공학석사학위논문

# Synthesis of Biocompatible and X-ray Opaque Iodinated Polymeric Microparticles as an Embolic Material

## 생체 적합성과 엑스레이 비투과성이 확보된 색전물질용 고분자 마이크로 입자의 합성

2016 년 2 월


서울대학교 대학원

재료공학부

이 새 봄

# Synthesis of Biocompatible and X-ray Opaque Iodinated Polymeric Microparticles as an Embolic Material

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이 논문을 공학석사 학위논문으로 제출함

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# ABSTRACT

## Synthesis of Biocompatible and X-ray Opaque Iodinated Polymeric Microparticles as an Embolic Material

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New embolic materials based on 2,3,5-triiodovinyl benzoate (TIVB), vinyl benzoate (VB) and 4-*tert*-butylbenzoate (VtB) were designed, synthesized and characterized. Polymerization of each monomer was performed in bulk radical polymerization. PVB and PVtB were iodinated via electrophilic aromatic substitution using Selectfluor®. Purity of each product was confirmed by $^{1}H$ NMR. GPC analysis measured the molecular weight of PTIVB, PVB and PVtB to be 147K, 218K and 262K, respectively with the value of Mw/Mn as 1.18, 1.78 and 3.52, respectively. Formation particle of PTIVB was based on Self-Organized Precipitation (SORP) and microparticles of IPVB as well as IPVtB were prepared using oil in water

(O/W) emulsion solvent evaporation method. Microstructure of the particles was observed by an optical microscope after filtered through steel sieves with a pore size of 50, 100 and 200 μm. PTIVB particle size in diameter ranged from 30 to 2000 μm could be prepared by changing the viscosity of PVA solution, concentration of THF and stirring speed in SORP method. On the contrary, microparticles of IPVB and IPVtB prepared by O/W method were irregularly shaped and difficult to control the size, probably due to the low solubility of polymers in organic solvent. Radiopacity of iodinated polymer microparticle was determined under x-ray using C-arm with Visipaque$^{TM}$ and Lipiodol as controls. Microparticles made of PTIVB showed the highest x-ray opaqueness among the prepared micropaticles, which was strong enough for further application in *in vivo* study as a contrast agent, while x-ray opaqueness of iodinated PVB was not intense enough to be visualized under x-ray, probably due to a limited number of replaced iodine, and microparticles of IPVtB became highly viscous liquid after iodination.

**Keywords**: Embolization, Iodinated Polymeric Microparticles, Computed Tomography(CT), DC beads, Lipiodol, Contrast agent

**Student number**: 2014-21449

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# 1. INTRODUCTION

Transarterial chemoembolization (TACE) is a minimally invasive procedure by radiologic imaging methods using a mixture of an anticancer drug, embolic material and a contrast agent to navigate catheters to find a major blood vessel of feeding arteries to a targeted tumor [3] In TACE, assigning a catheter, within an arterial blood vessel, close enough to a cancer cells is more effective for treatment. Depending on the size and location of the tumor, the tip of the catheter was selectively placed in the arteries, especially in the tumor feeding branches. After safe positioning of the catheter, mixture of an anticancer agents and embolic materials were injected with a contrast agent. Procedure of TACE was described in Figure 1.

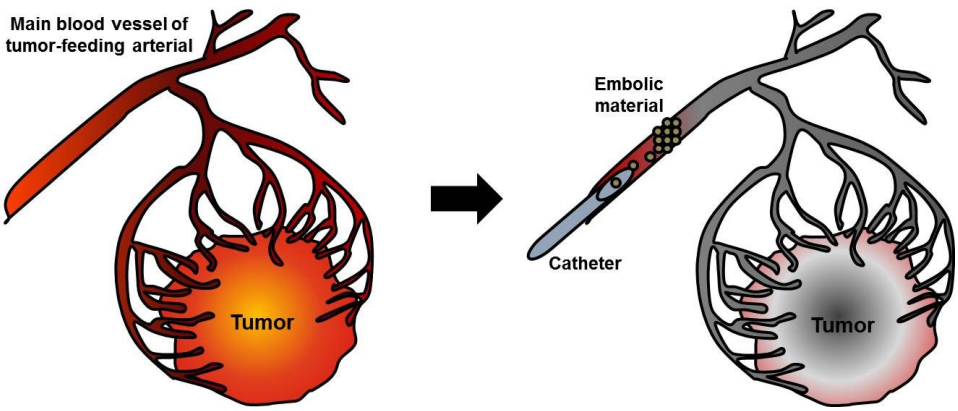



**Figure 1**. Transarterial chemoembolization (TACE)

There are three major embolic materials currently used in clinics; Histoacryl®, Onyx® and DC bead®. Histoacryl (n-butyl-2-cyanoacrylate, Germany) was approved by FDA in 2000 [7] (Figure 2) The cyanoacrylate derivative has ability to be polymerized without any catalysts upon contact with ionic fluids including blood. The fast polymerization due to highly electron deficient and reactive monomers immediately results in linear polycyanoacrylate, which causes rapidly increasing viscosity in the local site. As a result, solidified product of Histoacryl can be localized at a target position of arterial and functioned as embolic material [8]. For visualization of the materials during operation and controlling rate of solidification, Lipiodol®, iodinated oily contrast agents, is mixed with Histoacryl in different compositions.

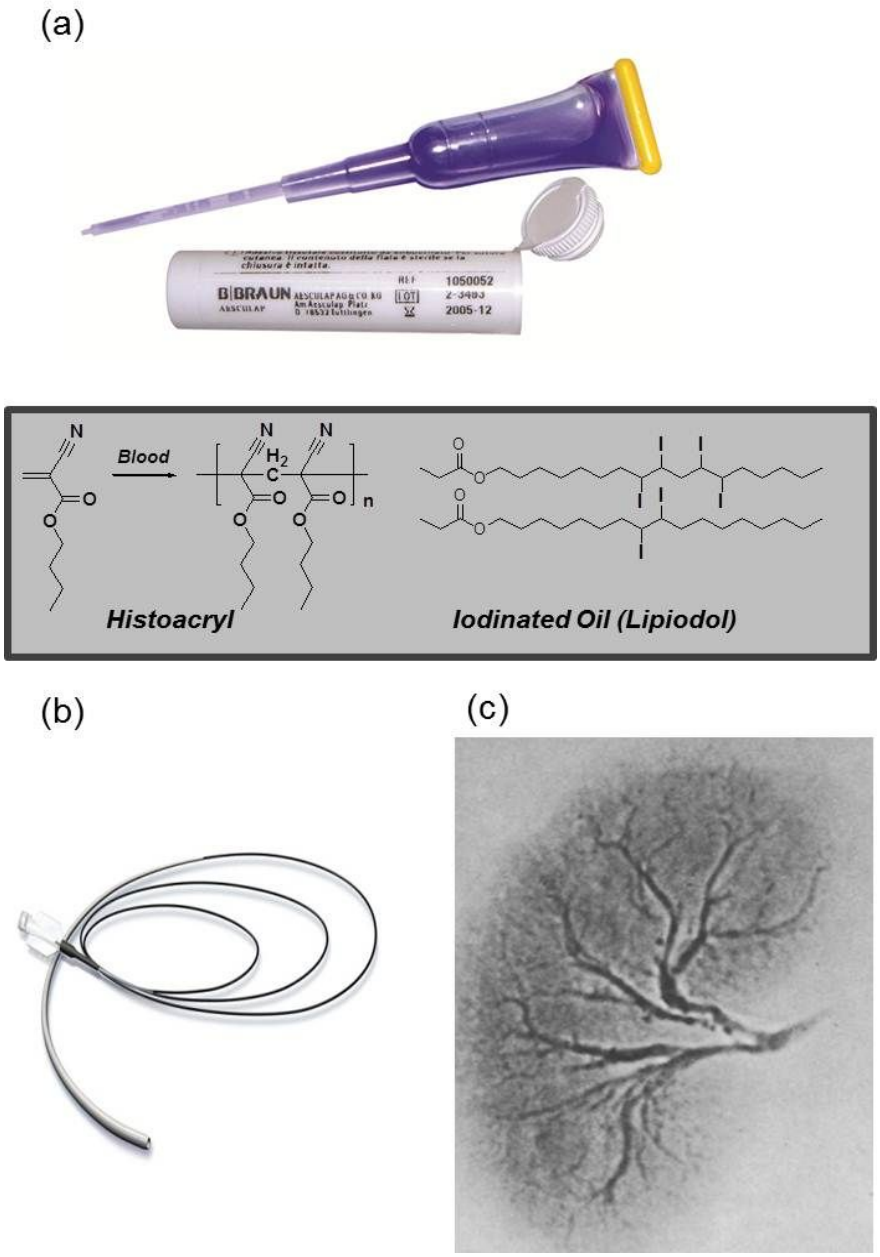



**Figure 2**. Histoacryl's (a) chemical structure and (c) CT image of kidney after injecting [8]. (b) Catheter for using TACE.

Rapid solidification rate of Histoacryl makes the polymers sticky and interact strongly with microcatheter tip, which might lead to a serious problem in withdrawing the catheter after injection. To overcome the disadvantage of Histoacryl, Onyx was developed and also approved by FDA[10]. Onyx consists of ethylene-vinyl alcohol copolymer dissolved in organic solvent of dimethyl sulfoxide (DMSO) and suspended micronized tantalum powder to provide CT response. The solidification of Onyx is based on precipitation of polymer when organic solvent is washed out on contact with blood flow [11]. The radiopacity, composition and precipitation of polymer from Onyx are shown in Figure 3. The main advantage of Onyx is that precipitated polymer does not adhere to the catheter. However, Onyx has many disadvantages due to the use of organic solvent, which causes side effects on the blood vessels and result in severe pain to patients when it is infused into vessels [12] and special microcatheter is required to safely handle the polymeric solution in DMSO..

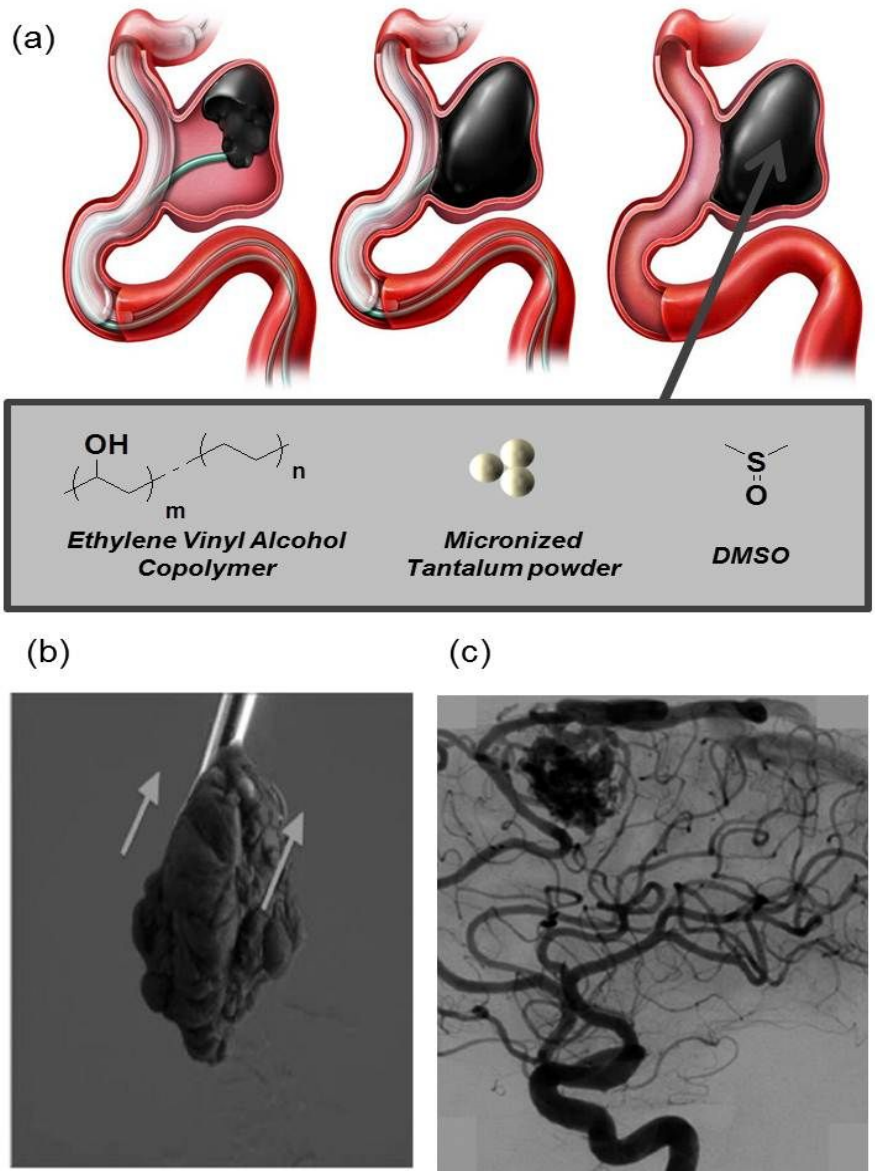



**Figure 3.** Description of (a) delivery procedure, (b) solidification and (c) CT image of brain after injecting of Onyx [11].

Avoiding the use of highly sensitive organic solvent in polymer solution, water solution based polymeric particle for embolization materials are widely studied in endovascular treatment. Various drug-eluting bead (DEB) was described in Table 1. Among them, DC Bead® (Contour, UK) is the first commercially available drug-eluting bead (DEB) as an embolic microsphere product. The beads are composed of polyvinyl alcohol polymer that has been modified with sulfonate groups to form a hydrogel of high water content (95%). Negatively charged sulfonate groups interact with positively charged protonated amine group of doxorubicin hydrochloride (Pharmacia & Upjohn, Kalamazoo, MI) by an ion-exchange process [12, 13]. This process also leads to a decrease in the equilibrium water content of the beads as some of the water molecules around the ionic groups are replaced by drug. Chemical structure of DC Bead, doxorubicin and irinotecan pointed the sites of binding interaction were illustrated in Figure 4 [14]. This device has the ability to release drug in a controlled and sustained manner. Drug loaded solution was prepared by soaking the beads in the solution of doxorubicin and Lipiodol (iodized oil). The soaking time is dependent on the concentration of drug loading solution and bead size. DC Bead was shown to rapidly sequester doxorubicin from solution and maximum loading levels of approximately 45 mg/mL of hydrated beads.

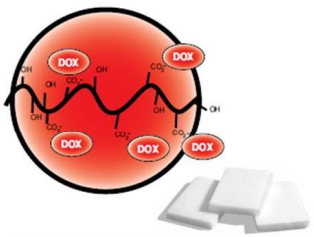
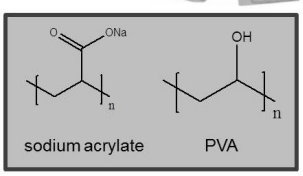
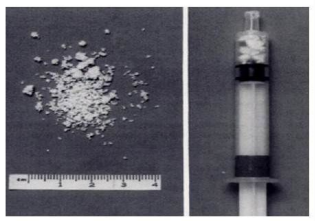
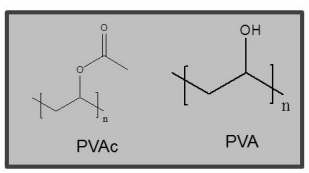
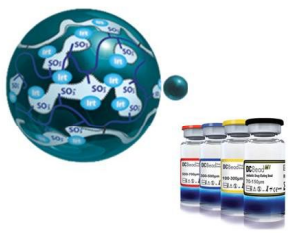
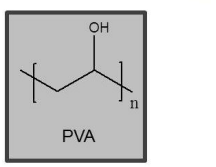
| Cutanplast® | Ivalon® | DC bead® |
|---|---|---|
| • Sponge-like sphere by sodium acrylate and vinyl alcohol copolymer     | • Sponge-like particle by hydroxylated polyvinyl acetal (PVAc)    | • Poly vinyl alcohol particle modified with sulfonate groups which are irregular shape and size    |

**Table 1**. Comparative features between a particle form of embolic material.

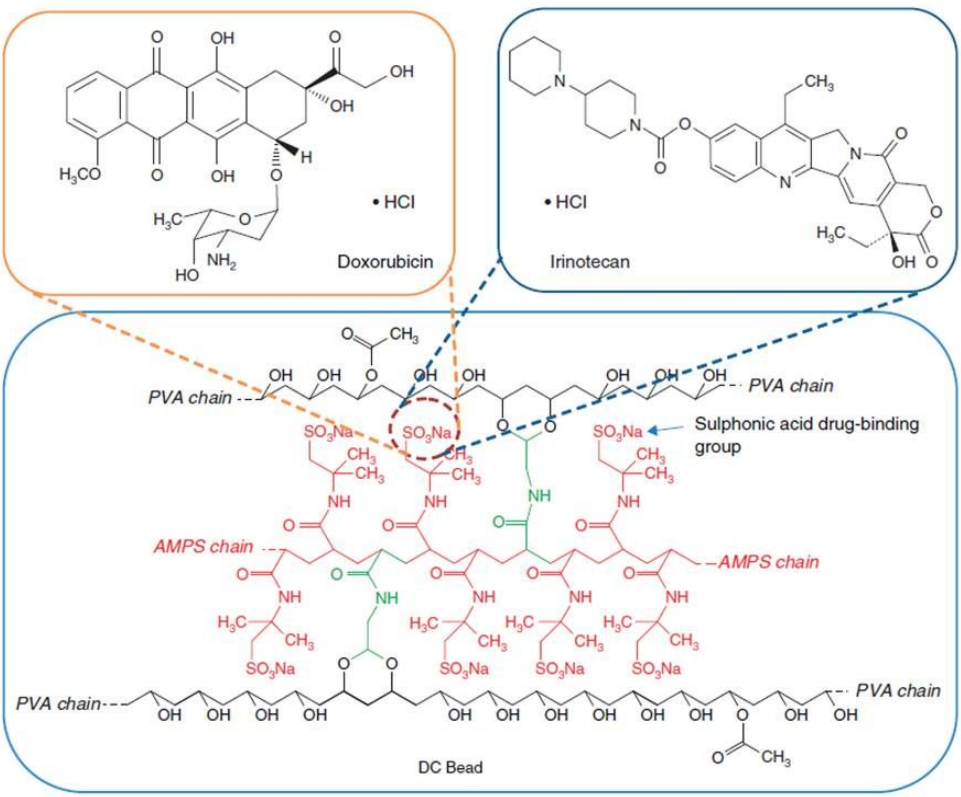



**Figure 4**. Chemical structure of DC Bead, doxorubicin and irinotecan pointing the sites of binding interaction [13].

The solid drug-loaded beads in the TACE procedure avoids the problems in using liquid embolic materials such as Histoacryl and Onyx [15, 16]. However, irregular particle size and shape have been reported to cause an inflammatory reaction in the wall of the embolized vascular tissue, which makes selective occlusion of targeted blood vessels difficult. In addition, commercial solid embolic materials are not inherently radiopaque and being used as a mixture with contrast agents in clinical use. As discussing above, there are both pros and cons in liquid and solid embolic system (Table 2). To endow the embolic materials with x-ray opaqueness, Histoacryl, DC bead or Onyx need to be combined with a CT contrast agents or tantalum powder. Based on these properties, there is a need for invention of a new embolic material which is safe in administration and x-ray opaque for easy and comfortable follow-up with radiologic imaging after administration. In this study, we designed and synthesized a new embolic material, that is polymeric microparticles contacting iodines, with inherent radiopacity.

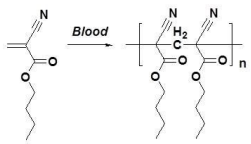
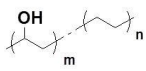
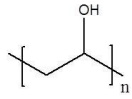
| | Histoacryl® | Onyx® | DC bead® |
|---|---|---|---|
| **Structures** |  N-butyl-2-cyanoacrylate |  Ethylene Vinyl Alcohol Copolymer |  Poly Vinyl Alcohol |
| **State** | Liquid monomer | Polymer dissolved In DMSO | Particle |
| **Contrast agents** | Lipiodol | Tantalum powder | Lipiodol |

**Table 2**. Comparative features between embolic materials

# 2. EXPERIMENTS

## 2.1 Materials

2,3,5-Triiodobenzoic acid (TIBA) and 2,2'-azoisobutyronitrile (AIBN) were obtained from TCI (Tokyo Chemical Industry Co., Ltd., Tokyo, Japan). AIBN was recrystallized from methanol and kept at 4 $^{o}$C before use.

Vinyl benzoate (VB), vinyl 4-*tert*-butylbenzoate (VtB), vinyl acetate (VAc), palladium(II) chloride ($PdCl_2$), lithium acetate (LiOAc), copper(II) bromide ($CuBr_2$), iodine ($I_2$), polyvinyl alcohol (PVA) Selectfluor® (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octanebis(tetrafluoro borate), F-TEDA-$BF_4$,), Celite® and acetonitrile (MeCN) were purchased from Sigma-Aldrich (St. Louis, MO, USA).

## 2.2. Instruments

$^{1}$H NMR analysis was performed by Bruker Advance-300 MHz spectrometer using DMSO-$d_6$ or $CDCl_3$-$d_6$ as a solvent at room temperature. Melting point was determined using a Stuart melting point apparatus SMP10 (Stuart Scientific Stone, Staffordshire, UK). The molecular weight and its distribution was analyzed by gel permeation chromatography (GPC) with a refractive index detector (Shimadzu RID-10A refractometer, Shimadzu SCL-10Avp, Shimadzu Corporation, Kyoto) equipped by Styragel® HR 3, HR 4 and HR 4E columns in series. The flow rate was 1 mL/min with tetrahydrofuran (THF) as an eluent and PS standards in the range of 1,400 ~ 250,000 Da were used for calibration. The microstructure of the product was observed using an optical microscope (OM, OLYMPUS, BX51M, Japan).

## 2.3. Synthesis of 2,3,5-triiodo vinyl benzoate (TIVB)

Previous synthetic procedure was modified for the synthesis of TIVB [17-20]. 1 L round bottom flask equipped with a dropping funnel was charged with $PdCl_2$ (0.05 mol), LiOAc (0.1 mol), and $CuBr_2$ (0.05 mol) dissolved in mixture of vinyl acetate (15.0 mol) and THF (10 mL) at room temperature. After the solution was heated to 60 $^oC$, 2,3,5-triiodobenzoic acid (TIBA) (1.0 mol) was added. The reaction continued with stirring at 80 $^oC$ for 3 days. The crude product was filtered by Celite® with ethyl acetate and purified by silica column chromatography (n-hexane /EA = 10/1, v/v).

$^1H$ NMR (DMSO, δ, ppm) : 4.83-4.85, 5.07-5.12, 7.32-7.39 (m, 3H, C(=O)OC*H*=C$H_2$), 7.90, 8.40 (d, 2H, ArH-$I_3$).

## 2.4. Polymerization of TIVB, vinyl benzoate (VB) and vinyl 4-*tert*-butylbenzoate (VtB)

TIVB (1.0 mol) and AIBN (0.008 mol) were added into 100 mL one neck round bottom flask under nitrogen atmosphere. Polymerization was completed at 130 $^{o}$C for 12 h [21]. Monomeric VB or VtB (1.0 mol) in 100 mL one neck round bottom flask was bubbled by $N_2$ for 1h and AIBN (0.008 mol) was added into the liquid monomer under nitrogen atmosphere [22-24]. Polymerization continued at 90 $^{o}$C for 12 h. The crude product was dissolve in acetone and precipitated into methanol to produce polymers. The obtained product were filtered and dried under vacuum at 45 $^{o}$C.

PTIVB $^{1}$H NMR (DMSO, δ, ppm) : 7.64, 8.18 (m, 2H, ArH-$I_3$), 2.23, 5.25 (m, 3H, $(CH_2$=CHOR)n ). PVB $^{1}$H NMR (DMSO, δ, ppm) : 7.19-7.62 (m, 5H, ArH-R), 2.07, 5.10 (m, 3H, $(CH_2$=CHOR)n ). PVtB $^{1}$H NMR ($CDCl_3$, δ, ppm) : 7.20, 7.73 (m, 4H, ArH-R), 2.08, 5.23 (m, 3H, $(CH_2$=CHOR)n ), 1.21 (m, 9H, $(CH_3$-CR$)_3$ )

## 2.5. Iodination of poly (vinyl benzoate) (PVB) and poly (vinyl 4-*tert*-butylbenzoate) (PVtB)

1 L round bottom flask equipped with a dropping funnel was charged with PVB or PVtB (0.01 mol) dissolved in 100 mL MeCN. $I_2$ (2.0 mol) and Selectfluor$^{TM}$ (2.0 mol) dissolved in the mixture of 10 mL THF and 50 mL MeCN were added into the polymer solution [25-28]. The reaction continued at 80 $^{o}$C under nitrogen atmosphere for 3 days. After complete removal of the solvent, the crude product was redissolved in dichloromethane and the solution was extracted with aqueous sodium thiosulfate pentahydrate (10%, w/w) solution. The organic layer was dried over anhydrous magnesium sulfate ($MgSO_4$) for 30 min and polymer was obtained after evaporation of the solvent. The iodinated polymer IPVB and IPVtB were kept under vacuum at 45 $^{o}$C.

IPVB $^1$H NMR (DMSO, δ, ppm) : 7.17-7.5 (m, 4H, ArH-I), 2.02, 5.12 (m, 3H, $(CH_2=CHOR)n$ ). IPVtB $^1$H NMR ($CDCl_3$, δ, ppm) : 7.15-7.96 (m, 4H, I-ArH-R), 2.08, 5.23 (m, 3H, $(CH_2=CHOR)n$ ), 1.16 (m, 9H, $(CH_3-CR)_3$ ).

## 2.6. Formation and characterization of particles with iodinated polymers

1.0 g PVA (Mw. 130,000) and 30.0 g $NaCl_2$ were dissolved in 100 mL water in 1 L beaker at 80 $^{o}$C. After the solution was cooled down to room temperature, 1.0 g PTIVB dissolved in 100 mL THF was added to the aqueous solution [29, 30]. The solution temperature was gradually increased up to 80 $^{o}$C and the mixture was magnetically stirred by 200 RPM for 24h. The crude product was washed using hot water and freeze-dried to isolate particles.

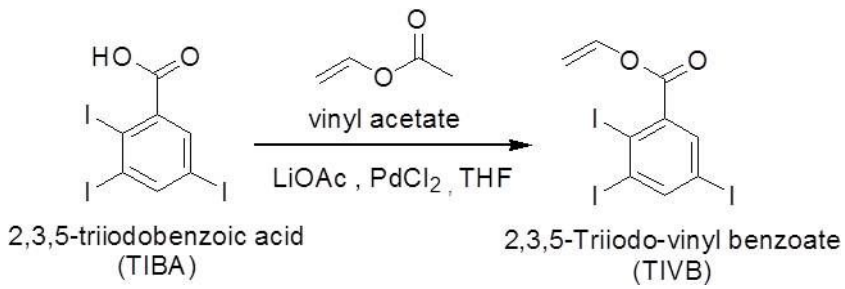
1.25g PVA was dissolved in 100 mL water in 500 mL one neck round bottom flask at 90 $^{o}$C. After the solution was cooled down to room temperature, 1.0g IPVB or IPVtB dissolved in 5 mL dichloromethane was added dropwise into the PVA solution. The stirring was continued at 40 ◦C with the rate of 1000 rpm for 12 h. The crude product was washed with water and freeze-dried to isolate particles [31, 32, 33].

The size of polymer particles was measured using an optical microscope after filtered through steel sieves with pore size 50, 100 and 200 μm. The x-ray opaqueness was qualitatively under a normal C-arm device in Seoul National University Hospital.

# 3. RESULTS AND DISCUSSION

## 3.1. Synthesis and characterization of iodinated polymer PTIVB, IPVB and IPVtB

Introduction of polymerizable vinyl group into the carboxylic acid of TIBA was completed by $PdCl_2$-catalyzed trans-esterification in the presence of vinyl acetate, LiOAc, and $CuBr_2$ [19, 20]. Synthetic scheme of TIVB was illustrated in Scheme 1. Characterization of the obtained product was performed by $^1H$ NMR and spectra of each compound were shown in Figure 5. Successful synthesis of TIVB was confirmed by $^1H$ NMR analysis based on new peaks from protons at vinyl group (-OC*H*=C$H_2$ : 4.83-7.39 ppm) next to ester group in TIVB and disappearance of a peak from carboxylic acid group of TIBA at 13.61 ppm. Isolated yield for the formation of TIVB was very low around 15-18 % and this trend has been previously reported for vinylation of aromatic carboxylic acids with sterically hindered structures [17-20]. It was assumed that heavy iodines with high atomic number on the benzene ring played a role of bulky groups in the previous study to reduce the reactivity of a compound of the reaction, which resulted in such a low yield.




**Scheme 1**. Synthetic procedure of TIVB

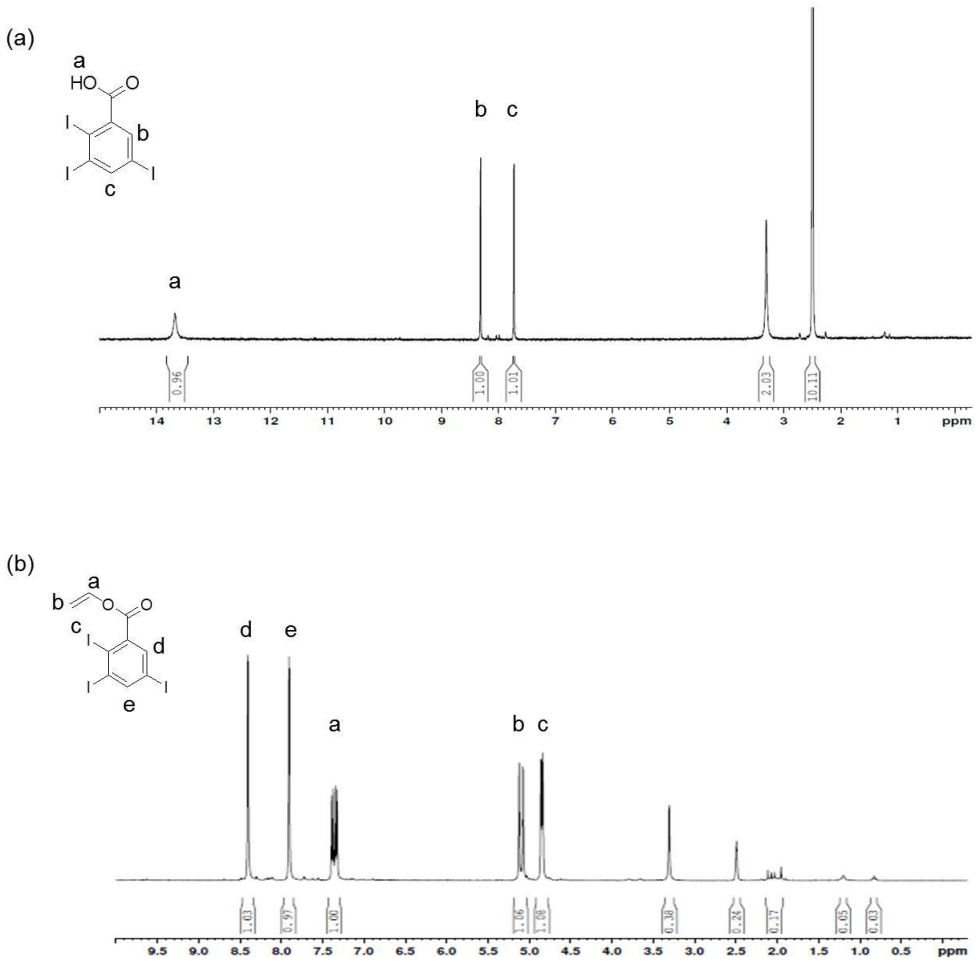



**Figure 5**. $^{1}$H NMR spectra of (a) TIBA and (b) TIVB

Melting point of TIVB was determined to be around 110 $^{o}$C by a Stuart melting point apparatus SMP10 (Figure 6). It was reported that monomers containing iodines were highly resistant to homo-polymerization and copolymerization with other monomers under normal conditions of free radical polymerization [21]. Polymerization of TIVB was completed by radical polymerization in bulk with AIBN at 130 $^{o}$C under the nitrogen atmosphere for 12 h. VB and VtB were also polymerized in bulk with AIBN at 90 $^{o}$C [21, 22, 23]. Synthetic scheme of the PTIVB, PVB and PVtB were illustrated in Scheme 2. Successful polymerization was confirmed by $^{1}$H NMR analysis based on disappearance of proton peaks from vinyl group (-OC*H*=C$H_2$ : 4.83-7.39 ppm) of monomers and appearance of widened peaks caused by extended relaxation time of polymer chains (Figure 7). Molecular weights and distributions of the polymers were determined by GPC and the traces were illustrated in Figure 8. Molecular weight of PTIVB, PVB and PVtB was 147K, 218K and 262K, respectively with the value of Mw/Mn to be 1.18, 1.78 and 3.52, respectively.

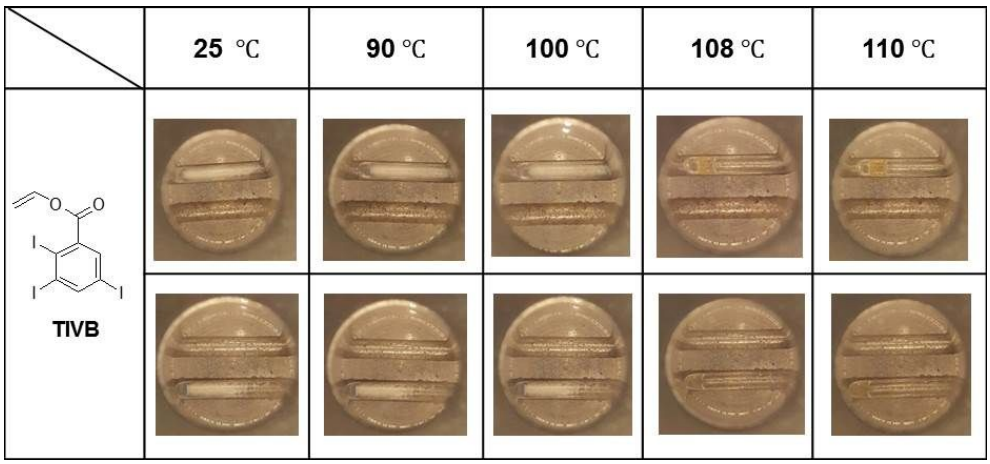
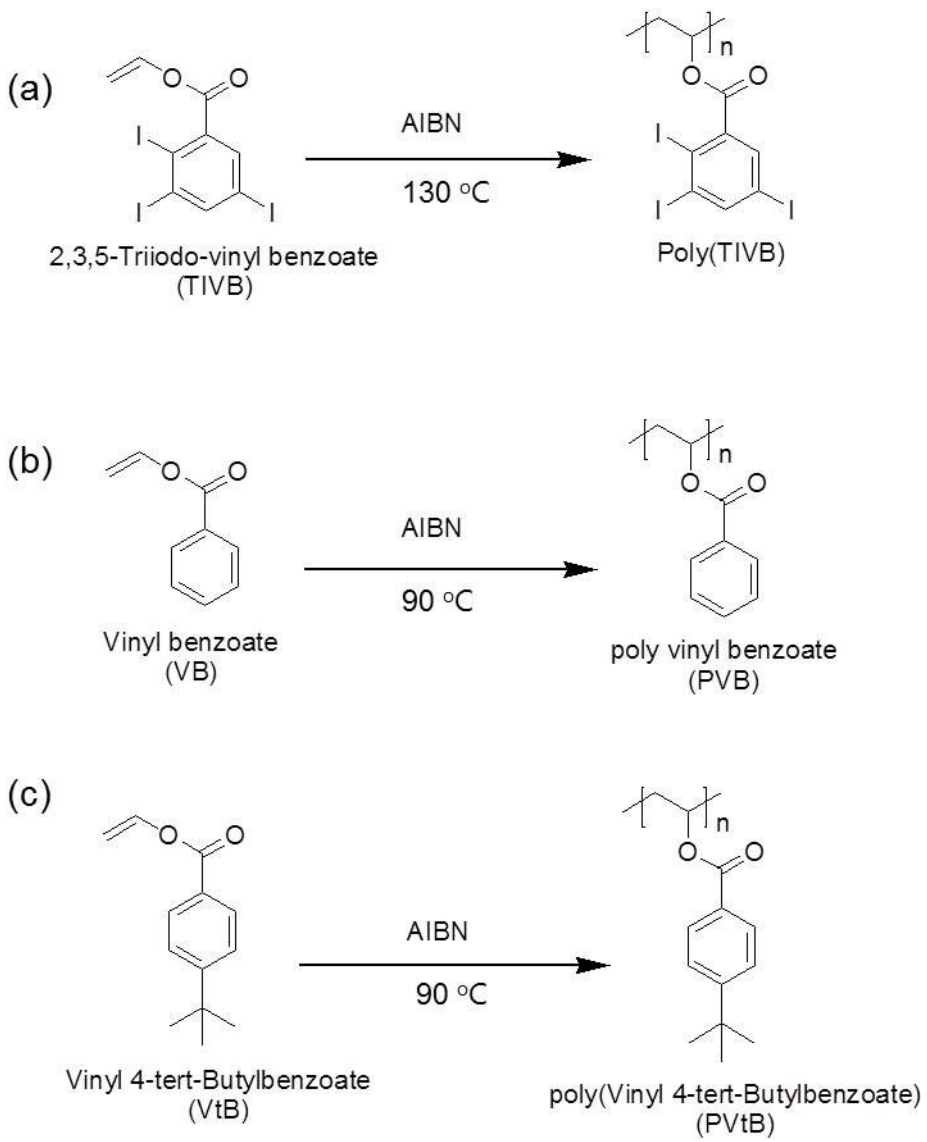



**Figure 6**. Melting point measurement of TIVB




**Scheme 2**. Polymerization scheme of (a) TIVB, (b) VB, and (c) VtB

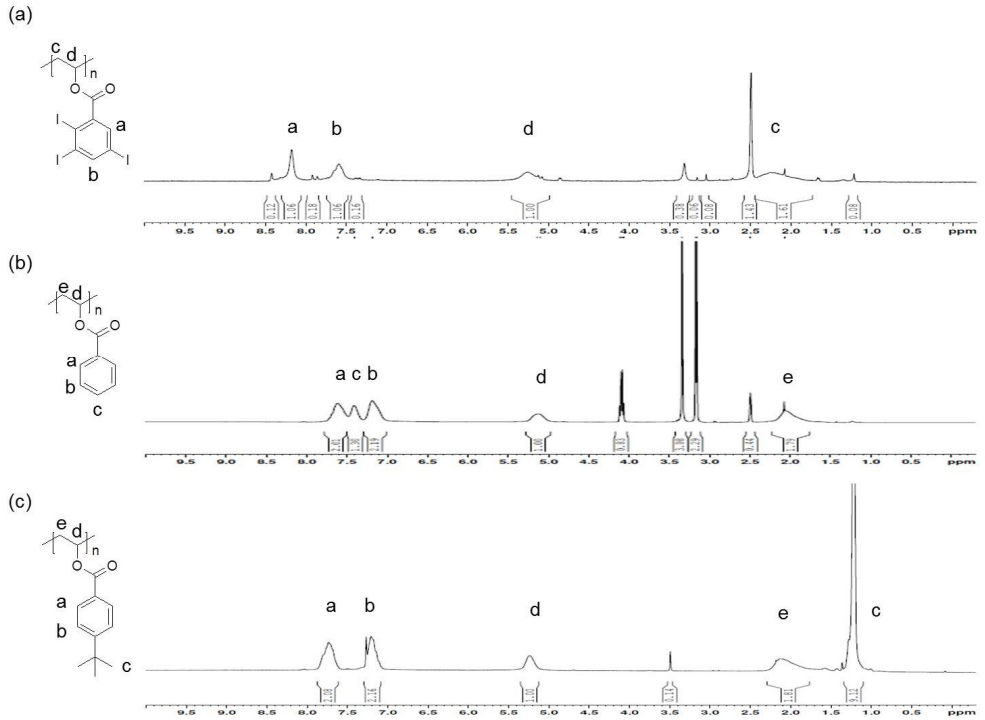



**Figure 7**. $^{1}$H NMR spectra of (a) PTIBA, (b) PVB and (c) PVtB

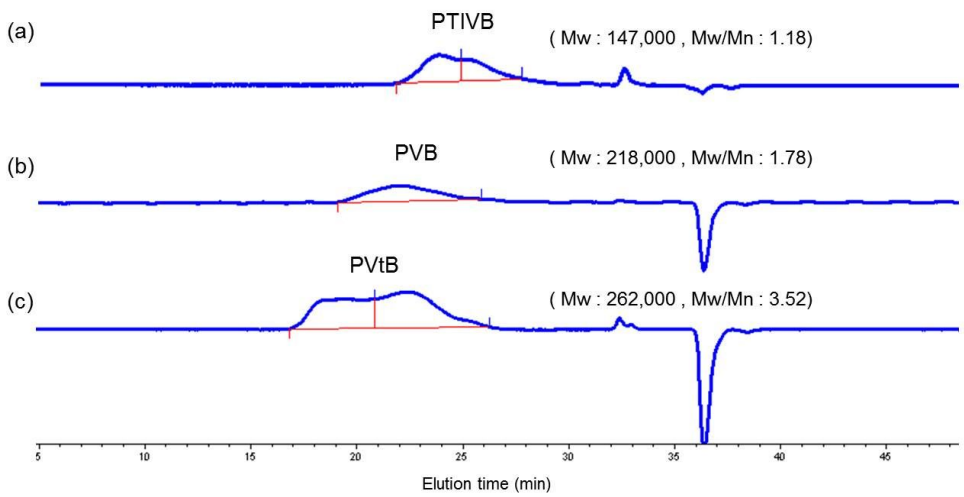
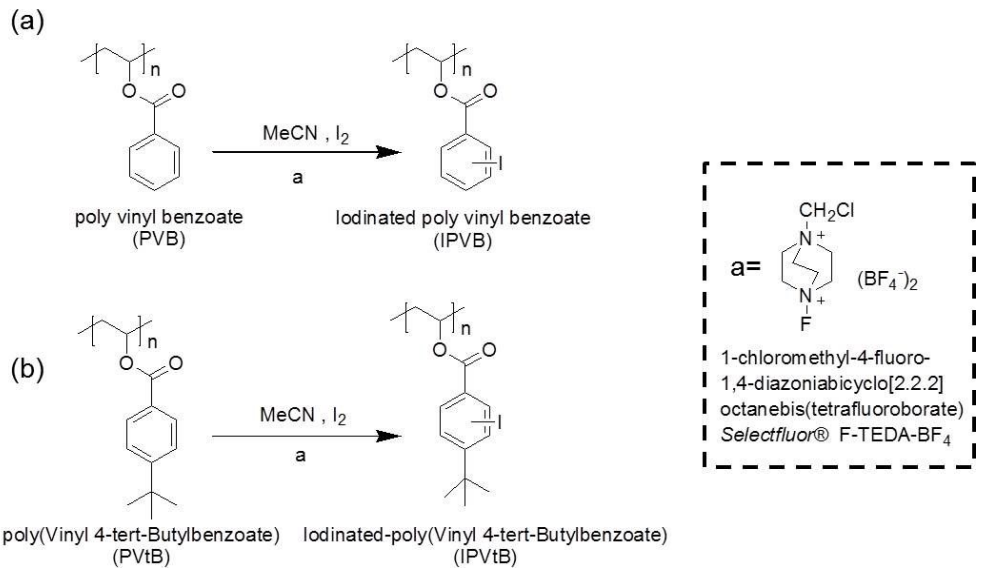



**Figure 8**. GPC trace of PTIVB, PVB and PVtB

Hydrogens of benzene rings were replaced via electrophilic aromatic substitution by electrophilic l iodine from polarization of the I-I bond by Selectfluor® (F-TEDA-$BF_4$, 1-chloromethyl-4-fluoro-1,4-diazoniabi cyclo[2.2.2]octanebis(tetrafluoroborate)) [25, 26]. Selectfluor® is one of the most powerful and effective mediator for electrophilic fluorinating reagent of organic compounds from the N-F family [27, 28]. Synthetic procedure of iodination of IPVB and IPVtB were illustrated in Scheme 3. Successful iodination of the polymers was confirmed by $^1$H NMR analysis based on decrease in peak intensities from protons at aromatic group (-Ar*H* of PVA : 7.04-7.79 ppm) of the monomers and shift of aromatic peaks after iodine substitution (Figure 9). Iodination did not produce a significant difference in molecular weights and distribution of polymers measured by GPC.




**Scheme 3**. Iodination procedure of PVB and PVtB

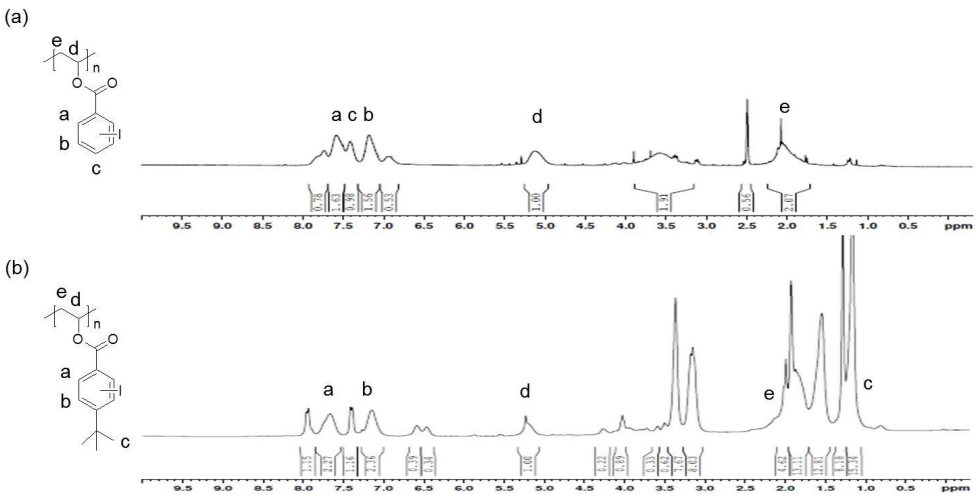



**Figure 9**. $^{1}$H NMR spectra of (a) IPVB and (b) IPVtB

## 3.2. Formation and characterization of microparticles

Microparticle of PTIVB was formed by phase separation between THF and aqueous phase, and the method for particle formation was reported as Self-ORganized Precipitation (SORP) in THF and water [29, 30]. Due to the low solubility of PTIVB in an organic solvent, excess amount of THF was employed in the particle formation. NaCl and PVA were dissolved in water, which increased viscosity of the aqueous phase and led to accelerated separation of the two phases.

THF solution of PTIVB was poured to the aqueous solution, and the mixture was slowly stirred at 70 $^{o}$C until THF was evaporated (Figure 10-a). After evaporation of the organic solvent, the product was washed with hot water for preventing PVA and NaCl recrystallization. The microstructure of the product was observed by an optical microscope after filtered through steel sieves with a pore size of 50, 100 and 200 μm. PTIVB particle sized under 50 μm was shown in Figure 11-a. Microspheres of different size in diameter ranged from 30 to 2000 μm could be prepared by changing the viscosity of PVA solution, concentration of THF and stirring speed. The size of particle was maximized to be 2000 μm without stirring and concentrated THF solution for 24 h at 80 $^{o}$C.

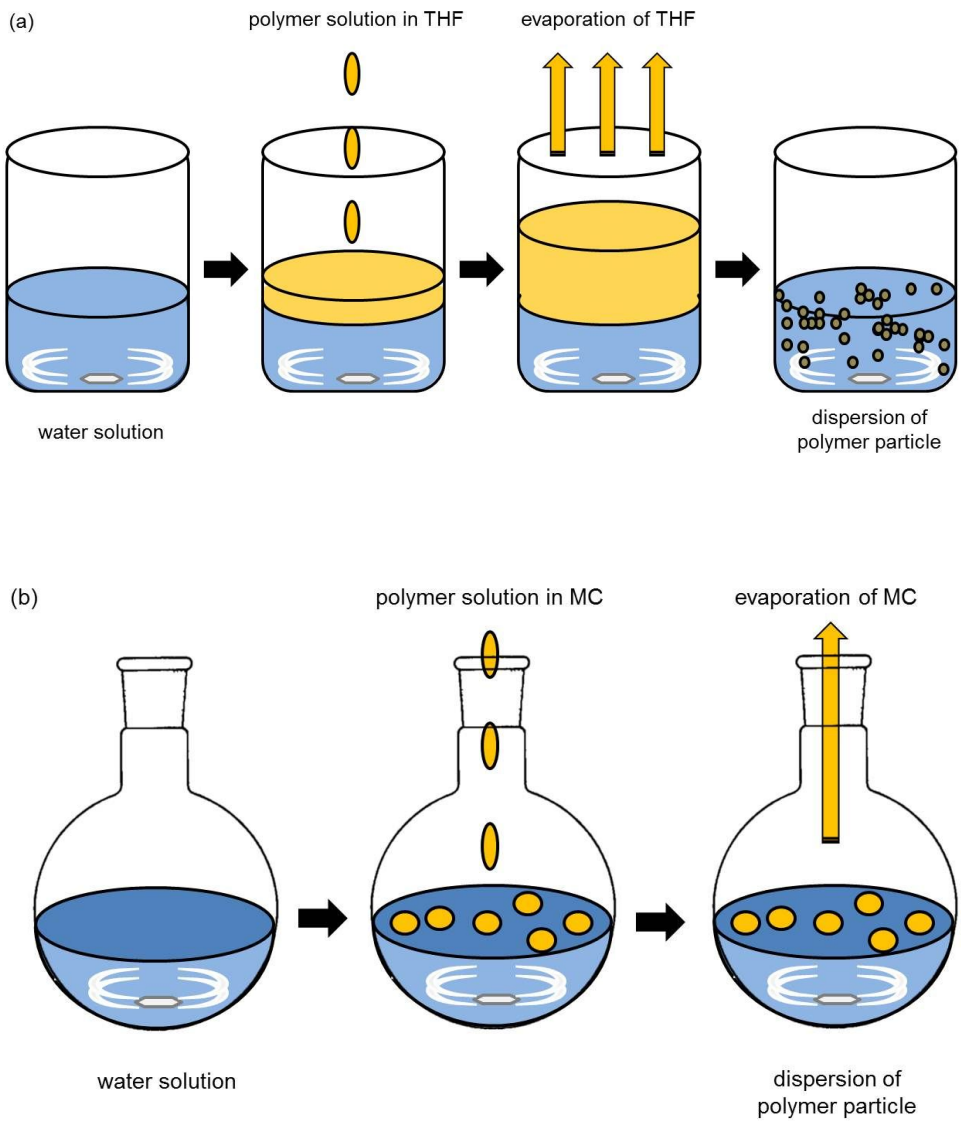



**Figure 10**. Formation of PTIVB particle sized 30-10000 μm

Microparticles of IPVB and IPVtB were prepared using oil in water (O/W) emulsion-solvent evaporation method (Figure 10-b)[31-33]. Polymer (IPVB or IPVtB) dissolved in MC was emulsified in 100 mL water containing PVA. The stirring speed and concentration of PVA in aqueous solution were controlled to produce a required particle size. The resulting oil-in-water (O/W) emulsion was stirred for 12h under ambient conditions to allow solvent to evaporate and microparticle formation. The microparticles were then collected by centrifugation and washed with distilled water. Immediately-formed microparticles in PVA or washed microparticles were sized by an optical microscope after size selection through steel sieves with a pore size of 50, 100 and 200 μm. Particles were irregularly shaped and difficult to control the size, probably due to the low solubility of polymers in organic solvent. Pictures of optical microscopy for IPVB and IPVtB particles are shown in Figure 11-b and c.

Radiopacity of iodinated polymer microparticle was determined under x-ray using C-arm (Figure 12). Visipaque™ is a representative CT contrast agent in clinical use with high x-ray opaqueness and Lipiodol is a poppyseed oil in clinical use as a biocompatible x-ray opaque contrast agent. Both contrast agents were employed as control groups to visually compare the x-ray opaqueness of prepared microparticles. Since Lipiodol is not

soluble in water, THF was used to dilute Lipiodol to emphasize the effect of concentration on x-ray opaqueness. The pictures are shown in Figure 12-a and Figure 12-b.

The polymers were dispersed in 0.4 % aqueous hyaluronic acid (w/w) for better dispersity and the solution was gently shaked before x-ray measurement. There was previous study for radiopactity of cyanoacrylate derivatives containing only one-iodine in the structure, which was as x-ray opaque as Ultravist and Lipiodol with multiple number of iodines in the structures. Based on this previous result, PTIVB with 3 iodines in every repeating unit was expected to display high radiopacity. X-ray opaqueness of PVB and IPVtB was believed to be dependent of the number of iodine substitution on the aromatic rings. As shown in Figure 12 c, PTIVB showed the highest x-ray opaqueness among the prepared micropaticles, which was strong enough for further application in *in vivo* study as a contrast agent. As shown in Figure12-d, the x-ray opaqueness of iodinated PVB was not intense enough to be used *in vivo* application, probably due to a limited number of replaced iodine, In case of IPVtB, x-ray opaqueness was acceptable, but the solid microparticles before iodination became highly viscous liquid after iodination. Viscous liquid is not suitable for the application as an embolic material because embolic materials administrated

at a target sites should display mechanical properties which is required to resist the pulsive pressure from the heart-beat (Figure 12-e). Based on the x-ray images, microparticles of iodinated PTIVB will be further developed as an x-ray opaque embolic materials. IPVtB and iodinated PVB showed limitations as an x-ray opaque material due to the low replacement ratio and poor mechanical properties.

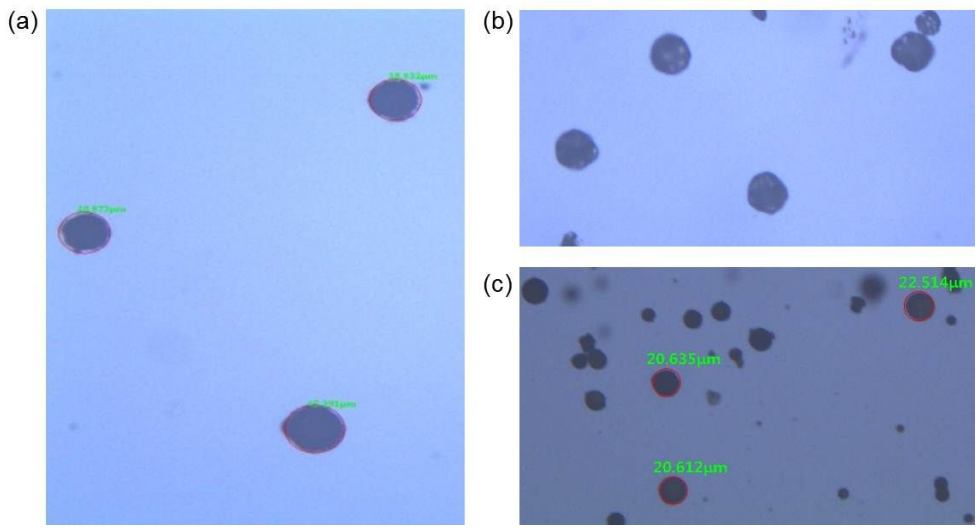



**Figure 11**. Observation particles of (a) PTIVB (b) IPVB and (c) IPVtB by optical microscope.

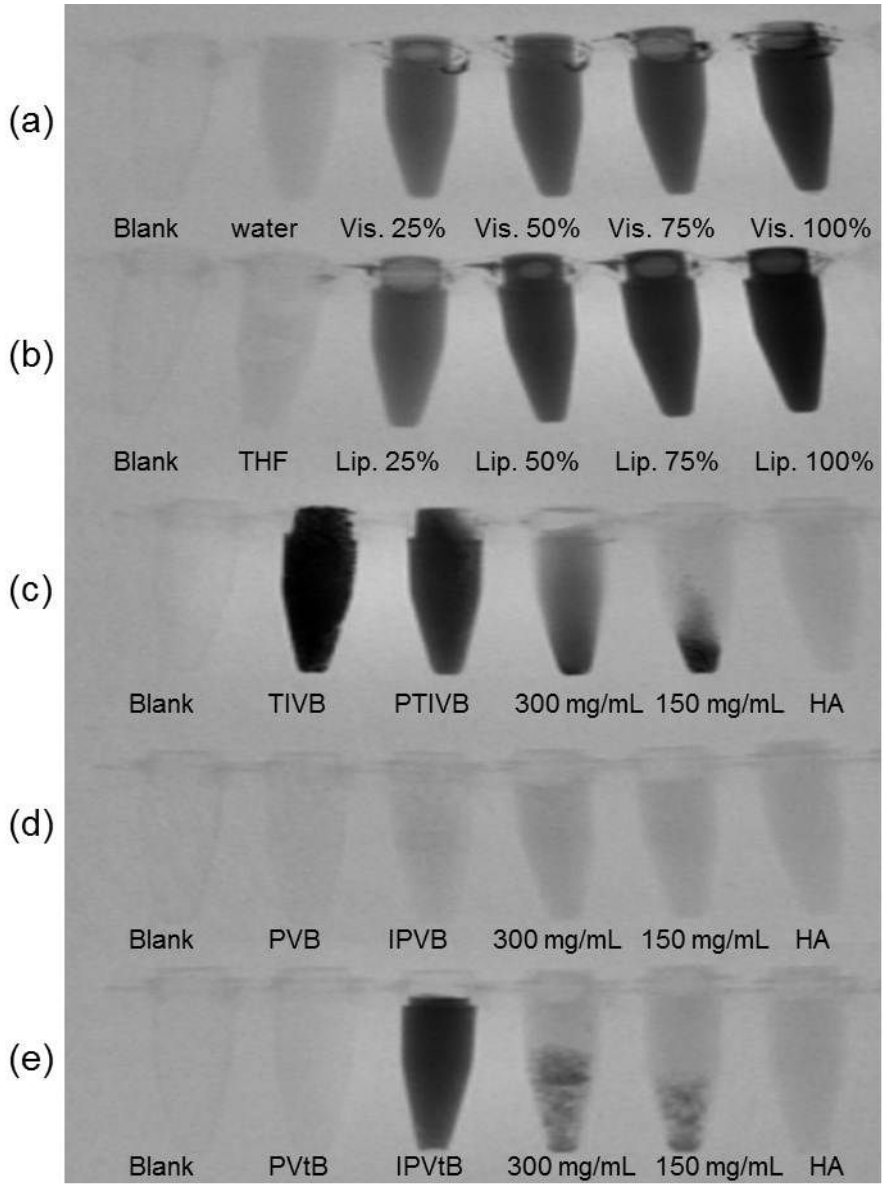



**Figure 12**. Observation radiopacity of (a) Visipaque, (b) Lipiodol, (c) PTIVB (d) IPVB and (e) IPVtB by computed tomography (CT)

# 4. CONCLUSION

In this study, we designed and synthesized a new embolic material and characterized its properties. 2,3,5-Triiodovinyl benzoate (TIVB) monomer was successfully synthesized from 2,3,5-triiodobenzoic acid (TIBA) using $PdCl_2$-catalyzed trans-esterification. TIVB. Vinyl benzoate (VB) and 4-*tert*-butylbenzoate (VtB) were polymerized by radical polymerization with AIBN in bulk under the nitrogen atmosphere. Iodination of PVB and PVtB polymers were completed using electrophilic aromatic substitution by activation of electrophilicity of elemental iodine by Selectfluor®. Purity of each product in the synthetic procedures was confirmed by $^1H$ NMR analysis, and molecular weight and distribution of polymers were determined by GPC. Formation particle of PTIVB was based on Self-Organized Precipitation (SORP) and microparticles of IPVB and IPVtB were prepared using oil in water (O/W) emulsion solvent evaporation method. The microstructure of the product was observed by an optical microscope and x-ray images were taken using a C-arm to determine x-ray opaqueness.

In conclusion, the microparticle composed of iodinated polymers displayed strong x-ray opaqueness enough for the further application as an embolic materials. Optimization of the particle size and selective hydrolysis from the particle surface will make the micropaticles an embolic materials with controlled hydrophilic surface and controlled particle density, which can be employed as an injectable materials into blood vessel via catheter.

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# 요약문

간암 화학색전술은 암세포가 혈액에 의존함에 착안하여 간암세포에 영양을 공급하는 주된 동맥을 찾아 항암제를 투여한 다음 혈관을 막아주는 치료법이다. 혈관조영제를 주사하면서 간동맥 CT 조영 사진을 얻어 종양의 위치, 크기 및 혈액 공급 양상 등의 정보를 얻어 항암제, 조영 물질 그리고 색전물질을 넣어 시술하게 된다. 기존 색전물질의 급격한 중합 속도로 인한 카테터의 흡착 위험과 유기용매를 고분자와 섞은 상태로 주입하는 방법을 피하기 위하여 물을 사용할 수 있는 구 형태의 색전물질들이 연구 되고 있다. 다양한 약물방출성 구슬입자 중에서 디씨비드®는 이온 교환을 통하여 항암제를 빠르게 흡수하고 색전 물질로 이용될 뿐만 아니라, 그 자리에서 항암제를 다시 방출 할 수 있다. 이때, 색전물질 시술의 CT 확인을 위하여 아이오딘을 포함한 기름형태의 조영제 리피오돌®을 함께 투입한다. 디씨비드의 시술은 절제술이 불가능한 암환자의 치료 및 생존율의 향상에 크게 기여하고 있으나, 불규칙적인 구형

사이즈와 모양은 혈관 내벽에서 의도하지 않은 염증성 반응을 일으킬 수 있다. 또한, 색전물질 스스로가 조영제로 쓰일 수 없어 정확한 색전 위치를 파악하고 관찰 하는데 한계가 있다.

본 연구에서는 아이오딘을 포함한 고분자를 합성하고 구형 물질을 만들어 혈관 내에 CT 조영이 가능 하면서 색전물질로 사용 가능한 새로운 구 형태의 색전 물질을 개발하였다. 색전물질은 아이오딘을 포함한 단량체를 사용하거나, 고분자에 아이오딘 첨가반응을 진행함으로서 CT 방사성 가능한 물질로 합성하였고, 이를 다양한 크기로 구형화 하면서 색전 물질로서의 특성을 갖게 하였다. 본 연구에서 설계된 새로운 색전물질은 기존 리피오돌®만큼 우수한 조영 효과를 보였으며 색전물질의 의료용 재료로써의 응용 가능성이 매우 높은 것으로 확인되었다.

**주요어:** 조영제, 색전물질, 색전술, 간암 화학색전술, 디씨비드, 리피오돌

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