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Biphase Drug Delivery Systems Carrying Nanocomposite Particles

Thomas Ende*

Department of Science, Academia Sinica, Taipei, Taiwan

Corresponding author: Thomas Ende

ende@scithomas.edu.in

Institute of Cytology and Genetics, Research Center of Virology and Biotechnology Vector, Greece

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Abstract

Magnetite nanoparticles and poly (D,L-lactide-co-glycolide) (PLGA) were combined to create drug-carrying magnetic nanocomposite spheres for magnetic targeted drug delivery. Through the chemical coprecipitation of ferric and ferrous chloride salts in the presence of a potent basic solution, magnetic nanoparticles of magnetite (average size: 13 nm) were created (ammonium hydroxide). For the synthesis of nanocomposite spheres, an oil-in-oil emulsion/solvent evaporation process was used, with agitation lasting 1.5 to 2 hours at 7000 rpm. Specifically, acetonitrile (oily phase I) was used to dissolve the PLGA and drug, which was subsequently mixed with magnetic nanoparticles. Next, Span 80- and viscous paraffin oil-containing droplets were added in a dropwise fashion (oily phase II). Using dynamic laser light scattering (DLLS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), and a superconducting quantum interference device, the nanocomposite spheres with various amounts (0%, 10%, 20%, and 25%) of magnetite were assessed in terms of particle size, morphology, and magnetic properties (SQUID). According to the findings, nanocomposite spheres with diameters ranging from 200 nm to 1.1 m are superparamagnetic over blocking temperatures close to 40 K and reach magnetization saturation beyond 5,000 Oe at ambient temperature.

Successful attempts have been made to synthesise and analyse pseudopolyrotaxanes made composed of polyethylene glycol axes with end thymine groups and -cyclodextrin rings. The principal drug delivery system, PPR-Fl, was created by conjugating fluorescein, a model drug, to the hydroxyl functional groups of the cyclodextrin rings of PPR via ester bonds. By forming hydrogen bonds with a complementary molecule like polycitric acid, citric acid, or adenine, the PPR-Fl was finally sealed off. This research sought to modulate the noncovalent interactions between stoppers and thymine end groups in order to regulate the release of fluorescein-cyclodextrin conjugates from PPR-Fl, which served as secondary drug delivery systems. It was discovered that pH had the ability to regulate the rate of Fl-CD release from PPR-Fl.

Keywords: Pseudopolyrotaxanes; Nanoparticles; Magnetite

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Introduction

The use of external forces such as magnetic fields, ultrasound, electric fields, temperature, light, and mechanical forces to concentrate medications within tumours has recently been explored by researchers in the development of targeted therapeutic systems [1]. These techniques involve externally generated forces that first localise the medication at a specific targeted region before activating it. The type under consideration targets particular sides of the body with magnetic particles carrying therapeutic molecules. Drug molecules are progressively released shortly after they have been concentrated on the desired area, increasing the therapeutic effectiveness of the medications by reducing the adverse effects of the drug's hazardous site on healthy cells or tissues [2]. It appears more likely that the

foundation of a drug localization system will be a magnetic targeted system with fields generated between 100 and 2500 Oe. Diffusion, degradation, and swelling followed by diffusion are the three primary methods for releasing drug molecules from the polymeric magnetic spheres into a blood artery or tissue [3]. Diffusion happens when drug molecules disintegrate in physiological fluids surrounding or containing the particles and move away from the particles. The drug molecules that were trapped by the polymer chains are released during degradation when the polymer chains hydrolyze into lower molecular weight species. Systems for swelling-controlled release are initially dry [4]. When they are implanted in the body, they expand to enhance internal pressure and porosity, allowing the drug molecules to diffuse from the swelling network. Based on internal and external circumstances, the release of active drug molecules can also be changed over a set period of time, as shown by diffusion. Because of its biodegradability, Poly (D,L-lactide-co-glycolide) (PLGA), which has been approved by the Food and Drug Administration (FDA) for drug delivery uses, is utilised as a host material. Oil-in-oil emulsion/solvent evaporation was used to embed a drug and magnetic nanoparticles (MNPs) into this polymer in the current study [5]. There were a range of MNP concentrations in PLGA, from 0% to 25%. Following their creation, biodegradable nanocomposite spheres were examined using a variety of techniques, including dynamic laser light scattering (DLLS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), and a superconducting quantum interference device, to ascertain their size distribution, morphology, and magnetic properties (SQUID) [6].

Utilizing supramolecular nanostructures for medication delivery is one of the key goals of nanomedicine. Nanostructures whose constituent parts are joined through covalent bonds are not adaptable, and their structure cannot be altered to suit changing environmental conditions. However, the constituent parts of nanostructures that are put together through noncovalent interactions may easily disassociate or associate [7]. Because of these characteristics, chemists and biologists may pre-design and prepare supramolecular nanostructures that can adapt to various biological barriers and modify their structure to pass through them and reach their target. Host-guest interactions are a noncovalent interaction type that is frequently employed in the creation of supramolecular nanostructures. Cyclodextrins rank among the most significant host molecules in supramolecular chemistry. The starch is broken down by the Bacillus macerans enzyme glycosyl transferase, which naturally produces cyclodextrins as a byproduct. The torus-shaped molecules are water soluble due to the remaining free hydroxyl groups of the glucose moieties that are situated on the rims of the molecules. The secondary hydroxyl groups at C-2 and C-3 of the glucose units are all located at the wider (on the wider edge of the ring), secondary rim of the molecule, where they form a network of intramolecular hydrogen bonds that give the structure rigidity, and the primary hydroxyl groups (C6) on the other edge. In addition to these cyclodextrins that are found naturally, other cyclodextrin derivatives have been synthesised. Typically, the amination, esterification, or etherification of primary hydroxyl groups outcomes in the production of these derivatives. Dendrosomes are now being built using cyclodextrin-polymer conjugates as biphase drug delivery methods. In these systems, dissociation of the dendrosome, a common drug delivery system, outcomes in the formation of a second, more compact drug delivery system [8].

The detachment of the rings from the axes is impeded by bulky groups at both ends of the axes in polyrotaxanes (PRs), which are highly functional supramolecules made up of many rings and one or more axes. Rings and axes are simply physically interlocked; there is no chemical interaction between them. Although polyrotaxanes, particularly those composed of polyethylene glycol axes and cyclodextrin rings, are used as a biocompatible and multivalent carrier to transport gene, drug, and biological active molecules, typically they are left by researchers after one or two reports and they have not been used as therapeutic agents by a group deeply [9].

The two important pairings of nucleobases, cytosine and guanosine and adenine and thymine, have long been considered to be the key to DNA's stability, replication, and capacity for information storage, with the hydrogen bonds between them playing a crucial role. By substituting nonnatural base pairs for base pairs, scientists have recently started to investigate the significance of these hydrogen bonds and other elements contributing to DNA's fascinating properties. Analogs of non-hydrogen-bonded base pairs have produced fascinating findings that have had and will continue to have a practical impact on a wide range of disciplines, including biology, medicine, materials science, supramolecular chemistry, medicinal chemistry, and organic chemistry.

In this article, we present a novel and exciting method for using PRs as biphase drug delivery vehicles. In these systems, stoppers that were attached to the end functional groups of PRs could be separated by stimuli present in biological media, and the cyclodextrins that were liberated could then be used to create new drug delivery systems through host-guest interactions [10]. To put it another way, the separation of the rings from the axes in PRs produced a vast number of tiny drug delivery systems that could cross biological barriers.

Material and Methods

Instrumentation

On a Bruker DRX 400 (400 MHz) apparatus, 1H nuclear magnetic resonance (NMR) spectra were captured using the solvent proton signal as a reference in CDCl3 and DMSO-d6 solvents. The X-ray power diffraction patterns of the products were captured on the D8-AdvancedBruker in the 2 range from 4 to 75. In order to capture the absorption spectra of materials in solution, a T80 UV-Visible spectrophotometer (PG Instruments Ltd.) was employed. Using an Avator 370, Thermo-Nikolt between 4000 and 400 cm1, KBr tablets for the solid state and CH2Cl2 solvent for the solution state, Fourier transform infrared (FT-IR) spectra were obtained with a resolution of 1 cm1. A Shimadzu, Japan-TGA50 was used for the thermogravimetric analysis (TGA) under a dynamic environment of an inert gas (Ar) at 10 (between room temperature and 800 °C).

Magnetic Nanoparticle Synthesis

50 mL of 2 M HCl and 55 mL of 5 M ammonium hydroxide (NH4OH) solutions were combined in a 100 mL beaker to create magnetic nanoparticles. 2 g of ferric chloride (FeCl36H2O) and 1.25 g of ferrous chloride (FeCl24H2O) were dissolved in 40 mL of 2 M HCl and 10 mL of 2 M HCl, respectively, in separate beakers. At a speed of 1200 rpm, the two solutions were combined and forcefully swirled. After that, 55 mL of 5 M ammonium hydroxide was added over the course of five minutes at room temperature. The 12.7 nm-diameter magnetite nanoparticles were subsequently collected using a Nd magnet and allowed to dry in an oven overnight. The size distribution of the magnetic nanoparticles as determined by TEM using Image software.

Magnetic Nanocomposite Spheres Synthesis

Two separate oil phases were synthesized in this procedure. During the first oil phase, 5 mL of the solvent (acetonitrile) and 1.25% w/v of PLGA (wt 40 000–75 000) were combined in a conical flask with a stopper. PLGA was entirely dissolved in acetonitrile using a tiny magnetic bar after the fluid was heated for 20 to 30 minutes. Before applying measure the concentration of the medication and magnetite nanoparticles to the same solution, the magnetic bar was taken out. The flask was then placed in a sonicator for around 10 minutes. Span 80 as a surfactant was added to 40 mL of a heavy liquid along with 1% v/v of it to prepare the second oil phase. After that, the mixture was run through an overhead mixer fitted with a high-shear impeller that had been particularly constructed and was running at 7000 revolutions per minute. It should be noted that this impeller's size and shape are crucial for producing nanocomposite spheres of a smaller size. The second step involved using a burette to add around 3 mL of the first phase to the second phase. Acetonitrile was allowed to evaporate and create nanocomposite spheres at high shear rates in the heavy oil by running the mixer for one hour and thirty minutes. Centrifugation at 17000 rpm for 30 minutes at 10°C was used to separate the nanocomposite spheres, which were then subjected to four n-hexane washings.

Preparation of Ditosylate Polyethylene Glycol

According to the method described in the literature, ditosylated polyethylene glycol was made. PEG (5 g, 5 mmol) was first dissolved in 30 mL of triethylamine, and then tosyl chloride (2.5 g, 13.5 mmol) was diluted in 15 mL of dichloromethane and added dropwise to this solution. For eight hours, the mixture was stirred at 45 C. The outcomes mixture was filtered, the solvent was evaporated, and it was then dissolved in dichloromethane (100 mL) and precipitated in diethyl ether at 0° C.

Functionalization of PEG by Thymine

Thymine functionalized polyethylene glycol using a nucleophilic substitution process involving PEG-diOTs and thymine. PEG-diOTs (2 g, 1.5 mmol) was dissolved in 30 mL of dimethylformamide before being dropwise added to a solution of potassium hydroxide (0.26 g, 4.5 mmol) and thymine (0.5 g, 4.5 mmol) in 5 mL of water. The mixture was mixed and refluxed for 48 hours. The outcomes mixture was filtered, the solvent was evaporated, the precipitate was then dissolved in dichloromethane (100 mL), precipitated in diethyl ether at 0°C, and the process was repeated. It was between 75 and 80 percent yield.

Preparation of PPR-Fl-Adenine Supramolecules

PPR-Fl (0.01 g) was dissolved in 1 mL phosphate buffers with pH values of 5.0 and 7.4 to create PPR-Fl-adenine. Adenine (0.01 g) was then added to the PPR-Fl-adenine solution. For 30 minutes, the mixture was shaken on a shaker with a setting of 100 rpm and room temperature.

Dissociation of Supramolecules to Obtain the Secondary Drug Delivery System: The Release Experiment

The manufactured supramolecules (0.02 g) were dissolved in 1 mL of pH 7.4–5 PBS buffer solution, then squeezed in a filtration process bag (Mn cutoff 2000). Then, 50 mL of phosphate buffers (pH = 7.4 and 5) were added to the dialysis bag (Mn cutoff 2000). Samples of a specific volume were completely disconnected from the external solution, and their UV-visible spectra were captured. The calibration curve was used to determine the fluorescein release rate and concentration from supramolecules.

Results

To ascertain the size distribution of the samples made up of nanocomposite materials and their size distributions, four samples with various MNP and drug contents were constructed. The nanocomposite sphere size also steadily grows from 0% to 25% MNP concentration. The aggregation of the nanoparticles in the initial oil phase, changes in viscosity, and reduced shear forces acting on the spheres could all be contributing factors. Applying SEM, the samples created at each concentration were evaluated. the SEM pictures of samples 2 and 3, which all have PLGA with 10% and 20%, respectively, of magnetite nanoparticles. The majority of the nanocomposite spheres are rounded in shape and range in diameter from 200 nm to 1.1 m. This demonstrates that DLLS variation in sphere size and shape in each concentration correlates to changes in fabrication system parameters such as viscosity and heat generation.

The goal of this effort was to create biphase drug delivery systems made up of a polyrotaxane with thymine end groups and complementary molecules or macromolecules that could interact noncovalently with these end groups. As a model drug, fluorescein was attached to the hydroxyl functional groups of polyrotaxanes. Primary drug delivery mechanism was the name given to these polyrotaxanes. Cyclodextrin-fluorescein conjugates were produced as the secondary drug delivery mechanism as a outcomes of the controlled dissociation of polyrotaxanes. Polyethylene glycol (Mn 1000) with end thymine groups was made to prepare the principal drug delivery system (Scheme 1). End thymine groups operate as hydrophobic domains that enhance interactions between polyethylene glycol and cyclodextrin cavities, which produces pseudopolyrotaxane with a high yield and quickly.

Discussion

Magnetization for nanocomposites is typically temperature-dependent. Before a 1 000-Oe field was applied, the sample 3 was

first chilled to a temperature close to that of liquid helium (about 4 K). After that, the sample was heated up to 300 K in stages in order to conduct magnetization measurements. Nanocomposite spheres exhibit a paramagnetic-type behaviour as temperature rises, with the magnetism first increasing to a peak at 40 K and then decreasing after that. The blocking temperature is typically referred to as 40 K, and this represents the superparamagnetic properties of the nanoparticles. Also evident is the plateau region in the zero field cooled (ZFC) curve and the beginning of the merger of the field cooled (FC) and ZFC curves at about 125 K. Although the two curves blend at a much lower temperature in dextran-coated magnetite with a comparable size distribution and blocking temperature, the ZFC lacks the characteristics shown in our sample. In the aforementioned study's Ferro fluid, which is based on water, magnetite particles were uniformly disseminated. The polymeric nanocomposite spheres in our study's investigation, however, had the magnetic particles that were randomly distributed. In turn, this affects how the particles interact with one another dipolarly. These energies have greatly contributed to the characteristics of the ZFC curve that have been found because it is known that the dipolar interaction energies of these particles are of the same order as their anisotropy energy barriers.

When citric acid, polycitric acid, and corresponding molecules or macromolecules of adenine are not present in the buffer at pH 7.4, the cumulative release percent of fluorescein-cyclodextrin conjugate (the secondary drug delivery system) from the primary drug delivery system is calculated. As can be seen, the secondary drug delivery system releases rapidly from the primary drug delivery system; when it is not capped by a complementary molecule, 100% of this system releases in four hours. The rate of release, on the other hand, reduces and systems exhibit a delayed release when they are bound by supramolecular interactions. When polyrotaxane is encapsulated by citric acid, the release is seen to be the slowest. Two weight ratios of citric acid have been employed for capping polyrotaxane in order to study the influence of citric acid on the rate of release of secondary drug delivery systems. As can be seen, the rate of release decreases slightly as the weight ratio of citric acid to polyrotaxane increases by two, demonstrating that the 0.01 W/W ratio of citric acid is sufficient to create a strong interaction with the thymine end groups of polyrotaxane, lock secondary drug delivery systems sufficiently, and ultimately prevent a fast release. Polycitric acid is the second best agent for stopping cyclodextrin-fluorescein conjugates and sufficiently slowing down their rate of release.

Conclusion

In this study, an oil-in-oil emulsion/solvent evaporation method is used to create drug-carrying magnetic nanocomposite spheres. By using DLLS and SEM, which produce spheres with sizes ranging from 200 nm to 1.1 m, it was possible to measure the impact of magnetic particles (13 nm) on the size and shape of the product. Magnetite nanoparticles are predominantly grouped and randomly distributed in the PLGA matrix, according to TEM images. The nanocomposite spheres behave as nanostructured materials, according to SQUID data. Overall, the application of focused administering drugs in the future may benefit from this research. As biphase drug delivery methods, fully supramolecular polyrotaxanes were created. pH and other stimulation variables regulated how quickly the secondary drug delivery systems were released from the original drug delivery system. They are attractive systems for delivering therapeutic agents like anticancer medications to target tissues because of the adaptability of the supramolecular connections between capping agents and pseudopolyrotaxanes.

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Conflicts of Interest

The author has no known conflicts of interested associated with this paper.

References

1 Islam KN, Bakar MZ BA, Ali ME (2013) A novel method for the synthesis of calcium carbonate (aragonite) nanoparticles from cockle shells. Pow Techn 235: 70-75.

2 Deepika S, Hait SK, Christopher J, Chen Y, Hodgson P, et al. (2013) Preparation and evaluation of hydrophobically modified core shell calcium carbonate structure by different capping agents. Pow Tech 235: 581-589.

3 Hadiko G, Han YS, Fuji M, Takahashi M (2005) Synthesis of hollow calcium carbonate particles by the bubble templating method. Materials Letters 59: 2519-2522.

4 Jin Y, Liu W, X Wang J, J Fang, Gao H (2009) (Protamine/dextran sulfate) 6 microcapules templated on biocompatible calcium carbonate microspheres. Physico chemical Eng 342: 40-45.

5 Auriemma G, Mencherini T, Russo P, Stigliani M, Aquino RP (2013) Prilling for the development of multi-particulate colon drug delivery systems: pectin vs. pectin-alginate beads. Carbohy Poly 92(1): 367-373.

6 Galindo Rodríguez SA, Allémann E, Fessi H, Doelker E (2005) Polymeric nanoparticles for oral delivery of drugs and vaccines: a critical evaluation of *in vivo* studies. Crit Rev Ther Drug Car Syst 22(5): 419-464.

7 Gaucher G, Satturwar P, Jones M C, Furtos A, Leroux JC (2010) Polymeric micelles for oral drug delivery. Eur J Pharma Biopharm 76(2): 147-158.

8 Patel MM (2011) Cutting-edge technologies in colon-targeted drug delivery systems. Exp Opin Drug Deliv 8(10): 1247-1258.

9 Ferrari PC, Souza FM, Giorgetti FL (2013) Development and *in vitro* evaluation of coated pellets containing chitosan to potential colonic drug delivery. Carbohy Polym 91(1): 244-252.

10 Maroni A, Del Curto MD, Zema L, Foppoli A, Gazzaniga A (2013) Film coatings for oral colon delivery. Int J Pharm 457(2): 372-394.