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Nanocomposite: An Overview

Aalok Basu and Jadupati Malakar

Department of Pharmaceutics, Bengal College of Pharmaceutical Sciences and Research, Durgapur–713212, West Bengal, India.

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ABSTRACT

Nanocomposite which is a multiphase solid material such as particle layers or fibers containing at least one phase in nanoscale, have been extensively accepted as a new arena as well as an unique delivery system in pharmaceutical research. Several application of above mentioned system like polymeric nanocomposite, nano-fibers composite and iron oxide nanoparticle composite with their respective delivery system and characterization are discussed in this review article. Moreover, nanocomposite is now introduced in cancer therapy in order to provide better therapy with minimal toxicity.

Introduction

The field of nanotechnology is one of the most popular areas for current research and development in basically all technical disciplines. This obviously includes polymer science and technology and even in this field the investigations cover a broad range of topics. This would include microelectronics (which could now be referred to as nanoelectronics) as the critical dimension scale for modern devices is now below 100 nm. Other areas include polymer-based biomaterials, nanoparticle drug delivery, microemulsion particles, fuel cell electrode polymer bound catalysts, layer-by-layer self-assembled polymer films, electrospun nanofibers, imprint lithography, polymer blends and nanocomposites.

Nanocomposites have attracted considerable amount of interest in the area of industrial and academic research for as bio-molecule carriers for an effective drug delivery system. Nanocomposites can be defined as multiphase solid material, where at least one phase has one, two or three dimensions at nano-size range, or structures having nano-scale repeat distances between the different phases that make-up the material [1]. The properties of nanocomposites depend not only on the properties of their individual parent components but also on their morphology and interfacial characteristics. The interaction between filler components of nanocomposites at the nanometer scale enables them to act as molecular bridges in the polymer matrix. This is the basis for enhanced mechanical properties of the nanocomposite as compared to conventional microcomposites [2]. The physicochemical and biological properties of nano materials differ from the properties of individual atoms and molecules or bulk matter. By creating nano particles, the basic properties of materials, such as their melting point, magnetic characteristics, charge capacity, flame retardancy, chemical resistance and optical clarity can be effectively controlled without changing the material's chemical composition [3]. Nanocomposites have a wide range of applications in drug delivery, biological implant materials, electronic packages, and automobile or aircraft components. Although some of the properties are similar among the applications, others are quite different.

The addition of small amount of nanoparticles to polymers has been able to create new properties for the composite material, though the results depend on the surface treatment of the nanoparticles and its procedure. Prior to initiation of the process, it is also important to determine whether a nanomaterial can be successfully integrated into nanocomposites to achieve multiple desirable properties required for a given purpose. To assess the potential value of nanocomposites, it is important to determine which nanomaterials can be effectively integrated into nanocomposites and the featuring novel functions. Then it will be important to determine the effectiveness of dispersion of the nanoparticles in the matrix and how this affected the structure of the polymer to enable optimization of the desired property. Once the basic composite model has been developed, studies are conducted to determine how the mixing of multiple nanomaterials in a polymer affects the final structure of the nanocomposites [4].

Due to presence of nano-structured material in the composite system, molecular permeability and control over drug release can remarkably be improved. The nanostructures materials play an important role in the creation of novel properties exhibiting multi-functional, high-performance characteristics beyond those of conventional macro-phase materials in the field of biomedicine. The controlled release of drug from nano-composite systems aim at delivery for temporal control (extended duration), distribution control, increased efficacy and increased patient compliance.

This review provides a brief idea on the application of nano-composites as means of drug delivery. The nanocomposites are generally found in form of nanoparticles which are of polymeric, solid-lipid or ferric oxide forms. Others types of composites include nanofibers, nanorods and thermogels.

Nanoparticle Composite for Drug delivery

Drug particles in nanometer size range have unique characteristics that can lead to enhance performance in a variety

Tele:

E-mail addresses: jadupati_pharma@yahoo.co.in

of dosage forms. Scientists use nanotechnology to approach classical and novel drug delivery applications. Controlled and targeted deliveries are the most enviable requirements expected from a carrier, which involves multi-disciplinary site specific or targeted approach. Nanoparticulate drug delivery system may offer platform of advantages over conventional dosage forms, which includes improve efficacy, reduced toxicity; enhance bio-distribution with improved patient compliance. Pharmaceutical nanoparticles are sub-nanosize based structure, contain drug or bioactive substances with in them and constituted of several tens or hundreds of atoms or molecules with a variety of sizes (from 5-300 nm) and morphologies (amorphous, crystalline, spherical, needles, tubes etc.).Nanoparticles are composed of organic or inorganic materials in which active agents can be dissolved, entrapped or encapsulated within the particle, or adsorbed onto the particle's surface. The active materials may exist as a solution, solid solution or a crystalline or amorphous solid in the nano-particles. Organic nano-particles possess good biocompatibility, good biodegradability, and high loading efficiency. Polymeric nanoparticles, Submicron liposomes, solid-lipid nanoparticles (SLN), micelles and dendrimers are examples of organic nanoparticles. Inorganic nanoparticles are of lesser importance, though lots of studies are done on silica nanoparticles and iron oxide nanoparticles. Sometimes, different substances are incorporated to impart desirable properties to the nanoparticle drug delivery systems. For instance, stabilizers are added to decrease free surface energy. The surfaces of nanoparticles are often decorated with specific molecules to impart novel function such as extended circulation time and specific-targeting. Nanoparticles with the above mentioned properties are termed as "Nanoparticle composites". Thus, nanoparticle composites may be defined as a drug delivery system in which at least one phase is made from nanoparticles, although excluding the active agents, there should be at least two or more components in the system. Some of the latest advances in the application of organic and inorganic nanoparticles composites have been briefly summarized in the following section:

Polymeric nanoparticle composites

The use of natural polymers has been extended to the nanotechnology and biomedical fields, due to its biocompatibility for in vivo applications as well as its stabilization of nanostructures. Several authors have used natural polymers for surface modification of nanomaterials, preparation of nanoparticles and nanocomposites and also as stabilizing or capping agents [5, 6]. Nanoparticles derived from natural polymers, such as chitosan, alginate and hyalouronic acid that have been fabricated for the delivery of drugs, proteins and genes. Among them, chitosan nanoparticles are mostly used due their cationic and mucoadhesive properties. The other unique properties of chitosan are biodegradability, bioactivity and non-toxicity as well as good adhesion and sorption, which largely contribute to its multiple applications [7].

Chitosan is also a valuable component of polymer blends and composites. Using an appropriate technological process one may obtain films, fibers, gels and foams as well as chitosan beads of different sizes and morphology. Numerous in vitro studies have analyzed the response to chitosan by smooth muscle cells, macrophages, osteoblasts, chondrocytes, erythrocytes and whole blood [8]. Studies revealed that when alginate is incorporated into chitosan, they stabilize the drug, increase loading efficiency, extend residence time at the site of drug absorption and also achieve desired drug release profiles. Vijay Kumar Malesu et.al studied the release kinetics of anticancer drug curcumin by fabricating biodegradable Chitosan-alginate nanocomposite blended with Cloisite 30B (a medical clay) of varying ratios [9]. Chitosan/alginate nanoparticle composites are used for oral and nasal delivery of insulin. Chitosan/hyaluronic acid nanoparticles composites have been found effective in ocular delivery of plasmid, while chitosan/cyclodextrin combination has been utilized for delivery of protein or peptides.

Gelatin is one kind of novel and promising biomaterial characterized by several advantages including low cost, biodegradability, non-toxicity and biocompatibility. None the less, problems related to low mechanical integrity and thermal properties of gelatin had to be tackled before the application of high-performance gelatin or gelatin-based composites is perfected. Polycaprolactone (PLC) is a kind of biodegradable polymer which can be blended with gelatin to impart better properties to the later. Related studies were conducted by Rashmirekha Sahoo et al., who prepared Gelatin/Montmorillonite (MMT) hybrid nanocomposite loaded with Placitaxel for Bladder cancer therapy. MMT was incorporated in the formulation as a matrix material component which also acts as a co-emulsifier in the nanocomposite preparation [10]. From time to time, various authors have proposed several types of drug release mechanisms from matrices. It has been proposed that drug release from matrices usually implies water penetration in the matrix, hydration, swelling, diffusion of the dissolved drug (polymer hydro fusion), and/or the erosion of the gelatinous layer.

Nanofiber composites

Multifunctional polymer composites are importance in effective and targeted drug delivery system. Since Kenawy et al. first examined the drug release properties from electrospun fibrous mats [11], drug delivery systems based on nanofibers have attracted an increasing interest in the pharmaceutical field. The controlled drug delivery systems are used to improve therapeutic efficacy and safety of drugs by delivering them at a rate dictated by the need of the physiological environment over a period treatment to the site of action [12]. By using various electrospinning techniques such as conventional, coaxial and emulsion electrospinning, a number of different drug-loading methods have been developed. For example, drugs can be coated onto the nanofibers through exposure of the nanofibers into drug solutions [13], embedded within the nanofibers through electrospinning the mixture solution of the polymers and drugs [14], or encapsulated within the nanofibers by emulsion electrospinning [15,16]. Before proceeding further, it is essential to discuss the process of electrospining as it contributes a great deal in large scale preparation of various types of nanocomposites. A typical electrospining process involves dissolving the drug of interest and a polymer in an appropriate solvent. The solvent is then placed in a syringe followed by application of high voltage. Increasing the applied voltage further results in the initiation of a charged fluid jet that follows a chaotic trajectory of stretching and bending until it reachs the grounded target. When the charge is increased above a critical voltage, stable jet is formed. The presence of molecular entanglements in the polymer solution prevents the jet from breaking into droplets. The process results in the formation of fiber in nanometer or micrometer range.

The delivery of drug from composite nanofibers can be controlled by applying an external magnetic field. This type of composite is generally composed of biocompatible and biodegradable polymer that may prove to be of ample interest in a wide variety of medicinal application especially for targeted drug delivery. Drug delivery with polymer nanofibers is based on the principle whereas dissolution rate of a particulate drug increases with increasing surface area of both the drug and the corresponding carrier if needed. Kenawy et al. investigated delivery of tetracycline hydrochloride based on the fibrous delivery matrices of poly (ethylene-co-vinyl acetate), poly (lactic acid), and their blend [17]. Ignatious & Baldoni [18] described electrospun polymer nanofibers for pharmaceutical compositions, which can be designed to provide rapid, immediate, delayed, or modified dissolution for sustained and/or pulsatile release characteristics. Song et.al stated that poly (N-iso-propylacrylamide)-co-polystyrene nanofibers with functionalized gold complex would form a new nanocomposite that facilitated the accumulation of daunorubicin inside leukemia cell. The synergistic enhancement effects of nanocomposites on the uptake of daunorubicin in drug-resistant leukemia cell were analyzed by electrochemical and confocal fluorescence microscopy.

Furthermore, the results revealed that such nanocomposites would be effectively applied in the area of biomedicine to facilitate drug delivery and provide an early diagnosis of cancer cells. Nanocomposites fibrous carriers showed advantages in drug delivery applications as compared to traditional bulk materials and single component nanomaterials in term of effective targeting, sustained release and potential cytotoxicity. Functional composite nanofiber materials have promised a versatile nanoscale controlled or targeting drug delivery system. These can be applied to the effective delivery of both small-molecule drugs and various classes of bio-macromolecules, such as protein, peptides and plasmid DNAs to the desired region of the body.

Solid-lipid nanoparticle composites

Solid lipid nanoparticles (SLNs) are particles of submicron range consisting of lipids that exist in solid form at both room and body temperatures. SLN were produced by high pressure homogenization of aqueous surfactant solutions containing the drug-loaded lipids in the melted or in the solid state.

Iron-oxide nanoparticle composites

Magnetic nanoparticles have been used mainly for bio-imaging and were found to be ineffective as drug carriers. Later they had undergone surface modification to form a composite characterized by increased stability, reduced toxicity and some novel functions. The majority of magnetic nanoparticles as targeted delivery systems are chemically iron oxides. Iron is essential to nearly all known organisms and even endogenic iron oxide nanoparticles were detected in the human hippocampus [19, 20]. However at the cellular basis, iron oxide causes direct cytotoxicity due to the generation of oxygen and nitrogen-based atoms with an unpaired electron *i.e.* reactive oxygen and nitrogen species (ROS and RNS) [21]. Therefore, magnetic nanoparticles are predominantly prepared through the use of core-shell methodology. As reviewed by Gupta and Gupta, the magnetic core of iron oxide nanoparticles is composed of magnetite (Fe_3O_4) and/or maghemite (γ-Fe_2O_3) whereas their shell surface coating can be of organic compounds including surfactants and synthetic or natural polymers or inorganic material such as silica, carbon, precious metals or oxides. [22.] The techniques for preparation of iron-oxide nanoparticle composites are polymeric coating, functional ligand conjugation, silica coating and entrapment in liposome. Targeted iron oxide nanoparticle composites conjugated with ligand have been studied in which the adopted ligand include folate and a urokinase plasminogen activator .

Zhanhu Guo et al. investigated the effect of particle functionalization by a bi-functional methacryloxy propyl-trimethoxy silane (MPS) on the vinyl ester resin curing process. The functionalized nanocomposites reinforced vinyl ester showed improved thermal and mechanical stability as compared with the nanocomposites reinforced with iron-oxide nanoparticles. The functionalization increases the adhesion and the dispersion of the nanofiller into the matrix [23]. Phanapavudhikul et al. reported the details of an iron oxide nanoparticle composite which was achieved by encapsulating nanosized magnetite with an acrylate-based cationic co-polymer made from methy-methacrylate (MMA), butyl acrylate (BA), and quinolinyl methacrylate (QMA) and modified with methoxy poly(ethylene glycol) methacrylate (MeOPEGMA) by using the water replacement method [24]. The composition of the co-polymer formulation was optimized through zeta-potential and freeze-thaw stability studies. Drug-loading and release mechanisms are based on the electrostatic interaction between the negatively charged model drug aspirin and positively charged co-polymer. The drug release kinetics showed a biphasic profile with initial burst release followed by a prolonged slow release.

Delivery of anticancer drugs

Surgery, radiation and chemotherapy remain the most widely used treatment options in the fight against cancer. Despite of recent progress in conventional methods, there is still a great need for new treatments that can eradicate cancer cells while causing much less damage to the normal cells. As a step forward in this direction, researchers around the world are making great efforts to incorporate nanotechnology into existing therapeutics and imaging in cancer treatment. Efficient delivery of anti-cancer drugs still pose a major challenge due to lack of specific site targeting and toxic effect of the candidate drug. Besides occurrence of multidrug resistance (MDR) is one of the major obstacle to the success of the tumor's chemotherapy [25, 26]. Nanoparticle composites have been widely used in drug delivery research for targeting and controlled release. Recently, some reports have demonstrated that anticancer drugs could be readily modified on the biocompatible nanomaterials covalently or non-covalently that could afford the sustained drug delivery for the target cancer cell lines and reduce the relevant toxicity toward normal cells and tissues [27- 29].

Jingyuan Li et al. fabricated biodegradable Poly (lactic acid) / gold [PLA/Au] nanpcomposites which facilitated the uptake of anticancer drug in target cells. Studies revealed that Daunorubicin conjugated with PLA/Au nanocomposites have a synergistic effect on the drug uptake in cancer cells and can be used in multidrug-resistant leukemia. From the specific nanostructure of the PLA nanofibers and the relevant nanocomposites as observed in Atomic Force Microscopy (AFM) study, it was concluded that the anticancer drug daunorubicin could be readily self-assembled on the surface of the new PLA/Au nanocomposites and hence this could be utilized as a new promising carrier for nano-medicine in cancer treatment [30]. A similar kind of work was carried out by Song et al. They described a daunorubicin loaded poly (N-isopropyl

acrylamide)-co-polystyrene (PNIPAM-co-PS) nanofiber where the composite nanofibers enhanced the cell permeation and uptake of daunorubicin into drug sensitive and drug resistant cancer cells. Results of AFM and confocal fluorescence microscopy indicated that interactions between the PNIPAM-co-PS nanofibers with candidate drug molecules on the membrane of leukemia infected cell line could affect the uptake of drug in a progressive manner and followed by accumulation of daunorubicin in drug-sensitive and drug resistant cancer cells.

Drug or gene targeting using magnetic nanoparticles is a one of the rapidly advancing area in cancer chemotherapy and cancer gene therapy. The idea of using magnetic microspheres as vehicles for drug delivery in cancer therapy was first introduced by Widder et al. [31].The rationale behind these two treatment modalities is based on binding either chemotherapeutics or nucleic acids onto the surface of magnetic nanoparticles which are directed to and/or retained at the tumor by means of an external magnetic field [32].

Di Zhao designed a novel multifunctional magnetic silver nanocomposite and Fe_3O_4/Ag conjugated to an epidermal growth factor receptor-specific antibody (C225) which can be potentially used for synchronous cancer therapy and diagnosis via magnetic resonance imaging. The design was successful in proving that Fe_3O_4/Ag/C225 combined with X-ray treatment could increase the sensitivity of CNEs to irradiation.

Characterization of nanocomposites

An important issue in the study of nanocomposite is to relate the performance with their morphology and other analytical results. One of the most frequently used characterization methods is the Wide angle X-ray diffraction (XRD). Wide-angle X-ray diffraction (WAXD) is a classical method for determining the gallery height (*d*-spacing distance) in clay particles [33]. The *d*-spacing can be determined by the diffraction peak in the XRD patterns and can be expressed by Bragg's equation (l= 2*d*001sinq), where *d*-001 is the interplanar distance of (001) diffraction face, q is the diffraction position and l is the wave length [34]. During intercalation, the insertion of polymer into the organoclay galleries forces the atoms apart and increases the *d*-spacing resulting in a shift of the diffraction peak to lower angles.

Small angle X-ray scattering, SAXS can be more informative and somewhat quantitative as explained by numerous authors [35-39]. However this technique has not been widely used except in a few laboratories probably because most laboratories do not have SAXS facilities or experience in interpreting the results. Other techniques like solid-state NMR and neutron scattering have also been used on a limited basis to explore clay dispersion [40-45].

A far more direct way of visualizing nanocomposite morphology is via transmission electron microscopy, TEM; however this approach requires considerable skill and patience but can be quantitative. Use of TEM is often criticized because it reveals the morphology in such a small region. However, this can be overcome by taking images at different magnifications and from different locations and orientations until a representative picture of the morphology is established. The major obstacle in obtaining good TEM images is not in the operation of the microscope but in microtoming sections that are thin and uniform enough to reveal the morphology. Fortunately, the elemental composition of the clay compared to that of the polymer matrix is such that no staining is required [46- 48].

Swelling study is conducted to determine the water absorption property of the polymer-drug conjugate. The samples were preconditioned at 50º C for 24h and then cooled in a desiccator before being weighed. The preconditioned samples were submerged in distilled water at 25º C for 24h.The samples were removed and dried with a paper towel before weighing. Water absorption was calculated as a percentage of initial weight. The soluble material loss was checked by weighting the specimens after drying them in an oven at 50º C for another 24h. It is generally known that the swelling behavior of the polymer network depends upon the nature of the polymer, polymer solvent compatibility and degree of cross-linking. However in the case of ionic networks, swelling behavior depends upon mass transfer limitations as well as ion exchange and ionic interaction [49].

FTIR spectra studies depict the various chemical interactions and bonds or cross linkages in polymer matrix. The data also confirms the chemical stability of the nanocomposite and suggests the intercalation of drug molecules in the polymer.

Conclusion

Nanocomposites have been an innovation subject in the area of research since last few years. This review provides a brief overview of the works carried out various researchers in the field of biomedicine and drug-delivery using nanocomposites. The art of designing the novel multifunctional nanocomposites aims to provide a controlled release dosage form with better drug loading capability and reduced toxicity. It should also be kept in mind that the polymer and filler used to fabricate the composites are biodegradable and can be fully eliminated from the body. In spite of rapid progresses, the nanocomposite field is largely new as evidenced by few studies as more projects should be conducted to study the interfacial interaction between the polymer, drug and the supporting fillers is impose full control over the release and targeting the specified sites. While researchers are seeking materials to meet difficult challenges with unique properties but there is no "rule of mixtures" to identify how to mix multiple nanomateials in a composite structure and all required properties. Nanomaterials often have unique properties that could enable composite materials with multiple unique properties simultaneously; however, it is often challenging to achieve these properties in large-scale nanocomposite materials.

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