Review

Sitian Zang, Shijie Chang, M. Babar Shahzad, Xiaoting Sun, Xiran Jiang, and Huazhe Yang*

Ceramics-based Drug Delivery System: A Review and Outlook

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Abstract: The drug delivery system (DDS) is a hot spot in the field of medicine due to their favorable characteristics, such as the realizability of targeted therapy, sustained and controlled release of drug. Ceramic materials have abundant desirable properties, such as simple preparation, adjustable size and structure, surface area to volume ratio, desirable stability under physiological conditions and excellent biocompatibility, etc. Hence they have been successfully applied in the field of DDS considerably in decades, acting as drug carriers. Traditional ceramic materials refer to inorganic solid compound. They are mainly composed of carbides, oxides such as hydroxyapatite, tricalcium phosphate, silica, zeolite, and zirconia, etc. This review summarized the applications of the ceramic materials in the field of DDS in recent years, meanwhile the outlooks of future development were also proposed.

1 Introduction

The drug delivery system (DDS) is the composite of drug and carrier where drugs are loaded inside or on the surface of the carriers through chemical or physical methods [1–4]. Drug carriers are classified in various types as shown in Figure 1. Size, structure and properties of carriers have effects on the loading capacity of drugs. Furthermore, the distribution and release rate of drug can be controlled, which is favorable for the accurate target and treatment of the lesion

site [5–9]. Effective dose requirements (ED₅₀) may also decrease because of high delivery efficiency of controlled, sustained and targeted DDS, which could help in cost reduction for patients. Especially, there is an increasing desire for local, homogeneous, controlled and sustained release of drug nowadays. Therefore, it is of great importance to prepare carriers with adjustable size and structure, desirable stability under physiological conditions, excellent biocompatibility and high uptake efficiency. From this perspective, ceramics are the desirable candidate material for carriers.

Figure 1: Classification of drug carriers

The ceramic-based drug carriers have attracted increasing attention with the developments in medicine, pharmaceuticals, and material science. Popular bioceramics include: beta tricalcium phosphate (β -TCP), hydroxyapatite, mesoporous silica, zirconia hydroxyapatite composite, etc. Meanwhile bioceramics are important parts of some inorganic-organic composites used as drug carriers.

The advantages of ceramic-based drug carriers are as follows: 1. Adjustable size and structure which are favorable for loading nano-sized drugs; 2. Low toxicity. Ceramics have good biocompatibility, biodegradability and biological stability; 3. Some ceramics are sensitive to environment, which can response to light, magnetism or heat, etc. These characteristics make them feasible for accurate targeted. Hence ceramic-based drug carriers have attracted

*Corresponding Author: Huazhe Yang: Department of Biophysics, School of Fundamental Sciences, China Medical University, Shenyang 110122; Email: hzyang@cmu.edu.cn

Sitian Zang: Department of Biophysics, School of Fundamental Sciences, China Medical University, Shenyang 110122

Shijie Chang, Xiran Jiang: Department of Biomedical Engineering, School of Fundamental Sciences, China Medical University, Shenyang 110122

M. Babar Shahzad: Institute of Metal Research, Chinese Academy of Sciences, Shenyang 110016, China

Xiaoting Sun: Department of Chemistry, School of Fundamental Sciences, China Medical University, Shenyang 110122

great attention of investigators from the fields of biomaterial, biophysics, biochemistry, bioengineering, pharmaceuticals and medicine. They mainly refer to hydroxyapatite, tricalcium phosphate, silica, zeolite, and zirconia, etc [10].

Bioceramics are considered as desirable drug reservoirs or matrix in DDS [11, 12]. The principle of drug-loading for ceramic-based DDS is shown in Figure 2. For instance, β -TCP can be manufactured to hollow structure with certain shape and size. They can degrade gradually in physiological environment under the action of body fluids, enzyme or cell. Pharmaceutical diffusing out via pores of ceramics depends on the concentration gradient and drug solubility, and porosity of ceramics drug carrier influence the diffusion of drugs. Drugs can be loaded inside or on the surface of the carriers by various method such as facile sono-chemical method [13–15].

Figure 2: Principle of ceramic-based DDS

However, most anticancer drugs (e.g. doxorubicin as a typical chemotherapeutic drug was used in the present therapy of cancer) without targeting ability exhibit side-effects to normal cells. Hence, exploring DDS for controlled, sustained and targeted release of anti-cancer drugs has attracted much attention from various fields to meet clinical requirements that maximum therapy effects along with minimal side effects.

2 Common ceramic drug carriers

2.1 Hydroxyapatite(HAP, $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$)

HAP is the main inorganic composition of hard tissues such as bone and teeth of vertebrates, etc. HAP occupies almost 60%~70% of bone mineral content in human body. Thus it has been applied abundantly in the field of bone repair. It can be synthesized automatically in the alive or-

ganic body, and it can resist the wet environment, avoid shrinkage and has adjustable hardness [16–20].

Nanostructured HAP has the following desirable properties: good biocompatibility, strong biological activity, biodegradability, osteoconductivity, nontoxicity, easy metabolism in vivo and hollow mesoporous structure. And hence it has been a desirable candidate for controlled and sustained release of proteins, genes and drugs in the field of DDS [21–23]. Plenty of studies have indicated their application in the field of targeted, controlled and sustained drug/protein/genes delivery system, which are summarized in Table 2.

Nowadays, researchers are facing plenty of challenges and limitations in this field, such as achieving targeted, controlled and sustained release of drugs, improving loading capacity of carriers, decreasing cytotoxicity of carriers and drugs, etc. Hence, numerous of researchers have carried out different studies to overcome the limitations.

Traditionally, drugs are taken 1-3 times a day via oral intake, however it is difficult to take drugs on schedule, especially for patients with depression, cancer and other chronic illness. In contrast, long-time DDS can release drug for several days or weeks. In recent years, many researchers are devoted themselves to achieving sustained drug release. Shyong *et al.* [24] synthesized HAP via co-precipitation method by mixing $\text{Ca}(\text{OH})_2$ and H_3PO_4 , then loaded antidepressant orchlorapine (OLZ) into porous hydroxyapatite to construct HAP-OLZ. They demonstrated that HAP-OLZ achieved long-time release of OLZ in rats with induced depression, which could be more than 3 weeks after intramuscular injection. And they found this system enhanced locomotor activity, and ability of studying and remembering in rats with induced depression. Hence HAP could be used as carrier for sustained release of OLZ, and HAP-OLZ was favorable to solve the non-adhesive drug intake that occurs in the therapy of antidepressant via intramuscular injection.

Meanwhile, enhancing loading performance of carriers is one of the most attractive parts in the field of DDS. Ma *et al.* [25] synthesized HAP microspheres via hydrothermal method and the study suggested that they had ideal loading capacity of Ibuprofen (IBU) with 413.65 mg/g, and the release of IBU was responsive to pH. In a similar study, Yu *et al.* [26] prepared HAP using ibuprofen (IBU) as model drug. It indicated that HAP nanorod-assembled porous hollow polyhedral had a better drug loading capacity, which is desirable for the sustained drug release.

It was found that the properties of HAP also have significant influence on the drug encapsulation efficiency and the time of sustained release. Shi *et al.* [27] synthesized nano-HAP and micro-HAP by mixing $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ and

Table 1: Experimental profiles of two kinds of HAP

properties	nano-HAP	micro-HAP
Shape	Rod-like	Miscropheres
Size of powders	Length of 150 nm, width of 20 nm	Diameter of 15 μm
Size of pores (nm)	3-4	3-4, 8-12
Surface areas (m^2/g)	84.48	17.31
The amount of LF on the surface (mg/m^2)	2.93	1.08
The maximum amount of adsorbed LF ($\mu\text{g}/\text{mg}$)	91.10	50.76

$(\text{CH}_3\text{O})_3\text{P}$ via sol-gel method, and functionalized HAP with lactoferrin(LF) to form HAP-LF. The experimental profiles are summarized in Table 1. Comprehensively, nano-HAP had larger surface areas, amount of LF on the surface and maximum amount of adsorbed LF than micro-HAP. They indicated that HAP-LF enhanced the biocompatibility of HAP. It turned out that HAP can be applied as a controlled release carrier of LF that might be applied in the field of enhancement of bone regeneration, also could be a new biomaterial.

Currently, one of the most attractive composite carriers is related to the organic-inorganic composite which can combine the advantages of both the inorganic and organic materials. Organic materials have the advantages of high hydrophilicity, desirable biodegradability and biocompatibility. Besides, inorganic biomaterials have high drug loading capacity and some are sensitive to magnetic field, heat, acidity, light and ultrasound. Hence, a lot of researchers modified inorganic particles with organics to overcome their respective shortages and enhance their performance in drug delivery. Meanwhile, organic-inorganic composite carriers not only had improved water solubility of drugs due to incorporation with high hydrophilic organic materials, but also possessed the characteristics of inorganic particles such as excellent drug loading capacity, controlled and sustained targeted delivery. For instance, carriers with high loading capacity and good targeted ability could be achieved through the hybrids of magnetic materials, ceramics and organic materials. Besides, it was found that the weight ratios of agents influence the properties of organic-inorganic composites. Therefore, organic-inorganic composite carriers have emerged rapidly as a novel class of versatile porous biomaterial for drug delivery application [28–34]. They are summarized in Table 4, 5, 6, 9.

Nowadays, many researchers have devoted themselves to optimize adsorption and release parameters of drugs/genes/proteins by controlling the crystallinity, structure and size of HAP. The concentration of modifiers (e.g., SDS (inositol hexakisphosphate and cyclohexane-

Figure 3: The process of CHAM synthesizing, drug loading and fluorescent labeling

1,2,3,4,5,6-hexacarboxylic acid)) have significant influence on the shape and size of HAP crystals. Qiao *et al.* [35] synthesized four kinds of hollow mesoporous carbonated HAP microsphere (CHAM) by mixing CaCO_3 and sodium dodecyl sulfate (SDS) via hydrothermal method. The process of CHAM synthesizing, drug loading and fluorescent labeling are shown in Figure 3, and some experimental results of 4 HAP groups are shown in Table 3. The concentration of SDS can be applied to controlling the structure, wall thickness and size of CHAM. It was found that the concentration of SDS contributed to increase drug entrapment efficiency, sustained release, biocompatibility and osteoconductivity. The pH-dependent drug release could be attributed to the degradation of CHAMs that was sensitive to pH. The shape of HAP crystals played an important role in the adsorption of proteins and drugs, and it can increase the drug entrapment efficiency and sustained drug release capacity by decreasing the crystallinity of HAP. As a whole, C group of CHAM might be the most desirable candidate for controlling and sustained release of cis-diaminedichloroplatinum (CDDP). The study suggested this system to be an ideal option for anti-cancer therapy because of their highest lethality on human squamous cell in vitro and entrapment of cis-diammineplatinum(II) dichloride (CDDP). In addition, this system might be applied in the therapy of cancer because of its satisfactory

Table 2: Synthesis method and potential application of HAP in the field of DDS

Synthesis method	Product	Model drug	Challenge	Experimental results	Potential application	Reference
Co-precipitation method	HAP	OLZ	Systemic side effects of OLZ, OLZ not releasing totally	HAP-OLZ achieved long-time release of OLZ which could be more than 3 weeks in rats with induced depression after intramuscular injection, and found out this system enhanced locomotor activity, and ability of studying and remembering in rats with induced depression.	HAP could be used as carrier for sustained release of OLZ, and HAP-OLZ was favorable to solve the non-adhesive drug intake that occurs in the therapy of antidepressant via intramuscular injection.	[24]
Hydrothermal method	HAP	IBU	Systemic side effects of ibuprofen. And ibuprofen did not release completely, might because of formed hydrogen bonding between -COOH in IBU and -OH in HAP	HAP had ideal loading capacity of ibuprofen (IBU) with 413.65 mg/g, and the release progress is responsive to pH. Meanwhile, cumulative release amount of IBU are stable in 38.55%, 40.42%, 64.95% at pH=4.0, 5.6, 7.4, respectively for more than 60h.	As targeted drug carrier, and could be applied in pH-sensitive DDS.	[25]
Hydrothermal method	nano-HAP	IBU and hemoglobin	Systemic side effects of ibuprofen and hemoglobin	HAP nanorod-assembled porous hollow polyhedral had a better drug loading capacity, which is desirable for the sustained drug release.	Sustained drug or protein carrier	[26]
Sol-gel method	nano-HAP and micro-HAP	Lactoferrin	Systemic side effects of ibuprofen	Nano-HAP had larger surface area, amount of LF on the surface and maximum amount of adsorbed LF than micro-HAP. They indicated that HAP-LF enhanced the biocompatibility of HAP.	They indicated that HAP-LF enhanced the biocompatibility of HAP. It turned out that HAP can be applied as a controlled release carrier of LF that might be applied in the field of enhancement of bone regeneration, also could be a new biomaterial.	[27]

Table 3: Some experimental results of 4 HAP groups

HAP group	A	B	C	D
SDS concentration (mg/ml)	1	2.33	4.66	10
Shape of crystals	Needle-like	Needle-like	Rod-like	Rod-like
Diameter of particles	90% under 3 μ m	About 3 μ m	3-5 μ m	Two sub-groups: 0.6 μ m and 5 μ m
Surfaces areas of particles (m ² /g)	17.58	-	-	25.12
Biodegradability	-	-	-	Fastest
Drug entrapment efficiency (%) at 24h	≈ 30	≈ 50	≈ 65	≈ 50
Cumulative drug release (μ g) at pH 5	≈ 70	≈ 95	≈ 120	≈ 100
Cumulative drug release (μ g) at pH 7	≈ 60	≈ 70	≈ 85	≈ 75
Tumor cell survival rate (%) at 24h	≈ 79	≈ 78	≈ 65	≈ 77
Tumor cell survival rate (%) at 72h	≈ 40	≈ 43	≈ 20	≈ 35

characteristics of sustained release of drugs, biodegradability and sensitivity to pH. In a similar study, Morsy R *et al.* [36] synthesized HAP/wollastonite (HAP/WT) composite by Two-Step co-precipitation method and the size of the as-prepared particles was less than 1 μ m. The study suggested that HAP/WT composites might be potential drug carriers and can be applied as bone repair materials.

Shuai *et al.* [37] fabricated sericin-HAP composite microspheres for loading DOX. They showed that controlled release of DOX was sensitive to pH, and sustained release of DOX could be realized. Furthermore, rate of DOX release was higher in acidic environment than in physiological environment which typical cancer and normal cells respectively possessed. This unique characteristic could decrease the toxicity to the normal tissue. This system had a potential application in DDS.

Simionescu *et al.* [38] prepared nano-HAP modified by biopolymers/poly(epsilon-caprolactone)/polyethylenimine by cryoablation. The as-prepared composites had controllable porosity, excellent biodegradation and lower cytotoxicity than pure PEI25-pDNA. It was found that the content of nano-HAP had sufficient influence on the cohesivity and uniformity of the composites. Besides, the composites released PEI25-pDNA over 22 days with high expression.

Zeng *et al.* [39] prepared Ba²⁺-doped HAP/Cu-doped quantum dots (QDs)/hyaluronic acid (HA) composites. In those composites Ba²⁺ used as CT contrast agent, Cu-doped quantum dots (QDs) as NIR fluorescent agent, and HA as fluorescent and cancerous cell targeting agent to target tumor and near infrared (NIR) imaging. The study indicated that the as-prepared composites not only could keep desirable dispersion of HAP but also had capacity of targeting tumor and NIR laser radiation at 700 nm, along with desirable photostability and excellent biocompatibility. Hence, it could be applied to CT and fluorescence bi-

modal imaging and early diagnosis and targeted therapy of tumor.

2.2 Tricalcium phosphate(TCP, Ca₃(PO₄)₂)

TCP can be divided into two types: α -TCP as high temperature phase and β -TCP as lower temperature phase. β -TCP has better biodegradability, biocompatibility and thermodynamic stability than α -TCP [40–43]. In this context, β -TCP has been applied as one of the most attractive carriers in the field of DDS with abilities of controlled, sustained and targeted release of drugs. And implementing regulator (sodium dodecyl benzene sulfonate) can regulate the size, distribution and shape of β -TCP. Lots of studies have indicated their application in the field of targeted, controlled and sustained drugs/proteins/genes delivery system, which are summarized in Table 5.

Hoover *et al.* [44] fabricated silver doped β -TCP with three concentrations of Ag₂O, 0.5 wt% Ag₂O, 1 wt% Ag₂O and 2 wt% Ag₂O. According to the immersion test, cumulative amount of Ag⁺ release was 80–90 μ mol in 60 days. Besides, it was favorable for the cell growth without obvious cytotoxicity even for 2 wt% of Ag₂O. The study indicated this system could achieve sustained release of silver.

Mirjalili *et al.* [45] fabricated β -TCP/carbon nanotube (CNT) composite and found no significant agglomeration with 1 wt% of CNT, and distribution of CNT, structure and size could be controlled by 2 wt% of sodium dodecyl benzene sulfonate (SDBS). Therefore, it might be feasible to apply β -TCP as both DDS and bone regeneration materials in the same time and make full use of the properties of β -TCP.

Lin *et al.* [46] synthesized PLGA/ β -TCP scaffolds with PLGA nanoparticles as DDS for loading OIC-A006. The drug release assay indicated that the pattern of OIC-A006

Table 4: Potential application of hybrid HAP in the field of DDS

Product	Model drug	Challenge	Experimental results	Potential application	Reference
CHAP, SDS as crystal growth regulator	CDDP	Choosing optical concentration of SDS because SDS exceeded more dispersed CaCO_3 instead of HAP.	Table 3. Quick release could originate from CDDP in the surface whilst the later sustained release could be caused the inner CHAP.	Cancer therapy, bone grating substitutes, pH-sensitive DDS	[35]
sericin-HAP	DOX	Systemic side effects of DOX	Controlled release of DOX was sensitive to pH, and sustained release of DOX could be realized. Furthermore, rate of DOX release was higher in acidic environment than in physiological environment which typical cancer and normal cells respectively possessed.	Controlled, sustained and targeted release of DOX for therapy of cancer, and regenerative medicine	[37]
nano-HAP/biopolymers/ poly(epsilon-caprolactone)/ polyethylenimine	PEI ₂₅ - pDNA	Systemic side effects of PEI ₂₅ -pDNA	The as-prepared composites had controlled porosity, excellent biodegradation and lower cytotoxicity than pure PEI ₂₅ -pDNA. It was found that the content of nano-HAP had sufficient influence on the cohesivity and uniformity of the composites. Besides, the composites release PEI ₂₅ -pDNA over 22 days with high expression.	Sustained and targeted drugs/genes delivery, regenerative biomaterials, gene-activated matrix	[38]
HAP/WT	-	The optimal ratio of HAP and WT	The composites ratio (HAP:WT) and the properties is relevant to the materials. The as-prepared particles with the size less than 1 μm	The composites might be potential drug carriers and can be applied as bone repair materials.	[36]
Ba ²⁺ -doped HAP/Cu-doped quantum dots(QDs)/HA composites, Ba ²⁺ as CT contrast agent, Cu-doped quantum dots (QDs) as NIR fluorescent agent, HA as fluorescent and cancerous cell targeting agent to target tumor and near infrared (NIR) imaging.	-	Systemic side effects of Cu-doped quantum dots (QDs) and HA	The as-prepared composites not only could keep desirable dispersion of HAP but also had capacity of targeting tumor and NIR laser radiation at 700 nm, along with desirable photostability and excellent biocompatibility.	It could be applied for CT and fluorescence bi-modal imaging and early diagnosis and targeted therapy of tumor.	[39]

Table 5: Potential application of β -TCP in the field of DDS

Synthesis method	Product	Model drug	Challenge	Experimental results	Potential application	Reference
Liquid porogen based method	Silver doped β -TCP	Ag ₂ O	Systemic side effects of Ag ₂ O	Cumulative amount of Ag ⁺ release was 80-90 μ mol in 60 days, increasing osteoblast cell proliferation along with osteoconductio without obvious cytotoxic even for the 2 wt% of Ag ₂ O.	Sustained release of antibiotics against infection in bone graft surgery.	[44]
Solution precipitation method	β -TCP/CNT	-	Optical concentration of SDBS	No significant agglomeration with 1 wt% of CNT, appearance of apatite layer on the surface of nanocomposites.	Bone graft biomaterials	[45]
Ice bath extraction and freeze-drying	PLGA/ β -TCP scaffolds with PLGA	OIC-A006	Systemic side effects of OIC-A006	The pattern of OIC-A006 release was biphasic, and sustained release of OIC-A006 had an effective impact on cell proliferation and adhesion. The system that OIC-A006 was loaded by PLGA/ β -TCP scaffolds with PLGA nanoparticles was favorable to osteoinduction and bone formation.	Osteoinduction and bone formation	[46]

release was biphasic, and sustained release of OIC-A006 had an effective impact on cell proliferation and adhesion. The system that OIC-A006 was loaded by PLGA/ β -TCP scaffolds with PLGA nanoparticles was favorable to osteoinduction and bone formation.

2.3 Silicon-based ceramics

Mesoporous SiO₂ nanopaticles (MSNs) have the following desirable characteristics: low cost, large specific surface area and specific pore volume, uniform and adjustable size of pores, mesoporous structure, high loading capacity of drugs, non-toxicity, desirable biocompatibility, biodegradation and stability. Accordingly, they have huge potential in the field of DDS for controlled and sustained release of drugs and targeted delivery. Usually, the synthesis method is the hydrolysis of tetraethyl lorthosilicate (TEOS, Si(OC₂H₅)₄) [47–52]. A number of studies indicating their applications in the field of targeted, controlled and sustained drugs/proteins/genes delivery system are summarized in Table 6.

Bardhan *et al.* [53] prepared MSNs with size of 150-200 nm by hydrolysis of tetraethyl lorthosilicate (TEOS, Si(OC₂H₅)₄). They used fluorescence anisotropy to monitor the trail of DOX loaded by MSNs. The most advantageous part was that the platform released drug at pH of cellular physiological microenvironment. The study demonstrated that MSNs/DOX system had stronger capacity of up-

take and stable release of DOX than free DOX in the therapy of primary non-keratinized squamous of oral mucosal. This unique characteristic could be applied for therapy of diseases, such as cerebral ischemia reperfusion injury and cancer.

Yang *et al.* [54] synthesized MSNs-Au loaded DOX where gold acted as gatekeepers of MSNs, these composites were applied as redox-sensitive DDS for chemophothermal synergistic therapy. It was shown that DOX released faster via stimulation of glutathione (GSH) or near infrared laser than free DOX.

Zhang *et al.* [55] prepared ZnO/MSNs composites. They found that the composites would release drug in the acidic microenvironment of tumor cells in comparison to zero release in the physiological microenvironment of the normal tissues. Besides, the cytotoxicity of ZnO QDs might endow composites with synergistic curative effect for tumor. Hence this system could improve the index of cancerous therapy and had significant potential for the therapy of cancer.

Wang *et al.* [56] prepared indocyanine green (ICG) loaded W₁₈O₄₉/MSNs. It showed that the system produced synergistic photothermal therapy and lethal effect to B16 tumor cells through the motivation of 808 nm NIR laser, and the shape of W₁₈O₄₉ can be controlled without surface modification. This system had potential application in the field of NIR-sensitive platform for therapy of cancer and the real-time track of photothermal therapy.

Table 6: Potential application of MSN in the field of DDS

Product	Model drug	Challenge	Experimental results	Potential application	Reference
MSN	DOX	Systemic side effects of DOX	As-prepared MSNs with size of 150–200 nm. The study demonstrated that MSNs/DOX system had stronger capacity of uptake and stable release of DOX than free DOX in the therapy of primary non-keratinized squamous of oral mucosal. The most advantageous part was that the platform released drug at pH in cellular physiological microenvironment	pH-sensitive DDS and targeted therapy of diseases, such as cerebral ischemia reperfusion injury and cancer.	[53]
MSN-Au, Au as gatekeeper	DOX	Systemic side effects of DOX	In vitro drug release studies showed that DOX released faster via stimulation of glutathione (GSH) or near infrared laser than free DOX.	Near infrared-responsive and redox-triggered DDS for chemo-photothermal synergistic therapy.	[54]
MSN/ZnO	DOX	Systemic side effects of DOX	The composites would release drug in the acidic microenvironment of tumor cells in comparison to zero release in the physiological microenvironment of the normal tissues. Besides, the cytotoxicity of ZnO QDs might endow composites with synergistic therapy for tumor. Hence this system could improve the index of cancerous therapy and had significant potential for the therapy of cancer.	pH-triggered, targeted DDS and synergistic therapy for tumor.	[55]
MSN/W ₁₈ O ₄₉	ICG	Systemic side effects of ICG	The system produced synergistic photothermal therapy and lethal effect to B16 tumor cells through the motivation of 808 nm NIR laser, and the shape of W18O ₄₉ can be controlled without surface modification.	This system had potential application in the field of NIR-sensitive platform for therapy of cancer and the real-time track of photothermal therapy.	[56]
MSN/HA	DOX	Systemic side effects of DOX	DOX release was responsive to redox and pH, and accompanied stronger cytotoxicity effects and cellular uptake to cancer cells.	Near infrared-responsive and pH-triggered targeted DDS for therapy of tumor.	[57]
MSN/HA	DOX	Systemic side effects of DOX	This system could release DOX faster, exhibited apoptosis more effectively than free DOX in cancer cells, and impeded growth of cancer cells with lower cytotoxicity to organism.	Therefore, the system responsive to HAase was a potential platform of DDS for targeted therapy of cancer cells that express HAase, such as colon cancer cells.	[58]
SiO ₂ /LDH/Bevacizumab composites	DOX	Systemic side effects of DOX	The system increased cellular uptake and targeted of DOX to cancer and brain, and decreased side effects of DOX, especially hepatic injury. Both of the in-vivo and in-vitro experiments indicated that the system had stronger effect of anti-angiogenesis and anti-neuroblastoma.	The composites have potential application for the targeted therapy of cancer where vascular endothelial growth factor (VEGF) expresses overly, such as neuroblastoma therapy.	[59]
MSN/PEI/lipid bilayers/IR-780 (iodide photosensitizer)	ZOL	Systemic side effects of ZOL	Drug release was responsive to NIR (808 nm) and accompanied negative cytotoxicity effects, and the compound had good dispersion stability.	It was found that PEI tethered core and shell and the high dispersion stability might attribute to lipid bilayers. The study suggested this system could be applied in the field of NIR-responsive and spatiotemporal controlled DDS for chemo-photodynamic therapy of tumor cells.	[60]

Table 6: ... continued

Product	Model drug	Challenge	Experimental results	Potential application	Reference
MSN/PD/SPION	chlorine6	Systemic side effects of chlorine6	PG layer connected MSNs and SPION could reinforce their colloidal stability. Experiment on a photosensitizer chlorine6 (Ce6) carried by MSNs/PD/SPION system suggested that Ce6 could be transported into target cells effectively directed by magnetism thereby enhancing the effect of photodynamic therapy.	Targeted drug delivery to enhance the effect of therapy, such as photodynamic therapy.	[61]
MSNs-PEG/PCL PEG/PCL worked as a thermal shock sensitive gatekeeper	DOX	Systemic side effects of DOX	The release of DOX was sensitive to thermal shock.	The study suggested the composites had potential application in the field of thermal shock sensitive DDS.	[62]
BMMs/ P(NIPAM-co-AA)	IBU	Systemic side effects of IBU	The nanocomposites could response to heat and pH. The mass fractal of P@BMMs was 2.51 in comparison with the mass fractal of BMMs was 2.36. Pharmoco-kinetics assay of P(NIPAM-co-AA)@BMMs demonstrated that the mechanism of ibuprofen release was non-Fickian diffusion, and in accord with Korsmeyer-Peppas power law model.	Thermal/pH-sensitive DDS for the controlled release of ibuprofen.	[63]
SBA-15-SH-poly(MPC-co-IA) composites	CDDP	Systemic side effects of CDDP	The composites had good loading capacity, biocompatibility and dispersity in water	DDS	[64]
Cubic nanoporous silica (SBA-16) modified by amine (A-SBA-16) and hematite SPIONs (Fe-SBA16)	indo	Systemic side effects of indo	The cumulative release of drug in 3 days is 91%, 63% and 68% for SBA-16, A-SBA-16 and Fe-SBA-16, respectively. Besides effective magnetic moment value of Fe-SBA-16 was about 384 μ B and the superparamagnetic did not change after loading drug.	Both A-SBA-16 and Fe-SBA-16 could be explored to sustained carriers of NSAID. Fe-SBA-16 also could be explored to targeted carrier of NSAID.	[65]
SiO ₂ /γ-Fe ₂ O ₃ nanocomposites, γ-Fe ₂ O ₃ as magnetic target inductor	-	-	The nanocomposites had desirable capacity of loading and sustained releasing drug, meanwhile it had satisfactory size, superficial area structure and biocompatibility.	They proposed this system might be applied in magnetic hyperthermia therapy and targeted drug delivery.	[66]
CD-MSN/UP38 where BBD worked as a thermal responder, and the temperature resolution of BBD was up to 0.2°C.	-	-	The most impressive part was that this system could be triggered by the heat energy of tumor. This system had strong therapeutic effects along with lower cytotoxicity effects.	Thermo-sensitive DDS to diagnose and remedy cancer.	[67]
MSNs/PAMMA dendrimers/CS	-	-	The composites possessed the impressing characteristic that preventing the fast clearance of PAMAM dendrimers. Meanwhile, PAMAM dendrimers and CS endowed the composites with fluorescence property which could omit using fluorescent labels, also made the drug release sensitive to pH. Furthermore, CS founded in osseous tissue possessed ability of target and could link dendrimers, and enhanced the delivery performance.	pH-sensitive and targeted DDS	[68]

Table 6: ... continued

Product	Model drug	Challenge	Experimental results	Potential application	Reference
Eu ³⁺ -doped calcium silicate	-	-	Eu ³⁺ -doped calcium silicate had size of 100 nm, and could radiate intense red luminescence at 612 nm, along with excellent biocompatibility and large specific surface area. The most fascinating part was that the composites had unique characterization of obvious decreasing intensity of radiation after loading drugs.	The composites could be applied to monitoring the trail of the release of drugs. And it might be a potential platform for sustained and controlled release of drugs, diagnosing disease and cells imaging.	[69]

Lin *et al.* [57] synthesized MSNs-hyaluronic acid (HA) loaded DOX where MSNs functionalized by HA as a redox and pH dual stimulate-sensitive DDS. The results indicated that DOX release was responsive to redox and pH, and accompanied stronger cytotoxicity effects and cellular uptake to cancer cells, which enable the composites to be applied in the field of tumor therapy.

Zhang *et al.* [58] synthesized MSNs/hyaluronic acid (HA) as hyaluronidase (HAase) sensitive DDS. This system could release DOX faster, exhibited more effective apoptosis than free DOX in cancer cells, and impeded growth of cancer cells with lower cytotoxicity to organism. Therefore, the system responsive to HAase was a potential platform of DDS for targeted therapy of cancer cells that express HAase, such as colon cancer cells.

Zhu *et al.* [59] fabricated SiO_2 /lactate dehydrogenase (LDH)-Bevacizumab composites as DDS to load DOX. Besides, vascular endothelial growth factor (VEGF) was applied as a target because of its abnormal expression in tumor. The study demonstrated that this system increased cellular uptake and targeted of DOX to cancer and brain, and decreased side effects of DOX, especially hepatic injury. Both of the in-vivo and in-vitro experiments indicated that the system had stronger effect of anti-angiogenesis and anti-neuroblastoma. Hence the composites have potential application for the targeted therapy of cancer where vascular endothelial growth factor (VEGF) expresses overly, such as neuroblastoma therapy.

Liu *et al.* [60] synthesized MSNs-zoledronic acid (ZOL)/tethered with lipid bilayers (tLB)-IR-780 iodide system as a NIR-responsive DDS. The study indicated that drug release was responsive to NIR and accompanied negative cytotoxicity effects, and the compound had good dispersion stability. The study suggested this system could be applied in the field of NIR-responsive DDS for tumor cells.

Yang *et al.* [61] prepared the MSNs/PG/SPION system where MSNs were coated by super paramagnetic iron oxide nanoparticles (SPION). The study revealed polyglycerol (PG) layer connected MSNs and SPION could reinforce their colloidal stability. Experiment on a photosensitizer chlorine6 (Ce6) carried by MSNs/PG/SPION system suggested that Ce6 could be transported into target cells effectively directed by magnetism thereby enhancing the effect of photodynamic therapy.

Cho *et al.* [62] structured MSNs-PEG/PCL where polyethylene glycol (PEG)/polycaprolactone (PCL) worked as a thermal shock sensitive gatekeeper. The assay indicated that the release of DOX was sensitive to thermal shock. The study suggested the composites had potential application in the field of thermal shock sensitive DDS.

Jin *et al.* [63] fabricated bimodal mesoporous silica nanoparticles (BMMs)/poly(N-isopropylacrylamide)-co-poly(acrylic acid) (P(NIPAM-co-AA)) to load ibuprofen. This system was responsive to temperature and pH. Pharmacokinetics assay of P(NIPAM-co-AA)@BMMs demonstrated a non-Fickian diffusion mechanism of ibuprofen release, and in accord with Korsmeyer-Peppas power law model.

Huang *et al.* [64] fabricated SBA-15-SH-poly(MPC-co-IA) composites to load CDDP, and synthetic route was shown in Figure 4. It was found that the composites had good loading capacity, biocompatibility and dispersity in water.

Figure 4: The synthetic route of CHAM and drug loading

Zelenak *et al.* [65] investigated the properties of cubic nanoporous silica (SBA-16) modified by amine (A-SBA-16) and hematite SPIONs (Fe-SBA-16) loaded with indomethacin (indo), a typical nonsteroidal anti-inflammatory drug (NSAID). The cumulative release of drug in 3 days was 91%, 63% and 68% for SBA-16, A-SBA-16 and Fe-SBA-16, respectively. Besides, effective magnetic moment value of Fe-SBA-16 was about $384 \mu_B$ and the superparamagnetic property did not change after loading drug. Hence both A-SBA-16 and Fe-SBA-16 could be explored to be sustained carriers of NSAID. Fe-SBA-16 could also be explored to be targeted carrier of NSAID.

Wan *et al.* [66] prepared walnut kernel-like $\text{SiO}_2/\gamma\text{-Fe}_2\text{O}_3$ composite by doping $\gamma\text{-Fe}_2\text{O}_3$ into mesoporous SiO_2 . It was found that the nanocomposite had desirable capacity of loading and sustained releasing drug, meanwhile it had satisfactory size, superficial area structure and biocompatibility. They proposed that this system might be applied in magnetic hyperthermia therapy and drug targeted delivery.

Dong *et al.* [67] fabricated CD-MSN/UP38 where 4-Benzylamino-7-nitro-2,1,3-benzoxadiazole (BBD) was used as a thermal responder by chemical synthesis and nanotechnology, and the temperature resolution of BBD was up to 0.2°C. The most impressive part was that this system could be triggered by the heat energy of tumor. This system had strong therapeutic effects along with lower cytotoxicity effects, which enable it to be applied in the field of thermal-sensitive DDS to diagnose and remedy cancer.

Xu *et al.* [68] assembled MSNs/polyamidoamine (PAMMA) dendrimers/chondroitin sulfate (CS) by layer-by-layer assembly method. The composites possessed the impressive characteristic that preventing the fast clearance of polyamidoamine (PAMAM) dendrimers. Meanwhile, PAMAM dendrimers and CS endowed the composites with fluorescence property which helped to avoid the need of external doping of fluorescent substances, and made the drug release sensitive to pH. Furthermore, CS found in osseous tissue possessed ability of targeting, linking dendrimers, and enhancing the delivery performance.

In addition, some silicon-contained materials are also considered as good candidate for carriers. For instance, in the study of Zhang *et al.* [69], it was found that the size of Eu^{3+} -doped calcium silicate was 100 nm, and could radiate intense red luminescence at 612 nm, along with excellent biocompatibility and large specific surface area. The most fascinating part was that the composites had unique characterization of obvious decreasing intensity of radiation after loading drugs, which could be applied to monitor the trail of the release of drugs. And the composites might be potential platform for sustained and controlled release of drug, diagnoses of disease and cells imaging.

2.4 Zeolitic Imidazole Framework (ZIFs)

The applications of conventional materials for DDS were restricted by their cytotoxicity and uncontrolled drug release, etc. Herein, ZIFs have emerged rapidly as a novel class of versatile porous biomaterial for application in the field of DDS owing to their unique priority of structural diversity, high specific surface area, desirable chemical and thermodynamic stability, non-toxicity and desirable biocompatibility [70–72].

Adhikari *et al.* [73] investigated the performance of 2 types of carriers, i.e., ZIF-7 and ZIF-8, for the release of DOX. It was shown that DOX was encapsulated easily by both carriers, and delivery duration of DOX was 10 h and 3 h for ZIF-7 and ZIF-8, respectively. Besides, controlled drug delivery time was 10 h owing to rigidity of ZIF-7. Furthermore, ZIF-8 was sensitive to pH and could release DOX in acidic

environment which tumor cells possess typically, that was not found in ZIF-7. Experimental results were shown in Table 7. Therefore, the drug release could be controlled by using various characteristics of different ZIFs. This provided reference for future exploration of DDS for therapy of diseases, such as cancer.

Table 7: Experimental results of 2 groups

Experimental results	DOX loaded ZIF-7	DOX loaded ZIF-8
pH-sensitive	✓	×
Controlled drug delivery time (h)	10	3

2.5 Ceramics based on iron oxide nanoparticles

Nowadays, iron oxide nanoparticles (Fe_3O_4 and Fe_2O_3) had been used in the field of DDS as magnetic metal organic frameworks (MOFs) and inductor for targeted delivery in terms of its unique magnetic property. A lot of studies indicated their application in targeted, controlled and sustained DDS are summarized in Table 8-9.

Table 8: Synthesis method of iron oxide nanoparticles in the field of DDS

Synthesis method	Product	Reference
Microwave irradiation technique	$\text{Fe}_3\text{O}_4\text{-NH}_2/\text{MIL101-NH}_2$ nanocomposites	[74]
Copolymerizing	$\text{Fe}_3\text{O}_4/\text{P(NIPAM-co-MAA)}$	[75]
W/O/W emulsion technique	$\text{Fe}_3\text{O}_4/\text{PLGA}$ or HAP/PLGA .	[76]
Ultrasound assisted precipitation method	$\text{Fe}_3\text{O}_4/\text{SiO}_2/\text{HAP}$ nanocomposites functionalized by APTES	[78]
Co-precipitation approach	Iron oxide nanoparticles ($\text{IONP(Fe}_3\text{O}_4/\text{Fe}_2\text{O}_3)$) dual-coated by HAP and NaAlg	[79]

Li *et al.* [74] fabricated DOX-loaded $\text{Fe}_3\text{O}_4\text{-NH}_2/\text{MIL101-NH}_2$ composites as DDS. The system had great surface areas (96.04 m^2/g) and volume (22.07 cm^3/g), and the loading capacity of 36.02%. Furthermore, DOX release was sensitive to pH. In addition, the system had desirable biocompatibility and low cytotoxicity, which is better than the

Table 9: Potential application of iron oxide nanoparticles in the field of DDS

Product	Model drug	Challenge	Experimental results	Potential application	Reference
$\text{Fe}_3\text{O}_4\text{-NH}_2/\text{MIL101-NH}_2$ nanocomposites	DOX	Systemic side effects of DOX	The nanocomposites had great surface areas ($96.04 \text{ m}^2/\text{g}$) and volume ($22.07 \text{ cm}^3/\text{g}$), as well as diameters was $140\text{-}330 \text{ nm}$ and the loading capacity of 36.02% . Furthermore, DOX release was sensitive to pH and aperture size of nanocomposites. In addition, the system had desirable biocompatibility and low cytotoxicity, which is better than the one with pure MIL101-NH ₂ as carrier. The intensity of magnetism of this system was 20.47 emu/g	Controlled release of DOX for diseases, such as therapy.	[74]
$\text{Fe}_3\text{O}_4/\text{P}(\text{NIPAM-co-MAA})$	DOX	Systemic side effects of DOX	The composites possessed a lower critical solution temperature (LCST) at about 37.2°C , which was close to normal physiological temperature of human. Furthermore, drug release capacity of $\text{Fe}_3\text{O}_4/\text{P}(\text{NIPAM-co-MAA})$ was sensitive to thermal controlled by laser with 808 nm wavelength. In addition, rate of DOX release was fast and cumulative rate increased 25% . Hydrodynamic diameters of the nanocomposites were increased with increasing content of PLGA and were unrelated with loading capacity. Their excellent biocompatibility was demonstrated in cytotoxicity experiments in vitro.	Multi-sensitive DDS of microgels, such as photothermal and chemotherapy DDS.	[75]
$\text{Fe}_3\text{O}_4/\text{PLGA}$ or HAP/PLGA	-	-		They had promising application in DDS.	[76]
$\text{Fe}_3\text{O}_4/\text{Fe-metal-organic framework@HAP}$, Fe_3O_4 as core, Fe-metal-organic framework as shell, HAP as pH-sensitive gatekeeper	DOX	Systemic side effects of DOX	Loading capacity of DOX was 75.38 mg/g , saturation magnetization was 34 emu/g .	Magnetic targeted and pH-sensitive DDS for therapy of tumor with lower cytotoxicity to normal cells.	[77]
$\text{Fe}_3\text{O}_4/\text{SiO}_2/\text{HAP}$ nanocomposites functionalized by APTES	Atenolol	Systemic side effects of atenolol	The size and morphology of nanocomposites are influenced by weight ratios of agents and calcining heat. The nanocomposites had desirable porosity (13.37 nm) and surface area ($55.88 \text{ m}^2/\text{g}$) for DDS of controlled release of atenolol. Furthermore, cumulative atenolol release amount was 100% and 15.6% at different pH, i.e., 6.8 and 1.2 respectively in 30 h .	Controlled release of atenolol, especially for the therapy of hypertension.	[78]
IONP dual-coated by HAP and NaAlg	Curcumin and 6-gingerol	Systemic side effects of curcumin and 6-gingerol	Curcumin and 6-gingerol release performance demonstrated that the drugs release was higher when pH was 5.3 than pH was 7.4 and the release time were both over 7 days at 37°C .	The system could be used in pH-dependent DDS, and had a potential application in controlled and targeted release of curcumin and 6-gingerol for the therapy of cancer.	[79]

one with pure MIL101-NH₂ as carrier. The intensity of magnetism of nanocomposites was 20.47 emu/g, which hinted that the system was sensitive to magnetism.

Qi *et al.* [75] fabricated Fe₃O₄/poly(N-isopropylacrylamide)-co-poly(methacrylic acid) (P(NIPAM-co-MAA)) by copolymerizing poly(N-isopropylacrylamide) with methacrylic acid in water phase that containing Fe₃O₄ modified by oleic acid. Assay indicated that the composites possessed a lower critical solution temperature (LCST) at about 37.2°C, which was close to normal physiological temperature of human. Furthermore, drug release capacity of Fe₃O₄/P(NIPAM-co-MAA) was sensitive to thermal controlled by laser with 808 nm wavelength. In addition, rate of DOX release was fast and cumulative rate increased by 25%. Hence, the composites had potential application in multi-sensitive DDS of microgels, such as photothermal and chemotherapy DDS.

Bootdee *et al.* [76] fabricated composite composed of Fe₃O₄/poly(D,L-lactide-co-glycolide)(PLGA) or HAP/PLGA. The weight ratios of Fe₃O₄ or HAP in the PLGA varied from about 5 to 60 wt% with various weight percent of Fe₃O₄ or HAP and PLGA in the oil phase. Hydrodynamic diameters of the nanocomposites were increased with increasing content of PLGA and were unrelated with loading capacity. Their excellent biocompatibility was demonstrated in cytotoxicity experiments in vitro. They had promising application in DDS.

Yang *et al.* [77] fabricated pH-responsive drug delivery system: Fe₃O₄/Fe-MOF/HAP which had a magnetic core coated Fe-MOF (metal-organic framework). In this system, HAP was pH-responsive gatekeeper to control the release of drug. The study indicated their loading capacity of doxorubicin (DOX) was 75.38 mg/g and their intensity of magnetic field was 34 emu/g, which endowed this system with targeted ability on tumor tissue while decreasing toxicity to normal cells.

Sobhan *et al.* [78] synthesized Fe₃O₄/SiO₂/HAP nanoparticles functionalized by 3-aminopropyl triethoxysilane (APTES). The system had desirable porosity (13.37 nm) and surface area (55.88 m²/g) for DDS of controlled release of atenolol. Furthermore, cumulative atenolol release amount was 100% and 15.6% at different pH, i.e., 6.8 and 1.2 respectively in 30 h.

Manatunga *et al.* [79] fabricated iron oxide nanoparticles (IONP) dual-coated by HAP and sodium alginate (NaAlg) to be pH-dependent DDS. Curcumin and 6-gingerol release performance demonstrated that the drugs release was higher when pH was 5.3 than pH was 7.4 and the release time both lasted for over 7 days at 37°C. The system could be used in pH-dependent DDS, and had a

potential application in controlled and targeted release of curcumin and 6-gingerol for the therapy of cancer.

2.6 Alginate-brushite

Besides, Dabiri *et al.* [80] fabricated composites composed of alginate-brushite (Alg-Bru) and hydrogel by a novel in-situ synthesizing strategy to load IBU. It was found that the composites were sensitive to acidity, meanwhile the mechanical properties of composites were improved by the brushite, swelling ratio of alginate was limited by brushite. However, brushite did not increase entrapment efficiency (%EE). The most impressive part was that brushite led the composites to release drug in a controlled gradual manner to avoid burst drug release of alginate.

3 Conclusions

Ceramics materials have numerous of merits such as simple method of preparation, adjustable size and structure, low toxicity, desirable stability under physiological conditions and biocompatibility, especially some are sensitive to environment, such as magnetic field, acidity and heat. Therefore, they have been widely applied in the field of DDS. However, some of them have limitations such as high cost, low encapsulation and uncontrollable dose. Hence, it is very important and challenged to improve the loading capacity, targeted and controlled release properties of the DDS to maximize efficiency of drugs and minimize the cytotoxicity to the normal tissue and cells. In addition, it is also of great importance to optimize the synthetic process to decrease the cost of ceramic-based carriers.

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