

Polymer Particle Preparation Methodology with Ternary System-Based

Emulsion Castings

(三成分系エマルジョンを鋳型に用いた高分子微粒子製造法)

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Thesis for Doctor of Philosophy in Engineering

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March 2022

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ABSTRACTS

There are many kinds of polymer forms in social life and for industrial application, such as fibers, films, foams, and moldings. Spherical particles are one of the most important polymer forms with narrow distribution, because various kinds of products, for example, spacers for LCD, toners for paper printing, raw material for 3D printer, basements for pharmaceuticals, or rheology control additive for lubricant, painting, cosmetics or composite materials are used in our lives.

Spherical polymer particles have mainly developed with emulsion polymerization technique for a long time. This technique is usually implemented by radical polymerization in an aqueous media so that it is easy to treat on an industrial scale. However, since the materials which are obtained by this technique are restricted in only vinyl-type polymers, such as acrylic-type polymer and polystyrene, the prepared particles are not suitable for high heat-resistance applications.

Polymer particle for carbon fiber reinforced plastic (CFRP) is a typical example that required more heat-resistance property. CFRP, which is composed of carbon fiber and epoxy resins, is an attractive material with high specific strength but toughness is usually deficient. For solving the problem, polymer particles are employed as toughness improvement additive in epoxy resins. And also heat resistance property is required to toughness improvement additive. However, vinyl-type polymers, such as acrylic rubber, is generally inferior about the property.

Engineering polymers, for example, polyamide, polyester, or polyphenylene sulfide, are well known as high heat-resistance polymers. However, these materials had been difficult to process to particles because of those heat and solvent resistant properties of themselves. So, an innovative process for those polymer particles has been expected.

In this thesis, an advanced polymer particle preparation methodology and the particles' application from the method have been investigated. A specific phase separation phenomenon of polymer solution is the central principle in this thesis. The original phenomenon was discovered by Scott in 1949. For a long time, it has been just recognized as a physicochemical phenomenon then it has not been utilized to a practical application.

The author succeeded to implement this phenomenon for producing various polymer particles. The particles have spherical shapes and narrow particle distributions. Furthermore, by controlling a crystallinity or other property of polymer, the characteristic appearance polymer particles enable to be produced.

The fundamental principle of the methodology of this study is that a target polymer to prepare a particle and a phase separation polymer dissolved in a solvent at a ratio which

enables to form a phase separation state and formed oil-in-oil emulsion, after that poor solvent of the target polymer was added, then the target polymer particle was prepared.

In Chapter 1, previous polymer particle manufacturing methods were reviewed and the problems and the prospects have been referred.

In Chapter 2, the author firstly demonstrated the new polymer particle preparation method by using ternary system emulsion of polymer solution as castings to engineering polymers. Polar solvents were selected as solvents to form oil-in-oil emulsion because of the limitation of the solubility of engineering polymers. The emulsion offers spherical templates for the casting of condensation polymers. The ternary system has enabled the production of fine particles of various engineering plastics with narrow size distributions.

In Chapter 3, to expand the methodology, ethylcellulose as a target polymer was focused. The author demonstrated that ternary system-based oil-in-oil emulsion castings can produce fine porous and spherical particle of biocompatible ethylcellulose with a narrow size distribution using ethanol as a solvent. Several analytical techniques, including X-ray diffraction, linseed oil absorption tests, transmission electron microscopy, scanning electron microscopy in combination with energy dispersive X-ray spectroscopy, and X-ray computed tomography scan have revealed that pore networks are constructed throughout the particles, which provides the large pore volumes.

In Chapter 4, the author demonstrates encapsulation of pigments in polymer particles prepared by oil-in-oil emulsion casting in a ternary system. Acrylonitrile-butadiene-styrene polymer (ABS) was used as a polymer matrix for pigment encapsulation, while polyvinyl alcohol and N-methyl pyrrolidone were used as a phase separation polymer and solvent, respectively. Some of pigments were successfully encapsulated into the ABS polymer particles. And also, the surface free energies were discussed as the key factor of efficient encapsulation.

The conclusion and the future problems of this thesis were discussed in Chapter 5.

和文要旨

繊維、フィルム、発泡体および成形体など、社会生活や産業応用において様々な高分子の形態が存在している。球状で粒度分布の狭い微粒子も最も重要な高分子の形態の一つであり、液晶ディスプレイのスペーサー、印刷用のトナー、3Dプリンターの原料、医薬品の基材、潤滑剤、塗料、化粧品あるいは複合材料の粘度調整用添加剤など、我々の生活の中の多くの場面で使われている。

球状ポリマー微粒子は長い間、主にエマルジョン重合技術と共に発展してきた。この技術は通常、水系溶媒中でラジカル重合により実施されるため、工業的には取り扱いやすい。一方、この技術で作られる材料は、アクリル系ポリマーやスチレンなどのビニル系ポリマーに限定される。しかし、これらの材料はそれほど耐熱性が高くなく、ある特殊な用途では使用することができない。

例えば、炭素繊維複合材料（CFRP）用のポリマー微粒子は、より耐熱性が求められる典型的な例である。炭素繊維とエポキシ樹脂からなる構成される CFRP は、その比強度特性の点で非常に魅力的な材料であるが、一般的に靱性が十分ではなく、ポリマー微粒子は靱性改良剤としてエポキシ樹脂中に添加されて使用される。この靱性改良剤にも耐熱性が求められるが、アクリルゴム粒子のようなビニル系のポリマー微粒子では耐熱性は十分でなく、ポリアミド粒子が使用されている。

ポリアミド、ポリエステル、ポリフェニレンスルフィドのようなエンジニアリングポリマーは、高耐熱性ポリマーとして良く知られている。しかし、これら材料は、材料そのものの耐熱性および耐溶剤性のため、粒子への加工が難しい。したがって、これらのポリマー微粒子のための革新的加工法が望まれていた。

本博士論文では、先進的なポリマー微粒子の製造の方法論とその方法で得られるポリマー微粒子の応用例について研究を進めた。この論文では、高分子溶液の特徴的な相分離現象が中心原理として取り扱っている。この現象は1949年に Scott により発見されたものであるが、長い間、単なる物理現象のひとつとしてしか認識されておらず、高分子の加工法として応用されてはいなかった。

筆者は、様々なポリマー微粒子を製造するために、この現象を利用することに成功した。この粒子は真球状で狭い粒度分布を持つだけでなく、ポリマーの結晶性や他の特性を活かすことにより、特徴的な形態を持つポリマー微粒子を作ることが可能である。本研究の基本的原理は、粒子化する目的のポリマーと相分離を引き起こすポリマーを単一の溶媒に、相分離を形成する比率で溶解し、オイルインオイルエマルジョンを形成させ、その後目的とするポリマーの貧溶媒を添加することで、微粒子を得るというものである。

第1章では、これまでのポリマー微粒子の製造法を振り返り、その問題点と可能性について言及した。

第2章において、筆者は高分子溶液の三成分系エマルジョンを鋳型として用いた新しい

ポリマー微粒子の製造法を初めて実現した。エンジニアリングポリマーの溶解性の限界から、オイルインオイルエマルジョンを形成する溶媒として極性溶媒を選定した。このエマルジョンは、縮合系ポリマーの球状鑄型になり、この三成分系は、様々なエンジニアリングプラスチックのポリマー微粒子を狭い粒度分布で製造することを可能にした。

第3章では、この方法論の拡張のためにエチルセルロースに焦点を当てた。筆者は、この高分子溶液の三成分系エマルジョンの実現に向け、安全性を踏まえ、溶媒としてエタノールを用い、生体親和性を有するエチルセルロースの真球状微粒子を狭い粒度分布で製造することができることを示した。また、X線回折、亜麻仁油吸油量評価、透過型電子顕微鏡、エネルギー分散型走査型電子顕微鏡、X線コンピューター断層撮影などの、いくつかの分析技術を用い、この粒子内に多孔ネットワーク構造が形成され、大きな孔体積を有していることを明らかにした。

第4章では、この三成分系オイルインオイルエマルジョンを用い、高分子微粒子内に顔料を内包させることを実現した。アクリロニトリルブタジエンスチレンポリマー（ABS）を顔料内包のためのマトリックスポリマーとし、ポリビニルアルコールを相分離剤、N-メチルピロリドン（NMP）を溶媒としたところ、いくつかの顔料についてABS内に内包させることに成功した。そしてさらに、表面自由エネルギーが内包化効率の重要ファクターになる点を論じた。

第5章では、この研究の結論と今後の課題に関し、まとめた。

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INTRODUCTON

1.1 BACKGROUND AROUND POLYMER PARTICLES

Polymer particles are one of the most practical methods for the treatment of polymers, such as fibers, films, foams, and moldings. They generally have a small diameter ranging from 100 nm to several microns; therefore, applications that take advantage of their characteristics are numerous. Polymer particles have low density, space controllability, and are optically, electrically, physically, and biologically harmless to external areas. Therefore, they have an important role in many fields.

Printing toners are one of the most important and large-volume applications. To express fine pixel descriptions in printing, fine controllability and ease of fixation on paper are required for laser toner [1]. Therefore, thermal plasticity, chargeability, binding ability, and flowability of the polymer particles are extremely suitable.

For paints, polymer particles are used as additives to control the viscosity [2][3] and capsule form, preventing the dripping of paints. They do not affect the color tone directly, and their specific gravity is lighter than that of any other small inorganic or metal material. In liquid crystal displays, polymer particles are used as light diffusion materials [4] or space gap adjusting materials [5][6] between the backlight unit and the display film. Another well-known application of polymer particles is as a drug basement for drug delivery systems [7][8], where a drug is loaded on polymer particles and covered by other polymers, and then the release speed is controlled. One of the high-end applications is the cosmetics industry, as polymer particles can easily change the texture, viscosity, or appearance of cosmetics. In particular, polymers have a softness and smooth texture, being suitable raw materials for cosmetic foundations.

In the preparation process of polymer particles, the “top-down” approach is generally used. “Top-down” means break down from bulk polymer materials; thus, mechanical grinding and pulverization are the most utilized methods (**Fig. 1- 1**). However, the particle shapes and sizes prepared by these methods are irregular and have a wide distribution. Other major approaches are solvent methods, such as the dissolution-precipitation and spray-drying methods [9]. However, it is very difficult to prepare highly solvent-resistant polymer particles using these methods because of the high solubility of the solvent in the target polymer. Moreover, because it is difficult to control the particle size and distribution using these techniques, the size distribution is extremely wide, and the particle shape is irregular.

Recently, the membrane emulsification method [10][11] (**Fig. 1- 2**) and microfluidics methods [12–14] (**Fig. 1- 3**) have been developed as frontier approaches. These methods

are interpreted as a combination of mechanical and solvent methods.

As the most representative preparation method for polymer particles, emulsion polymerization has been mainly researched for a long time. “Emulsion” is defined in the dictionary as any mixture of liquids that do not mix together, such as an oil and water system. Micelle colloids in the emulsion system become castings for polymer particles during emulsion polymerization. This technique is recognized as a polymerization method and is widely applied on an industrial scale to prepare vinyl polymers, such as acrylic polymers, polystyrene, and polyvinyl esters.

The advantage of emulsion polymerization is the controllability of the polymer particle properties. The mean size and particles distribution can be controlled by the polymerization conditions, such as the micelle concentration and polymerization temperature. The physical properties, such as elasticity, hardness, and transparency, can be designed by controlling the copolymerization monomer ratio. However, the selection of monomer combinations is limited, for example, vinyl-type substances as chemical compounds. As the heat resistance of the vinyl polymer cannot be adjusted to more than 150 ° C because of the main chain stability of the polymer, the polymer particles prepared by the emulsion method cannot be applied at high temperature conditions, such as automobile and aerospace parts.

Engineering plastics are widely recognized as heat-stable polymers. For example, polyamide and polyesters are the leading materials in engineering plastics and are used in textiles, fabrics, plastic bottles, etc. Moreover, polyphenylenesulfide, polyethersulfone, and polyetherketone are well known as super-engineering plastics and are widely used in many areas such as electrical and electronic components, medical equipment, auto-mobile parts, and aerospace-related parts. However, these materials have not been utilized in particle forms.

1.2 ENGINEERING POLYMER PARTICLE, DEMAND, POSSIBLE APPLICATION, AND PROBLEM

Although several polymerization techniques have developed and applied for preparation of polymer particles, such as emulsion polymerization, dispersion polymerization, and suspension polymerization, acrylic polymers suffer from a lack of heat resistance and durability. In recent years, selective laser sintering has become widespread; therefore, expectations for engineering polymer particles produced using this method have increased.

Although there are no clear academic definitions of engineering polymers or engineering plastics [15][16], they are generally considered as heat-resistant plastics with thermal deformation temperatures higher than approximately 100 °C. In the industrial sector, the categorization of engineering plastics is usually exhibited with “Plastic Triangles” or “Plastic

Pyramid” (Fig. 1- 4).

Most engineering plastics are synthesized by condensation polymerization, such as polyester or polyamide, and desalting polycondensation, such as polyphenylenesulfide or polyetheretherketone (Fig. 1- 5). Using these polymerization methods, by-products are generally produced during the course of the reaction. As the existence of water usually becomes in many cases a polymerization reaction inhibitor owing to reaction equilibrium, the oil-in-water emulsion casting system cannot be used for particulation. For the above reasons, other preparation methods must be developed for engineering plastic particle production.

In many cases, mechanical production methods, which are “top-down” approaches from bulk polymer solid by crushing or milling, have been adopted. Engineering plastics have toughness properties, hindering their pulverization at ambient temperatures.

Freeze crushing is a well-known method. Watanabe [17] applied this method to obtain a polyphenylene sulfide powder. The particles developed as three-dimensional (3D) printing raw materials; thus, fluidity was required for its use. However, as the obtained powder had irregular shape, the powder fluidity was insufficient. Nano-silica powder was used as an external additive to solve the low fluidity. However, an external additive can cause other problems in that the pieces formed from the powder become fragile. In another recent case of freeze crushing, a patent of liquid crystal polymer particles [18], which have more heat-resistant properties, was also applied. In other words, these techniques are still considered the standard method for obtaining engineering polymer particles.

In another mechanical approach, a polymer blending technique was developed with a twin-screw extruder [19 – 24] (Fig. 1- 6). The principle of the method is that an objective particulating polymer and a water-soluble polymer blend together, forming a polymer alloy composed of a water-soluble matrix phase and an objective polymer as the disperse phase, and then the water-soluble polymer is extracted by water. A recent trial applied a method for producing liquid crystal polymer particles [25]. This method requires heating these polymers at high temperatures to melt them; therefore, the melt viscosity ratio of these polymers is important. However, because the ratio is based on the nature of polymers, it is difficult to control the particle diameter as desired.

As an alternative mechanical approach to prepare engineering plastic particles, the following two methods with solvents are selected.

The spray-drying system is commonly used and can easily form polymer particles. This method consists of dissolving a polymer in a solvent and drying it, for instance, using dedicated equipment. As engineering polymers have low solubility in easily vaporized solvents, a solvent with a high boiling point should be chosen to use the system. As a result,

a few examples [26] (**Fig. 1- 7**) have been demonstrated, but the particle form and distribution are not acceptable. The most conventional system is the dissolution-precipitation method [27, 28].

In the latest article by Hejmady, an advanced method for reforming a particle after milling was reported [29] (**Fig. 1- 8**). The concept is a combination of a mechanical method and a solvent method. It appears to be a good approach to obtain a spherical particle; however, there is a problem in particle size controllability.

With regard to particle preparation for a few types of specific polymers, such as polycaprolactam [30], polylauro lactam [31], and polyester for low-temperature fixed toner [32], there are well-known particle preparation methods, but they are not versatile.

In conclusion, a polymer particle preparation method that can be widely applied to polymers with high heat resistance and high solvent resistance is strongly required.

1.3 EMULSION SYSTEMS AND OIL-IN-OIL EMULSION

Emulsion is a well-known liquid condition defined as a liquid dispersion in a liquid. Incidentally, a solid dispersion in liquid is called a suspension, and a gas dispersion is called foam. Emulsions have been applied in many fields, and related reviews have been published, for example, in oil and energy [33][34], food and nutrition science [35 - 38], environment science [39][40], polymer chemistry [41][42], and cosmetology [43]. Emulsions are roughly categorized into three types in almost all reviews: oil-in-water emulsion (O/W emulsion), water-in-oil emulsion (W/O emulsion), and double emulsion (O/W/O emulsion or W/O/W emulsion) (**Fig. 1- 9**). Emulsions are also classified according to their size. The macro emulsion is the general term for a diameter of micrometer or more. The macro emulsion is thermodynamically unstable; therefore, an additive chemical substance, such as a surfactant emulsifier and surface-active molecules, is needed to maintain it for a certain period. A microemulsion is a term for a emulsion smaller than the macro emulsion, formed spontaneously, and whose diameter is under 100 nm; therefore, it does not require an additive-like emulsifier. Nano-emulsions occur by mechanical shearing, and their diameter is less than 100 nm. Recently, microemulsions and nano-emulsions have been considerably applied to various advanced areas.

These emulsion types, composed of water and oil, are different types of solvent emulsions. Exceptionally, the same type of solvent emulsion is possibly formed with polar solvents and hydrocarbons, for instance, a combination of methanol with hexane or acetonitrile with decane. However, these combinations have not been utilized for the preparation of polymer particles because the solubility of polymers in alcohol and hydrocarbons is poor. Hence, this system has not been used on the preparation of polymer particles.

Oil-in-oil emulsions and their applications have been undeveloped areas to prepare particles; thus, pursuing an emulsion system for polymer particles is theoretically meaningful.

1.4 SCOTT SYSTEM, ITS HISTORICAL DEVELOPMENT, AND APPLICATIONS

One of the most attractive oil-in-oil emulsion systems is the ternary system polymer solution called the Scott system. However, this has not received considerable attention.

The first cohesive report of the phase-separating phenomenon in a polymer solution was presented by Dorby [44] in 1947. The author confirmed the mixing aspect with 14 polymers, such as cellulose, vinyl, and acrylic derivative polymers, and 13 solvents. Then, the phase separation phenomenon was found in 78 combinations, and these phase phenomena were classified in the triangle phase diagram. In 1949, Scott considered these phenomena from the perspective of polymer physics, and reported them as a ternary system of a polymer/polymer/solvent mixture [45].

Flory [46], Scott et al. [47], and Guggenheim [48] studied a polymer blend system consisting of a polymer/polymer mixture and not a solvent system. They assumed the free energies of each constituent using the following equations when both polymers were blended:

$$\Delta F_1 = RT \left[\ln \phi_1 + \left(1 - \frac{m_1}{m_2} \right) \phi_2 + m_1 \mu_{12} \phi_2^2 \right]$$

$$\Delta F_2 = RT \left[\ln \phi_2 + \left(1 - \frac{m_2}{m_1} \right) \phi_1 + m_2 \mu_{12} \phi_1^2 \right]$$

where ϕ_1 and ϕ_2 are volume fractions, m_1 and m_2 are degrees of polymerization, V_1 and V_2 are molecular volumes, $m_1 = V_1/V_0$, $m_2 = V_2/V_1$, μ_{12} is a constant value related to the interaction and heat generation between two polymers.

Scott expanded his studies to the polymer/polymer/solvent system; thus, he expressed the total free energy of the system and that of each constituent when mixing in the following three equations, which was the first report of a ternary system of a polymer solution, and obtained a phase separation condition at complete immiscible approximation.

$$\begin{aligned}
\Delta F_0 &= RT \left[\ln \phi_0 + \left(1 - \frac{1}{m_1}\right) \phi_1 + \left(1 - \frac{1}{m_2}\right) \phi_2 + \mu_{10} \phi_1^2 + \mu_{20} \phi_2^2 \right. \\
&\quad \left. + (\mu_{10} + \mu_{20} - \mu_{12}) \phi_1 \phi_2 \right] \\
\Delta F_1 &= RT \left[\ln \phi_1 + (1 - m_1) \phi_0 + \left(1 - \frac{m_1}{m_2}\right) \phi_2 \right. \\
&\quad \left. + m_1 \{ \mu_{10} \phi_0^2 + \mu_{12} \phi_2^2 + (\mu_{10} + \mu_{12} - \mu_{20}) \phi_0 \phi_2 \} \right] \\
\Delta F_2 &= RT \left[\ln \phi_2 + (1 - m_2) \phi_0 + \left(1 - \frac{m_2}{m_1}\right) \phi_1 \right. \\
&\quad \left. + m_2 \{ \mu_{20} \phi_0^2 + \mu_{12} \phi_1^2 + (\mu_{20} + \mu_{12} - \mu_{10}) \phi_0 \phi_1 \} \right] \\
\mu_{12} &= V_0 / RT (\delta_1 - \delta_2)^2 \quad \cdot \cdot \cdot \text{Solubility Parameter}
\end{aligned}$$

[Phase separation condition (at complete immiscible approximation)].

$$\ln \phi'_0 + \left(1 - \left(\frac{1}{m_1}\right)\right) (1 - \phi'_0) + \mu_{10} (1 - \phi'_0)^2 = \ln \phi''_0 + \left(1 - \left(\frac{1}{m_2}\right)\right) (1 - \phi''_0) + \mu_{20} (1 - \phi''_0)^2$$

From the 1950s to the 1980s, only a few articles reported on ternary systems, and these papers referred to the physical properties of these systems. Bigelow [49] presented a relationship between viscosity and concentration with polystyrene, polyvinylalcohol, and polymethyl methacrylate as polymers and benzene, toluene, and xylene as solvents. He demonstrated that the polymer concentrations had changed, and he found a viscometrical critical concentration in the system. In 1968, Edmond [50] performed sedimentation equilibrium experiments using dextrans, polyethylene glycol, and NaCl aq. and measured the osmotic pressures. In addition, by using simple thermodynamic expressions, he obtained the interaction coefficient for these materials. This article presented an example of an aqueous ternary system polymer solution. In 1969, Cenrry [51] described the free energy changes of ternary system polymer solutions with the interaction between solute and solvent by Maron's theory [52], which treated a general thermodynamic behavior for a nonelectrolyte solution. Then, they succeeded in obtaining a means of evaluating the polymer-polymer interaction parameters. Liu [53], using a perturbed hard-chain theory, argued that a polymer-polymer-solvent ternary system is miscible in view of the solvent contact agilities of each consistent.

After these fundamental discussions, some studies with instrumental analysis started in the mid-1980s and expanded the treated polymer and solvents. Most of the reports aimed at

discussing an emerging mechanism of phase separation in ternary system polymer solutions using the Flory-Huggins theory. Recently, Es-haghi [54] treated the equation of mass and heat diffusion behavior in a ternary polymer system .

In 1988, Einaga [55] employed a ternary system polymer solution consisting of polystyrene/polybutylene/N-dimethylformamide to describe the phase diagram. This was the first report on the use of a polar solvent in a ternary system polymer solution. Following this report, in 1996, Matsumoto [56] investigated another ternary system polymer solution formed by polyethersulfone/polysulfone/N-methylpyrrolidone. This was a primary report of engineering plastic to ternary system polymer solutions.

Various studies were conducted until the mid-2000s; however, they only focused on the physicochemical behavior of ternary system polymer solutions.

In contrast, a polymer/solvent/solvent ternary system, which was also investigated by Scott [57] in the aforementioned series article, was applied to process a polymer. For example, Yin [58] used a polymer/solvent/solvent ternary system for spinning a polyamic acid fiber. Polyamic acid, which is a precursor of polyimide, is widely used because of the difficulty in processing polyimide. Usually, a polyimide product is formed in the polyamic acid precursor, and then the precursor is induced to polyimide by a chemical reaction. Polyamic acid is polymerized in polar solvents; however, as it is difficult to precipitate from the solvent, polyamic acid/dimethylacetamide/water, was applied. As another example, in 2019, Kurada [59] prepared a conductive polymer membrane with non-solvent/solvent/polypyrrole and polysulfone and analyzed the formation mechanism of the membrane from solution. Although two polymer solutions of the system were used to prepare the membrane, the aim was to co-precipitate polymers from a solvent with a nonsolvent rather than phase separation between the polypyrrole solution phase and polysulfone solution phase.

Although there are some applicable studies on polymer/solvent/solvent ternary systems, no application for polymer processing using a polymer/polymer/solvent ternary system was found. To the best of our knowledge, the polymer/polymer/solvent ternary system has not been employed in practical applications.

1.5 OBJECTIVE AND SCOPE OF THIS THESIS

Polymer particles have become an attractive material because of their demand for frontier applications, such as 3D printers and advanced pharmaceuticals; however, only vinyl-type polymers have been used.

As previously mentioned, vinyl-type polymer particles and their preparation methods have been developed by precise polymer design and synthetic control concept of radical polymerization with O/W emulsion. Not all mechanical approaches can be applied to every

polymer material, and the approaches are insufficient in terms of precision to form fine particles, adequate particle distribution, particle shape, and regularity. In other words, these methods have limited applications to condensation polymers or non-vinyl-type polymers; therefore, the use of these polymer particles has not been addressed. Thus, one of the critical problems regarding polymer particles is the development of a new methodology to prepare fine polymer particles for non-vinyl-type polymers.

Accordingly, as the major objective of this doctoral thesis, a general methodology to prepare polymer particles for various polymers has been investigated.

Although O/W emulsions have been used as castings for their precursors to prepare polymer particles for a long time, an oil-in-oil emulsion based on the phase separation phenomenon of a polymer solution, the so-called Scott system, was selected in this study. In this study, a target polymer to prepare a particle and a phase separation polymer were dissolved in a solvent at a ratio that enabled the formation of a phase separation state and formation of an oil-in-oil emulsion. In sequence, a poor solvent of the target polymer was added, and the target polymer particles were prepared. This concept leads to the use of alcohol solvents, polar solvents, acetonitrile, and so on, which are theoretically impossible to form a O/W emulsion or a W/O emulsion due to the compatibility with water. Accordingly, using those O/O emulsions allows using a safer solvent than before or expanding kinds of polymer which enable to process into particles form.

First, the engineering polymer particle preparation method and its scope and limitations are discussed in Chapter 2. In this chapter, polar solvents were selected as solvents to form oil-in-oil emulsions because of the limited solubility of engineering polymers. Polar solvents are water-compatible and have not been used as solvents for oil-in-water emulsions; however, the Scott system can be used as an emulsion solvent.

Next, on the basis of expanding the methodology, Chapter 3 focused on ethyl cellulose as a target polymer, which is a useful biocompatible polymer. The former preparation methods of ethylcellulose particles consist of using a harmful solvent, which results in risks in using the particles in the pharmaceutical area. To solve this issue, ethanol, which has been approved by regulations in many countries, was utilized as a solvent. Ethanol is also a water-compatible solvent. In this chapter, the possibility of forming a particle with ethanol in this system and the mechanism of occurrence of the porous structure are discussed.

Finally, the functionalization of polymer particles using this concept is explained in Chapter 4. A polymer particle is inferior in physical functions to inorganic particles, such that a composite of a polymer and a specific functional material is usually formed to add value. This chapter focuses on the encapsulation of pigments in polymer particles with an oil-in-oil emulsion system, and the principle of encapsulating material in the polymer

particles is also discussed.

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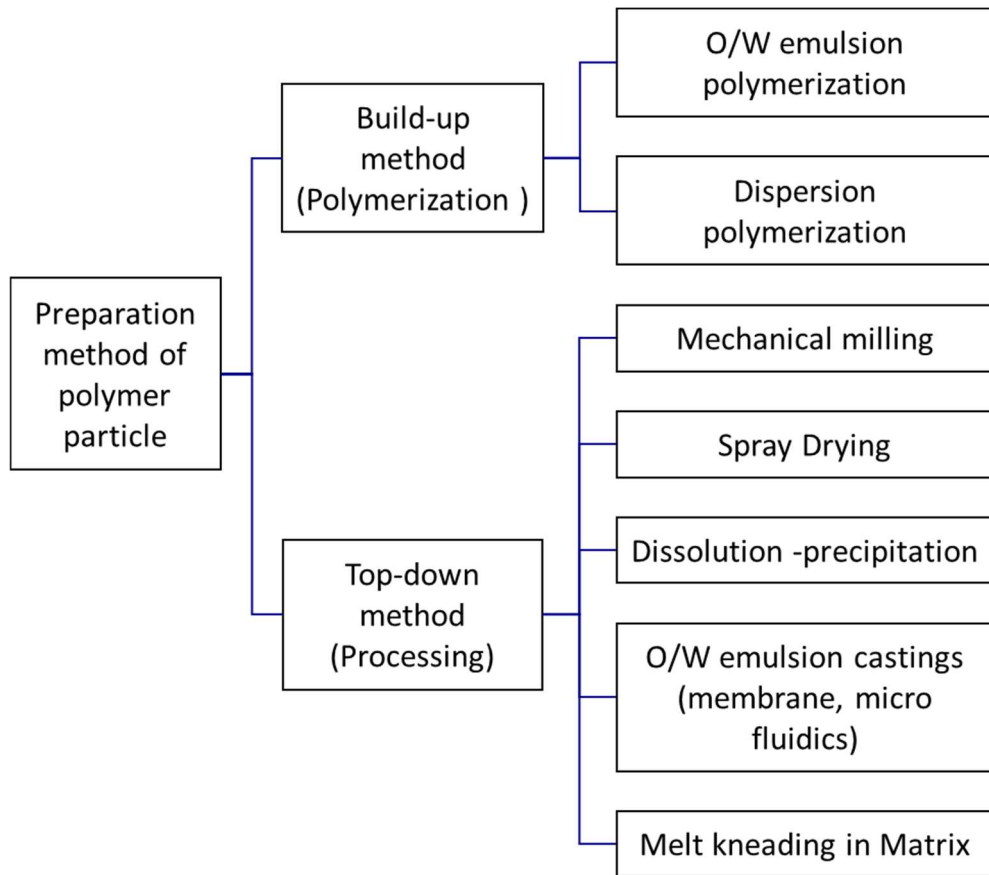


Fig. 1- 1 Classification of polymer particle preparations.

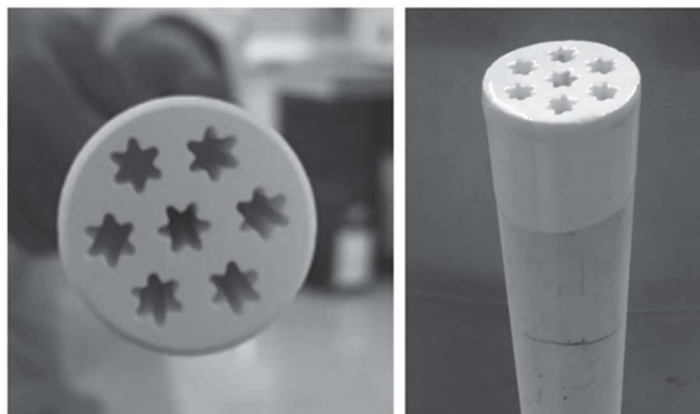
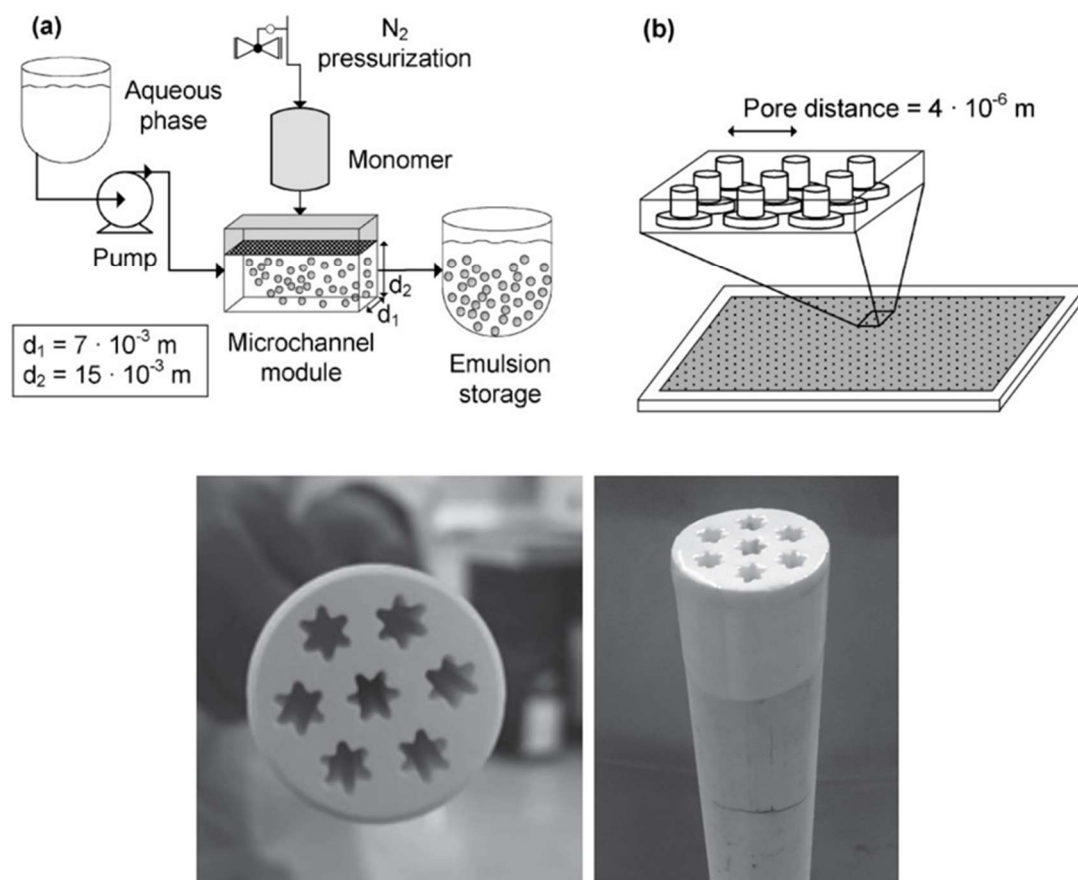


Fig. 1- 2 Examples of a membrane emulsification systems. (upper) microchannel emulsification system with microsieves ^[10], (lower) ceramic membrane with the seven star-shaped internal channels ^[11].

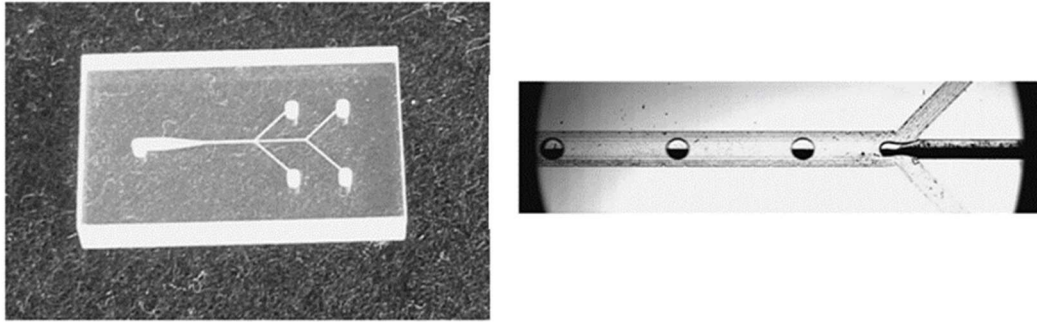


Fig. 1- 3 Examples of a microfluidics ^[13], (left) Micro-Channel chip (25mm × 15mm), (right) generation of bichromal droplet in micro channel duct.

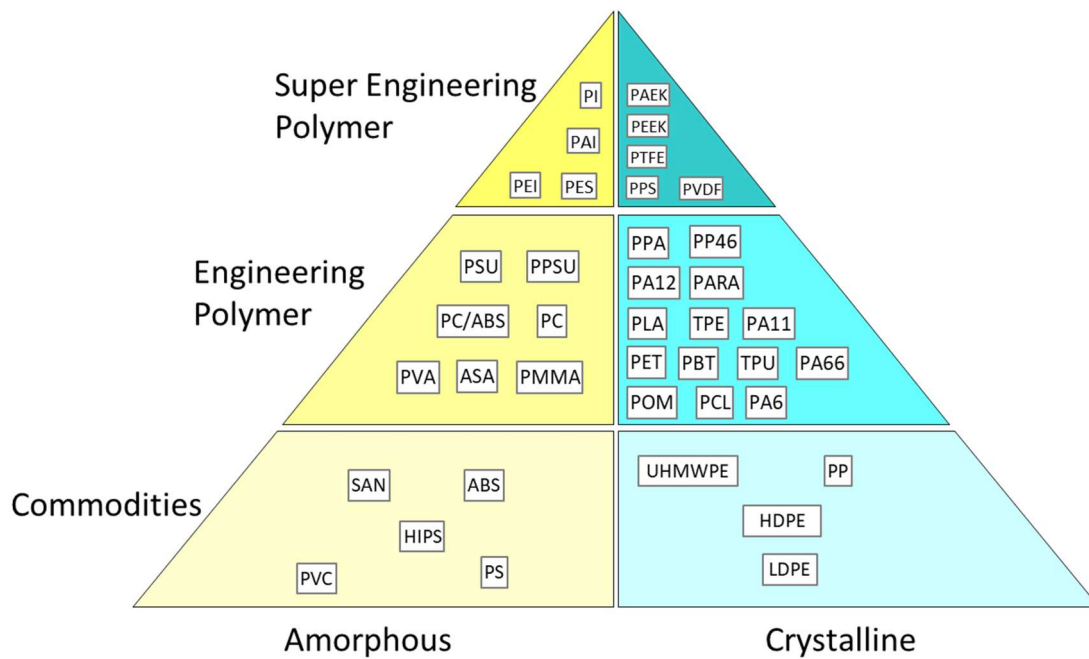


Fig. 1- 4 An example of Plastic Pyramid ^[16].

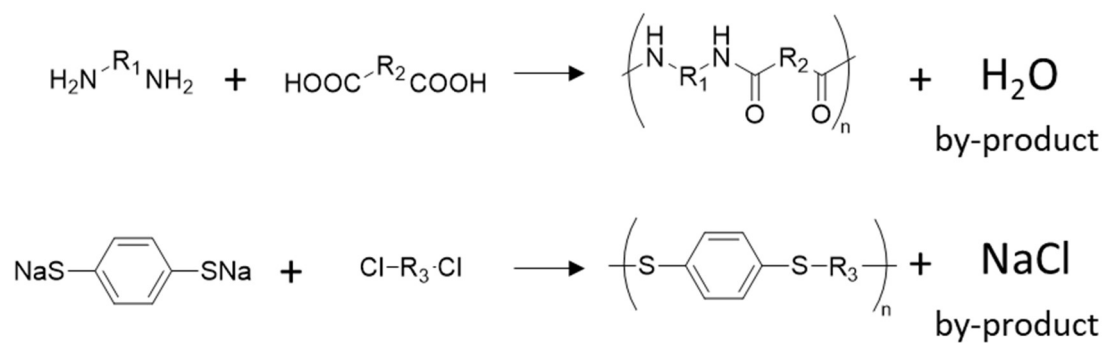


Fig. 1- 5 Condensation reactions and by-products.

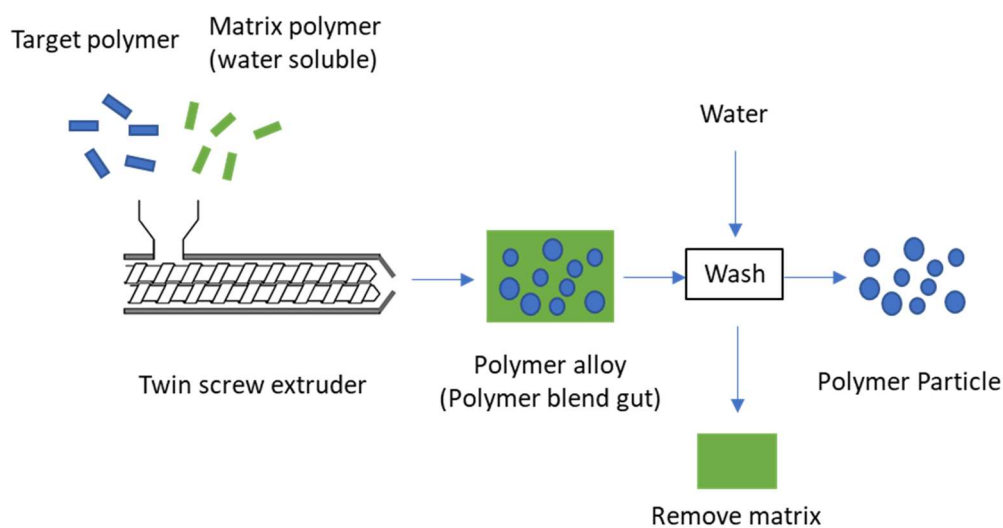


Fig. 1- 6 Melt kneading method.

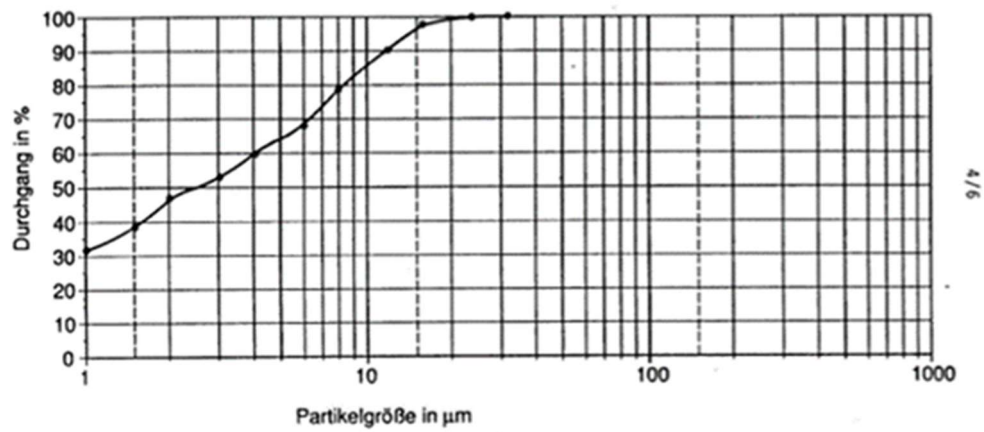


Fig. 1- 7 An example of a particle distribution by spray-drying [26].

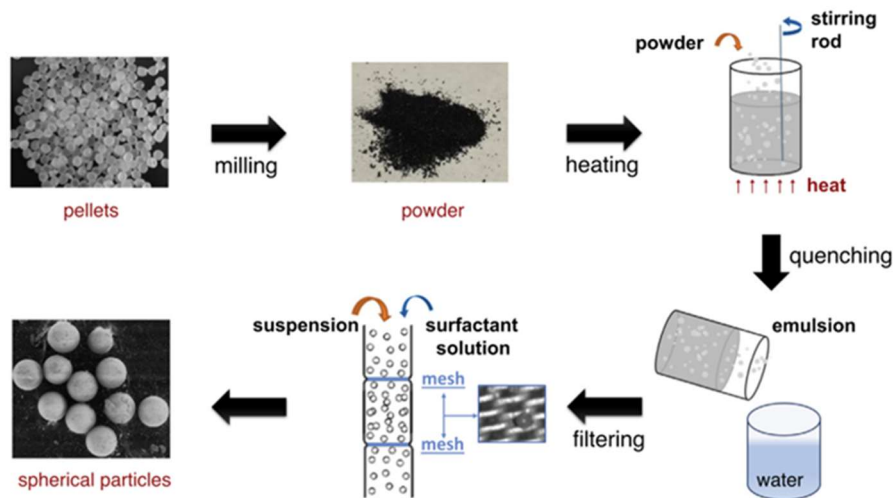
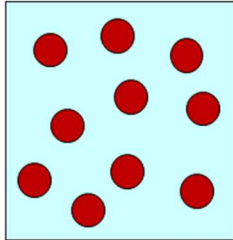
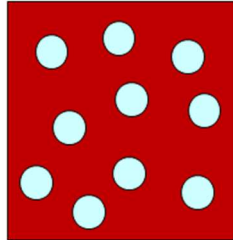


Fig. 1- 8 Recent example for perpetrating of engineering polymer particle [29].

Oil in Water (O/W) emulsion



Water in Oil (W/O) emulsion



Multiple emulsion
(O/W/O or W/O/W)

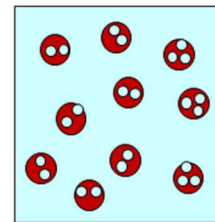
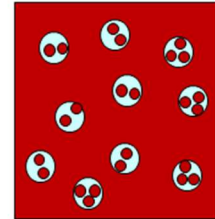


Fig. 1- 9 General Types of Emulsion Systems.

CHAPTER 2

ENGINEERING PLASTIC FINE PARTICLES: EMULSION CASTINGS ENABLED BY A TERNARY SYSTEM

CHAPTER 2

ENGINEERING PLASTIC FINE PARTICLES: EMULSION CASTINGS ENABLED BY A TERNARY SYSTEM

2.1 INTRODUCTION

Polymer fine particles have occupied a substantial fraction of current materials chemistry research. Their chemical and/or physical properties can be controlled through manipulation of the composition, particle size, and morphology. The mechanical functions are highly appreciated for various advanced applications, such as binders for toners, extenders for cosmetics, thickeners for paints, and spacers for liquid crystal displays. Fine particles, not only of traditional radical polymers such as polyacrylates and polystyrenes, but those of engineering plastics such as polyamides [1] and polyesters [2] are also in high demand in a wide range of applications since their chemical and/or physical properties have been improved.

Production methods for polymer fine particles can roughly be categorized into two approaches: building-up from respective monomers or casting of pre-synthesized polymers. In both cases, emulsions play a key role as spherical templates to produce polymer fine particles. Polymerization in oil in water (O/W) emulsions, either in the presence or absence of particular surfactants, would be the first option to access polymer fine particles and enable the production of polyacrylate or polystyrene fine particles via radical polymerization [3-6]. However, this approach is not directly applicable for condensation polymers, including engineering plastics, because aqueous conditions are required and they usually inhibit condensation reactions. To address this issue, emulsion castings could be alternatives to produce condensation polymer fine particles. In this approach, polymer solutions and aqueous media, which are immiscible with each other, are combined to form O/W emulsions in the presence or absence of particular surfactants. The thus formed spherical droplets that contain polymers are then precipitated via the evaporation of solvents [7-12] or the addition of poor solvents [13-15]. Significant solubility of the polymers in typical less-polar solvents that are immiscible with aqueous media is a prerequisite for this approach to be successful; otherwise, it would be difficult to form O/W emulsions. For these reasons, the production of fine particles of condensation polymers that are insoluble in typical less-polar solvents remains a challenge. Furthermore, polar solvents such as *N*-methylpyrrolidone (NMP) are excluded from this approach, because they are miscible with aqueous media and emulsions are not formed. Therefore, oil in oil (O/O) emulsions would be promising spherical templates to produce condensation polymer fine particles that are soluble only in polar solvents.

Since the pioneering work by Scott [16], ternary systems composed of two different polymers and one solvent have attracted fundamental interest in the field of polymer (physical) chemistry research [17-20]. Heterogeneous biphasic conditions can be formed even in a single solvent because different polymers show essentially poor affinity to each other. For example, polyethersulfone (PES) and polysulfone (PSF) in NMP can form a biphasic system that consists of an upper PSF solution layer and a lower PES solution layer [21]. Under mechanical stirring, the heterogeneous biphasic system provides apparent uniform dispersion conditions and could be regarded as O/O emulsions. I have questioned whether such O/O emulsions could offer spherical templates to produce fine condensation polymer particles. Described herein is the production of engineering plastic fine particles with narrow size distributions that have been enabled with such ternary systems.

2.2 EXPERIMENTAL

2.2.1 Materials

Unless otherwise stated, all materials were obtained from commercial suppliers and were used as received.

PES (Table 2- 2, Entry 1): Sumikaexcel® 4800P, supplied by Sumitomo Chemical.

ABS (Table 2- 2, Entry 2): Toyolac® T100, supplied by Toray Industries.

PC (Table 2- 2, Entry 3): Lupiron® E2000, supplied by Mitsubishi Engineering-Plastics Corporation.

PAN (Table 2- 2, Entry 4): Supplied by Sigma-Aldrich.

PPE (Table 2- 2, Entry 5): Supplied by Sigma-Aldrich.

a-PAM (Table 2- 2, Entry 6): Grilamid® TR55, supplied by EMS Werke.

PEI (Table 2- 2, Entry 7): Ultem® 1010, supplied by GE Plastics.

PAR (Table 2- 2, Entry 8): U-polymer®, supplied by Unitika.

c-PAM (Mw: 17,800) (Table 2- 3, Entry 1): TROGAMID® CX7323, supplied by Daicel-Evonik.

c-PAM (Mw: 22,500) (Table 2- 3, Entry 2): HiProlon® 200NN, supplied by Suzhou Hipro Polymers.

c-PAM (Mw: 38,000) (Table 2- 3, Entry 3): Rilsan® AESNOTL-44, supplied by Arkema.

PEE (Table 2- 3, Entry 4): Hytrel® 8238, supplied by Du Pont.

PVA (Separating Polymer): Gohsenol® GL-05, supplied by Nippon Synthetic Chemical Industry.

2.2.2 Equipment

The volume mean particle diameter and particle diameter distribution of each polymer particle were measured by Shimadzu Corporation SALD -2100 or Nikkiso Microtrac MT3300. The morphology of polymer particles was observed by JEOL JSM-6301NF scanning electron microscope (SEM).

2.2.3 Particulation Procedure

General Procedure for **Table 2- 2**.

The respective target polymer (2.5 g) and polyvinyl alcohol (2.5 g) were added to N-methyl-2-pyrrolidone (45 g) and the resulting reaction mixture was stirred until the polymers were dissolved (Note: O/O emulsion conditions with cloudy appearance would form). To an emulsion of the polymers stirred at room temperature ion-exchanged water (50 g) was slowly added to precipitate the respective target polymer. Thus, precipitated polymer fine particles were filtered, washed with ion-exchanged water, and dried in vacuo.

General Procedure for **Table 2- 3**.

The respective target polymer (2.5 g) and polyvinyl alcohol (2.5 g) were added to N-methyl-2-pyrrolidone (45 g) and the resulting reaction mixture was stirred at 180 °C in the glass autoclave reactor (**Fig. 2- 1**) under nitrogen atmosphere until the polymers were dissolved (Note: O/O S16 emulsion conditions with cloudy appearance would form). To an emulsion of the polymers stirred at 180 °C in the glass autoclave reactor ion-exchanged water (50 g) was slowly added through a highpressure pump to precipitate the respective target polymer. Thus, precipitated polymer fine particles were filtered, washed with ion-exchanged water, and dried in vacuo.

2.3 RESULTS AND DISCUSSION

The present work began with investigation of a ternary system composed of PES as a target polymer, polyvinyl alcohol (PVA) as a separating polymer, and NMP (**Fig. 2- 2 to Fig. 2- 4**). The phase diagram for the ternary system shows that dispersion conditions with cloudy appearance, which could be regarded as an O/O emulsion, are formed at relatively high polymer concentrations (>7%). Furthermore, the formation of dispersion conditions was also found to be sensitive to the PVA content, while the PES content did not have a significant impact on the dispersion behavior. The ternary system became highly viscous at higher polymer concentrations; therefore, PES/PVA/NMP = 5/5/90 (w/w/w) was used for

further investigations as a standard.

To precipitate PES selectively, the choice of poor solvents must be creative because PVA should remain in solution. In this context, water was found to simply function as an ideal poor solvent, and enabled the selective precipitation of PES over PVA from the ternary system. In particular, the rates of water addition to the ternary system were a key to the production of PES fine particles (**Table 2- 1**). When water was quickly added to the ternary system, most PES became aggregated and only a limited amount of fine particles was recovered (**Fig. 2- 5**). In contrast, slow water addition over longer time periods gave much better results; undesired aggregation was prevented to a significant extent and PES fine particles were afforded almost quantitatively. Negligible aggregation was observed under optimized conditions to give PES fine particles with a narrow size distribution (**Fig. 2- 6**). It should be noted that the ternary system was not restricted to NMP, but dimethyl sulfoxide (DMSO) was also applicable to produce PES fine particles (**Fig. 2- 7**). Although acetonitrile, acetone, and tetrahydrofuran were not available for the production of fine PES particles, this was simply because of the poor solubility of the polymer.

Engineering plastics are in high demand for a wide range of applications because they have improved chemical and/or physical properties. This also means that their solubility in typical solvents is generally poor, so that emulsion casting can be challenging. NMP is known as a good solvent for many polymers, including engineering plastics, and is widely used in both academic and industrial settings; however, some polymers are not soluble to a sufficient extent. The ternary system with NMP and PVA was found to be effective for the production of various polymer fine particles, including acrylonitrile butadiene styrene copolymer (ABS), polycarbonate (PC), polyacrylonitrile (PAN), polyphenylene ether (PPE), amorphous polyamide (a-PAM), polyetherimide (PEI), and polyarylate (PAR) (**Table 2- 2**, **Fig. 2- 8** to **Fig. 2- 14**). Although the average particle sizes were in the range from 0.57 to 30.7 μm , fine particles were quantitatively recovered in most cases with narrow size distributions. PC particles (**Table 2- 2 Entry 3 and Fig. 2- 9**) and PPE particle (**Table 2- 2 Entry 5 and Fig. 2- 11**) have misshapen surface compared with other polymer particles which have real smooth surfaces. I considered that the crystallinity of PC and PPE caused those shape. In general, those polymers were recognized as amorphous. But when a crystallization rate is slow, those polymers show crystallinity. In this method particulation period took two hours. Therefore, the crystallinity of those particles affects surface properties.

However, the ternary system was not directly applicable to crystalline polyamides (c-PAM) and polyester elastomer (PEE), because of their poor solubility in NMP. To address this issue, I turned my attention to the use of an autoclave reactor for the production of fine

particles that would otherwise be difficult to achieve. The polymers were solubilized in NMP at 180 ° C and precipitation was also conducted at this temperature via the addition of water to the reactor. This modified procedure with the autoclave reactor enabled the production of fine particles of c-PAM and PEE with various molecular weights. The average particle sizes were 9.1-15.8 μm and fine particles were quantitatively recovered in most cases with narrow size distributions (**Table 2- 3** and **Fig. 2- 15** to **Fig. 2- 18**).

The particulation mechanism was considered. As the polymer solubility changed by adding a poor solvent in the emulsion, segments of an expanded polymer chain in a polar solvent shrank via the theta state. The polymer chains aggregated with each other and solidified into polymer particles.

This polymer particle method provides a narrow particle distribution, which was considered to be caused by a small interface tension due to the same solvent between the dispersant and continuous phases. In case of PES particulation condition, the difference of surface tension between dispersant and continuous phases was 0.3 mN/m (PES/ PVA/ NMP = 5/ 5/ 90) and 1.9 mN/m (PES/ PVA/ DMSO = 5/ 5/ 90). In contrast, the interface tension between water and chloroform, which is generally used to form an oil-in-water emulsion, was 45 mN/m. Therefore, this assumption is acceptable.

The emulsion has a low tendency to coalesce owing to the low interfacial tension. Thus, the emulsion formed by mixing remained stable. In sequence, the emulsion turned into polymer particles, and the particle distribution became narrow.

Comprehending the relationship between emulsion diameter and particle diameter is significant to reveal the particulation mechanism; thus, a few trials were conducted to observe the emulsion diameter.

A digital microscope was inserted into a flask to observe the emulsion directly; however, it was difficult to distinguish the dispersed phase from the continuous phase because of their similar refractive indexes. Owing to the lack of time resolution in the equipment, the emulsion diameter could not be measured under stirring conditions.

Furthermore, observation trials were conducted using a Rheo-Microscope (Anton Paar). The emulsion sizes were successfully captured according to particular shear rates, but the shear rate could not be associated with the particle diameter from the captured emulsion size.

Almost all the polymer particles were spherical in shape in this study. It was estimated that the droplets shrank isotropically in the case of amorphous polymers, and the emerged polymer particle had a spherical shape. In contrast, in the case of polycarbonate and polyphenylene oxide, crystallization occurred in the droplet during the particulation period, followed by partial arrangement of polymer molecules; therefore, the surfaces of these

particles lost smoothness. Although these two polymers are generally recognized as amorphous polymers, crystallization can be induced when a polymer solidifies slowly. It took two hours to form a particle by pouring a poor solvent. It was considered that the system changed from droplet to particle at a slow pace, and partial crystallization progressed in the particles.

Polymer particles can be adulterated with a separating polymer. To confirm this, NMR analysis was conducted using PES particles. The particles dissolved in d-DMSO and the remaining PVA were evaluated. As a result, no significant amount of PVA was detected. Soxhlet extraction of PES particles by water was also implemented, but PVA could not be detected from the extract. Based on these results, I concluded that no more than 1% of contamination occurred.

2.4 CONCLUSION

In conclusion, I have successfully demonstrated that a ternary system, typically using NMP and PVA, is highly effective for producing fine particles of engineering plastics with narrow particle size distributions. O/O emulsions are likely to form below conditions; a solvent enable to dissolve target polymer, a difference of polar polarities between target polymer and phase separating polymer is wide, and phase separating polymer and total concentration of polymers is high (generally 5% or more); which offer spherical templates for the casting of condensation polymers. The ternary system was determined to be applicable to many engineering plastics, in combination with an autoclave reactor. I consider that this system can find unique applications for the production of fine particles of engineering plastics that are in high demand in various research fields.

2.5 REFERENCES

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Fig. 2- 1 Autoclave equipment for particulation in high temperature.

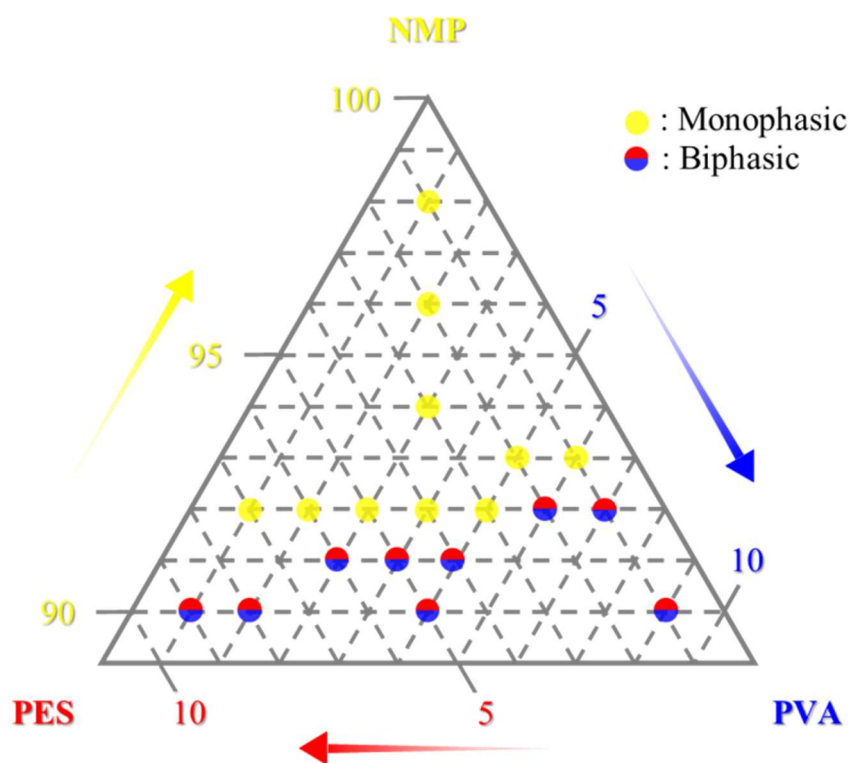


Fig. 2- 4 Phase Diagram of Ternary System.

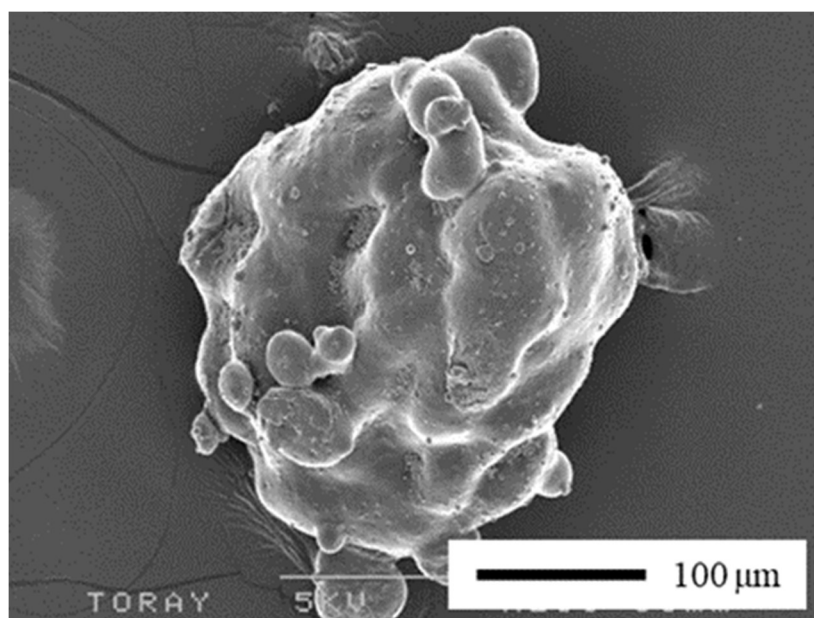


Fig. 2- 5 SEM Image of Aggregation Fraction of PES (Table 2- 1, Entry 1).

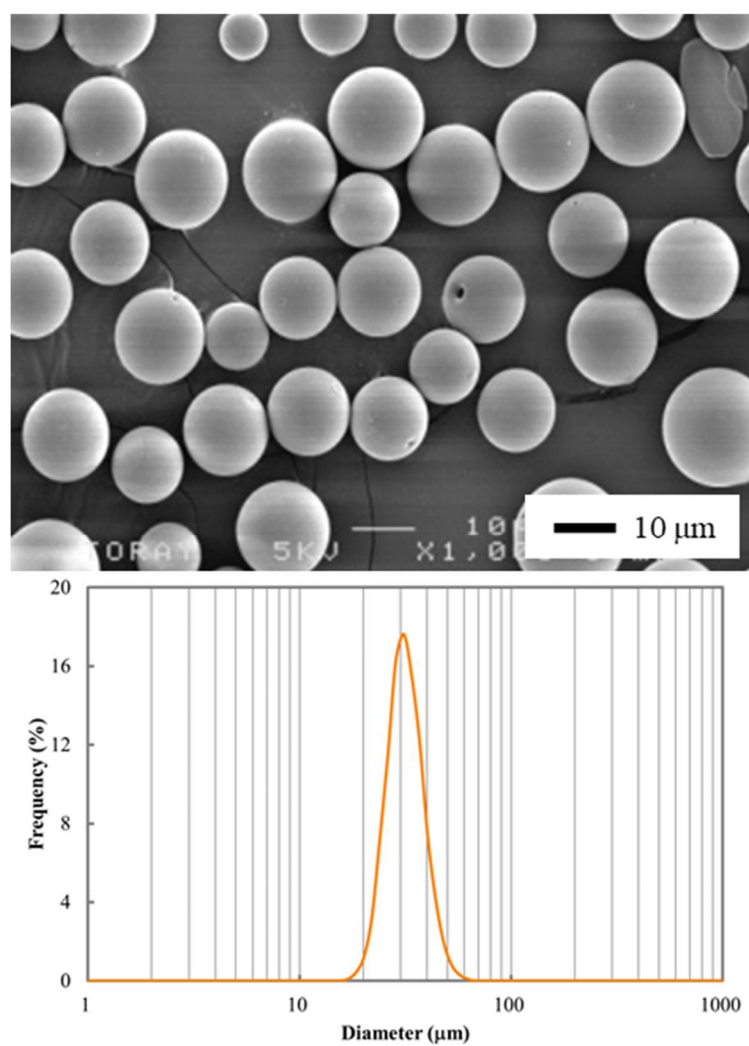


Fig. 2- 6 SEM Image and Size Distribution of PES Fine Particles (Table 2- 1, Entry 4).

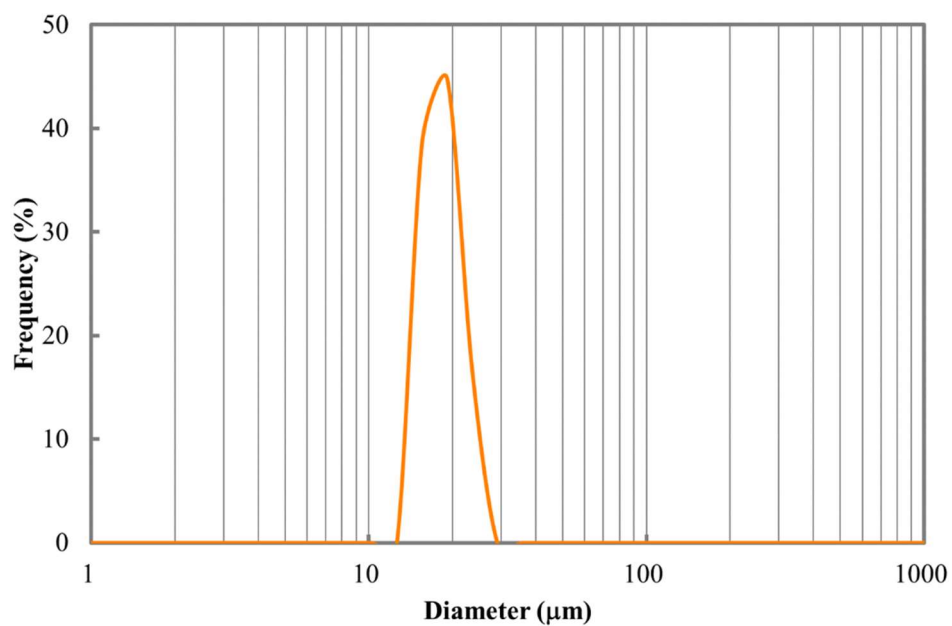


Fig. 2- 7 Size Distribution of PES Fine Particles Produced by Using DMSO instead of NMP (PES/PVA/DMSO = 2.5/5/92.5 (w/w/w)).

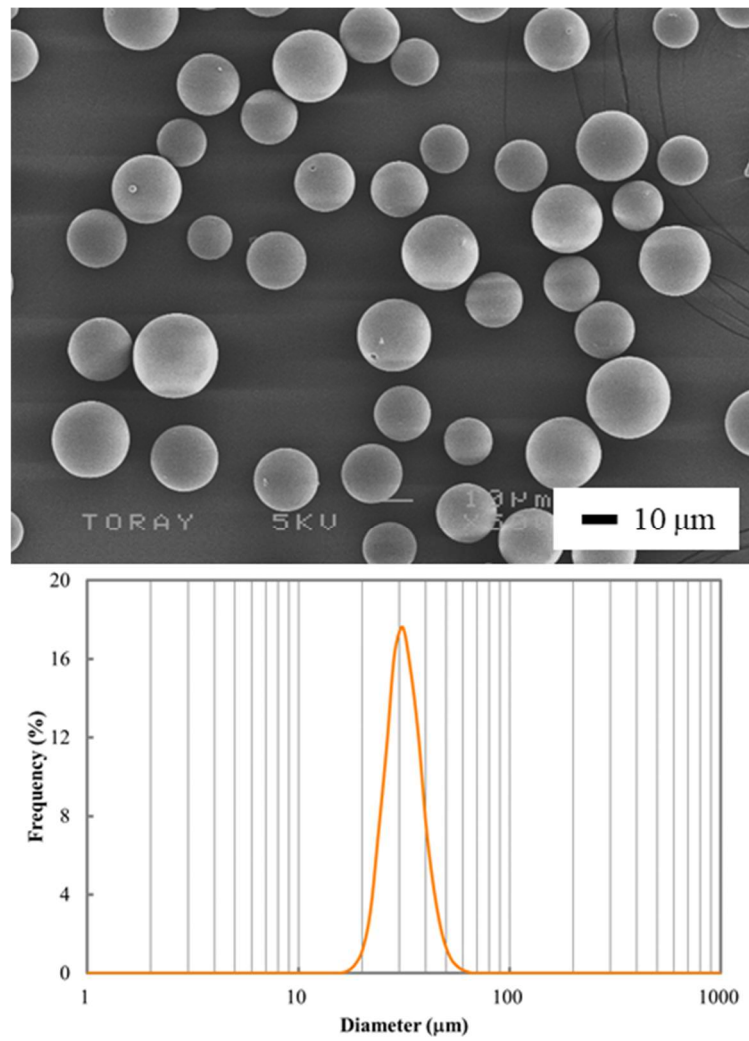


Fig. 2- 8 SEM Images and Size Distributions of ABS Fine Particles (Table 2- 2, Entry 2).

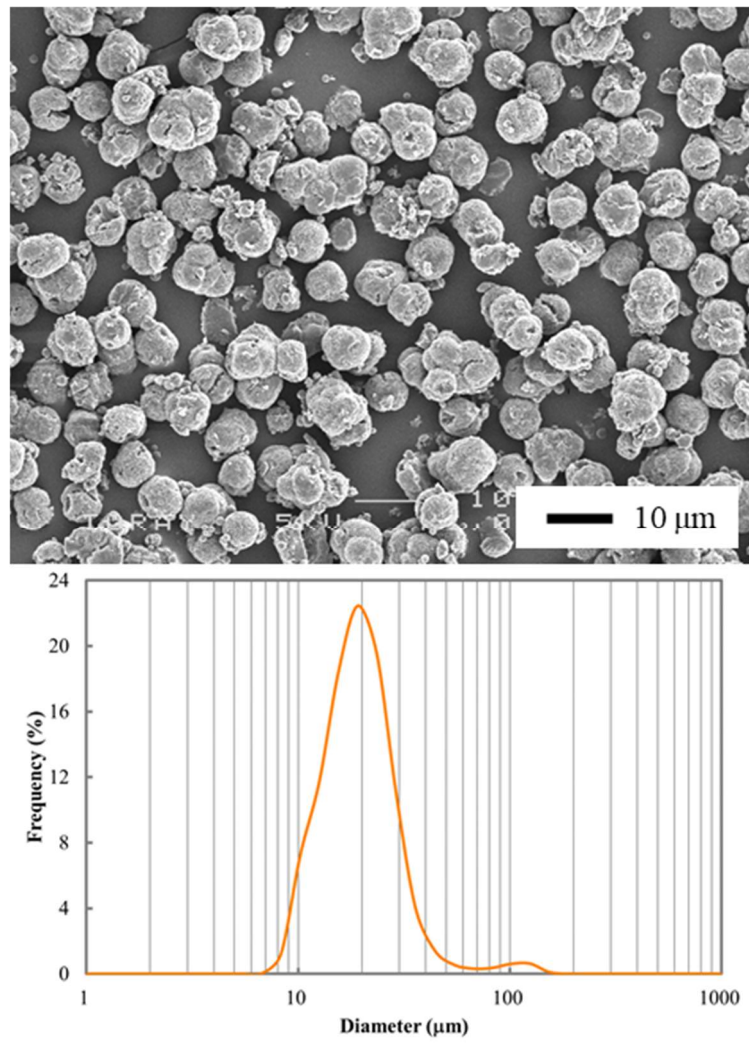


Fig. 2- 9 SEM Image and Size Distribution of PC Fine Particles (Table 2- 2, Entry 3).

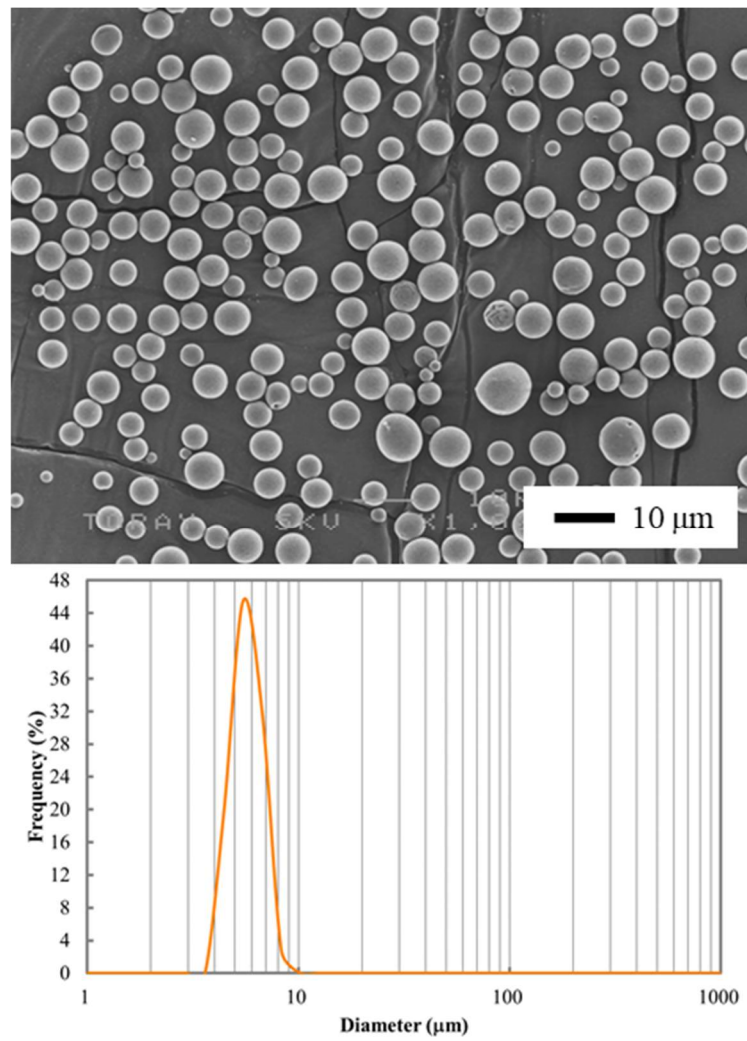


Fig. 2- 10 SEM Images and Size Distributions of PAN Fine Particles (Table 2- 1, Entry 4).

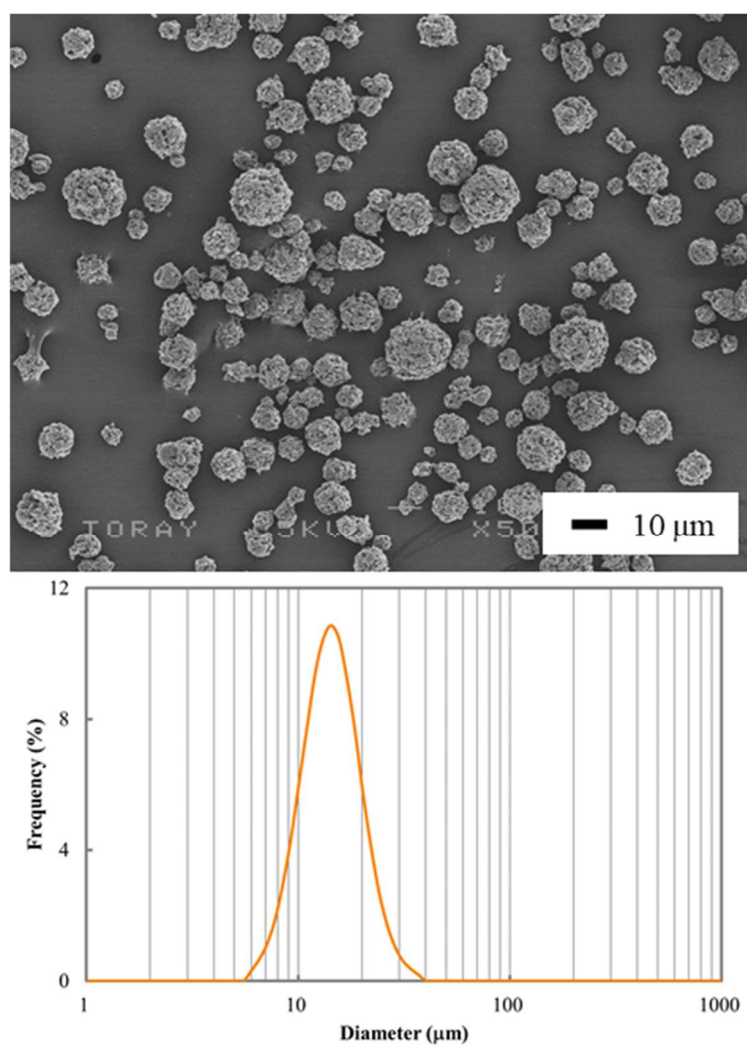


Fig. 2- 11 SEM Image and Size Distribution of PPE Fine Particles (Table 2- 2, Entry 5).

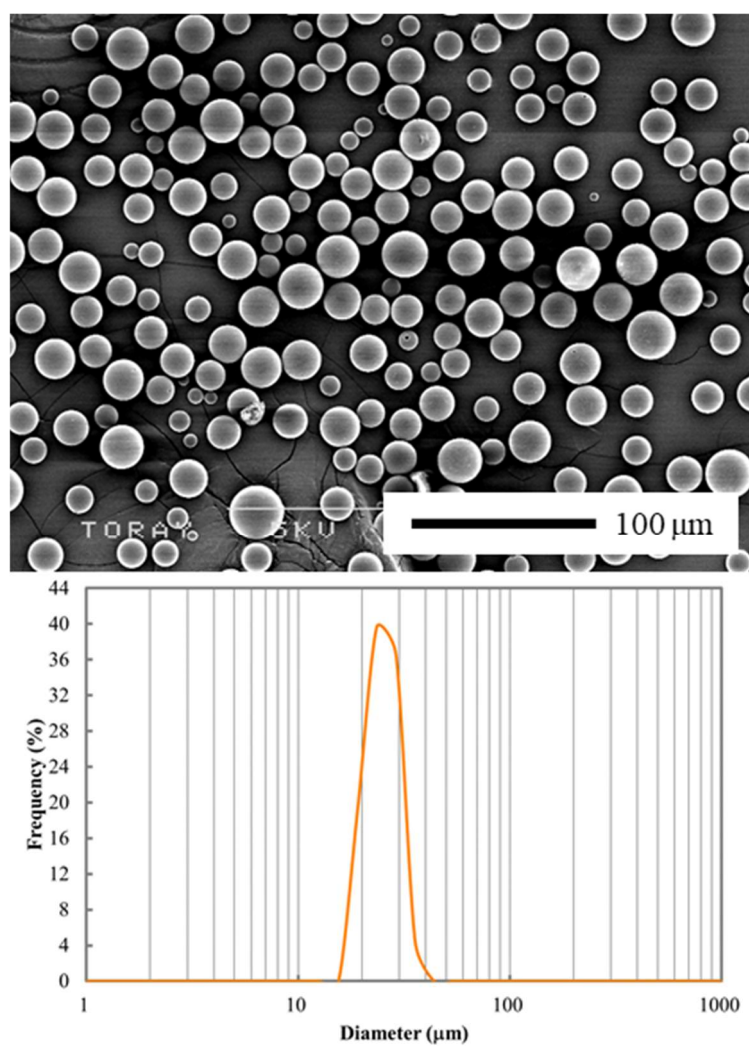


Fig. 2- 12 SEM Image and Size Distribution of a-PAM Fine Particles (Table 2- 2, Entry 6).

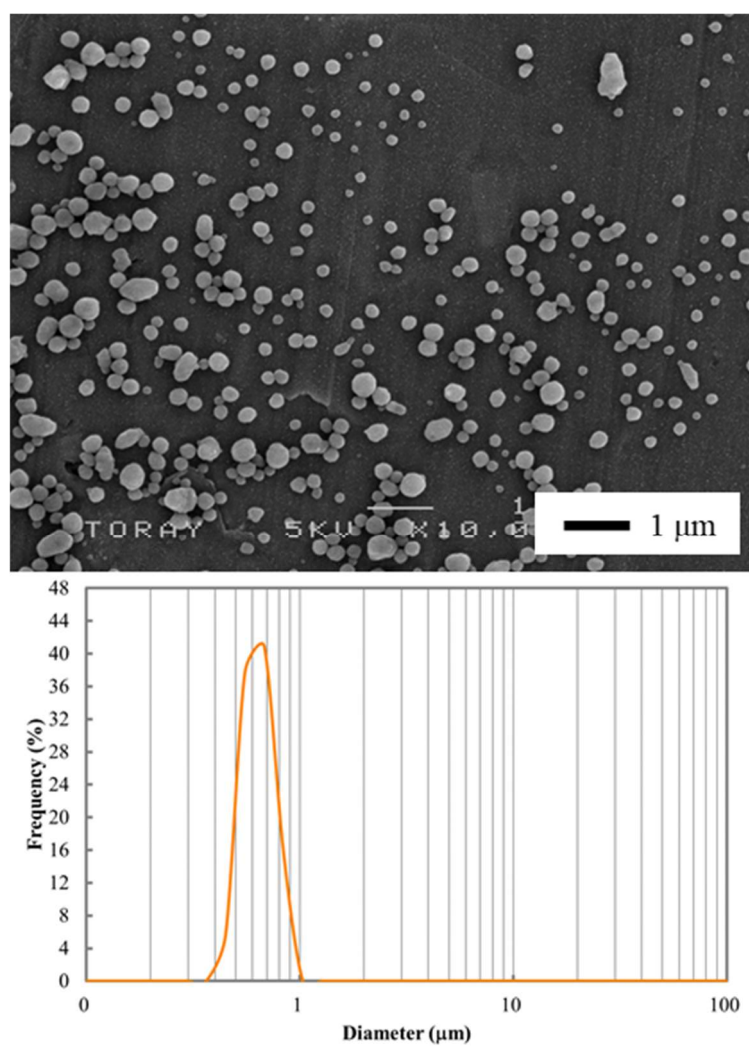


Fig. 2- 13 SEM Image and Size Distribution of PEI Fine Particles (Table 2- 2, Entry 7).

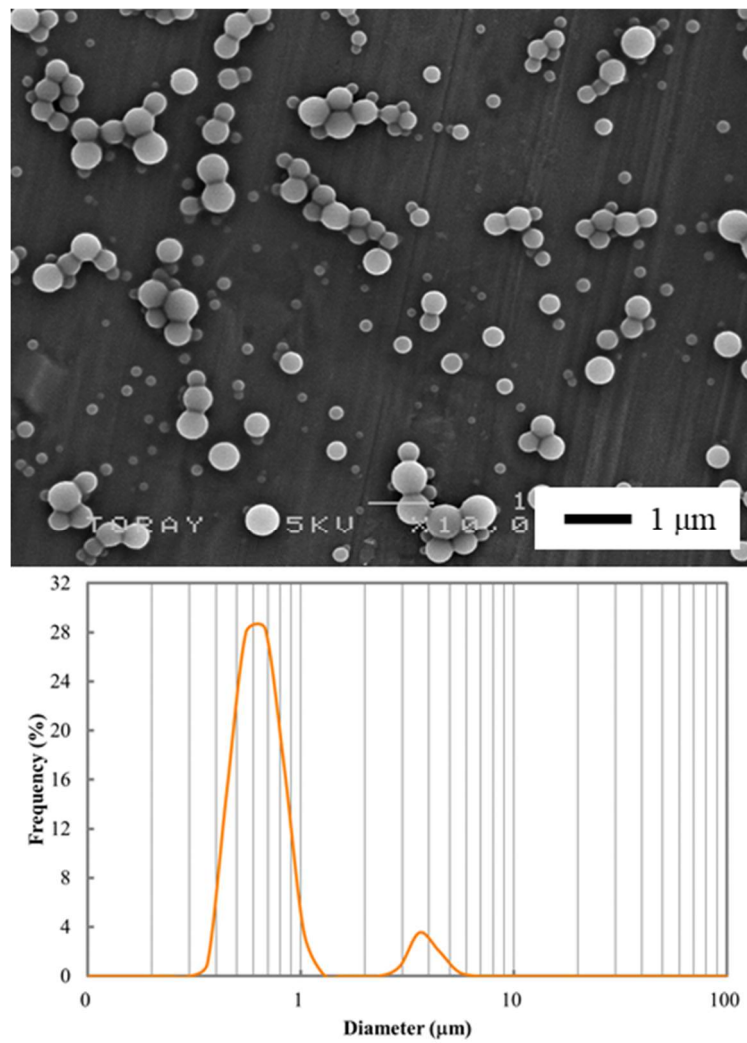


Fig. 2- 14 SEM Image and Size Distribution of PAR Fine Particles (Table 2- 2, Entry 8).

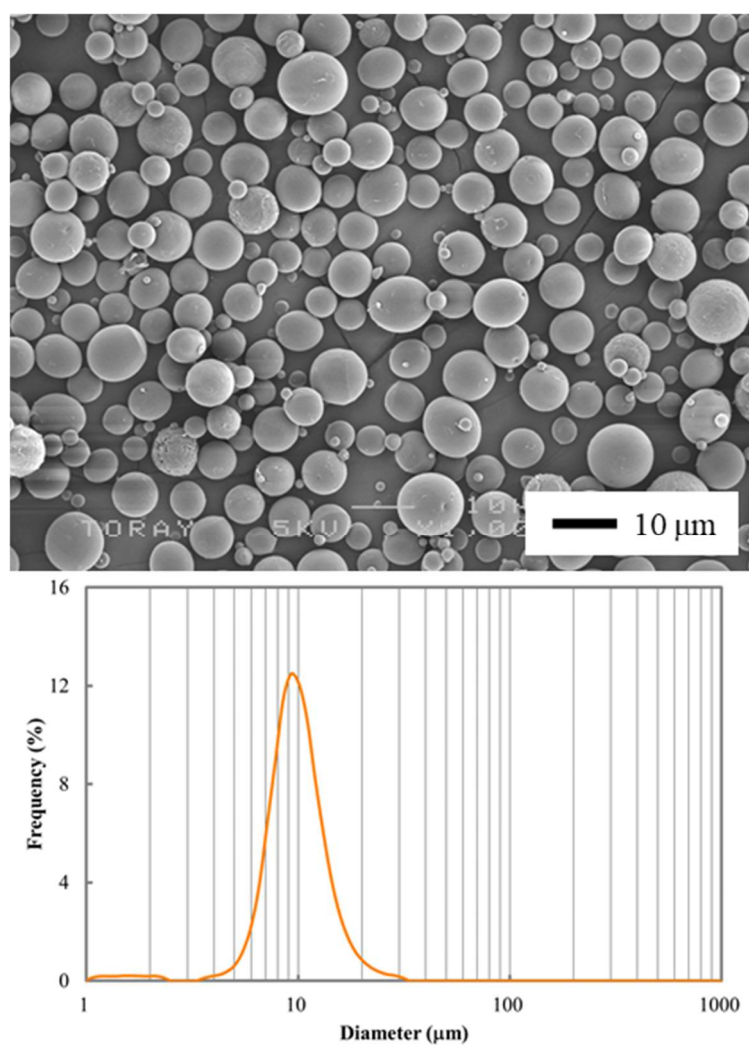


Fig. 2- 15 SEM Image and Size Distribution of c-PAM Fine Particles (Table 2- 3, Entry 1).

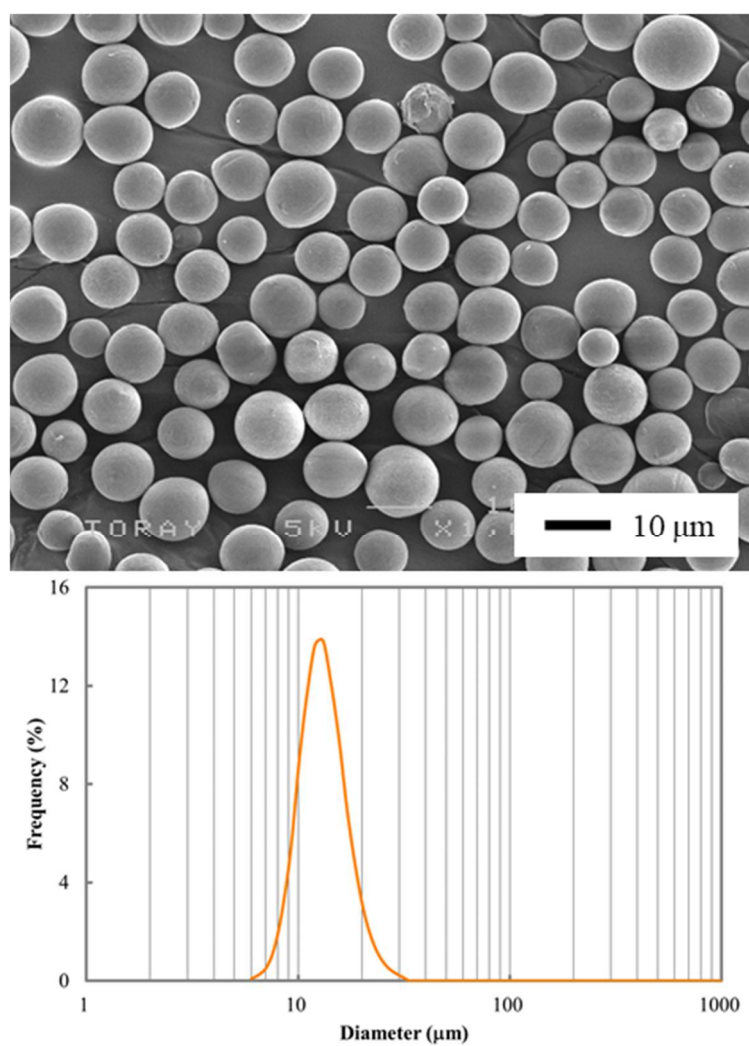


Fig. 2- 16 SEM Image and Size Distribution of c-PAM Fine Particles (Table 2- 3, Entry 2).

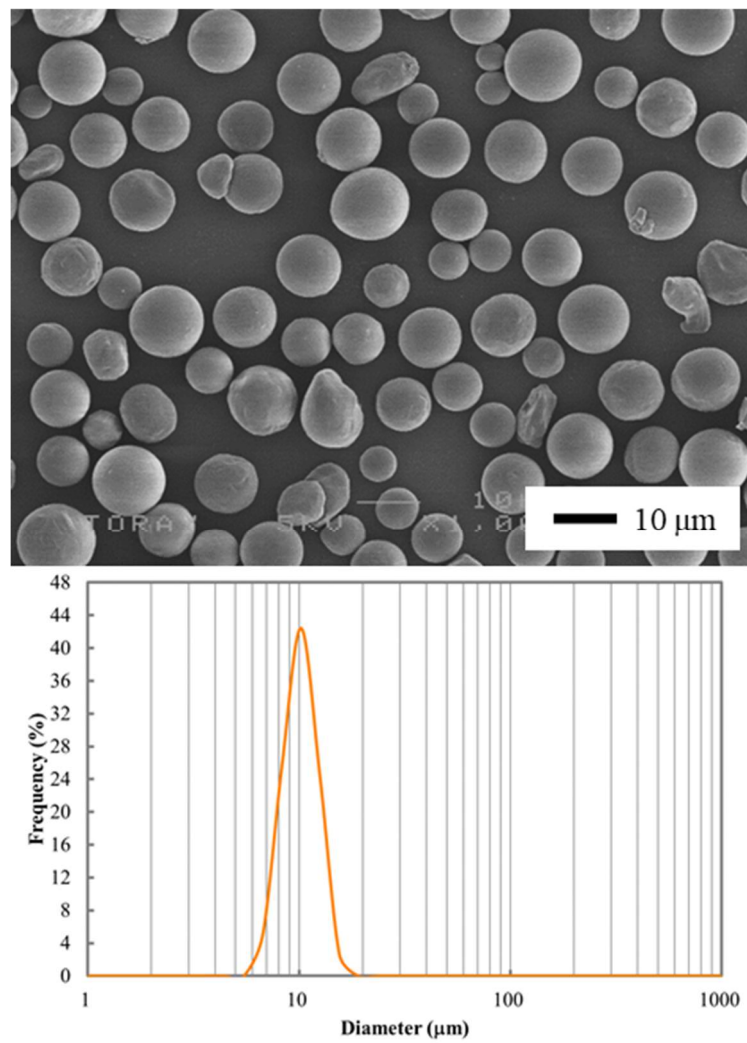


Fig. 2- 17 SEM Image and Size Distribution of c-PAM Fine Particles (Table 2- 3, Entry 3).

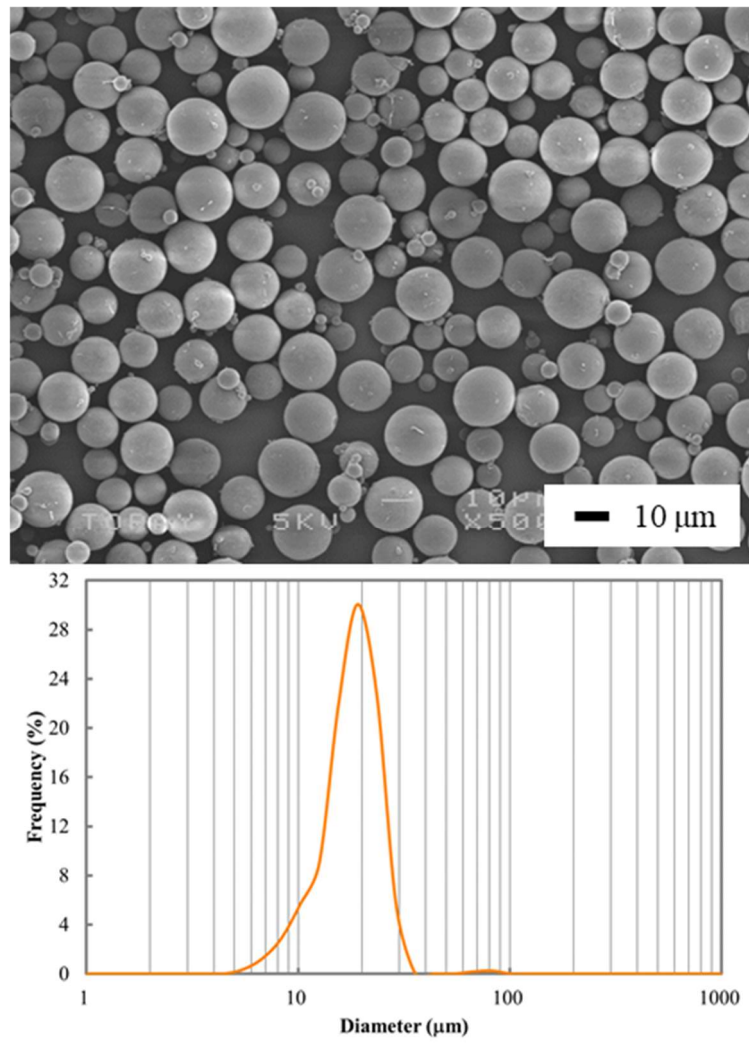


Fig. 2- 18 SEM Image and Size Distribution of PPE Fine Particles (Table 2- 3, Entry 4).

Table 2- 1 Optimization of the Production Method of PES Fine Particles.

Entry	Rete (mL/min)	Particle Fraction (wt%) ^a	Diameter (μm) ^b	Aggregation Fraction
1	50	23	0.8	77
2	1.1	>95	36.7	3
3	0.42	>95	36.7	0.9
4	0.21	>95	33.3	0.4

^aAdding rate of water.

^bMeasured by laser diffraction scattering method (volume-based).

Table 2- 2 Production of Various Polymer Fine Particles.

Entry	Target Polymer	Particle Fraction (wt%)	Diameter (μm) ^a	Distribution Index
1	PES	96	30.7	1.12
2	ABS	97	14.4	1.13
3	PC	86	17.6	1.27
4	PAN	92	5.1	1.16
5	PPE	78	14.3	1.35
6	a-PAM	90	22.4	1.18
7	PEI	80	0.57	1.13
8	PAR	78	0.64	1.13

^aMeasured by the laser diffraction scattering method (volume-based).

Table 2- 3 Production of Various Fine Polymer Particles using an Autoclave Reactor.

Entry	Target Polymer ^a	Particle Fraction (wt%)	Diameter (μm) ^b	Distribution Index
1	c-PAM (17,800)	95	9.8	1.16
2	c-PAM (22,500)	97	12.9	1.20
3	c-PAM (38,000)	95	9.1	1.11
4	PEE	95	15.8	1.63

^aMolecular weight given in parentheses.

^bMeasured by the laser diffraction scattering method (volume-based).

CHAPTER 3

POROUS AND SPHERICAL ETHYL CELLULOSE FINE PARTICLES PRODUCED BY TERNARY SYSTEM-BASED EMULSION CASTINGS

CHAPTER 3

POROUS AND SPHERICAL ETHYL CELLULOSE FINE PARTICLES PRODUCED BY TERNARY SYSTEM-BASED EMULSION CASTINGS

3.1 INTRODUCTION

Pharmaceutical research and development cover a wide range of subjects. Screening potential molecules to find active pharmaceutical ingredients (APIs) has traditionally been the initial focal point for drug discovery. With promising candidates, practical synthetic routes are then established to provide sufficient quantities for further clinical investigations. Drug delivery systems (DDSs) are also of significant importance to maximize the advancements of drug discovery. The growing toolbox of DDS carriers, which includes organic (soft) and/or inorganic (hard) materials, enables the controlled and/or targeted release of APIs, possibly with extended lifetimes. The design and production of novel functional carriers is a key for such a DDS technology to be successful. Biocompatibility is a prerequisite for DDS carriers to minimize undesired side effects on the human body. In this context, some fine polymer particles have proven to be promising options as biocompatible materials for DDS carriers, especially due to their high processability. For instance, dextran [1], polyethylene glycol [2], poly(lactic-co-glycolic acid) [3-5], chitin [6, 7], chitosan [8-11], and poly(acrylic acid) and their derivatives [12, 13] are currently applied for therapeutic use and have found effective applications in this field. Among the most common biocompatible polymers are cellulose derivatives, such as hydroxypropyl cellulose [14], carboxymethyl cellulose [15], and ethyl cellulose (EC) [16], due to their availability and safety. Several hydroxy groups offer efficient modification sites for the fine tuning of their hydrophilicity/hydrophobicity, crystallinity, and stability in biological environments.

Fine biocompatible polymer particles containing APIs are typically produced by polymer casting in the presence of APIs, where the polymer and API are both dissolved in a solvent and are particulated in one step to produce fine particles with API coated at the surface and/or included therein. Oil in water (O/W) emulsions are widely used as templates and the thus-formed spherical droplets containing both polymer and API are then precipitated via the evaporation of solvents [17-21] or the addition of poor solvents [22, 23]. However, this method has several limitations, such as the significant solubility of both the polymer and API is required in typical less-polar solvents that are immiscible with aqueous media to form O/W emulsions. Furthermore, residual solvents must be controlled to extremely low levels since they may be hazardous to human health. For these reasons, loading APIs into pre-cast fine polymer particles (two step method) would be a flexible alternative since the particulation and loading conditions can be optimized separately. For this method to be

successful, the production of porous polymer fine particles is key, or else the loading amount of the APIs would be insufficient [24]. While the production of porous fine particles of poly(acrylic acid) and their derivatives has been reported so far, that of ECs remains challenging.

I have developed ternary system-based oil in oil (O/O) emulsion casting in previous chapter, which enables the production of fine particles of engineering plastics (**Fig. 3- 1**) [25]. Such ternary systems were found and intensively studied by Scott [26]. I have revisited O/O emulsion casting as spherical templates for the casting of engineering plastics. In this method, a target polymer and a separating polymer are both dissolved in one solvent to form O/O emulsions since the affinity between the two different polymers is essentially low. The target polymer is then selectively precipitated from the ternary system by the addition of a poor solvent to produce fine particles of engineering plastics. I questioned whether such ternary system-based emulsion castings could also be applied to produce biocompatible polymer fine particles, ideally without the use of hazardous solvents. Described herein is my serendipitous finding that O/O emulsion castings enable the production of porous and spherical fine particles of biocompatible polymers, using EC as a model (**Table 3- 1**). This method has enabled me to access porous fine particles of ECs that are otherwise difficult or impossible to produce.

3.2 EXPERIMENTAL

3.2.1 Materials

All materials were obtained from commercial suppliers and were used as received.

EC-1: AqualonTM (EC) N50, supplied by Ashland Inc.

EC-2: AqualonTM (EC) T50, supplied by Ashland Inc.

EC-3: AqualonTM (EC) K50, supplied by Ashland Inc.

PVP (Separating Polymer): Luvitec[®] K-85N (weight-average molecular weight: 1,100,000) and Luvitec[®] K-30 (weight-average molecular weight: 50,000), supplied by BASF.

EtOH: Extra pure grade (>99.5 vol%), supplied by Amakasu Chemical Industries.

3.2.2 Analysis equipment and procedure

Size distribution of the EC fine particles was measured by laser-diffraction analysis (Nikkiso, Microtrac MT3300). EC fine particles were characterized by X-ray diffraction analysis (XRD, Rigaku, RINT 2100), transmission electron microscopy (TEM, Hitachi High-Tech, H-7100), scanning electron microscopy (SEM, JEOL, JSM-6319NF), X-ray

computed tomography scan analysis (X-ray CT, Zeiss, Xradia 510), FT-IR (Shimadzu, Prestige-21), DSC (TA, Q20), and mercury porosimeter (Micrometrics, AutoPore IV 9510). The specific surface area of the fine particles was determined based on Brunauer-Emmett-Teller (BET) theory using adsorption isotherms for krypton (BEL JAPAN, BELSORP-max)

General Procedure for Linseed Oil Absorption Test (**Fig. 3- 13**).

Linseed oil (ca. 60% α -linolenic acid) absorption test was carried out by using Japan Industrial Standards (JIS) K5101 “Pigment Test Method: Refined Linseed Oil Method”.

Procedure for SEM-EDX Analysis (**Fig. 3- 16**):

Sodium salicylate was absorbed into EC-2 fine particles, which were then embedded in an epoxy resin. A flat cross section was prepared by a microtome and the surface was coated with Pt (10 nm) by a sputtering method. Thus Pt-coated cross section was analyzed by Hitachi High-Tech Corporation FE-SEM SU 8020 and FE ESM S-4800 and Bruker Corporation AXS QUANTAX FlatQUAD Xflash 55060FQ.

Procedure for X-ray CT Scan Analysis (**Fig. 3- 17**):

EC-2 fine particles were fixed to the edge of a commercially available mechanical pencil lead (graphite rod) by instant glue. Thus prepared sample was analyzed by Zeiss Corporation Xradia 510 Versa in tube voltage 80 kV and tube power 7 W.

3.2.3 General Procedure for EC Fine Particles Production

The respective EC (2.5 g) and PVP (Luvitec® K-85N, 2.5 g) were added to EtOH (45 g) and the resulting reaction mixture was stirred at 70 °C for 2 h (Note: O/O emulsion conditions with cloudy appearance would form). To an emulsion of the polymers stirred at 70 °C ion-exchanged water (50 g) was slowly added over 2 h to precipitate the respective target EC. Thus precipitated EC fine particles were filtered, washed with ion-exchanged water, and dried in vacuo.

3.3 RESULTS AND DISCUSSION

The present work began with the construction of ternary system-based O/O emulsions that can be used as spherical templates for the casting of EC. After the investigation of numerous combinations, PVP and EtOH were selected as the separating polymer and solvent, respectively, mainly since they are non-hazardous materials. In addition to the essentially low affinity between the two different polymers, there is a significant gap in the solubility

parameters of EC and PVP; therefore, an effective phase separation to form emulsions would be expected. When EC-1 and PVP were co-dissolved in EtOH (5/5/90, w/w/w), the ternary system showed a cloudy appearance, which suggests that O/O emulsions were formed via phase separation (**Fig. 3- 1** and **Fig. 3- 2**). The picture of phase separation states looks cloudy because the state might not be perfectly separated. A part of droplets might sink into the lower phase due to the slight difference of density. To selectively precipitate EC from the ternary system, water was selected as the poor solvent since it is miscible with EtOH and PVP is highly soluble in water (see Supplementary data for further details). To my delight, EC fine particles with a narrow size distribution were collected quantitatively by the addition of water to the ternary system (**Fig. 3- 3**). Although some coalescence was evident in the scanning electron microscopy (SEM) observations, most particles seemed to be spherical, at least in the initial stage.

The hydrophilicity/hydrophobicity, crystallinity, and stability of EC in a biological environment can be fine-tuned by changing the ethoxy content; therefore, several grades of commercially available EC were employed. Having established the ternary system-based emulsion casting for the production of EC-1 fine particles, this method was then applied for particulation of other grades of EC. EC/PVP/EtOH = 5/5/90 (w/w/w) was used as a standard composition to construct the respective ternary systems, from which EC was selectively precipitated by the addition of water as a poor solvent. To my surprise, when EC-2 and EC-3 were used instead of EC-1, fine spherical and highly porous particles with a narrow size distribution were obtained (**Fig. 3- 5**, **Fig. 3- 6** and **Fig. 3- 4**). Although the mechanistic aspect remains an open question, the ethoxy content of EC has a significant impact on the particulation process. The SEM images in **Fig. 3- 5** suggest that the particles have pores with somewhat structural regularity and not totally random. X-ray diffraction (XRD) analysis shows that the crystalline structure of the starting ECs and their fine particles are significantly different (**Fig. 3- 7** to **3- 9**), which indicates that this method involves recrystallization (see **Fig. 3- 10** to **3- 12** for further characterizations).

The emerging porosity of EC particles was considered to be related to the polymer crystallization mechanism, nucleation and growth mechanism, or spinodal decomposition-type phase separation. The morphology of the EC particles appeared to have a periodic porous structure. If porosity emerged based on a nucleation and growth mechanism, the EC particle shape and morphology would become irregular like polycarbonate particles or polyphenylene oxide particles in Chapter 2. Therefore, the porosity of the EC particles was considered to be a spinodal decomposition-type phase separation mechanism. The solubility of EC in droplets was decreased by pouring water, and crystallization occurred via the metastable phase. As EC-2 and EC-3 were more likely to crystallize related to the ethoxy

contents, they were considered to have highly regular porous structures.

The linseed oil absorption test, which has been widely used in the field of pigment research, was then conducted to evaluate the pore volumes of the EC fine particles (**Fig. 3- 13**). The results clearly suggest that the pore volumes of the EC-2 and EC-3 particles are much larger than that of EC-1, which confirms the porous features. Such large pore volumes indicate that the pores are not only located at the surface, but also spread inside the particles, although direct observation of the particle interior remains challenging. To address this issue, cross sectional transmission electron microscopy (TEM; **Fig. 3- 14** and **Fig. 3- 15**) and SEM observations in combination with energy dispersive X-ray spectroscopy (SEM-EDX, **Fig. 3- 16**) were conducted. Although the pore volume of the EC-3 particles was larger than that of the EC-2 particles, the latter was used as a model for further investigations, mainly due to its morphological uniformity. EDX measurements were conducted using sodium as an indicator, which was absorbed as the salicylate salt into the fine EC-2 particles. To my satisfaction, the cross sectional SEM image of the fine EC-2 particles clearly suggests that the pores are spread inside the particles and are also overlapped with the EDX distribution of sodium (**Fig. 3- 16**). This result indicates that the pore networks were constructed throughout the particles since sodium salicylate was able to penetrate inside the pore network.

X-ray computed tomography (CT) scan analysis was performed to further study three-dimensional internal structure of the EC fine particles (**Fig. 3- 17**). In the sequential tomographical images of the internal structure of the particles, an area with an identical color indicates a continuous pore (except green, which also exhibits isolated pores at the surface). The pores observed here are macropores with diameters >50 nm, as micropores and mesopores are too small to be detected. The average pore diameter was measured to be $0.43\ \mu\text{m}$ by using mercury porosimeter (**Fig. 3- 18**), which is in good accordance with the TEM, SEM-EDX, and X-ray CT observations. This result indicates that not all the pores are connected with each other; however, many macropore networks are apparent throughout the particles, resulting in large pore volumes.

3.4 CONCLUSION

In conclusion, I have successfully demonstrated that porous and spherical biocompatible EC fine particles with a narrow size distribution can be produced by ternary system-based emulsion casting using EtOH and PVP. The two- and three-dimensional internal structures of the particles were thoroughly studied using several analytical techniques, including XRD, the linseed oil absorption test, TEM, SEM-EDX, and X-ray CT. The results clearly indicate that pore networks are constructed throughout the particles and these provide large pore

volumes. Although the mechanistic aspect remains an open question, the hydrophilicity/hydrophobicity and/or crystallinity of EC have a significant impact on the particulation process. I believe that the EC fine particles obtained in this work would be promising DDS carriers.

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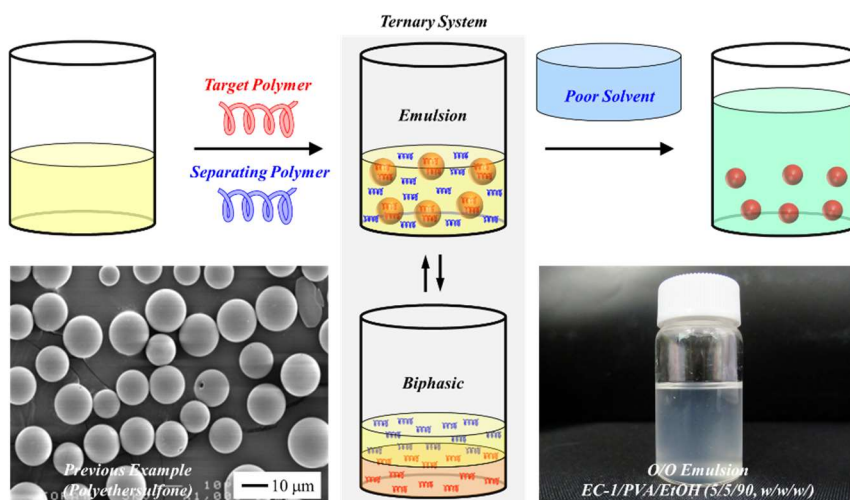


Fig. 3- 1 Schematic illustration of a ternary system.

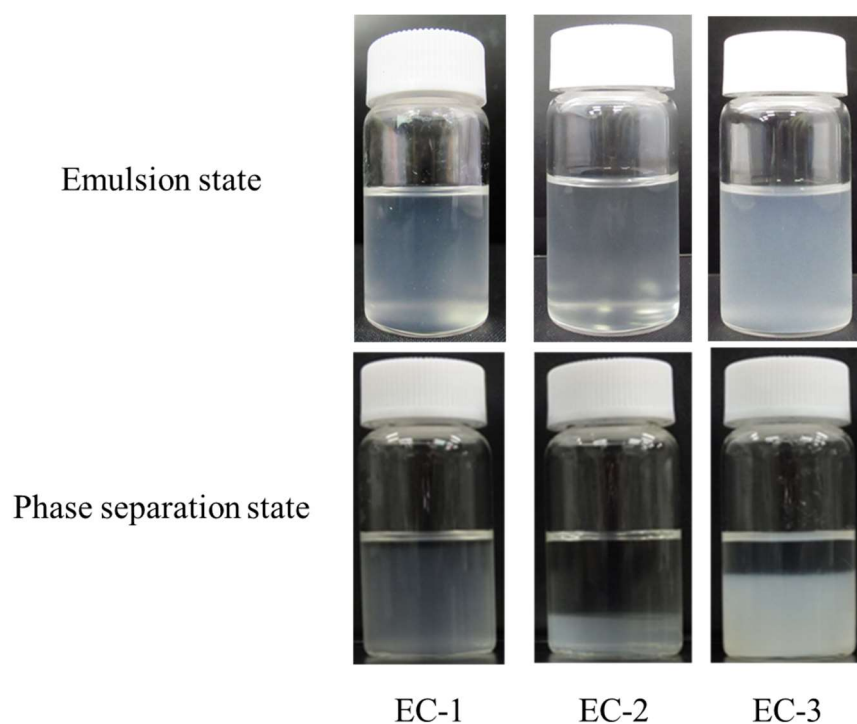


Fig. 3- 2 Photographs of the ternary system-based O/O emulsions taken at EC/PVP/EtOH= 5/5/90.

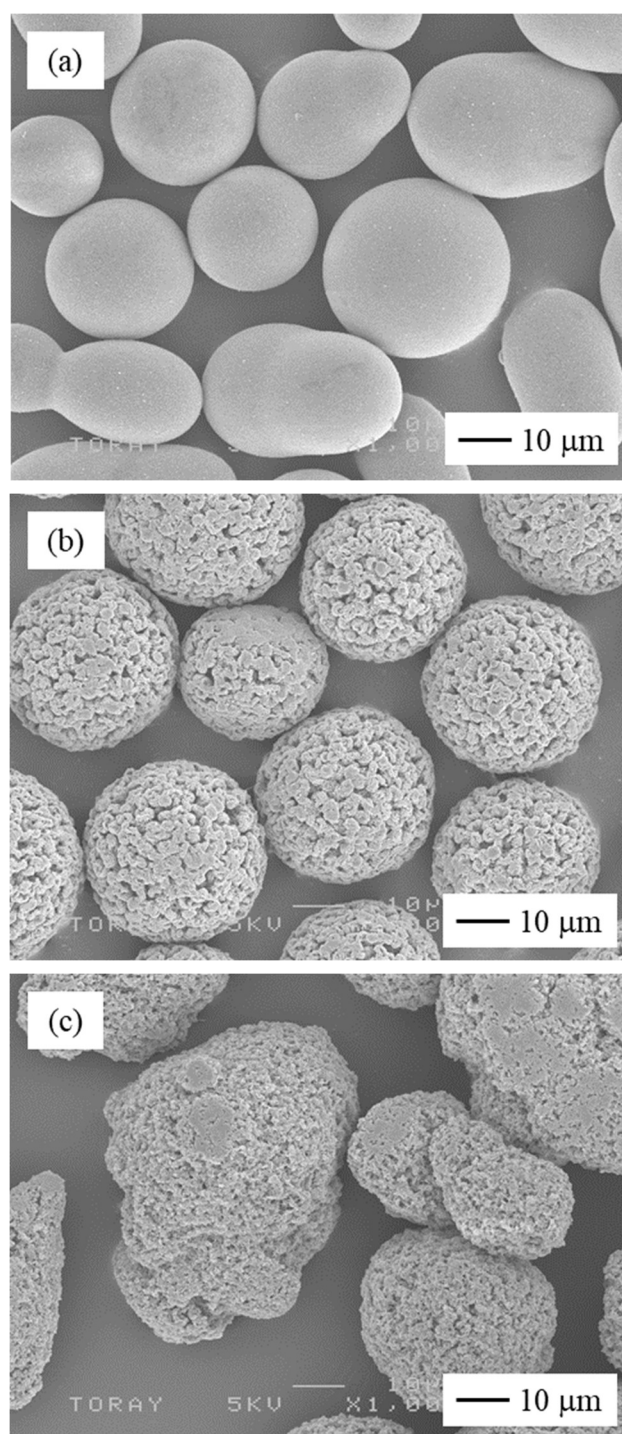


Fig. 3- 3 SEM images of (a) EC-1, (b) EC-2, and (c) EC-3 fine particles.

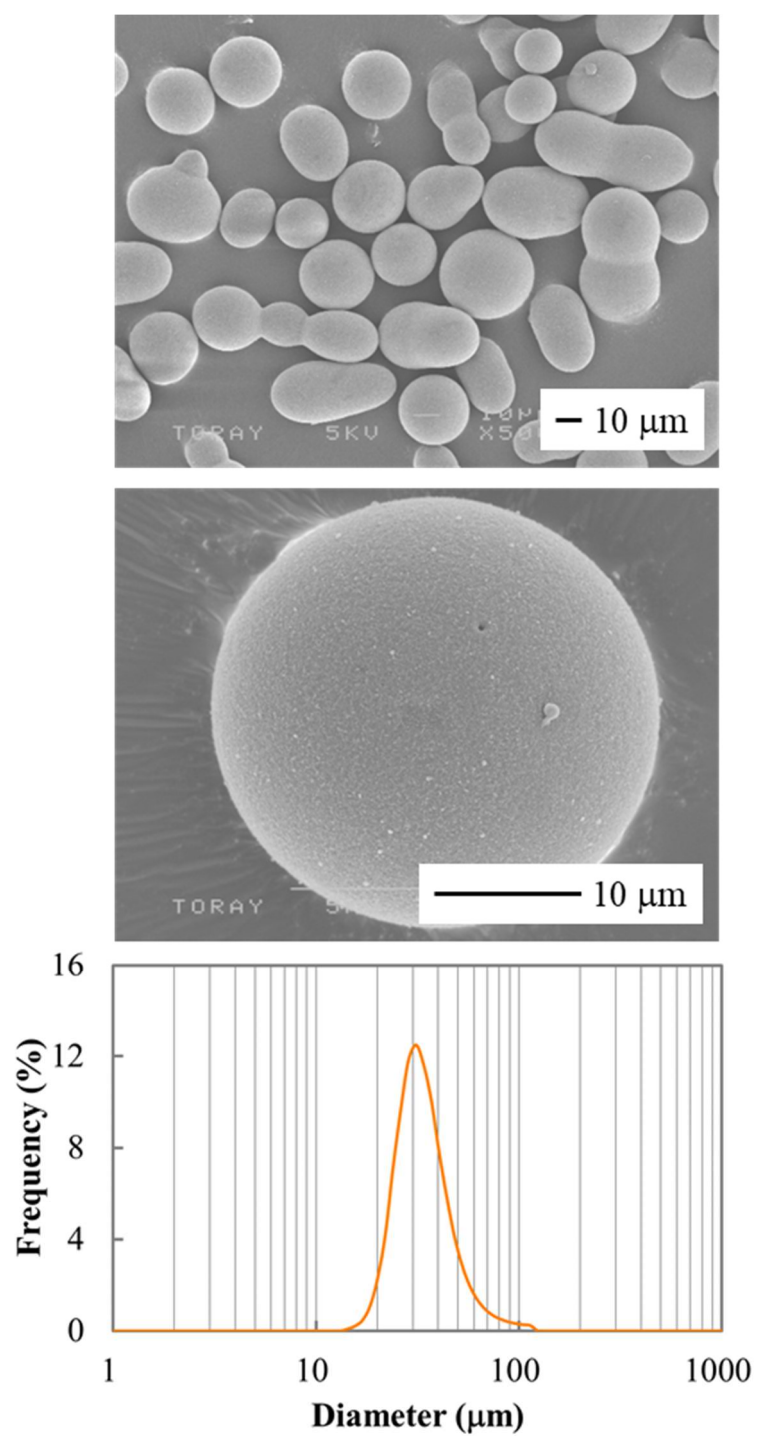


Fig. 3- 4 SEM images and particle size distribution of fine EC-1 particles.

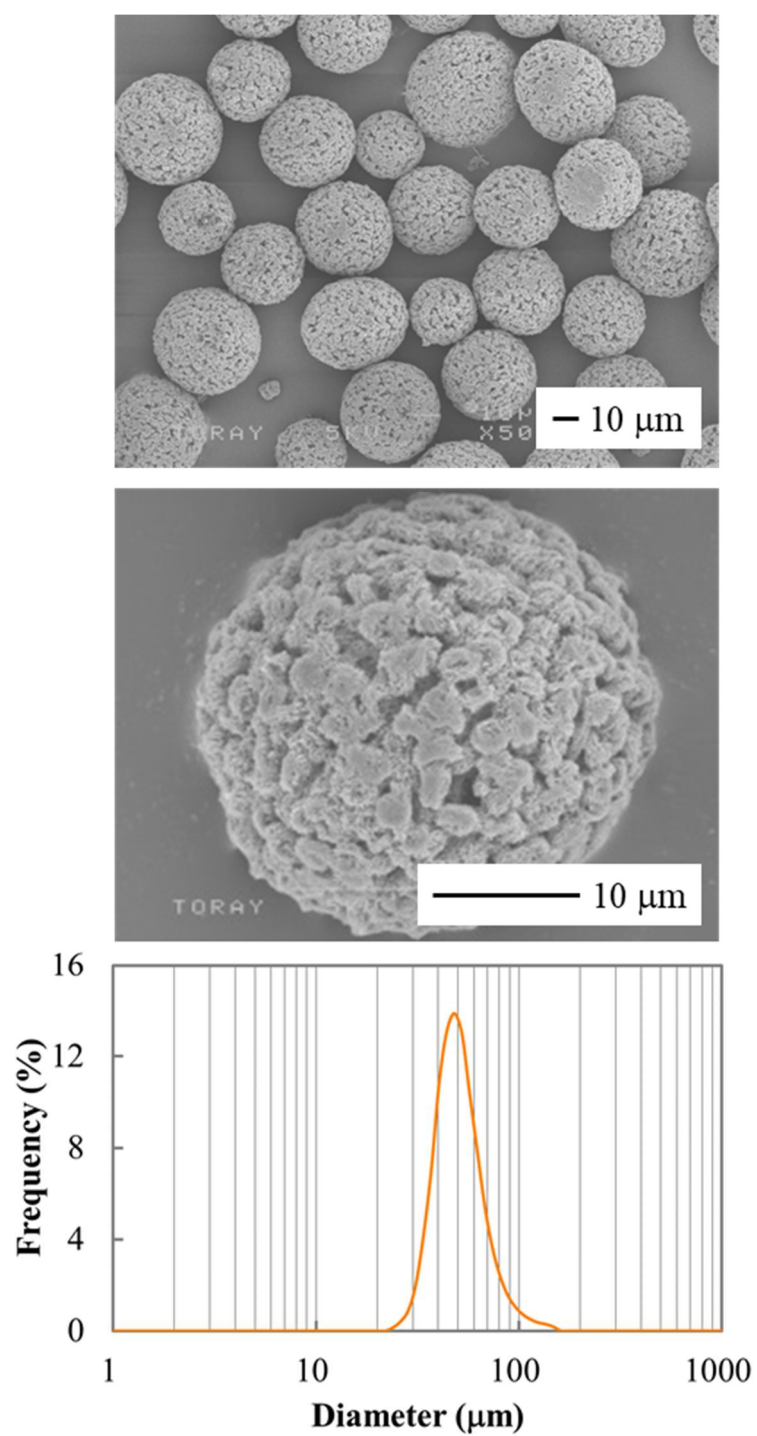


Fig. 3- 5 SEM images and particle size distribution of fine EC-2 particles.

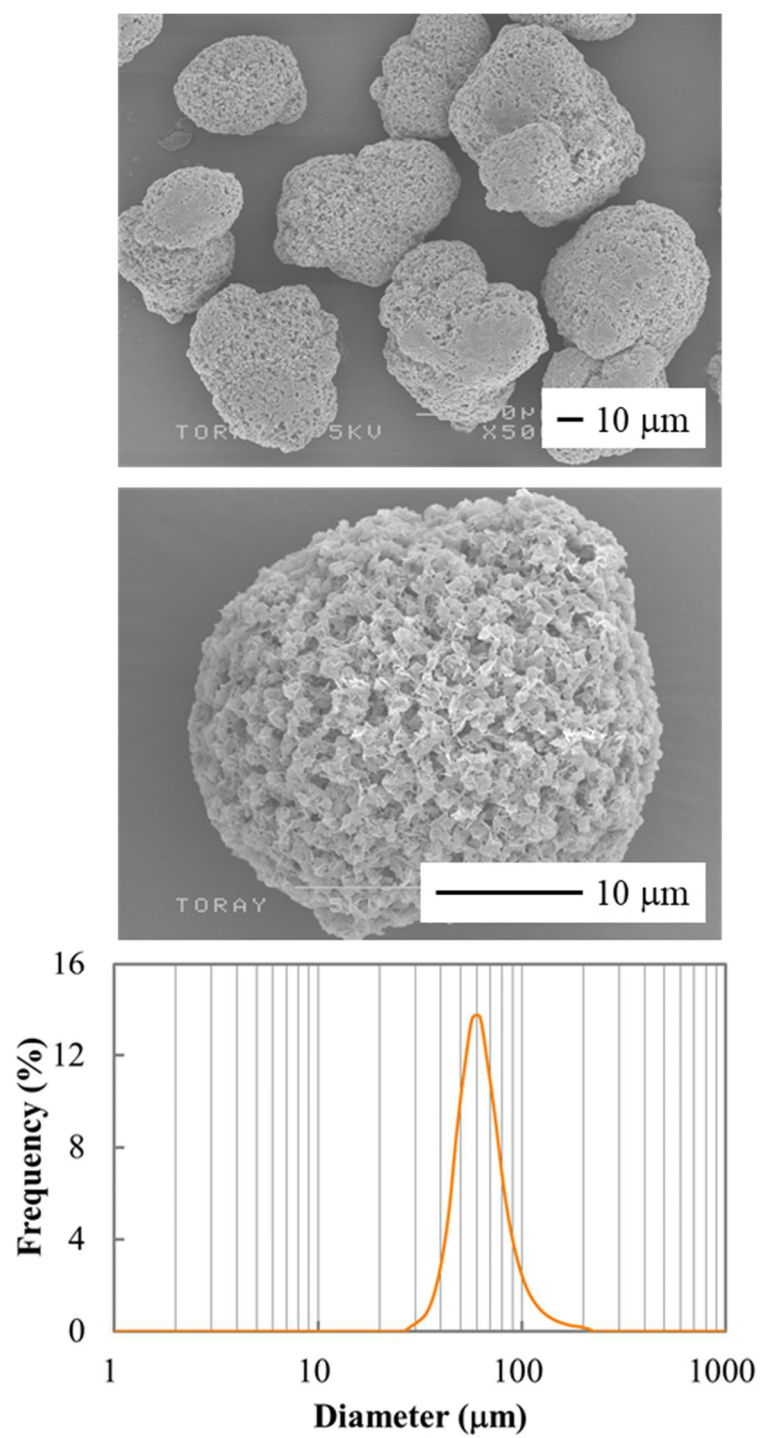


Fig. 3- 6 SEM images and size distribution of EC-3 fine particles.

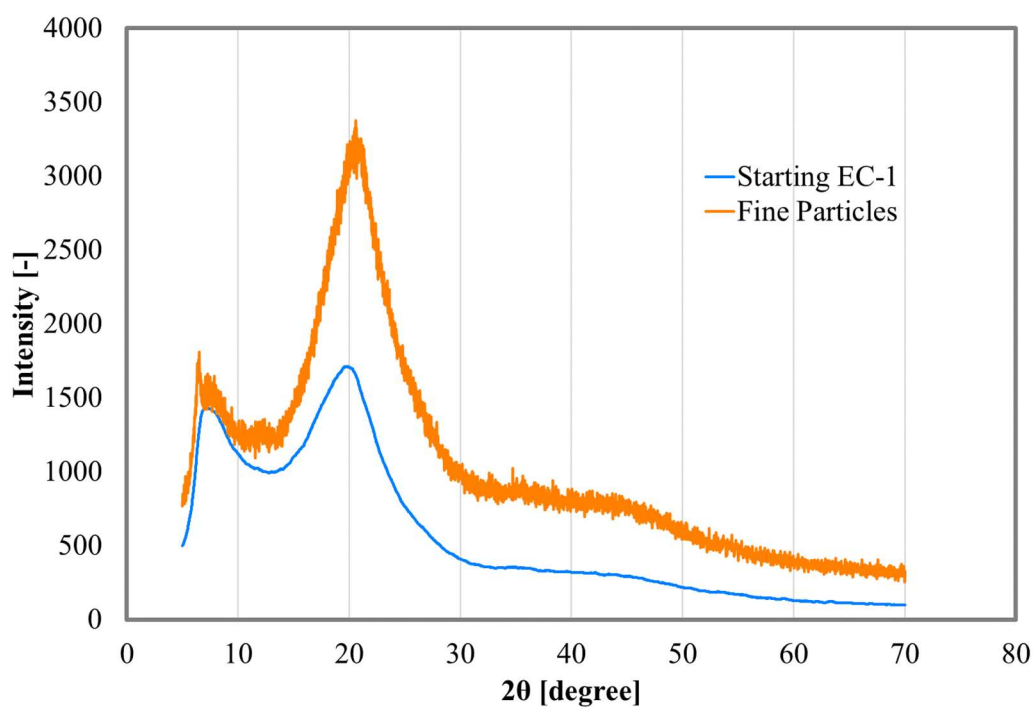


Fig. 3- 7 XRD patterns of starting polymer and its fine particles (EC-1).

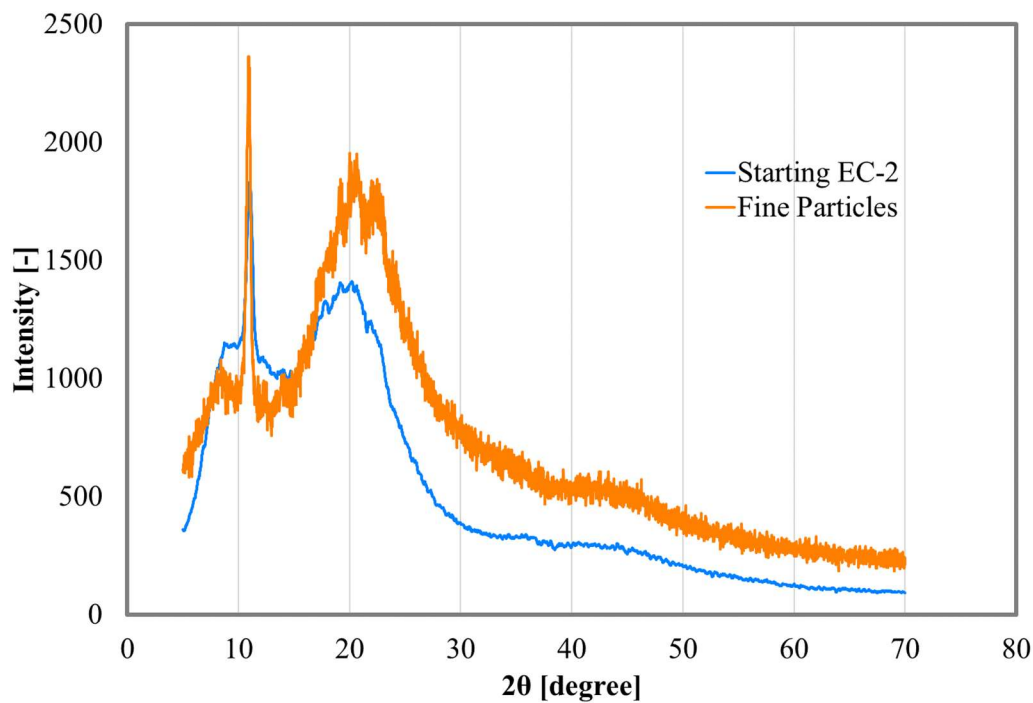


Fig. 3- 8 XRD patterns of starting polymer and its fine particles (EC-2).

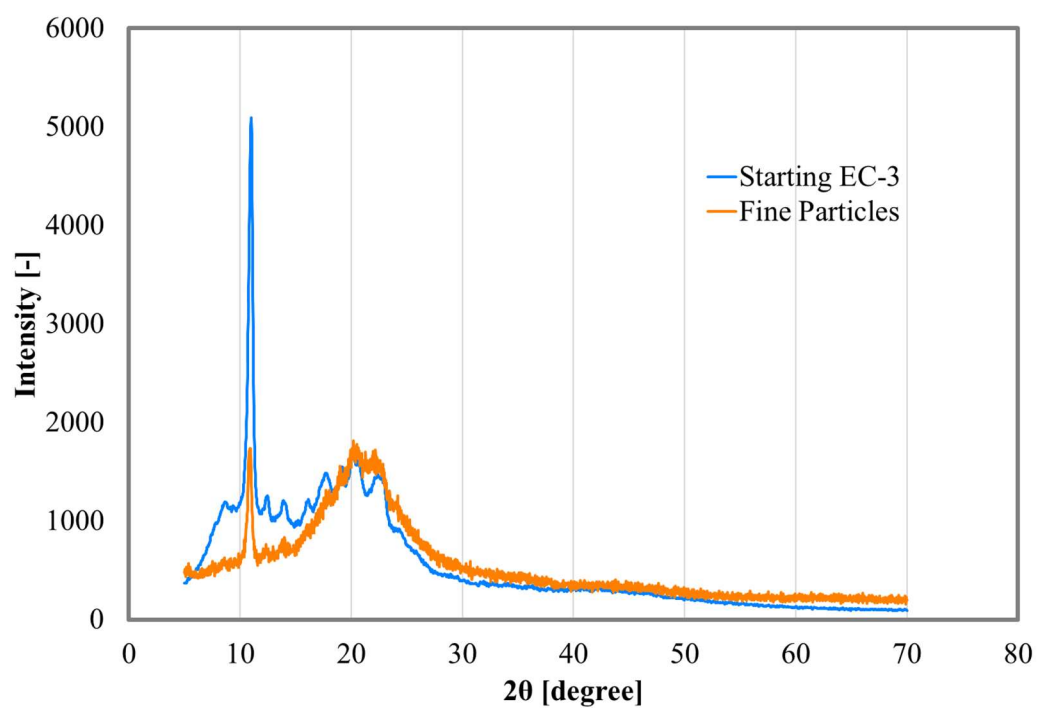


Fig. 3- 9 XRD patterns of starting polymer and its fine particles (EC-3).

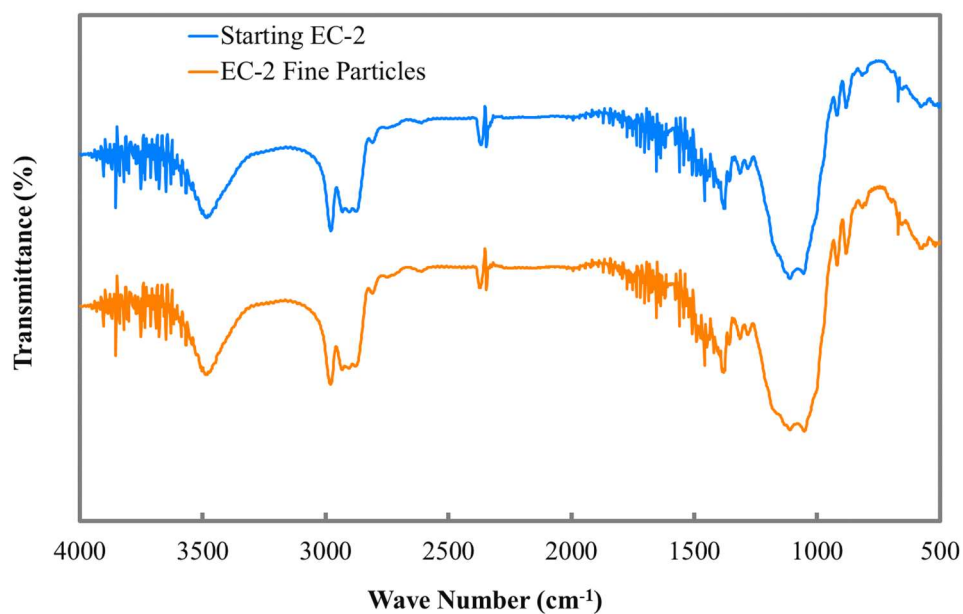


Fig. 3- 10 FTIR spectra of starting EC-2 and the fine particles.

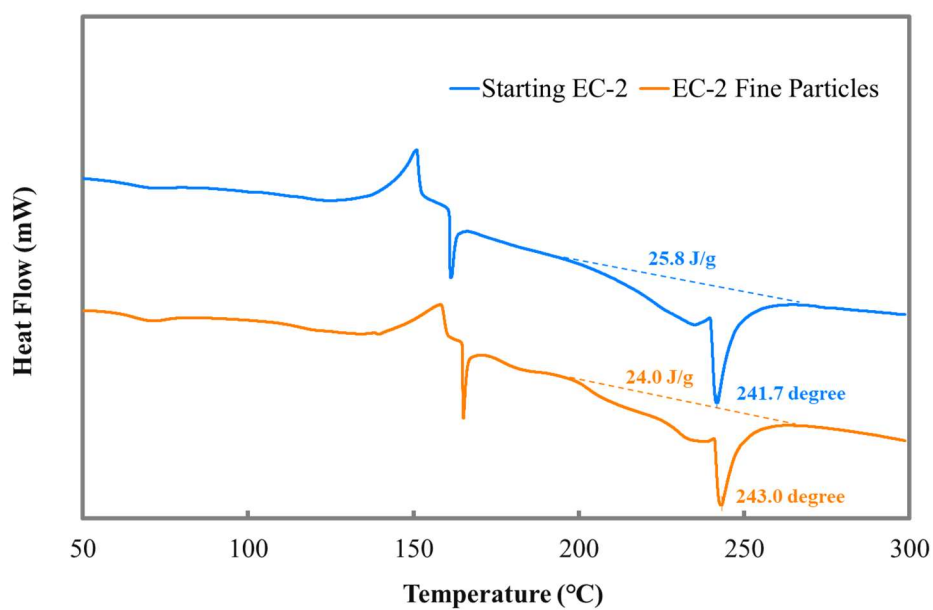


Fig. 3- 11 DSC charts of starting EC-2 and the fine particles.

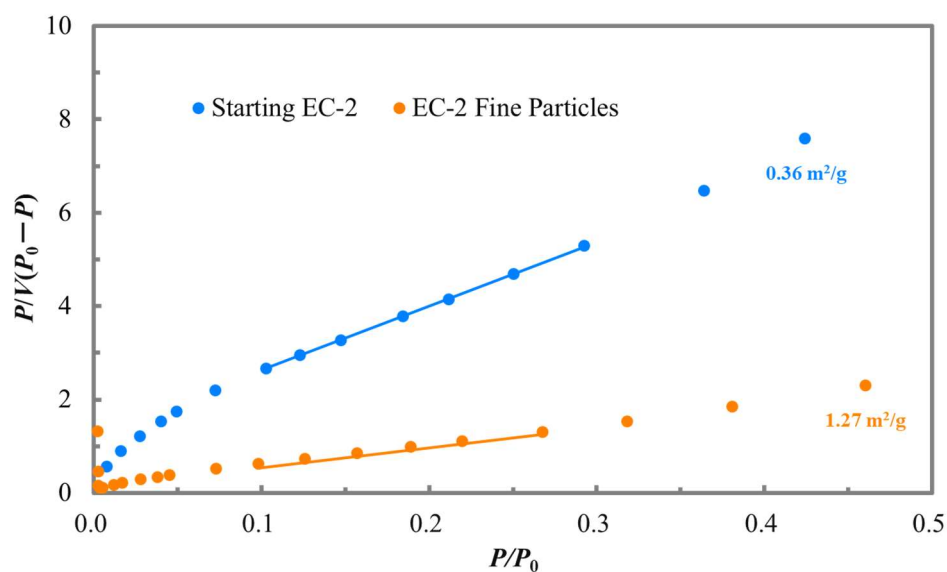


Fig. 3- 12 Adsorption isotherms of starting EC-2 and the fine particles using krypton.

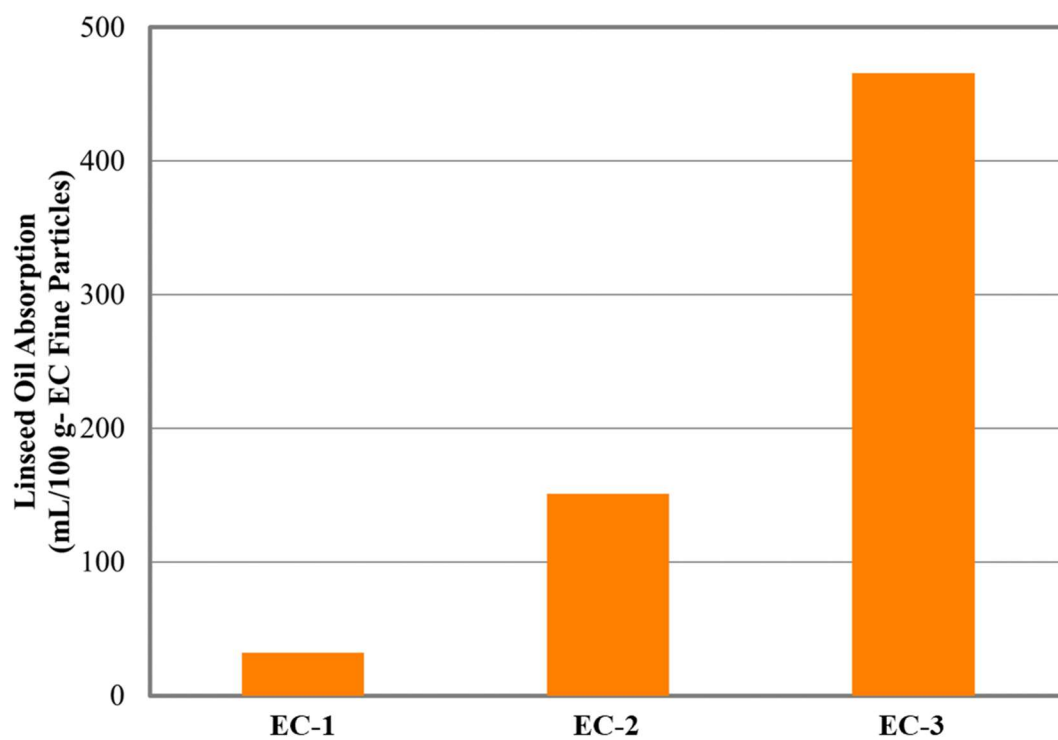


Fig. 3- 13 Linseed oil absorption test for the EC fine particles.

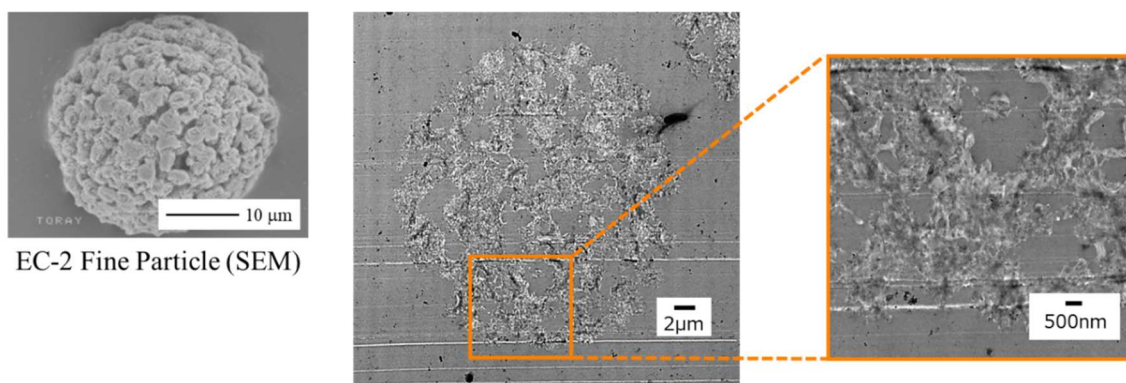


Fig. 3- 14 Cross sectional TEM images of the EC-2 fine particles.

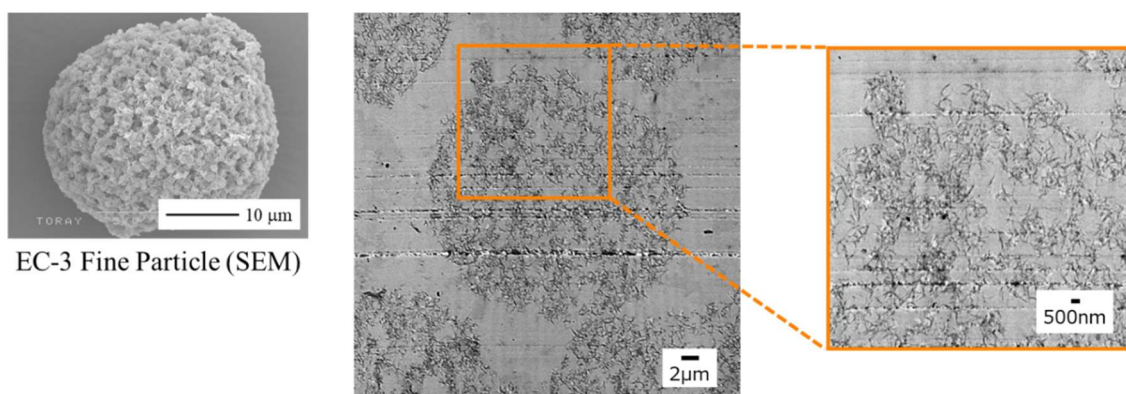


Fig. 3- 15 Cross sectional TEM images of the EC-3 fine particles.

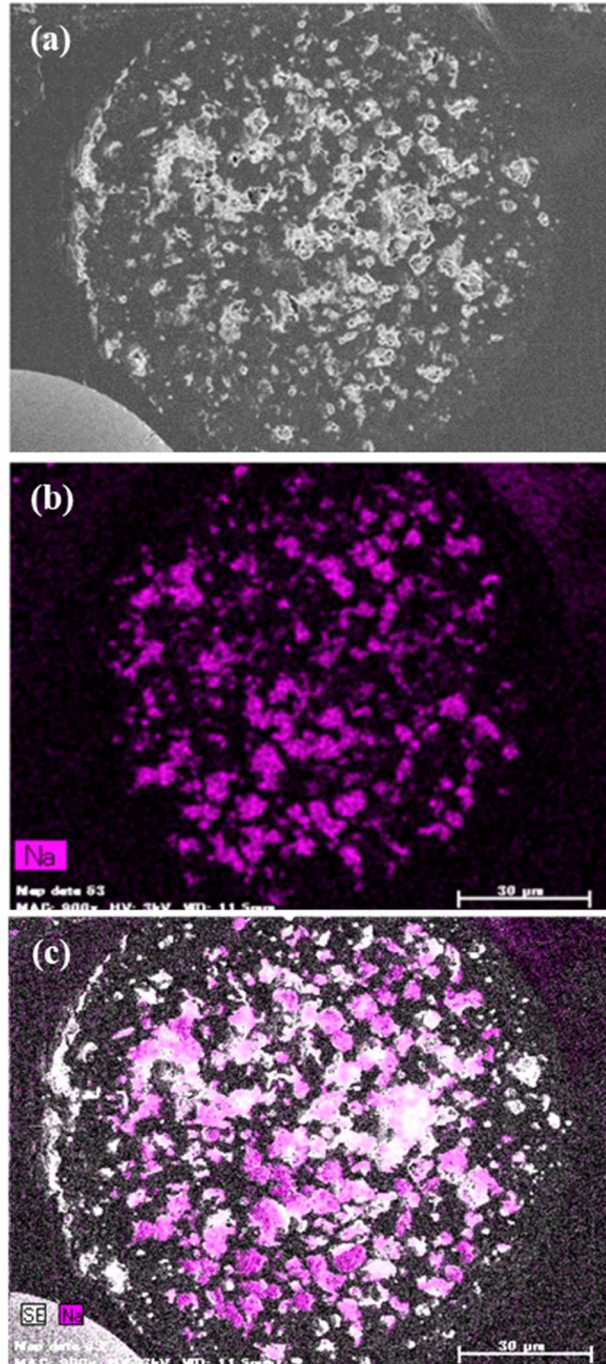


Fig. 3- 16 (a) Cross sectional SEM image of a fine EC-2 particle, and (b) EDX mapping of Na in the pores of the particle. (c) Merged SEM image and EDX map.

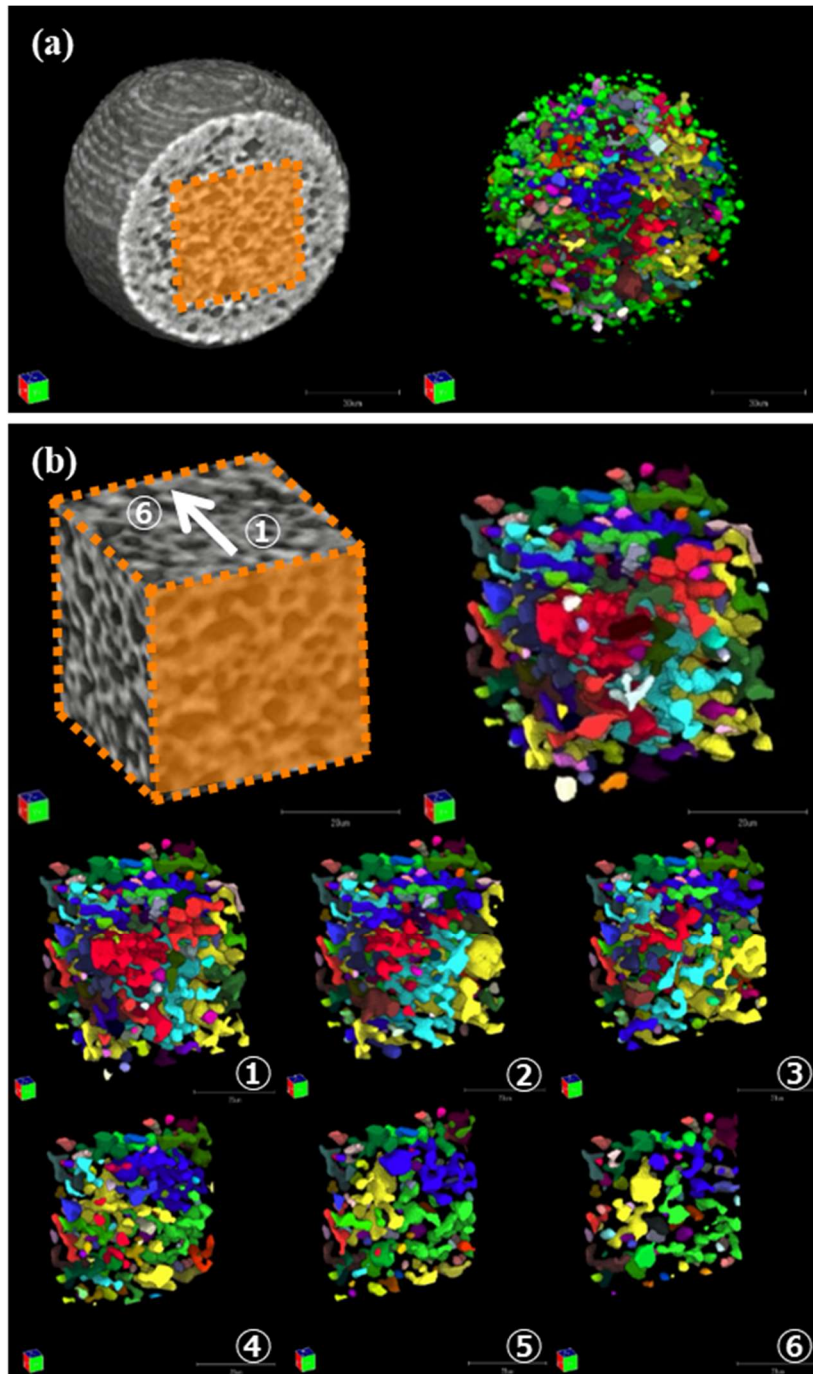


Fig. 3- 17 X-ray CT images of (a) a fine EC-2 particle, and (b) the sequential internal structure ($40 \times 40 \times 40 \mu\text{m}$).

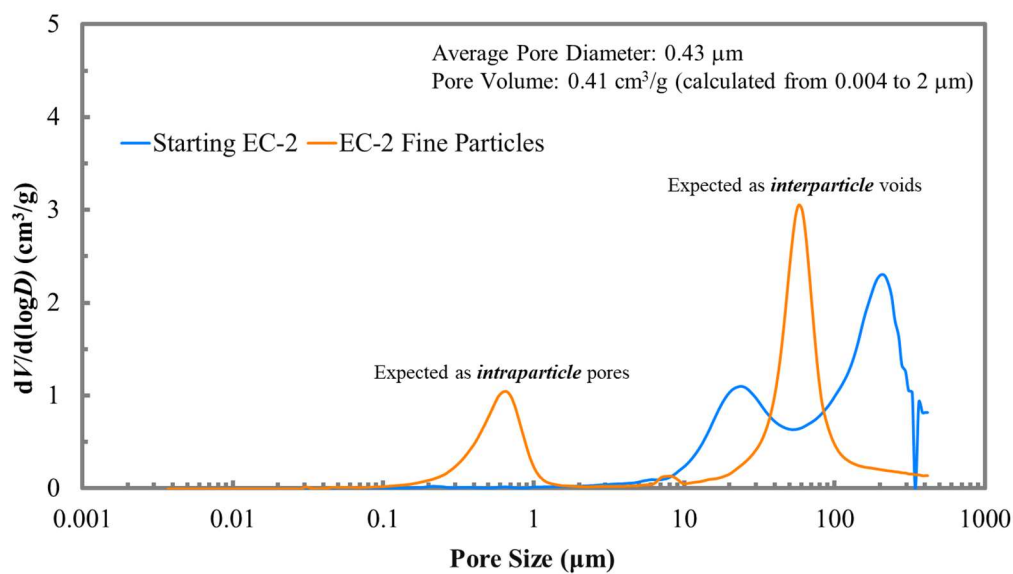


Fig. 3- 18 Porosity distributions of starting EC-2 and the fine particles measured by mercury porosimeter.

Table 3- 1 Ethyl cellulose samples used in this work.

	Ethoxy content (wt%)	Viscosity (mPa•s) ^a
EC-1	45.8	42
EC-2	49.0	47
EC-3	50.3	41

^aMeasured as 5 wt% solution in toluene/ethanol (80/20, w/w) at 25 ° C

CHAPTER 4

PIGMENT ENCAPSULATED SPHERICAL POLYMER PARTICLES PREPARED BY TERNARY SYSTEM-BASED EMULSION CASTINGS

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4.1 INTRODUCTION

Pigments are insoluble coloring powders that have been applied primarily to paint, cosmetics, or synthetic resins. The powders are affected by pH alternation, ultraviolet light, and other disturbances, and various methods for encapsulating pigments have been developed to prevent disturbances. Pigments hardly dissolve or disperse in the most conventional organic solvents; therefore, O/W emulsions cannot be used to encapsulate them in a polymer matrix. Several studies on this topic have been conducted.

Emulsion polymerization [1-2], mini-emulsion polymerization [3-5], surface medicated on pigment polymerization [6-9], sol-gel spray drying method [10], dry hybrid method [11], and phase separation method [12, 13] are well-known methods for encapsulating pigments. In particular, the method of containing pigments in the oil-in-water emulsion made by a monomer followed by its polymerization is one of the most typical encapsulation techniques.

The method to polymerize the monomer emulsion, which is used as castings to encapsulate a pigment, is quite different for the molecular structure of each pigment. Therefore, it is necessary to design a polymerization technique and choose an adequate monomer according to each pigment; thus, the polymers used for the encapsulation matrix are limited.

A novel method was developed to prepare polymer particles using a ternary emulsion system as castings [14, 15]. The ternary system emulsion, which is an emulsion using the phase separation phenomenon called Scott System [16], is composed of two polymers (polymers 1 and 2) whose polarity is different, and dissolved in a solvent at a specific ratio, and mixed to form an emulsion. Moreover, a polymer particle is formed by adding a poor solvent of polymer 1 to the emulsion and solidifying polymer 1 selectively from the emulsion. This is a polymer particle preparation method using the ternary system emulsion casting method. In general, the preparation of engineering polymer particles is difficult because engineering polymers can only dissolve in a polar solvent, hindering the formation of an oil-in-water emulsion. The author has successfully demonstrated the preparation of engineering polymer fine particles with a ternary system emulsion, which can be considered an oil-in-oil emulsion.

Therefore, in this study, as a new method to encapsulate pigments in polymer particles, spherical pigment-encapsulated polymer particles were prepared using a ternary system emulsion with a transparent polymer as the matrix and a polar solvent (**Fig. 4- 1**).

In this trial, acrylonitrile-butadiene-styrene (ABS) was chosen as a transparent matrix

polymer because of its availability, usability, and versatility, and a few coloring pigments with different chemical structures were selected.

4.2 EXPERIMENTAL

4.2.1 Materials

ABS, “Toyolac” T-500 supplied by Toray Ind. Inc, selected as matrix polymer 1, has transparency and was used to encapsulate and prevent color development of a pigment. As polymer 2 for a phase separation polymer, polyvinyl alcohol, “Gohsenol” GL-05, supplied by The Nippon Synthetic Chemical Industry Co. Ltd., which is hydrophilic and has a polarity different from that of ABS, was used. *N*-methylpyrrolidone (general grade supplied by Mitsubishi Chemical Corporation) was employed as a solvent to dissolve both polymers. Ion-exchanged water was used as a poor solvent to solidify the ABS. Four pigments shown in **Fig. 4- 2**, which are representative pigments and used with versatility, were selected to demonstrate their encapsulation into ABS polymer particles. The particles of these pigments were determined by image analysis to have 0.2 to 0.5 μm of diameter.

4.2.2 Representative production method for pigment encapsulated spherical polymer particles

A total of 2.5 g of ABS as polymer A, 45 g of *N*-methyl-2-pyrrolidone as an organic solvent, 2.5 g of polyvinyl alcohol as the polymer B, and 25 mg of pigment (**Table 4- 1**) were placed in a 100-ml four-neck flask. In sequence, the mixture was heated at 80 °C and stirred for 2 h until the polymer dissolved. After forming an O/O emulsion with pigment, 50 g of ion-exchanged water were added at 0.42 g/min via feed pump while maintaining at 80 °C and stirring. Next, ABS was precipitated to form the particles, and the slurry solution of ABS particles was filtered and washed with hot water at 80 °C three times. The separated wet particles were vacuum-dried at 80 °C overnight, thereby providing pigment-encapsulated polymer particles. The yield was calculated from the ratio of the weight of the isolated materials to the total weight of the added polymer and the pigment.

4.2.3 Evaluation method of pigment encapsulated polymer particle

The average particle diameter was measured by laser diffraction analysis (Nikkiso, Microtrac MT3300 EX II) in water. To observe the particle shape or encapsulation conditions of the pigment, a digital microscope (Keyence, VHX-5000) was used. The properties of the particles were examined by field-emission scanning electron microscopy (FE-SEM, JEOL, JSM-6301NF) after Pt vapor deposition. To confirm the pigment dispersion condition in the particle, the particle cross section was observed using FE-SEM

(Hitachi, H-7100). The cross-section was prepared by embedding a pigment-encapsulated particle in an epoxy resin, cutting an ultra-thin section to a thickness of 80 nm, and then staining the pigment parts of the section with osmium tetroxide and ruthenium tetroxide. The amount of encapsulated pigment in ABS particles was determined by dissolving a pigment-encapsulated particle in NMP, pouring the solution into a cell for optical analysis with an optical path length of 10 mm, and measuring the absorbance using an ultraviolet-visible-infrared spectrophotometer (JASCO, V-560). Each pigment was dissolved in NMP and diluted adequately to obtain a proportionality of absorbance to concentration, and the pigment concentration was measured with a calibration curve at maximum absorbance of a pigment. The encapsulation efficiency was calculated as the ratio of the weight of an encapsulated pigment, which was measured above the method and the weight of the raw material used.

To distinguish the encapsulating property of a pigment, the water wettability of the pigment was evaluated by measuring the contact angle between water and the pigment. A pigment was filled in a round mold with a diameter of 1.3 cm, and a pigment tablet was formed with a load of 6 t in a vacuum. A pigment tablet contact angle meter (Kyowa Interface Science, DM-501) was used to measure the contact angle of a drop of water on a pigment tablet. A press film of a pigment-encapsulated particle was demonstrated as a practical application, compared to that made from the dry-blending powder of pigment and ABS particles. The press film method was as follows: approximately 100 mg pigment-encapsulated particles were held between aluminum foils (thickness of 100 μm). Then, the aluminum foil was placed between the iron plates at 200 °C and 30 MPa for 2 min. Subsequently, the foils were removed from the plates and cooled. The appearance of the obtained films was compared. The relationship between additive volume and encapsulation volume was evaluated with Pigment Blue 15 as a representative example by preparing a particle with 5 to 15% pigment using the method described in Section 4.2.2, and the encapsulating volume was determined using the abovementioned method with optical analysis.

4.3 RESULTS AND DISCUSSION

4.3.1 Property of the pigment encapsulated polymer particle

Four pigments were selected and each pigment-encapsulated polymer particle was prepared by adding 1% pigment. The particle diameter distribution graph of a pigment-encapsulated ABS particle is shown in **Fig. 4- 3**. The encapsulation yields and encapsulation efficiency by measuring the pigment concentration after dissolving the particles in NMP are shown in **Table 4- 1**. The obtained pigment-encapsulated polymer particles had an average

volume particle diameter of approximately 20 to 30 μm , which was larger than that of normal ABS polymer particles except Pigment Yellow 110, in which the encapsulated weight was 63%. In addition, these particles had similar lognormal distributions and showed relatively sharp particle distributions. Pigment IV had a relatively larger average particle diameter, and the particle diameter distribution tended to be broad.

The observation results of the particles by digital microscope are shown in **Fig. 4- 4**. All the particle states of the images correspond to the particle distributions in **Fig. 4- 3**.

The observed pigment-encapsulated ABS particles had spherical shapes in the case of Pigments I, II, and III. It was observed that each pigment was present in each particle. However, in the case of Pigment IV, the pigment was not included in the ABS particles, and rather it existed outside the surface of the particles. The unencapsulated pigments affected the mode average diameter and particle diameter distributions.

The SEM images are shown in **Fig. 4- 5**. The particles that included pigment blue I, pigment II, and pigment III had smooth surfaces and true spherical shapes. No pigments could be recognized outside the polymer particles. Thus, it was considered that all pigments were located inside the particles. Alternatively, dozens of pigments seemed to exist outside of the particles in the case of Pigment Yellow 110. As the solubilities of the pigments are low, the pigments were considered to disperse as tiny pieces-states in the emulsion in which particles emerged. Hence, it was considered that the surface of the pigments affected this condition.

TEM cross-section observations of pigment I-encapsulated particles are shown in **Fig. 4- 6**. Black tiny particles are polybutadiene particles, and white particles are pigment I particles. In this figure, pigment I appears to be well dispersed in the matrix ABS resin.

To determine the existing condition of Pigment IV inside the particle, the complete aspect and a cross section of the particle were observed with STEM-EDX and are shown in **Fig. 4- 7**.

As a result, the chlorine atoms that were characteristically derived from the molecular structure of Pigment IV are indicated as yellow color in the images. It was evident that Pigment IV was located outside of the particles.

To demonstrate a practical application, a colored polymer sheet was prepared from a pigment-encapsulated polymer particle with Pigment I using a versatile thermal press method. A colored polymer sheet was also prepared from dry blend mixed powders with Pigment I powder and ABS fine polymer particles as a comparative example. The results of the aspects of the sheets are shown in **Fig. 4- 8**. In the case of the pigment encapsulated particles, the sheet from which blue color comes out could be obtained in only 1% pigment, and the color appearances of the sheet were homogeneous. On the contrary, in the case of

dry blend mixed powders with Pigment I powder and ABS particles, the sheet had a striped pattern in the perimeter, and the center had a dark color. Overall, the color appearance of the sheet was heterogeneous.

The distinction of fluidity between pigment and ABS in thermal press at 200 °C caused only ABS to flow from the center of the film, Pigment I remained there, and a heterogeneous film was formed. In contrast, in the case of pigment-encapsulated particles, a homogenous polymer film was formed because the encapsulated pigment flowed with melt ABS at the same time.

4.3.2 Relationship of pigment species with encapsulation state

To consider the phenomenon of changes in the pigment encapsulated state depending on pigment species, the author focused on the affinities of pigments to ABS resin. First, the phase separation behavior of the O/O emulsion was observed. Although the O/O emulsion of the Scott system is very stable, resting for a long time allows separation into macro phases. The separating states after rest are shown in **Fig. 4- 9**.

The upper phase was an ABS-contained-NMP phase and the lower phase was a PVA-contained-NMP phase. In the case of Pigments I, II, and III, the upper phases were highly cloudy and the lower phases were transparent, such that these pigments appeared to be distributed into the ABS contained-NMP phase. In contrast, Pigment IV appeared to distribute to the lower phase more than the upper phase because of its transparency. As the solvent of both phases was NMP, the author supposed that pigment distribution could be attributed to the affinity of the pigments to ABS or PVA. The differences in the affinity would be considered to affect the differences in the degree of pigment encapsulation in the ABS particles.

To evaluate the affinities of each pigment with ABS or PVA, the surface energies were determined from the contact angles to water with the pellets of the pigments using the Young-Dupré equation (1) (**Fig. 4- 10**). Pellets were prepared using the compression molding method. The results are shown in **Table 4- 1**:

$$W_{SL} = \gamma_L (1 + \cos \theta), \quad (1)$$

where γ_L is the surface tension of water, 72.75 mN/m, θ is the contact angle between the pigment palette and water, and W_{SL} is the free surface energy of each pigment.

ABS and PVA had free surface energies of 66.41 mN/m and 132.34mN/m, respectively. The surface tension of Pigment IV was the highest and closest to that of PVA among the four pigments. The values of the surface tension decreased in the following order; Pigment III, Pigment I, Pigment II, and Pigment III, which was the closest to that of ABS. The closer the

surface tension of the pigment to ABS, the greater the affinity of the pigment for ABS. These results suggest that the encapsulating efficiency increased. As the upper and lower phases had a common solvent in this system, a polymer property was considered to affect the encapsulation efficiency of the pigment. To the best of our knowledge, no research reports related to the distribution phenomenon of a dispersoid in a polymer solution of a polymer/polymer/solvent system were found; thus, the theoretical clarification is a future task. The authors believe that the results of this study are a starting point to clarify these aspects.

4.3.3 Effect to an encapsulated particle state with added weight of pigment

The particle aspects were evaluated when the added weights of the pigments increased by up to 15 % with Pigment I, which were rarely observed outside of the particle in the 1% pigment using a digital microscope. The results of the encapsulation weight% and the encapsulation efficiencies are shown in **Table 4- 2** and the particle size distributions of the encapsulated particles are shown in **Fig. 4- 11**.

In this examination, when a pigment that had a high affinity with ABS was used, the dependency on pigment encapsulation for the pigment concentration was low. A total of 77% of the pigment was encapsulated when 15% of the pigment was added. Therefore, increasing the pigment weight did not seem to affect the encapsulation result. In contrast, the average particle size increased, and the particle size distribution became wider as the added pigment weight was increased. The viscosity of the polymer solution increased with increasing pigment weight. When the viscosity increased, the same stirring condition of the emulsion was not sufficient to prepare the particles because of the lack of shear force for micronizing the emulsion size. The lack of shear force caused the emulsion size to be larger, the particle size distribution was estimated to be wider, and the average particle size seemed to be larger. The mode particle diameter and its distribution may be controlled within a certain range by adjusting the shearing force with a stirring speed or stirring blade pattern.

Consequently, when the pigment disperses well in hydrophilic solvents such as NMP, and when the surface energy of a polymer close to that of the pigment is selected or the wettability of the pigment can be controlled, this methodology enables the encapsulation of a pigment over a wide concentration range. This methodology can also be applied to encapsulate other functional materials into polymer particles.

4.4 CONCLUSION

By applying the polymer particle preparation method using O/O emulsion, Pigment Blue 15, Pigment Red 177, and Pigment Red 254 were successfully encapsulated in ABS particles

at a concentration of 0.8 to 1%. Further, Pigment Blue 15 was confirmed to encapsulate up to 11.6% of ABS particles. In contrast, in the case of Pigment Yellow 110, many pigments were detected outside the ABS particles, and the encapsulation was not successful. As the affinity between polymers and pigments seemed to affect the encapsulation efficiency, the surface energies of ABS, PVA, and pigments were evaluated by measuring the contact angles of each material with water.

As a result, the smaller the difference in the surface free energy of the pigment with ABS, the more pigment tended to be encapsulated in the ABS particle. The author considered that it was successful to obtain an elementary guideline for encapsulating a pigment into polymer particles.

The key point of this method is the difference in the surface free energy of the polymers. Therefore, this method could be applied to other functional materials to encapsulate polymer particles by controlling their surface energy.

4.5 REFERENCES

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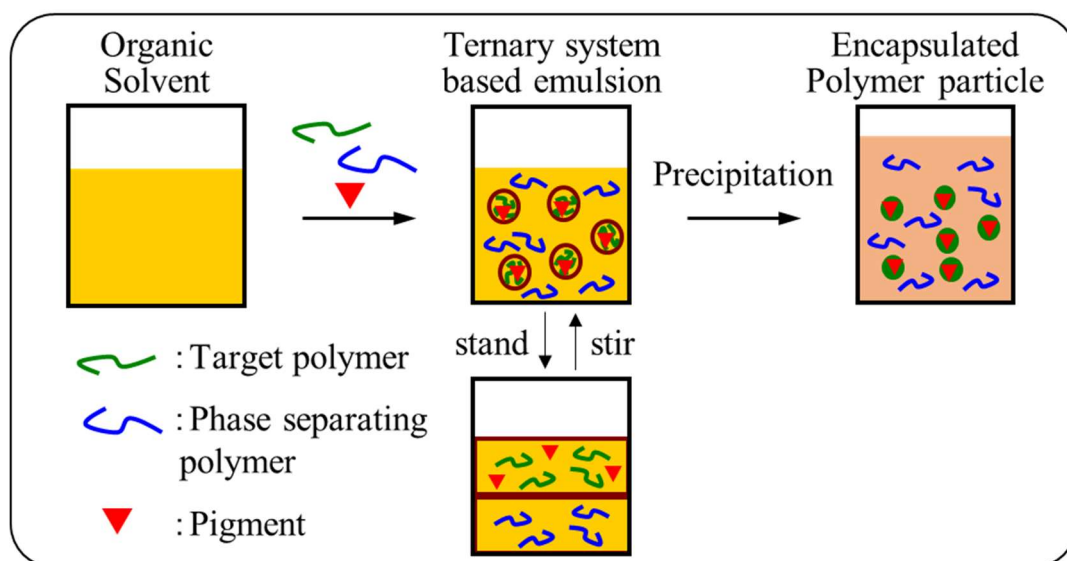
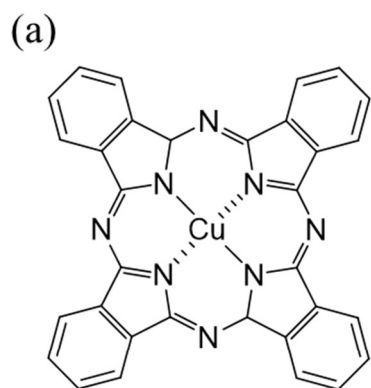
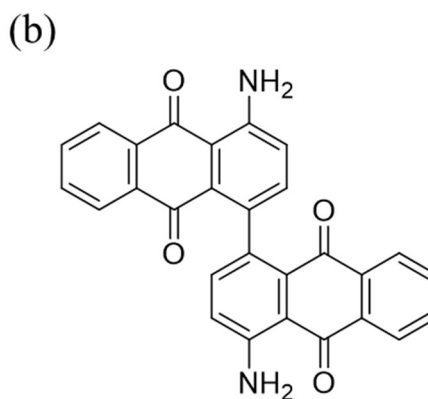


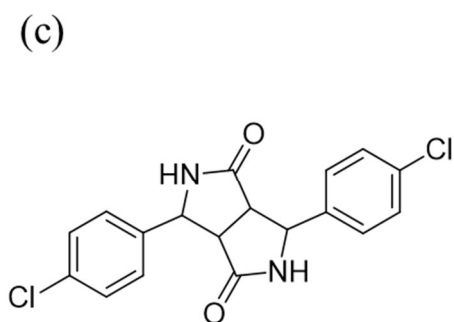
Fig. 4- 1 Concept of spherical polymer particles preparation and encapsulation of pigment particles in polymer particles by using Ternary system-based emulsion casting.



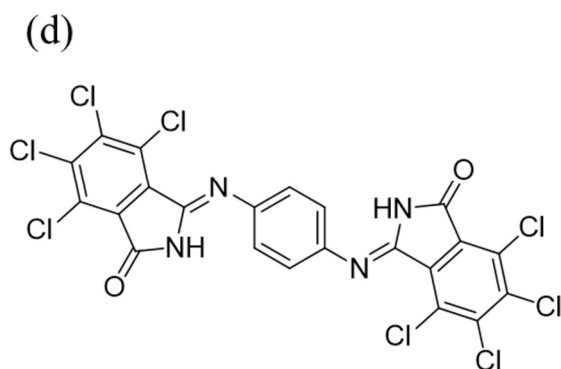
Copper(II) phthalocyanine



4,4'-Diamino-[1,1'-bianthracene]-
9,9',10,10'-tetraone



3,6-Bis(4-chlorophenyl)-2,5-
dihydropyrrolo[3,4-c]pyrrole-1,4-
dione



3,3'-(1,4-Phenylenediimino)
bis[4,5,6,7-tetrachloro-1H-
isoindol-1-one

Fig. 4- 2 Chemical structures of pigments (a) I (Pigment Blue 15), (b) II (Pigment Red 177), (c) III (Pigment Red 254), and (d) IV (Pigment Yellow 110).

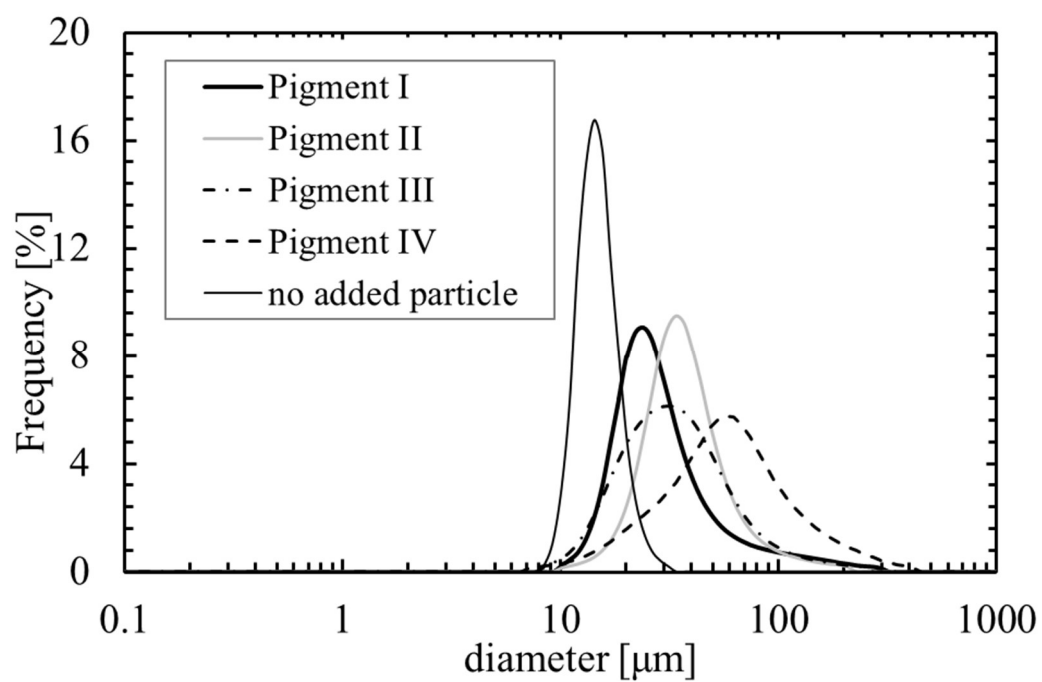


Fig. 4- 3 Effect of pigment materials on particle diameter distribution of pigments-encapsulating composite polymer particles.

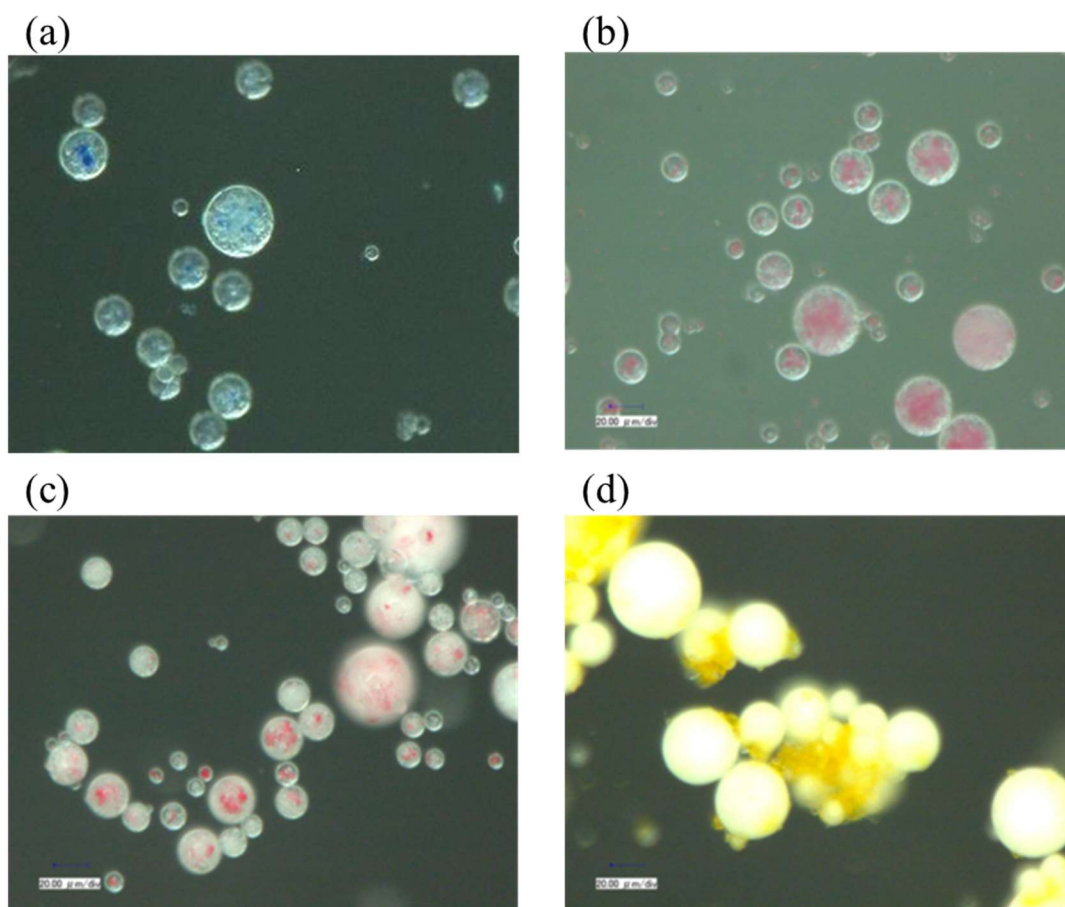


Fig. 4- 4 Digital microscope images of pigment encapsulated ABS spherical particles (a) Blue, (b) Red (c) Red and (d) Yellow. Amount of pigment added in each particle preparation was about 1 mass%.

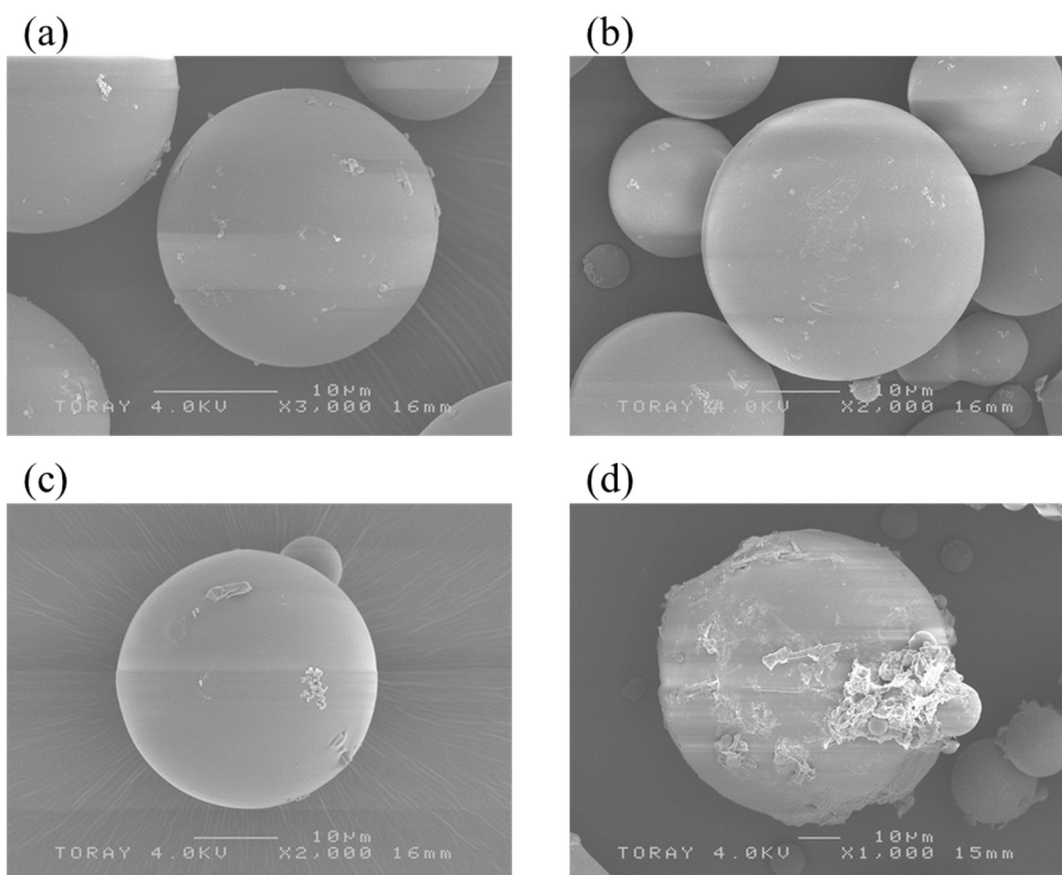


Fig. 4- 5 SEM observation of pigment encapsulated ABS spherical particles in Fig. 4 (a) I (Pigment Blue 15), (b) II (Pigment Red 177), (c) III (Pigment Red 254), and (d) IV (Pigment Yellow 110).

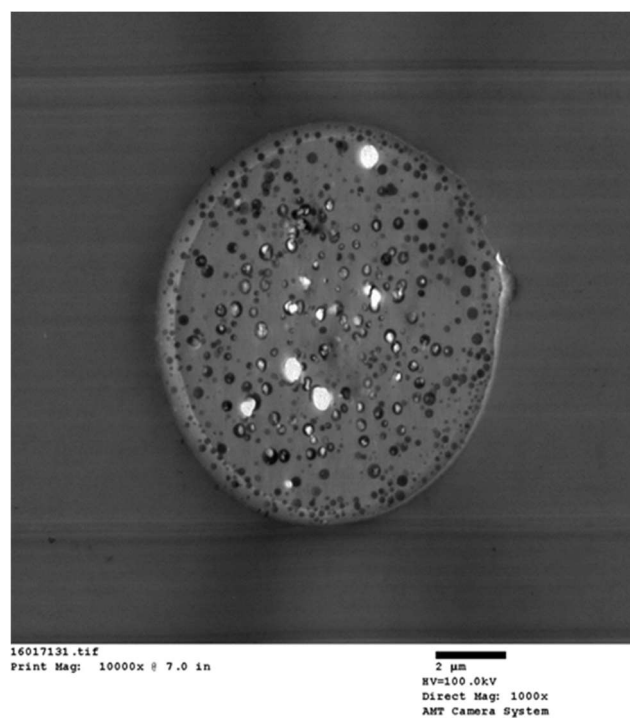


Fig. 4- 6 TEM cross section observation of pigment I encapsulated particles.

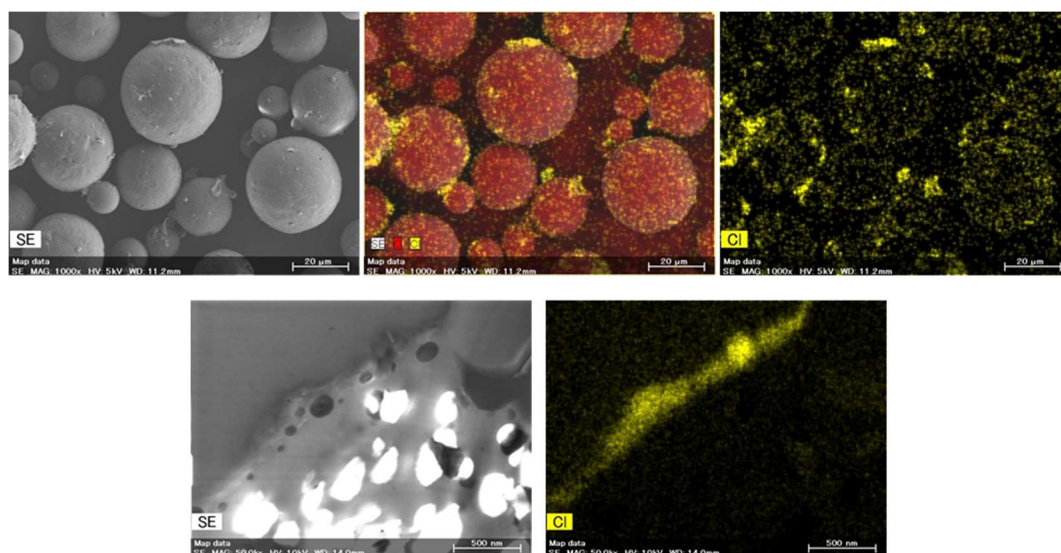
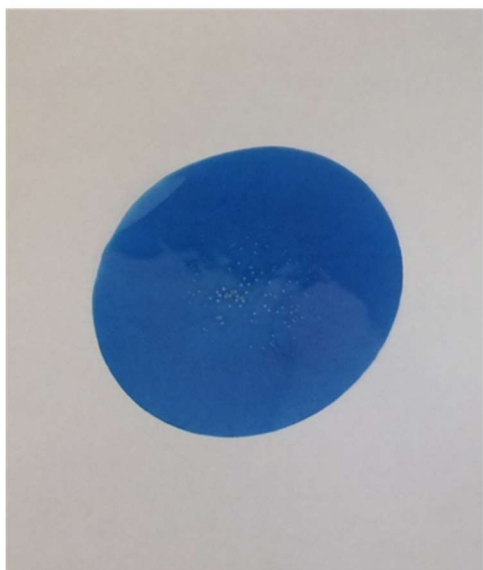


Fig. 4- 7 STEM-EDX observation of pigment IV encapsulated particles. (Upper row: whole particle images, lower row: cross section images).

(a)



(b)

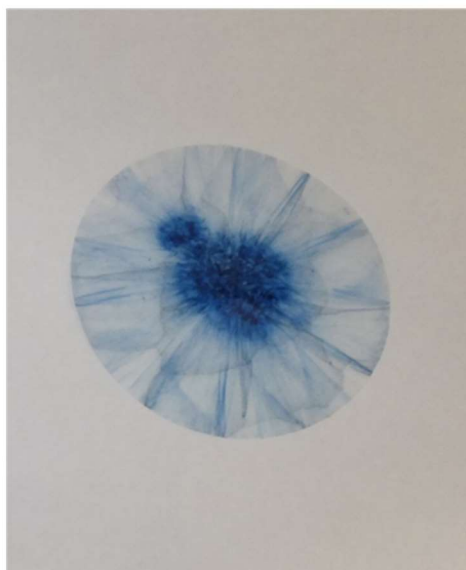


Fig. 4- 8 ABS polymer film with dispersion of blue pigment prepared from, (a) Pigment encapsulated composite polymer particles, (b) Dry mixture of pigment and uniform ABS polymer particles.

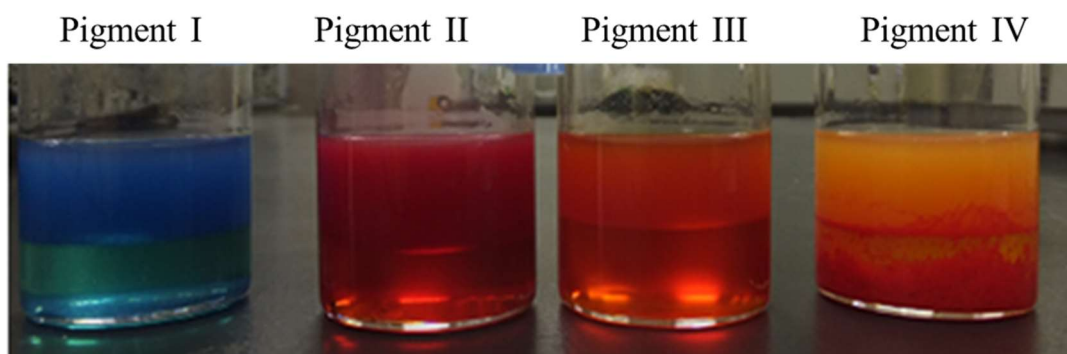


Fig. 4- 9 Phase separation of O/O emulsion with different pigment after long time standing for overnight.

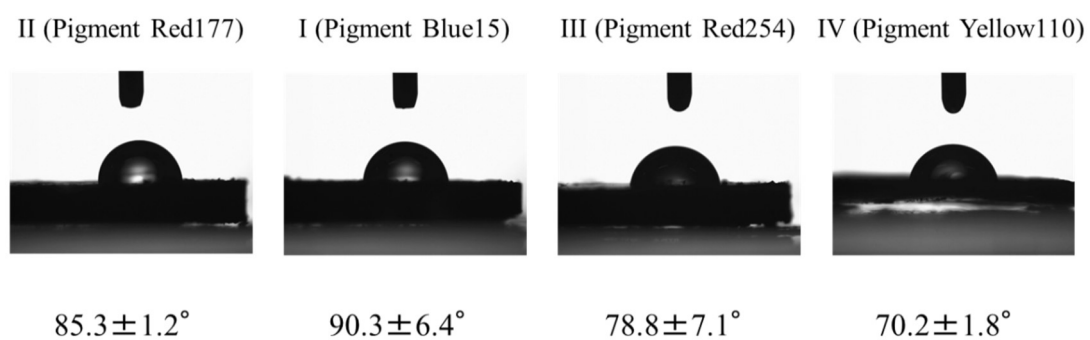


Fig. 4- 10 Contact angle observation of each pigment green body with pure water.

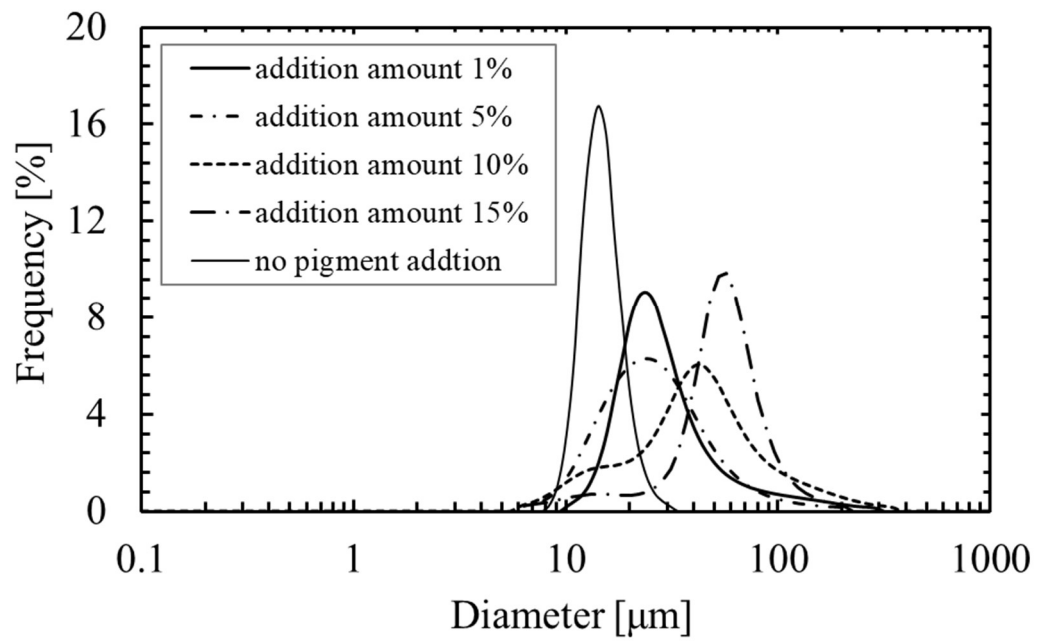


Fig. 4- 11 Effect of additive content on size distribution of composite particles in Pigment I.

Table 4- 1 Encapsulation result, contact angle with pure water on the surface of each pigment green body and estimated surface free energy of each pigment.

Pigment	Yield [%]	Encapsulation Efficiency [%]	Contact angle [°]	Surface free energy [mN/m]
I	93	80	85.3 ± 1.2	78.7
II	95	>99	90.3 ± 6.4	72.4
III	95	87	78.8 ± 7.1	86.9
IV	95	63	70.2 ± 1.8	97.4
ABS	—	—	95.0 ± 1.8	66.4
PVA	—	—	35.0 ± 1.9	132.3

Table 4- 2 Effect of pigment additive content on encapsulated efficiency in Pigment I.

Addition amount [%]	Encapsulated weight [%]	Encapsulation efficiency [%]
1	0.8	80
5	3.3	66
10	6.4	64
15	11.6	77

CHAPTER 5

GENERAL CONCLUSION

CHAPTER 5

GENERAL CONCLUSION

For my doctoral thesis, I investigated a polymer particle preparation methodology using a polymer/polymer/solvent ternary system.

First, the novel concept of the polymer particle preparation using a ternary system is exemplified with the processing of engineering polymers into particles, as described in **CHAPTER 2**. The polymer/polymer/solvent ternary system, which is referred to as the Scott system, formed an oil-in-oil emulsion, which was employed as castings for processing polymer particles. Any solvent fundamentally enables the formation of a ternary system when two polymers are dissolved in it. It has been long since an effective method of preparing particles from engineering polymers that dissolve in a polar solvent was developed because water-compatible polar solvents do not facilitate the formation of an oil-in-water emulsion. To overcome this issue, an engineering polymer and polyvinyl alcohol (PVA) were dissolved in *N*-methylpyrrolidone (NMP) to form an oil-in-oil emulsion. Thereafter, water, which is a poor solvent for the engineering polymer, but a good one for polyvinyl alcohol, was slowly added to the emulsion, when the particles of the engineering polymer emerged. This concept has been demonstrated with numerous engineering polymers, including polyether sulfone, polyamide, polyphenylene ether, polyester elastomer, and other condensation polymers. The polymer particles produced by this method have micron-order sizes and a narrow size distribution. Further, particles of poorly soluble polyamides with high heat resistance can also be produced using an autoclave.

This versatile methodology for forming particles of engineering polymers is unprecedented, and this is the first instance of the use of a Scott system in such polymer processing.

In **CHAPTER 3**, the polymer particle formation methodology developed for the ternary system was applied to generate particles of ethyl cellulose, a representative biocompatible polymer. Biocompatible polymer particles are utilized as basements of pharmaceuticals, vascular embolization materials, and sustained release capsules in pharmaceutical and medical fields. As harmful and volatile organic solvents, such as acetone, chloroform, or ethyl acetate, are used in the manufacture of these particles, strict safety management protocols are generally required for eliminating residual solvents in many cases. The key reasons for using these solvents are that these solvents enable the formation of oil-in-water emulsions and can be easily evaporated after they serve their purpose. On the other hand, ethanol, which is a relatively safer solvent than those solvents, does not enable the formation of oil-in-water, and is therefore not considered as a solvent candidate in polymer particle manufacturing processes. Hence, I attempted to process ethyl cellulose particles using a

ternary system consisting of ethanol. In this investigation, polyvinylpyrrolidone, a water-soluble polymer that is widely used in the pharmaceutical industry, was used as a separating polymer. Thus, 50–100 μm ethyl cellulose particles and particles of other engineering polymers were produced successfully. Moreover, porous ethyl cellulose particles were found to form under certain conditions. The structure of the porous particles was analyzed by oil-absorption evaluation, SEM, X-ray CT, and mercury porosimetry to discover that the porous ethyl celluloses particles contained continuous micron-sized pores. The results of DSC and powder X-ray diffraction analysis indicated that the pore formation was due to the crystallinity of ethyl cellulose. That is, during the formation of particles from the oil-in-oil emulsion, self-organization occurred owing the crystalline nature of this polymer. Although the conventional preparation of porous polymer particles requires a porogen, such as a gas or a liquid, the author speculates that the self-organization of polymers using an oil-in-oil emulsion affords a new approach for the production of porous particles.

Eventually, in **CHAPTER 4**, the author developed a preparation method for functionalized polymer particles based on the oil-in-oil (O/O) emulsion casting methodology. In particular, the main focus of this study was to investigate the encapsulation of pigments in polymer particles formed using a polymer/polymer/solvent ternary system and the related mechanism and principles are discussed. To demonstrate the encapsulation of pigments and evaluate the encapsulation conditions and encapsulation efficiency of Pigment Blue 15, Pigment Red 177, Pigment Red 254, and Pigment Yellow 110, acrylonitrile-butadiene-styrene (ABS) was selected as the polymer matrix, while PVA was chosen as the separating polymer and NMP was used as the solvent. When the emulsions of the ternary systems added with pigments underwent macro phase separation, the pigment molecules were observed to selectively partition into the ABS/NMP phase in the case of systems with good encapsulation efficiency. In contrast, in the cases of systems with low encapsulation efficiencies, the pigment existed in both the ABS/NMP phase and PVA/NMP phase. The author considered that the affinity of ABS, PVA, and pigment affected the partition of the pigment in the two phases. Therefore, the water contact angles of these compounds in pellet form were measured and their surface free energies were compared. As the surface energy of ABS is much lower than that of PVA, pigments I, II, and III with low surface energies selectively partitioned into the ABS/NMP phase rather than the PVA/NMP phase in the ternary system. Moreover, Pigment IV with intermediate surface energy partitioned into both the ABS/NMP and PVA/NMP phases, and the encapsulation of this pigment in the ABS polymer was inefficient. This phenomenon of surface energy matching can be a critical factor for assessing the encapsulation capability of other functional materials. The encapsulated particles could be readily processed into uniform films with a heat transfer

press. Thus, a novel and facile encapsulation method was successfully developed.

FIGURE CAPTIONS

Fig. 1- 1 Classification of polymer particle preparations.

Fig. 1- 2 Examples of a membrane emulsification systems. (upper) microchannel emulsification system with microsieves ^[10], (lower) ceramic membrane with the seven star-shaped internal channels ^[11].

Fig. 1- 3 Examples of a microfluidics ^[13], (left) Micro-Channel chip (25mm × 15mm), (right) generation of bichromal droplet in micro channel duct.

Fig. 1- 4 An example of Plastic Pyramid ^[16].

Fig. 1- 5 Condensation reactions and by-products.

Fig. 1- 6 Melt kneading method.

Fig. 1- 7 An example of a particle distribution by spray-drying ^[26].

Fig. 1- 8 Recent example for perpetrating of engineering polymer particle ^[29].

Fig. 1- 9 General Types of Emulsion Systems.

Fig. 2- 1 Autoclave equipment for particulation in high temperature.

Fig. 2- 2 Schematic Illustration of Ternary System.

Fig. 2- 3 Emulsion and Phase separation state of PES/ PVA/ NMP.

Fig. 2- 4 Phase Diagram of Ternary System.

Fig. 2- 5 SEM Image of Aggregation Fraction of PES (Table 2- 1, Entry 1).

Fig. 2- 6 SEM Image and Size Distribution of PES Fine Particles (Table 2- 1, Entry 4).

Fig. 2- 7 Size Distribution of PES Fine Particles Produced by Using DMSO instead of NMP

(PES/PVA/DMSO = 2.5/5/92.5 (w/w/w)).

Fig. 2- 8 SEM Images and Size Distributions of ABS Fine Particles (Table 2- 2, Entry 2).

Fig. 2- 9 SEM Image and Size Distribution of PC Fine Particles (Table 2- 2, Entry 3).

Fig. 2- 10 SEM Images and Size Distributions of PAN Fine Particles (Table 2- 1, Entry 4).

Fig. 2- 11 SEM Image and Size Distribution of PPE Fine Particles (Table 2- 2, Entry 5).

Fig. 2- 12 SEM Image and Size Distribution of a-PAM Fine Particles (Table 2- 2, Entry 6).

Fig. 2- 13 SEM Image and Size Distribution of PEI Fine Particles (Table 2- 2, Entry 7).

Fig. 2- 14 SEM Image and Size Distribution of PAR Fine Particles (Table 2- 2, Entry 8).

Fig. 2- 15 SEM Image and Size Distribution of c-PAM Fine Particles (Table 2- 3, Entry 1).

Fig. 2- 16 SEM Image and Size Distribution of c-PAM Fine Particles (Table 2- 3, Entry 2).

Fig. 2- 17 SEM Image and Size Distribution of c-PAM Fine Particles (Table 2- 3, Entry 3).

Fig. 2- 18 SEM Image and Size Distribution of PPE Fine Particles (Table 2- 3, Entry 4).

Fig. 3- 1 Schematic illustration of a ternary system.

Fig. 3- 2 Photographs of the ternary system-based O/O emulsions taken at EC/PVP/EtOH= 5/5/90.

Fig. 3- 3 SEM images of (a) EC-1, (b) EC-2, and (c) EC-3 fine particles.

Fig. 3- 4 SEM images and particle size distribution of fine EC-1 particles.

Fig. 3- 5 SEM images and particle size distribution of fine EC-2 particles.

Fig. 3- 6 SEM images and size distribution of EC-3 fine particles.

Fig. 3- 7 XRD patterns of starting polymer and its fine particles (EC-1).

Fig. 3- 8 XRD patterns of starting polymer and its fine particles (EC-2).

Fig. 3- 9 XRD patterns of starting polymer and its fine particles (EC-3).

Fig. 3- 10 FTIR spectra of starting EC-2 and the fine particles.

Fig. 3- 11 DSC charts of starting EC-2 and the fine particles.

Fig. 3- 12 Adsorption isotherms of starting EC-2 and the fine particles using krypton.

Fig. 3- 13 Linseed oil absorption test for the EC fine particles.

Fig. 3- 14 Cross sectional TEM images of the EC-2 fine particles.

Fig. 3- 15 Cross sectional TEM images of the EC-3 fine particles.

Fig. 3- 16 (a) Cross sectional SEM image of a fine EC-2 particle, and (b) EDX mapping of Na in the pores of the particle. (c) Merged SEM image and EDX map.

Fig. 3- 17 X-ray CT images of (a) a fine EC-2 particle, and (b) the sequential internal structure ($40 \times 40 \times 40 \mu\text{m}$).

Fig. 3- 18 Porosity distributions of starting EC-2 and the fine particles measured by mercury porosimeter.

Fig. 4- 1 Concept of spherical polymer particles preparation and encapsulation of pigment particles in polymer particles by using Ternary system-based emulsion casting.

Fig. 4- 2 Chemical structures of pigments (a) I (Pigment Blue 15), (b) II (Pigment Red 177), (c) III (Pigment Red 254), and (d) IV (Pigment Yellow 110).

Fig. 4- 3 Effect of pigment materials on particle diameter distribution of pigments-encapsulating composite polymer particles.

Fig. 4- 4 Digital microscope images of pigment encapsulated ABS spherical particles (a) Blue, (b) Red (c) Red and (d) Yellow. Amount of pigment added in each particle preparation was about 1 mass%.

Fig. 4- 5 SEM observation of pigment encapsulated ABS spherical particles in Fig. 4 (a) I (Pigment Blue 15), (b) II (Pigment Red 177), (c) III (Pigment Red 254), and (d) IV (Pigment Yellow 110).

Fig. 4- 6 TEM cross section observation of pigment I encapsulated particles.

Fig. 4- 7 STEM-EDX observation of pigment IV encapsulated particles. (Upper row: whole particle images, lower row: cross section images).

Fig. 4- 8 ABS polymer film with dispersion of blue pigment prepared from, (a) Pigment encapsulated composite polymer particles, (b) Dry mixture of pigment and uniform ABS polymer particles.

Fig. 4- 9 Phase separation of O/O emulsion with different pigment after long time standing for overnight.

Fig. 4- 10 Contact angle observation of each pigment green body with pure water.

Fig. 4- 11 Effect of additive content on size distribution of composite particles in Pigment I.

TABLE CAPTIONS

Table 2- 1 Optimization of the Production Method of PES Fine Particles.

Table 2- 2 Production of Various Polymer Fine Particles.

Table 2- 3 Production of Various Fine Polymer Particles using an Autoclave Reactor.

Table 3- 1 Ethyl cellulose samples used in this work.

Table 4- 1 Encapsulation result, contact angle with pure water on the surface of each pigment green body and estimated surface free energy of each pigment.

Table 4- 2 Effect of pigment additive content on encapsuled efficiency in Pigment I.

PUBLICATIONS

- (1) Hiroshi Takezaki, Itaru Asano, Yuji Echigo, Hiroshi Kobayashi, Hidehiro Kamiya, and Yohei Okada, Engineering Plastic Fine Particles: Emulsion Castings Enabled by a Ternary System, *Industrial & Engineering Chemistry Research* **2021** 60(2), 1067-1070
- (2) Hiroshi Takezaki, Takahiko Otsubo, Yuji Echigo, Hidehiro Kamiya, and Yohei Okada, Porous and spherical ethyl cellulose fine particles produced by ternary system-based emulsion castings, *Powder Technology* **2022** 395, 663-668
- (3) Hiroshi Takezaki, Yuji Echigo, Tomohiko Nakamura, Yuka Sato, Ayaka Miyazaki, and Hidehiro Kamiya, Pigment encapsulated spherical polymer particles prepared by Ternary System-based Emulsion Castings, *Journal of the Society of Powder Technology, Japan*, **2022** 59(2), 72-78

PATENTS

- (1) Method for producing polymer fine particle, WO 2009/142231, 2009/11/16, Itaru Asano, Yuji Echigo, Hiroshi Takezaki
- (2) Cellulose ether derivative fine particles, WO 2017/73626, 2017/5/4, Takahiko Otsubo, Kotoe Ohta, Yuji Echigo, Hiroshi Takezaki, Suguru Takaki, Satoshi Minakami, Akinori Ito, Hisashi Miyama
- (3) 着色ポリマー微粒子およびその製造方法, 特開 2017-155218, 2017/9/7, 中村友彦、浅野到、竹崎宏

SUMMARY IN JAPANESE

和文概要

三成分系エマルジョンを鋳型に用いた高分子微粒子製造法

1. 緒言

1. 1 ポリマー微粒子の背景

ポリマー微粒子は、繊維、フィルム、発泡体、および成形体と同様に、ポリマーを取り扱う上での実用的な形態の一つである。ポリマー微粒子は、一般的に 100nm から 100 μ m 程度の粒径を有し、その特徴を活かし、応用範囲はとても広い。ポリマー微粒子の共通な特徴としては、比重の低さや微小空間の制御性、さらには光学的、電氣的、物理的や生化学的の観点で外界に影響を与えないという点などがあげられる。

プリンターナーは、ポリマー微粒子における非常に大きなアプリケーションの一つである[1]。印刷における細かい描写をするためには、レーザートナーに対し、微細な制御性と易定着性が求められる。このため、ポリマー微粒子の熱可塑性は最適な特性である。

塗料では、ポリマー微粒子は粘度調整のための添加剤として用いられる[2][3]。ポリマー微粒子は色合いに直接影響を与えず、砂、ガラス金属などの他の微小添加剤に比べ比重も軽いことから、これらの特性は塗料用の添加剤として好ましい。液晶ディスプレイにおいては、ポリマー微粒子は光拡散材[4]やバックライトユニットとディスプレイ用フィルムの間のスペーサー[5][6]として用いられている。また、薬はポリマー微粒子上に担持され、他のポリマーでコートされることで徐放性スピードが制御される[7][8]。ハイエンドの応用事例としては化粧品があげられる。ポリマー微粒子を化粧品に添加することにより、その触感や粘度、外観を簡単に変えることができる。特にポリマーの持つ柔らかさとスムーズな触感は化粧品ファンデーション用の原料として最適である。

ポリマー微粒子を製造するためには、一般的にトップダウンアプローチが用いられる(Figure 1)。トップダウンアプローチとはバルクポリマーを細かくすることを意味しており、機械的なすりつぶしや粉碎などが最も簡単な方法である。しかし、この方法による粒子の形状は不定形である。他の主要な方法は、溶解析出やスプレードライ[9]などの溶媒を用いる方法である。これらのアプローチは、微粒子化する対象のポリマーの溶媒への溶解性が高いことが求められる。そのため、耐溶剤性の高いポリマーにとっては不利な方法である。さらには、これらの方法では、微粒子のサイズの調整が難しく、粒度分布も広い。

近年、膜乳化法[10][11]やマイクロ流路法[12 - 14]などの先進的な方法が開発されている。これらの方法は、機械的手法と溶媒を用いる方法を組み合わせた手法と解することができる。最も代表的な微粒子の製造法として、乳化重合は長年主要なものとして研究が進められてきた。

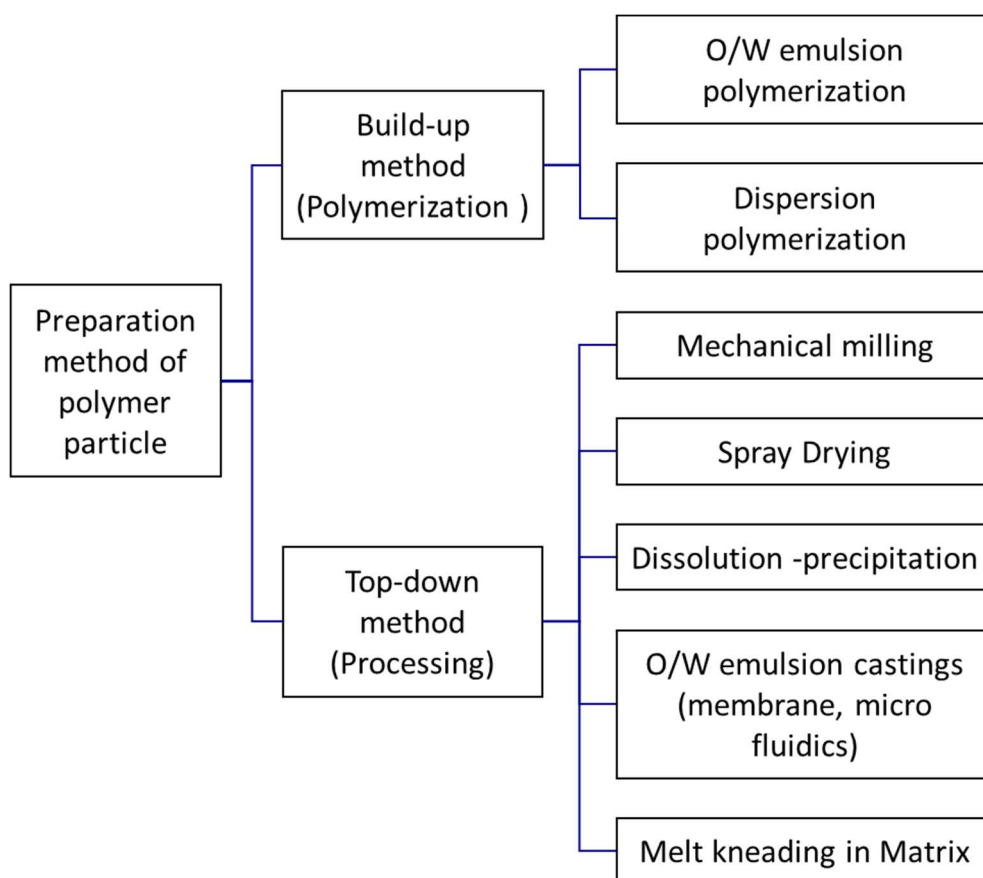


Figure 1 Classification of polymer particle preparations.

エマルションとは、辞書では互いに交じり合わない液体の混合物として定義されており、水と油の組み合わせが良く知られており、オイルインウォーター系は一般的に用いられる。エマルション系のミセルコロイドは、乳化重合における微粒子の鋳型の役割を果たし、微小なアクリル粒子を容易に作ることができる。この方法は重合法のひとつとして認識されており、工業スケールでアクリルポリマー、ポリスチレン、ポリビニルエステルなどのビニル系ポリマーなどに応用されている。

乳化重合の利点としては、ポリマー微粒子の特性の制御性にある。その粒径は、ミセル濃度や重合温度などの重合条件で調整できる。また粘弾性や硬さ、透明性などの物理特性は、モノマーの共重合組成で設計できる。しかしモノマーの組み合わせは分子内にビニル結合を有するものに限定され、得られるポリマーの主鎖の安定性から、その耐熱性を 150 度以上に調整するのは難しい。厳しい環境における微粒子の耐熱性としては十分ではなく、さらなる広範な応用に向けては、より高耐熱なポリマー微粒子の創出が必要であった。

一方エンジニアリングプラスチックは、高耐熱なポリマーとして知られている。ポリアミドやポリエステルはエンジニアリングプラスチックの代表的な材料であり、テキスタイルや繊維物、プラスチックボトルなどに使われている。さらにポリフェニレンスルフィド、

ポリスルホン、ポリエーテルケトンはスーパーエンジニアリングプラスチックとして知られており、電気電子部品、医療用材料、自動車材料や航空宇宙関連部品などに広く使われている。しかし、これらの材料が、微粒子の形態で使われることはそれほど多くはなかった。

1. 2 エンジニアリングポリマー微粒への期待、応用の可能性と課題

ポリマー微粒子は、エマルジョン重合や分散重合、懸濁重合など、重合技術の周辺で発展してきた。しかし、その技術で合成されるアクリル系ポリマーは耐熱性や耐久性の点で課題があった。近年、レーザー焼結タイプのアディティブマニュファクチャリングなどの微粒子に対し新たな用途が創出され、それに対して、エンジニアリングポリマーの微粒子への期待が益々高まっている。

エンジニアリングポリマーやエンジニアリングプラスチック[15][16]について、学術的な明確な定義は存在しないものの、概ねその耐熱性が 140 度以上のものを指すといわれている。工業的には、エンジニアリングプラスチックは **Figure 2** に示す“プラスチックピラミッド”としてまとめられることが多く、耐熱性が重要な指標となる。

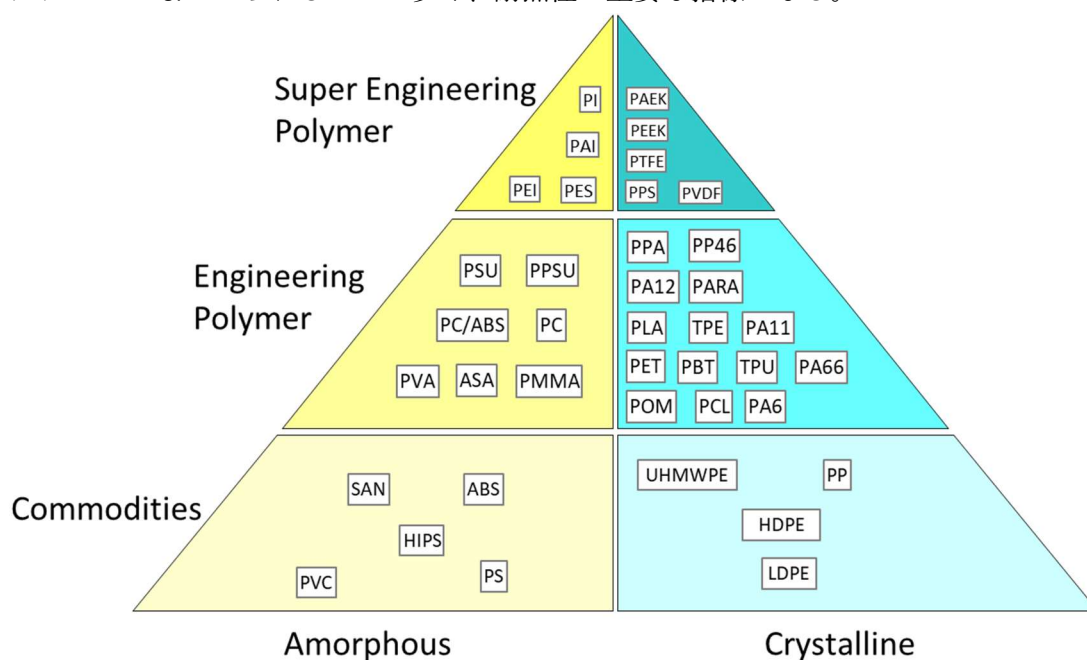


Figure 2 An example of Plastic Pyramid [16].

大部分のエンジニアリングプラスチックは、ポリアミドやポリエステルのように縮合重合やポリフェニレンスルフィドやポリエーテルエーテルケトンなどのように脱塩重縮合で合成される(**Figure 3**)。

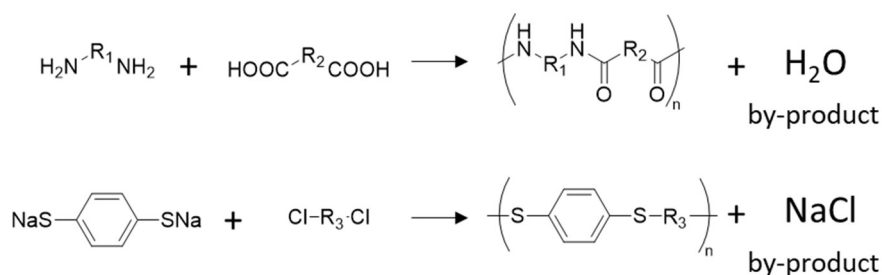


Figure 3 Condensation reactions and by-products.

これらの重合法は反応の進行と共に副生物が生成する。多くの場合、反応の平衡のため、水の存在は重合反応の阻害要因になり、オイルインウォーターエマルジョンを鋳型とする手法は、エンジニアリングプラスチックの粒子化の手法として用いることはできなかった。そのため、他のアプローチでの製造が試みられていた。

多くの場合は、粉碎やすりつぶしなど、いわゆるトップダウン法といわれる機械的手法が適用されてきた。しかし、エンジニアリングプラスチック類は、その靱性から常温での粉碎は困難である。

これに対し凍結粉碎は良く利用される方法のひとつであり、例えば渡辺ら[17]は、この方法を応用し、ポリフェニレンスルフィドの粉体を製造している。この方法で得られた粉体は形状が不定形であり、流動性が悪化することが課題になっている。この問題を解決するためにナノシリカを外部添加剤として加えている。しかし、外部添加剤は別の問題をもたらす可能性がある。凍結粉碎の他の最近の例として、さらに耐熱性の高い液晶ポリマーの特許[18]が出願されており、現状ではこの方法が標準的な技術レベルであると考えられる。

他の機械的なアプローチは、2 軸押出機を用いたポリマーブレンド技術を発展したものが非常に興味深い[19 – 24] (Figure 4)。この方法の原理は、微粒子化する目的のポリマーと水溶性のポリマーを共にブレンドし、水溶性ポリマーをマトリックス相、微粒子化を狙うポリマーを分散相にしたポリマーアロイを形成し、水で水溶性ポリマーを除くことにある。この方法は最近、液晶ポリマーに対しても応用されている[25]。この方法はポリマーを熔融するために高温に加熱することから、熔融状態での2つの粘度比が重要である。しかし、その比率はポリマー固有の特性によるものであることから、望みの粒子径に調整するのは難しい。

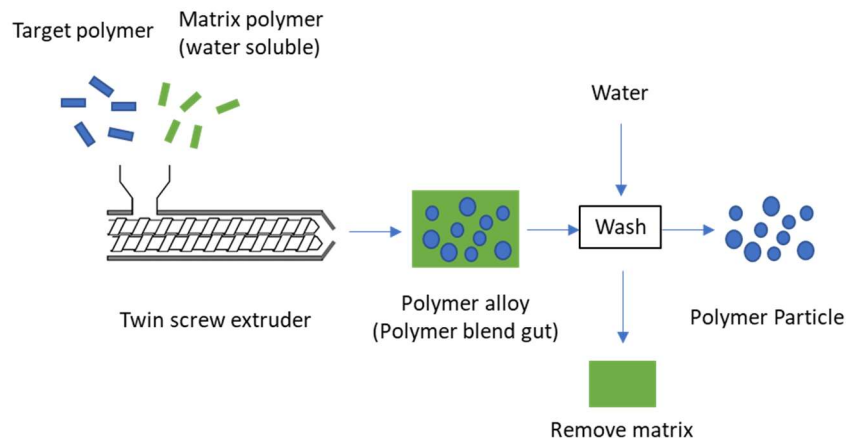


Figure 4 Melt kneading method.

また、エンジニアリングプラスチック微粒子の製造法の機械的手法の代替法として、以下の2つの溶媒法が挙げられる。スプレードライ法はポリマー微粒子を得るには良く知られており簡便である。この方法の要素は、ポリマーをある溶媒に溶解し、専用の装置で瞬時に乾燥させる点にある。エンジニアリングポリマーの場合、気化しやすい溶媒には溶解性が低く、このシステムを使いためには、沸点の高い溶媒を用いなければならない。その結果、実際に応用される例[26] (Figure 5)はあまりなく、その粒度分布は受け入れられるものではない。また、エンジニアリングプラスチック微粒子の製造法のもっとも簡便な方法は、溶解析出法である[27][28]。

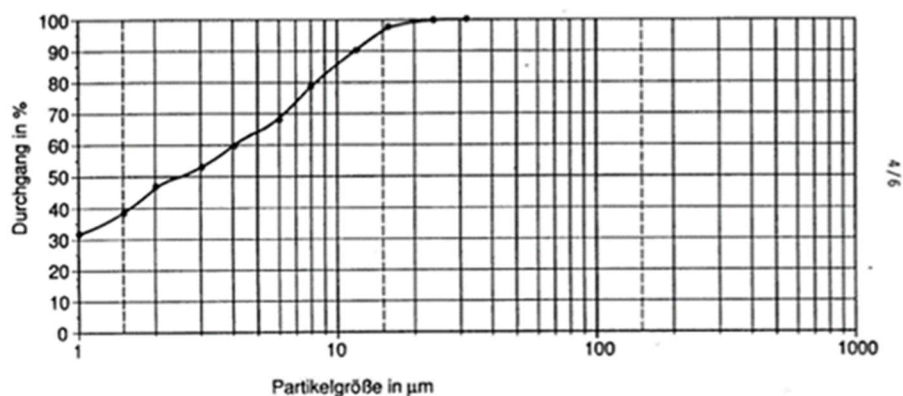


Figure 5 An example of a particle distribution by spray-drying [26].

最近の先進的な事例として、ミル粉碎をした後に粒子を再成形する方法が Hejmady によって報告されている[29]。この方法は機械的手法と溶媒法とを組み合わせた手法と位置づけられる。この方法は真球状粒子を得るのに有用な方法に見えるが、粒子径サイズの制御性に課題がある。

またポリカプロラクタム[30]やポリラウロラクタム[31]や低定着トナー用のポリエステル[32]などの特殊なポリマーに対する製造法に限って言えば、良く知られた微粒子製造法は存在している。しかし、これらの方法には汎用性があるとはいえない。

以上の結果から、高耐熱ポリマーや耐溶剤性の高いポリマーに広く適用できる製造法が強く期待されていた。

1. 3 エマルションシステムとオイルインオイルエマルション

エマルションとは、もちろん良く知られた液体状態であるが、液体の中に液体が分散したものとして定義される。液体中に固体が分散したものはサスペンションと呼ばれ、ガスが分散したものはフォームと呼ばれる。エマルションは、幅広い分野に応用されており、そのレビューも多数出されている。例えば、石油エネルギー分野[33][34]、食品栄養学[35-38]、環境科学[39][40]、高分子化学[41][42]、化粧品分野[43]などがあげられる。

エマルションの形態は、オイルインウォーターエマルション(O/W emulsion)、ウォーターインエマルション(W/O emulsion)、およびダブルエマルション(O/W/O emulsion or W/O/W emulsion)の3つに大きく分類される(**Figure 6**)。

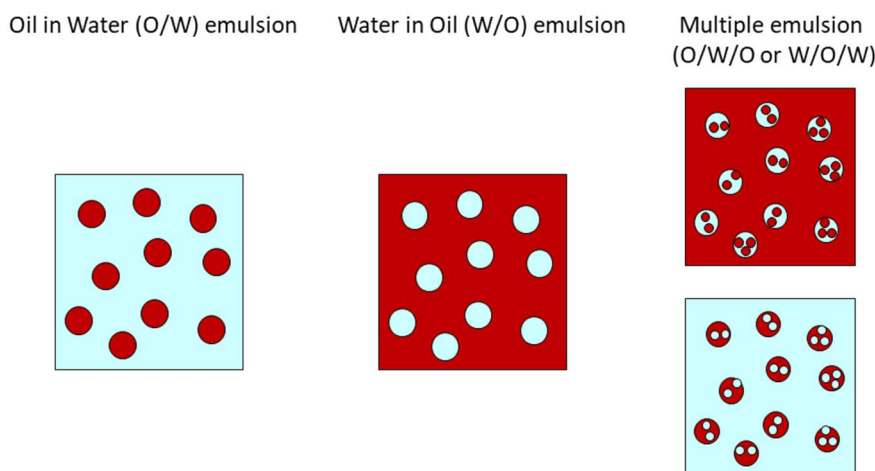


Figure 6 General Types of Emulsion Systems.

また、エマルションのサイズによっても分類される。マクロエマルションは、一般的にエマルション粒径が μm メーター以上のものを指す。マクロエマルションは熱力学的には不安定であるため、その状態を維持するため、通常、乳化剤や界面活性剤に代表される添加物が必要である。マイクロエマルションは、マクロエマルションよりも小さいものの用語として用いられ、通常 100nm 以下の粒径を持ち、自発的に形成される。このため、乳化剤のような添加物を必要としない。一方、ナノエマルションは機械的剪断によって発生させられ、その粒径は 100nm 以下になる。近年、マイクロエマルションやナノエマルションは、精力的に先端分野に応用されている。

これらのエマルションはいずれも水と油で形成された、いわば異種溶媒のエマルションと言える。例外的にメタノールとヘキサンや、アセトニトリルとデカンなど、極性溶媒と炭化水素の組み合わせのような同種溶媒でエマルションを形成することも可能である。しかしこれらの組み合わせでは、ポリマーの溶媒に対する溶解性が低いため、ポリマー微粒子の製造には使われていない。

つまり、オイルインオイルエマルションとその応用に関しては、これまで微粒子製造に対して未開拓な分野であり、ポリマー微粒子に関してエマルションシステムを見直すことは意義あることであると言える。

1. 4 スコットシステム、その歴史的発展と応用

魅力的なオイルインオイルエマルションシステムの一つに、いわゆるスコットシステムといわれる 3 成分系ポリマー溶液が挙げられる。しかしこの方法は、これまで余り注目されてこなかった。

高分子溶液の相分離現象に関し、1947 年 Dorby[44]らにより、最初にまとまった報告がなされた。彼らは、セルロース誘導体、ビニルポリマー誘導体、アクリル誘導体など 14 種のポリマー類と 13 種の溶媒とを実験的に混合した結果を記したものである。相分離現象は 78 の組み合わせで見つかり、それらの現象は 3 相図を用いてまとめられた。1949 年 Scott は、高分子物理の観点からこれらの現象について考察をまとめ、高分子／高分子／溶媒系の混合物による 3 成分系として報告した[45]。ちょうど同時期に、Flory[46]、Scott、Magat[47]、そして Guggenheim[48]が、高分子と高分子との混合である、溶媒を含まない高分子ブレンド系に関しての研究を進めていた。彼らは、2 種の高分子を混合したときのブレンドに関する混合自由エネルギーを下記 2 式のように仮定していた。

$$\Delta F_1 = RT \left[\ln \phi_1 + \left(1 - \frac{m_1}{m_2} \right) \phi_2 + m_1 \mu_{12} \phi_2^2 \right]$$

$$\Delta F_2 = RT \left[\ln \phi_2 + \left(1 - \frac{m_2}{m_1} \right) \phi_1 + m_2 \mu_{12} \phi_1^2 \right]$$

ϕ_1, ϕ_2 : 混合時の体積分率, m_1, m_2 : 高分子の重合度、 V_1, V_2 : 分子容、

$m_1 = V_1/V_0$ 、 $m_2 = V_2/V_1$ 、 μ_{12} : 2 つの高分子間の分子レベル以下での相互作用熱生成に関する定数

Scott は、この考えを高分子／高分子／溶媒系に拡張し、混合時の系の全自由エネルギーと個々の成分の自由エネルギーを以下の 3 つの数式で表わし、さらに完全に相互溶解しないという前提での相分離条件を導き出し、高分子溶液の 3 成分系として最初に報告した。

$$\begin{aligned}
\Delta F_0 &= RT \left[\ln \phi_0 + \left(1 - \frac{1}{m_1}\right) \phi_1 + \left(1 - \frac{1}{m_2}\right) \phi_2 + \mu_{10} \phi_1^2 + \mu_{20} \phi_2^2 \right. \\
&\quad \left. + (\mu_{10} + \mu_{20} - \mu_{12}) \phi_1 \phi_2 \right] \\
\Delta F_1 &= RT \left[\ln \phi_1 + (1 - m_1) \phi_0 + \left(1 - \frac{m_1}{m_2}\right) \phi_2 \right. \\
&\quad \left. + m_1 \{ \mu_{10} \phi_0^2 + \mu_{12} \phi_2^2 + (\mu_{10} + \mu_{12} - \mu_{20}) \phi_0 \phi_2 \} \right] \\
\Delta F_2 &= RT \left[\ln \phi_2 + (1 - m_2) \phi_0 + \left(1 - \frac{m_2}{m_1}\right) \phi_1 \right. \\
&\quad \left. + m_2 \{ \mu_{20} \phi_0^2 + \mu_{12} \phi_1^2 + (\mu_{20} + \mu_{12} - \mu_{10}) \phi_0 \phi_1 \} \right] \\
\mu_{12} &= V_0 / RT (\delta_1 - \delta_2)^2 \quad \cdot \cdot \cdot \text{Solubility Parameter}
\end{aligned}$$

[Phase separation condition (at complete immiscible approximation)].

$$\ln \phi'_0 + \left(1 - \left(\frac{1}{m_1}\right)\right) (1 - \phi'_0) + \mu_{10} (1 - \phi'_0)^2 = \ln \phi''_0 + \left(1 - \left(\frac{1}{m_2}\right)\right) (1 - \phi''_0) + \mu_{20} (1 - \phi''_0)^2$$

1950 年代から 1980 年代にかけては、3 成分系に関しては、数件しか報告例がなく、これらは主に系の物理的特性に言及したものであった。Bigelow[49]は、ポリマーとして、ポリスチレン、ポリビニルアルコール、および PMMA を、溶媒として、トルエン、キシレンと取り上げ、その濃度と粘度を明らかにした。彼らはポリマーの濃度を変え、粘度変化に決定的なポイントがあることを見出した。1968 年 Edmond[50]らは、デキストラン、ポリエチレングリコールと食塩水を用い、溶解沈殿平衡に関する実験を行い、その浸透圧を測定している。そして簡単な熱力学的表現を用い、これらの物質に関する相互作用係数を導き出している。この文献は、水系高分子溶液に関する 3 成分系である。1969 年、Cenrry[51]は、マロン[52]の理論による溶媒と溶質間の相互作用を用いて、3 成分系高分子溶液の自由エネルギー変化について詳述している。そして、高分子高分子間の相互作用を評価する手段を入手することに成功している。Liu[53]らは、高分子－高分子－溶媒の 3 成分系における混和に関し、perturbed hard chain 理論を用い、各成分の溶媒の contact agility の観点から議論している。

これらの基礎的議論の後、1980 年代中旬から機器分析を用いた研究が始まり、対象となる高分子や溶媒なども広がっていった。多くの報告が、Flory-Huggins theory を基に高分子溶液の 3 成分系においての相分離の発生を議論することが主眼であった。最近では、Es-haghi[54]らが、高分子溶液の 3 成分系に関する物質拡散と熱拡散の挙動を取り扱っている。

1988 年に Einaga[55] らは、高分子溶液の 3 成分系の相変化の説明に関し、ポリスチレンとポリブチレンと *N*-ジメチルホルムアミドからなる系を用いている。この報告は、高分子溶液の 3 成分系に極性溶媒を用いた最初の例である。この報告に続き、Matsumoto[56] らは、ポリエーテルスルホン／ポリスルホン／*N*-メチルピロリドンを用いて形成される高分子溶液の 3 成分系について検討をしている。これは、エンジニアリングプラスチックが高分子溶液の 3 成分系に適用された最初の例である。

様々な研究が 2000 年代中盤まで実施されてきたが、これらの文献は高分子溶液の 3 成分系の物理化学的挙動に焦点を当てただけのものである。

一方、高分子／溶媒／溶媒の 3 成分系においては、ポリマーの加工への適用がなされている。高分子／溶媒／溶媒の 3 成分系もまた Scott[57]により、前述の文献に続いて報告されている。例えば、Yin ら[58]は、高分子／溶媒／溶媒の 3 成分系を、ポリアミック酸繊維の紡糸に用いている。ポリアミック酸は、ポリイミドの前駆体であるが、ポリイミドの難加工性の点から良く用いられる。通常、ポリイミド製品は、ポリアミック酸の状態で成形し、この前駆体は、化学反応によってポリイミドに誘導される。ポリアミック酸は極性溶媒中で重合されるが、極性溶媒から沈殿させるのが難しいため、ポリアミック酸／ジメチルアセトアミド／水の系が応用された。他の例としては、Kurada[59]らが、2019 年に導電性膜の形成に非溶媒／溶媒／ポリピロールおよびポリスルホンの系を用い、溶液からの膜へ形成されるメカニズムについて詳細に検討した。この系の 2 つのポリマー溶液は膜形成のために使用されたが、これはポリピロール溶液相とポリスルホン溶液相との間の相分離というよりも、溶媒から非溶媒を用いて、これらポリマーの共沈殿を狙ったものであった。

高分子／溶媒／溶媒の 3 成分系に関する応用研究の例はあるものの、高分子／高分子／溶媒系を用いた高分子加工の応用例は見つかっていない。すなわち、筆者の知る範囲においては、高分子／高分子／溶媒の 3 成分系は実用的な応用はこれまでなされていなかった。

1. 5 本研究の目的

ポリマー微粒子は、3D プリンターや先端医薬品などの最新用途からのニーズも相まって、益々魅力的な材料になってきている。しかし、ポリマー微粒子の主要な材料は、長らくビニル系ポリマーに限られてきた。

既に述べたように、ビニル系ポリマーとそれらの製造方法は、オイルインウォーターエマルジョンを用いたラジカル重合の精密なポリマー設計と合成制御コンセプトによって発展してきた。また、機械的アプローチはすべてのポリマー材料に適用できるわけではなく、そのアプローチは微粒子を形成する上での精密性について十分なものではなかった。言い換えれば、これらの方法は、縮合系ポリマーや非ビニル系ポリマーへの応用には限界があり、それ故にこれらのポリマー微粒子については、その利用に対して焦点が当てられていなかった。つまり、ポリマー微粒子に関する決定的な問題として、非ビニル系ポリマーに

対する微粒子を製造するための新しい方法論の開発が残っていた。

この博士論文の主要な目的として、筆者は様々なポリマーに対するポリマー微粒子の一般的な方法論について研究を進めた。

オイルインウォーターエマルションは、ポリマー微粒子を調整するための鋳型として用いられてきたが、本研究では、高分子溶液の相分離現象いわゆるスコットシステムと呼ばれるオイルインオイルエマルションをその鋳型として取り上げた。このエマルションは、本研究における共通の重要な現象である。本研究の基盤となる方法論は、微粒子を形成するための目的ポリマーと相分離を形成するためのポリマーを単一の溶媒に、相分離を形成することのできる比率で溶解し、オイルインオイルエマルションを形成し、目的ポリマーの貧溶媒を添加した後に、そのポリマー微粒子を製造するものである。

最初に、第2章において、エンジニアリングポリマー微粒子の製造法とその対象と限界についてまとめた。この章では、エンジニアリングポリマーの溶解性の制限から、極性溶媒をオイルインオイルエマルション形成用の溶媒として選んだ。極性溶媒は水と相溶するため、ウォーターインオイルエマルション用の溶媒として使われることはなかった。しかし、スコットシステムは極性溶媒をエマルション溶媒として用いることを可能にした。

次にこの方法論の拡張の観点で、第3章では目的ポリマーとして、生体適合性ポリマーであるエチルセルロースの微粒子化に焦点を当てた。これまでのエチルセルロース微粒子の製造法には、有害な溶媒を使用するという問題点が残っており、このため医薬品分野でこの粒子に用いることに一定のリスクが存在していた。この問題を解決するために、多くの国の規格で承認されているエタノールを溶媒として用いた。エタノールもまた、水溶性溶媒である。この章では、この系でエタノールを用いた粒子の形成の可能性を述べ、さらに多孔質構造の発生のメカニズムについて言及した。

最後にこのコンセプトを用い、ポリマーの機能化について第4章で述べた。ポリマー微粒子は、無機粒子に比べ物理的機能の点で劣っているため、ポリマーと特殊機能物質との複合体は、価値をつけるために通常形成される。この章では、オイルインオイルエマルションを用いたポリマー微粒子中への顔料を内包化について焦点を当て、さらポリマー微粒子中への内包材料の原理について言及した。

2. 第2章 エンジニアリングプラスチック微粒子：三成分系エマルション鋳型の利用

エンジニアリングプラスチックを含む縮合系ポリマー微粒子は、その化学的物理的特性が、古くからあるラジカル重合系ポリマーと比べ、改善されていることから、幅広い用途に対して高い期待が存在する。しかし、縮合系ポリマー微粒子の製造法は、オイルインウォーター重合系が適用できず、オイルインウォーターエマルション鋳型は、それらポリマーの水溶性媒体と非相溶の低極性溶媒中への溶解性の限界から、創造的なものであった。ここでは、2種のポリマーと溶媒とから形成される三成分系で形成されるオイルインオイルエマルションを縮合系ポリマーの鋳型を真球状のテンプレートとして用いた。この三成分

系は様々なエンジニアリングプラスチックを狭い粒度分布で製造することを可能にした。

3. 第3章 三成分系エマルジョン鋳型による多孔真球エチルセルローズ微粒子

微細な孔を有し、真球状な生体適合性なポリマー微粒子は、ドラッグデリバリーシステムの精密なキャリアになりうる。活性な医薬添加物を含む生体適合性微粒子は典型的にはオイルインウォーターエマルジョン鋳型を用いて製造されるが、これらの方法には、オイルインウォーターを形成するために求められる水溶性溶媒と非相溶な低極性溶媒中に対する高分子と生理活性物質の重要な溶解性のような点で限界がある。ここで我々は、オイルインオイルエマルジョン鋳型が、微多孔で真球状の粒度分布の狭い生体適合性のエチルセルローズ微粒子の製造を可能にする実例を示した。X線散乱、亜麻仁油吸油量試験、透過型電子顕微鏡、エネルギー分散型X線分光法を組み合わせた走査型電子顕微鏡、および3次元X線CTにより、この粒子が多孔ネットワークを有し、大きな孔体積を有することを明らかにした。

4. 第4章 三成分系エマルジョン鋳型法による顔料内包高分子球形粒子の製造

本研究は、2種の高分子と溶媒からなる三成分系によるオイルインオイルエマルジョン鋳型によって作られる微粒子中に顔料の内包化を行った。アクリロニトリルブタジエンスチレン（ABS）を顔料内包化のマトリックス樹脂に、ポリビニルアルコールとN-メチルピロリドンが、それぞれ相分離ポリマーと溶媒として用いられた。顔料I、IIおよびIIIはがABS中への内包化に成功した一方、顔料IVは内包化できなかった。内包化粒子は熱プレスにより均一なフィルム形成が可能である。ABSの表面エネルギーは、PVAの表面エネルギーに比べ低く、低表面エネルギーの顔料I、IIおよびIIIは、三成分系のPVA/NMP相よりもABS/NMP相に選択的に移動していた。一方、顔料IVの表面エネルギーは中間的性質を持っていたことから、ABS/NMP相にもPVA/NMP相にも移動せず、ABSポリマー中への内包化は不十分であった。

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