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Recent Advances in Polymeric Nanocomposite Carriers of Various Active Ingredients for Controlled and Sustained Drug Release: A Review

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ABSTRACT

Controlled and sustained drug delivery has emerged as a transformative strategy for overcoming the limitations of conventional pharmaceutical formulations, including poor bioavailability, rapid drug clearance, systemic toxicity, and non-specific distribution. Among the numerous delivery platforms investigated, polymeric nanocomposite carriers have attracted considerable attention because they integrate the excellent biocompatibility, biodegradability, and processability of polymers with the unique physicochemical, mechanical, optical, magnetic, and therapeutic properties of inorganic nanomaterials. This review provides a comprehensive and critical evaluation of recent advances in polymeric nanocomposite-based drug delivery systems, highlighting the synergistic interactions between natural and synthetic polymers and a broad spectrum of nanofillers, including metal and metal oxide nanoparticles, carbon-based nanomaterials, nanoclays, mesoporous materials, and electrospun nanofibers. The influence of nanocomposite composition, fabrication strategies, and physicochemical characteristics on drug loading, encapsulation efficiency, release kinetics, targeting capability, and biological performance is systematically discussed. Furthermore, representative therapeutic applications in cancer therapy, wound healing, antimicrobial treatment, tissue engineering, neurological disorders, and regenerative medicine are critically compared to establish structure–property–performance relationships. This review primarily summarizes individual carrier systems, preparation methods, release mechanisms, and biomedical applications into a unified framework while identifying current limitations related to nanoparticle aggregation, long-term biocompatibility, biodegradation, large-scale manufacturing, regulatory approval, and clinical translation. This review provides valuable insights for researchers working on the rational design of advanced polymeric nanocomposites with enhanced therapeutic efficacy, improved safety, and accelerated clinical applicability.

Keywords: controlled drug delivery, polymeric nanocomposites, precision nanomedicine, smart nanocarriers, stimuli-responsive drug delivery, sustainable nanomanufacturing, therapeutic nanoplatforms.

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1. Introduction

Over the past years, scientists have become increasingly interested in organic-inorganic composite (OIC) materials, which are composed of two or more different types of components. OIC materials display a wide range of features because they might differ from both organic and inorganic materials in certain ways [1]. Bioactive organic–inorganic composites can be created by combining different organic polymers with inorganic components [2]. As technology advances, active ingredients (drugs) and sustained release remain significant challenges in the field of drug delivery and development. This is because conventional drug therapies have limitations in terms of selectivity, pharmacodynamics, side effects, short lifetime, and limited drug solubility [3]. Novel effective medication delivery techniques are practically crucial for avoiding unnecessary changes to the stability and characteristics of drugs. In this situation, drug delivery is designed to (i) precisely target the desired organ to reduce drug side effects and (ii) control drug release to prevent traditional overdose or underdose. The drug delivery system (DDS) is a combination of a drug and a carrier in which the pharmaceuticals are loaded either chemically or physically onto the carrier's surface

[4]. One of the most promising uses of human health care is DDS, which is a constantly developing area of the medical sciences. The development of organic–inorganic composites as a suitable carrier that is effective for drug delivery to the body with a maximum benefit-to-risk ratio remains a critical problem for scientists despite the rapid advancements in DDS [5]. DDS also enhances the concentration of the medications of interest in the target tissues and shields them from quick removal or degradation [6]. The active pharmaceutical ingredient can be released to produce the desired therapeutic effect thanks to the drug delivery mechanism. Tablets, capsules, syrups, ointments, and other traditional drug delivery methods are unable to offer sustained release due to their low bioavailability and fluctuations in plasma drug levels [7]. Essential benefits of sustained drug delivery are reduced doses, fewer adverse effects, less blood-stream concentration changes, decreased risks of dose-dumping, improved bioavailability, site specificity, and improved drug stability [8]. Many formulations for controlled drug release were created, including tablets, beads, buccal patches, capsules, implants, microparticles, nanoparticles, etc. These drug release systems are frequently made with a variety of ingredients, including inorganic materials (such as metal powders and bioceramics) and natural, synthetic, and semi-synthetic polymers. To maintain the release of certain medicinal compounds for as long as feasible, a range of polymeric nanoparticles and inorganic composites were recently created as fibers or particles at the nano- or micron-scale. Polymeric nanoparticles and inorganic materials combined to generate better loading and encapsulation of several pharmaceutically active substances, more sustainable drug release, and superior mechanical characteristics [9]. Generally speaking, composites are material mixes composed of two or more materials that interact chemically or physically. Each component maintains its unique properties while the other serves as the matrix phase (ceramics, polymers, or metals) and the reinforcing phase (sheets, particles, or fibers). In fact, these materials give the composites additional physico-mechanical characteristics [10]. Composites are classified as either inorganic/inorganic (metal/metal composites, ceramic/ceramic composites, etc.), organic/inorganic (polymer/metal composites, polymer/ceramic composites, etc.), or organic/organic based on the composition of the matrix reinforcement [11]. Numerous composites have recently been created for a range of biomedical applications, including drug delivery, antibacterial agents, cancer treatment, wound dressing, steam cell therapy, and biosensors [12]. A review based on OIC materials for controlled release of active ingredients. A few possibilities for creating organic–inorganic composites for drug delivery are shown in Fig. 1. Composite materials made of organic and inorganic components have long been the subject of intensive research. A review based on OIC materials for controlled release of active ingredients.

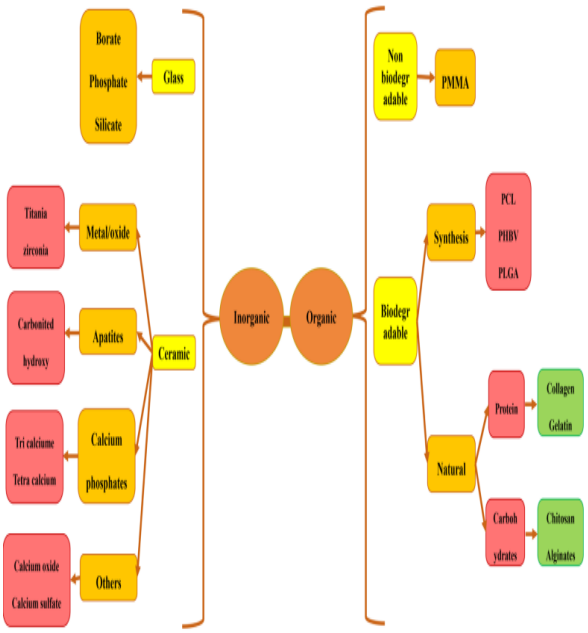

Fig. 1 - Several possibilities for producing organic-inorganic composites for drug delivery [13]

2. Organic–inorganic composite (OIC)

Materials that combine organic and inorganic elements into a single structure are known as organic–inorganic composites. Organic-inorganic composites are referred to as nanocomposites when their inorganic portions reach nanoscale size. Nanotubes, layered silicates (like montmorillonite (MMT) and saponite), metal nanoparticles (like Ag and Au), metal oxides (like TiO_2 and Al_2O_3), semiconductors (like PbS and CdS), and so on are examples of inorganic nanoscale building blocks. Of these, SiO_2 is thought to be particularly significant. As a result, polymer/silica nanocomposites have garnered a lot of attention from both academia and industry. By combining the unique properties of both kinds of materials, these materials aim to create a synergistic set of features. Blending the properties of inorganic and organic components is actually the aim of organic–inorganic composites.

For example, the flexibility and low weight of mechanical strength and thermal stability of inorganic materials. These materials are used in a wide range of OIC applications, such as electronics, sensors, tissue engineering materials, catalysis, and controlled drug release systems [14]. Numerous procedures, such as the sol–gel method [15], solution–processing (SP), soluation casting, electrospinning, chemical vapor deposition (CVD) method [16], in situ polymerization, polyelectrolyte complex (PEC) [17], layer–by–layer (LbL) assembly [18], the Langmuir–Blodgett technique [19], melt processing, atomic layer deposition (ALD) technique [20], and the molecular layer deposition (MLD) techniques that allow for the creation of organic–inorganic networks [21].

2.1. Method of preparation of organic–inorganic composite materials

In order to create several types of OIC materials, including films and fibers, different processing techniques have been used. These composite materials are frequently prepared using important techniques including electrospinning, sol-gel, solution casting, and in situ polymerization.

2.1.1. Sol-gel method (SG)

One way of bottom-up synthesis is the sol-gel procedure. During this process, several irreversible chemical reactions are carried out to create the final compounds. The sol-gel method is one of the essential techniques. The two chemical processes, sol and gel, are referred to as sol-gel. Gel is the interconnected network created between phases, whereas sol is a colloidal suspension of solid particles in a liquid phase [22]. The two primary processes in the sol-gel process are condensation and hydrolysis. Both are sequential processes with multiple steps. Hydrolysis is the cleavage of an organic chain bond to metal followed by a nucleophilic addition that replaces it with -OH groups. The hydrolyzed metal is left as an alcohol (alcoxolation) by the protonated species. The primary reaction parameters include temperature, water, solvent concentrations, metal reactivity, and the employment of complicated agents or catalysts. The compatibility of the sol-gel method with polymers and polymerization processes, which permits the production of nanoparticles in the presence of organic molecules, is one of its most interesting benefits [23]. Fig. 2 shows the sol-gel process technique.

organic polymers can be combined with the

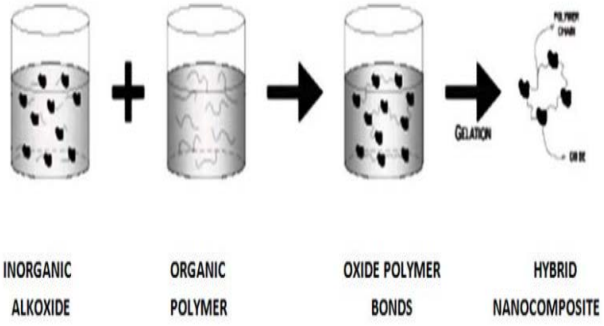

Fig. 2 - Sol-gel polymerization process [24]

2.1.2. Solution casting method

Solution casting is when thick mixtures with polymers, additives, and medicines are dried in a flat layer to create polymer films (Fig. 3). Although this process is simple, it can take a lot of time, and the materials used have a major impact on the final films' stability and qualities [25]. Usually, an organic solvent is used to dissolve or disperse polymers before they are placed onto a supporting surface. A solid layer develops on the substrate when the solvent evaporates during drying. Sometimes the solution contains particles of particular sizes, usually salts. After drying, the mixture is formed into its final shape. To dissolve the particles and leave a porous structure, the composite material can also be immersed in a bath. These solution-cast polymer films are ideal for serving as the base layer in multi-layered compositions because they have improved integrity in structure [26].

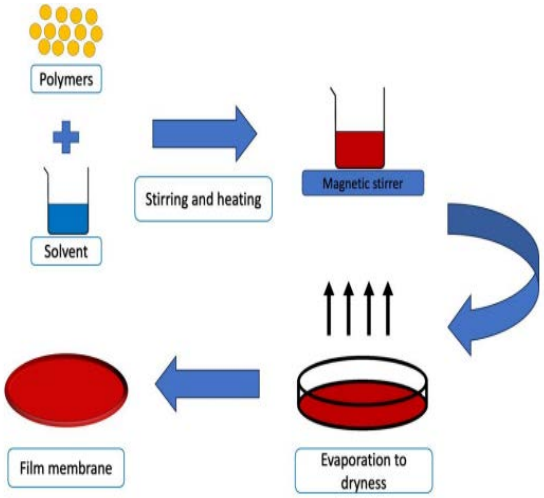

Fig. 3 - Solution casting method [27]

2.1.3. Electrospinning

A flexible technique, electrospinning is used to produce polymeric fibers with a high surface area to volume ratio and superior diffusion characteristics. Because of these qualities, it is useful for wound care applications, helping to reduce bleeding, absorb extra wound fluid, and promote tissue regeneration [28]. Typically, the electrospinning process uses an elevated direct current, or DC, voltage between a few kilovolts (10–20 kV). The application of this voltage creates electrical charges in a stream of polymer solution, which subsequently dries and forms polymer nanofibers. (Fig. 4). The compatibility of the selected polymer or polymers, the solvent or solvents, and any extra additives or active ingredients determines the stability, uniformity, and production efficiency of the electrospinning process. Indeed, in order to produce polymer nanofibers for wound care applications, electrospinning entails a number of crucial steps: Successful electrospinning is largely dependent on the compatibility and characteristics of the solvent and polymer. The syringe tube that is a component of the electrospinning apparatus is then carefully filled with the polymer solution. The solution inside the syringe is subjected to a powerful electric field produced by the electrical voltage differential between the tip of the needle and the collector that holds the solution. At the needle's tip, charges build up on the surface of the polymer solution droplet due to the electric field. The metal collector, which could be a stationary plate or a revolving drum, is where the nanofibers are gathered. On the collector's surface, the fibers create a nonwoven mat. The quality and homogeneity of the nanofibers depend on stable environmental factors, such as temperature and humidity. The ideal fiber qualities are obtained by optimizing variables including chamber temperature, solution vapor pressure, and the distance between the needle and collector. In general, the manufacturing of thin polymer nanofibers with specific qualities for a range of uses, including wound care, is made possible by the intricate yet tightly regulated process of electrospinning. Better absorption, moisture control, and cell contact are just a few of the increased wound healing properties that the resultant nanofibrous mats can offer [29].

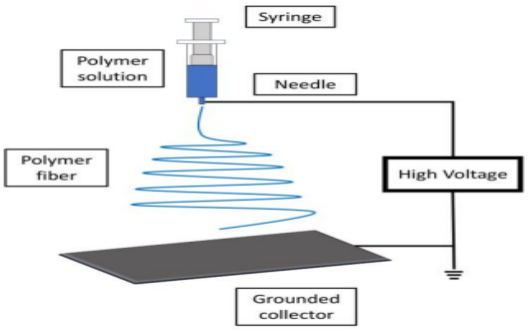

Fig. 4 - System of electrospinning [27]

2.1.4. In situ polymerization

The conducting filler is uniformly dispersed using in situ polymerization, which also preserves the aspect ratio and strengthens the link between the polymer and the filler. It is especially helpful for creating polymers that cannot be made using melt mixing (thermally unstable polymer) and solution (insoluble polymer) procedures. The monomer serves as the starting ingredient in this process. It entails dispersing carbons and polymers in a solvent. This enables the carbons to serve as a template for the growth of the polymer. After that, the mixture is agitated and sonicated to promote growth. Filtration or evaporation to dryness is then used to separate these composite structures from the fluid [30]. Fig. 5 shows a general schematic illustration of the in situ polymerization method. This process creates composite materials that are more conductive. The enhanced interaction between the polymer and the carbons could be the source of this. The product's more advantageous morphology could potentially be the cause.

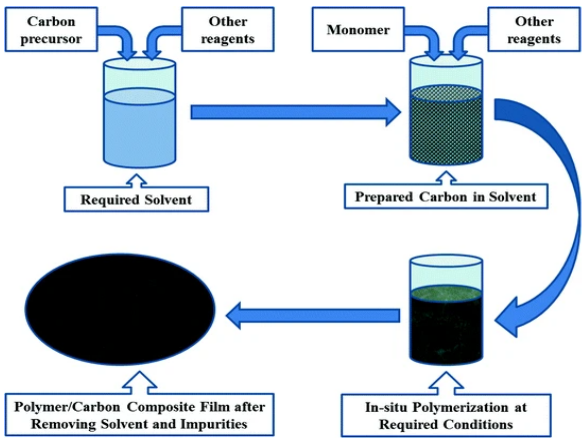

Fig. 5 - Schematic illustration of the in situ polymerization method [27]

3. Drug delivery system (DDS) nanocarriers

The process of delivering drugs to specific body locations and releasing them at the right rate is known as drug delivery. Locally released medications can help reduce the side effects of systemic drugs while maintaining a greater optimal drug concentration. DDS may also increase a drug's bioavailability [31]. Drug carriers, such as hydrogels, implants, films, spheroids, gels, dendrimers, beads, biocomposites, scaffolds, and microparticles, are used in DDS to load and encapsulate medications [32]. Thus, protecting the drug from degradation or destruction and facilitating precise delivery of the drug to the site of action are the main objectives of using polymeric nanoparticle carriers [33]. Drug delivery can therefore be controlled, targeted, or consistent. Common DDS that work with drugs come in bulk, micro, or nanoforms. Drug delivery techniques at the nanoscale offer significant benefits. Richard Feynman, a scientist, is credited with creating the idea of nanotechnology. The use of nanotechnology for medical purposes is known as nanomedicine, and it is a relatively recent scientific discipline. Drug delivery systems such as liposomes, niosomes, micelles, nanospheres, nanocapsules, nanoparticles, microparticles, microspheres, microbubbles, polymeric systems, dendrimers, colloidal gold, gold nanoshells, quantum dots, superparamagnetic particles, carbon nanotubes, cyclodextrins, and sphingosomes are frequently used for the diagnosis and/or treatment of a variety of diseases (Fig. 6 and Table 1) [34].

Table 1 - DDS nanocarriers for the diagnosis or therapy of a variety of diseases

Nanocarriers	Particles Size (nm)	Advantages	Disadvantages
Liposomes, Niosomes, phingosomes	20-3500	May be labeled with various radionuclides. Contrast enhancement for imaging in target and therapy enhancement.	The necessity of a long, time-consuming radiolabeling process and carefull controlling for reproducible efficiency
Micelles	-10 (Very small)	Easily prepared and radiolabeled, and removal by RES decreases depending on hydrophilic polymer shells.	The design of amphiphilic chelators should be given attention.
Nanoparticles, Solid Lipid nanoparticles	10-1000	These systems can be actively or passively targeted to the desired cell or tissue. They can escape from RES uptake. May be labeled with a variety of radionuclides.	Limited control of the size distribution and polydispersity.
Dendrimers	-10 (Very small)	Multivalent conjugation of radionuclides; biodistribution is enhanced depending on low polydispersity and spherical shape.	Toxicity may be formed depending on the positive charge of dendrimers.
Gold Nanoparticles	1-100	They have unique optical properties which are affected by shape and size. They can be used for cancer diagnosis and photothermal therapy.	It is important to discern the toxicity of the nanoparticle core and that of its capping ligands.
Microbubbles	≤10000	Act like red blood cells within the capillaries. Safer than molecular imaging modalities such as radiolabeled imaging.	Have low circulation time due to rapid RES uptake. Heat increase can be formed due to increase in frequency, which should be carefully monitored.
Magnetic Nanoparticles	10-50	They can be functionalized and manipulated with a selective molecule, and magnetic properties can be controlled with a magnetic field produced by an electromagnet or permanent magnet.	Metallic magnetic materials such as iron, cobalt and nickel are toxic and generally susceptible to oxidation. Uncoated magnetic nanoparticles should be chemically stabilized against degradation.
Quantum dots	(Typically <10)	Process long-term, multiplexed, and quantitative imaging and detection. They can be used for ultrasensitive and multicolor imaging of molecular targets.	Their delivery process across cells may be dangerous for the cell and may destroy it. In other cases, a QD may be toxic for cells.

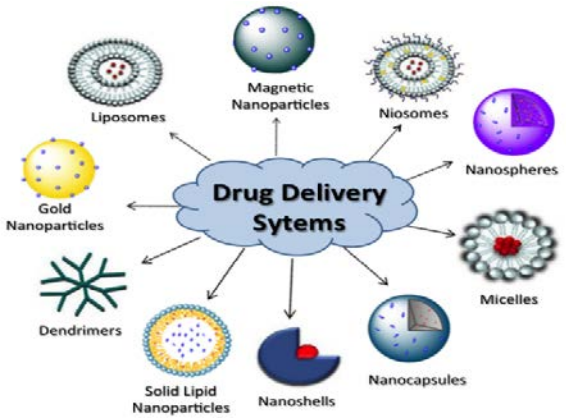

Fig. 6 - DDS nanocarriers for the therapy of various diseases [35]

3.1. Advantages of nanocarriers as delivery systems

Nanotechnology, a multidisciplinary scientific field that is expanding quickly, is the creation of systems and technologies at the molecular level [36]. Nanocarriers can be used to improve the poor solubility, penetration, low bioavailability, poor stability, or uncontrolled release of active substances [37]. As Davies *et al*. [38] reported, the chemical stability, photostability, antioxidant activity, and skin penetration of resveratrol and lipoic acid were all enhanced by their co-nanoencapsulation. Through the lipid-core nanocapsules, the nanoencapsulation also produced a more regulated release [39]. To summarize, the effectiveness of cosmetic goods has been increased through the use of nanocarriers as delivery vehicles **(**Fig. 7).

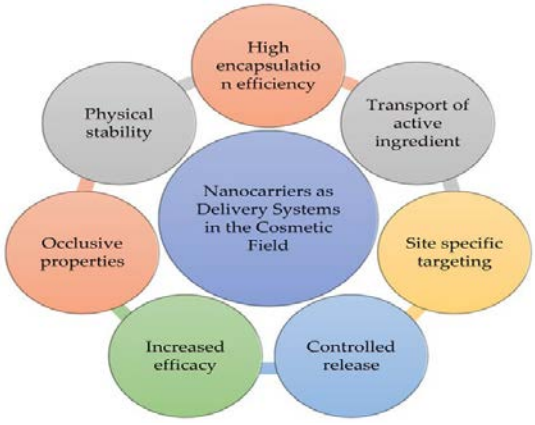

Fig. 7 - Advantages of employing nanocarriers as delivery systems [39]. Copyright 2022. Adapted from MDPI

3.2. Controlled drug delivery systems (CDDS)

Over the past few decades, CDDS have become a very effective technique for addressing issues with traditional dose forms, including frequent dosing, systemic adverse effects, low bioavailability, inefficient drug targeting, and stability, among others [40]. The polymer has become a crucial component of the contemporary pharmaceutical industry to overcome these disadvantages, but there is still a great need for the development of newer polymers that could better control drug release and be used to target bioactives; in other words, they should behave more intelligently [41]. In therapy, the DDS has several benefits (Fig. 8), such as lowering toxicity, raising the drug's therapeutic index, and avoiding frequent, costly, and uncomfortable dosing [5]. There are two ways to accomplish drug loading: integration and impregnation. During preparation, the medication is encapsulated by nanocomposites in the inclusion process. By incubating the nanocomposites in a solution, the impregnation process entraps the medication. Instead of using the impregnation approach, the inclusion method can produce nanocomposites with higher entrapment efficiency [42]. Because active materials may lose their activity during the incorporation process, the impregnation method is marginally better than the incorporation method. It has been suggested that sorption and release kinetic data be examined using a variety of isotherms in order to determine the mechanism of drug binding associated with the impregnation process (such as linear, Freundlich, Langmuir isotherms, and the BET model) [43]. Consequently, the following approaches should be used in drug release investigations depending on the identification of the release mechanism: reverse dialysis sac [42]. Determining the most effective formulations also requires consideration of the drug release from nanobiocomposites and the subsequent biodegradation [44].

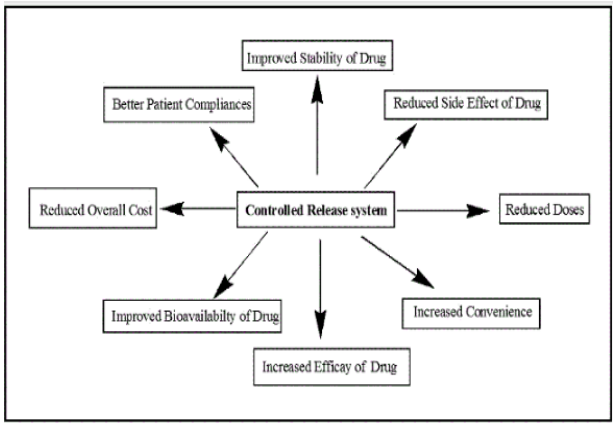

Fig. 8 - Benefits of controlled release of drug delivery system (DDS) [45]

4. Organic polymers as carrier for pharmaceutical applications

Polymers have been used in tissue engineering, DDS, gene therapy, and bioimaging, indicating their interest in pharmaceutical and medical difficulties. In general, polymers can be divided into two categories: synthetic and natural. Before being utilized for controlled drug administration, all natural or synthetic polymers must go through a number of purification, modification, and derivatization steps to guarantee their compatibility and safety for human health [42]. Based on their origin and chemical makeup, Raizada *et al.* [46] have divided commonly used polymers in pharmaceutical applications into six classes. It has been shown that (a) water-soluble artificial polymers, (b) insoluble water polymers that degrade, (c) cellulose-based polymers, (d) starch-based polymers, (e) rubber/plastics-based polymers, and (f) hydrocolloids make excellent scaffold materials for cell culture, especially in bone tissue regeneration strategies [47]. Compared to natural polymers, synthetic polymers that are produced through controlled and reproducible techniques and that are highly pure to prevent harmful effects appear to be more desirable. Among other characteristics, both groups of polymers can be hydrophilic or hydrophobic, hard or soft, thermoplastic or thermosetting, swellable, or degradable. This allows for a wide range of materials to match the anticipated use. Biodegradable polymers are needed for tissue engineering applications [48]. Biodegradable polymers of natural origin, such as polysaccharides (e.g., chitosan (CS), alginate, starch, gelatin, guar gum, carrageenan, albumin, and cellulose), as well as synthetic polymers such as polyorthoesters, polyanhydrides (PA), polyphosphoesters, polyesters (e.g., poly(lactic acid) (PLA) [49], polycaprolactone (PCL) [50], polyethylene glycol (PEG) (Fig. 9) [27], poly(lactic-co-glycoilc acid) (PLGA) [51], polyamides, polyurethane (PU), which are the most commonly used artificial polymers for regulated medication administration [42].

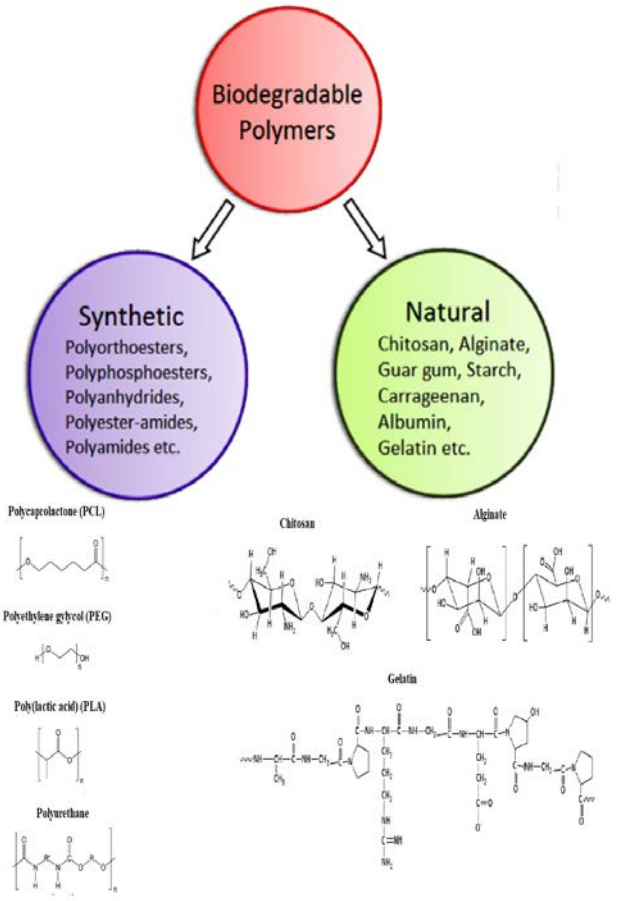

Fig. 9 - Biodegradable polymers classification for pharmaceutical applications [52]. Copyright 2019. Reproduced with permission from Elsevier

5. Inorganic materials in polymer composites

High electrical and thermal conductivity, high antibacterial activity, superior magnetic properties, chemical inertness, ease of surface functionalization, and biocompatibility are just a few of the exceptional qualities of many inorganic materials. Inorganic magnetic nanoparticles give polymeric matrices remarkable characteristics that can be used in a variety of biomedical applications, including medicine administration, therapy, and diagnostics. Numerous inorganic components are used in polymeric nanoparticle composites for drug delivery applications; a few of these are enumerated in the sections that follow (Fig. 10).

Fig. 10 - Inorganic materials that can be mixed with polymers to create organic-inorganic composites that have a lot of potential for use in drug delivery [53]

6. Nanocomposite

"Nanocomposite" is a word used when one of the structural units, in two ways inorganic or organic, falls within a certain size range of 1–100 nm. Generally, inorganic units produced in situ by molecular precursors like sol–gel reactions are referred to as hybrid materials, while separate components of structure in the correct dimension range are known as nanocomposites. Nanoparticles are examples of distinct inorganic units used in nanocomposites, such as nanorods, carbon nanotubes, and galleries of clay minerals [54]. These components are often incorporated into organic polymers to create a nanocomposite.

6.1. Type of nanocomposite

Nanocomposites have been divided into three classes based on the literature: intercalated, flocculated, and exfoliated, as shown in Fig. 11. Intercalated or layered nanocomposites are composites in which the extended polymer is inserted within the host polymers in organized multilayered structures. In flocculated and exfoliated composites, the host polymer may be nanoscale and should be distributed throughout the continuous polymer matrix [42]. The interfacial interactions between extended and host polymers serve as the basis for the classification [55]. We see the following concerning these three groups:

a. Intercalated nanocomposites are composites in which organic components or polymers (referred to as expanded polymers or inorganic materials) are frequently inserted into another polymer (the host polymer), irrespective of the ratio of polymer to inorganic material or polymer to polymer. The composites have characteristics of ceramic materials and are frequently interlayered.

b. Flocculated and intercalated nanocomposites differ only in the way the extended polymer is arranged within the host polymer.

c. Exfoliated nanocomposites: these depend on the loading of the filler to determine the mean space between the extended polymer layer and the continuous polymer matrix. Comparing the various forms of nano-biocomposites, it has been found that the filler amount is generally lower.

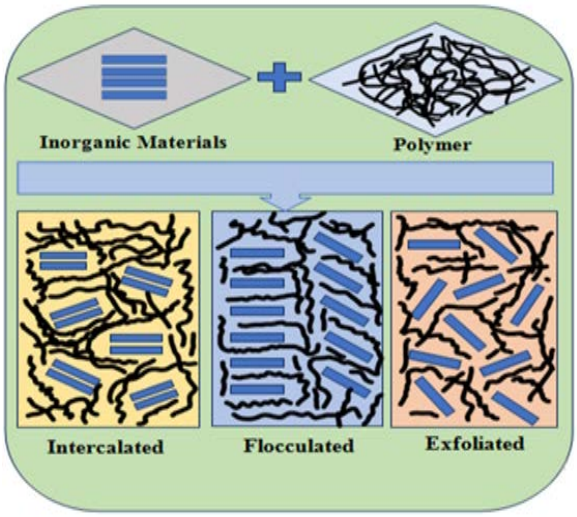

Fig. 11 - Schematic illustration of three main types of nanocomposite [42]

6.2. Properties of polymer nanocomposites

The properties of nanocomposites are influenced by a wide range of factors, such as the method of fabrication, the kinds of filler materials and their orientations, the degree of two-phase mixing, the type of adhesion at the matrix interface, the volume fraction of nanoparticles, the characteristics of the nanoparticles, the type of interphase formed at the matrix interface, the size and shape of the nanofiller materials, and the morphology of the system [56]. The novel family of composite materials known as nanocomposites regularly demonstrates exceptional mechanical, chemical, optical, electrical, and rheological qualities [57]. The nanoparticles must be evenly distributed throughout the matrix material in order to produce improved nanocomposites; if this is not done, the particles will aggregate, and the materials' qualities will decline. Since these aggregates will function as flaws and restrict the nanocomposite's ability to improve its properties, the nanoparticles should be evenly distributed

throughout the matrix to maximize this improvement [58].

6.3. Nanoparticles (NPs)

Materials with at least one dimension smaller than 100 nm are referred to as nanoparticles (NPs) [59].

These materials can have a 0D, 1D, 2D, or 3D overall shape [60]. When researchers found that a substance's size can influence its physicochemical properties, including its optical properties, the importance of these materials became clear. Since NPs are not simple molecules in and of themselves, they are composed of three layers. The surface layer is the first layer and can be functionalized with a variety of metal ions, polymers, surfactants, and small molecules. (b) The shell layer, which is completely chemically distinct from the core, and (c) the core, which is essentially the NPs' center and is usually used to refer to the NPs themselves [61].

6.3.1. Classification of nanoparticles

Nanoparticles can be classified as either inorganic (like metal and metal oxide nanoparticles like iron, zinc oxide, silica, and silver), carbon-based (like fullerenes, graphene, and carbon nanotubes), or organic (like ferritin, denderimers, micelles, liposomes, lipid-based NPs, polymeric nanoparticles, and micelles) [62] (Fig. 12). Because of their nanoscale size and high surface-area-to-volume ratio, nanoparticles can quickly move through the bloodstream and absorb large amounts of medication. Their larger surface area gives them special qualities that improve their mechanical, magnetic, optical, and catalytic properties, which enables a greater variety of medical applications.

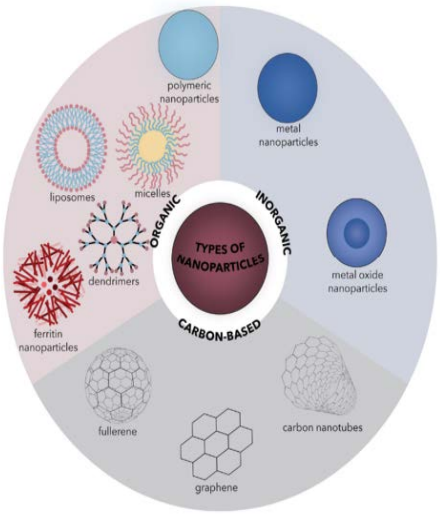

Fig. 12 - Schematic representation of the main classifications of nanoparticles [63]. Copyright 2021. Adapted from MPDI

6.3.1.1. Inorganic metal nanoparticles

In medicinal applications, gold nanoparticles (AuNPs) and silver nanoparticles (AgNPs) have garnered a lot of interest [63], as well as more generally in the development of technology, particularly because of their exceptional optical properties. Interestingly, these NPs exhibit surface plasmon resonance (SPR) behavior, which happens when light stimulates electrons at the material's interface between the conductor and insulator components [64]. These NPs' spectral characteristics are mostly form- and size-dependent; hence, the SPR is likewise influenced by the NPs' size, shape, and composition [65]. Metal nanoparticles' surfaces absorb light, causing electrons to collectively oscillate. This produces local heat that can be used in biomedical applications.

6.3.1.2. Inorganic metal oxide nanoparticles

Researchers are interested in inorganic metal oxide nanoparticles because of their appealing characteristics, which include easy surface functionalization, porosity, high stability, customizable form, and simple manufacturing procedures. Numerous biological applications, including medical imaging, medication transport, gene therapy, treatments linked to hyperthermia, antioxidant treatment, photodynamic therapy, dentistry, and wound healing techniques, have been studied for inorganic metal oxide nanoparticles. Inorganic substances, including gold nanoparticles, ZnO nanoparticles, TiO_2 nanoparticles, and silica-based nanoplatforms. Platforms known as metallic nanocarriers are helpful for the controlled and targeted delivery of macro- and micromolecules in the treatment of disease. These benefits resulted from ligands' variety in dimensions and forms, their high carrier capacity, their ability to form long-lasting interactions [66].

6.3.1.3. Carbon -based materials

Carbon-based nanomaterials include graphene (2D), carbon nanotubes (1D), nanodiamonds (1D), and carbon dots (CDTs) as well as fullerenes (0D), as illustrated in Fig. 13. The incorporation of polymeric nanoparticles into carbon nanomaterials gives them additional desirable characteristics like improved drug encapsulation ability, active functional groups, and superior mechanical stability. Impart qualuities such stability, active fuctional groups, improved drug encapsulation capacity, cellular responsiveness, increased solubility, antibacterial activity, and biocompatibility

that are appropriate for biomedical applications [67].

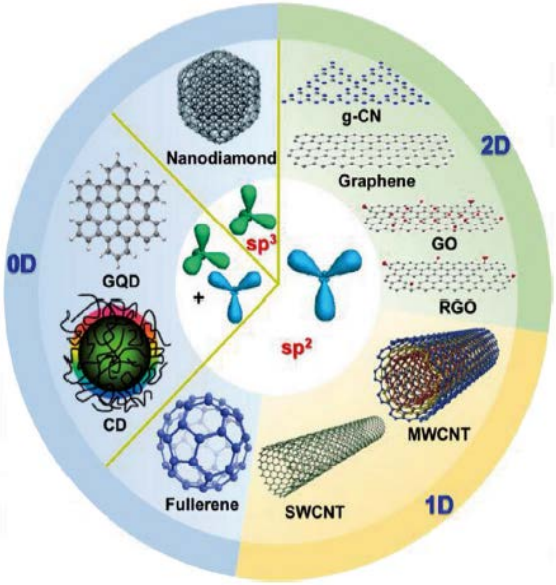

Fig. 13 - Carbon-based nanomaterials are classified according to their dimensionalities and carbon atom orbital hybridization [67].
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6.3.2. Polymeric nanoparticles (PNPs)

The majority of PNPs have nanosphere or nanocapsular shapes [68]. The matrix particles have an overall mass that is frequently solid, while the other molecules are adsorbed at the outer edge of the spherical surface. The solid mass in the latter case is completely contained within the particle [69]. We now have access to a large variety of polymers that can be turned into nanoparticulate carriers for different active ingredients thanks to recent developments in nanotechnology. The creation of nanoparticles has already made use of a wide range of natural and synthetic polymeric materials, including biodegradable, biocompatible, and nonbiodegradable compounds. The most prevalent ones are Polycaprolactone (PCL) [70], poly(lactide-co-glycolide) (PLGA), and poly(lactide) (PLA). Polymeric materials with satisfactory biocompatibility include poly(ethylene-co-vinyl acetate) (PEVA) and poly(methylmethacrylate) (PMMA). However, Eudragits® and poly(ethylene glycol) (PEG) are examples of synthetic polymeric materials that are not biodegradable.

6.3.2.1. Classification of polymeric nanoparticles

Polymeric nanoparticles can be classified as either nanospheres or nanocapsules based on their composition [71]. Fig. 14 shows schematic representations of both configurations. Numerous factors, including the drug's physicochemical properties, the medium's pH, the nature of the polymer or NPs' surface characteristics, the quantity of drug added to the formulation, and whether the drug was added before or after the formation of nanostructures [59].

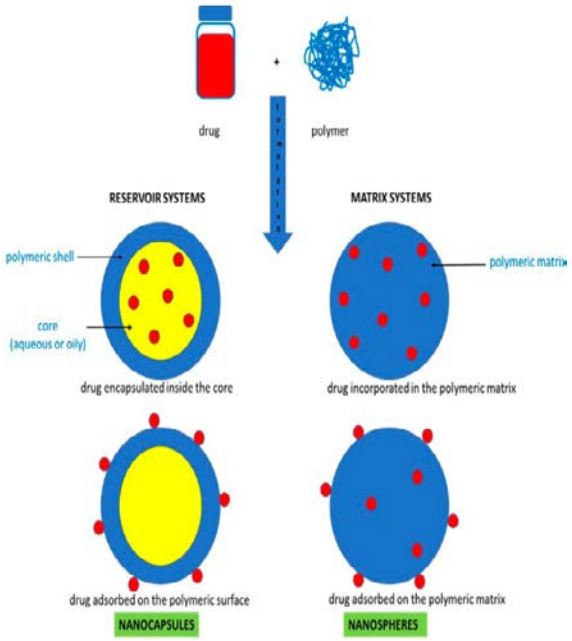

Fig. 14 - Polymeric nanoparticle types based on composition [72]

Drug molecules are adsorbed on a polymeric shell or enclosed in the core of the nanoparticle in nanocapsule systems. The drug is either embedded in the polymeric framework of the nanoparticle or adsorbed on the nanosphere's surface [72]. Both synthetic and natural polymers can serve as the basis for polymer matrices utilized as drug transporters. One can distinguish between natural polymers that come from bacteria, fungi, algae, plants, and animals. Excellent biocompatibility and biodegradability are characteristics shared by all of these matrices. Conversely, polyglycolic acid (PGA), PLA, PLGA [73], PCL [74], and polyvinyl alcohol (PVA) are the most often employed biodegradable synthetic polymers in the creation of nanoparticles.

7. Method of preparation of polymeric nanoparticles (PNPs)

Various techniques have been used to synthesize PNPs, contingent on the physicochemical characteristics of the medication and the application needs. Depending on the specific application, PNPs qualities must be optimized [75]. The kind of polymeric matrix, nanofiller, and desirable qualities for the finished goods are taken into consideration while choosing a process [76].

The process to produce polymeric nanoparticles was illustrated in Fig. 15.

Fig. 15 - Polymeric nanoparticle preparation methods [77]

7.1. Solvent evaporation

Solvent evaporation was the method developed to produce polymeric NPs from a premade polymer [75]. This process first requires the creation of an oil-in-water (O/W) emulsion, which results in the synthesis of nanospheres [78]. The active ingredient (like a medication) is added by dissolution or dispersion after the polymer has been dissolved in a polar organic solvent. Although they were used more often in the past, dichloromethane (DCM) and chloroform ($CHCL_3$) have been used extensively. The entire procedure is depicted in Fig. 16 [79]. Because of their toxicity, ethyl acetate has taken their place. Because of its better toxicological profile, it is more suitable for use in biomedical applications. Additionally, it has long been standard procedure to create an aqueous phase with a surfactant, like polyvinyl acetate (PVA) [80]. Following its emulsification in the aqueous phase with a surfactant, the organic solution is processed using high-speed homogenization or ultrasonication to create a dispersion of nanodroplets [75] To create a suspension of NPs, the polymer solvent diffuses and evaporates throughout the emulsion's continuous phase. After the solvent has evaporated, the solidified nanoparticles can be collected, cleaned by centrifugation, and then freeze-dried for long-term storage. This method enables the production of nanospheres [81].

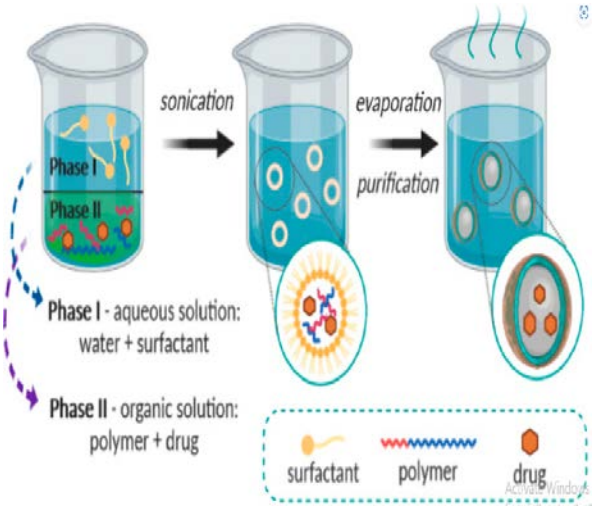

Fig. 16 - Schematic demonstration of the solvent evaporation technique [82].
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7.2. Emulsification/solvent diffusion

This procedure creates an O/W emulsion by mixing an aqueous solution with a surfactant and a solvent that is somewhat water-soluble and contains a polymer and medication [83]. This emulsion's internal part is composed of a somewhat hydrophilic organic solvent, such as benzyl alcohol or ethyl acetate, which has been saturated with water beforehand to guarantee that the two phases initially thermodynamically balance at room temperature [84]. When the dispersed droplets are subsequently diluted with a sizable amount of water, the resulting solvent diffuses from the droplets into the outside phase, producing colloidal particles. This process is often used to create nanospheres; however, adding a tiny quantity of oil (such as triglycerides C6, C8, C10, and C12) to the organic phase can also result in nanocapsules. Lastly, this step can be removed by evaporation or filtration, depending on the organic solvent's boiling point [75]. Fig. 17 provides a schematic illustration of this technique. In the end, NPs with sizes ranging from 80 to 900 nm can be produced. This method is frequently used to create PNPs, even though it requires a significant amount of the aqueous phase, which must be extracted from the suspended distribution, and there is a chance that the hydrophilic drug will diffuse into the aqueous phase [85].

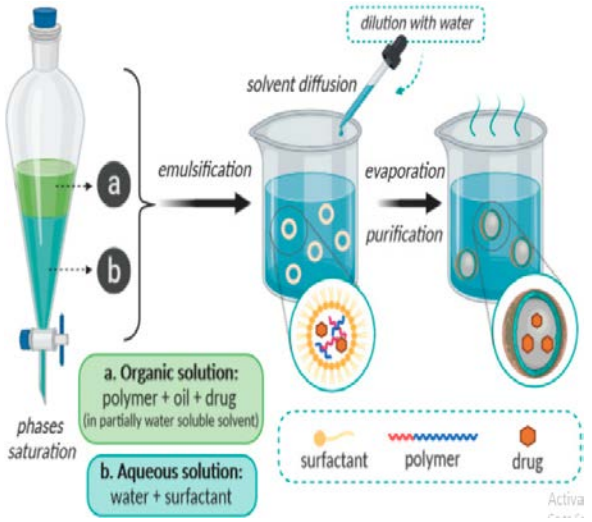

Fig. 17 - Schematic illustration of the emulsification/solvent diffusion technique [82]. Copyright 2020. Adapted from MDPI

7.3. Emulsification/reverse salting-out

This technique can be changed to incorporate the previously described emulsification/solvent diffusion method. The salting-out method, which divides a hydromiscible solvent from an aqueous solution, is based on the salting-out effect, which can result in the formation of nanospheres [86]. The main difference is that the aqueous phase consists of a gel, a colloidal stabilizer, and a salting-out agent, whereas the o/w emulsion is composed of a water-dispersed polymer solvent such as acetone or ethanol [87]. Appropriate salting-out agents include electrolytes such as magnesium chloride ($MgCl_2$), calcium chloride ($CaCl_2$), or magnesium acetate [$Mg(CH_3COO)_2$], as well as non-electrolytes like sucrose. Acetone and water become less miscible when the aqueous phase reaches saturation, enabling the other miscible phases to form an o/w emulsion [75]. The O/W emulsion is created while being vigorously stirred at room temperature. The emulsion is then diluted with an appropriate volume of deionized water or an aqueous solution to aid in the diffusion of the organic solvent to the exterior phase, the precipitation of the polymer, and eventually the formation of nanospheres. The salting-out agent and remaining solvent are eliminated by cross-flow filtering. Complete miscibility between the organic solvent and water facilitates the execution process, though it is not required [[86], [88]]. Fig. 18 shows a schematic representation of this approach. The size of the nanospheres created using this method ranges from 170 to 900 nm. The average size can be adjusted to values between 200 and 500 nm by varying the volume of the external phase and the concentration of polymers in the internal phase [89].

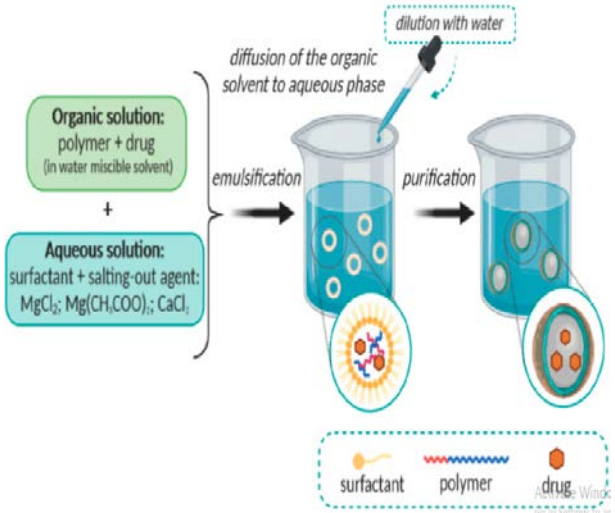

Fig. 18 - Schematic illustration of the emulsification/reverse salting-out technique [82]. Copyright 2020. Adapted from MDPI

7.4. Nanoprecipitation

This method, also called the solvent displacement method, requires two miscible solvents (Fig. 19). The internal phase consists of a polymer dissolved in a miscible organic solvent, such as acetone or acetonitrile [90]. Because they are immiscible in water, they are readily removed by evaporation. Essentially, this process involves the displacement of an organic solvent from a hydrophilic solution to the aqueous phase, followed by the interfacial deposition of a polymer. Following the polymer's dissolution in a water-miscible, intermediately polar solvent, the solution is progressively added to an aqueous solution while being stirred (dropwise) or at a controlled rate. The rapid spontaneous migration of the polymer solution into the aqueous phase causes the nanoparticles to form instantly in an attempt to avoid the water molecules [91]. As the solvent diffuses out of the nanodroplets, the polymer precipitates as nanospheres or nanocapsules. The process can be reversed without influencing the formation of nanoparticles, even though the organic phase is frequently added to the aqueous phase [92]. Surfactants can usually be added to the process to maintain the stability of the colloidal suspension, but their presence is not required to guarantee the formation of nanoparticles. The resultant nanoparticles have a well-defined size and a limited size dispersion, making them frequently superior to those produced by the emulsification

solvent evaporation process. The process of nanoprecipitation is widely employed to create polymeric nanoparticles (PNPs) with a diameter of around 170 nm [93]. However, it also enables the production of nanospheres or nanocapsules [75]. Nanospheres are created when the active ingredient dissolves or spreads throughout the polymeric solution. The drug is first dissolved in an oil and then emulsified in an organic polymeric solution to form nanocapsules, which are then dispersed in the external phase of the emulsion [94].

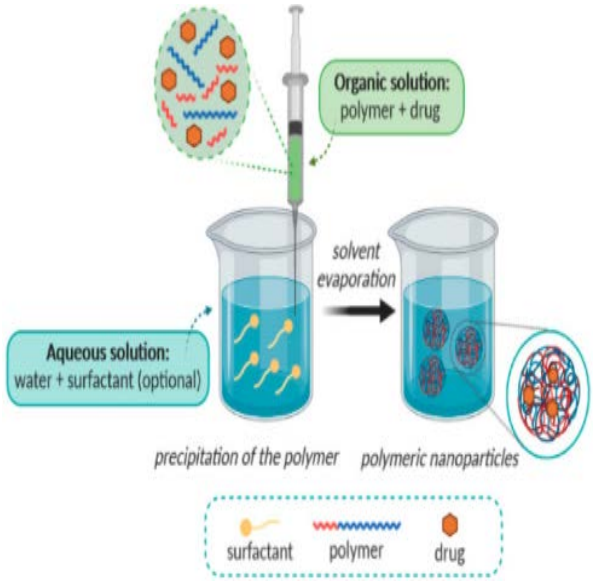

Fig. 19 - Schematic representation of the nanoprecipitation technique [82]. Copyright 2020. Adapted from MDPI

8. Polymer nanocomposite as carriers for active ingredients

The use of polymer-based nanocomposites as drug carriers has been extensively investigated because of their special mechanical and electrical features. Due to their ability to deliver therapeutic agents at the site of action in large and controlled doses, polymer nanocomposites are also being considered as possible drug delivery applicants. There are numerous bioapplications for the polymer-based polymer composites (Fig. 20). These polymer-based nanocomposites are designed with features that create new opportunities for creating advanced biomaterials for a range of biomedical applications, including cancer treatment, wound dressing, drug delivery, and tissue engineering, to meet various functional requirements.

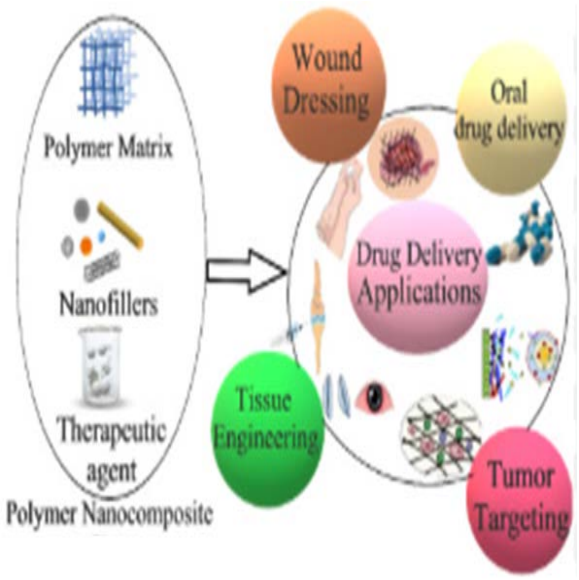

Fig. 20 - Application of polymer nanocomposites as carriers for active ingredients [95]. Copyright 2024. Reproduced with permission from Elsevier

8.1. Polymer nanocomposite-based metal nanoparticles

Pure metal precursors make up metal nanoparticles. Metal nanoparticles (MNPs) are gaining popularity because of their renowned LSPR (localized surface plasmon resonance) properties as well as other intriguing features related to their nanosizes, including optoelectrical, conducting, catalytic, mechanical, sensing, and superparamagnetic properties. Despite these advantageous characteristics, NPs' high toxicity rate, strong reactivity from surface charges, and innate propensity for aggregation are restricting their use in the biomedical industry. In the field of nanomedicine, inorganic nanoparticles such as gold (Au NPs), copper (Cu NPs), silver (Ag NPs), magnetic, silica, and quantum dots are frequently used.

As an antimetabolite, 5-fluorouracil (5-FU, 5-fluoro-2,4-pyrimidinedione) is a pyrimidine A pyrimidine equivalent. When used alone or in combination with other anticancer medications, It has a broad range of effects on solid tumors of the head, neck, brain, breast, ovary, pancreas, and gastrointestinal tract [96]. The main drawbacks of 5-FU use include its extremely low bioavailability, short plasma half-life, and non-specificity, which can result in systemic toxicity. As a result, large dosages are used, which causes adverse effects. Furthermore, the clinical uses of 5-FU have been significantly restricted due to tumor cell resistance development [97]. For instance, silver nanoparticles (AgNPs) are frequently used in biomedical

composites to improve anticancer activity, antibacterial efficacy, and drug encapsulation surface area [98]. N, N, N-trimethyl chitosan chloride (TMC) and carboxymethyl kappa-carrageenan (CMKC)/AgNPs were synthesized for use with different nanocomposites via polyelectrolyte complex PEC, according to Hanna *et al*. [99]. The results indicated that the produced nanocomposite, which was used as a natural carrier for 5-FU anticancer medicines, showed a prolonged and delayed release, hitting 96.3 ± 0.81% for 24 hours at pH 7.4 medium (TMC/CMKC/Ag 3%). The results demonstrated strong antibacterial and biodegradable qualities against several bacterial strains. AgNPs based on green biosynthesis also lessen harmful substances. All things considered, SNC, 3%, can be recommended as a successful solution for both regulated medication administration and antibacterial activity.

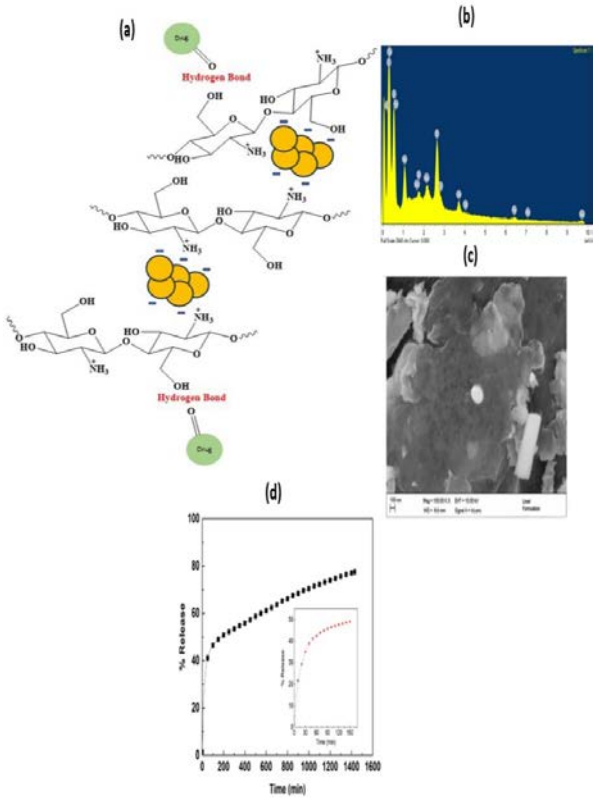

Fig. 21 - (a) Interaction between drug and CS-AuNPs, (b) EDX spectrum of CS-AuNPs nanoparticles, (c) SEM image, and (d) Release profiles of the drug from drug loaded-CS-AuNPs at pH 7.4 [100]. Copyright 2024. Adapted from Materials Research

Since AChE degrades ACh in the nucleus basalis and related regions, donepezil (Donz), a centrally acting, reversible, and noncompetitive acetylcholinesterase (AChE) inhibitor, raises the amount of ACh in the brain and improves cholinergic neurotransmission. Donz is used to treat mild to moderate Alzheimer's disease symptoms in patients [100].

Donz-loaded chitosan/gold nanocomposite (Donz-CS/AuNPs) was made by Saleh Al-Sarayra *et al.* [100] using a co-precipitation method.The produced nanocomposite is used for Alzheimer's disease. Donz and CS/AuNPs' anticipated interaction (Fig. 21a). Strong Au signals (1.5–2, 2–2.5, and 9.5–10 keV) were detected in the EDX data, confirming the particular gold peaks from the Donz-CS/AuNPs that were displayed in Fig. 21b. The AuNPs' spherical forms were visible in the SEM images (Fig. 21c). The results revealed Donz's regulated release profile (Fig. 21d).

8.2. Polymer nanocomposite-based metal oxide

Titanium dioxide (TiO_2) nanoparticles are especially beneficial due to their great chemical stability, low toxicity, high biocompatibility, and anticancer photocatalytic effectiveness [101]. The model drug norfloxacin (NFX) is a member of the fluoroquinolone class of antibiotics. In direct sunshine, it breaks down to produce ethylene and formyl piperazine, and it remains thermally stable up to 200 °C. An NFX overdose can also cause seizures, fever, nausea, breathing difficulties, tendon swelling, etc. [102]. Therefore, to keep the concentration of these medications within the therapeutic window for an extended amount of time, a sustained-release formulation is required. By lowering the frequency of dosages, the sustained-release approach also increases the drug's and the receiver's bioavailability.

For instance, a PLA/TiO_2 (spheres (S), rods (R)) nanocomposite loaded with NFX was made by solution casting and ultrasonication, Salahuddin *et al.* [103]. The produced nanocomposites showed antibacterial and anticancer characteristics. With a modest cellular damage efficiency on regular cell lines, the results validate the formation of the generated nanocomposites, which exhibit the intended antibacterial activity for the treatment of bacterial infections and are a suitable carrier and a good replacement for tumor cell lines. With minor cytotoxicity on normal cell lines, the results validate the production of the nanocomposites, which exhibit the required antibacterial activity for the treatment of bacterial infections and are a suitable carrier and good alternative for tumor cell lines.

8.3. Polymer nanocomposite/carbon-based materials

One famous anticancer drug is gefitinib, which is used to treat non-small cell lung cancer. Its low bioavailability results from its poor solubility in

aqueous solutions with a pH greater than 7. Gefitinib's limited water solubility necessitates a large dose during therapeutic use, which could result in more harmful reactions and side effects [104].

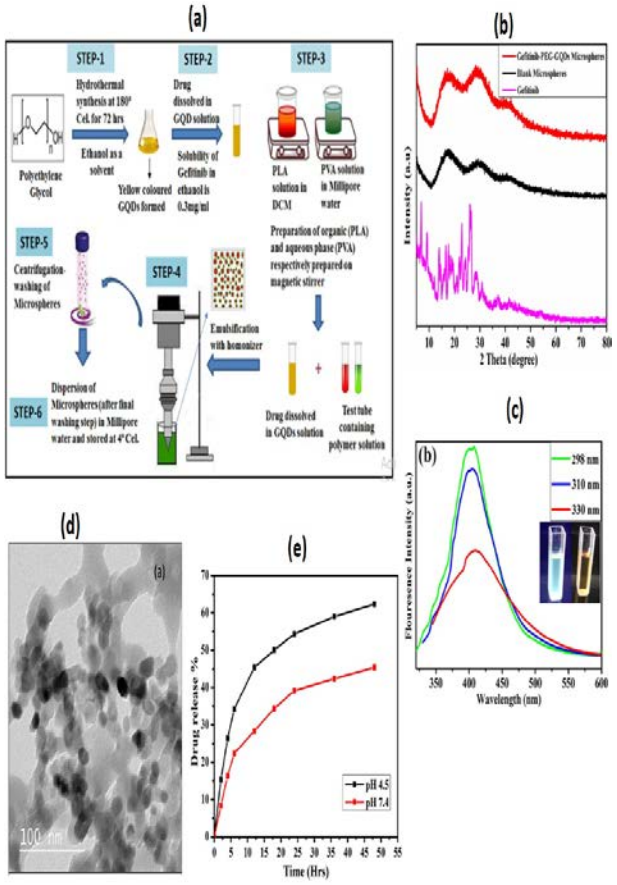

Fig. 22 - (a) Schematic view of the illustration of the creation of anticancer drug-loaded microspheres, (b) spectra of PEG-GQDs at the various excitation wavelengths, (c) X-ray diffraction patterns of drug, PLA/PVA microspheres, and drug-loaded GQD-embedded microspheres, and (d) HRTEM images of GQDs, and (e) Release profile for Gefitinib-loaded microspheres at different pH [105]. Copyright 2022. Adapted from Heliyon

Gautam and Pal [105] mentioned the preparation of gefitinib-loaded PEG-GQDs nanocomposites via the solvent evaporation technique and single emulsification technique using poly(vinyl acetate) (PVA) as a surfactant (Fig. 22a). The prepared nanocomposite was investigated by XRD and FE-FTIR. According to XRD, the obtained nanocomposite does not display any detectable peaks regarding gefitinib (Fig. 22b). The generated nanocomposite exhibits outstanding dispersibility in solvent and fluorescence that falls within the range of blue spectra in the VIBGYOR spectra (Fig. 22c). HRTEM shows that the graphene quantum dots have a constant diameter of 4–26 nm and are nearly evenly distributed. (Fig. 22d). The result showed that controlled release occurred at pH 7.4. (Fig. 22e). Additionally, this drug delivery method can be more effective than oral drug delivery and is appropriate for direct drug delivery to the lung cancer active site.

A nanomaterial made of sp2-bonded carbon atoms arranged in a flat honeycomb structure lattice is called two-dimensional (2D) graphene [106]. Graphene's exceptional biofunctionality and biocompatibility, together with its electrical conductivity, mechanical strength, thermal stability, and structural qualities, have garnered a lot of attention [107]. The most commonly used medication for treating breast cancer is doxorubicin (DOX). It belongs to the anthracycline group of organic compounds. Interaction with the DNA chain and replication inhibition is the foundations of the anti-cancer effect [108]. Ghamkhari *et al.* [109] mentioned the preparation of doxorubicin-loaded graphene oxide/poly(2-hydroxyethylmethacrylate)-g-poly(lacticde)-b-polyethyleneglycol-b-poly(2-hydroxyethyl methacrylate)-g-poly(lactide) nanocomposite was manufactured via reversible addition fragmentation chain (RAFT) and ring open polymerization (ROP). The outcomes demonstrated that the nanocomposite's anticancer medication efficacy was noticeably higher than that of free DOX. This nanoformulation may be studied as a potential delivery system to enable the oral administration of DOX to cancer patients due to its effective solubilization and controlled release properties.

8.4. Polymers nanocomposite-based clay

Clay is a layer of silicates made up of negatively charged silicate layered in layers. Polymer-nanoclay composites exhibit notable enhancements in mechanical and barrier properties when compared to polymers that use silica nanoparticles. Although nanoclay doesn't have antibacterial properties, it can become antimicrobial through chemical modification. Alkylphosphonium ions (Cloisite 30B) have been added to naturally existing montmorillonite clay (Cloisite Na^+) to provide it with antibacterial qualities [67]. The creation of antibacterial materials also makes use of these nanocomposites. Recently, certain morphologies, characteristics, and structures of polymer/clay nanocomposites have drawn attention. The interaction between the polymer and the clay is crucial in regulating mechanical behavior.

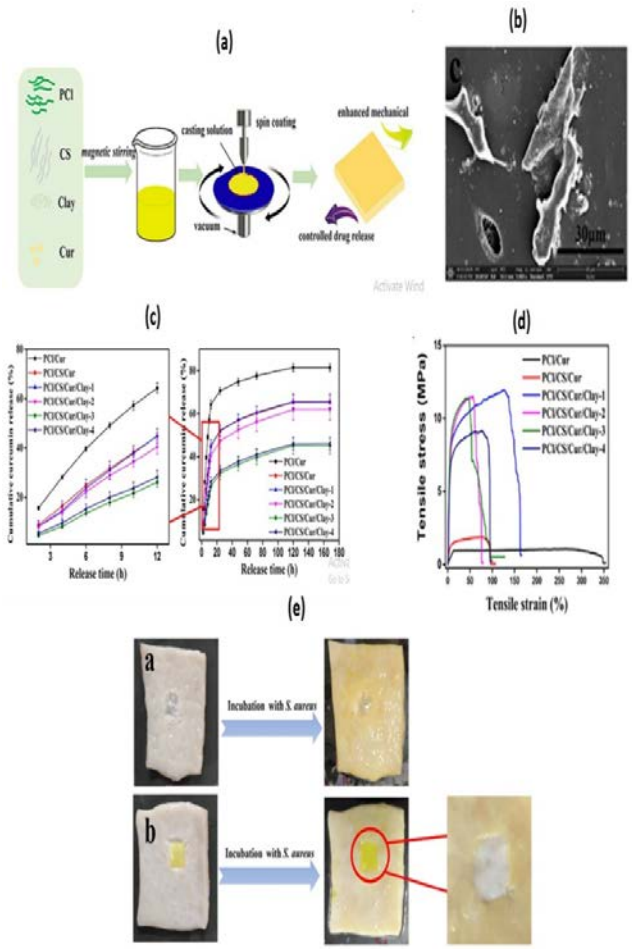

Fig. 23 - (a) Preparation of curloading with/without clay-enhanced flat membrane, (b) SEM image of PCl/CS/Cur/Clay-1, (c) The resulting membranes' in vitro release profiles within 12 and 168 hours of Cur, (d) tensile stress−strain curves of the Cur-loading membranes, and (e) Images of S. aureus infection for pig skin with an open wound and pig skin with a PCl/CS/Clay-3 film covering the wound [111].

Curcumin, often known as Cur, is a polyphenolic active substance obtained from plants that has broad-spectrum antibacterial qualities. It is used for antimicrobial treatment. Its structural characteristics and generation of antioxidant compounds prevent bacteria from growing. By means of the bacterial quorum regulator, it inhibits the adherence of bacteria to host receptors. When exposed to blue light, curcumin functions as a light sensitizer, causing phototoxicity and preventing bacterial growth [110]. For example, Huang *et al.* [111] mentioned the preparation of clay-reinforced polycaprolactone/chitosan/Cur (PCl/CS/Clay/Cur) nanocomposite film via the method of spin coating as shown in Fig. 23a. According to the SEM image (Fig. 23b), porous sponge-like morphology with disconnected structures was obtained. Good clay dispersion in the composite films was demonstrated by the physical and chemical characteristics. Compared to membranes without clay, the resulting nanocomposite film showed superior controlled-release profiles of Cur (Fig. 23c). It was discovered that adding nanoclay greatly increased the tensile strength (Fig. 23d). Additionally, the obtained film effectively prevented bacterial infection of the wound (Fig. 23e). The composite films' good biocompatibility was validated by cytotoxicity analysis. The obtained nanocomposite film would be promising candidates for wound dressing.

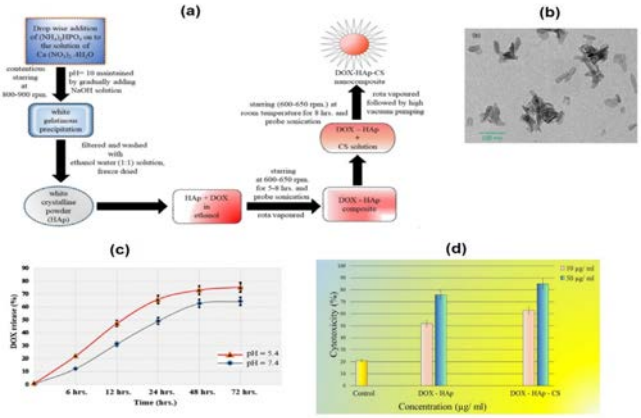

Fig. 24 - (a) Preparation of HAp and DOX-HAp-CS nanocomposite, (b) TEM images of DOX-HAp-CS nanocomposite, (c) In vitro DOX release patterns from the obtained nanocomposite under different pH, and (d) Cytotoxicity activity of drug loaded-HAp and drug loaded-HAp-CS [113]. Copyright 2019. Reproduced with permission from Springer.

Bone is a hard, mineralized tissue made up of strong, intricate hierarchical structures. The inorganic mineral nanohydroxyapatite (HAp) crystals, which are occasionally found in the osteoid matrix, make up human bone tissue. The hardness and stiffness of bone tissue are attributed to HAp. The calcium and phosphate combination HAp [$Ca_{10}(PO_4)_6(OH)_2$] has a molar ratio of Ca/P of approximately 1.67 [112]. According to Ghosh *et al.* [113], the preparation of DOX-loaded hydroxyapatite (HAp)-chitosan (CS) nanocomposite via the in situ precipitation method (Fig. 24a) was mentioned. It is used as an anticancer agent for osteosarcoma inhibition. Reducing the outermost energy of HAp particles and then regulating their size resulted in less agglomeration between the particles in the resulting nanocomposite, according TEM (Fig. 24b). The resultant nanocomposite offers outstanding mechanical properties with controlled drug release (Fig. 24c). The produced nanocomposite produces no significant cytotoxicity

towards cultured osteosarcoma cells (Fig. 24d). The obtained nanocomposite could be a promising drug carrier for cancer therapy.

8.5. Polymer nanocomposite-based nanofibers

For a variety of wound healing applications, tetracycline hydrochloride (TCH), a hydrophilic antibiotic, is used to prevent and treat bacterial infections that occur in burns, cuts, and surgeries [114].

For intense drug release, tetracycline hydrochloride (TC)-loaded polycaprolactone (PCL) nanofibers were prepared by electrospinning for regulated drug administration, according to Karuppuswamy *et al.* [115]. According to the observed results, TC loading for the controlled release caused the PCL to gradually change from a hydrophobic to a hydrophilic condition (TC, 5%). Drug-loaded membranes demonstrated the maximum tensile strength (3.9 MPa) at 2% drug membrane and the highest resistance to deformation. As the drug concentration rose, so did the fibrous scaffolds' porosity. According to in vitro release trials, the drug's burst release occurred within the first hour at the lowest and was followed by 8-day continuous controlled release. The resulting nanofibers may hold promise for use in biomedicine and healthcare applications, including medication delivery.

In another study, the creation of DOX-loaded PLGA/Atapulgite (ATT) nanocomposite using electrospinning was described by Wang *et al.* [116]. The obtained nanocomposite nanofibers exhibit better mechanical durability and a homogeneous, smooth morphology. The payload was continuously released from the generated nanofibers under both neutral and acidic pH settings. Furthermore, the released DOX from the nanofibers may considerably slow the proliferation of malignant cells. Because ATT/DOX-doped PLGA nanofibers can greatly enhance the mechanical properties of electrospun PLGA nanofibers and have a much lower burst release profile, they may be employed as a functional material for tissue engineering scaffolds for more effective local tumor treatment applications. To demonstrate the anticancer efficacy of these composite nanofibers, more in vivo studies had to be conducted.

PCL/gelatin nanofibers embedded with Dox-loaded mesoporous silica nanoparticles/silver nanoparticles were prepared by blow spinning, according to Tavira *et al.* [117]. The obtained nanocomposite exhibited a slow-release profile of AgNPs and DOX together with high encapsulation effectiveness. Furthermore, in addition

n to blocking AgNP infection, the obtained nanocomposite has the potential to efficiently eliminate melanoma cancer cells. The ability of normal cells to adhere to the scaffold made of fibrous mats loaded with nanoparticles demonstrated the potential for repairing melanoma cancer wounds.

For instance, TCH-loaded PLA/polyvinylpyrrolidone (PVP)/TCH-MWCNTs composite fibrous mats were prepared by electrospinning (Fig. 25a) according to Emre Bulbul *et al.* [118] SEM shows a smooth morphology free of bead defects (Fig. 25b). AFM reported that the surfaces of all the electrospun fibrous mats were smooth (Fig. 25c). Additionally, MWCNT-loaded electrospun mats showed a much more controlled drug release manner, reduced the burst release of TCH, and significantly increased the drug encapsulation efficiency (EE%) (Fig. 25d). According to in vitro cytotoxicity tests, the generated nanocomposite mats did not cause any harm to human umbilical vein endothelial cells (HUVECs). The resulting composite nanofiber mats may find use in biomedical applications as therapeutic materials or drug delivery systems.

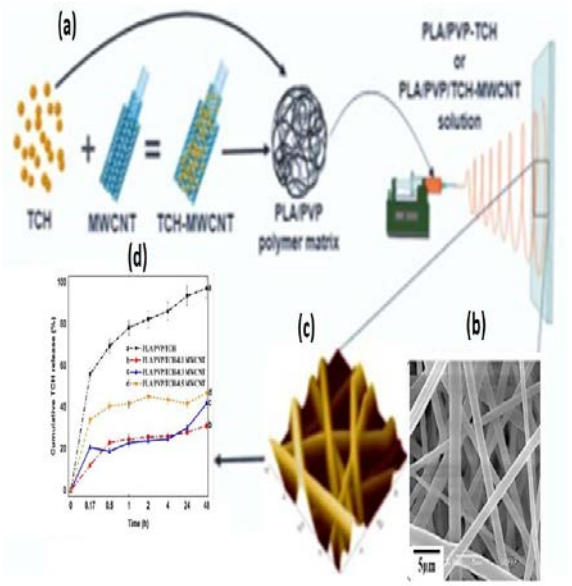

Fig. 25 - (a) Electrospinning method, (b) SEM image of the prepared nanofiber at 0.3 MWCNT, (C) 3D AFM images of the electrospun nanofiber at 0.3 MWCNT, and (d) Cumulative release profile of Drug the electrospun fibrous mats PLA/PVP/TCH, PLA/PVP/TCH-MWCNT at different concentration of MWCNT [118]. Copyright 2019. Reproduced with permission from Elsevier.

Table 2 - Method of preparation of various polymeric nanocomposites as carrier of various active ingredients for controlled drug release

Polymeric nanocomposite	Active ingredients	Method of preparation	Resultes	References
TMC/carboxymethyl kappa-carrageenan (CMKC)/ AgNPs nanocomposite	5-Flourouracil (5-FU)	Polyelectrolyte complex (PEC)	- Controlled drug delivery. - Exhibited good biodegradability and antimicrobial properties against different bacterial strains. -Acts as an effective carrier for anticancer drug at 3% Ag.	[99]
Chitosan/gold (CS/AuNPs) nanocomposite	Donepezil (Donz)	Co-precipitation technique	- Exhibited controlled release profile of Donz. -The produced nanocomposite was used for Alzheimer's Disease Therapy.	[100]
PLA/ Titanium dioxide nanocomposite	Norfloxacin (NFX)	Ultrasonic/ solution casting method	- Exhibited antibacterial and antitumor Activities. - Showed moderate cytotoxicity efficacy on normal cell lines and the formulation, making it a good substitute and appropriate carrier for tumor cell lines.	[103]
PEG-GQDs nanocomposite	Gefitinib	Solvent evaporation /single emulsification method	- Act as an effective carrier for anticancer drug. - Exhibited controlled release at PH 7.4. – Exhibited a suitable approach for direct drug delivery to the lung cancer's active site, which may be more effective than oral drug delivery.	[105]
GO/poly(2-hydroxyethyl methacrylate)-g-poly(lacticde)-b-polyethyleneglycol-b-poly(2-hydroxyethyl methacrylate)-g-poly(lactide)	Doxorubicin (DOX)	Reversible addition fragmentation chain (RAFT)/ ring-opening polymerization (ROP)	-Exhibited superior anticancer efficacy when compared to free DOX. - Demonstrated the capacity to effectively solubilize DOX and offer controlled release. -Serves as a potential delivery vehicle so that DOX can be given orally to cancer patients.	[109]
Clay-reinforced polycaprolactone/chitosan (PCl/CS/Clay) nanocomposite film	Curcumin (Cur)	Spin coating method	- Showed porous sponge-like morphology. - Demonstrated superior Cur controlled-release profiles compared to membranes devoid of clay - Protected the wound from bacterial infection. -The tensile strength was found to be considerably increased by the addition of nanoclay. - Proved good biocompatibility. -It would be promising candidate films might be promising candidate for wound dressing.	[110]

Hydroxyapatite (HAp)-chitosan (CS) nanocomposite	Doxorubicin (DOX)	In situ precipitation method	-It is used as an anticancer agent for osteosarcoma inhibition. - Provides outstanding mechanical properties with controlled drug release. -The produced nanocomposite produces no significant cytotoxicity towards cultured osteosarcoma cells. -The obtained nanocomposite could be a promising drug carrier for cancer therapy.	[112]
Polycaprolactone (PCL) nanofibers	Tetracycline hydrochloride (TC)	Electrospinning	- Sustained controlled release of TC. - Exhibited the highest tensile strength of 3.9 MPa at 2% drug membrane. - The obtained nanofibers could be promising for drug delivery applications in biomedicine and healthcare.	[115]
Poly(lactic-co-glycolic acid)/ Attapulgite (ATT) nanocomposite nanofibers	Doxorubicin (DOX)	Electrospinning	-Exhibited a smooth and uniform morphology. -Exhibited sustained controlled release of ATT/DOX-doped PLGA nanofibers. - The released DOX from the nanofibers may considerably slow the growth of tumor cells. -Reduced burst release profile of ATT/DOX-doped PLGA nanofibers. -Improved the mechanical properties. - It serves as a useful component for tissue engineering scaffolds, which improves the application of local tumor therapy. -Exhibited antitumor efficacy of produced nanofibers.	[116]
PCL/gelatin nanofibers embedded	Doxorubicin (DOX)	Blow spinning	-Exhibited good encapsulation efficiency with a slow-release profile of DOX and AgNPs. -Preventing infection by AgNPs. -The obtained nanocomposite could effectively destroy melanoma cancer cells. - It is used to heal wounds caused by melanoma cancer.	[117]
Poly (lactic acid) (PLA) /polyvinylpyrrolidone (PVP)/ MWCNTs composite fibrous mats	Hydrochloride (TCH*)*	Electrospinning	-Smooth morphology and smooth surfaces. -Displayed a significantly more regulated drug release mechanism. -Demonstrated a significant improvement in drug encapsulation efficiency. Decreased TCH burst release. -Showed no harmful effects on the endothelial cells of the human umbilical vein (HUVECs). -It serves as a therapeutic material for drug delivery systems in biomedical applications.	[118]

According to Mosallanezhad *et al.* [119], PCL/chitosan-loaded zinc oxide nanoparticles and curcumin (Cur) were prepared by electrospinning. SEM examination revealed bead-free, silky nanofibers. The elemental analysis also demonstrated that ZnO was distributed well among the scaffolds. The addition of ZnO greatly enhanced the mechanical properties, and the sample with 3 weight percent Cur had the maximum water uptake value. After a quick release, the Cur medication stabilized in around twenty-four hours. When applied to experimental data, the Peppas model yielded the best results. Effective inhibition of bacterial growth was demonstrated by the resulting nanocomposite. Additionally, research conducted in vitro showed that a high Cur content reduces cell attachment and survival. Table 2 provides an overview of the many alterations that can be used to challenge the characteristics of various drug-loaded polymeric nanocomposites as carriers for controlled drug release.

9. Conclusion

Polymeric nanocomposites have emerged as a transformative class of multifunctional drug delivery platforms by integrating the favorable biocompatibility, biodegradability, and structural versatility of polymeric matrices with the unique physicochemical properties of nanoscale fillers. Recent advances in nanomaterial engineering, surface functionalization, and fabrication technologies have enabled the development of carriers with enhanced drug-loading capacity, programmable release kinetics, improved targeting efficiency, and superior therapeutic performance. The convergence of natural and synthetic polymers with metallic nanoparticles, metal oxides, carbon-based nanomaterials, nanoclays, mesoporous nanostructures, and electrospun nanofibers has expanded the scope of applications in cancer therapy, antimicrobial treatment, wound healing, regenerative medicine, neurological disorders, and other precision therapeutic strategies. Collectively, these developments demonstrate the significant potential of polymeric nanocomposites to overcome many limitations associated with conventional drug delivery systems.

Despite these remarkable advances, several scientific and translational challenges continue to hinder widespread clinical implementation. Achieving reproducible large-scale manufacturing while maintaining consistent nanoparticle dispersion, structural homogeneity, and batch-to-batch reproducibility remains a major obstacle. Long-term biosafety, biodegradation behavior, immunogenicity, nanoparticle accumulation, and chronic toxicity require comprehensive in vivo evaluation using standardized experimental protocols. In addition, the complexity of nano–bio interactions, limited understanding of pharmacokinetic and pharmacodynamic behavior, insufficient long-term clinical evidence, and the absence of internationally harmonized regulatory guidelines continue to delay regulatory approval and commercialization. Economic considerations, manufacturing costs, process scalability, sterilization compatibility, storage stability, and quality assurance further complicate industrial translation. Addressing these multidisciplinary challenges will require close collaboration among materials scientists, pharmaceutical researchers, biomedical engineers, clinicians, toxicologists, regulatory agencies, and industrial partners.

Future research should focus on the rational design of intelligent, multifunctional polymeric nanocomposites capable of simultaneously integrating targeted delivery, controlled drug release, real-time therapeutic monitoring, and diagnostic imaging within a single platform. Greater emphasis should be placed on stimuli-responsive systems that respond to physiological and pathological triggers, including pH, temperature, enzymatic activity, redox potential, magnetic fields, ultrasound, and light, thereby enabling highly localized and personalized therapy. Furthermore, environmentally sustainable manufacturing based on green chemistry principles, renewable biopolymers, solvent-free processing, and energy-efficient production should become a central objective for future research to minimize environmental impact while improving industrial feasibility.

Looking ahead, the convergence of advanced polymer science, nanotechnology, computational intelligence, additive manufacturing, and precision medicine is expected to redefine the next generation of drug delivery systems. Continued interdisciplinary innovation, combined with rigorous biological validation, standardized characterization methods, and well-designed clinical studies, will be essential for translating laboratory-scale discoveries into clinically approved therapeutic products. Ultimately, polymeric nanocomposites are poised to play a pivotal role in the development of safer, smarter, and more effective therapeutic platforms that support personalized healthcare and improve patient outcomes across a broad spectrum of diseases.

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Бақыланатын және ұзақ мерзімді дәрілік заттардың шығарылуына арналған әртүрлі белсенді ингредиенттердің полимерлі нанокомпозиттік тасымалдаушыларындағы соңғы жетістіктер: шолу

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ТҮЙІНДЕМЕ

Дәрі-дәрмектерді бақылаумен және ұзақ уақыт бойы жеткізу дәстүрлі фармацевтикалық препараттардың шектеулерін, соның ішінде биожетімділігінің төмендігі, дәрі-дәрмектерді тез жою, жүйелік уыттылық және спецификалық емес таралуды жеңудің трансформациялық стратегиясына айналды. Зерттелген көптеген жеткізу платформаларының ішінде полимер нанокомпозиттік тасымалдаушылар айтарлықтай назар аударды, себебі олар полимерлердің тамаша биоүйлесімділігін, биоыдырағыштығын және өңдеуге қабілеттілігін бейорганикалық наноматериалдардың бірегей физика-химиялық, механикалық, оптикалық, магниттік және терапиялық қасиеттерімен біріктіреді. Бұл шолу полимер нанокомпозиттеріне негізделген дәрілік заттарды жеткізу жүйелеріндегі соңғы жетістіктерді кешенді және сыни бағалауды ұсынады, табиғи және синтетикалық полимерлер мен металл және металл оксиді нанобөлшектері, көміртегі бар наноматериалдар, наноклейлер, мезокеуекті материалдар және электроспинделген нанобөлшектер сияқты кең ауқымды нанобөлшектер арасындағы синергетикалық өзара әрекеттесуге баса назар аударады. Нанокомпозиттік құрамның, өндіріс стратегияларының және физика-химиялық сипаттамаларының дәрілік заттардың жүктелуіне, капсулалау тиімділігіне, босату кинетикасына, нысанаға алу мүмкіндігіне және биологиялық өнімділікке әсері жүйелі түрде талқыланады. Сонымен қатар, қатерлі ісік терапиясындағы, жараларды емдеудегі, микробқа қарсы емдеудегі, ұлпалық инженериясындағы, неврологиялық бұзылуларда және регенеративті медицинадағы типтік терапиялық қолданыстар құрылым, қасиеттер мен сипаттамалар арасындағы байланысты анықтау үшін сындарлы түрде салыстырылады. Бұл шолу негізінен жеке тасымалдаушы жүйелерді, дайындау әдістерін, босату механизмдерін және биомедициналық қолданыстарды бір жүйеде қорытындылайды, сонымен қатар нанобөлшектердің агрегациясына, ұзақ мерзімді биоүйлесімділікке, биоыдырауға, ірі көлемді өндіріске, , реттеуші органдардың бекітуіне және клиникалық енгізуге қатысты қолданыстағы шектеулерді анықтайды. Бұл шолу терапиялық тиімділігі, қауіпсіздігі және жеделдетілген клиникалық қолданылуы бар озық полимерлі нанокомпозиттерді рационалды жобалаумен айналысатын зерттеушілер үшін құнды ақпарат береді.

Түйін сөздер: бақыланатын дәрілік заттарды жеткізу, полимерлі нанокомпозиттер, полимер нанокомпозиттері, дәлме-дәл наномедицина, ақылды нанотасымалдаушылар, тітіркендіргіштерге жауап беретін дәрілік заттарды жеткізу, тұрақты наноөндіріс, терапиялық наноплатформалар.

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Последние достижения в области полимерных нанокомпозитных носителей различных активных ингредиентов для контролируемого и пролонгированного высвобождения лекарственных средств: обзор

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АННОТАЦИЯ

Контролируемая и пролонгированная доставка лекарственных средств стала преобразующей стратегией для преодоления ограничений традиционных фармацевтических препаратов, включая низкую биодоступность, быстрое выведение лекарственных средств, системную токсичность и неспецифическое распределение. Среди многочисленных исследованных платформ доставки полимерные нанокомпозитные носители привлекли значительное внимание, поскольку они сочетают в себе превосходную биосовместимость, биоразлагаемость и технологичность полимеров с уникальными физико-химическими, механическими, оптическими, магнитными и терапевтическими свойствами неорганических наноматериалов. В данном обзоре представлена всесторонняя и критическая оценка последних достижений в области систем доставки лекарственных средств на основе полимерных нанокомпозитов, с акцентом на синергетическое взаимодействие между природными и синтетическими полимерами и широким спектром нанонаполнителей, включая наночастицы металлов и оксидов металлов, углеродсодержащие наноматериалы, наноглины, мезопористые материалы и электроформованные нановолокна. Систематически обсуждается влияние состава нанокомпозита, стратегий изготовления и физико-химических характеристик на загрузку лекарственного средства, эффективность инкапсуляции, кинетику высвобождения, способность к таргетной доставке и биологические характеристики. Кроме того, критически сравниваются типичные терапевтические применения в лечении рака, заживлении ран, антимикробной терапии, тканевой инженерии, неврологических расстройствах и регенеративной медицине для установления взаимосвязи между структурой, свойствами и характеристиками. Этот обзор в основном обобщает отдельные системы-носители, методы получения, механизмы высвобождения и биомедицинские применения в единой системе, выявляя при этом существующие ограничения, связанные с агрегацией наночастиц, долгосрочной биосовместимостью, биоразложением, крупномасштабным производством, получением разрешений регулирующих органов и клиническим внедрением. Данный обзор предоставляет ценную информацию для исследователей, работающих над рациональным проектированием передовых полимерных нанокомпозитов с повышенной терапевтической эффективностью, улучшенной безопасностью и ускоренным клиническим применением.

Ключевые слова: контролируемая доставка лекарств, полимерные нанокомпозиты, прецизионная наномедицина, интеллектуальные наноносители, доставка лекарств в ответ на внешние воздействия, устойчивое нанопроизводство, терапевтические наноплатформы

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