Pharmaceutical Formulation Using Polymer Nanocomposites

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ABSTRACT

A polymer matrix and nanometer-sized reinforcements (nanofillers), such as nanoparticles, nanotubes, or nanoclays, combine to form nanocomposites. To improve or give the composite material new qualities, these nanofillers—which are usually between 1 and 100 nanometers in size—are added to the polymer matrix. Comparing nanofillers to the unaltered polymer, the former enhances qualities including mechanical strength, thermal stability, chemical resistance, and barrier qualities. In the pharmaceutical industry, nanocomposites can be utilized to create sophisticated drug delivery systems. The nanofillers give targeted distribution to particular body regions, improve stability, increase drug solubility, and allow controlled drug release. Nanocomposites are very useful in a variety of medical and therapeutic applications because of the nanofillers' enormous surface area and tiny size, which enable improved interaction with biological systems. Hydrogels, films, microspheres, liposomes, nanotubes, emulsions, gel systems, micelles, coatings, injections, and many other are among the types that are involved. The mechanical strength and bioadhesiveness of the delivery systems can be enhanced by the synergistic effects of adding nanomaterials such as metal oxide nanomaterials, silica nanoparticles, or carbon nanotubes to polymer matrices.

Keywords: Nanocomposite, Pharmaceutical formulation, Application.

INTRODUCTION

A solid composed of at least one phase that is one, two, or three dimensions at the nanometre scale is called a nanocomposite. The nanoscale phase process aims to achieve synergy among diverse components. Nanomaterials found in nanocomposites include: nanoparticles, nanofibers, and nanoclays. Material properties change when the size of the material constituents falls below a certain threshold, referred to as 'critical size' (1).Reducing material dimensions to the nanometer range fosters interactions at phase interfaces, which play a crucial role in enhancing material properties. The ratio of surface area to volume of the reinforcing material used in nanocomposite preparation is directly linked to understanding the structure-property relationship(2). The nanocomposite material (with at least one component on the nanometric scale (10^{-9} m)), made from non-metallic, metallic, and polymer materials through a specific process, offers the additional benefit of maintaining primary characteristics to mitigate defects and showcase new attributes. Such materials represent a multiphase crossover of the matrix and reinforcing materials. The reinforcing material is a dispersed phase, typically fibrous materials such as glass Fiber and organic fiber, while the matrix material is a continuous phase, consisting of metallic, inorganic on-metallic, and polymer matrix materials (2).Nanocomposites present a novel alternative to address the current limitations of micro composites and monolithic, positioning them as materials for the future.

The primary advantages of nanocomposites over other composite materials are(3):

- a high surface/volume ratio allows for smaller filler sizes and reduced distances between fillers;
- superior mechanical properties, offering high ductility without loss of strength and scratch resistance;
- enhanced optical properties (light transmission varies with particle size).

The drawbacks of applying nanocomposites mainly involve toughness and impact performance linked to the incorporation of nanoparticles into the bulk matrix of the composite (4);

- limited understanding of the formulation/property/structure relationship, the need for simpler particle exfoliation and dispersion;
- cost-effectiveness.

Nanocomposite materials are categorized into three groups based on their matrix materials(5):

1. Ceramic matrix nanocomposites (CMNC)
2. Polymer matrix nanocomposites (PMNC)
3. Metal matrix nanocomposites (MMNC)

Ceramic matrix nanocomposites

Ceramic matrix composites are materials that intentionally incorporate one or more distinct ceramic phases to improve wear resistance and thermal and chemical stability. However, the primary drawback of ceramics is their brittleness and low toughness, which limits their industrial use.

This challenge is addressed through the development of ceramic-matrix nanocomposites (CMNC).An example of CMNC is a matrix containing energy-dissipating components (fibers, platelets, or particles)that are integrated into the ceramic matrix to reduce brittleness and enhance fracture toughness (8).

Processing Raw materials

The raw materials for CMNC matrices include Al2O3, SiC, SiN, etc.

Generally, the reinforcements in all nanocomposites are sized at the nanoscale.

Iron and other metal powders such as TiO2, silica, and clays have been utilized for crystalline reinforcement. The most commonly used materials are clays and layered silicates due to their availability in very small particle sizes and well-researched chemical interactions(6,7). Incorporating clay and layered silicates, even in small amounts, enhances the properties of the matrix (8).

Processing methods

Various methods have been created for synthesizing CMNC (9,10). New approaches primarily involve single-source-precursor techniques based on the melt spinning of hybrid precursors, followed by curing and pyrolyzing the fibers.

Some traditional methods include the conventional powder method(11); polymers precursor route (2,12), spray pyrolysis (11); and vapor techniques (13) (CVD and PVD).

Chemical methods encompass the sol-gel process, colloidal and precipitation techniques, and template synthesis (14).

Structure of CNMC:

The structure of the nanocomposites consists of a matrix material embedded with nano-sized reinforcement components (particles, whiskers, fibers, nanotubes).

Ceramic is a rigid material that is highly brittle and can fracture easily through crack propagation (15). The addition of a ductile metal phase into the ceramic matrix can improve the ceramics' durability, leading to enhanced mechanical properties (hardness and fracture toughness) due to the interaction among the many stages, reinforcements, and matrix. The relationship between the surface area and volume of the reinforcement materials is vital for understanding the structure-property linkage in CMNCs(16).

As previously mentioned, significant improvements in fracture strength and toughness, along with high-temperature resistance, can be achieved in comparison with micro counterparts and monolithic matrix components(17).

Application of CMNCs:

From this perspective, metal and ceramic nanocomposites can significantly impact a wide range of industries, including aerospace, the automotive sector, electronics, and military applications (14).

Some innovative uses of ceramic nanocomposites include the removal of acid fuchsin (15), various photocurrent applications (18) and biomedical uses.

Ceramics used in biomedical applications are referred to as bio ceramics. Nano-phased ceramics are also involved in research addressing various structural and bio-related issues. One example is the incorporation of Nano metrics in prosthetics to reduce the risk of rejection and promote the proliferation of osteoblasts (bone-forming cells). The application of monocrystalline ceramic materials in biomedical applications presents several advantages:

- Higher resistance/hardness
- Improved toughness/durability
- Diminished ductility and flexibility
- Reduced rejection risk

Table 1: Advantages and limitations of CNMC processing methods(14)

Method	Advantages	Limitations
Powder process	Simple	Agglomeration, high temperatures, low formation and phase dispersion rates
Polymer precursor process	Possibility of preparing finer particles, better reinforcement dispersion	Phase segregation results from the agglomeration and dispersion of ultra-fine particles.
Sol-gel process	Simple, versatile, chemical homogeneity	Compact, minimal void creation when compared to the mixing technique.

Metal matrix nanocomposites (MMNC)

Metal matrix nanocomposites (MMNC) are multiphase materials made of a ductile metal or alloy matrix containing nano-sized reinforcement material.

The properties of MMNC include high ductility, toughness, strength, and modulus.

MMNC can be applied in various sectors such as aerospace and automotive industries (19).

Processing Raw materials

The metal matrices used for producing MMNC include Al, Mg, Pb, Sn, W, and Fe.

The reinforcements for MMNC are the same as those for CMNC and PMNC (19).

Synthesis

The most commonly utilized techniques for preparing MMNC are: spray pyrolysis(20,21), liquid metal infiltration (22), rapid solidification (23), vapour techniques (18) (PVD, CVD), electrodeposition(22) and chemical methods, which encompass colloidal(23)and sol-gel processes.

Table 2: Advantages and limitations of MMNC processing methods

Method	Advantages	Limitations
Spray pyrolysis	Producing homogenous, spherical, and ultrafine powders in multicomponent systems efficiently.	The cost of producing homogeneous, nanoparticles on a big scale.
Sol-gel process	High purity products, strict stoichiometry control, good chemical homogeneity, low processing temperature, and effectiveness and versatility.	Porous, weakly bonded, and having little wear resistance
Rapid solidification process (RSP)	Simple, dependable, and effective.	The disadvantage of metal-metal nanocomposites is that they are non-homogeneous and agglomerate.

Some innovative methods for MMNC include the melt falling-drop quenching method(24) and one-pot synthesis of the nanocomposite of carbon dots nanocomposite (CDs) and AuNPs (gold nanoparticles)(25).

Applications of MMNC:

Metal nanocomposites have extensive applications across various industries, including automotive, aerospace, electronics, and military(26).

Polymer-metal nanocomposites, which use polymer as a matrix and metal nanoparticles as nanofillers, may find applications in several biomedical fields and medical devices (27).

Polymer matrix nanocomposites (PMNC):

Nanocomponents in PMNC are typically referred to as fillers and categorized as:

- 1D - linear (e.g. carbon nanotubes),
- 2D - layered (e.g. montmorillonite),
- 3D - powder (e.g. silver nanoparticles(28).

As a result of the interaction between the polymer matrix and the nanofiller at the molecular level, an attractive effect among the nanocomposites is observed. Therefore, adding a small quantity of nanofiller with dimensions under 100 nm to the matrix alters the properties of the composite material. The production of nanocomposites can be accomplished using the same techniques that are employed for traditional composites, such as: in-situ, solvent method, or by blending melted polymer matrix. The features of PMNCs include: high thermal stability, enhanced mechanical properties (high abrasion resistance), and reduced gas permeability (higher barrier capacity)(7).

Processing methods of polymer matrix

Various techniques have been utilized for preparing polymer nanocomposites.

The most commonly used include:

- Intercalation of the polymer or pre-polymer from solution;
- In-situ intercalative polymerization;
- Melt intercalation;
- Template synthesis (Sol-gel technology)(29).

In-situ intercalative polymerization: is a method that allows for polymer formation between the intercalated sheets. It relies on the swelling of layered silicate in the liquid monomer, followed by initiation of polymerization through heat or radiation, diffusion of an appropriate initiator, or an organic initiator(30). Initially, this method was used in the production of nylon–montmorillonite nanocomposite, and later it was applied to other thermoplastics. In-situ polymerization is a suitable technique for thermoset–clay nanocomposites(31).The drawbacks of in-situ intercalative polymerization include: slow reaction rates; reliance on clay exfoliation through processes such as swelling of clay; diffusion rate of monomers in the clay layer gallery; and oligomers may form due to incomplete polymerization(32).

Melt intercalation: This method does not require a solvent and consists of layered silicate in a molten state. By employing conventional techniques like injection moulding or extrusion, the thermoplastic polymer is mechanically blended with organophilic clay at elevated temperatures(33).During this phase, polymer chains are exfoliated, resulting in the formation of nanocomposites. This approach is particularly useful for preparing thermoplastic nanocomposites. If in-situ polymerization fails or the polymers are unsuitable, this technique can be utilized. A limitation of this method is its restricted application to polyolefin, which represent the majority of polymers used(19).

Template synthesis (sol-gel technology): This technique involves synthesizing clay minerals within the polymer matrix by using an aqueous or gel solution containing the polymer and silicate building blocks. During the process, nucleation takes place, enabling the polymer to facilitate the growth of inorganic host crystals while they are confined within the layers.

In theory, the sol-gel technique can promote the dispersion of silicate layers in a single-step process, without the presence of the onium ion, but it has several disadvantages. Firstly, the synthesis of clay minerals necessitates high temperatures, which may lead to polymer decomposition. Additionally, there is a tendency for aggregation during silicate growth. The sol-gel technique is often employed for synthesizing double-layer hydroxide-based nanocomposites but is considerably less versatile for layered silicates(34).

Table 3. Overview of polymer nanocomposites method

Method	**Application**	**Advantage**	**Disadvantage**
In-situ intercalative polymerization	Manufacturing of thermoplastics and nylon–montmorillonite nanocomposite.	Linking is enabled by the tethering effect.	Reaction rate is slow; clay exfoliation is dependent.
Melt intercalation	Manufacturing of nanocomposites made of thermoplastic	In-situ polymerisation substitution technique	Polyolefin applicability is limited.
Template synthesis (Sol-gel technology	Creation of nanocomposites based on double-layer hydroxide	In a single step, encourage the silicate layers to disperse.	High temperatures are necessary for the synthesis of clay minerals, which leads to polymer breakdown and an aggregation propensity during silicate growth.

Types of Pharmaceutical formulation including Nanocomposite:

Nanocomposite Hydrogel:

Hydrogels are natural or synthetic polymer chains that are linked to one another by cross-linkers, forming a hydrophilic material with a gel-like macro-molecular structure. They can absorb several times their weight when dry and may contain as much as 99% water or biological fluids(35). This three-dimensional (3D) highly hydrated porous structure can replicate the natural tissue microenvironment, and they are typically designed to hold, release, or capture materials(35,36). There are two categories of hydrogels based on their production methods:

chemical (thermosetting) gels and physical (thermoplastic) gels. Chemical gels are cross-linked covalently through various methods, such as polymerization in the presence of a cross-linker or linking an existing polymer via methods like heating, ultrasound, UV, or γ-irradiation, among others. Physical gels are amorphous networks of hydrophilic polymers bonded together by noncovalent interactions, such as Van der Waals forces and hydrogen bonding. Chemical gels swell but do not dissolve in water, while physical gels eventually dissolve in water and can be melted with heat (3). When choosing materials for hydrogel preparation, key properties should be assessed, including swelling, mechanical properties, diffusion rates, and chemical functionality. These properties are influenced by the cross-linking density, distance between cross-links, macro-molecular structures in the gel, and residual chemicals (monomers, initiators, etc.)(37). A notable limitation of hydrogels is their low mechanical strength (32), particularly when applied as tissue engineering scaffolds or in situations that require high mechanical strength, along with good compression tolerance and elasticity (e.g., cartilage tissues).Their low mechanical characteristics complicate handling and loading in different body areas. Recent strategies are focusing on enhancing the mechanical and chemical properties of hydrogels for targeted biomedical applications. The high surface-to-volume and aspect ratios of nanoparticles and nano-layers make them suitable for integration within polymeric material networks(37). The physical/chemical crosslinking of polymeric chains with various nano-scaled structures forms a network with distinct new properties, referred to as nanocomposite hydrogels(35,36). New properties and behaviours emerge following the nanoscale dispersion of fillers in the composite. This dispersion can also enhance certain properties already present in the unfilled matrices(35,38). Different types of nanomaterials are utilized to create nanocomposite hydrogels. Examples of these nanomaterials include carbon-based nanomaterials (carbon nanotubes or CNTs, graphene, nanodiamonds), polymeric nanoparticles (dendrimers and hyper-branched polymers), inorganic/ceramic nanoparticles (hydroxyapatite, silicates, and calcium phosphate), and metal/metal oxide nanoparticles (gold, silver, and iron oxides) (36). This integration introduces unique properties into hydrogels, including the following (36): – Responsiveness to stimuli such as radiation, temperature, and electric or magnetic fields. Stimuli can trigger swelling, water expulsion, absorption, and the release of contents encapsulated within the network. Smaller hydrogels exhibit faster responses(39). These characteristic positions hydrogel as promising candidates for drug/gene delivery systems and bio devices/biosensors. Enhanced mechanical toughness, resulting from increased polymer network entanglements due to nanoparticle incorporation. Nanoparticles serve as bridges between the polymer chains

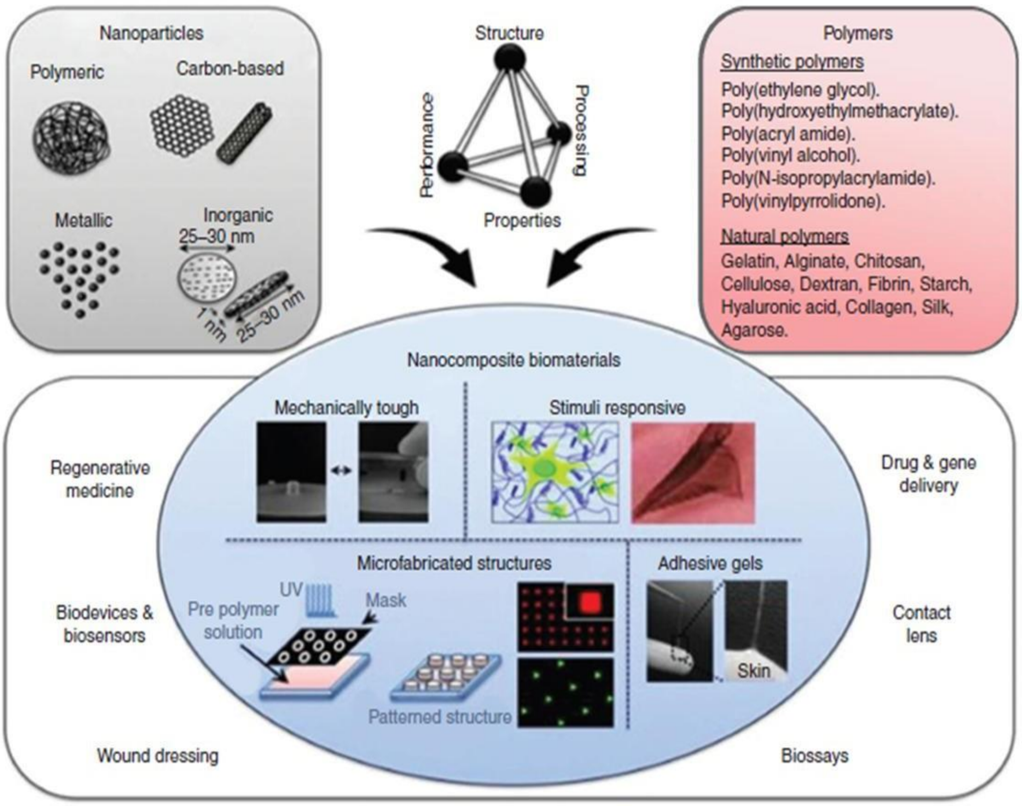

Figure 1: The nanocomposite hydrogels for biomedical applications (36)

The optimized mechanical strength is an essential characteristic for biomaterials utilized in regenerative medicine, wound dressings, and contact lenses.

Adhesion to surfaces, particularly skin or soft tissues, positions hydrogels as a viable option for wound dressing materials, facilitating easy application and removal on the body surface. This adhesion results from the surface roughness of nanocomposites achieved by incorporating nanoparticles into the network, allowing for interlocking with the irregularities of the target surface. The capability to create micro fabricated structures represents a physical approach to manufacturing entities with Nano/micro scale components. Cells are primarily cultured on 2D surfaces. These traditional culture conditions significantly contrast with the natural 3D tissue environment, potentially leading to abnormal cell behaviour. Therefore, it is crucial to develop 3D cell culture systems that can replicate native tissue conditions. This necessitates the creation of cell-friendly biomaterials using microfabrication techniques. In the development of nanocomposites, the challenge lies in how to construct macroscopic components that leverage the distinctive physical and mechanical properties of the nanoscale entities contained within them. (37).

- **Carbon-based nanocomposite hydrogels:** Carbon-based nanomaterials, such as carbon nanotubes (CNTs), graphene, fullerene (C60), and nanodiamonds, hold promise for applications in biomedicine. Notably, CNTs and graphene are frequently employed due to their excellent electrical conductivity, mechanical strength, and optical properties. CNTs are hollow cylindrical structures made of carbon (graphite) characterized by a high aspect ratio (∼1000) and sp2 hybridization. Ideal (defect-free) CNTs differ from graphite in having very few or no chemically active dangling bonds. A characteristic of CNTs is the presence of varied specific distances attributed to the Van der Waals forces. CNT pores are easily accessible to ions of various sizes and charges. The charging mechanism is described by the equation below. $C{=}O + H^+ + e^-$ COH (1) With these properties, carbon-based nanomaterials are suitable candidates for developing electrically conductive tissues, such as nerve, muscle, and cardiac tissues. The rigidity of CNTs is due to the strength of the C-C bonds within individual shells. Additionally, CNTs can serve as a nanoscale heat sink, preventing the composite material from overheating and subsequent destruction. The optical properties of CNTs are significantly influenced by the symmetry, the presence or absence of caps (CNT ends), and the number of constituent carbon atoms(40).

- **Polymer-based nanocomposite hydrogels:** Dendrimers or hyperbranched polymers, liposomes, polymeric micelles, nanogels, and core-shell polymeric particles are examples of nanoparticles that can encapsulate hydrophobic or hydrophilic drugs, proteins, genes, and other bioactive substances. These hybrid hydrogels have attracted interest in the pharmaceutical and biomedical fields due to their ability to release drugs in a controlled manner. This capability arises from the stimuli-responsiveness of these polymeric nanoparticles. Stimuli-responsiveness refers to a significant alteration in properties in response to minor changes in environmental conditions such as temperature, light, concentration, or pH. Ionizable polymers with a pKa value ranging from 3 to 10 are suitable for pH-responsive systems. Weak acids and bases such as carboxylic acids, phosphoric acids, and amines, respectively, show a change in ionization state when pH varies. This results in a conformational change in the swelling behavior of the hydrogels when these ionizable groups are connected to the polymer structure.(41).

Nanocomposite Films:

Nanocomposite films are sophisticated materials made up of two or more phases, with at least one having dimensions in the nanometer range (1-100 nm). These films integrate characteristics from their components to provide improved mechanical, thermal, electrical, or optical properties. The nano-scale structure fosters distinctive interfacial interactions and high surface-to-volume ratios, rendering these materials adaptable for various sectors, including healthcare, electronics, and environmental protection(42).

Types of Nanocomposite Films:

1. **Polymer Matrix Nanocomposites (PMNCs):** These consist of a polymer base containing embedded nanoparticles such as clay, carbon nanotubes, or metallic oxides. They are lightweight, flexible, and applicable in packaging, biomedical devices, and electronic component(40).

2. **Ceramic Matrix Nanocomposites:** Built on a ceramic base, these films incorporate nanoscale reinforcements like silicon carbide or zirconia. They are suitable for uses that necessitate high-temperature resistance and mechanical strength, such as in aerospace and thermal barriers (43).
3. **Metal Matrix Nanocomposites:** These films are metal-based and include nanocrystals or particles like titanium carbide or aluminium oxide. They are frequently utilized in wear-resistant coatings, cutting tools, and magnetic storage devices (44).
4. **Hybrid Nanocomposites:** These combine organic and inorganic elements, resulting in multifunctional films. Examples include graphene-oxide-polymer composites, which improve electrical conductivity and mechanical properties(44).

Synthesis Techniques: Various methods exist to produce nanocomposite films, including: (45)

a. **Solution Casting**: Involves dissolving the polymer and filler in a solvent, followed by evaporation to create a film
b. **Layer-by-Layer Assembly**: Involves the alternating deposition of polymer and filler layers to achieve accurate control over film thickness.
c. **In Situ Polymerization**: Nanoparticles are dispersed in a monomer solution before polymerization occurs.
d. **Physical Vapour Deposition (PVD)** and **Chemical Vapor Deposition (CVD)**: Common methods for ceramic and metallic nanocomposites.

Applications of Nanocomposite Films(46–48)**:**

1. **Healthcare and Biomedical Applications:**

   - Utilized in drug delivery systems due to their biocompatibility and ability to regulate release rates.
   - Antimicrobial coatings for medical devices and implants help to minimize infection risks.
   - Biosensors for diagnostics benefit from their high sensitivity and specificity.

2. **Electronics and Optoelectronics:**

   - Nanocomposite films are essential for flexible electronic displays, solar cells, and LEDs due to their improved electrical conductivity and transparency.
   - They are also utilized in microelectronic components, where miniaturization and high performance are critical.

3. **Environmental Applications:**

   - Employed in water purification membranes, they provide high selectivity and durability for contaminant filtration.
   - Coatings for corrosion resistance in industrial settings lower maintenance costs and prolong equipment lifespans.

4. **Energy Storage and Conversion:**

   - In lithium-ion batteries and super capacitors, nanocomposite films enhance energy density and cycling stability.
   - Thermoelectric materials efficiently convert waste heat into electricity.

5. **Packaging Industry:**

   - The barrier properties of polymer nanocomposite films extend the shelf life of food products by preventing moisture and oxygen penetration.
   - They are also utilized in biodegradable and sustainable packaging solutions.

6. **Aerospace and Automotive:**

   - High-strength, lightweight nanocomposites enhance fuel efficiency and structural integrity in vehicles and aircraft.
   - Their thermal stability makes them appropriate for high-temperature applications like jet engines.

7. **Tribology:**

   - Nanocomposite coatings diminish friction and wear, increasing the longevity of mechanical components such as gears and bearings.

Future Prospects: Progress in nanotechnology is broadening the possibilities of nanocomposite films. New synthesis methods, including atomic layer deposition and sol-gel processes, are facilitating the creation of materials with customized features for upcoming applications such as quantum computing, neural interfaces, and environmental sensors.

Nanocomposite Nanotubes:

Before discussing the different aspects of nanotube/polymer composite systems, we first present carbon nanotubes. There are various types of nanotubes, which differ significantly based on the methods employed in their synthesis. This section offers a brief summary of nanotubes, their origins, and some key properties essential for understanding nanotube/polymer composites (49). Carbon nanotubes are elongated cylinders composed of covalently bonded carbon atoms. The ends of these cylinders may be capped with hemi fullerenes or left exposed. The two main categories of CNT are single-wall carbon nanotubes (SWNT) and multi-wall carbon nanotubes (MWNT). SWNT can be viewed as a single graphene sheet (graphene being a monolayer of sp2-bonded carbon atoms) rolled into a continuous cylinder. The carbon atoms within the cylinder exhibit partial sp3 character, which increases as the cylinder's radius of curvature decreases (50). MWNT consist of nested graphene cylinders arranged concentrically around a central hollow core, with interlayer spacing’s of approximately 0. 34 nm, representing the inter-plane distance of graphite (51). A specific type of MWNT is the double-wall nanotubes (DWNT), which are made up of two concentric graphene cylinders. DWNT are anticipated to demonstrate greater flexural modulus than SWNT due to the presence of two walls and enhanced toughness compared to typical MWNT due to their reduced size (52). The nanotubes can be filled with foreign elements or compounds, such as C60 molecules, creating hybrid nanomaterials with distinctive intrinsic properties, including transport properties (52). While these hybrid nanomaterials are currently in limited supply, increasing production may present a new opportunity for polymer nanocomposites. The different methods for rolling graphene into tubes are characterized by tube chirality (or helicity or wrapping), as defined by the circumferential vector, CBh) nab1 + mab2, where the integers (n, m) represent the number of steps along the unit vectors (ab1 and ab2) of the hexagonal lattice (53). Using this (n, m) nomenclature, the three types of orientation of the carbon atoms around the nanotube circumference are classified as armchair (n) m), zigzag (n) 0 or m) 0), or chiral (all other configurations). The chirality of nanotubes significantly influences their transport characteristics, particularly their electronic properties. All armchair SWNT are metallic with a band gap of 0 eV. SWNT with n - m) 3i (where i is an integer and 0) are semi-metallic, exhibiting a band gap on the order of a few meV, while SWNT with n - m 3i are semiconductors with a band gap of approximately 0.5-1 eV (54). Each MWNT encompasses various tube chiralities, resulting in more complex predictions of their physical properties. Currently, MWNT and SWNT are predominantly produced using three methods, each with its unique characteristics: arc discharge, laser ablation, and chemical vapour deposition (CVD). Several reviews (51,53) are available on these production methods. Arc discharge and laser ablation techniques involve the condensation of hot gaseous carbon atoms generated from solid carbon evaporation. In CVD, a gaseous carbon source (hydrocarbon, CO) is catalytically decomposed, leading to the deposition of nanotubes on a substrate or their growth from a substrate. Compared to with arc and laser methods, CVD may provide greater control over the length and structure of the generated nanotubes, and the process seems scalable for industrial production. Indeed, Hyperion Catalysis International Inc. manufactures MWNT (trade name FIBRIL nanotubes) utilizing a CVD technique. Carbon Nanotechnology Inc. (Houston, TX) produces SWNT using a floating catalyst CVD method known as high-pressure catalytic decomposition of carbon monoxide or HiPco (55).As previously noted, currently, all established methods of CNT preparation yield mixtures of nanotube chirality, diameters, and lengths along with various quantities and types of impurities. This heterogeneity in CNT has significant consequences for the purification of carbon nanotubes and the fabrication of nanotube/polymer composites. For instance, smaller diameter SWNT are more vulnerable to both thermal degradation and chemical functionalization, thus the diameter distribution may change between SWNT synthesis and nanotube/polymer composite production. A typical average diameter for SWNT is about 1. 2-1. 4 nm, and the minimum diameter of a stable free-standing SWNT is constrained by curvature-induced strain to approximately 0. 4 nm. 18 The variation in SWNT diameter is also demonstrated by the presence of different wrap configurations (n, m), where the circumferential vectors are utilized to determine the nanotube diameters. MWNT can have diameters ranging from several nanometres to several hundred nanometers. The reported lengths of nanotubes vary from several tens of nanometers to several centimeters.19 The properties of nanotube/polymer composites will differ considerably based on the distribution of the type, diameter, and length of the nanotubes.

Synthesis Methods(56–58)**:**

- **Ex-Situ Methods**

  Nanotubes are produced separately and then added to the matrix. Techniques such as high-energy ball milling or solvent mixing are used for consistent dispersion..

- **In-Situ Polymerization**

  Nanotubes are synthesized directly within the matrix, resulting in improved integration and enhanced properties..

- **Sol-Gel Processes**

  This method entails creating a colloidal solution that develops into a gel, embedding nanotubes during synthesis for ceramic or polymer-based nanocomposites.

- **Electrochemical Deposition**

  This method is used to deposit nanotube layers within a matrix, frequently applied in sensor manufacturing.

Nanotube suspension:

A genuine solvent for pure nanotubes has not yet been identified.

The high aspect ratio of the nanotubes, together with a strong natural van der Waals attraction among them, results in the formation of ropes and bundles of carbon nanotubes (CNT), especially in single-walled nanotubes (SWNT), where the attractive force is -0.5 eV per nanometre of contact between nanotubes (54). Ropes are clusters of SWNT that possess a uniform diameter, allowing them to create a hexagonal lattice, while bundles consist of monocrystalline groups of SWNT or multi-walled nanotubes (MWNT). Through the process of ultra-sonication, nanotubes can be moderately dispersed in specific solvents, such as dimethyl formamide and dichlorobenzene, resulting in nanotube suspensions. Comprehending nanotube suspensions is crucial for managing various solvent-based procedures (phase separation, chemical privatization, etc.) linked to the preparation of nanotube/polymer composites since the initial nanotube dispersion can affect the nanotube distribution within the polymer matrix. Three key questions arise concerning nanotube suspensions.

What is the size distribution of suspended nanotube objects?

This is essential, as isolated tubes enable significant chemical derivatization in suspension and present the largest interfacial area for stress transfer to the polymer matrices. Considering the variability in diameters and lengths, size characterization is most effectively performed using an imaging technique, specifically atomic force microscopy (AFM) (55,59). If it is assumed that the objects on the substrate accurately reflect the suspension, a detailed analysis of diameter (inferred from height), length, and aspect ratio can be performed.

Secondly, to what degree do the nanotubes (isolated, ropes, bundles) exhibit behaviour akin to rigid rods while suspended?

When CNT behaves as rigid rods, various rigid-rod theories can be applied to assess the physical properties of nanotube suspensions and nanotube/polymer composites(60).

This inquiry can be conveniently addressed using scattering methods (61–63), though some researchers have found success employing rheological (64) characterizations. A limited number of studies have utilized small-angle X-ray, neutron, or light scattering with wave vectors Q in the range of 10-3-100 nm-1 (corresponding to length scales of 1-1000 nm) to examine the structures of nanotubes in suspension. A suspension of isolated rigid rods with diameter D and length L demonstrates a scattering intensity that changes according to Q-1 for wave vectors $2\pi/L < Q < 2\pi/D$. With typical nanotube aspect ratios exceeding 100 and SWNT diameters approximating -1 nm, the criteria for isolated rigid rods with good dispersion require a very low nanotube concentration and consequently low scattering intensities from nanotube suspensions, presenting a significant challenge. Using small angle neutron scattering and a dilute suspension of SWNT (0.01-0. 1 wt. %) in water combined with the surfactant sodium dodecyl benzene sulfonate (NaDDBS), In the range $0.003 < Q < 0.02$ Å-1, Zhou et al. (65) observed that the scattered intensity decreased with Q-1, which is consistent with an isolated rigid-rod behaviour in these suspensions. The scattered intensity, on the other hand, followed a power law dependence with exponents in the range of -2 to -3 over the whole range of Q when the aforementioned suspensions were made with Triton X-100, a surfactant with a less effective ability to disperse nanotubes, indicating some kind of network of ropes (65). According to Wang et al., the exponent of Q can be used as a semi-quantitative indicator of the degree of dispersion in nanotube suspensions; higher dispersion is indicated by exponents near -1. The reported persistence length that causes the -1 dependence may be minimal in relation to the nanotube length, which is a warning for these scattering techniques. Thirdly, how do the suspensions of nanotubes change throughout time? The handling of nanotube suspensions during processing and in applications is influenced by their stability. Although few have been employed, nanotube suspensions can be tracked throughout time using the experimental techniques mentioned above to examine size and stiffness. Overall, research on nanotube dispersions is still ongoing, with an emphasis on evaluating the stiffness, stability, and size distribution of suspended nanotube objects (59).

Challenges and Future Directions

Despite the enormous potential of nanocomposite nanotubes, issues such as agglomeration of nanotubes, production scalability, and expensive costs prevent their widespread use. To solve these problems, cost-effective synthesis methods and improvements in dispersion techniques are essential. It is anticipated that future studies would concentrate on multifunctional composites, incorporating characteristics like environmental responsiveness and self-healing. Nanocomposite nanotubes have the potential to transform industries by utilising their exceptional qualities to provide inventive, efficient, and sustainable solutions.(30)

Nanocomposite Emulsion: Nanocomposite Synthesis

To incorporate nanomaterials into polymer matrices, various techniques can be employed depending on the characteristics of the nanomaterial and polymer matrix. These techniques typically include template synthesis, melt compounding, in situ polymerization, and mixing (blending) (66–69). In the template synthesis method, which predominantly involves inorganic nanoparticles, the nanomaterials are produced concurrently with the polymer matrix. This simultaneous synthesis helps minimize nanoparticle aggregation. However, this approach is constrained by the high temperatures often required for nanoparticle manufacturing (>130 °C) (70). The melt compounding method is frequently utilized in commercial nanocomposite production (67). Here, the polymer is heated to a high temperature and subsequently combined with nanoparticles under shear stress. It is essential to select the right temperature to achieve an optimum viscosity for the polymer melt, enabling it to endure the shear forces from the compounding process while also preventing degradation of both the polymer and nanoparticles during synthesis (67,69). In situ polymerization differs from the template synthesis method in that the nanoparticles are prepared beforehand (67–69). Polymerization techniques such as dispersion, suspension, emulsion, miniemulsion, and Pickering emulsion are employed. In this approach, the polymerization of monomers takes place in the presence of the nanomaterial.

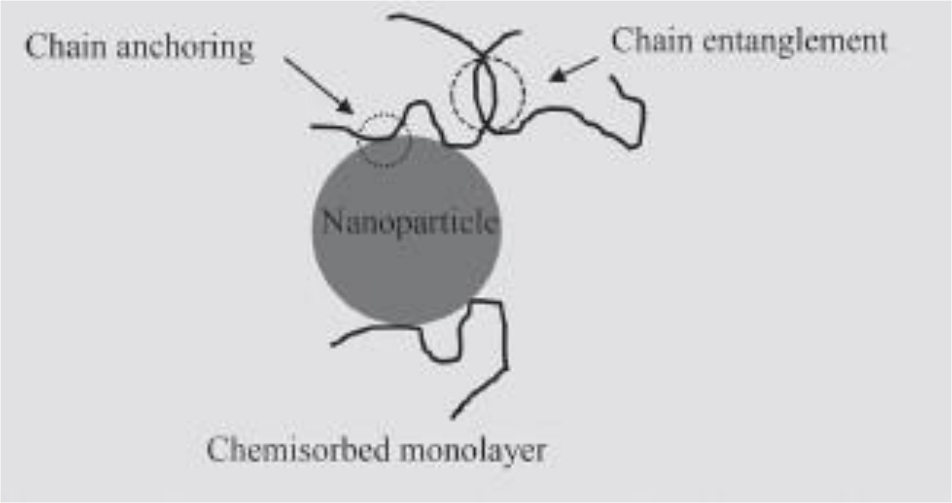

Fig. 2 Schematic of the interphase region between a nanoparticle and polymer matrix(71)

Except for the dispersion polymerization technique, which employs a solvent as the reaction medium, the other polymerization methods are water-based and tend to be less hazardous (66–69). Lastly, the mixing or blending technique entails combining pre-prepared polymers and nanomaterials (66–68). In some situations, the polymer may be in a suspended latex form (i.e., a colloidal dispersion of polymer particles in water) or dissolved in a solvent (i.e., aqueous or non-aqueous based on the polymer's solubility).The blending method generally involves low-shear mixing; however, in certain cases, high-shear mixing or sonication may be necessary to enhance the dispersion of nanomaterials within the polymer matrix (72). Additional details on the water-based latex process are outlined below. Uniformly dispersing nanoparticles in a liquid medium and maintaining their dispersed state in the final product is vital in nanocomposite synthesis since the unique properties of nanoparticles are conveyed only in their dispersed form (30). Insufficient dispersion can cause nanoparticles to aggregate into soft or hard clumps, depending on the synthesis conditions and surface chemistry (73). This aggregation effectively increases the size of the nanomaterial and diminishes its specific surface area. Consequently, this leads to a reduced interfacial area between the nanoparticles and polymer matrix, preventing the anticipated performance from being realized. Generally, interparticle interactions are influenced primarily by factors such as particle surface chemistry, shape, aspect ratio, interparticle distance, and polydispersity (74). In a nanocomposite polymer matrix, the development of a robust interphase layer between the nanoparticles and the bulk polymer matrix significantly enhances mechanical properties, given that the structure and characteristics of the interphase layer differ from those of its components (75–77). The interphase structure is composed of flexible polymer chains, typically arranged in sequences of adsorbed segments (such as contact points, anchors) on the surface of the nanoparticle. and unadsorbed segments (loops and tails) that become intertwined with neighbouring chains (77). The unique characteristics of the interphase govern the load transfer between the polymer matrix and the nanoparticles (75–77). It is believed that at the percolation threshold, strong interactions among the surfaces of the nanoparticles can create a rigid network within the polymer matrix. A minimum amount of nanofiller is necessary to establish a cluster that spans the polymer matrix (71). However, a more flexible network may form if the nanoparticles are connected through their surface interactions with the polymer chains (78). The percolation threshold is influenced by the shape of the nanoparticles and their dispersion traits. Nanoparticles with high aspect ratios, like CNTs, cellulose nanofibers, and CNCs, demonstrate significantly lower percolation thresholds compared to spherical nanoparticles. Consequently, adding threshold amounts of these nanoparticles can significantly improve the electrical conductivity and/or mechanical properties of polymer nanocomposites(78).

Surface Modification

Various surface modification methods can be utilized to enhance the compatibility of nanoparticles and the polymer matrix while largely preserving the bulk material properties (79). Surfaces of materials (whether the nanoparticle, the polymer, or both) can be altered and optimized using physical interactions, molecule adsorption onto their surface (e.g. , surfactants), or through chemical treatments(80). The chemical approach entails the covalent attachment of polymer (or oligomer) chains or small molecules (e.g., acetyl groups, amine groups) to the nanoparticle surface. This chemical surface modification, known as surface grafting, includes two distinct phases: surface activation followed by grafting. There are two primary grafting techniques: grafting-from (surface-initiated polymerization) and grafting-to .(65)

Grafting-From Technique

In the grafting-from technique, an initiator catalyzes the polymerization of monomers through the nanoparticle surface. In certain situations, it is advantageous to fix an initiator on the nanoparticle surface before commencing the polymerization (45,79). Initiators such as azo-bis-isobutyronitrile and phenyl pyrenyl methyl groups can be secured onto surfaces, followed by radicals created by oxidizing agents ,(81) ozone, and energy supplies (e.g. , heat, UV light) (82,83). Various in situ surface-initiated polymerization processes can be utilized, including radical, controlled radical, carbocation, anionic, and ring-opening polymerization (84). The primary benefit of the grafting-from technique is achieving high grafting densities on surfaces. Since chain length and density significantly influence the surface chemistry of the grafted polymer, efforts have been made to enhance the control over graft density and chain length (84). For instance, in the atom transfer radical polymerization grafting-from technique, the graft density can be regulated by incorporating “dummy initiators” that have the same anchoring groups as the initiator but do not initiate polymerization(85,86). The chain length can be regulated by modifying the termination rate in polymerization through sacrificial initiator molecules (84,86).

Grafting-To Method

In the grafting-to method, a polymer with terminal functionalities is synthesized and then adsorbed onto a substrate to create a chemical bond (i.e. , chemisorption). Various polymerization methods can be utilized to produce end functionalized polymers (87–89). In this approach, the produced polymers can be analyzed before grafting, while characterization is more complicated in the grafting-from method. Nevertheless, grafting-to methods have limitations regarding low grafting densities due to the steric hindrance caused by the grafted chains. In the grafting-to approach, high graft chain density can be achieved using self-assembled monolayers (SAMs) (90,91). SAMs can spontaneously create ordered molecular structures on a substrate. They are made up of three main elements: the head group, the functional group, and the assembling structure. The head group must have a strong attraction to the graphable substrate. For example, head groups with silanes are suitable for polymer and alumina substrates. Head groups containing alcohols are applied to iron oxide and silicon substrates. While the surface modification techniques mentioned earlier are beneficial for designing interfaces with control over graft density and chain length, determining which interface structures are most effective for achieving specific composite properties remains a challenge (76).

Nanocomposite Injectable:

Nanocomposite injectable formulations are a sophisticated type of materials intended to improve therapeutic results in medical settings. By combining nanoparticles with polymeric, ceramic, or metallic matrices, these formulations utilize the mechanical, chemical, and biological properties of their components (92,93). Their injectable form allows for minimally invasive administration, making them particularly appealing for use in drug delivery, tissue engineering, and regenerative medicine(94).

Method of preparation(95,96):

1. **In Situ Polymerization**: This technique mixes nanoparticles with monomers or pre-polymers that undergo polymerization after injection, enabling the material to solidify or gel at the site of interest.

2. **Sol-Gel Process**: A chemical procedure that transforms a solution into a solid gel phase to create nanocomposites. This approach is often employed in ceramic-based systems.

3. **Electrospinning and Electrostatic Assembly**: These techniques are utilized to produce nanofiber-reinforced composites, allowing for control over the distribution and orientation of nanoparticles.

4. **Shear Mixing and Sonication**: These physical techniques ensure a uniform distribution of nanoparticles within the matrix.

5. **3D Bioprinting**: An innovative method that prints nanocomposite formulations into precise geometries for tissue engineering.

Application(97–99):

1. Drug delivery:

   Nanocomposite injectable formulations are commonly utilized for localized and sustained drug delivery. Their capability to encapsulate therapeutic agents, safeguard them from degradation, and release them in a regulated manner makes them optimal for:

   - **Cancer Therapy**: Nanoparticles such as liposomes or mesoporous silica can be loaded with chemotherapeutic agents for targeted delivery.
   - **Antibiotic Delivery**: Silver nanoparticles embedded in hydrogels can offer antimicrobial properties for wound healing.

2. Tissue engineering:

   In regenerative medicine, nanocomposite injectable formulations serve as scaffolds that facilitate cell growth and tissue regeneration. Examples include:

   - **Bone Repair**: Calcium phosphate nanocomposites can replicate the mineral composition of bone.
   - **Cartilage Regeneration**: Injectable hydrogels infused with graphene oxide enhance mechanical traits and support chondrocyte development.

3. Immunomodulation:

   Nanocomposite formulations can convey immunomodulatory agents or function as adjuvants in vaccines. For example, polymeric nanoparticles can improve the delivery of antigens to dendritic cells.

4. Pain management:

   Formulations that provide controlled release of analgesics such as lidocaine can offer extended pain relief without the need for repeated doses.

5. Diagnostics application:

   Metallic nanoparticles, including gold or iron oxide, integrated into injectable matrices can act as contrast agents for imaging methods such as MRI or CT scans.

Advantages(100,101)**:**

1. **Minimally Invasive Delivery**: Injectable formulations decrease surgical complications and enhance patient adherence.
2. **Controlled Release**: The inclusion of nanoparticles enables a customizable release of drugs or growth factors.
3. **Enhanced Mechanical Properties**: Nanoparticles can strengthen the matrix, making it appropriate for load-bearing situations.
4. **Customizability**: The surface modification of nanoparticles and matrix materials permits adaptation to specific applications.

Challenges(102,103)*:*

1. **Stability Issues**: It can be difficult to maintain a consistent dispersion of nanoparticles within the matrix.
2. **Biocompatibility**: The risk of cytotoxicity or immunogenicity requires comprehensive assessment.
3. **Scalability**: Manufacturing techniques need to be optimized for large-scale production.

4. **Regulatory Hurdles**: Guaranteeing safety and efficacy while adhering to regulatory requirements can be a prolonged process.

Future approach(104–106):

The field of nanocomposite injectable formulations is progressing swiftly, with research concentrating on:

1. **Smart Materials**: Formulations responsive to stimuli such as pH, temperature, or magnetic fields.
2. **Personalized Medicine**: Customizing solutions for each patient through 3D bio printing and precision medicine techniques.
3. **Advanced Imaging**: Merging diagnostic and treatment functions in theranostic products.
4. **Sustainable Manufacturing**: Creating environmentally friendly and economical production processes.

Nanocomposite Gel:

Nanocomposite gels represent an intriguing blend of nanotechnology and material science, providing diverse applications in areas including biomedicine, electronics, and environmental science. These materials are created by incorporating nanoparticles or nanostructures into a gel matrix, leading to distinct combinations of mechanical, chemical, and physical properties. This document offers a comprehensive examination of nanocomposite gel formulation, detailing its components, synthesis methods, characterization, and applications(107).

Components of Nanocomposite Gels:

The formulation of a nanocomposite gel includes two main components:

Gel Matrix:

The gel matrix acts as the continuous phase, offering the structural foundation that contains the nanomaterials. Common types of gel matrices consist of (108,109):

- **Polymeric Gels**: Made of cross-linked polymer networks that can hold considerable amounts of solvent. Examples include polyacrylamide, polyethylene glycol (PEG), and natural polymers like alginate and gelatin.
- **Hydrogels**: These hydrophilic polymeric gels can absorb large quantities of water while keeping their structure intact. Hydrogels are frequently employed in biomedical applications.
- **Organogels:** Created using low molecular weight organogelators or polymers in organic solvents.
- **Composite Gels**: Combinations of natural and synthetic polymers, enhancing particular properties such as biocompatibility or mechanical strength.

Nanomaterials:

Nanomaterials serve as the dispersed phase in nanocomposite gels and are key to the improved properties of the final product. Types of nanomaterials include (110–112):

- **Metal Nanoparticles**: Such as gold, silver, and platinum, which provide antibacterial, catalytic, and optical properties.
- **Carbon-Based Nanostructures**: Including graphene, carbon nanotubes (CNTs), and fullerenes, prized for their electrical conductivity and mechanical strength.
- **Ceramic Nanoparticles**: Such as silica, titanium dioxide, and alumina, contributing thermal stability and chemical resistance.
- **Quantum Dots**: Semiconductor nanocrystals that display unique optical properties such as photoluminescence.
- **Magnetic Nanoparticles**: For example, iron oxide nanoparticles are utilized in targeted drug delivery and magnetic resonance imaging (MRI).

- **Biomimetic Nanomaterials:** Such as hydroxyapatite, which imitates natural bone tissue.

Synthesis Technique:

The synthesis of nanocomposite gels involves merging the gel matrix and nanomaterials through methods that guarantee uniform distribution and strong interactions between components. Key techniques include(58,113–115):

In situ Polymerization:

Nanomaterials are dispersed in a monomer solution, followed by polymerization to create the gel matrix. This approach ensures homogenous dispersion and robust interfacial bonding. Examples comprise free-radical polymerization and sol-gel processes.

Physical mixing:

Nanoparticles are physically blended with a pre-existing gel. Although straightforward, achieving uniform dispersion can be difficult and may necessitate sonication or surfactants.

Chemical Grafting:

Nanomaterials undergo chemical modification to attach polymer chains onto their surfaces. This improves compatibility with the gel matrix and enhances mechanical properties.

Layer-by-Layer Assembly:

This technique entails the sequential deposition of alternating layers of nanomaterials and polymers to build the composite gel. It is particularly effective for constructing multi-layered or gradient structures.

Electrospinning and Electro spraying:

Electrospinning can fabricate Nano fibrous gels, while electro spraying disperses nanomaterials within the gel matrix. These methods are beneficial for producing high-surface-area materials.

Sol-Gel Process

A chemical synthesis technique where a colloidal solution (sol) is converted into a solid gel phase. It is widely used for integrating ceramic nanoparticles.

Characterization of Nanocomposite Gels:

Comprehensive characterization is essential for assessing the properties and performance of nanocomposite gels. Important characterization techniques include(116–119):

Morphological Analysis:

- **Scanning Electron Microscopy (SEM):** Analyzes surface morphology and nanoparticle distribution.
- **Transmission Electron Microscopy (TEM):** Offers high-resolution images of the internal structure and nanomaterial arrangement.
- **Atomic Force Microscopy (AFM):** Assesses surface roughness and topology.

Mechanical properties:

- **Rheology:** Evaluates viscoelastic characteristics, including storage and loss modulus.
- **Compression and Tensile Testing**: Measures mechanical strength and elasticity.

Thermal properties:

- **Differential Scanning Calorimetry (DSC):** Examines thermal transitions such as glass transition

temperature (Tg).
- **Thermogravimetric Analysis (TGA):** Evaluates thermal stability and degradation behaviour.

Chemical properties:

- **Fourier Transform Infrared Spectroscopy (FTIR**): Detects functional groups and chemical interactions.
- **X-ray Photoelectron Spectroscopy (XPS**): Studies surface chemistry and elemental composition.

Electrical and optical:

- **Conductivity Measurements**: Measures electrical conductivity for electronic applications.
- **UV-Vis Spectroscopy**: Investigates optical characteristics, including absorption and transmittance.
- **Photoluminescence Spectroscopy**: Assesses fluorescence or emission characteristics.

Swelling and porosity:

- **Swelling Ratio:** Evaluates the gel's capacity to absorb solvents.
- **Porosity Analysis:** Measures pore size and distribution, using techniques like mercury intrusion porosimetry or Brunauer-Emmett-Teller (BET) analysis.

Applications:

Nanocomposite gels are utilized in various fields, taking advantage of their distinct characteristics (120–123):

Biomedical applications:

- **Drug Delivery:** Nanocomposite hydrogels facilitate controlled and targeted drug release through stimuli-responsive behaviour.
- **Tissue Engineering:** These gels act as scaffolds for cell proliferation and tissue regeneration due to their biocompatibility and mechanical strength.
- **Wound Healing:** Gels infused with silver nanoparticles demonstrate antimicrobial properties, accelerating healing.
- **Diagnostics:** Quantum dot-containing gels are used in bioimaging and biosensing.

Environmental applications:

- **Water Purification:** Gels with photocatalytic nanoparticles (e.g., TiO2) break down organic pollutants.
- **Oil Spill Clean-up:** Superabsorbent gels can capture significant amounts of oil.
- **Heavy Metal Removal:** Magnetic nanocomposite gels aid in the adsorption and elimination of toxic metals from water.

Energy application:

- **Super capacitors:** Nanocomposite gels containing conductive fillers (e.g., graphene) serve as electrolytes.
- **Solar Cells:** Improve light absorption and charge transportation in photovoltaic devices.
- **Batteries:** Function as solid electrolytes or separators in lithium-ion batteries.

Electronics and optoelectronics

- **Flexible Electronics:** Conductive gels support the creation of stretchable and wearable devices.
- **Sensors:** Applied in chemical, biological, and pressure sensors due to their sensitivity to external stimuli.

Industrial applications:

- **Coatings:** Nanocomposite gels are used as protective and functional coatings, providing corrosion

resistance and self-cleaning features.
- **Adhesives and Sealants:** Enhanced mechanical and thermal properties make them suitable for industrial applications.

Challenges(124–127)**:**

- **Uniform Dispersion:** Achieving a consistent nanoparticle distribution is a notable challenge.
- **Scalability:** Mass production of nanocomposite gels with uniform quality poses difficulties.
- **Cost:** Elevated production expenses hinder commercial feasibility.
- **Stability:** Improvement is needed for the long-term stability of nanocomposite gels in various environmental conditions.

Future Directions(128,129):

- **Green Synthesis:** Innovation of sustainable synthesis methods.
- **Advanced Functionalities:** Combining multifunctional nanomaterials for integrated applications.
- **Personalized Medicine:** Customized nanocomposite gels for patient-specific treatment requirements.
- **Artificial Intelligence (AI) Integration:** Applying AI for predictive modelling and optimization of gel attributes.

Nanocomposite Liposomes:

Nanocomposite liposomes represent an advanced and promising area in drug delivery systems, combining the advantages of liposomal carriers with nanocomposite materials to improve stability, drug loading, and controlled release. This document explores the detailed aspects of nanocomposite liposome formulation, including their structure, composition, preparation techniques, benefits, challenges, and possible applications in medicine and biotechnology (130). Liposomes are spherical vesicles made up of one or more phospholipid bilayers that encase an aqueous core. They are widely utilized in drug delivery due to their biocompatibility, capacity to encapsulate both hydrophilic and hydrophobic drugs, and potential for targeted delivery. Nonetheless, traditional liposomes often encounter challenges such as low stability, quick clearance from the bloodstream, and uncontrolled drug release. In contrast, nanocomposites are materials consisting of a matrix embedded with nanoparticles, which provide improved mechanical, thermal, and chemical attributes. By incorporating nanocomposite materials into liposomal systems, the resulting nanocomposite liposomes show enhanced features that address the limitations of conventional liposomes (131–133).

Structural and compositional features:

Nanocomposite liposomes generally include(134–137):

1. **Lipid Bilayers**: The main component, typically made of phospholipids like phosphatidylcholine, phosphatidylethanolamine, or synthetic lipids like DOTAP (1,2-dioleoyl-3-trimethylammonium-propane).

2. **Nanoparticle Core or Shell**: Incorporated or coated nanoparticles such as gold, silica, carbon nanotubes, or magnetic nanoparticles boost functionality.

3. **Encapsulated Drugs**: Therapeutic substances, including small molecules, proteins, nucleic acids, or imaging agents, are either contained within the aqueous core or integrated into the lipid bilayer.

4. **Surface Modifications**: Polyethylene glycol (PEG) and targeting ligands (e.g., antibodies, peptides) are commonly attached to the surface to enhance circulation time and allow for active targeting.

Preparation methods:

Various techniques are used to create nanocomposite liposomes, designed to achieve specific characteristics such as particle size, encapsulation efficiency, and surface properties (138–141):

1. **Thin-Film Hydration Method**:

- A combination of lipids is dissolved in an organic solvent and evaporated to create a thin film.
- The film is hydrated with an aqueous solution that contains the drug and nanoparticles.
- Following this, sonication or extrusion produces liposomes of the intended size.

2. **Solvent Injection Method**:

- Lipids dissolved in a water-miscible organic solvent are injected into an aqueous phase containing the nanoparticles and drug.
- Rapid solvent exchange prompts the self-assembly of liposomes.

3. **Reverse Phase Evaporation**:

- An emulsion is formed by blending lipids in an organic solvent with an aqueous drug solution.
- Evaporation of the organic phase generates unilamellar or multilamellar liposomes.

4. **Nanoparticle Embedding or Coating**:

- Nanoparticles are either embedded in the aqueous core, inserted into the lipid bilayer, or coated onto the liposome surface using methods such as electrostatic adsorption or chemical conjugation

5. **Microfluidic Approaches**:

- New technologies employ microfluidic devices to manage liposome formation at the nanoscale, ensuring consistent size distribution and reproducibility

Characteristics Feature(135,137,142,143)**:**

1. **Enhanced Stability**:

   Nanocomposite liposomes are resistant to aggregation and decay, prolonging shelf life and stability under physiological conditions.

2. **Controlled Drug Release**:

   Integration of nanoparticles allows for stimuli-responsive release provoked by pH, temperature, light, or magnetic fields.

3. **Improved Drug Loading**:

   The hybrid structure boosts the encapsulation efficiency for both hydrophilic and hydrophobic drugs.

4. **Targeting Capabilities**:

   Surface modifications with targeting moieties facilitate selective delivery to particular cells or tissues, thereby minimizing off-target effects.

5. **Multifunctionality**:

   These systems can concurrently deliver therapeutic agents and imaging agents for theranostic purposes.

Applications:

Nanocomposite liposomes have significant potential in various fields(144,145):

1. **Cancer Therapy**:
    - Encapsulating chemotherapeutics such as doxorubicin or paclitaxel in nanocomposite liposomes improves efficacy and reduces systemic toxicity.
    - Magnetic nanoparticles enable hyperthermia therapy alongside drug delivery.
2. **Gene Delivery**:
    - Nanocomposite liposomes safeguard nucleic acids like siRNA or DNA from enzymatic degradation and guarantee efficient cellular uptake.
3. **Antimicrobial Therapy**:
    - Loading antibiotics into nanocomposite liposomes enhances penetration into biofilms and decreases resistance development.
4. **Imaging and Diagnostics**:
    - Functionalized liposomes carrying imaging agents (e.g., quantum dots or gold nanoparticles) provide accurate diagnostics via MRI, CT, or fluorescence imaging.
5. **Vaccines**:
    - Liposomal formulations with adjuvants and antigen-loaded nanoparticles enhance immune responses and ensure prolonged antigen release.

Advantages over conventional system(146)**:**

- **Synergistic Properties**: Merging the biocompatibility of liposomes with the durability of nanocomposites improves overall functionality.
- **Reduced Toxicity**: Controlled release mechanisms diminish systemic side effects.
- **Versatility**: Nanocomposite liposomes can be customized for various applications and payloads.
- **Stimuli-Responsiveness**: Sensitivity to environmental factors allows for precise regulation of drug release.

Challenges(147,148)**:**

1. **Complex Manufacturing Processes**:

    Scaling up production while preserving consistency and quality poses a notable challenge.

2. **Cost**:

    The incorporation of nanoparticles and surface modifications raises formulation expenses.

3. **Regulatory Hurdles**:

    The intricacy of nanocomposite systems presents challenges for gaining regulatory approval.

4. **Stability Concerns**:

    Although nanocomposite liposomes enhance stability, specific formulations may still encounter problems such as leakage or fusion during storage.

5. **Potential Toxicity**:

    The long-term biocompatibility and clearance of incorporated nanoparticles require thorough examination.

Nanocomposite Nanoclays:

Nanocomposites have received considerable interest in materials science because of their improved mechanical, thermal, and barrier characteristics. Among different types of nanocomposites, those that include nanoclays are especially noteworthy for their cost-effectiveness, ease of processing, and diverse applications. This document offers a thorough analysis of nanocomposite nanoclay formulations, covering their structure, preparation, properties, and applications(7). Nanoclays are a category of naturally occurring or synthetically modified clays with nanometer-scale thickness and high aspect ratios. The common types of nanoclays include montmorillonite, kaolinite, hectorite, and saponite, with montmorillonite being the most frequently used in nanocomposite formulations(7).

The primary attributes of nanoclays include(149):

- **Layered Structure**: Nanoclays have a layered silicate structure with spaces between the layers that can accommodate ions or organic molecules.
- **Surface Modification**: Their surfaces can be treated with organic or inorganic compounds to enhance compatibility with various polymer matrices.
- **High Surface Area**: This attribute leads to excellent interaction with the matrix material, resulting in improved composite properties

Types of Nano clays:

Nanocomposites are categorized based on how well the nanoclays are dispersed in the polymer matrix (150):

- **Intercalated Nanocomposites**: In these composites, nanoclay layers are partially separated, with polymer chains inserted between them, leading to moderate enhancement of properties.
- **Exfoliated Nanocomposites**: Here, nanoclay layers are completely separated and evenly dispersed in the polymer matrix, resulting in superior mechanical, thermal, and barrier properties.
- **Phase-Separated Nanocomposites**: In these cases, nanoclays remain clustered, resulting in limited improvement in composite properties.

Surface modification:

Raw nanoclays typically need surface modification to achieve compatibility with hydrophobic polymer matrices. Surface treatments include ion exchange or grafting with organic compounds like quaternary ammonium salts (151). These adjustments enhance interfacial adhesion between the clay and polymer, allowing for better dispersion and improved properties.

Methods of preparation:

Several methods are utilized to create nanoclay-based nanocomposites(152,153):

a. Solution intercalation: In this approach, nanoclays are dispersed in an appropriate solvent, and the polymer is dissolved in the same solvent. The amalgamation of the two solutions enables polymer chains to intercalate between the nanoclay layers. After solvent evaporation, the nanocomposite is obtained.

b. Melt intercalation: This solvent-free technique involves blending nanoclays and polymers at elevated temperatures. The shear forces resulting from mixing facilitate the dispersion of nanoclays throughout the polymer matrix.

c. In situ polymerization: Nanoclays are mixed with monomers, followed by polymerization triggered by heat, radiation, or catalysts. This method guarantees uniform dispersion of nanoclays and robust interfacial bonding.

d. Sol-gel processing: This technique entails the hydrolysis and condensation of alkoxide precursors in the presence of nanoclays, resulting in a hybrid organic-inorganic nanocomposite.

Properties of nanoclay based Nanocomposite:

The addition of nanoclays provides a variety of enhanced properties to the polymer matrix (146,154,155):

i. Mechanical properties: Nanoclay nanocomposites demonstrate increased tensile strength, modulus, and toughness due to the even distribution of nanoclays and strong interfacial bonding.

ii. Thermal stability: The incorporation of nanoclays enhances thermal stability by limiting polymer chain movement and serving as a heat barrier.

iii. Barrier properties: Nanoclays create a complex pathway for gas and liquid molecules, greatly decreasing permeability and improving barrier characteristics.

iv. Flame Retardancy: Nanoclays serve as a barrier against heat and oxygen, postponing the beginning of combustion and minimizing the emission of flammable gases.

v. optical clarity: In exfoliated nanocomposites, the nanoscale distribution of clays ensures minimal light scattering, preserving the optical clarity of the polymer.

Factors affecting Nanocomposite performance:

The performance of nanoclay-based nanocomposites is influenced by several factors (156,157):

- **Clay Type and Loading**: The selection of nanoclay and its concentration affect the level of dispersion and the resulting properties.
- **Surface Modification**: Appropriate surface treatment improves compatibility and interfacial adhesion.
- **Processing Conditions**: Factors such as temperature, mixing speed, and duration influence the quality of dispersion.
- **Polymer Matrix**: The inherent properties of the polymer, including molecular weight and polarity, impact the final composite properties.

Application(158,159)**:**

Nanoclay-based nanocomposites are employed across various industries due to their versatile characteristics:

i. Automotive Industry:

- Lightweight and durable components for enhanced fuel efficiency.
- Improved thermal stability and flame retardancy for under-the-hood applications

ii. Packaging:

- Excellent barrier properties to guard against moisture, gases, and UV radiation.
- Biodegradable nanocomposites for sustainable packaging options.

iii. Construction:

- High-strength materials for infrastructure uses.
- Coatings with improved weather resistance and durability.

iv. Electronics:

- Nanocomposites with enhanced dielectric properties for electronic devices.

- Shielding materials to prevent electromagnetic interference (EMI).

v. Biomedical application:

- Drug delivery systems that use nanoclay's ability to adsorb and release therapeutic agents.
- Antimicrobial coatings for medical instruments.

vi. Aerospace:

- Lightweight and high-performance materials for aircraft and spacecraft.
- Thermal and flame-resistant composites for extreme environments.

Challenges:

Despite their benefits, nanoclay-based nanocomposites encounter challenges that need to be addressed for wider use (82,160,161):

- Dispersion issue: Achieving consistent dispersion of nanoclays remains difficult, especially at higher concentrations. Advanced mixing strategies and surface adjustments are necessary to resolve this issue.

- Processing cost: The expenses related to surface modification and specialized processing equipment can be high.

- Environmental concern: While nanoclays are naturally occurring, their modification and the linked polymer matrices may have environmental effects. Research into biodegradable polymers and eco-friendly modification methods is essential.

- Scale-up challenges: Transitioning lab-scale processes to industrial production necessitates addressing factors like reproducibility, consistency, and scalability.

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