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Preparation of SKL-AG20 loaded Microparticles by Oil-in-water Emulsion Solvent Evaporation and Spray Drying for Sustained Drug Delivery

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Preparation of SKL-AG20 loaded Microparticles by Oil-in-water Emulsion Solvent Evaporation and Spray Drying for Sustained Drug Delivery

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Abstract

Controlled drug delivery systems employing microparticles offer lots of advantages over conventional drug dosage formulations. Microencapsulation technique have been conducted with biodegradable polymers such as poly(lactic-*co*-glycolic acid) (PLGA) and poly(lactic acid) (PLA) for its adjustable biodegradability and biocompatibility. In this study, we evaluated two techniques, oil-in-water (o/w) emulsion solvent evaporation and spray drying, for preparation of polymeric microparticles encapsulating a newly synthesized drug, SKL-AG20, for the long-term drug delivery of this low-molecular-weight drug with a very short half-life. Drug-loaded microparticles prepared by the solvent evaporation method showed a smoother morphology; however, relatively poor encapsulation efficiency and drastic initial burst were discovered as drawbacks. Spray-dried drug-loaded microparticles had an imperfect surface with pores and distorted portions so that its initial burst was critical (70.05-87.16 %) when the preparation was carried out with a 5 % polymeric solution. By increasing the concentration of the polymer, the morphology was refined and undesirable initial burst was circumvented (burst was reduced to 35.93-74.85 %) while retaining high encapsulation efficiency. Moreover, by encapsulating the drug with various biodegradable polymers using the spray drying method, gradual and sustained drug release, for up to 2 weeks, was achieved.

Key words: Biodegradable polymers, polymeric microparticles, solvent evaporation, spray drying

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1. Introduction

Optimized drug delivery systems have been the focus of intensive research for decades. A sustained drug release system reduces the frequency of drug administration and provides patients convenience and safety with just a single application.[1] In particular, a new fabrication method is needed for the delivery of low-molecular-weight drugs which have a very short half-life. In one of the traditional methods, drugs are encapsulated with biodegradable polymers and applied to specific sites. Poly(lactic-*co*-glycolic acid) (PLGA) and poly(lactic acid) (PLA) have been used for drug-encapsulation due to their biocompatibility and biodegradability. PLGA is a Food and Drug Administration (FDA)-approved biodegradable polymer. Its ester linkages degrade by hydrolysis in water, giving it biocompatibility.[2] The biodegradability can be adjusted, as the duration of the PLGA degradation varies depending on the ratio of monomers (lactide and glycolide). PLGA with a higher lactide unit ratio needs more time to be degraded.

One of the simplest methods to encapsulate drugs is the oil-in-water (o/w) emulsion solvent evaporation technique. This method comprises 3 major steps: preparing an organic solvent including the drug and the biodegradable polymer, dispersing the organic solvent into an aqueous

solution and evaporating the volatile solvent for several hours.[3, 4] Another method, spray drying, has also been widely used because of its convenience and remarkable encapsulation efficiency. This technique is a one-step procedure. After dissolving the drug and polymer into an organic solvent, polymeric microparticles are easily acquired by spray drying the solvent at a high temperature.[5, 6]

SKL-AG20 is a newly synthesized compound developed by SK Corporation (Daejeon, Korea) which has a very short half-life of less than 30 min in the body of animals. The drug needs to be fabricated for prolonged drug delivery *in vivo*. In this study, the oil-in-water (o/w) emulsion solvent evaporation method and the spray drying method were used to prepare various drug-loaded microparticles with 3 types of polymer and several drug-to-polymer ratios. Morphological characterization, size analysis, evaluation of drug content, and *in vitro* drug release studies were conducted to select microparticles with optimized properties among those produced by these methods.

2. Materials and Methods

Materials

PLGA (504H, 50:50, viscosity [dl/L] 0.45-0.60), (755S, 75:25, viscosity

[dl/L] 0.50-0.70), PLA (205S, viscosity [dl/L] 0.55-0.75) were purchased from Boehringer Ingelheim (Ingelheim, Germany). SKL-AG20 was a kind gift from the SK Corporation (Daejeon, Korea) and poly(vinyl alcohol) (PVA, MW 30,000-70,000) was purchased from Sigma (St. Louis, MO, USA). All other reagents were analytical and high-performance liquid chromatography (HPLC) grade and used without further purification.

Methods

Polymeric microparticles containing SKL-AG20 were prepared by the oil-in-water (o/w) emulsion solvent evaporation technique. Five hundred milligrams of PLGA (504H, and 755S) and PLA (205S) were each dissolved in 10 ml of methylene chloride to prepare 5 % (w/v) polymeric solutions. Twenty-five milligrams of SKL-AG20 was then suspended in the organic phase. The solution was dropped in 100 ml of the 5 % (w/v) PVA aqueous solution by stirring at 800 rpm to volatilize the organic solvent. Additional PLGA (755S), PLA (205S) microparticles were prepared by varying the volumes of the organic solvent (10 ml and 7.5 ml) and the amounts of the drug (25 mg, 50 mg and 100 mg). After 3 hours of stirring, the aqueous suspension was centrifuged and washed twice with distilled water, then freeze-dried and stored at -70 °C.

Polymeric microparticles were also produced by the spray drying method.

Two-and-a-half grams of PLGA (504H, and 755S) polymers were dissolved in methylene chloride to obtain a 5 % (w/v) solution and 125 mg of the drug was suspended in the organic solution. Homogeneous solutions were spray-dried using a mini spray dryer (Buchi 290, Switzerland), operating in a co-current mode and equipped with two fluid nozzles. A 0.7 mm spray nozzle was used. The operating parameters were set as follows: inlet air temperature, 45 °C; outlet air temperature, 39-40 °C; aspirator control, 100 %; air flow, 601 L/h; feed spray rate, 360 ml/h. The preparation was magnetically stirred at a moderate speed and the organic solution was fed into the spray-dryer with a peristaltic pump. The microparticles produced were carefully recovered in a cyclone separator. Additional preparations were processed using 10 % of PLGA (504H, and 755S) and PLA (205S) polymeric solutions at the equivalent conditions. The collected microparticles were withdrawn, vacuumed for 2 days to remove the remaining organic solvent, and stored at -70 °C.

Morphological Characterization

The surface morphology of SKL-AG20-loaded polymeric microparticles was identified using scanning electron microscopy (SEM, JSM-840A, JEOL, Tokyo, Japan). Ten milligrams of each sample were suspended in 1 ml of 0.05 % (w/v) Tween 20 in phosphate-buffered saline (PBS, pH 7.4)

and sonicated for 1 minute. The samples were placed on an aluminum stub and coated with platinum for 100 seconds before taking photographs at an accelerating voltage of 15 kV.

Particle Size Analysis

The size of drug-loaded polymeric microparticles was measured using SEM images. Fifty microparticles were selected randomly in each microparticle image and analyzed using ImageJ 1.33u (available at http://rsb.info.nih.gov/ij/) software to determine the diameter of microparticles and to analyze the size distribution.

Evaluation of Drug Content and Encapsulation Efficiency

The drug content and encapsulation efficiency of drug-loaded polymeric microparticles were measured by UV spectrometry at 277 nm (UV-1601PC, Shimadzu, Japan). Three milligrams of each drug-loaded polymeric microparticle preparations was dissolved in 10 ml of dimethyl sulfoxide (DMSO). The content (w/w) of the drug-loaded polymeric microparticles was determined in triplicate. The encapsulation efficiency (w/w) was calculated as the ratio of actual-to-theoretical drug content.

$$\textit{Drug content (\%)} = \frac{\text{Drug weight determined}}{\text{Actual drug weight}} \times 100$$

$$\textit{Encapsulation efficiency (\%)} = \frac{\text{Drug weight determined}}{\text{Theoretical drug weight}} \times 100$$

In vitro drug release studies

In vitro drug release patterns of polymeric microparticles were analyzed using HPLC at 277 nm (Agilent Technologies, 1200 series, USA). A solution of 0.05 % (w/v) Tween 20 in PBS (pH 7.4) was used as the release media. Drug-loaded polymeric microparticles were suspended in 10 ml of the release media (n = 3), incubated at 37 °C, and rotated vertically. After centrifugation, 3 ml of the supernatant was extracted from the sample tubes at specified time intervals (1, 3 and 7 hours, and 1, 3, 5, 7, 10 and 14 days). The drug retained in the microparticles was extracted using 1 ml DMSO, and the total amount of drug in each samples was determined by summing the amounts in the supernatant and the microparticle extract. The amount of the drug in each samples was then divided by the total amount of microparticles to calculate a cumulative percentage. All experiments were repeated 3 times.

3. Results and Discussion

Morphology and size of drug-loaded polymeric microparticles

In this study, microparticles were prepared by two different methods, oil-in-water (o/w) emulsion solvent evaporation and spray drying. The morphology of drug-loaded polymeric microparticles prepared by the solvent evaporation method was assessed by SEM (Figure 1). Microparticles exhibited a perfect spherical shape regardless of the types of polymer and drug-to-polymer ratios. The morphology of the particle is generally influenced by polymer precipitation at the solvent evaporation step.[3] As the organic solvent is evaporated, the polymer precipitates gradually. Solvent evaporation and precipitation of polymers are slow processes in the oil-in-water (o/w) emulsion solvent evaporation method, because these steps depend on natural volatilization of the solvent, rather than evaporation at high temperature. The presence of PVA also helps the formation of a smooth surface, since PVA acts as a powerful stabilizer during the step. The analysis of the size of the particles showed increasing diameters with reducing volume of the organic solvent, although the change was not dramatic (Table 1). The diameter of particles prepared by this method increased up to 50 μm, using 5 ml of the organic solvent, which is too big and undesirable for injection (data not shown).

Spray drying is conducted under harsher conditions, in which the temperature is sufficiently high to evaporate organic solvents. An aspirator draws in newly produced microparticles continuously and with great force, which is probably why the spray-dried microparticles exhibited a spherical shape with many pores, like a golf ball, along with some distorted portions (Figure 2). This imperfect morphology may be solved by increasing the concentration of polymers.[7] When the concentration of polymers was raised from 5 % to 10 %, a comparatively improved morphology was observed, with an intact and smooth surface. The size of the microparticles is listed in Table 2. Furthermore, as the concentration of the polymer was increased, larger microparticles were produced, up to 20-25 μm, a size that is approximately twice as large as those obtained with the 5 % solution. This increase in size can be explained by an increase in the viscosity of the internal phase of the emulsion. Typically, when the viscosity of the internal phase is increased, stronger stirring is needed to separate the emulsion into smaller droplets; if not, the size of microparticles becomes larger.[3] The size of the microparticle in a drug delivery system is very critical since it determines the rate of drug release. If microparticles are small, the surface area per unit volume will increase and the diameter of particles will be smaller, which causes rapid diffusion of the encapsulated drug.[8] Therefore, manufacturing microparticles of appropriate size is very important to

achieve prolonged drug release.

Drug loading

To evaluate the drug content of microparticles prepared using various polymers, ratios of drug-to-polymer, and volumes of organic solvent, a defined amount of microparticle was dissolved in DMSO and the drug was detected by UV spectrometry at a wavelength of 277 nm. As shown in Table 1, the higher the amount of drug, the higher the encapsulation efficiency of the microparticles. However, the difference in drug contents between the two groups of microparticles with different drug-to-polymer ratios (1:20 and 1:10) was not significant. During the preparation, an organic solution containing a hydrophobic drug is dispersed into the aqueous phase and agitated by mechanical force for several hours. SKL-AG20, used in this study, is relatively hydrophilic; therefore, severe drug loss would occur in the aqueous phase due to its low solubility in water, especially when fierce mechanical stirring is accompanied. Therefore, the encapsulation efficiency of drug-loaded polymeric micropartcles was rather low in samples with 1:20, and 1:10 drug-to-polymer ratios. In samples with a 1:5 drug-to-polymer ratio, much of the drug could be encapsulated in microparticles, although there was still substantial drug loss. Additional microparticles were prepared by decreasing the volume of the organic

solvent from 10 ml to 7.5 ml and varying the amounts of the drug. Encapsulation efficiency slightly increased the presence of reduced volumes of the solvent (Table 1). In this method, organic solvent must be diffused into an aqueous phase and evaporated at the water/air interface with mechanical stirring due to develop hard microspheres. However, as the volume of solvent decreased, the time required to precipitate the microparticles by solvent removal is shorter. The shorter precipitation time results in the fast formation of harder microparticles, because of rapid evaporation of the organic solvent and the increase in the viscosity of the internal phase of the emulsion while the polymer weight remains constant. Therefore, the drug may be retained better in the organic phase, and not diffused easily. For these reasons, the drug loss decreases which results in high drug encapsulation efficiency.

As demonstrated from many previous studies, high encapsulation efficiency is a striking advantage of the spray drying technique.[7] In this study, microparticles containing SKL-AG20 at extremely high encapsulation efficiencies were obtained relatively easily using the spray drying method. Therefore, drug-to-polymer ratio was fixed at the lower ratio (1:20) and various polymers were used to fabricate spray-dried drug-loaded microparticles. Indeed, microparticles prepared by spray drying had high encapsulation efficiencies, as reported by many previous studies.

More than 90 % of the drug was captured in particles (Table 2).

In vitro drug release studies

To analyze the drug release pattern, the specified amount of microparticles prepared by the oil-in-water (o/w) emulsion solvent evaporation method was weighed in a test tube in which 10 ml of the release media and rotated vertically. In a preliminary study, almost 60 % of the initial burst was observed in a PLGA (504H) drug-loaded microparticle. PLGA (755S), and PLA (205S) polymers were used to prepare microparticles that could serve as an improved long-term drug delivery system. Consequently, PLGA (755S) and PLA (205S) microparticles, having almost the same drug content (approximately 1.0 %), exhibited 18.22 % and 6.44 % of the initial burst (~1 day), respectively. Further, the greater lactide ratio in the PLGA (755S)/PLA (205S) microparticles elicited a more gradual drug release pattern than that of the PLGA (504H) microparticles over 14 days (Figure 3). In the light of the improved drug release pattern, additional *in vitro* drug release studies were carried out with four groups of microparticles. PLGA (755S) microparticles prepared with 10 ml methylene chloride (drug content [d.c.] = 2.49 %), PLGA (755S) microparticles made with 7.5 ml of the organic solvent (d.c. = 4.59 %), PLA (205S) microparticles made with 10 ml of the organic solvent (d.c. = 1.78 %), and lastly, PLA (205S)

microparticles made with 7.5 ml of the organic solvent (d.c. = 3.52 %) were evaluated using identical drug release assays (n = 3). Drug release studies, *in vitro,* of microparticles loaded heavily with drugs (> 7 %) were not conducted because critical initial burst was estimated. The drug release profiles are presented in Figure 4. A drastic initial burst occurred as the drug content increased because of the high gradient of drug between the inside and outside of the microparticle. PLGA (755S) and PLA (205S) drug-loaded microparticles released the drug for 2 weeks while the PLGA (504H) microparticles released the drug for only one week. However, rapid initial burst (~1 day) can be a serious disadvantage in the drug delivery system, despite the improved encapsulation efficiency and sustained drug release as shown in Figure 4.

To address this advantage, spray-dried microparticles were prepared and an *in vitro* drug release study was carried out. Spray-dried microparticles generally show higher drug content. All microparticle groups prepared by this method had a drug content desirably higher than 4 %, which was sufficient to justify *in vitro* drug release studies. The drug release patterns of spray-dried microparticles, which were observed for 7 days in all groups, are presented in Figure 5. Firstly, spray-dried PLGA (755S) and PLA (205S) drug-loaded microparticles showed 87.16 % and 70.05 % respectively of

the initial burst, as in microparticles made with the low concentration of the polymer (5 % [w/v]). Such drastic initial burst results from the imperfect morphology of microparticles, with many pores and dented surfaces caused by the evaporation of the solvent and also their small size.[9] Therefore, to prolong the drug release, spray-dried microparticles were prepared with a higher concentration of polymers (10 %) and additional PLA (205S) polymer. When the concentration of the polymers was increased, the initial burst of spray-dried drug-loaded microparticles was much lower than that in microparticles prepared with a lower polymer concentration. This desirable change is probably due to a change in the morphology of the microparticles, to one with relatively smooth surface and with less pores of larger size, which in turn lowered the initial burst and yielded an improved drug release pattern.[10] The different groups of PLGA (504H, and 755S) and PLA (205S) microparticles exhibited initial bursts of 74.85 %, 42.40 %, and 35.93 %, and also a release rate in 14 days of 98.67 %, 72.37 %, and 62.93 %, respectively. By using the spray drying technique, most targeted drugs or proteins can be encapsulated at more than 90 %, which confirms that at smoother morphology and appropriate size of microparticles are important factors in establishing a sustained drug delivery system. The morphology and size can be controlled by manipulating many factors, including the volume of organic solvent, the amount of polymer, and also

by parameters of the instrument used in preparation.

4. Conclusion

Emulsion solvent evaporation and spray drying are widely used methods for encapsulating targeted drugs or proteins. In this study, we found that it was difficult to achieve both high encapsulation efficiency and sustained drug release for drug compound, SKL-AG20, using the oil-in-water (o/w) emulsion solvent evaporation method. As observed in spray-dried microparticles, however, an undesirable initial burst could be reduced while maintaining high encapsulation efficiency by increasing the amount of polymer. Furthermore, increasing the ratio of the lactide led to a more sustained drug release pattern up to 2 weeks. Additional studies in animal models need to be conducted to clarify the correlation between the *in vitro* and *in vivo* drug release patterns.

5. References

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6. Tables and Figures

Polymer type	Drug: Polymer	Drug content (%)	Encapsulation efficiency (%)	Mean size (μm)	Burst (%)
(a) 755S	1:20	1.02 (± 2.98)	21.39 (± 2.39)	9.51	18.22
	1:10	1.16 (± 8.62)	12.76 (± 9.07)	10.45	-
	1:5	2.49 (± 9.02)	14.95 (± 8.68)	11.08	65.59
(b) 205S	1:20	0.98 (± 3.09)	20.57 (± 2.98)	10.15	6.44
	1:10	1.21 (± 8.34)	13.32 (± 7.92)	11.93	-
	1:5	1.78 (± 3.79)	10.69 (± 4.06)	10.89	44.78
(c) 755S	1:20	1.10 (± 7.85)	23.11 (± 7.44)	11.21	-
	1:10	1.59 (± 9.19)	17.50 (± 8.72)	12.39	-
	1:5	4.59 (± 2.12)	27.55 (± 2.38)	13.62	70.45
(d) 205S	1:20	1.19 (± 3.56)	24.98 (± 3.09)	11.38	-
	1:10	3.52 (± 10.62)	38.73 (± 8.96)	13.19	56.62
	1:5	7.12 (± 7.03)	42.72 (± 6.87)	13.52	-

Table 1. Characterization of SKL-AG20-loaded polymeric microparticles using solvent evaporation method

(a)-(b), prepared with 10 ml organic solvent; (c)-(d), prepared with 7.5 ml organic solvent

Polymer type	Polymer (%)	Drug content (%)	Encapsulation efficiency (%)	Mean size (μm)	Burst (%)
504H	5	4.52 (±19.27)	94.92 (±18.27)	7.50	87.16
755S		4.48 (± 9.91)	94.08 (±10.27)	5.67	70.05
504H	10	4.68 (± 12.88)	98.28 (±12.77)	10.32	74.85
755S		4.61 (± 22.51)	96.81 (±21.27)	9.43	42.40
205S		4.57 (± 18.50)	95.97 (±19.01)	10.52	35.93

Table 2. Characterization of SKL-AG20-loaded polymeric microparticles using spray drying method

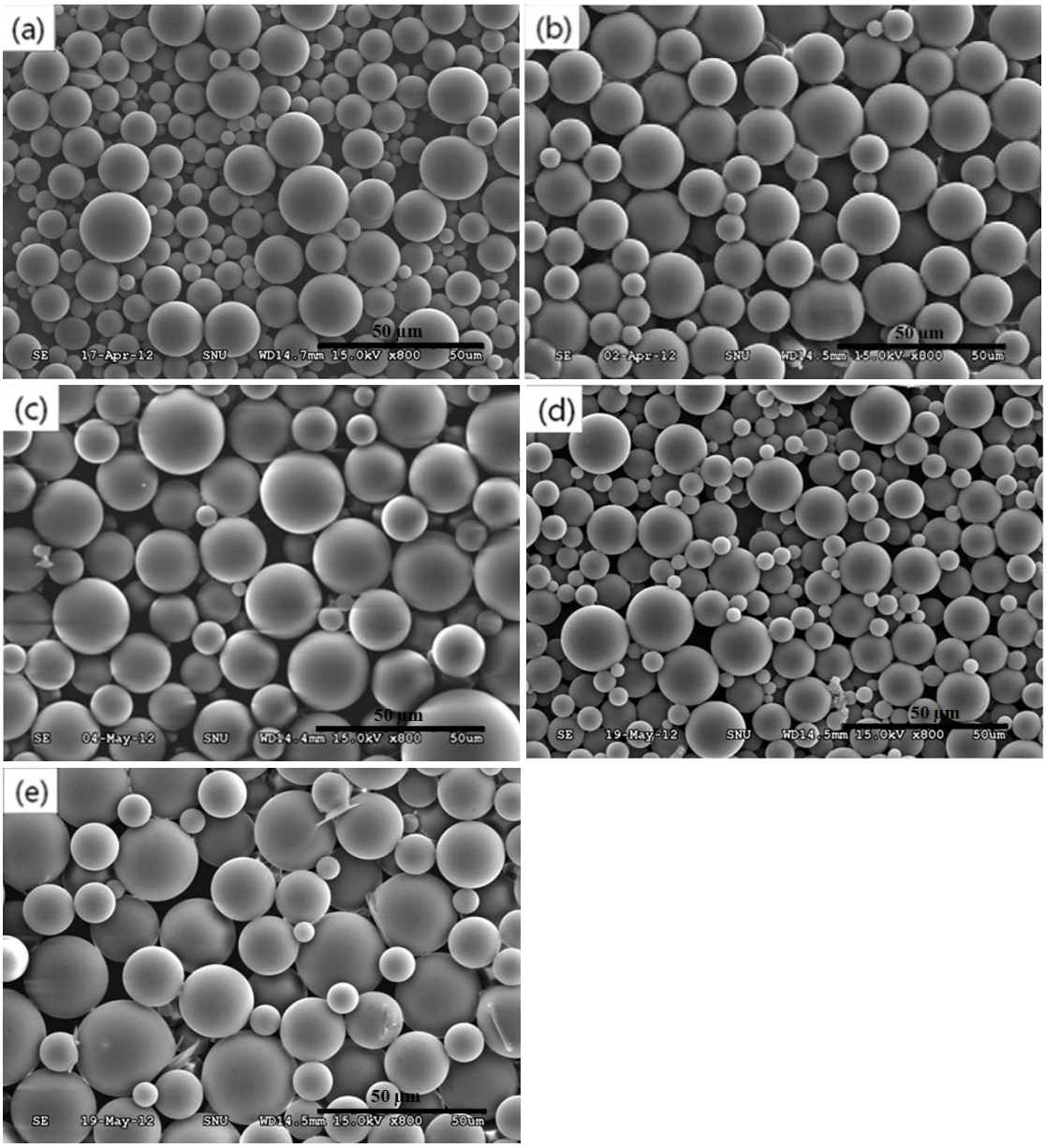

Figure 1. Assessment of the morphology of SKL-AG20-loaded polymeric microparticles fabricated using the solvent evaporation method using SEM. (a) 504H, 10 ml of the organic solvent, 1:20 (drug:polymer), (b)-(c), 755S; (b) 10 ml organic solvent, 1:5 (drug:polymer) (c) 7.5 ml organic solvent, 1:5 (drug:polymer) (d)-(e), 205S; (d) 10 ml organic solvent, 1:5 (drug:polymer) (e) 7.5 ml organic solvent, 1:10 (drug:polymer)

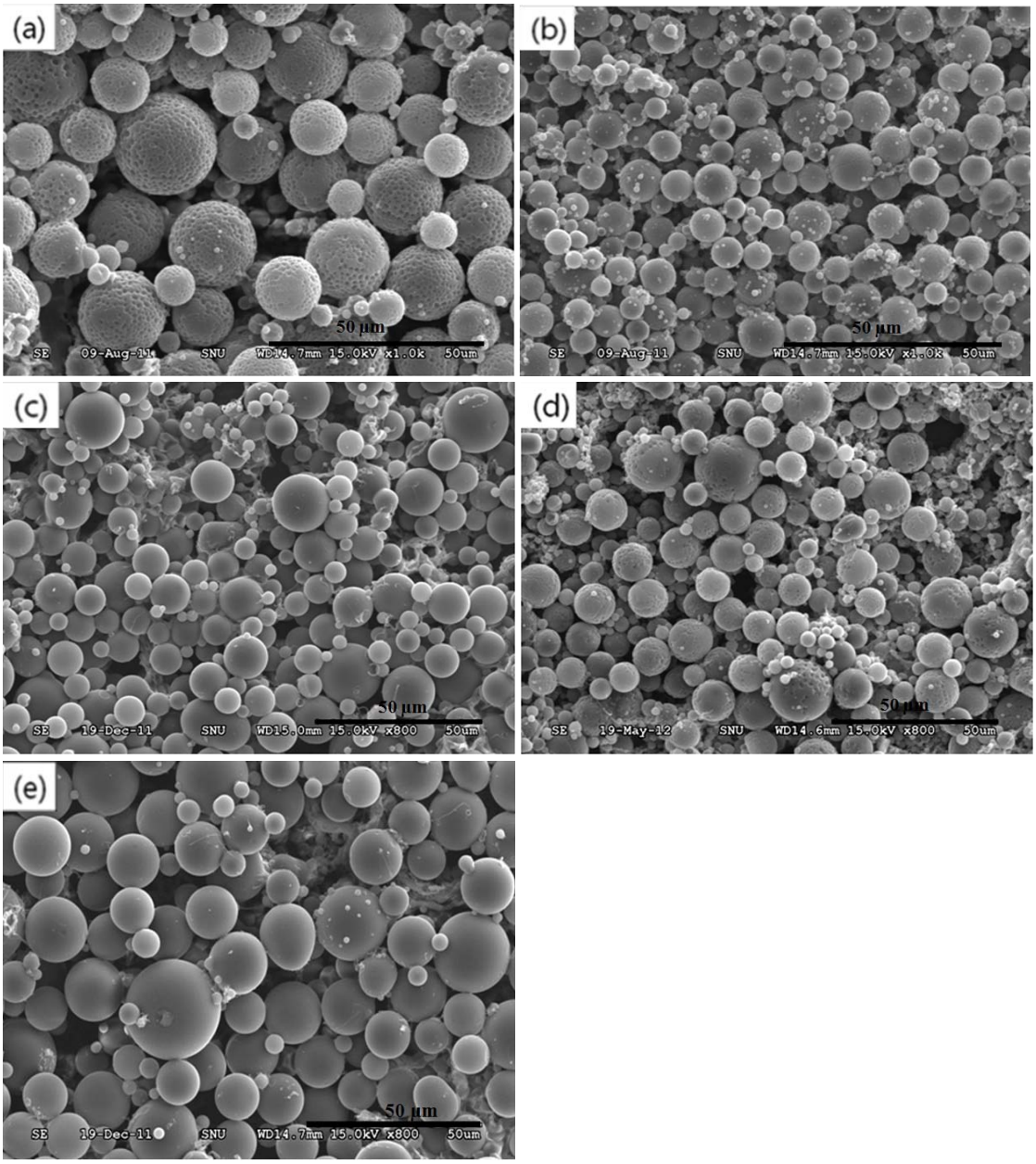

Figure 2. Assessment of the morphology of fabricated SKL-AG20-loaded polymeric microparticles using the spray drying method using SEM. (a)-(b), 5 % polymeric solution, (a) 504H and (b) 755S; (c)-(e), 10 % polymeric solution, (c) 504H, (d) 755S, and (e) 205S

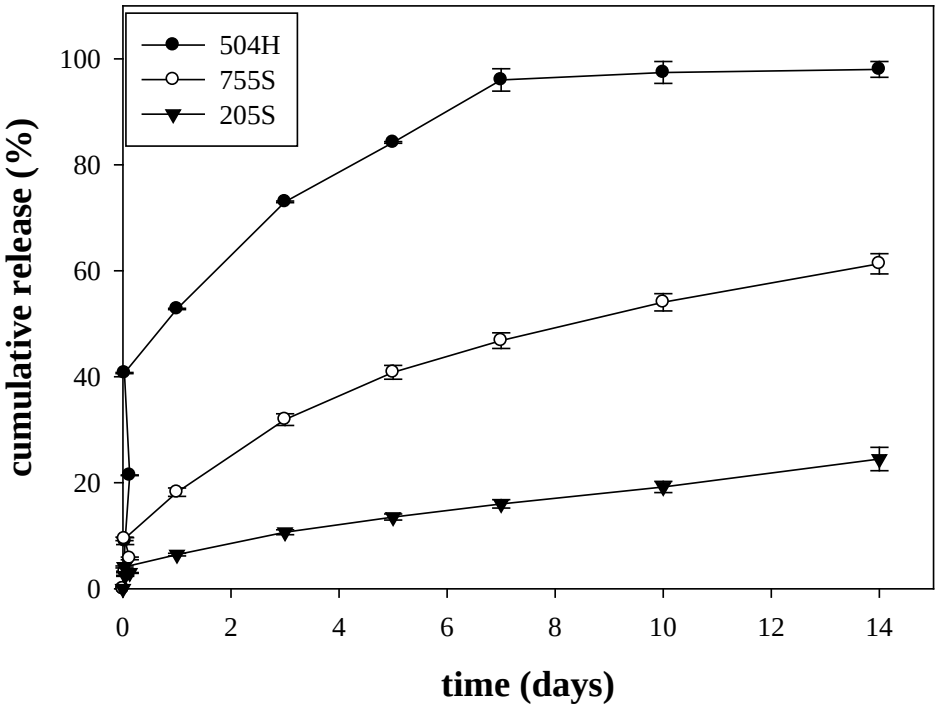

Figure 3. Effect of different polymers on SKL-AG20 release rates from polymeric microparticles fabricated by solvent evaporation method

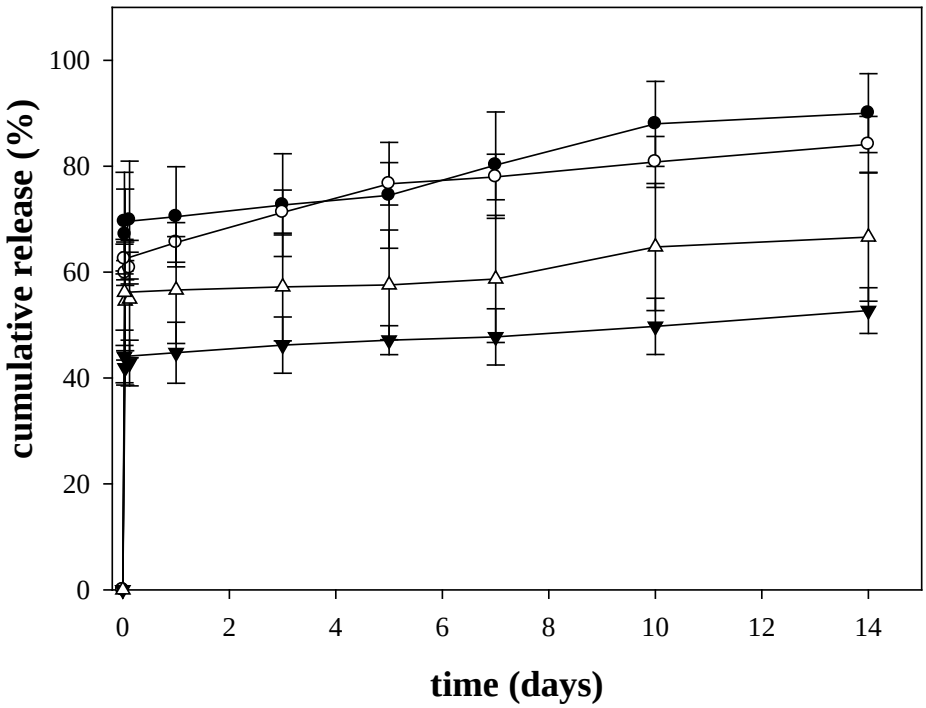

Figure 4. SKL-AG20 release pattern of microparticles fabricated with various polymers, volumes of solvent, and amounts of the drug by solvent evaporation method. Displayed are the drug release patterns of microparticles prepared with 7.5 ml PLGA (755S) solution, 1:5 (drug:polymer) (filled circles), 10 ml PLGA (755S) solution, 1:5 (drug:polymer) (open circles), 7.5 ml PLA (205S) solution, 1:10 (drug:polymer) (open triangles), and 10 ml PLA (205S) solution, 1:5 (drug:polymer) (filled triangles).

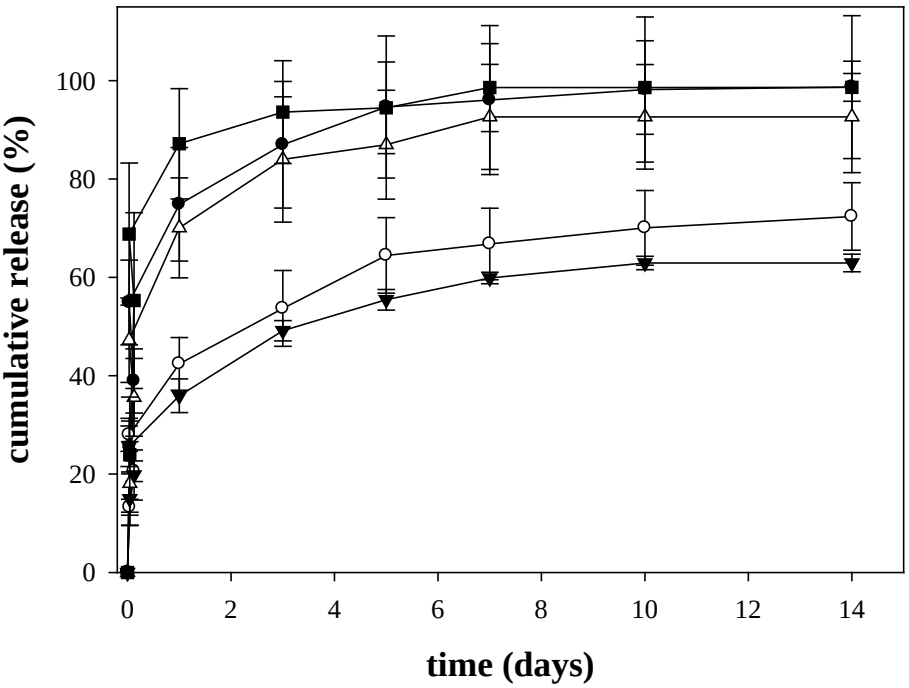

Figure 5. SKL-AG20 release pattern of spray dried microparticles fabricated with different polymers and solution concentrations. The release of the drug from microparticles prepared with 5 % PLGA (504H) solution (filled squares), 10 % PLGA (504H) solution (filled circles), 5 % PLGA (755S) solution (open triangles), 10 % PLGA (755S) solution (open circles), and 10 % PLA (205S) solution (filled triangles) are shown.

국문 초록

낮은 분자량으로 인하여 체내에서 짧은 반감기를 나타내 낮은 약물의 효율을 보이며 잦은 약물 투여를 필요로 하는 SKL-AG20과 같은 약물은 새로운 약물 전달체계를 필요로 한다. 생분해성을 가지는 고분자를 이용하여 약물을 감싸 지속적인 약물의 방출을 유도하고자 에멀젼 용매 증발법과 분무 주사법, 두 가지로 고분자성 마이크로 입자 그룹을 만들어 *in vitro* 환경에서 실험을 하였다. 그 결과, 사용된 용매의 양이나 고분자와 SKL-AG20의 비율에 따라 입자의 크기, 약물의 포획 정도, 약물의 방출 패턴 등이 영향을 받는 것으로 나타났다. 또한 PLGA 고분자의 단위체의 비율에 따라 약물의 방출 패턴을 보다 효율적으로 조절할 수 있었다. 특히, 용매의 양과 고분자의 농도 조건을 바꾸어 주사 분무된 고분자성 마이크로 입자에서 크기가 더 크고 매끄러운 표면을 가진 입자를 관찰할 수 있었다. 그 결과, 표면적의 감소로 인해 약물의 초기 방출량이 줄어들어 보다 더 지속적인 약물 방출 효과를 보였다. 결과적으로, 다양한 고분자성 마이크로 입자 시스템을 이용하여 생분해성이 강한 약물을 효과적으로 전달할 수 있게 되었고, 많은 양의 약물을 포함하면서도 2 주일에 걸쳐 고른 속도로 약물을 방출하는 약물 전달 시스템을 구현함으로써 보다 더 편리하고 효과적인 치료가 가능해졌다.

주요어: 생분해성 고분자, 고분자성 마이크로입자, 용매 증발 법, 분무 주사법

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