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막유화법에 의한 생분해성 Polycaprolactone 마이크로캡슐의 제조와 약물방출 특성

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Preparation of Polycaprolactone Microcapsules by Membrane Emulsification Method and Its Drug Release Properties

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요 약: SPG (Shirasu porous glass) 관형 막이 설치된 회분식 막유화 장치를 사용하여 이온성 약물이 담지된 단분산 polycaprolactone (PCL) 마이크로캡슐을 제조하기 위한 막유화 공정변수의 최적조건을 결정하였다. 마이크로캡슐에 담지된 이온성 약물로는 양이온성인 lidocaine·hydrochloride, 중성인 sodium salicylate와 음이온성인 4-acetaminophen의 3가지를 사용하였으며, PCL 마이크로캡슐로부터 이들 모델약물의 방출거동을 검토하였다. 캡슐제조에 사용된 PCL의 농도와 분자량, 막간 압력차, 분산상과 연속상에 첨가시킨 유화제의 농도, 연속상의 교반속도가 막유화법으로 제조된 PCL 캡슐의 크기와 크기분포에 미치는 영향을 검토하였다. 이들 공정변수의 조절을 통해 평균 크기 약 5 μm의 균일한 마이크로캡슐을 제조할 수 있었다. 약물 방출실험 결과 산성조건에서 알칼리조건으로 방출환경이 변화됨에 따라 약물 방출속도가 증가하였다.

Abstract: Uniform microcapsules containing ionic model drugs were prepared by controlling various conditions of emulsification procedure using a lab-scale membrane emulsification system with a SPG (Shirasu porous glass) tubular membrane. We observed the effects of various emulsification parameters [concentration and molecular weight of polycaprolatone (PCL) polymer, transmembrane pressure and emulsifier concentration in disperse phase and continuous phase, stirring speed] on the mean size and size ditribution of microcapsules containing lidocaine·hydrochloride (cationic drug), sodium salicylate (nonionic drug) and 4-acetaminophen (anionic drug) used as a model drugs. Also, release characteristics of a model drugs from PCL microcapsules were investigated. Controlling membrane emulsification parameters, uniform PCL microcapsules with about 5 μm of the mean size were finally prepared. The release rate and the burst effect of microcapsules were decreased in condition of the acidic solution, but it was increased in condition of the base solution.

Keywords: *Membrane emulsification, SPG membrane, Microcapsule, Polycaprolactone, Drug release*

1. Introdution

The stability of an emulsion greatly depends upon the emulsifying agent, droplet size, net charge and mechanical and physical properties of the adsorbed film on emulsions [1]. In particular, the distribution of emulsion droplet size is the most important parameter in characterizing any emulsions. Stability and resistance to creaming, rheology, chemical reactivity and physiological efficiency are influenced by both the relative emulsion size and the size distribution [2].

Various instruments exist both on the industrial and laboratory scale to produce emulsions, e.g. colloid mills, toothed discs, dispersing machines and high-pressure homogenizers [2,3]. The emulsions made by those

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instruments show considerable polydispersity such that the droplet size distribution is usually between 0.1 and 100 μm. The preparation of uniform emulsions is considered to be more difficult using the above instrument.

A new emulsifying technique, called membrane emulsification, was proposed by Nakashima et al. [4]. In this method, a microporous glass membrane with a narrow pore size distribution was used as an emulsifying tool. The concept of this method is that a dispersed phase is permeated as uniform droplets through the pore of membrane into a continuous phase flowing alongside the membrane surface by constant pressure, and then formed droplet are detached on the membrane surface and suspended into the continuous phase [5]. This technique has the capability of producing not only uniform emulsions, but also multiple emulsion such as W/O/W emulsions.

A microcapsulated drug is one of prospective drug delivery system because it has obvious advantages, such as improving the therapeutic effect, prolonging the biological activity, controlling frequency, and so on. It is especially important for anticancer drugs, which can be target administration to increase the drug concentration in the disease area with reduced toxicity of drug in the healthy area, as well as lowing the side effect of the drug. Therefore, the study of microparticle preparation has attracted much interest for the past decade [6-9]. By controlling the size of microspheres, the targeted delivery of drugs to the required area of various organs becomes realizable. Polydisperse microspheres of biodegradable polymer have been developed for a hormone delivery device settled under the skin. Highly monodisperse microspheres smaller than 1 μm can be applied to the targeting of drug delivery to various organs, such as the lungs, liver, kidney and especially the brain. Since Nakashima et al. [4] reported the preparation method of monodispersed microspheres using SPG (Shirasu porous glass) membrane, various kind of monodisperse microspheres with a narrow size distribution have been developed [10-13].

Biodegradable polymers are widely used as drug carriers for drug-controlled release and as operation repairing material in medical surgery [9,14]. polycaprolatone (PCL) is one of the biodegradable polymers that can be degraded by hydrolysis and is the widely used biodegradable polymer due to its good drug permeability and biocompatibility. Considering its good drug transportability, PCL is a potential biodegradable polymer for used in the biomedical field. However, the degradation rate of PCL is not fast since its crystallinity is too strong to be hydrolyzed [18]. With the aim of improving and controlling the degradability of PCL, a number of PCL copolymers that comprise ε-caprolactone and other lactones such as glycolide, lactide and valerolactone have been synthesized [19,20]. In particular, PCL demonstrates a low melting point (57°C) and low glass-transition temperature (-62°C). PCL, as matrix of microparticles, can be degraded by microorganism as well as by hydrolytic mechanism under physiological condition and also decomposed into non-toxic and low molecular weight species with release of the drug and then metabolized or absorbed by organism. Therefore, many investigation have focused on the application of biodegradable microparticle drugs in recent years [15-17].

In this paper, the monodisperse microcapsules of a biodegradable polymer, PCL were prepared by controlling various conditions of membrane emulsification procedure using a lab-scale system to prepare PCL microcapsules containing a drugs with different ionic properties that were a lidocaine·hydrochloride (cationic drug), 4-acetaminophenol (nonionic drug) and sodium salicylate (anionic drug). Also, release characteristics of drugs with different ionic properties from PCL microcapsules were investigated. In the experiment, we considered various conditions of membrane emulsification procedure such as the weight ratio of PCL, concentration of emulsifier, stirring speed of continuous phase, and transmembrane pressure.

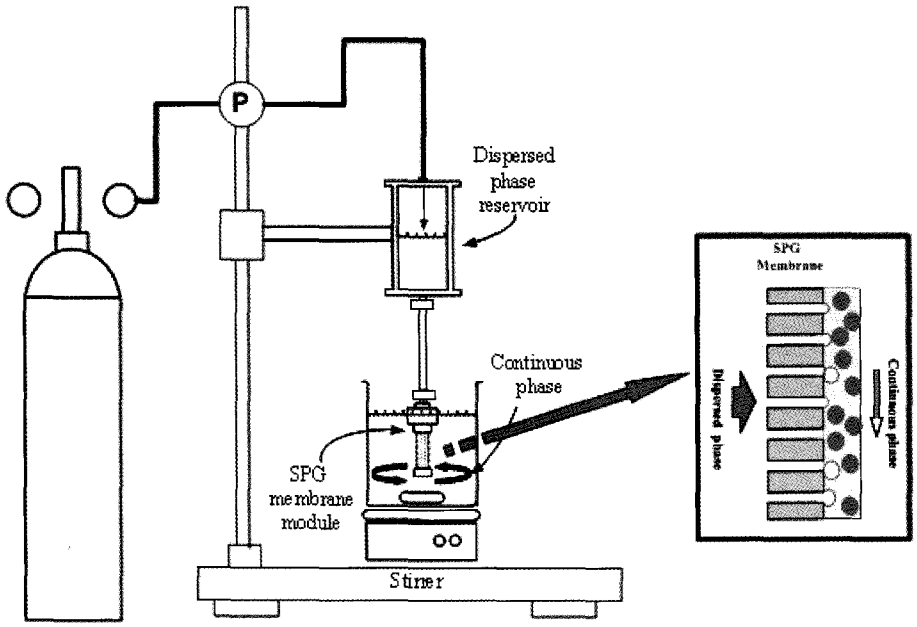


Fig. 1. Schematic diagram of membrane emulsification system.

2. Experimental

2.1. Materials

Polycaprolactone used as a dispersed phase was purchased from Sigma Co., USA. Deionized water used throughout the process as a continuous phase was prepared from Milli-Q Ultra-pure Water System, USA. Sodium dodecyl sulfate used as a emulsifier was provide from Acros Organics Co., USA. Methanol and acetone were provided from Merck Co., Germany. All chemicals were used without further purification. SPG membranes of average pore sizes, 2.6 μm, were purchased from Ise Chemical Co., Japan. Lidocaine · hydrochloride, sodium salicylate and 4-acetaminophen used as a model drugs that have different ionic properties were provide from Sigma Co., USA. Phosphate buffer solution (pH 2.0 pH 7.4 and pH 9.0) were respectively purchased from Shinyo Pure Chemicals Co., Japan.

2.2. Membrane Emulsification System

Fig. 1 shows the membrane emulsification apparatus. Used SPG membrane tubes were 10 mm outer diameter, 1 mm thickness and 250 mm length. The dispersed phase was stored in the dispersed reservoir which was connected to a nitrogen gas tank. The continuous phase was stirred gently with a magnetic bar in a tall beaker (250 mL) to prevent the aggregation of the droplets. By applying a given pressure of nitrogen gas, the dispersed phase will permeate through the uniform pore of the SPG membrane into the continuous phase to form the droplets, then be stabilized by polyvinylalcohol (PVA) and sodium dodecyl sulfate (SDS) dissolved in the continuous phase.

2.3. Preparation of Polycaprolactone Microcapsules

A typical procedure for the preparation of PCL microcapsules was shown in Fig. 2. PCL was dissolved in a mixture of dichloromethane and PVA, and was used as an oil phase. The aqueous phase where SDS and model drug were respectively dissolved was used as continuous phase. Typically, the dispersed phase was prepared as 0.1 g of SDS and 0.1 g of drug dissolved in 10 mL of water, and oil phase was prepared as 1.0 g of PCL dissolved in 23 mL dichloromethane. Then the dispersed phase was added into the oil phase and sonicated for 3 min in 2 kW, 20 kHz to form W/O emulsion.

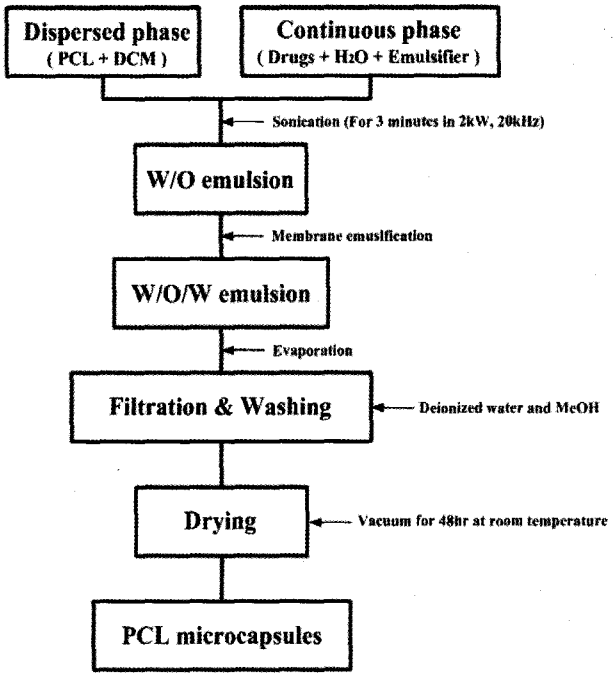


Fig. 2. Preparation procedure of PCL microcapsules using membrane emulsification method.

W/O emulsion prepared as a dispersed phase was added into dispersed phase reservoir. The W/O emulsion permeated through the uniform pores of a SPG membrane by the pressure of nitrogen gas into the aqueous phase as a continuous phase to form the droplets. Then dichloromethane was evaporated at room temperature for 24 hr. Finally, the produced microcapsules were collected by filtration, washed with distilled water and methanol, and dried by vacuum for 48 hr to obtain powder-like PCL microcapsules.

2.4. Determination of Size and Size Distribution of Microcasules

The volume-averaged diameter of the PCL microcapsules and their size distribution were measured with a light scattering particle size analyzer (Mastersizer 2000, Malven Instrument Ltd., UK). The size distribution was evaluated with the Span value defined as follow [18] :

$$Span = \frac{D_{90\%} - D_{10\%}}{D_{50\%}} \quad (1)$$

Here, $D_{N\%}$, (N = 10, 50, 90) means that the volume percentage of microcapsules with diameters up to N%. The smaller span value indicates the narrower size distribution.

2.5. Morphology of PCL Microcapsules

PCL microcapsules were well dispersed in deionized water and then air-dried onto a piece of aluminum foil. The samples were coated with gold and then observed with a field emission scanning electron microscope (LEO-1530FE, LEO Instrument Co., Germany).

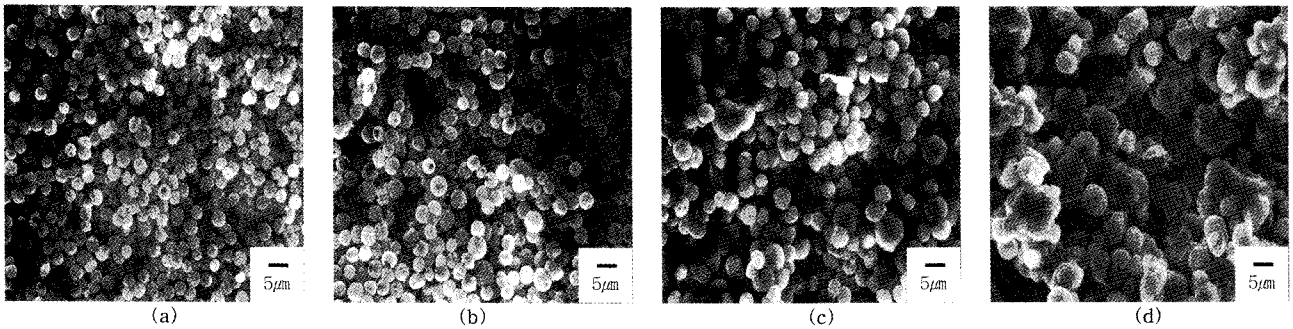
2.6. Determination of Drug Content

To evaluate the drug content that was loaded from different ionic properties in the PCL microcapsules, the known amounts of microcapsules were weighed and completely dispersed in the phosphate buffer solution (PBS, pH 9.0) of 30 mL. Then, the PCL microcapsules dispersed in PBS were sonicated for 3 min. They were left to a shaking bath at the shaking rate of 150 rpm for 2 days to be completely dissolved. To determine the percentage of drugs loaded per dry weight of PCL microcapsules (w/w), it was calculated with a below equation.

$$Drug\ loading\ (\%) = \frac{weight\ of\ drugs\ loaded\ (g)}{weight\ of\ microcapsules\ dried\ (g)} \times 100 \quad (2)$$

2.7. Determination of Drug Release

Drug release from PCL microcapsules was studied under sink condition in pH 2.0, pH 7.0 and pH 9.0 phosphate buffer solution. PCL microcapsules (70 mg) were suspended in 20 mL release medium in a glass vial placed in a shaker bath at 60 cycles/min and at 37°C. The samples were collected at various time point. filtered through a 1.2 μm filter (Wattman) and assayed by using a UV/Vis spectrophotometer at 193 nm for lidocaine · hydrochloride, at 207 nm for sodium salicylate and at 197 nm for 4-acetaminophen.



(a) (b) (c) (d)

Fig. 3. SEM images of PCL microcapsules prepared with different PCL concentrations (Mn = 42,500 g/mol). (a) 3.3% (w/w) solution, (b) 5.0% (w/w) solution, (c) 6.7% (w/w) solution, (d) 10.0% (w/w) solution.

3. Results and Discussion

3.1. Preparation of PCL Microcapsules

3.1.1. Effect of PCL Concentration

The effect of PCL polymer concentration on the mean size of the microcapsules prepared by membrane emulsification method was investigated. Fig. 3 shows SEM images of the prepared microcapsules with various PCL concentration. The concentration was varied form 3.3 to 10% (w/w).

When the concentration of PCL solution was 10% (w/w), the dispersed phase had high viscosity and difficult to control continuing emulsification since the microporous glass membrane was hardly wetted owing to high viscosity of the PCL solution. Also, the prepared microcapsules were easily crushed due to their good solidity. Therefore, prepared microcapsules using the high concentration of PCL solution were not uniform in shape, suggesting that the use of low concentration lead to the uniform of PCL microcapsules. Hence, the microcapsules tend to crush because the structure of the matrix becomes strong when the high PCL concentration are used. On the other hand, the PCL solution of 3.3% (w/w) concentration had relatively low viscosity and easy to pass through the pores of membrane without applying higher pressures to disperse phase.

The effect of PCL concentration in the dispersed phase on mean particle size and size distribution were shown in Fig. 4. As shown in Fig. 4, it observed that the mean size of microcapsules increased gradually with increase in PCL concentration. That is to say, the mean size of the microcapsules at high concentration of PCL solution was larger than that at low concentration because of the increase in viscosity.

On basis of the above facts, monodispersed microcapsules were obtained when the concentration of the PCL solution was 3.3% (w/w). Thus, as the PCL concentration is decreased the mean size is also decreased.

3.1.2. Effect of Molecular Weight of PCL

Fig. 5 shows SEM images of the microcapsules prepared with various molecular weight of PCL. Also, the effect of different molecular weight of PCL on the mean size and the size distribution of prepared microcapsules was shown in Fig. 6. As shown in Fig. 5, although molecular weight of PCL was varied, the mean particle size and size distribution was nearly uniform. As a result of this, we were confirmed that the mean particle size and size distribution of PCL microcapsule prepared by membrane emulsification methods are not affected on PCL molcular weight.

3.1.3. Effect of Emulsifier Concentration

The mean size, size distribution and span value of the microcapsules with change of emulsifier concentration in the continuous phase were shown in Fig. 7. The emulsifier concentration in continuous phase was changed with 0.2, 0.4, 0.6, 0.8 and 1% (w/w). As shown in Fig. 7, it was observed that the mean size and size distribution of the microcapsules decreased gradually with increasing emulsifier concentration in the continuous phase. When the emulsifier concen-

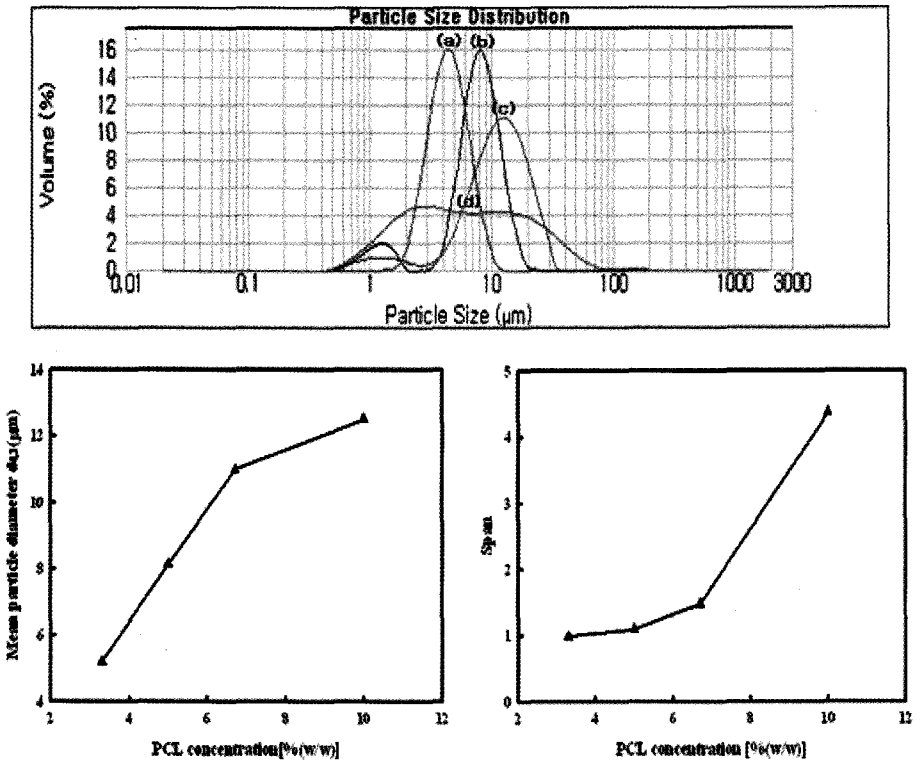
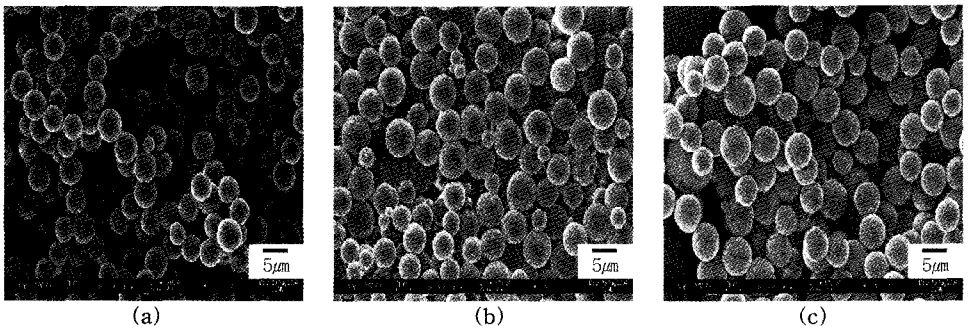


Fig. 4. Effect of PCL concentration on mean size, size distribution and span value of microcapsules (Mn = 42.500 g/mol). (a) 3.3% (w/w) solution, (b) 5.0% (w/w) solution, (c) 6.7% (w/w) solution, (d) 10.0% (w/w) solution.



(a) (b) (c)

Fig. 5. SEM images of the PCL microcapsules prepared with different molecular weight of PCL. (a) 10,000 g/mol, (b) 42,500 g/mol, (c) 80,000 g/mol.

tration in continuous phase was 1% (w/w), the mean size of microcapsules was the smallest. Therefore, it was considerable that microcapsules were increased emulsifying power and stability by increasing emulsifier concentration in the continuous phase.

Also, the effect of emulsifier concentration in the disperse phase were shown in Fig. 8. The emulsifier concentration in disperse phase was changed with 0.2, 0.4, 0.6, 0.8 and 1% (w/w). As shown in Fig. 8, it was observed that the mean size and size distribution of the microcapsules decreased gradually with increasing emulsifier concentration in the disperse phase. When the emulsifier concentration in disperse phase was 1% (w/w), the mean size of microcapsules was the smallest. Therefore, it was considerable that microcapsules were increased emulsifying power and stability by increasing emulsifier concentration in the disperse phase.

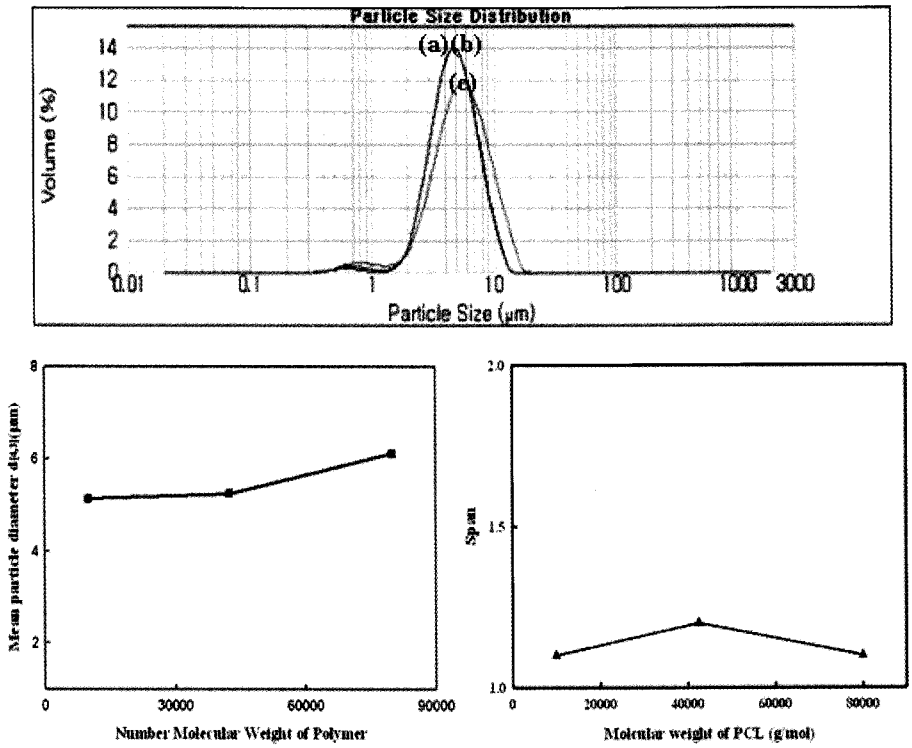


Fig. 6. Effect of molecular weight of PCL on mean size, size distribution and span value of microcapsules. (a) 10,000 g/mol, (b) 42,500 g/mol, (c) 80,000 g/mol.

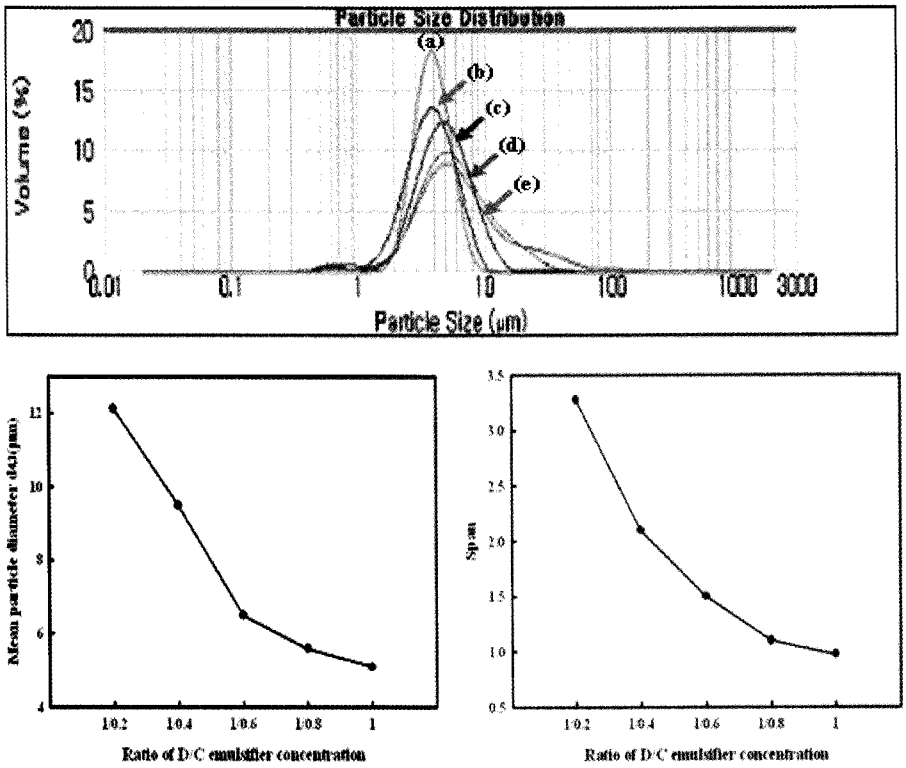


Fig. 7. Effect of emulsifier concentration in continuous phase on mean size, size distribution and span value of microcapsule. Weight ratio of D/C emulsifier concentration : (a) 1.0/1.0, (b) 1.0/0.8, (c) 1.0/0.6, (d) 1.0/0.4, (e) 1.0/0.2.

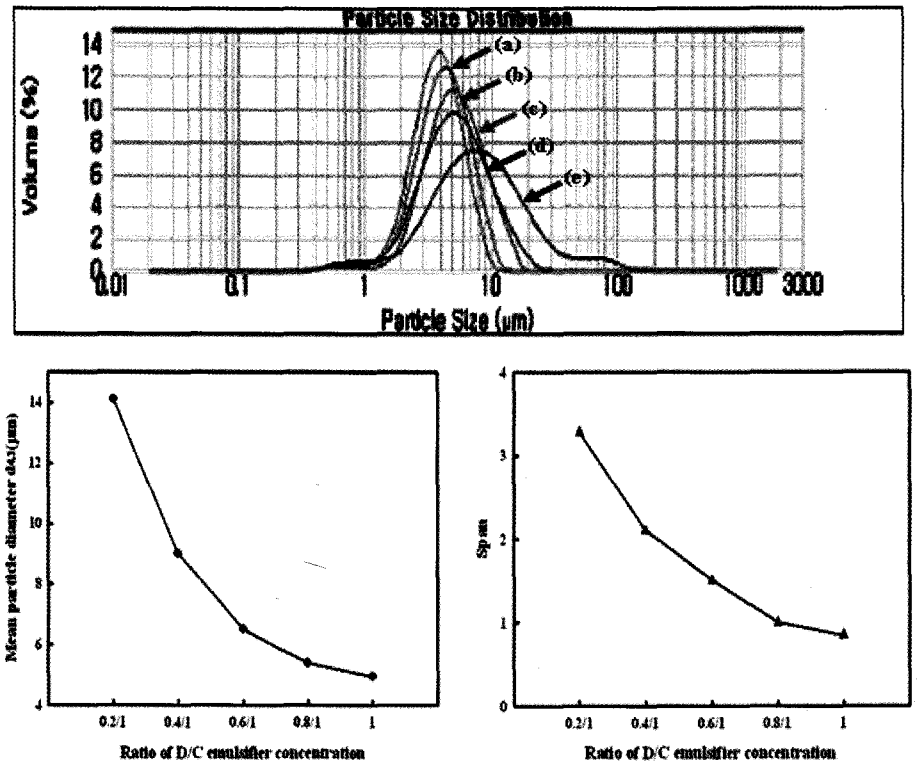


Fig. 8. Effect of emulsifier concentration in dispersed phase on mean size, size distribution and span value of microcapsules. Weight ratio of D/C emulsifier concentration : (a) 1.0/1.0, (b) 0.8/1.0, (c) 0.6/1.0, (d) 0.4/1.0, (e) 0.2/1.0.

3.1.4. Effect of Stirring Speed

The stirring speed of the continuous phase is considered as one of the main parameters affecting the membrane emulsification technique because droplets formed on the surface of the membrane detach under the influence of the flowing of continuous phase. The effect of stirring speed of the continuous phase on the mean size, size distribution and span value of the microcapsules were shown in Fig. 9. The stirring speed was adjusted at 300, 400, 500, 600, 700, 800 and 900 rpm. As shown in Fig. 9, the largest change in the mean size of microcapsules occurred at lower stirring speed range. These results can be explained as follows; At lower stirring speed the formed droplet size increase rapidly and the size distribution becomes much broader because the droplets grow and coalesce at the membrane surface before finally being detached. However, there is no significant influence on the mean size and the size distribution of microcapsules at high stirring speed.

3.1.5. Effect of Transmembrane Pressure

The effect of transmembrane pressure on the mean size, size distribution and span value of the microcapsules is shown in Fig. 10. Transmembrane pressure was adjusted with 30, 40, 50, 60 kPa. As shown in Fig. 10, it was observed that the mean size and the size distribution of microcapsules increased sharply with the increase in transmembrane pressure because the droplet grew and coalesced on the membrane surface at high pressure before finally being detached.

3.2. Drug Release Properties

3.2.1. Drug Loading Contents

Cationic drug (lidocaine · hydrochloride), nonionic drug (4-acetaminophenol) and anionic drug (sodium salicylate) were loaded into the microcapsules. The amount of the drug loading was set at the ratio of drug to PCL; 0.1 : 1, 0.2 : 1, 0.3 : 1, 0.5 : 1, respectively. To increase the amount drug loading in the microcapsules, the disperse phase was strongly stirred for

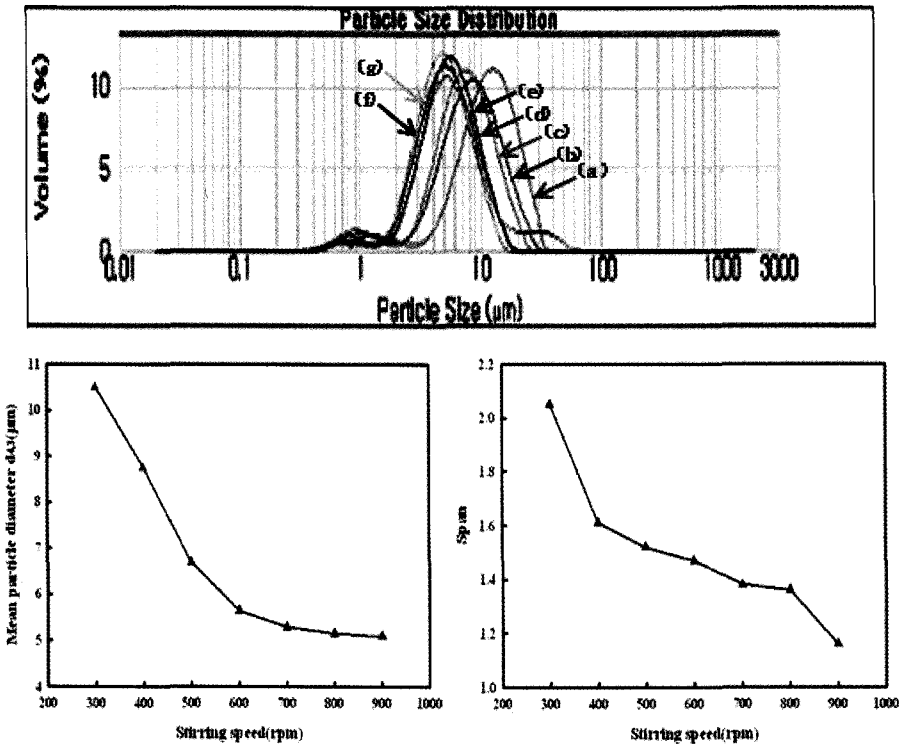


Fig. 9. Effect of stirring speed on mean size, size distribution and span value of microcapsules. (a) 300 rpm, (b) 400 rpm, (c) 500 rpm, (d) 600 rpm, (e) 700 rpm, (f) 800 rpm, (g) 900 rpm.

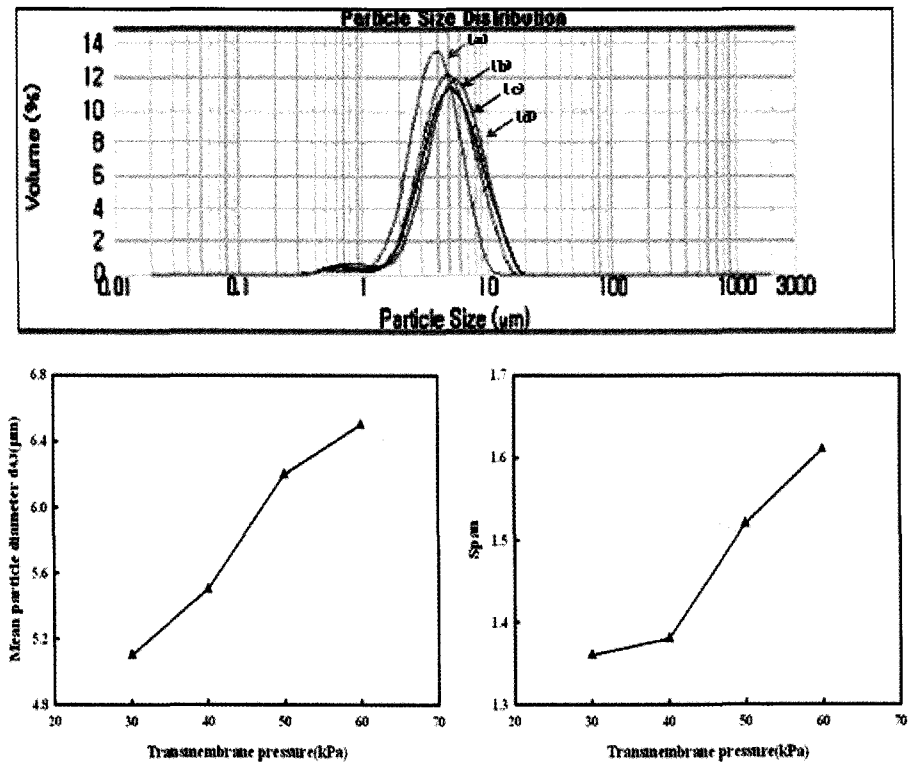


Fig. 10. Effect of transmembrane pressure on mean size, size distribution and span value of microcapsules. (a) 30 kPa, (b) 40 kPa, (c) 50 kPa, (d) 60 kPa.

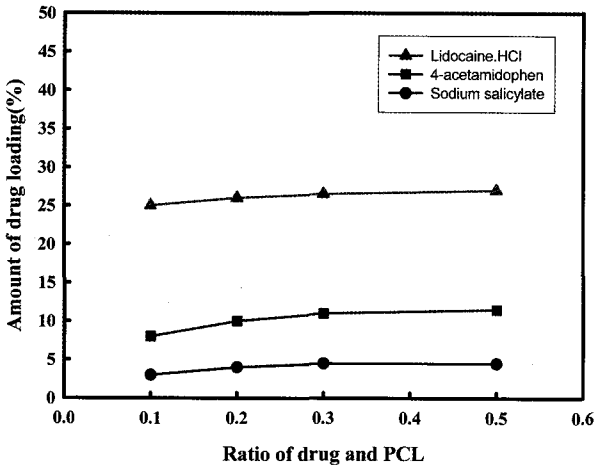


Fig. 11. Amount of drug loading with change of the ratio of drug and PCL.

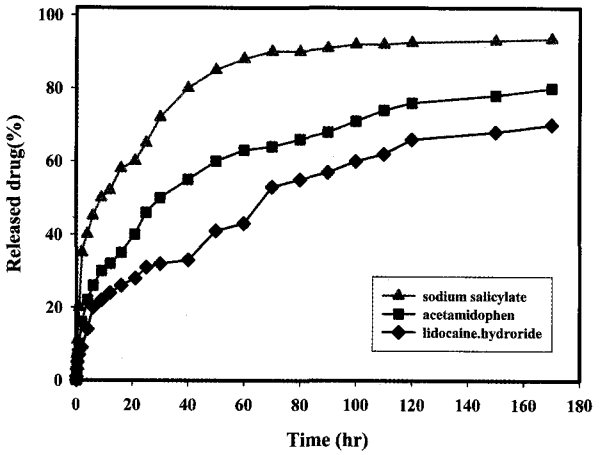


Fig. 12. Release profiles of drugs with different ionic properties in phosphate buffer solution of pH 7.4 at 37°C (Mn = 42,500 g/mol).

perfect mixing of the PCL and the drug solutions during emulsification. To determine the amount of drug loadings in the microcapsules, the dissolution experiments in phosphate buffer solution with pH 9.0 was performed. Fig. 11 shows the amount of drug contents in the microcapusles. As shown in Fig. 11, the loading amount of different drugs was increased in the following order, anionic< nonionic< cationic drug, respectively. Due to ionic repulsive or attractive force between drugs and carbonyl group in PCL, the cationic drug has attractive force with PCL but the anionic drug has repulsive force with PCL. Cationic drug (lidocaine · hydrochloride) was loaded 27.0% (w/w)

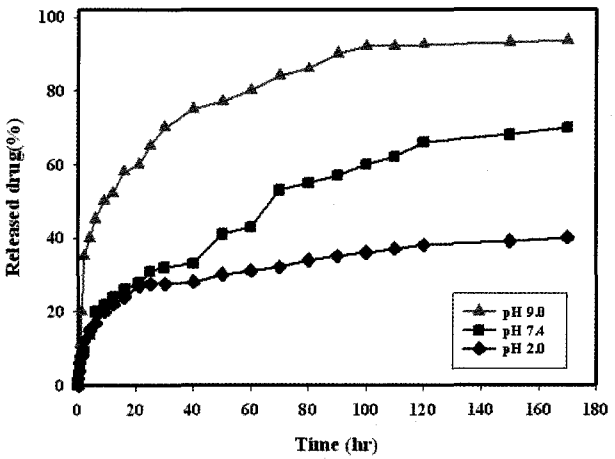


Fig. 13. Release profiles of lidocaine-hydrochloride in phosphate buffer with pH 2.0, 7.4 and 9.0 at 37°C (Mn = 42,500 g/mol).

when the ratio of drug and PCL was 0.5 : 1. Also, the amount of loading for 4-acetaminophen (nonionic drug) was 11.5% (w/w) and 4.5% (w/w) for sodium salicylate (anionic drug).

3.2.2. Drug Release with Different Drugs

Three kind of drugs loaded in the microcapsules were released using pH 7.4 phosphate buffer solutions in shaking incubator for 7 days. Drug release percentage vs. time curve is shown in Fig. 12. Cationic drug more retard than anionic one and the initial release of anionic drug was faster than that of cationic drug. It is shown that negative charges of the microcapsule matrixes and ionic characterisitcs of drug influence the drug release rate. i.e. : PCL microcapsules have ester groups of negative charge, so that they have attractive force between microcapsules and with positive buffer solution.

3.2.3. Drug Release with Different pHs

Fig. 13 represents drug release behaviors in buffer solution with different pHs for 7 days. These drug release profiles indicated that the release was sustained in acidic medium. The release experiments for the three selected drugs showed slower release behavior in pH 2.0 than in pH 9.0 and exhibited the retarded release characteristics during the overall release time. For

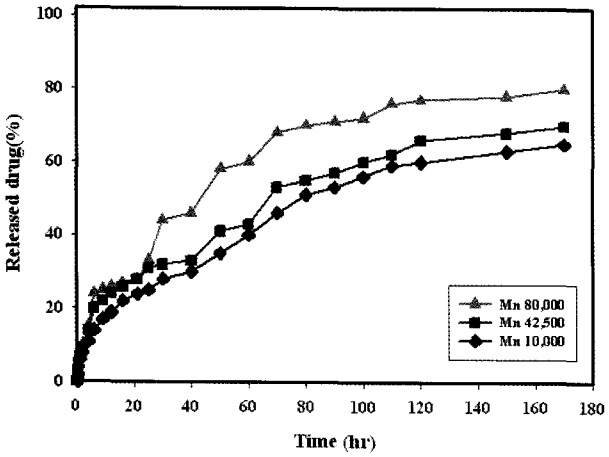


Fig. 14. Release profiles of the PCL microcapsules containing 10% lidocaine · hydrochloride with different polymer molecular weight in phosphate buffer solution of pH 7.4 at 37°C.

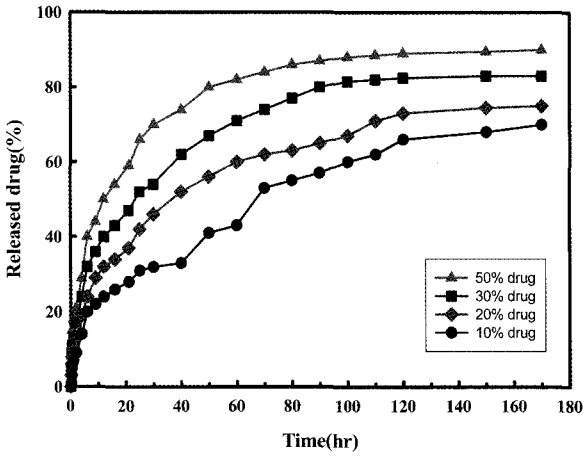


Fig. 15. Released profiles of lidocaine·hydrochloride from the PCL microcapsule containing different amount of lidocaine · hydrochloride in pH 7.4 at 37°C (Mn = 42,500 g/mol).

the release of lidocaine · hydrochloride, the release rate was delayed in pH 2.0. The initial release was retarded and showed the half amount of other drug releases. We confirmed that the release of drug loaded in microcapsules had pH sensitive characteristics.

3.2.4. Drug Release with Different PCL Molecular Weight

Fig. 14 shows a drug release from PCL microcapsules prepared with a different molecular weight PCL. When using the highest PCL molecular weight (80,000 g/mol), drug release occurred most rapidly. As the molecular weight increase, the crystallinity is considerably reduced, and long period length increase. Based on the facts, when the molecular weight is large, the amorphous region will be wide open and form a coarse crystalline microstructure through which the drug will diffuse rapidly. Thus, it was found that the internal crystalline plays an important role in drug release.

3.2.5. Drug Release with Different Drug Loading Contents

Fig. 15 shows total released of lidocaine · hydrochloride from the PCL microcapsules against drug loadings. As shown in Fig. 15, the larger the amounts of loaded lidocaine · hydrochloride, the faster drug release due to the hydrophilic drug properties. Therefore, as the drug becomes more hydrophilic by increasing the loading contents of drug, hydrophilic interaction is stronger and drug release is faster. Also, the reason of rapidly drug release was caused by a thin of outside wall thickness for microcapsule by increasing drug loading.

4. Conclusions

PCL microcapsules containing three kinds of ionic drugs were prepared by the membrane emulsification method using SPG membrane tubes. Effect of experimental conditions of membrane emulsification on the size and size distribution of PCL microcapsules and release characteristics of ionic drugs were investigated. Results are as follows :

1) Uniform microcapsules with the mean diameter of about 5 μm were finally prepared using membrane emulsification and the optimal conditions for preparation of those microcapsules were as follows : PCL concentration = 3.3% (w/w), emulsifier concentration = 1% (w/w), stabilizer concentration = 1% (w/w), trasmembrane pressure = 30 kPa, stirring speed = 700 rpm.

2) Although molecular weight of PCL was changed,

mean size and size distribution of the PCL microcapsules had not nearly an effect of it.

3) The increase of emulsifier concentration and stirring speed of the continuous phase decreased the mean size of PCL microcapsules, but the increase of transmembrane pressure increased the mean size of PCL microcapsules.

4) The more increased molecular weight of PCL, The better released drug of loaded in PCL microcapsules, because amorphous area of PCL microstructure is greatly by increasing PCL molecular weight.

5) The more increased drug loading contents of PCL, the better released drug in PCL microcapsules because increasing drug loading contents caused by a thin of outside wall thickness of microcapsule.

6) The release behavior of lidocainehydrochloride from PCL microcapsule in phosphate buffer solution of pH 9.0 was much faster than those of microcapsule in pH 2.0 and 7.4.

7) The release behavior of ionic drugs from PCL microcapsules in phosphate solution of pH 7.4 was made rapidly released of anionic drug rather than cationic drug and nonionic drug.

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