and foster a more circular and sustainable economy.

But issues like affordability, scalability, and general acceptance still need to be resolved. Overcoming these obstacles and promoting the broad use of biodegradable polymers will need cooperative efforts from academics, businesses, and legislators. With further development, these polymers have the potential to be extremely important in forming a more sustainable and environmentally friendly future.

REFERENCES:

1. Webb, A.R., Yang, J., & Ameer, G.A. (2008). A New Strategy to Characterize the Extent of Reaction of Thermoset Elastomers. *Journal of Polymer Science Part A*, 46, 1318-1328.
2. Kiran Dhaliwal, UCL Centre for Nanotechnology and Regenerative Medicine, Division of Surgery & Interventional Science, Royal Free London NHS Foundation Trust, Pond Street, London NW3 2QG, United Kingdom
3. Vroman, I. and Tighzert, L., 2009. Biodegradable polymers. *Materials*, 2(2), pp.307-344.
4. Ha CS, Gardella JA Jr. Surface chemistry of biodegradable polymers for drug delivery systems. *Chem Rev*. 2005 Nov;105(11):4205-32. doi: 10.1021/cr040419y. PMID: 16277374.
5. Taylor, M.S., Daniels, A.U., Andriano, K.P. and Heller, J., 1994. Six bioabsorbable polymers: in vitro acute toxicity of accumulated degradation products. *Journal of applied biomaterials*, 5(2), pp.151-157.
6. Ha, C.S. and Gardella, J.A., 2005. Surface chemistry of biodegradable polymers for drug delivery systems. *Chemical reviews*, 105(11), pp.4205-4232.
7. Gavasane, A.J. and Pawar, H.A., 2014. Synthetic biodegradable polymers used in controlled drug delivery system: an overview. *Clin Pharmacol Biopharm*, 3(2), pp.1-7.
8. Nair LS, Laurencin CT (2006) Polymers as Biomaterials for Tissue Engineering and Controlled Drug Delivery. *Adv Biochem Eng Biotechnol* 102: 47-90.
9. Nair, L.S. and Laurencin, C.T., 2007. Biodegradable polymers as biomaterials. *Progress in polymer science*, 32(8-9), pp.762-798..
10. Bhise, K., Kotwal, V., Saifee, M. and Inamdar, N., 2007. Biodegradable polymers: which, when and why. *Indian J Pharm Sci*, 69(5), p.616.
11. Mansoori, B., Mohammadi, A., Davudian, S., Shirjang, S. and Baradaran, B., 2017. The different mechanisms of cancer drug resistance: a brief review. *Advanced pharmaceutical bulletin*, 7(3), p.339.

12. Wicki, A., Witzigmann, D., Balasubramanian, V. and Huwyler, J., 2015. Nanomedicine in cancer therapy: challenges, opportunities, and clinical applications. *Journal of controlled release*, 200, pp.138-157.
13. Mogoşanu, G.D., Grumezescu, A.M., Bejenaru, C. and Bejenaru, L.E., 2016. Polymeric protective agents for nanoparticles in drug delivery and targeting. *International journal of pharmaceutics*, 510(2), pp.419-429.
14. Dang, Y. and Guan, J., 2020. Nanoparticle-based drug delivery systems for cancer therapy. *Smart Materials in Medicine*, 1, pp.10-19.
15. Palma, E., Pasqua, A., Gagliardi, A., Britti, D., Fresta, M. and Cosco, D., 2018. Antileishmanial activity of amphotericin B-loaded-PLGA nanoparticles: an overview. *Materials*, 11(7), p.1167.
16. Cosco, D., Federico, C., Maiuolo, J., Bulotta, S., Molinaro, R., Paolino, D., Tassone, P. and Fresta, M., 2014. Physicochemical features and transfection properties of chitosan/poloxamer 188/poly (D, L-lactide-co-glycolide) nanoplexes. *International Journal of Nanomedicine*, pp.2359-2372.
17. Cosco, D., Paolino, D., De Angelis, F., Cilirzo, F., Celia, C., Di Marzio, L., Russo, D., Tsapis, N., Fattal, E. and Fresta, M., 2015. Aqueous-core PEG-coated PLA nanocapsules for an efficient entrapment of water soluble anticancer drugs and a smart therapeutic response. *European journal of pharmaceutics and biopharmaceutics*, 89, pp.30-39.
18. George, A., Shah, P.A. and Shrivastav, P.S., 2019. Natural biodegradable polymers based nano-formulations for drug delivery: A review. *International journal of pharmaceutics*, 561, pp.244-264.
19. George, B. and Suchithra, T.V., 2019. Plant-derived bioadhesives for wound dressing and drug delivery system. *Fitoterapia*, 137, p.104241.
20. Gagliardi, A., Giuliano, E., Venkateswararao, E., Fresta, M., Bulotta, S., Awasthi, V. and Cosco, D., 2021. Biodegradable polymeric nanoparticles for drug delivery to solid tumors. *Frontiers in pharmacology*, 12, p.601626.
21. Paolino, D., Cosco, D., Celano, M., Moretti, S., Puxeddu, E., Russo, D. and Fresta, M., 2013. Gemcitabine-loaded biocompatible nanocapsules for the effective treatment of human cancer. *Nanomedicine*, 8(2), pp.193-201.
22. Islam, M.A., Barua, S. and Barua, D., 2017. A multiscale modeling study of particle size effects on the tissue penetration efficacy of drug-delivery nanoparticles. *BMC Systems Biology*, 11, pp.1-13.
23. Scheinberg, D.A., Villa, C.H., Escorcia, F.E. and McDevitt, M.R., 2010. Conscripts of the infinite armada: systemic cancer therapy using nanomaterials. *Nature reviews Clinical oncology*, 7(5), pp.266-276.
24. Tiwari, G., Tiwari, R., Sriwastawa, B., Bhati, L., Pandey, S., Pandey, P. and Bannerjee, S.K., 2012. Drug delivery systems: An updated review. *International journal of pharmaceutical investigation*, 2(1), p.2.
25. Gupta, S. and Kumar, P., 2012. Drug delivery using nanocarriers: Indian perspective. *Proceedings of the National Academy of Sciences, India Section B: Biological Sciences*, 82, pp.167-206.
26. Langer, R., 1998. Drug delivery and targeting. *Nature*, 392(6679 Suppl), pp.5-10.
27. Shaik, M.R., Korsapati, M. and Panati, D., 2012. Polymers in controlled drug delivery systems. *International journal of pharma sciences*, 2(4), pp.112-116.
28. Manthina M, Kalepu S, Padavala V (2013) Oral lipid-based drug delivery systems – an overview. 3: 361–372.
29. Kalepu, S., Manthina, M. and Padavala, V., 2013. Oral lipid-based drug delivery systems—an overview. *Acta Pharmaceutica Sinica B*, 3(6), pp.361-372..
30. Vyas, S.P. and Khar, R.K., 2002. Controlled drug delivery concepts and advances. *vallabh prakashan*, 1, pp.411-47.
31. Kwon, S.G., Kwon, Y.W., Lee, T.W., Park, G.T. and Kim, J.H., 2018. Recent advances in stem cell therapeutics and tissue engineering strategies. *Biomaterials Research*, 22(1), pp.1-8.]
32. Ueda, K., Ma, C., Izumiya, M., Kuroda, C., Ishida, H., Uemura, T., Saito, N., Aoki, K. and Haniu, H., 2023. Biocompatibility Evaluation of Carbon Nanohorns in Bone Tissues. *Nanomaterials*, 13(2), p.244.
33. Xiao-Gang, Z., Shahzad, K. and Li, C., 2012. One-stage total knee arthroplasty for patients with osteoarthritis of the knee and extra-articular deformity. *International orthopaedics*, 36, pp.2457-2463.
34. Jenkins, P.J., Clement, N.D., Hamilton, D.F., Gaston, P., Patton, J.T. and Howie, C.R., 2013. Predicting the cost-effectiveness of total hip and knee replacement: a health economic analysis. *The bone & joint journal*, 95(1), pp.115-121.
35. Tsagozis, P., Parry, M. and Grimer, R., 2018. High complication rate after extendible endoprosthetic replacement of the proximal tibia: a retrospective study of 42 consecutive children. *Acta Orthopaedica*, 89(6), pp.678-682.
36. Gore, D.R., 2001. The arthrodesis rate in multilevel anterior cervical fusions using autogenous fibula. *Spine*, 26(11), pp.1259-1263.

37. Schwartz, C.E., Martha, J.F., Kowalski, P., Wang, D.A., Bode, R., Li, L. and Kim, D.H., 2009. Prospective evaluation of chronic pain associated with posterior autologous iliac crest bone graft harvest and its effect on postoperative outcome. *Health and Quality of Life Outcomes*, 7, pp.1-8.
38. Dimar II, J.R., Glassman, S.D., Burkus, J.K., Pryor, P.W., Hardacker, J.W. and Carreon, L.Y., 2009. Two-year fusion and clinical outcomes in 224 patients treated with a single-level instrumented posterolateral fusion with iliac crest bone graft. *The Spine Journal*, 9(11), pp.880-885.
39. Jakoi, A.M., Iorio, J.A. and Cahill, P.J., 2015. Autologous bone graft harvesting: a review of grafts and surgical techniques. *Musculoskeletal surgery*, 99, pp.171-178.
40. Kombate, N.K., Walla, A., Ayoub, G., Bakriga, B.M., Dellanh, Y.Y., Abalo, A.G. and Dossim, A.M., 2017. Reconstruction of traumatic bone loss using the induced membrane technique: preliminary results about 11 cases. *Journal of orthopaedics*, 14(4), pp.489-494.
41. Yaacob, A. and Jamaludin, N.S., 2023. Biodegradable Polymers for Cardiac Tissue Engineering. In *Handbook of Biodegradable Materials* (pp. 979-1013). Cham: Springer International Publishing.
42. Javid-Naderi, M.J., Behravan, J., Karimi-Hajishohreh, N. and Toosi, S., 2023. Synthetic polymers as bone engineering scaffold. *Polymers for Advanced Technologies*.
43. Viguier-Carrin, S., Garnero, P. and Delmas, P.D., 2006. The role of collagen in bone strength. *Osteoporosis international*, 17, pp.319-336.
44. Rashedi, I., Talele, N., Wang, X.H., Hinz, B., Radisic, M. and Keating, A., 2017. Collagen scaffold enhances the regenerative properties of mesenchymal stromal cells. *PloS one*, 12(10), p.e0187348.
45. Modulevsky, D.J., Cuerrier, C.M. and Pelling, A.E., 2016. Biocompatibility of subcutaneously implanted plant-derived cellulose biomaterials. *PloS one*, 11(6), p.e0157894.
46. Beck, D.E., Cohen, Z., Fleshman, J.W., Kaufman, H.S., van Goor, H. and Wolff, B.G., 2003. A prospective, randomized, multicenter, controlled study of the safety of Seprafilm® adhesion barrier in abdominopelvic surgery of the intestine. *Diseases of the colon & rectum*, 46, pp.1310-1319.
47. Younes, I. and Rinaudo, M., 2015. Chitin and chitosan preparation from marine sources. Structure, properties and applications. *Marine drugs*, 13(3), pp.1133-1174.
48. Huang, L., Zhu, L., Shi, X., Xia, B., Liu, Z., Zhu, S., Yang, Y., Ma, T., Cheng, P., Luo, K. and Huang, J., 2018. A compound scaffold with uniform longitudinally oriented guidance cues and a porous sheath promotes peripheral nerve regeneration in vivo. *Acta biomaterialia*, 68, pp.223-236.
49. Ahmad, S., Minhas, M.U., Ahmad, M., Sohail, M., Abdullah, O. and Badshah, S.F., 2018. Preparation and evaluation of skin wound healing chitosan-based hydrogel membranes. *AAPS PharmSciTech*, 19, pp.3199-3209.
50. Ayoub, M.A. and El-Rosasy, M.A., 2014. Hybrid grafting of post-traumatic bone defects using β -tricalcium phosphate and demineralized bone matrix. *European Journal of Orthopaedic Surgery & Traumatology*, 24, pp.663-670.
51. Einhorn, T.A. and Gerstenfeld, L.C., 2015. Fracture healing: mechanisms and interventions. *Nature Reviews Rheumatology*, 11(1), pp.45-54.
52. Park, J.B., Kim, K.Y., Lee, W., Kim, H. and Kim, I., 2015. Combinatorial effect of stem cells derived from mandible and recombinant human bone morphogenetic protein-2. *Tissue Engineering and Regenerative Medicine*, 12, pp.343-351.
53. Yoshikawa, T., Ohgushi, H. and Tamai, S., 1996. Immediate bone forming capability of prefabricated osteogenic hydroxyapatite. *Journal of Biomedical Materials Research: An Official Journal of The Society for Biomaterials and The Japanese Society for Biomaterials*, 32(3), pp.481-492.
54. Salunke, P.A., Wagh, R.S., Patil, S.S. and Barhate, S.D., 2016. An overview: site specific drug delivery system. *INDO AMERICAN JOURNAL OF PHARMACEUTICAL SCIENCES*, 3(1), pp.57-72.
55. Grumezescu, A.M. ed., 2019. *Nanoarchitectonics in Biomedicine*. William Andrew.
56. Alaswad, S.O., Mahmoud, A.S. and Arunachalam, P., 2022. Recent Advances in Biodegradable Polymers and Their Biological Applications: A Brief Review. *Polymers*, 14(22), p.4924.
57. Ohshima, H. and Makino, K. eds., 2014. *Colloid and interface science in pharmaceutical research and development*. Elsevier.
58. Brahankar, D.M. and Jaiswal, S.B., 2009. *Biopharmaceutics and Pharmacokinetics: A treatise*. Vallabh Prakashan.
59. Karlsson, J., Vaughan, H.J. and Green, J.J., 2018. Biodegradable polymeric nanoparticles for therapeutic cancer treatments. *Annual review of chemical and biomolecular engineering*, 9, pp.105-127.
60. Tsung, T.H., Tsai, Y.C., Lee, H.P., Chen, Y.H. and Lu, D.W., 2023. Biodegradable Polymer-Based Drug-Delivery Systems for Ocular Diseases. *International Journal of Molecular Sciences*, 24(16), p.12976.
61. Salunke, P.A., Wagh, R.S., Patil, S.S. and Barhate, S.D., PHARMACEUTICAL SCIENCES.

62. Râpă, M.A.R.I.A., Popa, M.E., Cinelli, P., Lazzeri, A., Burnichi, R., Mitelut, A. and Grosu, E., 2011. Biodegradable alternative to plastics for agriculture application. *Romanian Biotechnological Letters*, 16(6), pp.59-64.
63. Reddy, P.C., Chaitanya, K.S.C. and Rao, Y.M., 2011. A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. *DARU Journal of Pharmaceutical Sciences*, 19(6), p.385.
64. Sahana, T.G. and Rekha, P.D., 2018. Biopolymers: Applications in wound healing and skin tissue engineering. *Molecular biology reports*, 45, pp.2857-2867.
65. Asokan, P., Firdoos, M. and Sonal, W., 2012. Properties and potential of bio fibres, bio binders, and bio composites. *Rev. Adv. Mater. Sci*, 30(3), pp.254-261.
66. Ehret, P., 1996. Biodegradable nonwovens. *ITB Nonwovens—Industrial Textiles*, (3), pp.29-30.
67. Ulery, B.D., Nair, L.S. and Laurencin, C.T., 2011. Biomedical applications of biodegradable polymers. *Journal of polymer science Part B: polymer physics*, 49(12), pp.832-864.
68. Din, F.U., Aman, W., Ullah, I., Qureshi, O.S., Mustapha, O., Shafique, S. and Zeb, A., 2017. Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. *International journal of nanomedicine*, pp.7291-7309.
69. Tiwari, G., Tiwari, R., Sriwastawa, B., Bhati, L., Pandey, S., Pandey, P. and Bannerjee, S.K., 2012. Drug delivery systems: An updated review. *International journal of pharmaceutical investigation*, 2(1), p.2.
70. Sinha, V.R. and Khosla, L., 1998. Bioabsorbable polymers for implantable therapeutic systems. *Drug development and industrial pharmacy*, 24(12), pp.1129-1138.
71. Basu, A., Kunduru, K.R., Doppalapudi, S., Domb, A.J. and Khan, W., 2016. Poly (lactic acid) based hydrogels. *Advanced Drug Delivery Reviews*, 107, pp.192-205.
72. Teleanu, D.M., Chircov, C., Grumezescu, A.M., Volceanov, A. and Teleanu, R.I., 2018. Blood-brain delivery methods using nanotechnology. *Pharmaceutics*, 10(4), p.269.
73. Cacciatore, I., Ciulla, M., Fornasari, E., Marinelli, L. and Di Stefano, A., 2016. Solid lipid nanoparticles as a drug delivery system for the treatment of neurodegenerative diseases. *Expert opinion on drug delivery*, 13(8), pp.1121-1131.
74. Patel, M., Souto, E.B. and Singh, K.K., 2013. Advances in brain drug targeting and delivery: limitations and challenges of solid lipid nanoparticles. *Expert opinion on drug delivery*, 10(7), pp.889-905.
75. Wichterle, O. and Lim, D., 1960. Hydrophilic gels for biological use. *Nature*, 185(4706), pp.117-118.
76. Sung, Y.K., Gregonis, D.E., John, M.S. and Andrade, J.D., 1981. Thermal and pulse NMR analysis of water in poly (2-hydroxyethyl methacrylate). *Journal of Applied Polymer Science*, 26(11), pp.3719-3728.
77. Ferreira, L., Vidal, M.M. and Gil, M.H., 2000. Evaluation of poly (2-hydroxyethyl methacrylate) gels as drug delivery systems at different pH values. *International journal of pharmaceutics*, 194(2), pp.169-180.
78. Hanak, B.W., Hsieh, C.Y., Donaldson, W., Browd, S.R., Lau, K.K. and Shain, W., 2018. Reduced cell attachment to poly (2-hydroxyethyl methacrylate)-coated ventricular catheters in vitro. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, 106(3), pp.1268-1279.
79. Tanaka, R., Ueoka, I., Takaki, Y., Kataoka, K. and Saito, S., 1983. High molecular weight linear polyethylenimine and poly (N-methylethylenimine). *Macromolecules*, 16(6), pp.849-853.
80. Gillies, E.R. and Frechet, J.M., 2005. Dendrimers and dendritic polymers in drug delivery. *Drug discovery today*, 10(1), pp.35-43.
81. Menjoge, A.R., Kannan, R.M. and Tomalia, D.A., 2010. Dendrimer-based drug and imaging conjugates: design considerations for nanomedical applications. *Drug discovery today*, 15(5-6), pp.171-185.
82. Törmälä, P., Pohjonen, T. and Rokkanen, P., 1998. Bioabsorbable polymers: materials technology and surgical applications. *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine*, 212(2), pp.101-111.
83. Pulapura, S. and Kohn, J., 1992. Trends in the development of bioresorbable polymers for medical applications. *Journal of biomaterials applications*, 6(3), pp.216-250.
84. Sung, Y.K. and Kim, S.W., 2020. Recent advances in polymeric drug delivery systems. *Biomaterials Research*, 24(1), pp.1-12.
85. Heller, J., Barr, J., Ng, S.Y., Abdellauoi, K.S. and Gurny, R., 2002. Poly (ortho esters): synthesis, characterization, properties and uses. *Advanced drug delivery reviews*, 54(7), pp.1015-1039.
86. Kumar, N., Langer, R.S. and Domb, A.J., 2002. Polyanhydrides: an overview. *Advanced drug delivery reviews*, 54(7), pp.889-910.
87. Kamaly, N., Yameen, B., Wu, J. and Farokhzad, O.C., 2016. Degradable controlled-release polymers and polymeric nanoparticles: mechanisms of controlling drug release. *Chemical reviews*, 116(4), pp.2602-2663.

88. Nicolas, J., Mura, S., Brambilla, D., Mackiewicz, N. and Couvreur, P., 2013. Design, functionalization strategies and biomedical applications of targeted biodegradable/biocompatible polymer-based nanocarriers for drug delivery. *Chemical Society Reviews*, 42(3), pp.1147-1235.
89. Li, L., Yang, J., Soodvilai, S., Wang, J., Opanasopit, P. and Kopeček, J., 2019. Drug-free albumin-triggered sensitization of cancer cells to anticancer drugs. *Journal of Controlled Release*, 293, pp.84-93.
90. Patra, J.K., Das, G., Fraceto, L.F., Campos, E.V.R., Rodriguez-Torres, M.D.P., Acosta-Torres, L.S., Diaz-Torres, L.A., Grillo, R., Swamy, M.K., Sharma, S. and Habtemariam, S., 2018. Nano based drug delivery systems: recent developments and future prospects. *Journal of nanobiotechnology*, 16(1), pp.1-33.
91. Li, L., Yang, J., Wang, J. and Kopeček, J., 2019. Drug-free macromolecular therapeutics exhibit amplified apoptosis in G2/M phase arrested cells. *Journal of Drug Targeting*, 27(5-6), pp.566-572.
92. Bagalkot, V., Farokhzad, O.C., Langer, R. and Jon, S., 2006. An aptamer–doxorubicin physical conjugate as a novel targeted drug-delivery platform. *Angewandte chemie international edition*, 45(48), pp.8149-8152.
93. Speck, O., Speck, D., Horn, R., Gantner, J. and Sedlbauer, K.P., 2017. Biomimetic bio-inspired biomorph sustainable? An attempt to classify and clarify biology-derived technical developments. *Bioinspiration & Biomimetics*, 12(1), p.011004.
94. Vincent, J.F., 2009. Biomimetics—a review. *Proceedings of the institution of mechanical engineers, part H: Journal of Engineering in Medicine*, 223(8), pp.919-939.
95. Smith, A.E., 1995. Viral vectors in gene therapy. *Annual review of microbiology*, 49(1), pp.807-838.
96. Sung, Y.K. and Kim, S.W., 2018. The practical application of gene vectors in cancer therapy. *Integrat Cancer Sci Therap*, 5, pp.1-5.

