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RAPID COMMUNICATION

Smart delivery system for cosmetic ingredients using pH-sensitive polymer hydrogel particles

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Abstract−pH-Sensitive P(MAA-co-EGMA) hydrogel microparticles were prepared and their feasibility as smart delivery carriers for cosmetically active ingredients such as arbutin, adenosine, and niacinamide was evaluated. P(MAA-co-EGMA) hydrogel microparticles were synthesized via dispersion photopolymerization. There was a drastic change in the swelling ratio of P(MAA-co-EGMA) microparticles at a pH of around 5. The loading efficiency of the cosmetic ingredients was affected by the electrostatic interaction between the hydrogel and the cosmetic ingredients. The P(MAA-co-EGMA) hydrogel microparticles showed a pH-sensitive release behavior. Thus, at pH 4 almost none of the cosmetic ingredients except adenosine permeated through the skin, while at pH 6 relatively high skin permeability was obtained. These results indicate that the P(MAA-co-EGMA) hydrogel microparticles synthesized in this study have the potential to be used as a smart carrier for cosmetic ingredients triggered by an external pH change for cosmetic applications.

Key words: Hydrogel Microparticles, Cosmetic Ingredients, Arbutin, Adenosine, Niacinamide, pH-sensitive, Smart Delivery System, Skin Permeability

INTRODUCTION

Since the 1980s, consumer demand for more effective cosmetics products that more substantively beautify the appearance has resulted in the introduction of more active ingredients, which may actually improve not just the appearance of the skin but also the health of the skin, into a number of cosmetics [1-4]. Thus, current cosmetics are intended to renew, restore, and rejuvenate, not just cleanse, protect, and moisturize the skin. In general, these active ingredients in the cosmetics are very unstable to air, light, heat, moisture, metal ions, oxygen, and base so that they easily decompose into biologically inactive compounds. Therefore, considerable efforts have been made to encapsulate or immobilize cosmetically active ingredients in order to protect them from the surrounding environment [5-10].

In this study, using pH-sensitive hydrogels, one of the environmentally responsive hydrogels, we have developed a smart delivery system of cosmetic ingredients triggered by an external pH change for cosmetic applications. In our design of a smart delivery system, the cosmetic ingredients are incorporated within pH-sensitive hydrogel microparticles and then stored in a cosmetic container where the pH is maintained lower than the pK_a of the hydrogel. In this low pH condition, the cosmetic ingredients cannot be released from the hydrogel particles due to the collapsed hydrogel network, so that the ingredients are protected. However, when the cosmetic ingredient-loaded hydrogel particles are applied to the skin, where the pH is always around pH 6 due to human homeostasis, the surrounding pH increases, leading to the release of the cosmetic ingredients from the particles and their absorption through the skin.

As a first step in the development of a smart delivery system for cosmetic ingredients, arbutin, adenosine, and niacinamide were used as model ingredients. Adenosine is one of the well-known anti-wrinkling agents [11-13], and arbutin and niacinamide are skin whitening agents used for skin lightening cosmetic products, such as lightening creams, anti-aging whitening creams, and age spot corrective creams [14-17]. The pH-responsive copolymer of MAA and PEGMA, designated P(MAA-co-EGMA), hydrogel microparticles were prepared and the feasibility of the P(MAA-co-EGMA) hydrogel microparticles as delivery carriers was evaluated with these cosmetic ingredients. The pH-responsive swelling and release behavior of the hydrogel microparticles, the loading efficiency of the cosmetic ingredients in the hydrogel microparticles, and the skin permeability of the cosmetic ingredients as a function of pH were investigated

MATERIALS AND METHODS

Methacrylic acid (MAA), poly(ethylene glycol) methacrylate (PEGMA, molecular weight 360), poly(ethylene glycol) dimethacrylate (PEGDMA, molecular weight 330), adenosine, silicon oil, and trifluoroacetic acid (TFA) were purchased from Sigma-Aldrich (USA). Arbutin, niacinamide, and dimethicone copolyol (DC) were obtained from Nabion (Korea). 1-Hydroxycyclohexyl phenyl ketone (otherwise known as Irgacure® 184) was purchased from Ciba Specialty Chemicals (USA). Acetonitrile (ACN) was purchased from Burdick & Jackson (HPLC grade, USA).

1. Synthesis of P(MAA-co-EGMA) Hydrogel Microparticles

P(MAA-co-EGMA) hydrogel microparticles were prepared by dispersion photopolymerization. Monomers with a feed composition (molar ratio) of 0.6 : 1 MAA : EG were mixed. In this monomer mixture, the PEGDMA was added as a cross-linker in an amount of 0.75 mol% of total monomers. Irgacure® 184, as a UV-light sensitive initiator, was added in an amount of 0.5 wt% of total monomers and this mixture was diluted with deionized water to 25 wt%

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of total monomers. The mixture was then purged with nitrogen gas for 10 minutes to remove dissolved oxygen that would act as an inhibitor of the reaction, and then added to 30 ml of silicon oil to which DC was added in an amount of 2.0 wt% of total monomers. DC was used as a dispersion stabilizer. The hydrophilic mixture was dispersed in the silicon oil with an ultrasonic processor (VCX750, Sonics & Materials) for 2 minutes. The dispersion solution was irradiated with UV light (intensity 1,000 mW/cm^2) for 300 seconds for the polymerization. Synthesized particles were then separated from oil by several repeated cycles of washing with deionized water, centrifugation and sonication. The washed particles were lyophilized using a freeze-dryer (Ecospin 3180C, Biotron) for 24 hours for future use.

2. Swelling Studies of P(MAA-co-EGMA) Hydrogel Microparticles

To determine the pH-responsive swelling behavior of the P(MAA-co-EGMA) hydrogel microparticles, the freeze-dried microparticles were weighed and then placed in phosphate-citrate buffer solutions with pH values of 4 and 6. The ionic strength of each buffer solution was adjusted to 0.5 M by the addition of potassium chloride. After swelling, the size of the particles was observed by dynamic light scattering (DLS, Nano S90, Malvern).

3. Incorporation and Release of Cosmetic Ingredients

Incorporation of cosmetic ingredients (arbutin, adenosine, and niacinamide) into the P(MAA-co-EGMA) hydrogel microparticles was carried out by soaking 0.05 g of particles in 25 ml of each stock solution (2.0 mg/ml) of cosmetic ingredients for 24 hours. At specific time points, 0.5 ml of sample was withdrawn and the concentrations of cosmetic ingredients were measured to calculate the loading efficiency, defined as the ratio of the amount of cosmetic ingredients incorporated into the hydrogel microparticles to the amount of cosmetic ingredients in the stock solution. After 24 hours, the cosmetic ingredient-loaded hydrogel microparticles were separated from the solution by centrifugation and then used for the release experiments. To release the cosmetic ingredients from the particles, 0.05 g of cosmetic ingredient-loaded hydrogel microparticles were placed in 25 ml of buffer solutions with pH values of 4 and 6. At specific time points, 0.5 ml of sample was withdrawn from the solution and the concentration of released cosmetic ingredients was measured. For loading and release experiments, HPLC was used to determine the concentration of cosmetic ingredients. The HPLC used in the analysis consisted of a Waters 600E controller, a Waters 600 pump, a Waters 717 plus autosampler, a Waters 996 photodiode array detector, and a column (TC-C18, C18, 5 μm, 250×4.6 mm, Agilent). For arbutin analysis, the mobile phase was 97.5% water and 2.5% ACN with 0.1% (v/v) TFA. The sample injection volume was 10 μL and the UV detection wavelength was 254 nm. For adenosine analysis the mobile phase was 80% water and 20% ACN with 0.1% (v/v) TFA. The sample injection volume was 10 μL and the UV detection wavelength was 280 nm. For niacinamide analysis, the mobile phase consisted of two solutions: solution A was water with 0.1% (v/v) TFA and solution B was ACN with 0.1% (v/v) TFA. The flow gradient was from 85 to 15% of solution A over 5 min and the flow rate was 1.4 ml/min. The sample injection volume was 10 μL and the UV detection wavelength was 290 nm. The calibration curves of each cosmetic ingredient concentration versus HPLC peak were prepared to obtain quantitative information on loaded and released cosmetic ingredients.

4. Skin Permeability Studies of Cosmetic Ingredients

Skin permeation experiments were carried out using Franz diffusion cells (FCDV-15, Labfine) and human epidermis which was purchased from Hans Biomed (Korea). A diffusion cell consisted of a donor chamber and a receptor chamber with the skin positioned between the chambers. The absorption surface area of the skin was 0.785 cm^2. Then 5 ml of the receptor chamber was filled with pH 4 or pH 6 buffer solutions. After equilibration of skin with the receptor phase, 2 mg of the cosmetic ingredient-loaded P(MAA-co-EGMA) hydrogel microparticles and 1 ml of buffer solution were introduced into the donor chamber. The receptor fluid was maintained in contact with the underside of the skin from the time of application until the end of the collection of the receptor fluid. The diffusion cell and skin were maintained at a constant temperature of 36 °C. The receptor solution was continuously agitated with a magnetic stirrer at 500 rpm. After 24 hours, 0.5 ml of sample was taken from the receptor chamber and each cosmetic ingredient concentration was measured using HPLC.

RESULTS AND DISCUSSION

pH-Responsive P(MAA-co-EGMA) hydrogel microparticles with MAA : EG=0.6 : 1 were synthesized by dispersion photopolymerization. The average diameters of the particles measured by DLS were 2.8 μm and 4.7 μm at pH 4 and pH 6, respectively. This difference of the average diameters between pH 4 and pH 6 was caused by the pH-responsive swelling behavior of the hydrogel microparticles. In general, the pH-sensitive swelling behavior of MAA-containing hydrogels results from the ionization or deionization of the carboxylic acid groups of the MAA in response to external pH changes. The carboxylic acid groups of MAA in the hydrogel become ionized as the pH of the external medium increases over the pK_a of the hydrogel. Thus, the presence of MAA in the P(MAA-co-EGMA) hydrogels resulted in a typical pH-responsive swelling behavior of the anionic hydrogel, i.e., low swelling ratios at low pH and high swelling ratios at high pH. Thus, for P(MAA-co-EGMA) hydrogel microparticles prepared in this study, there was a drastic change of the swelling ratio at a pH of around 5, which is the pK_a of PMAA. At a pH below 5, the hydrogels were in a relatively collapsed state, but at a pH higher than 5 the hydrogels swelled to a high degree. This sharp transition between the swollen and collapsed states at a specific pH makes it possible to use the hydrogels as carriers with which the release of the solute from the hydrogels can be controlled by external pH changes.

The loading efficiencies of arbutin, adenosine, and niacinamide at pH 6.5 were 32.4(±8.8)%, 10.5(±1.0)%, and 16.6(±2.0)%, respectively. The incorporation of loading materials into P(MAA-co-EGMA) hydrogel microparticles is affected by both the degree of swelling of the hydrogel and the electrostatic interaction between the hydrogel and the loading materials at the condition where the incorporation is carried out. In this experiment, however, since the hydrogel composition (MAA : EG=0.6 : 1) and the loading pH of 6.5 were at the same condition, the degree of swelling of the hydrogel did not affect the loading efficiency. Therefore, the difference of loading efficiencies of each cosmetic ingredient was explained by the electrostatic interaction between the hydrogel and each cosmetic

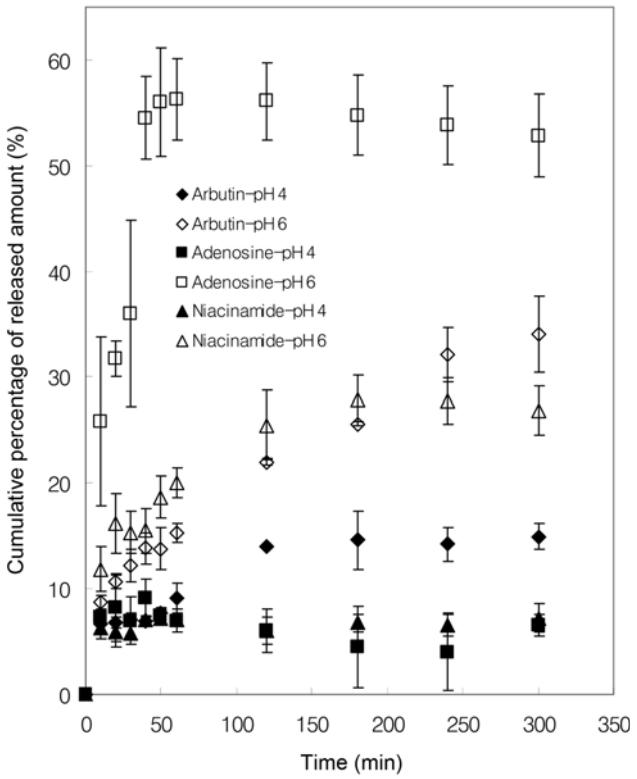

Fig. 1. Cumulative percentage of cosmetic ingredients released from P(MAA-co-EGMA) hydrogel microparticles with MAA : EG=0.6 : 1; arbutin at pH 4 (◆), adenosine at pH 4 (■), niacinamide at pH 4 (▲), arbutin at pH 6 (◇), adenosine at pH 6 (□), and niacinamide st pH 6 (△) (average±SD, n=3).

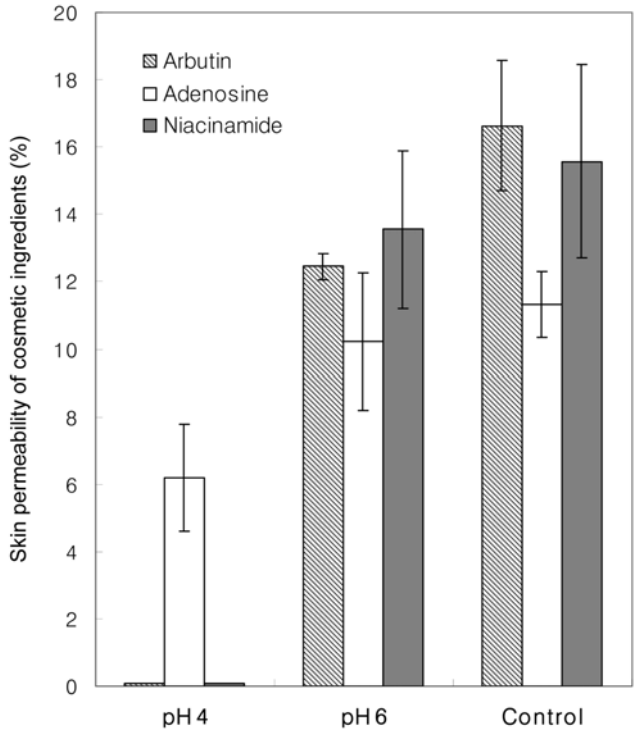

Fig. 2. Skin permeability of cosmetic ingredients from cosmetic ingredient-loaded P(MAA-co-EGMA) hydrogel microparticles with MAA : EG=0.6 : 1 at pH 4 and 6 for 24 hours (average±SD, n=3).

ingredient at pH 6.5.

To investigate the pH-responsive release behavior of cosmetic ingredients from the P(MAA-co-EGMA) hydrogel microparticles, the cosmetic ingredient-loaded microparticles were placed in pH 4 or pH 6 buffer solutions. The cumulative percentage of cosmetic ingredients released from the particles as a function of time is shown in Fig. 1. The P(MAA-co-EGMA) hydrogel microparticles showed a pH-responsive release behavior. Small amounts of cosmetic ingredients were released from the particles at pH 4, but at pH 6 relatively large amounts of cosmetic ingredients were released from the particles. At pH 6 about 2, 8, and 4 times more arbutin, adenosine, and niacinamide were released from the particles than at pH 4, respectively. This pH-sensitive release behavior of P(MAA-co-EGMA) hydrogel microparticles for cosmetic ingredients is due to the change in the mesh size of the hydrogel network depending on the external pH change. As the pH increased over the pK_a of the hydrogel, the electrostatic repulsion produced between the charged carboxylic acid groups of the MAA brought an increase of the mesh size of the hydrogel network and abrupt release of the cosmetic ingredients from the hydrogel particles. This pH-sensitive release behavior can be used as a smart carrier for a cosmetic ingredient such as arbutin, adenosine, or niacinamide, triggered by an external pH change. For instance, the P(MAA-co-EGMA) hydrogel microparticles are able to keep the cosmetic ingredients inside the particles when they are in the cosmetic container, where the pH is maintained at pH 4, and release the cosmetic ingredients from the particles when they are applied to the skin, where the external pH increases to around 6.

To verify the idea that the cosmetic ingredients can be released from the particles and absorbed through skin when the external pH changes from pH 4 to 6, permeation of cosmetic ingredients from the cosmetic ingredient-loaded hydrogel microparticles through the human epidermis was studied. Fig. 2 shows the skin permeability of the cosmetic ingredients (arbutin, adenosine, and niacinamide) from the particles as a function of pH. At pH 4 almost none of the ingredients except adenosine permeated through the skin, while relatively high skin permeability was obtained at pH 6 for all the cosmetic ingredients. This is because, as previously mentioned, the P(MAA-co-EGMA) hydrogel microparticles had a pH-sensitive release behavior for the loaded materials; in other words, at pH 6 more cosmetic ingredients were released from the particles and permeated through the skin than at pH 4. The skin permeability of the cosmetic ingredients at pH 6 reached about 75%, 90%, and 87% of the permeability of the control, which was the experiment using each cosmetic ingredient not loaded in the hydrogel at pH 6, for arbutin, adenosine, and niacinamide, respectively. This indicates that the cosmetic ingredient-loaded in P(MAA-co-EGMA) hydrogel microparticles could release the cosmetic ingredients, which then permeated through the skin as they were exposed to a pH condition higher than the pK_a of the hydrogel.

CONCLUSIONS

pH-Responsive P(MAA-co-EGMA) hydrogel microparticles were

synthesized by dispersion photopolymerization. There was a drastic change of the swelling ratio of P(MAA-co-EGMA) hydrogel microparticles at a pH of around 5, which is the pK_a of MAA. At a pH below 5 the hydrogels were in a relatively collapsed state, but at a pH higher than 5 the hydrogels swelled to a high degree. The loading efficiency of the cosmetic ingredients was affected by the electrostatic interaction between the hydrogel and the cosmetic ingredients. The P(MAA-co-EGMA) hydrogel microparticles showed a pH-sensitive release behavior. At low pH (pH 4) small amounts of cosmetic ingredients were released from the particles, while at high pH (pH 6) relatively large amounts of cosmetic ingredients were released from the particles. Thus, at pH 4 almost none of the cosmetic ingredients except adenosine permeated through the skin, while at pH 6 relatively high skin permeability was obtained. These results indicate that the P(MAA-co-EGMA) hydrogel microparticles synthesized in this study have the potential to be used as a smart carrier for a cosmetic ingredient such as arbutin, adenosine, or niacinamide, triggered by an external pH change for cosmetic applications.

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