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An overview of the development of composites containing Mg and Zn for drug delivery

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ABSTRACT

Drug delivery is known as the administration of drugs using suitable vehicle for achieving effective treatment with no unwanted effects. In recent years, various composite materials have been developed and evaluated for being used in different biomedical fields such as wound dressings, cardiac prosthesis, tissue engineering, and drug delivery. Zinc is the second most available element after Fe in our body. Nanoparticles based on metal oxides, such as zinc oxides and Zn-containing composites, can be considered as viable platforms for some biomedical uses, especially for drug delivery applications. Mg composite biomaterials are also suggested for diverse biomedical applications due to their good mechanical properties, biocompatibility, and bioactivity. This paper highlights applications of zinc and magnesium-based composites in development of drug delivery systems.

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1. Introduction

Drug delivery systems are designed for the administration of a pharmaceutical compound to promote its therapeutic effects in the animal or human body with minimum side effects [1, 2]. Through extensive studies on animals and humans, our understanding of pharmacodynamics and pharmacokinetic fundamentals has been improved widely. Based on these improvements, several attempts have been implied to improve drug effects in treatment. As a result of these attempts, controlled-release technology is developed, for instance, sustained release drug delivery systems, targeted drug delivery systems, on-demand drug delivery systems, etc. Such systems include tablets, capsules, liposomes, nanoparticles, hydrogels, microneedles and other medical devices [3, 4].

In the past few years, a wide range of composites has been developed and evaluated for different biomedical applications such as cardiac prosthesis, tissue engineering, and drug delivery [5-9]. For instance, for delivering a drug to the intestines, the structure of the composite should include an acid-resistant fatty acid surface covering the interlayers of lactate dehydrogenase (LDH) [10-12]. In recent years, there has been a great interest in the development of bioactive mesoporous materials for drug delivery and bone repair owing to their high pore volume as well as specific surface area. In this regard, a variety of bioactive mesoporous materials have been studied including mesoporous amorphous calcium silicate [13], silica-hydroxyapatite (HAp) composite [14], silica with different pore sizes [15], and $CaO–SiO_2–P_2O_5$ bioactive glasses [16-19].

Zinc is the second most abundant trace element found in our body [20, 21], 85% of which is stored in the bone and muscle [22]. It has been estimated that the zinc amount in our bone is between 110 to 300 mg/kg [23]. The combination of multifunctional properties of zinc and high bioactivity of HAp yields attractive characteristics for biomedical applications [24]. Zn has been termed 'calcium of the twenty-first century' [25]. Intrinsic physiological relevance, pro-regeneration properties, biocompatibility, and biodegradability of Zn has resulted in the emergence of Zinc-based degradable biomaterials [25]. Zn metal-organic frameworks (MOFs), Zn ceramic nanomaterials, and metallic Zn alloys are common Zn-based biomaterials [25, 26]. In the field of drug delivery systems, nanoparticles (NPs) have exhibited prospective performance resulting from facile synthesis and incorporation, high surface area, and high stability, making them suitable for targeting specific cell types and controlling drug release within various microenvironments [27]. PH-responsive drug carriers such as ZnS and ZnO nanoparticles can target tumor cells because the pH values of these cells are noticeably lower than those of normal cells [28, 29]. Nanocomposites are preferred materials for drug delivery due to their adsorption [29].

Mg alloys have attracted great interest among different biodegradable materials owing to their biosafety and desirable mechanical properties [30-32]. Several studies have concentrated on the application of magnesium alloys for temporary cardiovascular stents [33-40]. Furthermore, drug-eluting stents (DESs) have been developed after successfully placing temporary Mg-based cardiovascular stents into a preterm baby's left pulmonary artery [41]. Recently, some Mg alloy-based DESs, such as DREAMS and DREAMS 2G, have been developed, which have lower degradation rate compared to the bare Mg stent and release antiproliferative drug including paclitaxel or rapamycin. The BIOSOLVE-I and BIOSOLVE-II clinical trials of these stents were reported to be successful and no obvious scaffold thrombosis or death was observed, indicating optimal efficacy and biosafety [34, 40, 42]. The mentioned merits of biodegradable Mg-based alloys have encouraged researchers to investigate porous magnesium-based composites that offer higher fracture toughness as well as compressive strength for bone tissue engineering applications [43, 44]. Mg-based composite scaffolds have also shown favorable drug release profiles appropriate for bone infection treatment [45].

The objective of this paper is to review the progress and development of Mg and Zn-containing composites for drug delivery, their synthesis methods, mechanisms, and current challenges and future developments.

2. Drug delivery system

Controlled drug delivery systems (DDSs) are known as formulations or devices that can transport therapeutic agents in the body for their action at specific site, at desired rate, for specific time, and release of the drugs to the target location [46-48]. Therefore, these systems act as an interface between the drug and the patient and help us to develop personalized medicine including pharmaco proteomics, pharmacometrics, and pharmacogenomics. In addition to active pharmaceutical components, an improved delivery process provides a suitable pharmaceutical formulation containing a variety of inactive constituents [49, 50]. Any disease is treated by the specific concentration of therapeutic drugs in plasma with a special regimen [51], which is achieved by a specific drug dose taken at a particular interval in conventional drug therapy. The intervals and the dose of the drug are regulated only based on the half-life and therapeutic index of the drug. In general, fluctuations occur inevitably due to missed dose of the drug, improper patient compliance, over medication or under medication. In order for the drug to be released with an effective therapeutic concentration in a controlled release system, a definite drug release kinetics is required to be followed which is achieved through controlled drug delivery systems [52, 53].

The administration route also influences drug bioavailability. Various administration routes namely, parenteral (subcutaneous, intramuscular, and intravenous) or enteral (ocular, nasal, oral, or transmucosal) can influence the drug bioavailability by altering the biological barrier numbers a drug should cross or by altering the drug exposure to metabolic and pumping mechanisms [54, 55]. To overcome these limitations, it is required to use existing drug effectively and safely using concepts and techniques contributing to controlled/sustained and targeted drug delivery systems. Moreover, the attempts towards overcoming negative aspects of conventional drug delivery that are formed by compression of tablets, coating, and encapsulating bioactive drug molecules have resulted in technological advancements in drug delivery systems and revolution in medication methods [50, 56]. In this regard, computational simulations have also provided a unique insight into the mechanisms of drug diffusion and adsorption in porous carriers at the atomic level [57-60].

3. Composites in drug delivery

In recent decades, noticeable advancements have been observed in the design of chemotherapeutics. However, most chemotherapeutics have some limiting drawbacks such as high cytotoxicity, nonspecific and uncontrolled delivery, high drug dosing, lower solubility, poor absorption, and high side effects [61, 62]. Therefore, it is needed to develop ideal drug delivery systems with some particular properties such as biodegradability, biocompatibility, high drug loading capacity, and capability of drug release in a controlled way. In recent years, different drug delivery systems have been designed to address these parameters including dendrimer, liposomes, and polymers nanoparticles; however, they cannot address the mentioned factors independently [63-66].

The expected characteristics of an ideal drug delivery system could be provided by metal substrate composites. A composite system can offer some advantages like controlled drug release over a long time, stability improvement of drug delivery system, and drug bioactivity preservation in polymeric-based technology. Furthermore, in comparison with pure liposome, dendrimer, and polymeric-based systems, this integrated

system may increase the delivery efficacy [67, 68].

4. Composites containing Mg and Zn in drug delivery

4.1 Zinc and composites containing Zn in drug delivery

Owing to better biocompatibility as well as in vivo biodegradation rate for tissue therapy and regeneration, zinc is considered a preferred candidate for biodegradable metallic materials over Fe and Mg. The emerging theranostics field, such as drug delivery, cancer therapy, bioimaging, and tissue targeting, have extensively benefited from zinc-based ceramic nanomaterials [69, 70]. These ceramics possess several promising characteristics including a high surface-to-volume ratio, pH-responsive nanostructure, good biocompatibility, antibacterial activity, and photoluminescence [71]. Organic biomaterials based on Zn, mainly MOFs, are also promising materials for bioimaging, drug delivery, and cancer therapy due to pH responsiveness as well as large surface/volume ratios [25].

In mesoporous silica nanoparticles (MSNs), the ZnS and ZnO quantum dots, or nanoparticles, are incorporated to cover pores as a component in nanocomposites or cappers [25, 72-74]. In addition, ZnO can exhibit various nanostructures such as nanobels, nano rods, nano disks, nano sheets, nano spheres, quantum dots, etc. It can also be modified to provide excellent properties as a nanocomposite. The US Food and Drug Administration introduced ZnO as one of the safe metal oxides [75, 76]. Moreover, its high energy of excitation-binding around 60 meV, as well as its the wide spot gap around 3.37 eV, add positive properties to its long list of attractive features. Regarding the rewarding properties of ZnO together with its low cost, nanomaterials based on this metal oxide attracted attention in applications related to biomedicine [28, 77]. Furthermore, ZnO nanomaterials exhibit a high capacity of drug loading, have good biodegradability, and can be synthesized through different routes, making them prospective materials for drug delivery. Not only ZnO-based nanocarriers have been fabricated into various forms of nanostructures to deliver drugs to target sites but also they have designed to release the drugs in a controlled manner in response to the pathophysiological conditions [78, 79].

4.2. Magnesium and composites containing Mg in drug delivery

Mg, as one of the important elements in bone tissue and body fluids, has some key roles in the improvement of bone mineral density, reduction of bone fragility, and enhancement of the growth and adhesion of osteoblast cells leading to bony tissue development [31, 80, 81]. Because of the excellent biocompatibility, bioactivity, and mechanical properties of Mg-based biomaterials, they have been considered for local drug delivery systems as well as bone regeneration materials. These systems include forsterite (Mg_2SiO_4) [82], calcium phosphate bone cements doped by Mg [83, 84], magnesium-containing bioactive glasses, etc. [85]. To make biomaterials suitable for bone repair, they are preferred to exhibit a controllable drug delivery capacity in addition to bioactivity [86, 87]. The Mg alloy surface can be treated by bioactive agents to become suitable for this kind of application. Local drug release strategies have several advantages over traditional systemic drug delivery including avoiding systemic drug exposure as well as using a lower amount of drugs [88]. Until now, some drug release orthopedic implants based on Mg alloys have been reported containing antibiotics, e.g. antimicrobial peptide [89, 90], gentamicin [91], or gentamicin sulfate [92]. Magnesium alloy implants commonly suffer from an easy infection related to implantation along with the high rate of degradation. Dong et al [89] fabricated a surface drug delivery system based on Mg/Epoxy resin-ZnO/Polycaprolactone (PCL)-Ibuprofen using a dip coating method followed by spraying. It was suggested that the composite coating could be a promising alternative for biodegradable Mg-based drug delivery and implant applications.

5. Synthesis methods of composites containing Mg and Zn

5.1. Electrospinning method

In order to fabricate composite with well chemical composition and controlled morphology, many advanced methods have been employed. Meanwhile, electrospinning is considered the simplest and most adaptable technique. The fabrication of composites can easily be prepared via the electrospinning technique; however, the only restriction is that the second phase should be well dispersed or soluble in the primary solu-

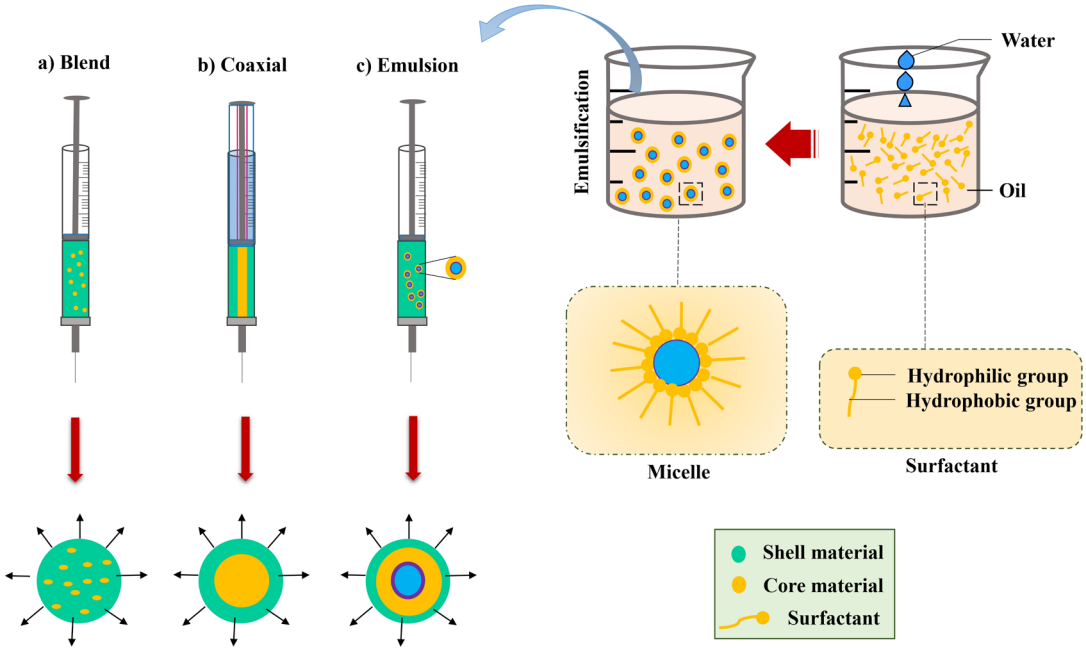

Fig. 1. Schematic illustration of composites containing bioactive agents by (a) blend, (b) coaxial, and (c) emulsion electrospinning.

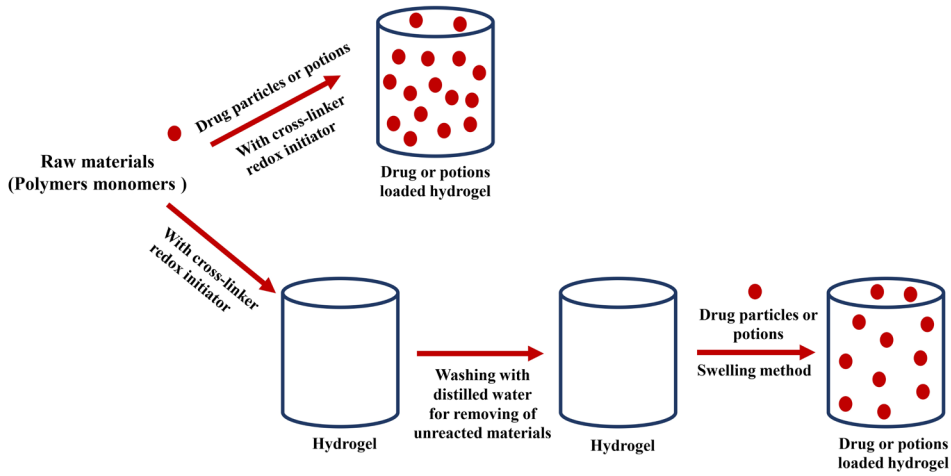

Fig. 2. Free-radical polymerization technique for the nanostructured hydrogel preparation.

tion. This technique has been developed approximately for a century and can be considered as sub-branches of the electrospray process [93-95]. During the electrospinning process, the elongation of the liquid drop occurs by increasing the electric field. A conical shape of the liquid drop is created by achieving a balance between the induced charge distribution on the drop surface and the liquid surface tension. The process is shown schematically in Fig. 1.

In the case of electrospinning, the fundamental setup is easily controlled and very simple. Mainly, it consists of an electrically conductive collector (an aluminum foil or silicon part), a high-voltage power supply, and a spinneret, however, all of these segments are not essential [96]. Therefore, to produce fibers instead of droplets, a number of processing parameters must be optimized actually e.g. fibers, droplets, or a beaded structure that depends on the different processing parameters, such as distance between collector and source [97].

5.2. Solvothermal technique

Another synthesis method for the composites is the solvothermal technique. The general procedure is similar to the hydrothermal technique, but organic solvents are utilized instead of water in the solvothermal method [98-100][96]. Through this technique, a transformation or chemical reaction occurs under supercritical temperature and pressure in an organic solvent such as toluene [101], 1, 4 butanol [102], and methanol [103]. To make the final material crystallized, it is required to perform a subsequent thermal treatment [104].

5.3. Co-precipitation method

A commonly used technique for the fabrication of layered double hydroxides (LDHs) and similar materials for drug delivery applications is co-precipitation [105-107]. For all co-precipitation variations, similar materials are required for initiation. The starting materials are composed of similar starting materials: 1) a divalent cation soluble source for the formation of the layers; 2) a trivalent cation soluble source for the formation of the layers; 3) a soluble ionic compound such as sodium nitrate and sodium carbonate as a source of interlayer anions; 4) a strong base including sodium hydroxide, urea, ammonia, and potassium hydroxide to cause LDH precipitation [105, 108, 109].

5.4. Sol-gel method

The sol-gel technique is an extensively used method to synthesize highly pure and homogeny products [93, 110, 111]. Depending on the homogeneity degree of the gel, two types of the sol-gel method are known: monophasic and diphasic. In case metal ions are dispersed at the atomic level, it is called a monophasic gel, while in diphasic one, the homogeneity scale is in the range of 1-100 nm [112]. The hybrid gel is a combination of monophasic and diphasic gels [113, 114]. The final material properties are determined by the rate of hydrolysis and condensation in the sol-gel process, which is dependent on different factors. These factors include starting materials, inorganic and organic additive addition, pH, water content, etc. [114, 115]. Recent developments in the sol-gel process have made it possible to embed organic compounds as well as other modified inorganic oxides in SiO_2 and also to control the release of these compounds from the matrix into the medium [116, 117]. Despite the remarkable advantages of these sol-gel carrier systems, they are not widely known for drug delivery applications. The sol-gel method is facile and versatile; the starting materials are inexpensive, inert, stable to heat and light, and benign for the environment or humans [118-121].

5.5. Water-in-oil-in-water (w/o/w) double emulsion method

According to Sahoo et al. [122] and Jaraswekin et al. [123], the most popular method for the preparation of poly(lactic-co-glycolic acid) (PLGA) microparticles (MP) or microsphere (MS) is the solvent evaporation method. In this technique, elevated temperatures or agents for inducing phase separation are not needed, and sterile microcapsules can also be produced by scaling up microencapsulation (ME) [124, 125]. Based on the drug state in the polymer solution and the dispersion medium, the emulsion method is categorized into oil-in-water (o/w), water-in-oil (w/o), and water-in-oil-in-water (w/o/w) double emulsion methods [126, 127]. Among the methods used for MS preparation, the w/o/w solvent evaporation is the most commonly practiced technique [128]. In order to provide the controlled drug release, degradation protection of the drugs, and alleviating adverse effects of the drugs in the body, pharmaceutical industries extensively use w/o/w by evaporation removal of the emulsion solvent technique [129, 130]. In this method, to internalize the active ingredient efficiently, the stability of the primary emulsion is considered to be a critical factor [131]. Low encapsulation efficiency is the result of unstable primary emulsion [132, 133].

5.6. Microemulsion method

The microemulsion method is employed for the preparation of high-T_c oxide of $YBa_2Cu_3O_7$, nanocrystalline Al_2O_3, TiO_2, Fe_2O_3, colloidal metals, colloidal AgCl, and colloidal Fe_3O_4 [134, 135]. Microemulsions consist of at least three components including a surfactant, a nonpolar phase (usually oil), and a polar phase (usually water). Microemulsions are thermodynamically stable solutions, isotropic, and macroscopically homogeneous. The polar and the non-polar regions are separated by an interfacial film formed by the surfactant molecules [136]. This method shows some significant advantages such as thermodynamic stability,

nanoparticle monodispersity, large interfacial area, and ultralow interfacial tension [137, 138]. Microemulsion has attracted attention in the preparation of nanoparticles mainly due to the versatility of microemulsion systems like the very small droplet size production, cost-effectiveness [139-141], simple procedure, and mild reaction conditions [142, 143].

5.7. Free radical polymerization method

In bioprinting, free radical polymerization is frequently utilized for the creation of cross-linked hydrogels [144]. Through using thermal or photo-initiator or redox reaction, polymerization of a polymer consisting of vinyl groups occurs leading to the formation of a hydrogel. This method is not a suitable technique for the fabrication of end-functional polymers. On the other hand, the situation has changed by the emergence of living radical polymerization, so that the production of end-functional polymers is also possible using this technique. Free radical polymerization is employed to synthesize composites containing polymers, metal, and metal oxide used in the drug delivery systems [145]. The processing steps are presented in Fig. 2.

5.8. Microwave radiation method

As a result of several rewarding properties of microwave stimulation including controllable operability, deep tissue penetration, and good thermal efficiency, it is being increasingly used in numerous smart drug delivery investigations [146]. Microwave is composed of both magnetic and electrical components with high-frequency radiation in the range of 300 MHz-300 GHz [147]. By the use of the electromagnetic and/or heating elements of the microwave, drug delivery systems can be processed and modified. The introduction of microwave radiation can be carried out directly onto the pre-formed products and/or upon the dosage form preparation. Furthermore, the microwave can be used in the excipients processing before using them in the drug formulation in delivery systems [148].

Qiu et al. [149] designed a microwave-sensitive drug microcarrier based on Fe_3O_4@ZnO@mGd_2O_3: Eu nanoparticles using poly [(N-isopropyl acrylamide)-co-(methacrylic acid)] as the microwave stimulus gate-keeper. By using a short-time high-frequency microwave device, it is possible to avoid the bulk heating, therefore, the construction of drug delivery systems based on MSN responsive to microwave radiation is feasible [150]. Shi et al. [146] fabricated NPs for drug delivery based on a doped ZnO@Fe_3O_4 core surrounded by a mesoporous silica shell. The silica shell was used due to its large pore volume and good biocompatibility, while the core exhibited high-performance microwave absorbance.

5.9. In-situ gelling procedure

The in-situ gel forming polymeric systems have been extensively studied as carriers for sustained drug delivery. Before administration in the body, these vehicles are in the form of sol or suspension and after administration, they undergo in-situ gelation [151-153]. In the formulation of these systems, a gelling agent is used to form a stable suspension/sol system containing dispersed drugs and other excipients. Due to the pH change in the gastric environment, the gelation of the sol/suspension system is triggered. The adopted formulation is a sodium alginate solution or gellan gum containing sodium citrate and calcium chloride, in which the free calcium ions turn into complexes and released only in the stomach acidic environment. Sodium alginate/gellan gum acts as a gelling agent producing textures in the final product, which can be in the form of hard, brittle, non-elastic gels of fluid gels [153-155]. Ca ions entrapped in sodium alginate or gellan gum polymeric chains enable polymer chains crosslinking to form matrix structure. In the gelation process, double-helical junction domains are first formed, then, these domains are re-aggregated forming a three-dimensional network by hydrogen bonding with water and complexing with cations [156, 157]. Some advances in the field of in-situ gelling include: overcoming the problem of poor conventional ophthalmic solution bioavailability by using gel drops that are instilled into eyes; increasing drug contact time at the maximum absorption site; reducing systemic drug absorption through the nasolacrimal duct and the resulting side effects; reducing the frequency of administration, and drug delivery with narrow windows of absorption in the small intestinal zone. Gastro-retentive drug delivery systems are beneficial for drugs that are absorbed through the stomach such as ferrous salts and also for the ones that are used for local treatment in the stomach and peptic ulcer disease treatment (e.g. antacids) [158-160].

6. Drug delivery mechanisms of composites containing Mg and Zn

There are slightly different ways for the definition of the term "release mechanism". It has been used for describing the process that determines the rate of release and also for describing the procedure through which drug molecules are released or transported. A number of processes or mechanisms have been demonstrated to be rate-controlling in drug release [161]. In recent years, the development of novel approaches for designing new controlled-release drug delivery systems has been at the center of attention [162]. The traditional drug delivery system works in a way that causes a rapid increase in the drug dosage in the blood following by a drop in the dosage [163, 164]. Drug plasma levels are described as under level and overhead, which are inefficient and toxic, respectively [165]. In an ideal drug delivery system, a suitable drug concentration should be transmitted to targeting sites while keeping other tissues safe [166, 167].The following two formulas (Eq. 1and Eq. 2) are used for the calculation of the levels of loaded and released drug [166]:

$$Drug\ loading\ of\ carrier\ (wt\%) = \frac{the\ amount\ of\ drug\ (g)}{the\ amount\ of\ nanohybride\ and\ drug\ (g)} * 100$$

$$\text{OR} \quad \%Drug\ loading = \frac{weight\ of\ drug\ in\ a\ sample}{weight\ of\ sample\ taken} * 100 \qquad (1)$$

$$\%Drug\ release = \frac{the\ amount\ of\ released\ drug\ (g)}{the\ amount\ of\ loaded\ drug\ (g)} * 100 \qquad (2)$$

The efficiency of drug encapsulation can be determined according to Eq.(3) [168]:

$$Encapsulation\ efficiency(\%) = \frac{Initial\ drug\ weight - Drug\ weight\ in\ supernatan}{Initial\ drug\ weight} * 100 \qquad (3)$$

The drug release of nanocomposite has been studied in the literature using mathematical models [169]. Eq.4 can determine the sample liquid uptake:

$$M_s = Kt^n \qquad (4)$$

where, K and n are constants. By using the mechanism of drug release, the following power law equation is obtained:

$$M_t/M_\infty = Kt^n \qquad (5)$$

where, the drug released fraction at time t and equilibrium is represented by M_t and M_∞, respectively. The characteristic of the drug and the samples determines the value of K and the diffusion exponent of n is used for the characterization of the drug release mechanism. The values of 'k' and 'n' are obtained by calculating the intercept and slope of the plot between M_t/M_∞ [170].

Das et al. [171] designed a colon-specific drug carrier based on Zn/pectin/chitosan composite microparticles. By studying the drug release,

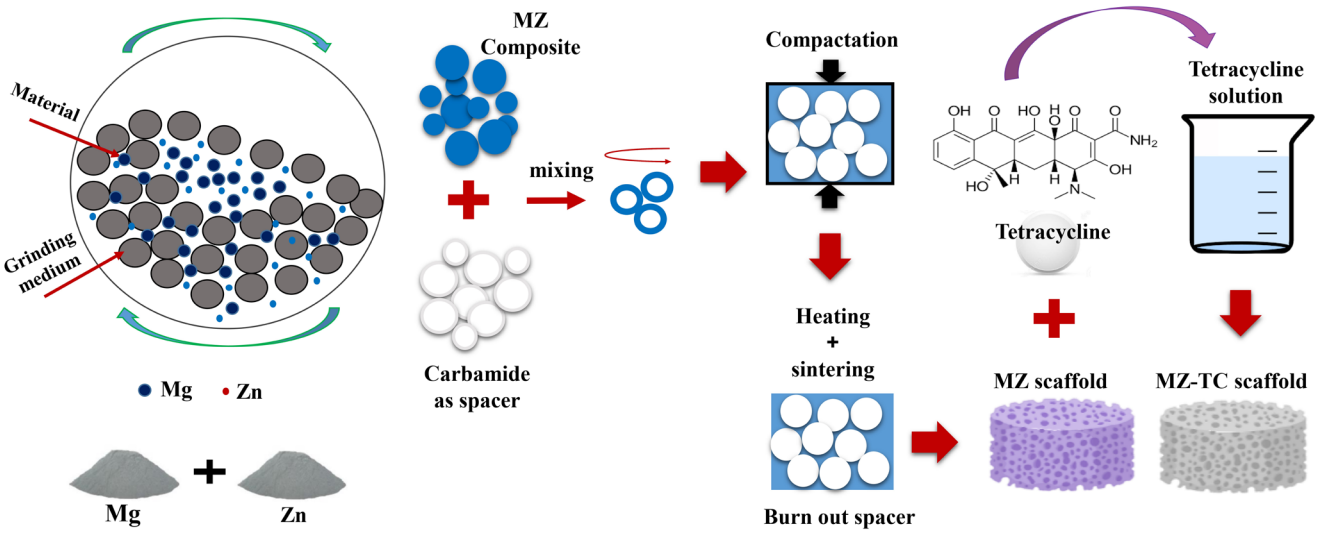

Fig. 3. Hydrogel beads containing ZnO NPs for the drug delivery application.

the formulation was optimized. The drug release pattern was shown to be significantly affected by formulation parameters. It was reported that the specific content of the colon-specific drug could be loaded without hampering its behavior. Results showed high encapsulation efficiency and stability of the drug in the formulation during storage time. Furthermore, *in vivo* drug release was observed from the optimized composite particle formulation in rats. Company et al. [172] developed a novel composite of zinc oxide nanoparticles and citric acid-based polyester elastomer (POC–ZnO). Results indicated that the original concentration of NPs in the composites affected the ZnO release kinetics for 15 days. Among all composites, POC–ZnO 5% was reported to have the zero-order release kinetics.

7. The state-of-the-art of composites containing Zn and Mg in drug delivery

Dodero et al. [173] used an electrospinning technique to embed ZnO nanoparticles within alginate-based nanofibrous membranes. In order to combine ZnO nanoparticle with the polymer through electrospinning, it is preferred to use medium-molecular-mass alginates with a low mannuronic and guluronic acid residues (M/G) ratio or low-molecular-mass alginates with a high M/G ratio. Composite scaffolds based on ZnO-polyetherimide (ZnO/PEI) with antibacterial activity were also developed by the electrospinning process [174]. The effectiveness of the developed scaffolds was reported by positive responses against gram-negative (*Escherichia coli*) bacteria as well as gram-positive (*Staphylococcus aureus*).

Javanbakht et al. [166] developed a novel drug delivery bio-nanocomposite based on carboxymethylcellulose (CMC)/zinc MOF/graphene oxide via the solvothermal method. It was reported that the prepared bio-nanocomposite could be used for anticancer drug delivery. Bhattacharjee et al. [175] successfully incorporated ZnO into Fe (III) trimesate metal-organic framework (MIL-100(Fe)) to deliver anticancer drugs of doxorubicin hydrochloride (DOX) by the one-pot in-situ method. The investigation rendered interesting insights into the incorporation of NPs into MIL-100(Fe) and its drug loading capacity as well as release rates. Kura et al. [176] loaded L-3-(3,4-dihydroxyphenyl) alanine as an anti-parkinsonian drug in a novel layered organic-inorganic nanocomposite based on Al-layered double hydroxide (LDH)/Zn via a direct co-precipitation technique. Sustained-release behavior was observed in these composites suggesting that they are suitable for controlled-release formulations. In comparison with pure levodopa, the synthesized nanocomposite showed enhanced cell viability of 3T3 cells after 72 h of exposure.

Seyfoori et al. [177] fabricated a robust nanostructure composite of $ZnFe_2O_4$ and $ZnFe_2O_4$-hydroxyapatite using the co-precipitation method for multiple applications of cancer treatment, bone filler, and drug delivery.

Nigam et al. [178] reported a successful synthesis of $Zn_xMg_{(1-x)}Fe_2O_4$ nanoparticles using the sol-gel method with the potential to be used for drug delivery. SiO_2–CaO mesoporous bioactive glass nanoparticles doped with Zn^{2+} ions were produced by Neščáková et al. [179] using the microemulsion assisted sol-gel method. It was reported that the nanoparticles have the potential for being used as drug delivery systems as well as bioactive fillers for various applications such as wound healing and bone regeneration. Thangaraj et al [180] synthesized superparamagnetic Ce_4−$xSr_{1+x}Fe_{5-x}ZnxO_{14+\delta}$ (x=0-0.45) nanocomposites by the nitrate-citrate sol-gel route for different applications such as drug delivery, sensor, dielectric, conductivity studies, and optical properties. Pathania et al. [181] studied the drug release kinetics of chitosan-*g*-poly(acrylamide)/Zn (CPA-Zn) nanocomposite synthesized by microwave radiations. The nature of the matrix and the pH of the medium were shown to affect the drug release behavior.

Zn-clinoptilolite/GO nanocomposite was introduced by Khatamian et al [182] for the preparation of drug delivery systems with high loading capacity. The reflux method and microwave-assisted hydrothermal method were used for the fabrication of the nanocomposites. As a cancer drug, the nanocomposite exhibited slow release for DOX, high loading capacity, and cytocompatibility. Nanocomposite hydrogel scaffolds based on chitosan-gelatin/ZnO with both drug delivery and inherent antibacterial properties were prepared using an in-situ method. The prepared scaffolds demonstrated high porosity and no agglomeration in the chitosan-gelatin matrix. Additionally, the nanocomposite scaffolds exhibited improved antibacterial, biodegradation, swelling properties, as well as a controlled release for naproxen [183]. Yadollahi et al [184] synthesized nanocomposite hydrogel beads of chitosan/ZnO by the in-situ generation of zinc oxide nanoparticles upon the chitosan bead formation. According to the results, the drug release from the chitosan beads was prolonged by the addition of ZnO nanoparticles. This was reported to be due to a longer drug migration path from the beads to the

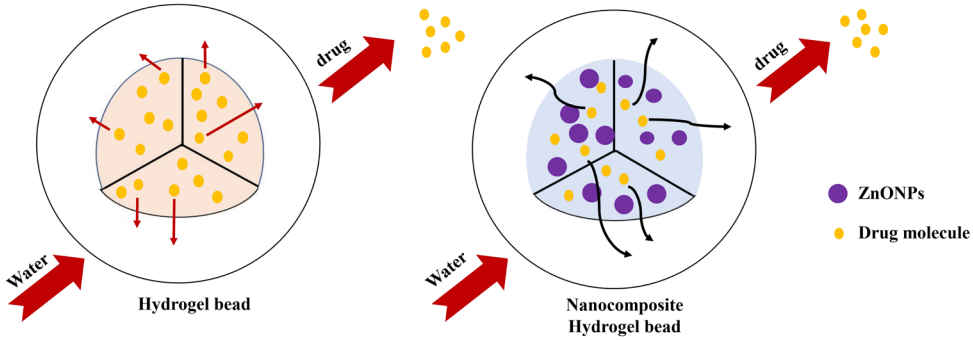

Fig. 4. Preparation of composite scaffolds by the space holder technique.

media. The nanocomposites showed promising behavior for developing controlled delivery of drugs. The drug release behavior of hydrogel beads containing ZnO particles is demonstrated in Fig. 3.

Yang et al [185] assembled flower-mesoporous carbon (FPCS)-magnetic Fe_3O_4 and pH-sensitive ZnO nanoparticles to construct the FPCS-Fe_3O_4-ZnO composite as microwave and pH bi-triggered drug carrier. Yang et al. [186] incorporated Mg particles into poly (l-lactic acid) (PLLA) microspheres to suppress inflammatory response induced by PLLA and regulate the drug release profile. It was shown that the internal connectivity of the microspheres was altered during hydrolytic degradation by changing the Mg particle sizes and contents, resulting in manipulating drug delivery with tunable release patterns. Foroughi et al. [168] developed a novel synthesis method (one-step modified reverse microemulsion) for the preparation of HAp-$MgFe_2O_4$ nanocomposite for the drug delivery application. It was demonstrated that the drug delivery rate of the nanocomposite was influenced by calcination temperature and textural properties.

In a study by Cheddadi et al. [187], the free radical polymerization method was used to synthesize poly (magnesium acrylate) hydrogel for drug delivery applications. They were suggested for oral drug delivery devices due to prospective drug release properties along with simplicity and low cost. In the work performed by Rijal et al. [188], the electrospinning technique was utilized to synthesize Mg incorporated polycaprolactone/low molecular weight chitosan (PCL/LMW-CS) composite nanofiber. They showed that the obtained nanofibrous were good candidates for applications in tissue engineering such as bone regeneration, wound healing, regenerative medicine, and drug delivery. Rijal et al. [189] used the electrospinning method to prepare composite nanofibers of MgO, chitosan (CS), and poly(ε-caprolactone) (PCL). They realized that the obtained new composite nanofibrous membranes were able to mimic the function and physical structure of the tissue extracellular matrix (ECM). This, in turn, suggested that they can be potentially used for various tissue engineering applications e.g. DDSs.

In another study, Mohammad et al. [190] prepared a composite of ethyl cellulose-magnesium hydrogen phosphate (EC-MgHPO4) via the sol-gel technique. Their results proved that the composite could be used in the fields of drug delivery, biosensor, bioanalytical, and scaffolding applications. Foroughi et al. [191] used a one-step reverse microemulsion method to synthesize nanoporous HAp-$MgFe_2O_4$ nanocomposite. They found that calcining the nanocomposite at 700 °C results in a core-shell structure with MS of ~9.5 emu/g. In addition, considering the IBU release behavior of all samples, the drug delivery rate of the nanocomposite could be altered by calcination temperature that in turn may change the textural properties of samples.

Bakhsheshi-Rad and his colleagues [45] synthesized composite scaffolds of Mg-Ca-TiO_2 (MCT). They loaded different concentrations of doxycycline (DC) in the scaffolds and used the space holder technique as a cost-effective, feasible, and novel method to have an appropriate corrosion rate, a network of interconnected pores, and appropriate compressive strength. A schematic presentation of this technique is shown in Fig. 4. Considering the drug release profiles, they found that DC loading MCT scaffolds showed sustained and burst drug release and by increasing the concentration of DC, the drug release rate was increased.

Tabia et al. [192] fabricated the Mg-doped bioactive glass nanoparticles (BG-NPs) through the sol-gel route. They loaded amoxicillin to the synthesized BG-NPs and investigated their drug release behavior. They concluded that by increasing Mg content the loading efficiency decreased. However, the release kinetics was increased by increasing magnesium content. They realized that the specific surface area and porosity were responsible for this advancement.

8. Conclusions and future insights

In this review, the drug delivery composite systems containing Mg and Zn either matrix or reinforcement are summarized. Both Zn and Mg have been applied in various areas of DDSs due to their amazing intrinsic properties i.e. biocompatible and biodegradable as well as being abundantly available. This has made them remarkably advantageous over their conventional counterparts. Besides, the synthesis methods of these excellent composites are also reviewed and their mechanism of drug release is discussed. It should be noted that studying the drug delivery properties of zinc/magnesium and their composites might lead to the realization of more effective drug delivery systems in the future.

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Conflict of interest

The authors declare that there is no conflict of interest.

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