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Prospective

# Recent Advances in Magnetoliposomes as Drug Delivery Carriers

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## Abstract

Liposome has been one of the most promising drug delivery carriers and has made their way to the market. Magnetic nanoparticles also have been attracting interest for therapeutic and imaging applications due to their unique magnetic properties. Integration of liposomes and magnetic nanoparticles gives great potential to the field of drug delivery, such as magnetic targeted drug delivery, image guided drug delivery, and controlled release using hyperthermia or alternating magnetic field. Here, we discuss the recent development of magnetoliposomes for drug delivery and their potentials.

**Keywords:** Magnetoliposomes; Liposomes; Magnetic nanoparticles; Drug delivery

## Introduction

Magnetic nanoparticles have great potential in a variety of applications including catalysis [1], data storage [2], environmental remediation [3], and biomedical applications [4-11]. Magnetic nanoparticles, especially iron oxide nanoparticles ($Fe_3O_4$ and $\gamma$-$Fe_2O_3$), have demonstrated their great capability for biomedical applications due to their unique magnetic properties and biocompatibility. They are used as contrast agents for magnetic resonance imaging (MRI) [4,5] because of the shortening effect on T2 relaxation time of neighboring regions [6]. Magnetic force exerted on magnetic nanoparticles under magnetic field gradient allows the nanoparticles to be used as carrier for magnetic targeting in drug delivery system [7,8] and gene transfection [9]. Heat generation of magnetic nanoparticles under AC magnetic field can be applied for hyperthermia (heat treatment of cancer) [8,10,11]. Liposomes are closed spherical vesicles consisting of lipid bilayers which encapsulate an aqueous phase [12]. Liposomal formulation is the first nanoparticle based drug delivery system made the transition to clinical application [13]. They have great advantages as drug carriers such as their biocompatibility, biodegradability which can be applied for sustained release, ability to encapsulate water soluble drugs within lipid bilayers and water insoluble drugs in between lipid bilayers, and drug protection against degradation factors [14]. For example, Doxil® is the first FDA approved liposomal drug which encapsulates doxorubicin in PEG coated (PEGylated) liposome. It can be delivered to tumor site by passive targeting using the enhanced permeability and retention (EPR) effect [15]. The combination of liposomes and magnetic nanoparticles, which is called magnetoliposomes, was first introduced by De Cuyper et al in 1988 [16]. Lauric acid coated magnetic nanoparticles were incorporated inside lipid bilayer for magnetophoresis. Since then, various magnetoliposomes have been reported for drug delivery, MRI imaging [17,18], and hyperthermia [19]. The integration of magnetic nanoparticles and liposomes gives magnetoliposomes great potentials for drug delivery such as magnetic targeting, image guided drug delivery using MRI or other imaging methods, and controlled release using hyperthermia and low frequency magnetic field (Figure 1). It is discussed in Section 4.

## Magnetic Nanoparticle Synthesis and Magnetoliposome Formation

### Synthesis of magnetic nanoparticles

Iron oxide nanoparticles are most commonly used magnetic nanoparticles for biomedical applications because of their biocompatibility and magnetic property. Iron oxide nanoparticles have been prepared by both of bottom up and top down. However, top down method has limitation on particle size and scale of production, thus bottom up

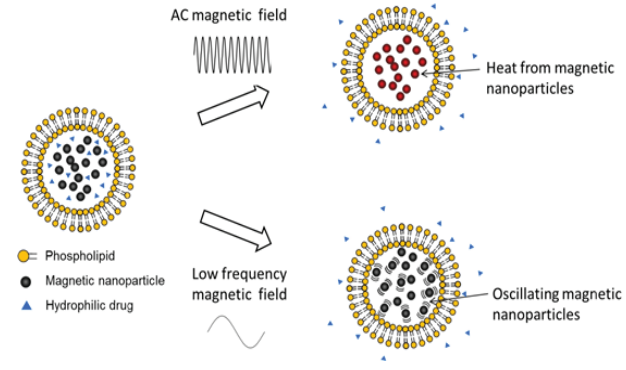


**Figure 1.** Schematic illustration of controlled drug release from magnnetoliposomes using magnetic nanoparticle hyperthermia and oscillation of magnetic nanopparticles under low frequency magnetic field.

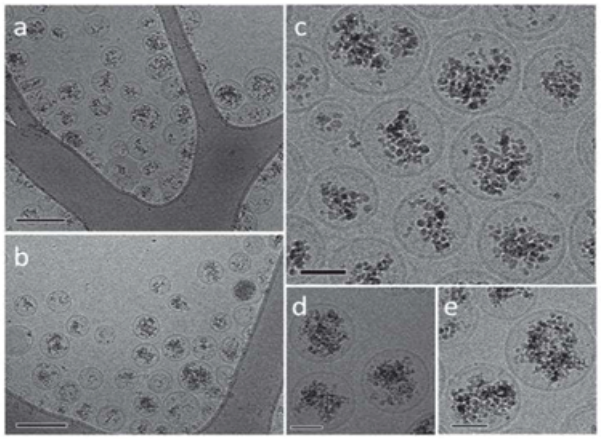


**Figure 2.** Gallery of cryo-TEM images of magnetoliposomes made from DOPC–cholesterol (75:25, mol:mol) containing an average number of 77 particles per liposome, equivalent to 5.6 mol iron per mol lipid. (a, b) Scale bars 200 nm; (c–e) scale bars 50 nm. Reprinted with permission from ref. [17], ©2012 John Wiley & Sons Inc.

method is preferred. Many bottom up method have been developed such as coprecipitation [20,21], thermal decomposition [22,23], hydrothermal [24], reverse micelle [25]. Each synthesis method has advantage and disadvantage on the easiness, size and shape control, monodispersity, and surface properties. Here, we introduce

coprecipitation and thermal decomposition. Coprecipitation is most widely used method because of the easy and simple steps. This method is based on the coprecipitation of $Fe^{2+}$ and $Fe^{3+}$ aqueous salt solutions at 1:2 molar ratio by addition of alkaline solution [20]. The control of size and shape of nanoparticles depends on the type of salts used (e.g. chlorides, sulphates, nitrates, perchlorates, etc.), pH of the media and capping agent such as chelating organic anions or polymers [21]. The disadvantage of this method is broad size distribution. Another widely used synthesis method is thermal decomposition. High-quality monodispersed iron oxide nanoparticles can be synthesized by decomposition of iron precursors such as iron oleate and iron pentacarbonyl under high temperature [22,23]. This method has advantages for producing highly crystalized particles with narrow size distribution. However, the nanoparticles synthesized by thermal decomposition are capped with surfactant, and resulting hydrophobic surface does not allow nanoparticles to be dispersed into water. Additional phase transfer process is required for biomedical applications. In the case of magnetoliposomes, this hydrophobic surface can help encapsulating nanoparticles in between bilayers of liposome.

## Formation of Magnetoliposomes

Figure 2 shows transmission electron microscopy (TEM) images of magnetoliposomes. Three different structures of Magnetoliposomes can be formed depends on the location of magnetic nanoparticles (Figure 3). Most widely used approach is encapsulating magnetic nanoparticles within lipid bilayers. Encapsulating magnetic nanoparticles in between lipid bilayers

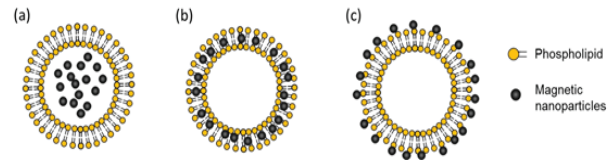


**Figure 3.** Magnetoliposomes encapsulate magnetic nanoparticles within lipidid bilayers (a), encapsulate magnetic nanoparticles in between lipid bilayers (hydrophobic sidee) (b), and bind magnetic nanoparticles on the surface of liposome (c).

(hydrophobic side) is another approach which has been gaining attention. Magnetic nanoparticles synthesized by thermal decomposition are used for this approach because of their hydrophobic surface. There is less report on binding magnetic nanoparticles on the surface of liposome [26]. A number of preparation methods have been developed for liposome formation such as thin film hydration [27,28], reverse-phase evaporation [27], and ethanol injection [28]. Most commonly used method for magnetoliposome preparation is thin film hydration. This method is followed by the processes of drying lipid, hydration of the dried lipid, and size reduction. For the magnetoliposomes which contains magnetic nanoparticles within lipid bilayers, magnetic nanoparticles are dispersed in the aqueous medium before hydration process. The size of liposome can be reduced by extrusion through polycarbonate filters with different pore sizes or sonication.

## Biomedical Applications

### Drug delivery system

Delivery of drugs to specific targeted sites and their release at the right time and period are essential for drug delivery system. It enables efficient treatment using minimal amount of drugs and reduces side effect from non-specific distribution. In addition to delivery and release of drugs, nanoparticles have the potential to achieve cell or tissue specific targeting, and image guided drug delivery [29]. Targeting of nanoparticle formulation can be achieved by both passive and active targeting. Current US Food and Drug Administration (FDA)-approved nano drug accumulates in tumor by passive targeting using enhanced permeability and retention (EPR) effect [30]. EPR effect is based on the enhanced extravasation and nanomaterial retention in tumor tissues which are permeable and leaky. Passive targeting requires nanoparticles to have long circulation time in the blood to have sufficient accumulation in tumor tissue. This long circulation time has been achieved by surface modification with polyethylene glycol (PEG) [31], called PEGylation, which builds a sterically repulsive shield that protects the particles from non-specific interactions [32] and avoids removal by the reticuloendothelial systems (RES). Active targeting uses targeting moiety (ligand) such as an antibody which binds to specific receptor in tumor cells [33][34], or stimuli responsive characteristics of nanoparticles to release drugs at targeted sites. Various stimuli responsive nanoparticles have been reported, such as pH-sensitive [35], temperature-sensitive [36], and ultrasound-

sensitive nanoparticles [37]. Magnetic nanoparticles are one of the great candidates for active targeting carrier. Magnetic targeting is based on magnetic force exerted on magnetic nanoparticles in the presence of a magnetic field gradient [8]. When external field gradient is applied from magnet, magnetic nanoparticles are attracted to magnet due to the magnetic force. This magnetic force is dependent on physical parameters such as magnetic field strength, gradient, and volumetric and magnetic properties of the particles. Hydrodynamic size is another parameter which should be considered to design nanoparticle formulation. It is generally agreed that optimal hydrodynamic size of nanoparticle formulation for in vivo application is 10–100 nm [38]. Nanoparticles smaller than 10 nm are rapidly removed by renal clearance, and larger nanoparticles (>200 nm) are removed by the reticuloendothelial system (RES) of spleen and liver [39].

**Hyperthermia**

Since hyperthermia based controlled release has been the major application of magnetoliposomes, we introduce hyperthermia using magnetic nanoparticles (called magnetic nanoparticle hyperthermia or magnetic fluid hyperthermia) and the mechanism of heat induction briefly. Hyperthermia is another biomedical application of magnetic nanoparticles, which treats cancer with increasing the temperature to higher than 42℃. It has been reported that the viability of cells significantly decreases after exposed to heat [40,41]. This hyperthermia treatment has great advantages of being less invasive to the body and less side effects compared to traditional cancer treatment such as surgical operation, chemotherapy, and radiation therapy. Magnetic nanoparticles have been a great candidate as a heat source for local hyperthermia treatment due to their ability for magnetic targeting and heat induction under AC magnetic field at specific region. Hyperthermia using magnetic materials has been investigated since 1957, when Gilchrist et al reported heating of various tissue samples with $\gamma$-$Fe_2O_3$ under ac magnetic field [42].

Heating of magnetic nanoparticles under AC magnetic field is caused by two processes: hysteresis loss and relaxation losses. When an external magnetic field is applied, magnetic materials possess hysteresis property between magnetic field and magnetization. Hysteresis loss is induced by this hysteresis property, and its value is given by its frequency multiplied by the area of the hysteresis loop in an external field [8]. However in the case of superparamagnetic nanoparticles such as superparamagnetic iron oxide nanoparticles (SPIONs), there is no contribution of hysteresis loss because of their superparamagnetic property without hysteresis [43]. For those small magnetic nanoparticles, relaxation losses are dominant for heat dissipation of the nanoparticles. Relaxation losses are caused by a delay in magnetic moment relaxation. Brownian relaxation loss and Néel relaxation loss are associated with magnetic moment rotation of the entire particle and within a particle, respectively [44]. The heating of the magnetic nanoparticles depends on the magnetic property, amplitude and frequency of AC magnetic field, and also surrounding environment. Therefore, optimization of magnetic field condition for each magnetic nanoparticles and surrounding environment is essential to control the temperature rise of magnetic nanoparticles.

**Drug delivery using magnetoliposomes**

The magnetic properties of magnetic nanoparticles make magnetoliposomes multifunctional drug delivery carrier with the potential for magnetic targeting, controlled release using temperature rise (hyperthermia) under AC magnetic field, and image guided delivery using MRI and other imaging methods. The magnetoliposomes developed as carrier of drug delivery in recent years were listed in Table 1. Controlled release of encapsulated drugs in response to the temperature rise of magnetic nanoparticle hyperthermia has been main focus of magnetoliposomes for decades [45-53]. Temperature sensitive magnetoliposomes have been developed using DPPC which have gel-to-liquid phase transition temperature (Tm) of 42 ℃, slightly above body temperature. Near their gel-to-liquid phase transition temperature, liposomes become highly leaky because of disorder at the boundaries between solid and fluid domains in the lipid [54]. Temperature sensitive magnetoliposomes which encapsulate Mn0.5Zn0. $5Fe_2O_4$ nanoparticles and antitumor drug $As_2O_3$ within lipid bilayers showed maximum drug release of 98.32% at 44 ℃ [47]. Lipid composition of liposomes is an important factor to control the transition temperature of liposomes. By adding DSPC which has higher transition temperature compared to DPPC (DSPC: 55℃, DPPC: 42℃) into the lipid composition, the temperature which triggers release of encapsulated fluorescent dye was increased from 35 ℃ to 40 ℃ [48]. PEGylated and ligand conjugated magnetoliposomes have been reported to improve their blood circulation time and targeting ability [49,50]. PEGylation, which is surface modification of nanoparticles with polyethylene glycol (PEG), is a well-known technique to enhance blood circulation of nanoparticles. The steric hindrance of PEG chain prevents plasma proteins to attach on the surface of nanoparticles, thus impart stealth properties [55]. Ligand conjugation on the surface of nanoparticles enhances active targeting to the specific site which expresses receptor [33,34]. Folate is one of the ligands used for anti-cancer targeting because of the folate receptor overexpressed in a large number of epithelial malignancies compared to healthy cells [56]. Folate conjugated magnetoliposomes showed higher uptake into human cervical cancer cells (HeLa), which have been shown to exhibit high folate receptor expression, and drug release [49]. Magnetoliposomes encapsulate magnetic nanoparticles in between lipid bilayers have been reported for controlled release based on magnetic nanoparticle hyperthermia [51-53]. The advantage of encapsulating magnetic nanoparticles in hydrophobic area between lipid bilayers is that no further surface coating is required for magnetic

nanoparticles synthesized by thermal decomposition. This structure is expected to have focused heating on lipid bilayers from encapsulated magnetic nanoparticles and maximize the drug release [51]. Amstad et al (2011) reported temperature sensitive magnetoliposomes encapsulate palmityl-nitroDOPA-coated iron oxide nanoparticles between lipid bilayers and calcein within bilayers [52]. The release of encapsulated calcein has been

**Table 1.** List of recently reported magnetoliposomes for drug delivery.

| Magnetic nanoparticles | Lipid | Structure | Encapsulated molecule | Release mechanism | Other feature | Ref. |
|---|---|---|---|---|---|---|
| Mn0.5Zn0.5Fe2O4 | DPPC, Cholesterol | Within bilayers | $As_2O_3$ | Temperature-sensitive, Controlled released by hyperthermia | | [47] |
| Resovist | DPPC DSPC Cholesterol | Within bilayers | Carboxy fluorescein | Temperature-sensitive, Controlled released by hyperthermia | | [48] |
| 5 nm γ-$Fe_2O_3$ Commercial | DOPC DPTAP Cholesterol PEG-DMPE NBD-DPPE DSPE-PEG-folate | Within bilayers | Doxorubicin | Temperature-sensitive, Controlled released by hyperthermia | PEGylation Folate targeting | [49] |
| 10 nm $Fe_3O_4$ Commercial | DPPC Cholesterol DSPE-PEG DSPE-PEG -folate | Within bilayers | Doxorubicin Calcein | Temperature-sensitive, Controlled released by hyperthermia | PEGylation Folate targeting | [50] |
| 5 nm γ-$Fe_2O_3$ Oleic acid coated Commercial | DPPC | In between | Carboxy fluorescein | Temperature-sensitive, Controlled released by hyperthermia | | [51] |
| 5, 10 nm Iron oxide Palmityl-nitro DOPA-coated iron oxide NPs | DSPC SOPC POPC PEG-PE | In between | Calcein | Temperature-sensitive, Controlled released by hyperthermia | PEGylation | [52] |
| $Fe_3O_4$ AOT-coated | Soybean lecithin | In between | Calcein | Temperature-sensitive, Controlled released by hyperthermia | | [53] |
| $CoFe_2O_4$ Coprecipitation | PC | Within bilayers | Carboxy fluorescein | Controlled release by ac magnetic field 0.2, 2.84, 5.82 kHz | | [59] |
| $CoFe_2O_4$ Coprecipitation Oleic acid Coating | PC | in between | Carboxy fluorescein | Controlled release by ac magnetic field 0.2, 2.5, 5.2 kHz | | [60] |
| $Fe_3O_4$ Carboxymethyl dextran coated Commercial | HSPC Cholesterol | Within bilayers | Carboxy fluorescein | Controlled release by AC magnetic field 20 kHz, 60 A/m | | [61] |
| 3–5 nm $Fe_3O_4$ Citrate coated Coprecipitation | Soy PC Cholesterol | Within bilayers | Doxorubicin | Controlled release by AC magnetic field 50 Hz, 45mT | Carboxymethyl dextran coated stealth liposomes | [62] |
| Fe/$Fe_3O_4$ Hydrophilic, amphiphilic, or hydrophobic peptide coated | DPPC DSPC Cholesterol | Within bilayers | $MgSO_4$, Carboxy fluorescein | Controlled release by magnetic field Ultrasound generation under pulsed magnetic fields | | [63] |

**Abbreviations:** EPC: Egg Phosphatidylcholine; DSPE-PEG: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000]; DPPC: 1,2-dipalmitoyl-sn-glycero-3-phosphocholine; DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; DPTAP, 1,2-dipalmitoyl-3-trimethylammoniumpropane; PEG-DMPE, 1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-750];NBD-DPPE:1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(7-nitro-2-1,3-benzoxadiazol-4-yl);DSPE-PEG-folate:1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[folate(polyethylene glycol) 2000]; DOPC: 1,2-dioleoyl-sn-glycero-3-phosphocholine; Nitro DOPA: Nitro L-dihydroxyphenylalanine; SOPC: 1-stearoyl-2-oleoyl-sn-glycero-3-phosphochline; POPC: 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine; PEG-PE: 1,2-Dioleoyl-sn-Glycero-3-Phosphoethanolamine-N-[Methoxy(Polyethylene glycol)2000]; AOT: Sodium bis (2-ethylhexyl) sulfosuccinate; HSPC: MaterialsHydrogenated soybean phosphatidylcholine; Soy PC: Soybean phosphatidylcholine

demonstrated under AC magnetic field. The heat from magnetic nanoparticles under AC magnetic field caused phase transition of the lipid bilayer from gel to liquid, and released encapsulated calcein out of the liposome. They also demonstrated greater release efficiency of the above magnetoliposomes compared to those which contain hydrophilic iron oxide nanoparticles within lipid bilayers. This is because of direct heat transfer from hydrophobic iron oxide nanoparticles to lipid bilayers. Constant hydrodynamic size of those magnetoliposomes before and after AC magnetic field exposure shows calcein release was caused by membrane permeability and not liposome rupture or fusion. Qiu et al. reported the repetitive release of encapsulated calcein from temperature sensitive magnetoliposomes with AOT-coated $Fe_3O_4$ nanoparticles between lipid bilayers [53]. The encapsulated calcein was released repetitively by switching AC magnetic field on and off. By turning off the AC magnetic field, the phase transferred back to gel without temperature, and stopped the release of calcein. There is an increasing interest in using low frequency magnetic field to enhance controlled release of drugs from drug carrier contains magnetic nanoparticles [57,58]. It has been reported that the movement of nanoparticles under low frequency magnetic field increase permeability of surrounding polymers [57]. Enhanced release of encapsulated molecule from magnetoliposomes after exposure to low frequency magnetic field was first reported by Nappini et al [59]. Significantly higher release rate of carboxyfluorescein was observed from magnetoliposomes encapsulate $CoFe_2O_4$ nanoparticles compared to those without nanoparticules after exposure to AC magnetic field at 5.82 kHz without rupture of bilayers. They also reported the different release behavior between magnetoliposomes which encapsulate $CoFe_2O_4$ nanoparticles within lipid bilayers and those encapsulate nanoparticles in between lipid bilayers [60]. Since then, there have been some reports showing controlled release of encapsulated molecules from magnetoliposomes by

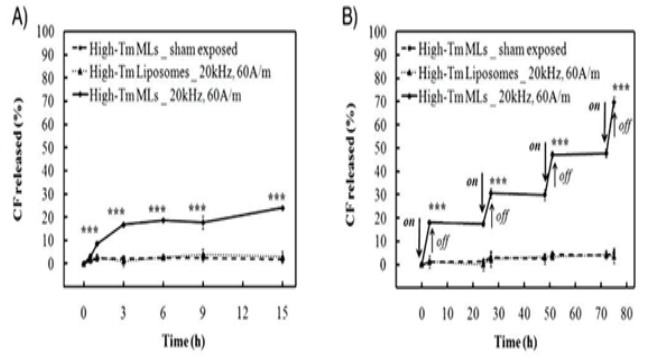


**Figure 4.** Effect of AMF exposure (20 kHz, 60 A/m at 37 °C) in continuous (A) and ON–OFF (B) modality on the cumulative release of CF from MLs and control liposome. The amount of CF released from MLs over time under isothermal sham exposure is reported for both strategies. Values (mean±S.D.) are the average of 7 independent experiments. Asterisks indicate significant differences between controls (sham exposure and control liposomes) and MLs (*** $p < 0.001$). Reprinted with permission from ref. [61], ©2015 Elsevier B.V.

oscillation of magnetic nanoparticles under ac magnetic field without heat generation [61,62]. Spera et al demonstrated the membrane permeation and carboxyfluoresein release from high-transition temperature magnetoliposomes which are not sensitive to temperature increase up to 50℃ under AC magnetic field [61]. Repetitive release of encapsulated carboxyfluoresein was obtained by switching AC magnetic field on and off without change in their size (Figure 4). Podaru et al demonstrated that magnetic nanoparticles generate ultrasound under pulsed magnetic field, and it causes disruption of lipid bilayers, resulted in release of encapsulated $MgSO_4$ and carboxyfluorescein [63]. Triggering drug release from magnetoliposomes using low frequency magnetic field or pulsed magnetic field is a new concept which has great potential for controlled drug release without heat induction. Although promising results have been reported, further studies are necessary to reveal the mechanism of drug release and to optimize lipid composition and the condition of magnetic field.

## Conclusion

Over the last 20 years, various magnetoliposomes have been developed and investigated for drug delivery. PEGylation of magnetoliposomes prolonged their blood circulation, and antibody conjugation improved active targeting to specific sites. Drug release behavior of magnetoliposomes with different lipid composition and different structures has been investigated. We also discussed recent advances on the controlled release of encapsulated molecule using magnetic nanoparticle hyperthermia and low frequency magnetic field. Although the potential of magnetoliposomes for drug delivery has been demonstrated in many reports, extensive research on their preparation and optimization of release condition is essential. Precise temperature control and high resolution in vivo temperature measurement will be necessary to avoid heating of surrounding healthy tissues for hyperthermia triggered controlled release. Compared to hyperthermia, the controlled release using low frequency magnetic field is still immature, and further investigation for release mechanism and optimization of field condition will be necessary. However, the drug release without heat from magnetic nanoparticles has great potential for on demand control release and drug delivery to the area which is sensitive to heat.

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