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사용자 편의성 향상을 위한 새로운 개념의 브러쉬-오프 필름 기반 구강 케어 패치

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A New Concept Oral Care Patch with an Easily Removable Brush-off Film for More Convenient and Comfortable Use

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초록: 브러쉬-오프 타입 구강 케어 패치 개발에 관한 최초의 연구로서, 에틸 셀룰로오스(EC)와 하이드록시프로필 메틸셀룰로오스(HPMC)로 구성된 고분자 블렌드 필름을 solvent casting 방법으로 제조하였다. 고분자 블렌드 필름의 브러쉬-오프 패치로서의 적합성을 평가하기 위해 접촉각 측정, 인장강도 시험 및 광학현미경을 이용한 수화 시간에 따른 표면 형상 변화 측정 등을 수행하였다. 본 연구에서 측정된 표면 특성, 인장강도 및 수화 특성 등과 같은 필름의 물리화학적 특성은 고분자 조성에 크게 의존하는 것으로 나타났다. 무엇보다도, 기계적 물성과 수화 특성 측면에서 EC와 HPMC가 1:1 또는 2:1의 비율로 제조된 고분자 블렌드 필름이 30분 브러쉬-오프 패치로서 가장 적합한 것으로 나타났다. 이 연구는 브러쉬-오프 필름 패치를 디자인하고 평가하는 구강 케어 성분 전달 관련 연구분야에 새로운 방법론을 제시할 것으로 기대한다.

Abstract: As the first study to develop a brush-off type oral care patch, the polymer-blended films composed of ethyl cellulose (EC) and hydroxypropyl methylcellulose (HPMC) were prepared by a solvent casting method. Contact angle measurements, tensile strength tests and optical topography measurements were performed to assess the suitability of the polymer blends as a brush-off patch film. The physicochemical properties of the polymer films were dependent profoundly on their composition. The morphologies of the blended polymer film were significantly altered upon contact with water over time. In terms of mechanical strength and hydration property, the polymer-blended films of EC and HPMC with a mass ratio of 1:1 or 2:1 were found to be highly suitable for a 30 min brush-off patch. We believe that this study can provide a new and versatile methodology of both designing and evaluating a brush-off film patch for oral care substance delivery.

Keywords: brush-off film, oral care patch, polymer blend, ethyl cellulose, hydroxypropyl methylcellulose.

Introduction

Oral conditions affect the lives of people worldwide. Oral health is an important contributor to overall health and well-being. Toothpaste is the most commonly used oral care product for maintaining good oral health. There are many kinds of toothpastes for sensitive teeth care, gingival care and teeth whitening. However, the mode of use of toothpaste involves brushing teeth within 1~3 min, followed by removal by rinsing with water. Generally, changes from the use of toothpaste are felt after two to six months because of the short contact time between the active ingredient and the target area.[1-3] Oral patch technology is therefore gaining attention as a means of extending the contact time.

This oral patch technology can be used for local action (target area) and the oral care substance can be retained for a longer period in the oral cavity for release in a controlled fashion.[4] Recently, oral patches have gained popularity and acceptance because of the extended contact time and faster effect.[5-8] These patches can adhere to target areas like the teeth and gingiva

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and can be removed after a certain amount of time by peeling off the film (peel-off type products).[5,6] However, most of these delivery systems are thin gels or dry, adhesive films containing active ingredients on a water-impermeable film such as a polyethylene (PE) patch, and therefore leave a lot of residue on the target area after use, which produces an uncomfortable and unpleasant feeling. This kind of patient inconvenience has led to the development of novel oral care substance delivery systems such as brush-off type patches. Brush-off type patches are removed by brushing after the designated contact time. The main difference between peel-off type and brush-off type films is the mechanism of removal after use. The designated contact time and usage time depend on the characteristics of the products. The operation mode of brush-off type films is as follows: 1) the oral care film containing the active ingredient is attached to the target area in the oral cavity; 2) the film becomes increasingly weaker after wetting in the oral cavity; 3) this weakened film can be removed from the target area by brushing (Figure 1).

For this purpose, in the initial stage of use of brush-off type films, the structure and mechanical properties must be maintained, whereas in the final stage, the film should undergo alteration to an abradable film that can be removed by brushing with a toothbrush. This film disintegrates readily and abruptly during brushing. The characteristics of the oral film depend mainly on the type of polymer. Selection of the polymers and polymer blends is a key point in the development of brush-off type films because the designated contact time and target area differ for each case. Adequate experimental methods are required to determine the optimal polymer blend. In this study, we aim to develop a thirty minute brush-off type film. For this purpose, ethyl cellulose was selected as a hydrophobic film and hydroxypropyl methylcellulose as a hydrophilic film. Hydroxypropyl methylcellulose is known as a rapid-release, water-soluble polymer for tablet coating, whereas ethyl cellulose is a known water-insoluble coating polymer.[9] Using contact angle measurements, a tensile tester, and an optical microscope (Videoscope), these polymers and their blend are evaluated and the efficacy of the experimental methods as tools for the development of various brush-off type films for oral health is discussed. Thus, the overarching aim of this study is to develop a newer oral care substance delivery system, i.e., a brush-off type film, for enhanced customer satisfaction and faster results.

Experimental

Preparation and Release Property of Adhesive Layers. Oral care patches consist of an adhesive layer and a backing layer (Figure 1). An active ingredient is loaded in an adhesive layer and released from the adhesive layer. In this study, an adhesive layer was prepared by solvent casting method. At first, polymers, active ingredients, plasticizers were dissolved and uniformly dispersed in water. This slurry was casted using

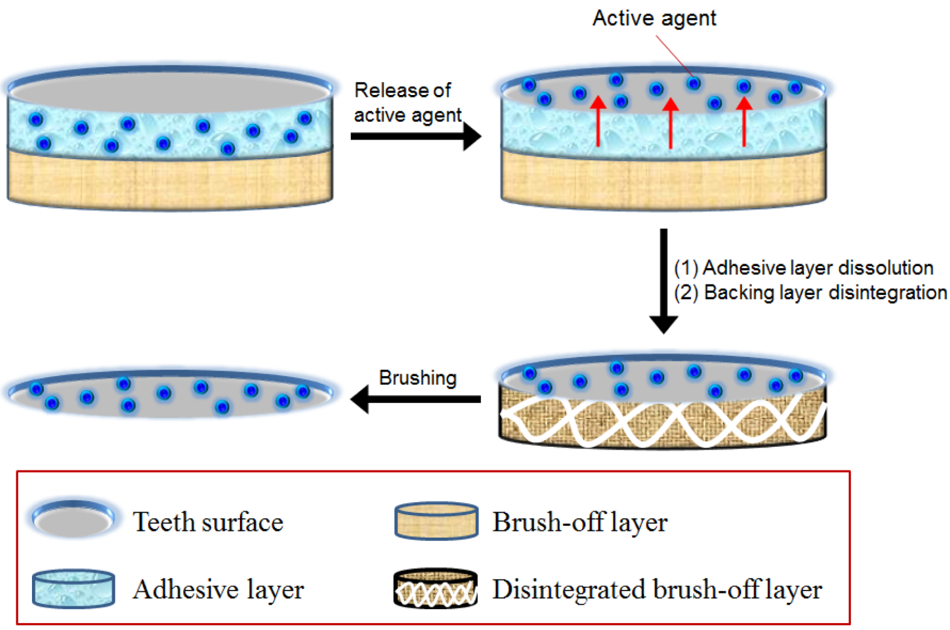

Figure 1. Schematic illustration of the operation mode of the brush-off type oral care patch for oral cavity.

a Mathis lab coater and dried to fabricate a film in an oven at 50 ºC. In this study, the drug release profile was investigated by the paddle 5 method of USP dissolution test for 30 min.[10]

Materials and Preparation of Brush-off Films. Ethyl cellulose (Aqualon EC N-22 Pharm) was purchased from Ashland. Hydroxypropyl methylcellulose (AnyAddy AN6 Food) was purchased from Lotte Fine Chemical. All other chemicals used were analytical or reagent grade.

Film casting was performed by using a Mathis lab coater and lab dryer. The polymer solutions were casted and then cut to predetermined sizes after drying. The polymer-blended films comprising HPMC and EC were prepared in varying ratios as follows: specified quantities of EC and HPMC and a plasticizer (castor oil and glycerin) were dissolved in ethanol to form a brush-off film. The adhesive layer containing the active agent and conferring tackiness was the same for all samples to facilitate comparison of the behavior of the backing layers (peel-off type or brush-off type).

Physicochemical Properties of the Prepared Films. Contact angle measurement was performed by using a Kruss drop size analyzer. The contact angle measurement is illustrated in the case of a drop (30 μL) of distilled water on a glass slide (VWR microslides) covered by a polymer film. After dropping one drop of distilled water onto the film-coated slide, the contact angle was monitored as a function of time.

The mechanical properties of the films were evaluated using a universal testing machine (Zwick Material Prufung tensile tester). Each film patch (1 cm×12 cm) was held between two tensile grips positioned at a distance of 10 cm. The force and elongation were measured when the films broke. Three determinations were performed.

An ITPlus videoscope instrument was used to monitor the surface characteristics of the polymer films before and after hydration. The changes in the surface of the polymer film on the glass slide were monitored by photographic imaging with the progress of time.

Results and Discussion

The drug loading efficacy of the adhesive layer proved to be ~100% when active ingredients were thermally stable at 50 ºC. In addition, the release amount was found to be more than 75% for 30 min when the oral care patch was tested by the paddle 5 method of USP dissolution test.[10] Here, we focused on the development of backing layer which are closely associated with the comfortable use of consumers.

The solvent casting method was used to prepare the films. Various brush-off films were prepared at different mass ratios of EC and HPMC by dissolving a polymer or the polymers in ethanol by agitation at 1400 rpm, and all other excipients were dissolved separately. The resulting solution was casted as a film and allowed to dry; the film was then cut into pieces of the desired size. The thickness of the film was measured by using calibrated digital Vernier Calipers. The thickness of the films was around 300 μm. Typically, oral care substance patches such as peel-off type films consist of two different layers; one is an adhesive layer and the other is a backing layer (Figure 1). Generally, the active ingredient is contained in an adhesive layer. The main difference in the removal mechanism depends on the characteristics of the backing layer. Polyethylene (PE) is one of main polymers used as the backing layer of peel-off type films and is generally manufactured by blow molding.

Contact angle measurements are used to assess the wetting behavior, disintegration time, and dissolution of oral films.[11] An appropriate brush-off type film must have an initially hydrophobic surface that becomes mechanically weaker and hydrophilic in the end. These changeable surface properties of the backing layer film can be assessed by contact angle measurement. On the other hand, if the surface of the backing film is consistently hydrophobic, the film is appropriate for use as a peel-off type film.

The initial contact angle of the water-impermeable, more hydrophobic PE film having no hydrophilic functional groups (which is used as a typical polymer for the backing layer of peel-off films) was close to 100º and did not change after contact with 30 μL of water for 600 s (Figure 2). The water-insol-

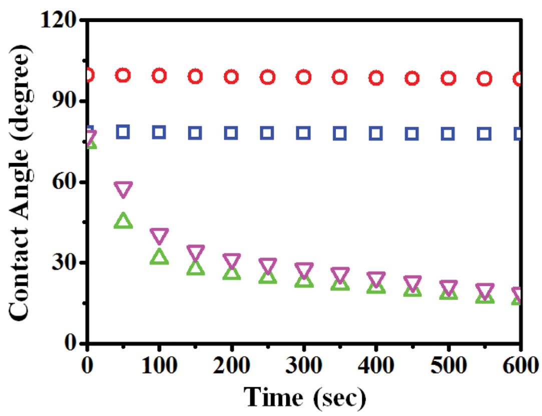

Figure 2. Contact angle of PE peel-off film (○), EC peel-off film (□) and brush-off films (EC/HPMC films with 1:1 (△) and 2:1 (▽) mass ratios).

uble, water-impermeable, and hydrophobic film of ethyl cellulose that has some hydroxyl groups on the repeating glucose unit had an initially measured contact angle of roughly 80°; the contact angle decreased, but by less than 20%, during 600 s of contact.

The polymer-blended film of EC and HPMC with a mass ratio of 1:1 gave rise to a very different pattern of contact angles (Figure 2). In the initial stage, the contact angle was around 80°, similar to that of the ethyl cellulose film. Within 60 s, the contact angle decreased by more than 50% and finally decreased to 16° in 600 s. The change of the contact angle to 16° means that the hydrated surface is very hydrophilic and is easily wetted. For use as a brush-off film, such properties are necessary, as previously mentioned. The variability of the contact angle within a short time is a desirable characteristic for a brush-off film and strongly suggests that the polymer blend of EC and HPMC should be a good candidate as a brush-off film.

The mechanical properties of oral films may critically affect the physical integrity during attachment and removal. For a more comfortable feel when an oral care patch is attached to the teeth or gingiva, the film should remain tightly attached within the humid oral cavity because people talk and swallow saliva continuously. High mechanical strength is required for peel-off films because they should be removed as an intact film. If the film rips during peeling, pieces of film may be left on the teeth or gingiva. In contrast, brush-off films require a different mechanical strength pattern. The mechanical strength of the polymer films was evaluated using a universal testing machine and the stress-strain curves of the polymer films were obtained depending on the polymers and polymer blends. The tensile strength of the film is defined as the resistance of the material to a force tending to tear it apart.[12-21] The Young's modulus is an indicator of the stiffness or how the film deforms in the elastic region.[22]

Soft and weak films may be more appropriate as brush-off type films than strong or brittle films. Morales *et al*. reported that the stress-strain curve can be used to investigate the mechanical properties of these films.[23] It is known that soft and weak films have low tensile strength, a low Young's modulus, and low elongation at break.[24] As shown in Figure 3, the EC film showed a mechanical pattern of "hard and strong", whereas the HPMC film had a pattern of "soft and brittle". The brush-off film comprising the polymer blend of EC and HPMC had a "soft and weak" mechanical pattern, which means that these films can fall apart and disintegrate into pieces upon brushing.

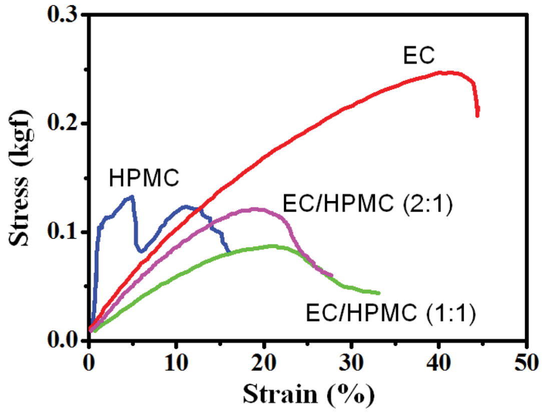

Figure 3. Stress-strain curves of oral care patches with different backing layers: EC (—), HPMC (—), and brush-off films (EC/HPMC films with 1:1 (—) and 2:1 (—) mass ratios.

Table 1. Tensile Strength of Oral Patches from Polymer Blends with Different Ratios of EC to HPMC

Ratio of EC to HPMC	Tensile strength (kgf)
EC:HPMC=1:0	0.26
EC:HPMC=2:1	0.13
EC:HPMC=1:1	0.07
EC:HPMC=1:2	0.05

The hard and strong properties of the EC film make it appropriate as a peel-off film. The film did not disintegrate and was simply divided into two parts. The HPMC film was too brittle to be stretched. The blended polymer films of EC and HPMC could be stretched and disintegrated when pulled with zigs.

Tensile strength analysis showed that relative to the EC only film, the polymer-blended films of EC and HPMC with a mass ratio of 1:1 became weaker and weaker as the HPMC proportion increased (Table 1). The tensile strength of films is deeply related to their mechanical strength and may serve as an indicator of adequate polymer blends and ratios for abradable, brush-off type films. Furthermore, the ratio can be chosen depending on how long the film should stay in the oral cavity.

The surface morphology of the brush-off films was monitored by optical microscopy. In the case of the EC film, one backing layer of the peel-off type film showed no change as time went on (Figure 4). Optical micrographs of the polymer blends with EC and HPMC revealed changes depending on time and the HPMC:EC ratio after hydration, as shown in Figure 4. When the composition of the films was the same with the ratio of HPMC to EC being the only difference, the surface morphology of the films differed after thirty minutes of hydra-

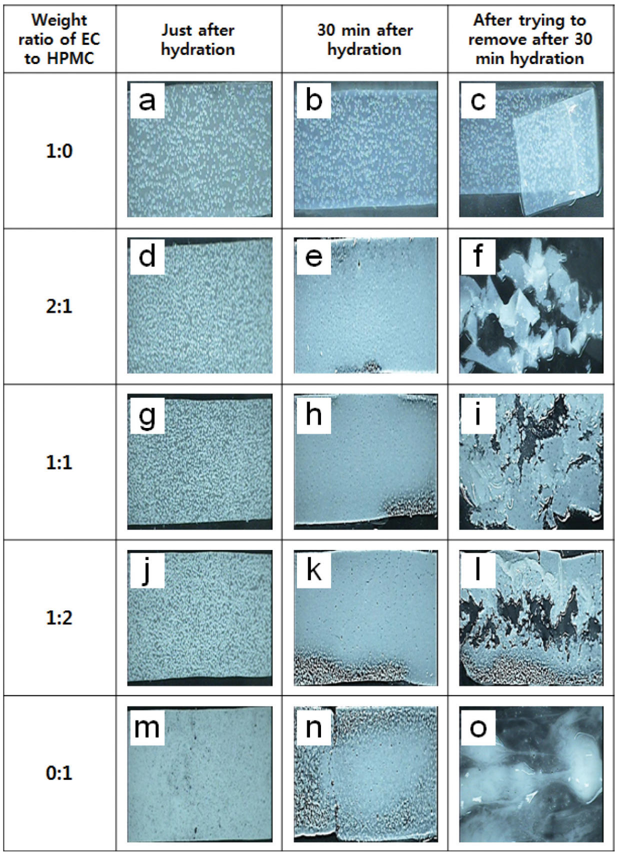

Figure 4. Morphology of various polymer films with hydration time.

tion. In detail, when EC only was used without HPMC, the film had no pores and showed no weakening with time, as shown in Figure 4(a-c). After 30 min hydration, the film did not fall apart when rubbed with the fingers. The film could only be removed by peeling-off as shown in Figure 4(c).

On the other hand, the HPMC only film without EC showed very a different pattern (Figure 4(m-o)). In this case, pores were observed just after hydration, and a huge crack was formed within 30 min (Figure 4(n)). When the film was touched with the fingers, it was easily crushed and looked like a gel (Figure 4(o)).

When the ratio of EC to HPMC was 2:1, as shown in Figure 4(d-f), pores slowly appeared in the film and became clear around 30 min (Figure 4(e)). The film was not crushed when manipulated with the fingers, but fell apart as pieces upon brushing (Figure 4(f)). The surface of the polymer film of EC and HPMC with a 1:1 mass ratio appeared to be weaker with the passage of time and pores were observed after hydration. Note that the EC/HPMC (1:2) film possessed many cracks (Figure 4(k)), similar to the pure HPMC film (Figure 4(n)). After 30 min, the film can be easily crushed even by a soft touch. The endurance time of the brush-off film could be tuned depending on the ratio of the two polymers and the hydration time. To stay on the target area, such as the gingiva and teeth, for 30 min, the film should maintain its shape and have some mechanical strength but not be too strong. For example, the EC only film seemed inappropriate because it is too strong. The HPMC film and the EC/HPMC (1:2) film were not appropriate as 30 min brush-off films because of the weakness of the film. In contrast, the EC/HPMC films with mass ratios of 1:1 and 2:1 appeared appropriate as 30 min brush-off films. We think that the most suitable film as 30 min brush-off films can be made through proper tuning in the composition.

These results can be explained as follows: ethanol is a good solvent for both of the two polymers; therefore, ethanol was used to dissolve the polymers for the fabrication of the blended film; however, water is a good solvent for HPMC only and a poor solvent for EC.[23] The incompatibility between these two polymers is known because there is no significant intermolecular interaction force when the polymer blend film is in contact with water.[25] Overall these results suggest that the polymer blends of EC and HPMC with a specific mixture ratio may serve as brush-off films for oral cavity under given conditions (e.g., contact time, additive types).

Conclusions

For the first time, we developed brush-off type oral care patch films composed of ethyl cellulose (EC) and hydroxypropyl methylcellulose (HPMC). These polymer blend films had soft and weak mechanical properties and exhibited endurance after hydration. The morphologies and mechanical properties of the films drastically changed after hydration. The polymer-blended films of EC and HPMC at 1:1 or 2:1 mass ratios were found to be highly suitable for a 30 min brush-off patch when considering their mechanical strength and hydration property. The results of this study suggest that contact angle measurement, tensile strength test and especially optical microscopic observation may be appropriate methods for proper selection of the optimal polymer blend and the best ratio of polymers for brush-off films. We believe that this approach can open a new way for the design of highly efficient oral care patches and the selection of brush-off film formulations.

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