Nano Hybrids and Composites
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Nanocomposites in Controlled & Targeted Drug Delivery Systems

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Abstract. In recent years, development of different types of nanocomposites have increased their utilization in the biomedical and pharmaceutical sciences. The nanometer size range and unique composition make nanocomposites a beneficial alternative to any single conventional material. The present chapter provides a general overview of nanocomposites, discusses different types of nanocomposites such as metal, ceramic and polymer nanocomposites. The discussion is further focused on different nanocomposite based controlled and targeted systems developed for delivery of various drugs including anti-cancer, anti-microbial, anti-inflammatory, anti-diabetic and cardiovascular drugs.

1.0 Introduction

Composites are defined as combinations of two different materials in which one is called the reinforcing phase which is in the form of fibers, sheets, or particles, and is embedded in the other phase called as matrix phase. Nanocomposites are therefore defined as composites in which at least one of the phases shows dimensions in the nanometre range (1 nm = 10^{-9} m) which is further embedded in a metal, ceramic, or polymer matrix [1]. Reinforcing material is a strong and low density material while the matrix is usually a ductile or tough material. In nanocomposites, the strength of the reinforcement phase is combined with the toughness of the matrix phase to achieve a combination of desirable properties not available in any single conventional material. Therefore, structure of nanocomposites typically comprises of the matrix material having the nanosized reinforcement components in the form of particles, whiskers, fibres, nanotubes, etc [2]. The properties of nanocomposites depend upon many variables such as the matrix material, loading, degree of dispersion, size, shape and orientation of the nanoscale reinforcing phase and interactions between the matrix and the reinforcing phase. On the basis of the nano range (≤ 100 nm), nanoscale reinforcing phase can be grouped into following categories:

a. 0D nanomaterials- all the dimension are within nanoscale with no dimension larger than 100 nm, e.g., nanoparticles. These nanoparticles can be crystalline or amorphous, metallic, ceramic, or polymeric.
b. 1D nanomaterials- needle like–shaped materials having one dimension in nano range. Examples include nanoplatelets, nanorods, nanoclays and nanosheets.
c. 2D nanomaterials- two dimensions in nano range. Examples include nanofibers, carbon nanotubes, nanorods and whiskers.
d. 3D nanomaterials- all three dimension in nano range. It include nanogranules, nanoclays and equiaxed nanoparticles [3].

Nanocomposites based on nanocellulose, nano- or microfibrilliar cellulose, cellulose nanofibers are new generation nanomaterials that possess wide range of applications in the field of pharmacology,

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medicine, tissue engineering, biosensors, microfluidics elements, materials for microencapsulation and drug delivery, as permoselective membranes and as a barrier to protect mucosal tissues [4, 5, 6, 7, 8, 9]. The nanocomposites possess a whole complex of unique properties typical for nanomaterials in general, such as high specific surface area, enhanced chemical reactivity, controlled release of the drug, high mechanical durability, together with biocompatibility, biodegradability, and non-toxicity, which makes it an excellent candidate for drug release applications [4, 9].

A variety of non-degradable and biodegradable polymer–inorganic composites and nanocomposites have been studied, including polydimethylsiloxane or poly(methyl methacrylate) combined with silicates [10], poly(vinyl alcohol) (PVA)–montmorillonite clay [11] poly(e-caprolactone) and tetraethoxysilane (TEOS), polycaprolactone–graphene [12], and poly(lactide-co- glycolides) with hydroxyapatite, bioactive glass or calcium phosphates [13]. Most of these composites were made with bioactive ceramics to promote bone regeneration and many of these composites have been evaluated for controlled release of other therapeutics, such as aspirin [14] or the antibiotic ceftazidime [15, 16]

2.0 Advantages of Nanocomposites

The advantages of nanocomposites are listed below:

1. Properties of the matrix material in nanocomposites can be improved by the addition of nanofiller materials in small amount as compared to conventional composites that require high concentration of micro particle in order to improve properties.
2. Nanocomposites are much lighter in weight compared to conventional composites due to the presence of nanofiller materials.
3. These nanomaterials enhance thermal, chemical, mechanical, optical, magnetic and electrical properties to a much greater extent than conventional composites.
4. They are highly dispersible in aqueous medium [3].

3.0 Types of Nanocomposites

Following is the list of different types of nanocomposites:

1. Metal matrix nanocomposites MMNC
2. Ceramic matrix nanocomposites CMNC
3. Polymer matrix nanocomposites PMNC
4. Polymer nanocomposites with layered silicates
5. Polymer-nanofibre/CNT/GO nanocomposites
6. Biopolymeric nanocomposites
7. Nanocomposites hydrogel
8. Layered double hydroxide (LDH) nanocomposites

3.1 Metal matrix nanocomposites, MMNC's

Metal matrix nanocomposites consist of ductile metal/alloy matrix in which nanoparticles are reinforced in order to exhibit physical, chemical and mechanical properties entirely different from those of matrix material. The nanoparticles are generally used to improve wear resistance, mechanical properties and damping features. Owing to superior properties due to nanoparticle embedment, MMNC's are being investigated by researchers for their wide range of applications in structural components [1, 3]. General methods used for the preparation of MMNC's are spray pyrolysis, liquid metal infiltration, rapid solidification, vapour techniques, electrodeposition and chemical method which include sol-gel processes. The two major methods for their production are *ex sit*u and *in situ* [17]. *Ex situ* method involves adding nano-reinforcements to the liquid or powdered metal, while *in situ* processes involves generation of ceramic nano-compounds by reaction during processing, for example by using reactive gases. Several methods have been

developed for *ex situ* synthesis of MMNCs among which different powder metallurgy and ultrasound-assisted casting techniques were effectively employed, which plays a particularly promising role for their high potential productivity. Ceramic compounds (SiC, Al_2O_3, etc.), intermetallic materials and carbon allotropes were used to reinforce Al, Mg, Cu and other metals and alloys. Particular importance is assigned to carbon nanotubes (CNT), which are characterized by very high strength and stiffness [18, 19, 17]. *In situ* MMNCs have been effectively prepared by liquid metallurgy processes. Melt stirring, high-pressure die casting and arc-discharge plasma method are other *in situ* methods [17]. Types of Metal Matrix Nanocomposites are Fe-Cr/Al_2O_3, Ni/Al_2O_3, Co/Cr, Fe/MgO, Al/CNT, Mg/CNT.

3.2 Ceramic matrix nanocomposites CMNC's

They are new generation of engineering materials with at least one phase in nano dimension, having a wide range of applications in industrial sector. They have exceptional electrical and mechanical properties due to microstructure of nanoceramic composites**.** Amongst numerous methods employed for the preparation of ceramic matrix nanocomposites, the common methods used in nanocomposites fabrication are conventional powder method, polymer precursor route, spray pyrolysis, and chemical methods such as sol-gel process, colloidal and precipitation approaches and template synthesis [1]. Types of ceramic matrix nanocomposites are Al_2O_3/SiO_2, SiO_2/Ni, Al_2O_3/TiO_2 and Al_2O_3/SiC.

3.3 Polymer matrix nanocomposites PMNCs

These mainly comprise of a matrix made from a polymeric material and the reinforcing phase having nanoscale dimensions dispersed within the matrix phase. Due to the nanoscale size of the reinforcing phase, the interface-to-volume ratio is significantly higher than in conventional composites owing to unique properties of PMNCs. The volume fraction of the second phase can be reduced without degradation of the desired properties. Polymer nanocomposites (PNCs) represent an alternative to conventional polymer composites due to their improved properties. PNCs are also easily extruded or molded to near final shape and high degrees of stiffness and strength using far less high-density inorganic material [1]. General methods used for the preparation of PMNCs are intercalation of the polymer or pre-polymer from solution, *in situ* intercalative polymerization, melt intercalation, direct mixture of polymer and particulates, template synthesis, *in situ* polymerization and sol-gel process**.** Types of polymer matrix nanocomposites are thermoplastic/thermoset polymer/layered silicates, polyester/TiO_2, polymer/CNT, polymer/layered double hydroxides.

3.4 Polymer nanocomposites with layered silicates

Drug delivery system having clay mineral composites exhibit unique hybrid properties superior to the components and have the ability to incorporate various drug substances [20, 21, 22]. Silicate clay minerals and graphite (Layered silicates) are the two types of nanoplatelet particle composites [23]. Hectorite, saponite, and montmorillonite are the most commonly used smectite type layered silicates used for the preparation of nanocomposites. Out of these, montmorillonite (MMT) has the widest acceptability for use in polymers because of their high surface area and surface reactivity. MMT is used both as excipient and active substance in pharmaceutical products [24]. It has enhanced gel strength, mucoadhesive capability to cross the gastrointestinal barrier, and ability to adsorb bacterial and metabolic toxins such as steroidal metabolites [25]. A way to outspread the applications of clay-polymer nanocomposites with improved properties, is to modify polymers by incorporation of inorganic fillers [26]. Due to novel physical and chemical properties, smectite clays intercalated by drug molecules have attracted great interest from researchers [27]. Polymer nanocomposites with layered silicates can be classified as follows:

a) **Phase separated or Conventional composite:** Phase separated composites are obtained when the polymer phase is unable to intercalate (or penetrate) between the silicate sheets. Their properties are same as those for traditional microcomposites. Methods used for

manufacturing of conventional composites are wet lay-up, pultrusion, resin transfer molding (RTM), vacuum assisted resin transfer molding (VARTM), autoclave processing, resin film infusion (RFI), prepreg method, filament winding, fiber placement technology, etc [23].

b) **Intercalated nanocomposite:** This technique involves in situ polymerization in between the intercalated sheets via swelling of the layered silicate within the liquid monomer which can be initiated either by heat or radiation or by an organic initiator [28, 29, 30, 31, 32]. This approach was successfully applied in manufacturing of nylon–montmorillonite nanocomposite, and later it was extended to other thermoplastics [33]. Kevadiya *et al.,* synthesized montmorillonite-alginate nanocomposites for the sustained intestinal delivery of thiamine hydrochloride (Vitamin B_1) and pyridoxine hydrochloride (Vitamin B_6) [34].

c) **Exfoliated nanocomposites:** The stacked layers of layered silicates can be easily dispersed in an adequate solvent system in which the polymer is soluble and the silicates are swellable, such as water, acetone, chloroform, or toluene. The polymer adsorption occurs onto the delaminated sheets and upon solvent evaporation, the sheets reassemble, sandwiching the polymer. This strategy can be used to synthesize epoxy–clay nanocomposites [35]. Exfoliated nanocomposites have higher phase homogeneity than the intercalated counterpart [36].

Iliescu *et al.,* synthesized montmorillonite–alginate nanocomposite as a drug delivery system for the delivery of irinotecan and showed that the release can be sustained without any burst effect [37]. In graphene based polymer nanocomposites, graphite and GO act as precursors to many graphene based materials and have been widely investigated as composite fillers [38]. Recently, graphene nanoribbons, produced by "unzipping" of multiwalled carbon nanotubes, have been investigated as composite filler [39]. In general, the organically modified silicate nanolayers are referred as 'nanoclays' or 'organosilicates' [40].

Moura *et al.*, investigated the intercalation of ibuprofen into MMT as a sustained release drug carrier [41]. Liu *et al.,* studied the intercalation of 5-fluorouracil with MMT as drug carrier [42]. Amin *et al.,* reported intercalation and release behavior of promethazine chloride and buformin hydrochloride from MMT [43]. Marandi *et al.,* studied the loading and delivery of sertraline using MMT K10 [44]. Anis *et al.,* synthesized the poly (d,l-lactide-co-glycolide)-MMT nanoparticles for oral delivery of paclitaxel by the emulsion-solvent evaporation method [20]. Cationic drugs can be intercalated into MMT by ion exchange [45, 46, 47]. Mahkam *et al.,* prepared Montmorillonite-pH-sensitive positively charged nanocomposites for an effective delivery of naproxen [89]. Melinte *et al.,* synthesized hybrid nanocomposites based on new triazeno copolymers and montmorillonite which can be a promising technique to create photosensitive systems for chemosensor or microlithographic applications. They also evaluated the impact of the organoclay in terms of structure and its interactions with the monomer molecules/polymers within the galleries on the properties and morphology of the final hybrid composites including a fluorescence study [49]. Salahuddin *et al.,* prepared microbicidal polyamide-montmorillonite nanocomposites of 1, 3, 4-Oxa (thia) diazoles. *In vivo* study of which showed that nanocomposites had good antimicrobial activity [50].

Wang *et al.,* prepared and characterized chitosan and chitosan/organic rectorite (OREC) nanocomposite films with different mass ratios of chitosan to organic rectorite by a casting/ solvent evaporation technique. These nanocomposite films were also successfully loaded with bovine serum albumin (BSA), as a model drug. Their bactericidal activity and *in vitro* release studies were carried out. The chitosan/OREC nanocomposites films are expected to have promising applications as antimicrobial agents, water-barrier compounds, anti-ultraviolet compounds, and drug-controlled release carriers [51].

3.5 Polymer-nanofibre/CNT/GO nanocomposites

Many inorganic fillers with micrometric dimensions such as calcium carbonate, glass beads and talc have been used widely in conventional polymer composites to augment the mechanical properties of polymers [52]. A further improvement of the mechanical properties can be achieved by using filler materials having nanometric dimensions and larger aspect ratio such as layered silicate and carbon nanotubes. Carbon nanotubes (CNTs) have a substantially larger aspect ratio (~ 1000) and stiffness in comparison with layered silicates (~ 200) [53, 54, 55]. CNTs also exhibit remarkable properties such as unique mechanical and electrical characteristics due to which CNTs are used to reinforce polymers from last few years [56, 55].

Justin *et al.,* developed strong and conductive chitosan–reduced graphene oxide nanocomposites for transdermal drug delivery and showed that introduction of rGO to chitosan improved the mechanical properties of the nanocomposites, with the strongest nanocomposite containing 1% rGO showing an increase of 91.3% for Young's modulus and 95.6% for ultimate tensile strength over pristine chitosan while maintaining the elongation at break at 10.8% [57].

3.6 Biopolymeric nanocomposites

Biopolymers are the best contrasting options to traditional nonbiodegradable polymers for controlled delivery of therapeutically active substances [58, 59]. Biopolymers are arranged into three noteworthy classifications. The first group is comprised of biopolymers specifically separated from biomass, for example, starch or cellulose. The second group is comprised of polymers obtained synthetically from biobased monomers, as poly(lactic acid). The third and last classification is comprised of polymers created by microorganisms or microscopic organisms, as poly(hydroxyl alkanoates) [59]. These polymers are utilized independently or in the blend to control drug delivery in various ways, including polymer disintegration, drug dispersion inside the polymer network or over a polymer film and polymer degradation. Some biopolymeric based nanocomposites are discussed below:

3.6.1 Cellulose based nanocomposites: The nanoscale cellulose possesses unique properties typical for nanomaterials, such as high specific surface area, enhanced chemical reactivity, and high mechanical durability, together with biocompatibility, biodegradability, and non-toxicity, which make it an excellent candidate for drug release applications. Galkina *et al.,* successfully synthesized drug delivery systems based on cellulose nanofibers – titania nanocomposites loaded with three different types of model drugs such as diclofenac sodium, penicillamine-D and phosphomycin that displayed distinctly different controlled long-term release profiles**.** They showed that the obtained nanocomposites could potentially be applied in transdermal drug delivery for anesthetics, analgesics and antimicrobial activity [9].

3.6.2 Starch-based nanocomposites: Starch is an excellent alternative to synthetic materials because it is abundant, renewable and low cost material with biodegradable and film forming properties [60, 61]. Kalambur and Rizvi., successfully prepared starch-based nanocomposites from starch-polycaprolactone (PCL) blends in the presence of montmorillonite (MMT) nanoclay by reactive extrusion processing. Their work showed significant improvement in the mechanical properties (strength, modulus or strain) of starch–PCL blends by addition of nanoclay [62]. Fama *et al.,* reinforced nanocomposite materials based on a starch matrix with very small amounts of multi-walled carbon nanotubes (MWCNTs) to synthesize biodegradable starch based nanocomposites with low water vapor permeability and high storage modulus. They showed that wrapping carbon nanotubes with a starch–iodine complex allows obtaining starch based nanocomposites with very small amounts of carbon nanotubes which exhibit important improvements in storage modulus and water vapor permeability properties with respect to the starch matrix [63].

3.6.3 Gelatin-based nanocomposites: Gelatin is one of the most versatile and widely used structural natural proteins in pharmaceutics because of its biocompatibility, biodegradability, low cost, and other applications. Also, gelatin based nanocomposites play a crucial role in various aspects of biology and medical sciences. Various cross-linkers used to improve the physicochemical behavior of gelatin nanocomposites (GNCs) have been reported [64]. Liu *et al.,* prepared and characterized gelatin-hydrogel based mucoadhesive nanocomposites as scaffolds for intravesical gene delivery. There was increased lentiviral retention and penetration from these hydrogels which further produced more localized, efficient *in vivo* intravesical transgene expression. [65].

3.6.4 Guar gum-based nanocomposites: Guar gum is a nontoxic, biocompatible and biodegradable biopolymer which is used extensively as a biomaterial in various biological and technological processes [66]. Ghosh *et al.,* developed silver nanocomposites embedded in cationic guar gum polymeric matrix which were further evaluated for wound healing application in rat punch wound model and showed superior wound healing efficacy of guar biopolymer silver nanocomposites [67]. Dziadkowiec *et al.,* prepared and characterized ibuprofen-loaded guar gum/montmorillonite bionanocomposites for controlled drug delivery [68].
Similarly, chitosan based nanocomposites for controlled drug delivery are also reported which are discussed later in this chapter.

3.7 Nanocomposite hydrogels
Recently, nanocomposite hydrogels have attracted interest of researchers as biomaterials and their properties can be easily altered by manipulating the properties of the hydrogel and the composite material [69]. Besides, hydrogel nanocomposites with magnetic particles have been proved as potential candidates for pulsatile drug delivery and soft actuator applications. Zrinyi and co-workers reported that magnetic composites of poly (vinyl alcohol) undergo quick, controllable changes in response to an applied magnetic field and thus can be used in soft actuator-type applications [70]. Further studies on magnetic composites of N-isopropylacrylamide (NIPAAm) have shown that magnetic particles do not affect the temperature sensitivity of the hydrogel network, including the lower critical transition temperature (LCST) [71, 72]. Satarkar *et al.,* synthesized magnetic nanocomposites of temperature-sensitive hydrogels by incorporation of superparamagnetic Fe_3O_4 particles in negative temperature-sensitive poly (N-isopropylacrylamide) hydrogels and confirmed to be responsive to alternating magnetic fields [73]. Jayakaran *et al.,* synthesized nanocomposite hydrogels of Harunganamadagascariensis leaf extract (HLE) for local drug delivery for the treatment of periodontal infections [74].
Taleb *et al*., synthesized and characterized sodium alginate/chitosan/hydroxyapatite nanocomposite hydrogels using gamma radiation-induced copolymerization and as cross linker for the oral delivery of doxorubicin (DOX)- an anticancer drug for liver cancer (Hepatocellular carcinoma) [75]. Results of their study showed that drug release is pH sensitive and higher release rate upto 95% was observed at pH 5.

3.8 Layered double hydroxide (LDH) nanocomposite
Layered double hydroxide (LDH) nanocomposite is a class of inorganic material with chemical composition represented by the general formula, $[M^{2+}_{1-x}\, M^{3+}_{x}\, (OH)_2]^{x+}\, [A^{n-}]_{x/n} \cdot mH_2O]$ where M^{2+} and M^{3+} are divalent and trivalent metal cations respectively [76, 77, 78]. The unique structure of LDH consisting of an outer positively charged metal hydroxide sheets and inner interlayer anions hydrated with water molecules aiding in its uptake and cellular penetration [76, 77]. They have ability to intercalate anions due to which number of pharmaceuticals can be incorporated within the LDHs and their stacked structure offers environmental protection to the intercalated drug [78]. Different types of LDH have been exploited for drug delivery in biomedical field. Even though they are still in the preliminary stage, but the results are promising and LDH are likely to join other delivery systems that have reached upto the level of clinical trials and use [79]. Ambrogi *et al.,*

reported 100% release over 100 min from a 50% (w/w) ibuprofen intercalated LDH, which showed improved controlled release compared to immediate release in commercial ibuprofen tablets [80, 78]. Deleon *et al.,* successfully intercalated ibuprofen into inorganic biodegradable polymer composites of LDH and Poly L-Lactic Acid (PLLA) and showed that cumulative drug release was significantly improved from the nanocomposite [78].

4.0 Drug Delivery Applications of Nanocomposites:

Some of the key drug delivery applications of nanocomposites are discussed below:

4.1. Nanocomposites as controlled release systems

An ideal drug delivery system should carry the preferred drug molecules to the targeted cells or tissues and liberate the drug in a controlled mode. One way to control the drug release is incorporation of the drug inside a substrate with particular chemical, biological and mechanical properties. Biopolymers of natural origin, such as chitosan are promising candidates for drug delivery applications due to their biodegradability, biocompatibility as well as low manufacturing and disposal costs [81]. Utilization of such biopolymers to synthesize the nanocomposites has increased the drug delivery efficiency of the nanocomposites & such systems have been successfully developed to deliver the drugs in the controlled manner, out of which few examples are mentioned below:

4.1.1 Controlled release of propranolol: Chitosan and clays can shape nanocomposites *via* electrostatic exchanges, with striking prospective as advanced drug delivery systems. These type of nanocomposites can be formulated as microparticles by means of spray-drying. Magnesium aluminum silicate (MAS) is a mixture of colloidal montmorillonite and saponite clays. MAS has found wide applications in the form of pharmaceutical excipient, as suspending and stabilizing agent. It is considered to be non-toxic and non-irritant at levels usually applied in pharmaceutical industry [82, 83]. Khlibsuwan *et al.,* successfully prepared propranolol HCl-loaded chitosan:MAS microparticles by spray-drying. The addition of MAS causes a number of changes in the resultant product like reduced microparticle swelling and slower drug release. It was found that propranolol release was sustained for several hours, at low and neutral pH, and no burst release was observed besides the fact that the microparticles were in the lower mm size range, and chitosan is soluble at acidic pH. It highlights the importance of “drug-chitosan” and “drug-MAS” interactions and gel formation with these systems. Further, the inclusion of small amounts of TPP, which serves as the crosslinking agent led to the decline in the release rate. These findings suggest that chitosan:MAS microparticles offer an interesting potential for controlled drug delivery (e.g. upon oral administration in capsules) [84].

4.1.2 Controlled delivery of ibuprofen: Graphene-based nanocarriers not only possess large specific surface area but also prevent drugs from impulsive discharge outside the target cells. Luo *et al*., uniformly embedded graphene oxide (GPO) into the three-dimensional (3D) porous network of bacterial cellulose (BTC) to form a novel BTC/GPO nanocomposite drug nanocarrier. The ibuprofen was loaded in nanocomposites *via in situ* biosynthesis technique. The BTC/ GPO nanocomposites can hold more drug than pure BTC. The drug release from IBP@BTC and IBP@ BTC/ GPO was found to be dependent on the pH of release medium. In addition, the formed IBP@BTC/GPO displayed a more sustainable release behavior than IBP@BTC, which suggests the significant role of GPO in promoting controlled release. The drug release was controlled by a non-Fickian diffusion mechanism for IBP@ BTC/GPO. The BTC/GPO nanocarrier may hold great promise as a new drug delivery system [85].

4.1.3 Controlled release of aceclofenac: Chitosan being a natural polymer & due to its variety of properties e.g. mucoadhesivity etc., has been widely used in the several particulate drug delivery systems (e.g. nanoparticles) for the controlled or sustained release of drugs [86, 87, 88. The ability

of CS to hold the drug & release the drug in the sustained manner has also been utilized to develop the nanocomposite systems. Jan *et al.,* developed a nanocomposites system of chitosan (CS) and Locust bean gum (LBG) using glutaraldehyde as a cross-linker. The variation in the polymer composition was found to modify the size of the nanocomposites as well as drug entrapment efficiency. The variation of either CS or LBG could be useful in controlling the release rate of drug from the nanocomposites. However, the existence of another polymer component in the composites was inevitable in suppressing the burst release of drug in the stomach and regulating the drug release profiles in variable pH environments of gastrointestinal tract, because only CS particles were insufficient to resist the burst effect at acidic pH of stomach. This novel nanocomposites system had potential to reduce burst release which further minimize the gastrointestinal side effects of drug by controlled drug delivery application [89].

4.1.4 Controlled release of metformin: The well-known oral antidiabetic drugs for type 2 diabetes mellitus (T2DM) are metformin (MET) unaided or in combination with the second generation sulfonylureas such as gliclazide, glimperide, glipizide and glibenclamide [90]. Metformin is an FDA approved and well acknowledged antidiabetic drug which has antagonistic result on pancreatic cancer proliferation [91, 92]. Moreover, diminished growth of pancreatic cancer xenografts in nude mice models administered with MET emphasizes its ability as a pancreatic cancer drug. The foremost troubles related to MET are its low bioavailability and short half-life period [93]. Thus, in order to overcome these problems, chitosan based nanocomposites for controlled MET antidiabetic drug delivery was developed which served the purpose of controlled release & exhibited prolonged stability in alkaline medium. Biocompatible nanocomposite films based on blended chitosan and poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol) (BP) polymers containing metformin (MET) drug and MCM-41 or MCM-41-APS (APS = aminopropylsilane) nanoparticles (NPs) were developed by Shariantinia *et al.,* in order to improve the hydrolytic stability, biocompatibility, mechanical properties and sustain the drug release for 15 days [70].

4.2. Nanocomposites in targeted drug delivery

Targeted drug delivery, also termed as smart drug delivery is a technique of conveying drug to a patient in a manner that increases the concentration of the drug in specific part or organ of the body relative to others. Targeted drug delivery generally employ nanosystems in order to overcome the limitations of conventional drug delivery. The objective of a targeted drug delivery system is to prolong, localize, target and have a confined drug interaction with the diseased tissue unlike conventional drug delivery system where drug is transported throughout the body organs. Nanocomposites systems have been successfully employed for the targeted delivery of drug, out of which some examples are discussed here.

4.2.1 Targeted delivery of doxorubicin: Rasoulzadeh *et al*., utilized the graphene oxide/carboxymethylcellulose nanocomposites for the targeted delivery of anticancer drug doxorubicin. Biodegradable carboxymethyl cellulose/graphene oxide (CMC/GO) nanocomposite hydrogel beads were prepared by physical crosslinking with $FeCl_3.6H_2O$ for controlled release of anticancer drug doxorubicin (DOX). The π-π stacking interaction between DOX and GO resulted in higher loading capacity and controlled release of the DOX from CMC/GO nanocomposites hydrogel. The release profile of DOX from hydrogel beads at pH 6.8 and 7.4 indicated it's strong pH dependence. Drug release from pure hydrogel was more than nanocomposite hydrogels and with increasing the amount of GO nanoparticles, drug release reduced due to strong interactions among amine groups of DOX and carboxylic groups of graphene oxide [94].

4.2.2 Targeted delivery of doxorubicin in glioma*:* Targeted delivery of drugs in a precise manner represent a potential technology in gliomas. Superparamagnetic Fe_3O_4 nanoparticles were loaded on the surface of GO by means of chemical precipitation process to outline GO@Fe_3O_4 nanocomposites. Lactoferrin (Lf), an iron-transporting serum glycoprotein that attaches to receptors

overexpressed at the surface of glioma cells and vascular endothelial cell of the blood brain barrier, was selected as the targeted ligand to create the targeted delivery system Lf@GO@Fe_3O_4 through EDC/NHS chemistry. The nano delivery structure had a high loading capability and demonstrated a pH-dependent release pattern. Compared with free DOX and DOX@GO@Fe_3O_4, Lf@GO@Fe_3O_4@DOX displayed greater intracellular delivery efficiency and stronger cytotoxicity against C6 glioma cells. The results demonstrated the potential utility of Lf conjugated GO@Fe_3O_4 nanocomposites for therapeutic application in the treatment of gliomas [95].

4.2.3 Delivery of methotrexate: MgAl-layered double hydroxide (MgAl-LDH) nanoparticles have great potential in drug and siRNA delivery. A nanodot-coating strategy was utilized to prepare SiO_2 dot-coated layered double hydroxide (SiO_2@MgAl-LDH) nanocomposites with good dispersibility and controllable size for drug delivery. Further SiO_2@MgAl-LDH nanocomposites were employed as a nanocarrier to deliver methotrexate (MTX), a chemotherapy drug, to the human osteosarcoma cell (U2OS) and found that MTX delivered by SiO_2@MgAl-LDH nanocomposite apparently inhibited the U2OS cell growth. In the optimal SiO_2@MgAl-LDH composition, the negatively charged SiO_2 nanodots were uniformly distributed on the positively charged LDH nanoparticles. The cellular uptake tests show that SiO_2@MgAl-LDH nanocomposites exhibited better dispersion within the cells after internalization, with effective inhibition of U2OS cancer cell growth. Therefore, monodispersed SiO_2@MgAl-LDH nanocomposites can be a promising nonviral delivery carrier for *in vivo* drug and gene delivery [96].

4.2.4 Supramagnetic nanocomposites for doxorubicin: Manganese ferrite/graphene oxide ($MnFe_2O_4$/GO) nanocomposites as controlled targeted drug delivery were prepared by a facile sonochemical method. The magnetization curve indicated superparamagnetic behavior of the obtained $MnFe_2O_4$/GO with saturation magnetization at room temperature. The *in vitro* cytotoxicity testing exhibited negligible cytotoxicity of as-prepared $MnFe_2O_4$/GO even at the high concentration. The as-prepared nanocomposites display high loading capacity of anti-cancer drug DOX, and the loaded DOX shows an interesting pH responsive release feature, which is favorable for avoiding quick drug release in neutral blood system but promoting drug release at acidic tumor sites or within cells [97].

4.3. Nanocomposites as antimicrobials

4.3.1 Carbonated hydroxyapatite (CHAp)/agarose composites for antimicrobial application: Kolanthai *et al.,* prepared the CHAp/agarose composites with CHAp nanorods encapsulated by agarose by solvo thermal method which resulted in nanorod composites. Additionally, the calcinations produced spherical particles and rods in pure HAp of a reduced size. The powder composites were mesoporous with low dissolution rate, high *in vitro* bioactivity, high hemocompatibility and non-cytotoxicity as compared to pure HAp. The composites showed a sustained drug (Amoxicillin, 5- Fluorouracil) release and high antimicrobial activity against common bacterial strains of *E. coli, S. aureus* and *S. epidermidis* in contrast to calcined (HAp) samples. The synthesized mesoporous nanopowder composites displayed an enhanced surface area, bioactivity, sustained drug release and high antimicrobial resistant against gram positive and gram native bacteria, enabling their void filling applications in bone and drug delivery system. The calcined samples can be used for the rapid release of the antibiotic and anti-cancer drug to damaged tissues [98].

4.3.2 Chitosan-based nanocomposite of ofloxacin: Chitosan is obtained from extensive deacetylation of chitin and has wide applications in the area of tissue engineering, controlled and targeted drug delivery system. Nanocomposites with chitosan as the matrix phase and nanosized reinforcements such as carbon nanotubes, organically modified nanoclays and biobased reinforcements results in more stable and stronger materials [99].
Synthesis of chitosan-g-poly(acrylamide)/CuS (CPA/CS) nanocomposite for controlled delivery of ofloxacin was carried out by Pathania *et al*. The drug release behavior was dependent upon the pH of medium and the nature of matrix. The maximum drug loading efficiency of 85% was recorded for CPA/CS. The maximum drug release was observed at acidic pH after 18 h from CPA/CS. Nanocomposites were tested for antibacterial activity against *Escherichia coli* bacteria and was found to be approximately 97% after 24 h [100].

4.4. Miscellaneous applications

4.4.1 Bone implant: The typical goal of a bone tissue engineering approach is to develop bone graft replacements that can repair bone defects without the need for allografts or autografts [101]. With this approach, the porous scaffold serves an important role in the manipulation of the functions of osteoblasts and a central role in the guidance of new bone formation into desired shapes [102, 103]. Chitosan-graft-poly(AA-co-AAm)/hydroxyapatite (HAp) nanocomposite scaffolds were synthesized as a bone implant and a drug carrier. It was found that mechanical strength of the scaffolds can be improved by either increasing the HAp nanoparticles amounts or reducing pore size of the scaffolds. The cytotoxicity of the prepared scaffolds' extracts was examined by determining the viability of human fibroblast gum (HUGU) cells using MTT assays. The results of the cell culture experiments demonstrated that the prepared scaffolds have good cytocompatibility without any cytotoxicity. It was also found that increasing amount of the HAp nanoparticles improves cell viability and proliferation on the scaffolds. The presence of the HAp nanoparticles affected the celecoxib loading and the encapsulation efficiency of the prepared scaffolds. Results from the Kopcha models revealed that the release of celecoxib from the prepared red biocompatible nanocomposite scaffolds can be used for studies for further *in vivo* assessment in bone tissue engineering [104].

4.4.2 Combinational drug delivery: A novel antibacterial clay/polymer nanocomposite with average particle size of 20–40 nm and two cationic compartments in polymer was synthesized *via* ion exchange by Zeynabad *et al.,* This multifunctional nanocomposite was used for dual drug delivery of anticancer drug methotrexate (MTX) and an antibacterial agent ciprofloxacin (CIP) with encapsulation efficiency of 90% for both drugs. CIP loaded nanocomposites showed enhanced antimicrobial activity in comparison to free CIP. The cytotoxicity studies demonstrated enhanced cytotoxicity of developed MTX loaded nanocomposite in comparison to free MTX against MCF7 cell lines. Cell cycle study showed that MTX-loaded nanocomposite caused S-phased arrest in MCF-7 cells compared to control nontreated cells. The dual CIP/MTX formulated NC provided the opportunity to deliver both MTX and CIP drugs in combination and pH dependent, sustained release [105].

4.4.3 Control release with MRI: Developing multifunctional theranostic platforms with complementary roles has drawn considerable attention in recent years. Wang *et al* synthesized doxorubicin loaded superparamagnetic cobalt ferrite/graphene oxide ($CoFe_2O_4$/GO) nanocomposites with integrated characteristics of magnetic resonance imaging and controlled drug delivery. The obtained $CoFe_2O_4$/GO exhibited superparamagnetic property and dose-dependent T2-weighted enhancement effect with negligible cytotoxicity. The nanocomposites were found to be able to efficiently transport DOX into the cancer cells and then cause cell death. The drug loading capacity of this nanocarrier was high and the drug release behavior demonstrated a sustained and pH-responsive release, which is favorable for avoiding quick drug release in neutral

blood system but promoting drug release at acidic tumor sites or within the cells. The results suggested that the prepared $CoFe_2O_4$/GO nanocomposites showed great potential as an effective multifunctional nanoplatform for magnetic resonance imaging and controlled drug delivery for simultaneous cancer diagnosis and chemotherapy [106].

4.4.4 Oral delivery of insulin: Drug-loaded montmorillonite nanocomposites were prepared by intercalation of insulin into the montmorillonite layers followed by TiO_2 coating. Incorporation of porous TiO_2 coating increased the drug entrapment and sustained the drug release. These nanocomposites can be used in converting the insulin utilization from injection to oral as the procedure is simple and cost-effective & utilizes pharmaceutically approved, biocompatible and non-polluting materials. Also, prevention of digestive degradation of the drug due to its entrapment in the nanocomposite system may potentially change the route for insulin delivery from injection to oral that presents a painless and more comfortable treatment for diabetics [107].

4.4.5 Light controlled metallo-drug delivery: Nesic *et al.,* studied the colloidal TiO_2 nanoparticles as a carrier for controlled delivery of the ruthenium complex to the melanoma cell line. The system demonstrated slower complex release upon visible and increased release rate upon UV light illumination. The light–dependent cytotoxicity of the system was also done on amelanotic melanoma cancer cell line. The cell death was enhanced by UV and reduced by red light in the presence of investigated nanocomposite system. Both components of the system acted as photosensitizers, by generating reactive oxygen species, which promoted cell death. Thus, the system might act dually, as photodynamic therapeutic agent and as the light tunable system for metallo-drug delivery and it might be of interest for development of more efficient drug delivery approaches by using a light as external stimulus [108].

4.4.6 Nanocomposites in tissue engineering: Tissue engineering, a technique to create biological substitutes meant to repair or replace failing organs or tissues, applies methods from materials engineering and life sciences. One of the most promising approaches is to grow cells on highly engineered porous structures known as scaffolds which act as temporary support for cells, facilitating the regeneration of the target tissues without loss of the three-dimensional (3D) stable structure. Polymeric scaffolds play a key role in tissue engineering through cell seeding, proliferation and new tissue formation in three dimensions [109]. The utilization of biodegradable polymers in biodegradable nanocomposites has great potential as tissue repair and/or regeneration in orthopaedics. Thiolated chitosan (TCS), one of the promising derivative of chitosan possesses improved solubility, processibility, mucoadhesive, and permeation properties over CS. It is proposed as a promising candidate as scaffold material for tissue engineering by Li *et al.,* [110]. Erisken et al., successfully fabricated functionally graded electrospun polycaprolactone and b-tricalcium phosphate nanocomposites for tissue engineering applications [111].

4.5 Magnetic, pH and temperature stimuli-sensitive nanocomposite in drug delivery

Response to stimulus is a basic process of living systems [112]. The human body has the capacity to react to certain conditions at sub-atomic to the macroscopic level [113]. This concept led to the development of "smart" materials that react to light, pH, temperature, mechanical stress or magnetic field.

Magnetic nanocomposites are multi-component materials which mainly contains nanosized magnetic materials to trigger the response to an external stimulus like an external static or alternating magnetic field [114]. Hervault *et al.,* developed magnetic nanocomposites (MNCs) made of an iron oxide core and a pH- and thermo-responsive polymer shell that can be used as both hyperthermic agent and drug carrier. Their study reported that conjugation of anticancer drug doxorubicin (DOX) to the pH- and thermo-responsive MNCs *via* acid-cleavable imine linker provides advanced features for the targeted delivery of DOX molecules *via* the combination of

magnetic targeting, and dual pH- and thermo-responsive behavior which offers spatial and temporal control over the release of DOX [115].

pH-responsive nanocomposites as controllable drug delivery system has been designed by incorporating positive charges in the framework of polymers, so that anionic molecules can be efficiently adsorbed inside of the carriers with minimal release under weak acidic pH value. Mahkam *et al.,* prepared and characterized montmorillonite-pH-sensitive positive charges nanocomposites as a drug delivery system. Naproxen was used as a model drug which is entrapped in these pH-sensitive positive charge nano carriers and the *in vitro* release profiles were established separately in both enzyme-free simulated gastric and intestinal fluids (SGF; pH 1) and (SIF; pH 7.4), respectively [116].

Ji *et al.,* developed coumarin-containing photo-responsive nanocomposites for NIR light-triggered controlled drug release. The potential application of this NIR-responsive biocompatible nanocomposite system is NIR light-triggered release of DOX. During the study, cytotoxicity and cellular uptake of the nanocomposite were also investigated [117].

Table no. 1 shows some of the reported nanocomposites based controlled and targeted drug delivery systems.

Table 1: Nanocomposites based controlled and targeted drug delivery systems

Sr. no	Name of nanocomposite	Application	Reference
1	Montmorillonite-alginate nanocomposite	Sustained delivery of irinotecan	[37]
2	MMT Nanocomposites	Sustained delivery of ibuprofen	[41]
3	Polyamide-montmorillonite nanocomposites	Antimicrobial activity of 1, 3, 4-Oxa (thia) diazoles	[50]
4	Chitosan/organic rectorite (OREC) nanocomposite films	Bactericidal activity of BSA	[51]
5	Magnetic composites	Soft Actuator-type application	[70]
6	Nanocomposite hydrogels of HLE	For local drug delivery for the treatment of periodontal infections	[74]
7	Sodium alginate/chitosan/hydroxyapatite nanocomposite hydrogels	For the oral delivery of doxorubicin (DOX)- an anticancer drug for liver cancer	[75]
8	Chitosan based naanocomposites	Controlled delivery of metformin	[81]
9	BTC/GPO nanocomposites	Controlled delivery of ibuprofen	[85]
10	Carbonated hydroxyapatite/agarose composites	Sustained drug release and antimicrobial application of Amoxicillin, 5- Fluorouracil	[87]
11	CS/LBG nanocomposites system	Controlled delivery of aceclofenac	[89]
12	Graphene oxide/Carboxymethylcellulose nanocomposites	Targeted delivery of anticancer drug doxorubicin	[94]
13	SiO_2 dot-coated hydroxide nanocomposites	Controlled delivery of methotrexate in human osteosarcoma	[96]
14	Manganese ferrite/graphene oxide nanocomposites	Controlled targeted drug delivery of doxorubicin	[97]
15	Chitosan-g-poly(acrylamide)/CuS(CPA/CS) nanocomposite	Antimicrobial application of ofloxacin	[100]

16	Chitosan-graft-poly(AA-co-AAm)Hydroxyapatite nanocomposites	Bone implant/Drug carrier	[104]
17	Clay/Polymer nanocomposite	Combinational drug delivery of anticancer drug methotrexate and antibacterial agent ciprofloxacin.	[105]
18	Superparamagnetic cobalt/graphene oxide nanocomposites	Control release of doxorubicin with MRI	[106]
19	Montmorillonite nanocomposites	Oral delivery of insulin	[107]
20	pH and thermo responsive nanocomposites	Targeted delivery of doxorubicin	[115]

5.0 Conclusion

Nanocomposites have wide applications in controlled and targeted drug delivery. The types of systems include inorganic, metal, magnetic and polymeric nanocomposites. Various stimuli sensitive, smart polymeric systems that responds to change in pH, temperature or a specific phase have also been developed as nanocomposites and have been effectively utilized to control the release of drugs. Nanocomposites systems have also been reported for biomedical and diagnostic applications.

List of abbreviations:

APS: Aminopropylsilane; BSA: Bovine Serum Albumin; BTC: Bacterial cellulose; CHAp: Carbonated hydroxyapatite; CIP: Ciprofloxacin; CPA: Chitosan-g-poly(acrylamide); CMC: Carboxymethylcellulose; CMNC: Ceramic matrix nanocomposites; CNT: Carbon nanotubes; CS: Chitosan; DOX: Doxorubicin; EDC/NHS: ethyl carbodiimide/N-hydroxysuccinimide; FDA: Food and Drug Administration; GPO: Graphene oxide; GNCs: Gelatin Nanocomposites; GO: Graphene oxide; HAp: Hydroxyapatite; HCl: Hydrochloric acid; HLE: Harunganamadagascariensis leaf extract; IBP: Ibuprofen; LBG: Locust bean gum; LCST: Lower critical transition temperature; LDH: Layered double hydroxide; Lf: Lactoferrin; MAS: Magnesium aluminum silicate; MET: Metformin; MMNC: Metal matrix nanocomposites; MTX: Methotrexate; MWCNTs: Multi-walledcarbon nanotubes; MNCs: Magnetic nanocomposites; NC: Nanocomposites; NIPAAm: N-isopropylacrylamide; NPs: Nanoparticles; NIR: Near infra-red; OREC: Organic rectorite; PLLA: Poly L-Lactic Acid; PMNC: Polymer matrix nanocomposites; PNCs: Polymer nanocomposites; PVA: Poly(vinyl alcohol); RFI: Resin film infusion; RTM: Resin transfer molding; SGF: Simulated gastric fluid; SIF: Simulated intestinal fluid; TEOS: Tetraethoxysilane; TPP: Tripolyphosphate ; T2DM: Type 2 diabetes mellitus; UV: Ultraviolet; VARTM: Vacuum assisted resin transfer molding;

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