DOI 10.1007/s11094-020-02203-0
Pharmaceutical Chemistry Journal, Vol. 54, No. 4, July, 2020 (Russian Original Vol. 54, No. 4, April, 2020)

ANTICANCER DRUG DELIVERY SYSTEMS BASED ON CURCUMIN NANOSTRUCTURES: A REVIEW

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Original article submitted January 9, 2020.

In recent years, the application of nanostructures in biomedical and pharmaceutical fields has increased. The special designs and compositions make nanocomposites very useful alternatives to conventional materials. Curcumin is a promising anti-cancer agent that has a positive and significant effect on chemotherapeutic achievements. The anticancer properties of curcumin have been widely investigated in different forms such as nanoparticles and nanocomposite structures. Chitosan-based nanocomposites, magnetic nanoparticles, polymer nanocomposites and blends, and montmorillonite- and alginate-based nanocomposites have been used in loading curcumin for various purposes. The anticancer preparations of curcumin nanoparticles and drug release systems employing curcumin-loaded nanoparticles, electrospun nanofibers, and hydrogel nanocomposites have been investigated. This review provides a summary of the applications of nanostructures containing curcumin, especially in controlled drug release systems. The curcumin nanoparticles and nanocomposites are suitable candidates for anticancer applications. On the nano-scale, curcumin has better aqueous solubility and, if used in a nanocomposite, there is a good ability for manipulating the drug delivery system properties.

Keywords: curcumin; controlled drug release; cancer; nanoparticles; nanocomposites;

1. INTRODUCTION

In recent years, nanocomposites as drug carriers found improved pharmaceutical applications. Nanocomposites represent composites with at least one component having dimensions in the nanoscale range (1 – 100 nm). These materials exhibit remarkable properties such as high mechanical strength, electrical conductivity, thermal stability, optical clarity, chemical resistance as well as drug release controlling ability [1 – 3]. Nanocomposites can provide a broad range of new properties for drug delivery systems. The aims of controlled drug release from nanocomposites are improved patient compliance, increased drug efficacy, and optimized dosage over extended periods. Among these nanocomposites, polymer-matrix based composites are suitable candidates for drug delivery as nanocarriers due to their special properties [4, 5].

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Nanocomposites are matrices in which filler components with the nanometer size are added to manipulate and reinforce the matrix properties. The small amount of nanosized reinforcement materials gives the matrix several advantages as compared to macrosized additions. Indeed, nanocomposites with high water uptake capacity, biocompatibility, non-toxicity, sensitivity to external stimuli, and biodegradability are great candidates for application in drug release systems [6. 7]. Nanocomposites are categorized as zero-, one-, two-, and three-dimensional nanomaterials. Nanoparticles are the most typical zero-dimensional nanomaterials, which have crystalline (single- or polycrystalline) or amorphous structure [8]. Nanowires, nanosheets, nanorods and nanoplatelets are one-dimensional nanomaterial. Nanofilms, nanolayers, nanocoatings, carbon nanotubes and nanowhiskers are two-dimensional nanomaterials. Finally, three-dimensional nanomaterials include nanogranules, equiaxial nanoparticles, and nanoclays [9].

The matrices of nanocomposites have ceramic, metallic or polymer chemical structures. The ceramic nanocomposites have wide industrial applications. The common ceramic matrixes of nanocomposites are Al_2O_3-SiO_2, SiO_2-Ni, Al_2O_3-TiO_2 and Al_2O_3-SiC [10]. Metal matrixes of nanocomposites are made from metal or alloy. The common metal

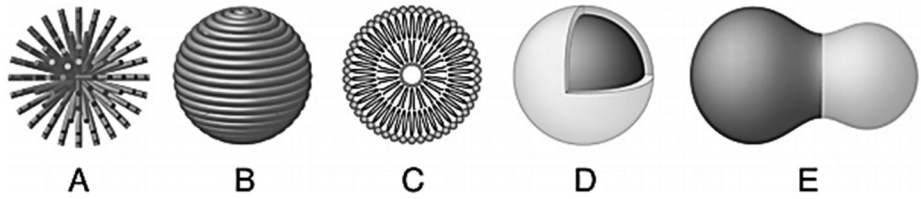

Fig. 1. Various methods of MNP modification for drug delivery systems: (A) end-grafted polymer coated MNP, (B) MNP fully encapsulated in polymer coating, (C) liposome encapsulated MNP, (D) core–shell MNP, (E) heterodimer MNP [35].

matrixes of nanocomposites are Fe/Cr-Al_2O_3, Ni-Al_2O_3, Fe-MgO, Co-Cr, Al-CNT, and Mg-CNT [11]. In polymer nanocomposites, both the matrix and nano-additives can involve a wide range of materials. Nanoparticles, nanofibers, nanotubes and layer-like materials are used regularly for polymeric nanocomposite preparation. This this type of nanocomposites has a wide range of applications because of high elasticity, light weight, barrier resistance, ease of production, and low cost [12].

Harmful side effects of chemotherapy, such as killing healthy cells, nausea and vomiting, diarrhea and hair loss, interest researchers to develop drug delivery systems. Manipulating different materials especially polymers to give them anticancer ability has been performed using different nanostructures as additives. The advantages of using nanocomposites in cancer drug delivery include entrapped drugs with high half-life and longer circulation in blood as well as the addition of nanostructures like graphene, graphene oxide, and magnetic Fe_3O_4 nanoparticles which ensure improved cancer cells targeting [13, 14]. The side effects of most chemotherapeutic drugs hardly tolerated by patients are hair loss, nausea, vomiting and diarrhea.

Curcumin is a hydrophobic herbal compound containing aromatic rings of phenol. It has been used as anti-inflammatory, antirheumatic and antimicrobial drug, and its cytotoxicity study showed good activity against cancer cells. The bioavailability and anticancer performance of curcumin depend on its stability and aqueous solubility, therefore poor solubility and stability caused low bioavailability and resulted in low anticancer activity. To overcome these limitations, curcumin can be included in polymer nanocomposites and used in drug delivery systems [15, 16].

2. PROPERTIES OF CURCUMIN

Curcumin is 1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione and appears as hydrophobic phytochemical molecule that can be extracted from turmeric. It was reported that curcumin exhibited anti-tumoral [17], antimicrobial and anti-inflammatory [18, 19], and anti-HIV [20] properties, as well as it has been demonstrated that curcumin can chelate iron in aplastic anemia [21]. Unfortunately, curcumin has limited medical applications because of poor aqueous solubility, rapid degradation and poor absorption through the gut [22]. To solve these problems, drug delivery systems made from polymeric micelles, hydrogels, nano and micro emulsions, cyclodextrins, liposomes and biodegradable microspheres with loaded curcumin have been developed. Biodegradable polymer nanocomposites have been used for the delivery of antitumor drugs with low side effects, destruction of tumor cells, high ability of crossing cell wall, as well as targeted and controlled drug delivery [23].

3. CURCUMIN LOADED NANOCOMPOSITES

3.1. Chitosan-Based Nanocomposites

Chitosan is a natural biopolymer composed of β-(1-4)-2-acetamino-2-deoxy-β-D-glucose derived from chitin. It is soluble in dilute acidic media, for example, formic, citric, lactic, acetic acids and ionic liquids. The NH_2 functional groups of chitosan protonated to NH_3^+ interact with negatively charged surfaces, and eventually the dissolution of chitosan molecules takes place [24]. Chitosan has wide applications due to excellent chemical and biological properties, including membranes, tissue engineering, biomedicine, environmental protection, food industry, etc. Chitosan exhibits biocompatibility, high biological activity, biodegradability, non-allergenicity, low toxicity and film forming capacity [25, 26]. Electrostatic interactions between positively charged chains of chitosan and negatively charged drug molecules such as curcumin allow drugs to be kept in chitosan-based composite and ensures prolonged drug release profile [27]. For these reasons, chitosan can be a promising candidate as nanocarrier for drug delivery [28]. Carbon nanotubes, montmorillonite, nanoclays, graphene oxide, noble metals, polymer and magnetic nanoparticles were added to chitosan to prepare carriers for drug delivery systems [29 – 31].

3.2. Magnetic Nanoparticles

Magnetite nanoparticles (MNPs) with good biocompatibility, adjustable nanoscale sizes, targeting ability and biological degradability [32] have been applied in biomedical and drug delivery system. Synthesis of chitosan/polyethylene glycol/poly(vinyl pyrrolidone) (CS/PEG/PVP) polymer

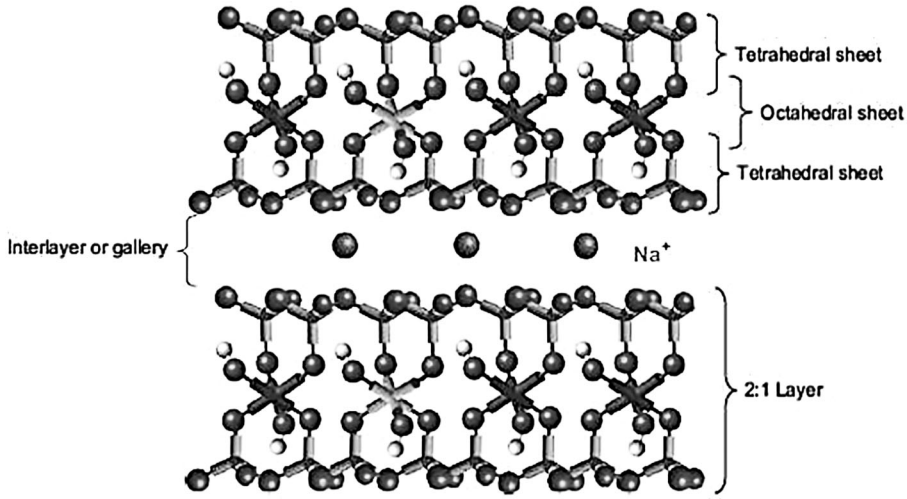

Fig. 2. Chemical structure of sodium montmorillonite [44].

nanocomposites have been performed using magnetite (Fe_3O_4) nanoparticles as nanosized component. Chitosan and Fe_3O_4 with nanoparticle sizes (20 – 80 nm) can be dissolved in acetic acid solution. Then curcumin solution has been prepared separately and mixed with magnetic chitosan solution to prepare a drug-chitosan magnetic solution. This solution has been added to the sodium tripolyphosphate (TPP) solution. The PEG and PVP solutions have been added to Fe_3O_4/CS/curcumin to form drug loaded nanocomposites of Fe_3O_4/CS/PEG and Fe_3O_4/CS/PEG/PVP. High drug loading, good drug encapsulation, slow drug release and low interaction with cancer cells were observed. Therefore, it has been established that that curcumin loaded Fe_3O_4/CS/PEG/PVP, Fe_3O_4/CS/PEG, and Fe_3O_4/CS nanocomposites have high potential for applications to cancer therapy [33]. In another study, nano and macro sizes of magnetic Fe_3O_4/carboxymethyl chitosan nanocomposite have been prepared. It was demonstrated that the amount of loaded and released curcumin depends on Fe_3O_4 particle sizes, and the chitosan composites with nanoparticle showed higher drug loading and lower drug release [34]. Various structures of MNPs have been used for drug carriers such as end-grafted polymer-coated MNPs, MNPs fully encapsulated in polymer coating, liposome encapsulated MNPs, core–shell MNPs and heterodimer MNPs. Figure 1 shows schematic diagrams of various methods for application of MNPs to drug carriers [35].

3.3. Polymer Nanocomposites and Blends

Synthetic polymers as well as natural polymers have been used in composites for curcumin-controlled release. A nontoxic alginate/chitosan/Pluronic composite was prepared and curcumin was encapsulated it. Briefly, calcium chloride and sodium alginate aqueous solutions were mixed. Then chitosan solution was added dropwise, followed by stirring and centrifuging. The curcumin encapsulation efficiency was been increased in the presence of Pluronic. It has been found that the curcumin loaded nanoparticles can be incorporated into HeLa cells, thus these composite also have potential application in cancer therapy and the hydrophobic drug delivery [36]. The biodegradability of starch/chitosan/montmorillonite nanocomposite was investigated and results showed that this property increased with increasing amount of chitosan. It was demonstrated that curcumin release depends on pH and components of polymer nanocomposite. The drug was suitable for basic environment [37]. As a film forming polymer nanocomposite, polyvinyl alcohol/chitosan films have been prepared and incorporation of curcumin successfully performed. The results of drug diffusion showed that higher amounts of PVA positively affected the rate of drug release from films because PVA had acceptable swelling ratio in water [38]. A polymer nanocomposite consisting of curcumin/silver nanoparticles in polyethylene glycol was prepared and used for antibacterial applications. Silver nanoparticles were prepared using an in-situ method in the presence of curcumin. The results showed this polymer nanocomposite to be an effective candidate for antibacterial applications [39].

3.4. Montmorillonite Based Nanocomposites

Montmorillonite (MMT) is a phyllosilicate type of minerals that has low price, large surface area, drug-carrying ability, good absorption capacity and cation exchange ability (Fig. 2). Montmorillonite showed high ability of swelling due to its peculiar structure [40]. Composites possessed rough and porous surface and thus showed excellent sorption properties [41]. The montmorillonite/chitosan (MMT/CS) nanocomposites exhibited good thermal strength, mechanical characteristics, and water uptake, and have been introduced as effective drug release systems [42]. These nanocomposites can absorb both negatively and positively charged drugs

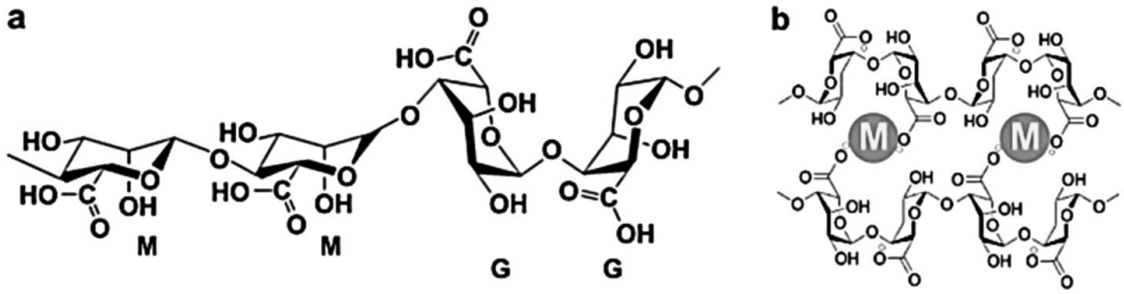

Fig. 3. (a) Alginate chemical structure and (b) interaction of alginate negative ions with divalent cations [51].

on their cationic chitosan and anionic clay components. Since MMT/CSnanocomposite had poor solubility at gastric pH, the stability and bioavailability of drugs must increase in the gastrointestinal tract [43].

3.5. Alginate Based Nanocomposites

Alginate is a polysaccharide that is biocompatible, naturally biodegradable, and widely used in pharmaceutical and biomedical applications [45]. Alginates are salts of alginic acid, including sodium, aluminum, calcium, barium and zinc alginates, and sodium alginate has most commercial applications among others [46]. Figure 3 shows the chemical structure of alginate and ionic interaction of alginate with divalent cations. Sodium alginate has good solubility in hot water. It can produce gelatinization by ionic interaction in the presence of various di- or trivalent metal cations [47]. The ionic cross-linking between carboxyl groups of alginate molecule and metal cations formed egg-like structures called "egg-box" model [46 – 48]. Curcumin loaded magnetic alginate/chitosan nanocomposites have been prepared to study of curcumin cytotoxicity on breast cancer cells of MDA-MB-231. The nanocomposites exhibited growth in cytotoxicity with increasing curcumin concentration and expected to be promising components for drug delivery systems for anti-cancer treatment [49]. The pharmaceutical characteristics of curcumin have been improved by alginate/pectin blend. Curcumin has been loaded in alginate/pectin beads in order to enhance its effect on colon cancer. Strong curcumin entrapment has been observed with beads immersed in the curcumin solution. The curcumin-loaded beads showed slow drug release in the model medium of upper parts of gastrointestinal tract and sudden release in colonic buffer medium [50].

4. CURCUMIN LOADED NANOMATERIALS FOR CANCER TARGETED DRUG DELIVERY

4.1. Curcumin Nanoparticles

Nanotechnology helps to improve of curcumin unfavorable properties in the drug delivery systems with controlled and slow drug release into cancer cells [52 – 54]. The curcumin nanoparticles of encapsulated in protein/peptide, cyclodextrin, liposomes, phospholipid and polymer nanoparticle (NP) were designed to delivery of curcumin in an aqueous medium. Because of biodegradable and bioavailability properties of polymer nanoparticles, they selected as carriers of curcumin drug [55 – 57]. Curcumin and superparamagnetic iron oxide nanoparticles (SPIONs) were dissolved in ethyl acetate, poly(lactide-co-glycolide) (PLGA) was added and the mixture was sonicated. Then, the mixture was added dropwise to polyvinyl alcohol solution, followed by stirring and centrifuging. The curcumin encapsulated-SPION-PLGA nanoparticles were prepared. These magnetic nanoparticles can destroy cancer cells of pancreatic (PANC-1 and MIA PaCa-2) [58].

Curcumin has also been encapsulated in polymers including polylactide and D-α-tocopheryl polyethylene glycol succinate (PLA–TPGS) copolymer, 1,3-β-glucan (Glu), O-carboxymethyl chitosan (OCMCs) polymer and OCMCs-folic acid (Fol). The results showed that these nanoparticles could be promising candidates for cancer therapy [59]. Other studies reported that curcumin was encapsulated in poly(lactide-co-glycolic acid) (PLGA) with polyvinyl alcohol and poly(L-lysine) as stabilizer [60], polyethylene glycol – PLGA [61] and poly(N-isopropylacrylamide) (PNIPAAm) – methacrylic acid [52] and tested for activity against cancer cells. The prepared curcumin-loaded nanoparticles showed increased inhibition of cancer cell growth as compared to free curcumin.

4.2. Curcumin/Nanoparticle Systems

Curcumin loaded gold/graphene oxide nanocomposites have been synthesized and used for controlled drug delivery. The drug release in such systems was pH sensitive and pH 5.3 was the best for drug release. These nanocomposites showed low toxicity for healthful cells and were biocompatible [62]. In another study, silver/reduced graphene oxide (Ag/RGO) and curcumin have been dispersed in tetrahydrofuran and added to the hyper-branched epoxy resin. The nanocomposites were biocompatible and suitable for antimicrobial applications because they could prevent fungal, bacterial and algal growth on surfaces [27]. Li, et al. [63] prepared γ-Fe_2O_3/polyaniline-curcumin (γ-Fe_2O_3/PANI-cur-

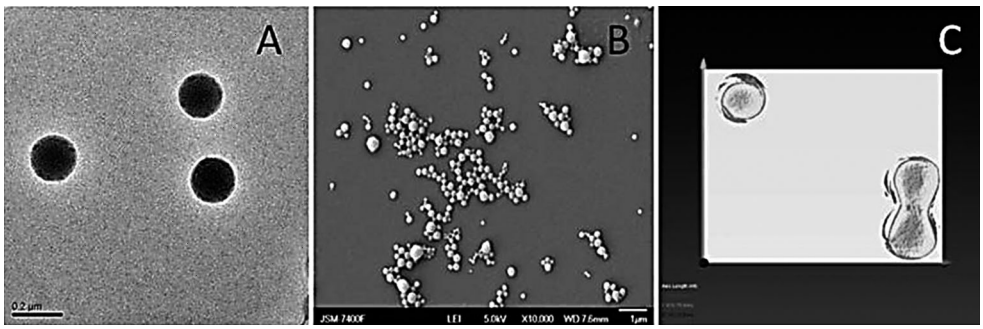

Fig. 4. (A) TEM micrograph; (B) SEM micrograph; and (C) 3D-TEM tomography image of encapsulated curcumin nanoparticles [65].

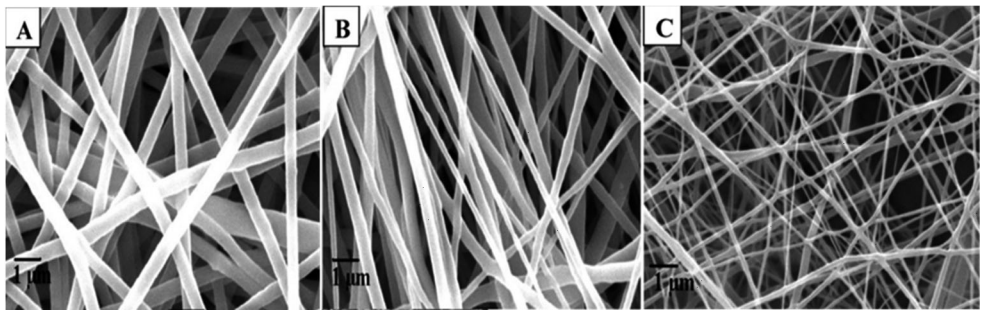

Fig. 5. SEM micrographs of (A) polyurethane, (B) polyurethane – dextran and (C) polyurethane – dextran – drug nanofiber mats [72].

cumin) nanocomposite and investigated its performance as anticancer drug delivery system. Another organic-inorganic hybrid prepared form curcumin loaded on ZnO nanoparticles has also been used for anticancer drug delivery and showed high antibacterial activity and potential toxicity against gastric cancer cells [64]. Figure 4 shows TEM micrograph, SEM micrograph, and 3D-TEM tomography images of encapsulated nanoparticles of curcumin with PLGA [65].

4.3. Electrospun Nanofibers

The electrospinning method can be a promising technique for the preparation of systems for controlled drugs delivery. The electrospun fibers have been used as carriers for anticancer drugs. They showed attractive properties of low cost, nanoporous structure, high production rate, high surface area, and ability for physical/chemical modification. These properties suggest having various applications in pharmaceutical field, especially drug delivery systems [66]. The electrospinning method has been used for preparation of a single system consisting of curcumin-loaded poly(3-caprolactone) – poly(ethylene glycol) – poly (3-caprolactone) nanofibers. The cytotoxicity study of these nanofibers indicated that they strongly affected the growth of glioma 9L cells [67]. Polyvinyl alcohol (PVA), polyethylene glycol (PEG), polylactic acid (PLA), and polyurethane (Fig. 5) are polymers that have been widely used in electrospun nanofibers for curcumin drug delivery [68, 69]. In [70], a mixture of PVA and PEG has been prepared, sonicated, and dried in oven to form a polymer film. In another mixture, curcumin was mixed with PLA and then electrospun on PVA – PEG film. The obtained flexible composite had wound-healing dressing and anticancer applications [70]. In other report, chitosan/PVA nanofibers were prepared by electrospinning method and then nanofibers were immersed into methanol/curcumin solution. The nanofibers of lower molecular weight such as chitosan showed higher rate of curcumin release because higher viscosity caused curcumin to be covered by a gel layer which hindered the curcumin release [71].

4.4. Hydrogel Nanocomposites

Hydrogels exhibit stimulus-responsive properties and are used for various applications including drug delivery [73, 74]. The crosslinking density of hydrogels is an important factor in hydrogel synthesis for controlled drug release. Due to their enhanced response to stimulus, hydrogels attracted considerable attention for use in these systems. A hydrogel-based curcumin drug carrier has been adopted using PVA and sodium alginate composition with few-layer graphene oxide (GO). SEM micrographs showed a three-dimensional structure of GO in this hydrogel (Fig 6). It was demonstrated that three-dimensional GO increased the swelling ratio up to 5 times and decreased drug release rate by 59% [75].

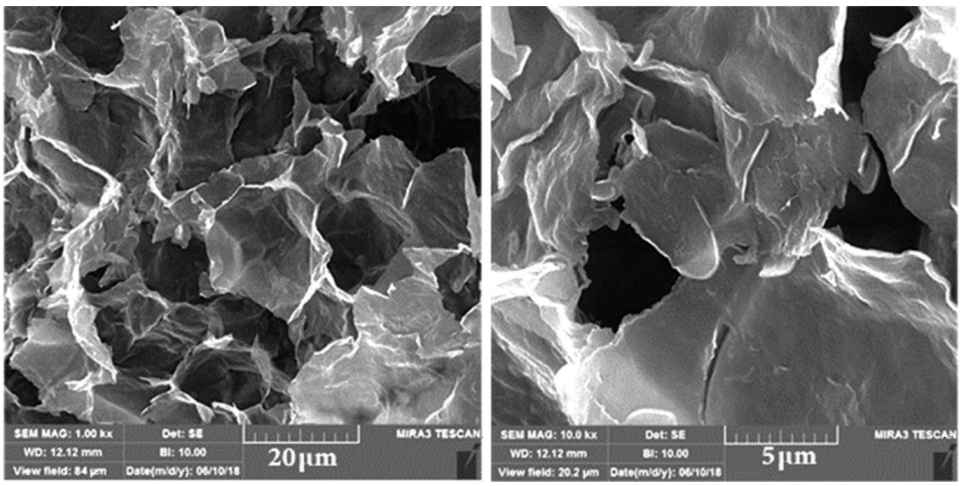

Fig. 6. SEM micrographs of three-dimensional graphene oxide in PVA-sodium alginate polymer blend as a hydrogel-based curcumin drug release system.

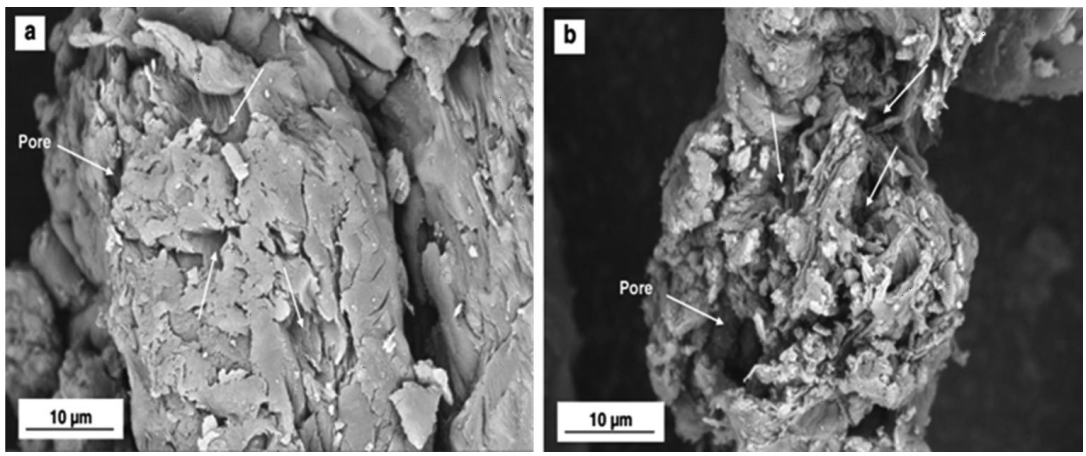

Fig. 7. (a) SEM micrographs of sodium alginate-g-p(acrylic acid-co-acrylamide) hydrogel and (b) sodium alginate-g-p(acrylic acid-co-acrylamide)/clinoptilolite hydrogel nanocomposites [77].

Poly(N-isopropylacrylamide-co-methacrylic acid) copolymer hydrogels are useful drug delivery systems for cancer therapy [63]. Doxorubicin-loaded poly(n-isopropyl acrylamide) thermo-sensitive hydrogel based on single-walled nanotubes was prepared for gastric cancer therapy [76]. Curcumin encapsulated in these hydrogels gave a perfect result by inhibiting the growth of MCF-7breast cancer cells. Figure 7 shows SEM micrographs of sodium alginate–g–p(acrylic acid-co-acrylamide) hydrogel, and sodium alginate-g-p(acrylic acid-co-acrylamide)/clinoptilolite hydrogel nanocomposites [77].

5. CONCLUSION

Nanocomposites are new materials that have wide applications in targeted and controlled drug delivery systems. The tapes of nanocomposites can be ceramic, metallic, and polymeric. Among these, polymeric nanocomposites have been developed for the control and release of drugs due to their being stimuli-sensitive and smart systems that respond to changes of pH, temperature, or illumination. Curcumin is a hydrophobic drug with attractive pharmaceutical properties, especially for cancer treatment. Unfortunately, poor aqueous solubility of curcumin restricts to decrease of its medical applications. However, curcumin loaded nanocomposites such as alginate or chitosan-based nanocomposites, magnetic nanoparticles, polymer nanocomposites, and montmorillonite can be used to solve this problem. The anticancer activity of curcumin has been reported in nanoparticle systems, electrospun nanofibers, and hydrogel nanocomposites, which proved to be suitable candidates for anticancer applications.

ACKNOWLEDGMENTS

The authors are grateful to the University of Kashan for supporting this work.

CONDLICT OF INGTEREST

The authors declare that they have no conflict of interest.

COMPLIANCE WITH ETHICAL STANDARDS

This work did not contain any studies with human and animal subjects performed by any of the authors.

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