論文 / 著書情報
Article / Book Information

題目(和文)	
Title(English)	Green processing of surface modification and extraction for biomedical nanoparticle productions
著者(和文)	WIJAKMATEE Thossaporn
Author(English)	Thossaporn Wijakmatee
出典(和文)	学位:博士(工学), 学位授与機関:東京工業大学, 報告番号:甲第12879号, 授与年月日:2024年9月20日, 学位の種別:課程博士, 審査員:下山 裕介,久保内 昌敏,多湖 輝興,松本 秀行,原田 琢也,Pachauri Vivek
Citation(English)	Degree:Doctor (Engineering), Conferring organization: Tokyo Institute of Technology, Report number:甲第12879号, Conferred date:2024/9/20, Degree Type:Course doctor, Examiner:,,,,,
学位種別(和文)	博士論文
Category(English)	Doctoral Thesis
種別(和文)	要約
Type(English)	Outline

Doctoral Thesis

(Outline)

Green processing of surface modification and extraction for biomedical nanoparticle productions

Thossaporn WIJAKMATEE

Academic supervisor (1): Prof. Dr. Yusuke SHIMOYAMA

Academic supervisor (2): Dr. Vivek PACHAURI

Department of Chemical Science and Engineering

School of Materials and Chemical Technology

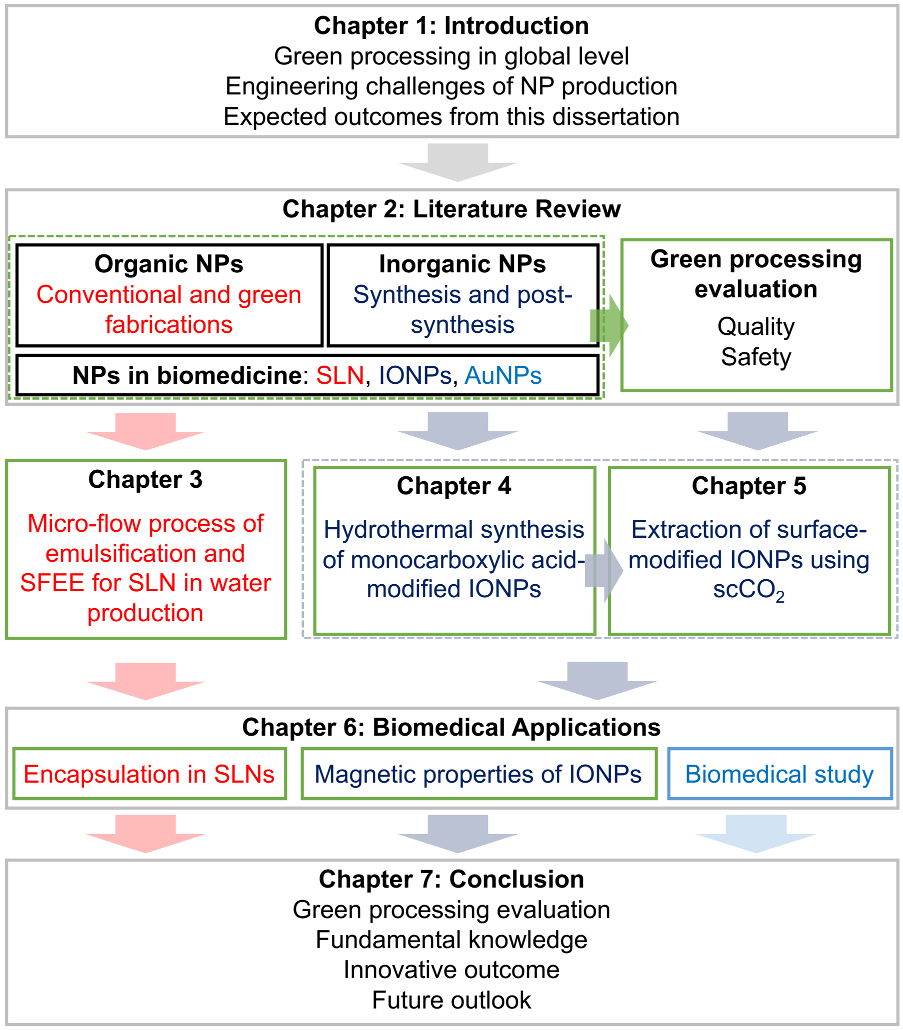
Tokyo Institute of Technology, Japan

&

Institute of Materials in Electrical Engineering 1 (IWE1)

Faculty of Electrical Engineering and Information Technology

RWTH Aachen University, Germany



Structure of this dissertation

Chapter 1 – Introduction

Chapter 1 provides the background and motivation for this dissertation. It emphasizes the importance of green processing, especially for environmentally friendly production of nanoparticles (NPs), which are widely used in cosmetics and biomedical treatments. NPs are classified into two main types: organic and inorganic. Organic NPs are primarily used as drug carriers, while inorganic NPs are applied in magnetic resonance imaging, hyperthermia, and diagnostics. The efficacy of NPs depends on their size, shape, and surface properties, making controlled production crucial. To address environmental and product efficacy concerns, green chemicals like supercritical CO_2 ($scCO_2$) and water are proposed for NP fabrication and purification, particularly in surface modification and extraction. This chapter outlines the structure of dissertation, summarizing the definition of green processing, the history and recent studies of organic and inorganic NPs, and their applications in Chapter 2. Chapters 3-5 present the development of green processing with fundamental knowledge and practical examples for production of both organic and inorganic NPs. Chapter 6 discusses the applications of NPs in biomedical activities, inhibiting the feasibility of a green cycle for biomedical NPs. Finally, Chapter 7 concludes with the outcomes of each chapter and directions for future studies.

Chapter 2 – Literature review

Chapter 2 defines green processing for NP production, aligning it with the principles of the green chemistry and the circular economy. Current issues in NP production are identified through a literature review to achieve green processing. Traditionally, organic NPs are produced using solvent evaporation methods, which often involve toxic solvents and high temperatures. Inorganic NPs are commonly produced via hydrothermal and solvothermal synthesis, raising concerns about toxic solvents and the need of understanding for core properties and surface control. Given these concerns with conventional techniques, green processing in NP production can be evaluated based on two main factors: (1) environmental and safety considerations, and (2) efficiency of fabrication and purification. For the first factor, the selection of chemicals is crucial, with $scCO_2$ and water recommended to avoid the use of organic solvents. The second factor depends on process design and parameter control to achieve product quality. This chapter reviews the characteristics of NPs, specifically stearic acid lipid NPs (SLNs), iron oxide NPs (IONPs), and gold NPs (AuNPs), obtained from traditional methods for comparison with the proposed methods in this dissertation.

Chapter 3 – Integrated micro-flow process of emulsification and supercritical fluid extraction of emulsion for stearic acid nanoparticle production

Chapter 3 provides the discussion about the development of an integrated micro-flow process combining emulsification and supercritical fluid extraction of emulsion (SFEE) for the fabrication of SLNs dispersed in an aqueous solution. The controllability of SLN production was investigated by varying the flow rates of oil and water phases, surfactant species, surfactant concentrations, and pressure. The study considered the utilization of two different surfactants for stabilizing oil droplets and SLNs in water. It was found that Tween 80, a hydrophilic surfactant, played a crucial role in achieving a homogeneous emulsion phase, which is essential for controlling particle size post-extraction. Additionally, lecithin, a hydrophobic surfactant, successfully narrowed the size distribution of SLNs by suppressing aggregation. The extraction efficiency achieved was over 97%. These results suggest that a combined surfactant system in the integrated micro-flow process is a promising approach for continuously fabricating stable and uniform SLNs for practical applications. From a green processing perspective, the results of new micro-flow system were compared with those from conventional methods, demonstrating the effectiveness of using $scCO_2$ as a green extraction medium and ethyl acetate (EA) as a low-toxic solvent.

The concept of selecting appropriate surface modifiers for controling particle characteristics and surface properties is not limited to only organic NPs but it also applies to inorganic NPs, as discussed in Chapter 4.

Chapter 4 – Hydrothermal synthesis and surface modification of iron oxide nanoparticles using monocarboxylic acids with various chain lengths

In Chapter 4, the hydrothermal synthesis and surface modification of IONPs were performed in a batch reactor at 200 °C for 20 min, using monocarboxylic acids with various alkyl chain lengths (C6 to C18) as surface modifiers. The short chain modifiers (C6 to C12) successfully produced surface-modified IONPs with uniform shapes and a magnetite structure, while the long chain modifiers (C14 to C18) resulted in IONPs with non-uniform shapes and a combined particles of magnetite and hematite in the products. Additionally, the synthesized IONPs exhibited single crystallinity and high stability. These results with the visualization of monocarboxylic acid-hot water system suggest the phenomena in the non-toxic reaction field and provide a selection guideline for surface modifiers to control the structure and surface properties of IONPs with high crystallinity and stability. This aligns with the principles of effective fabrication, enabling the production of high-quality products in non-toxic medium systems. Furthermore, understanding the modified surface properties offers insights into developing post-synthesis systems, particularly for separating and purifying surface-modified IONPs from unreacted components in water, as discussed in Chapter 5.

Chapter 5 – Supercritical carbon dioxide extraction of monocarboxylic acid-modified iron oxide nanoparticles

In this chapter, extractions of unmodified and monocarboxylic acid-modified IONPs from

Chapter 4 were performed using different extraction media, including hexane, cyclohexane, cyclopentane, and $scCO_2$, with both visual and quantitative analysis. Organic solvent extraction was conducted in a batch system. The extraction of IONPs with long-chain modifiers resulted in significant color changes in the solvent phase (from transparent to dark-brown) and the water phase (from dark-brown to light-brown or transparent), in contrast to the unmodified and short-chain modified cases. The extraction efficiency (*EE*), calculated from the iron concentration in the water phase, was significantly higher than that in the solvent phase, suggesting the presence of captured IONPs at the water-solvent interface. The extraction using $scCO_2$ revealed that the water-$scCO_2$ interfaces were transparent in the unmodified case and light-brown in the surface-modified case. Using $scCO_2$ provided a high *EE* for hydrophobic-surface NPs, with the highest *EE* of 96.0% achieved over a 1 h extraction. Kinetic analysis of extraction using non-polar media in a semi-batch system indicated that $scCO_2$ provided the highest extraction rate, with the highest *EE* of 99.8% at 100 min. This study indicates the potential of $scCO_2$ for efficient surface-modified NPs extraction and provides insights into optimizing particle extraction processes. Additionally, the high extraction performance reduces the number of operations and avoids the use of organic solvents. This aligns with the principles of a green chemistry and a circular economy, demonstrating strong evidence of efficiency in fabrication and purification, as well as environmental and safety considerations.

Chapter 6 – Biomedical applications of surface-modified nanoparticles produced from green processing

This chapter showcases the practical applications of NP products obtained through green processing in this dissertation. Specific investigations and characterizations were performed to demonstrate their potential. Considering the high waste generation in advanced biomedical studies, an efficient analytical method applying NPs is necessary to support the feasibility of a circular economy transformation, particularly in product consumption. Therefore, a simple analytical platform was developed by the author and colleagues at the Institute of Materials in Electrical Engineering 1 (IWE1), RWTH Aachen University, Germany, to support advanced biomedical studies using the unique characteristics of NPs. The practical examples include:

(1) Encapsulation in SLNs: β-Carotene, a model hydrophobic active ingredient, was introduced to test encapsulation in SLNs using the integrated micro-flow process of emulsification

and SFEE developed in Chapter 3.

(2) Magnetic Properties of IONPs: IONPs obtained from hydrothermal synthesis in Chapter 4 were characterized for their potential in biomedical applications, especially hyperthermia. The saturation magnetization and coercive field were compared with acceptable values from the literature.

(3) Image Acquisition of BioNanoconjugates for Advanced Biomedicines: Surface-modified inorganic NPs were recommended to be prepared for in-vitro biomedical studies using green processing of synthesis and post-synthesis methods from Chapters 4 and 5. An analytical platform was developed to study biomolecule-NP (BioNanoconjugate) interactions using optical analysis based on unique NP properties such as surface characteristics and hyperthermia. In this part, a real-time image acquisition and processing platform was implemented to elucidate interactions in a model BioNanoconjugate system, specifically amino acid-AuNP. Citrate-reduced AuNPs synthesized using the Turkevich method with varying trisodium citrate to gold(III) chloride ratios (1 to 8) were used to kinetically investigate physicochemical interactions in conjugate systems, induced by introducing various amino acids with different side chains (polar uncharged, positively charged, negatively charged, and thiolate). RGB values of each conjugate, extracted from over fifty thousand images recorded over 72 h, were used to elucidate different aggregation patterns and surface variations of AuNPs. Amino acids with polar uncharged side chains (asparagine, glutamine, glycine) showed negligible RGB value variations, indicating stable AuNP colloidal suspension. Conversely, amino acids with positively charged (arginine, lysine), negatively charged (glutamic acid), and thiolate (cysteine) side chains exhibited diverse RGB variation patterns, suggesting different physicochemical interactions among the amino acid-AuNP conjugates. To investigate the reliability of this system, dynamic light scattering (DLS) analysis confirmed particle size changes, while absorbance spectra analysis validated the change in aggregation state and surface properties of AuNPs from the selected conjugates. This platform offers a simple, cost-effective, and efficient documentation method, providing researchers with a comprehensive dataset for detailed analysis. This approach can enhance the understanding of interactions in further BioNanoconjugate systems for various applications, with reducing trial-and-error to select the appropriate conditions for detail analysis in advanced biomedical research.

Chapter 7 - Conclusion

Chapter 7 summarizes the key findings of this dissertation in terms of green processing evaluation, fundamental knowledge, innovative outcomes, and future outlook. The fabrication and purification processes of NPs discussed in Chapters 3-5 align well with green processing principles, producing high-quality NP products while using environmentally friendly chemicals. Each chapter provides fundamental knowledge on controlling the characteristics and surface properties of NPs in specific systems. Chapter 3 highlights the advantages of using combined hydrophilic and hydrophobic surfactants to produce stable SLNs in water. Chapter 4 discusses the effect of monocarboxylic acid chain length on solubility in hot water, leading to different patterns of IONP formation. Chapter 5 demonstrates the high extraction efficiency of IONPs from water using $scCO_2$ compared to organic solvents, due to the significantly higher self-diffusion coefficient of $scCO_2$. The innovative outcome presented in Chapter 6 introduces a simple, low-cost analytical screening method for studying interactions in BioNanoconjugate systems. This dissertation demonstrates that green processing for biomedical NP production can be achieved through the use of green chemicals and engineering design. For future outlook, feasibility studies such as economic analysis, life cycle assessment, data science analysis, and further exploration of time-dependent RGB analysis for various BioNanoconjugates are recommended. These efforts aim to achieve the transformation to a circular economy by 2050, in line with common targets set by various global organizations and governments.