유기겔을 이용한 약물전달시스템 개발

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Development of Drug Delivery System using Organic Gel

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1. Introduction

Various formulations such as ointments and wound dressings have been developed for thetreatment of severe skin wounds or ulcers including bedsores and burn wounds. Wound dressings are often used to protect the wound and/or enhance healing process. PVA is a hydrophilic, semicrystalline copolymer of vinyl acetate and vinyl alcohol. The PVA's biocompatibility has made it an excellent material for use in medical applications as a drug delivery device. PVA hydrogels are prepared by using freezing and thawing techniques of physical method. Physically cross-linked PVA hydorgel is a non-toxic, non-carcinogenic and good biocompatibility. Improvements in the characteristics of PVA hydorgel could be achieved by the addition of biological macromelecules. Sod.fusidate (SF) is a mono-anionic steroidal antibiotic used widely for the treatment of infectious diseases with methicillin-resistant or, more recently, multi-resistant *Staphylococcus aureus* strains. Thus, this wound dressing (PVA/PVP/SA hydrogel containging SF) was examined in vivo studies and mechanical characteristics

2. Experimental

2.1. Preparation of Physical Characterization of PVA hydrogel

PVA hydrogel was obtained by the previously described method with a slight modification. In brief, an aqueous solution of PVA was freezed at -20°C for 18 hrs and thawing at room temperature for 6 hrs, for three consecutive cycles. The effect of various excipients on physicochemical characteristics of these systems was evaluated. Mechanical properties such as tensile strength (N/mm2) and elongation at break (%) and bioadhesive strength to detach the hydrogel from tissue were characterized. To measure the swelling behavior of PVA hydrogel, samples were dried at 60℃ oven for 24hrs. The dry weights of hydrogels were immediately measured. Afterwards, hydrogels were soaked in PBS maintained at 37℃ then weighted at 8hrs to determine the wet weights.

2.2. Preparation of SF loaded PVA hydrogel

SF containing PVA was prepared as following: SF was incorporated into PVA/PVP/SA solution by simple mixing for an hour. Then a solution was freezed at -20°C for 18 hours and thawing at room temperature for 6 hours, for three consecutive cycles.

2.3. SF assay and released studies

The concentration of SF was determined using an Inertil ODS-2 column (C18, 150 x 4.6 mm i.d., 5 um particle size) and Hitachi HPLC instrument (L2200 detector, pump, Autosampler, column oven). The mobile phase was acetonitrile-sodium acetate solution (25:75 v/v) adjusted to pH 4.6 with H_3PO_4 with 1.0 ml/min of flow rate. SF was detected by a UV detector at 365 nm. The release of SF from the cross-linked hydrogels was evaluated in water by the paddle over disk method at 50 rpm. The concentration of SF present in the dialysate was sampled at selected time intervals and measured by HPLC.

2.4. Skin irritation test

The back of the animals (Six healthy rabbits of the New Zealand White) were clipped free of fur with an electric clipper at least 4 hours before application of the sample. A 0.5g sample was then applied to each site by introduction under a double gauze layer to an area of skin approximately 2.54cm X 2.54cm square. At a 48 hours after sample application, the test sites were examined for dermal reactions.

2.5. Permeation study of SF loaded PVA hydrogel

The permeation study of SF from PVA hydrogel was measured through the abdominal skin of hairless mouse. Permeation experiments were carried out for 24h at 37°C with Franz-type diffusion cell (Lab Fine Instruments, Korea).

2.6. In vivo wound healing study

Male SD rats weighting approximately 250~300 g was used to evaluate wound healing characteristics of hydrogels. Skin wounds of 1.5 cm x 1.5 cm area were prepared by excising the dorsum of rats and disinfected using 70 % ethanol. The excised wounds were covered with the PVA hydorgel containing Sod. fusidate and fixed with elastic adhesive bandage (Soft cloth tape®, 3M). After the experiment, rats were anesthetized by diethyl ether on 4, 6 days after surgery. The wounds were grossly examined and photographed for characteristics evaluation .

3. Results and discussion

The PVA of 10% was an optimal ratio to form bioadhesive hydrogel through cross-linking. In order to obtain a more ideal hydrogel administrated skin, gel was formulated with bioadhesive polymer such as carbomer, chitosan and PVP. Also sodium alginate (SA), swelling polymer, was added to make hydrogel that absorb wound exudates. A PVA/PVP hydrogel showed good effects on tensile strength and adhesiveproperty. But, mechanical and adhesive properties of PVA hydrogel were lower when the PVA hydrogel is mixed carbomer or chitosan rather than those of 10% PVA hydrogel. The additions of SA in the hydrogel showed 4-fold increase the degree of swelling, but decreased gel strength and elasticity. To make the effective hydrogel for fast healing of wound, PVA hydrogel is prepared with a topical anti-infective drug, sodium fusidate.

	Hydrogel methods		
Excipients	Swelling	Mechanical properties	adhesion
Carbomer	-	-	-
Chitosan	+	-	+
PVP	+	+	++
Sod.Alginate	++	-	-
Xanthan gum	-	-	-

Table1. Effect of Excipients on PVA hydrogel

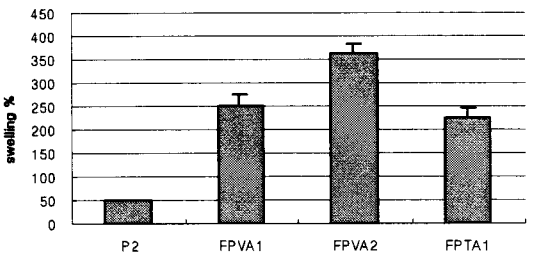

Figure 1. Swelling test of SF loaded PVA hydrogel

The release of drug from this hydrogel showed sustained release profile for 24hrs. Furthermore, when SF loaded PVA hydrogel was applied to rabbit, the hydrogel did not cause any irritation.

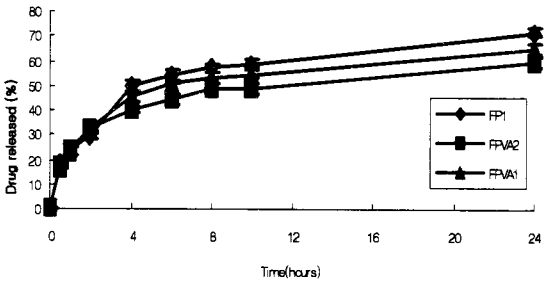

Figure 2. Dissolution test of SF loaded PVA hydrogel

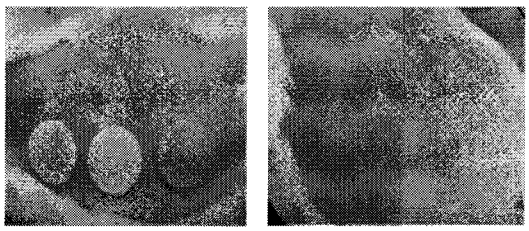

Figure 3. Skin irritation test of Sf loaded PVA hydrogel (left : 0 hour, right : 48 hours)

In vitro permeation study with hairless mouse skin showed sustained release and permeation amount of SF was greater than ointment preparation. Skin retention amount of SF was similar to the permeation result. In vivo wound healing study showed that SF loaded PVA hydrogel better wound healing ability compared with control.

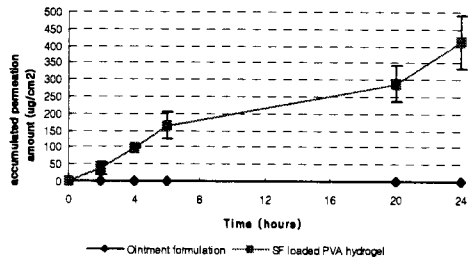

Figure 4. in vitro permeation study with hairless mouse skin

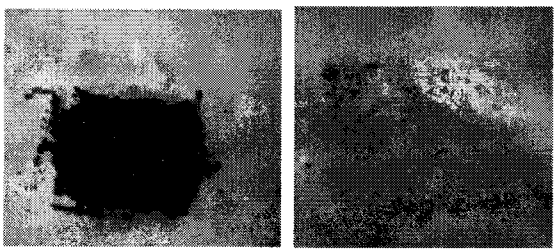

Figure 5. In vivo test of SF loaded PVA hydrogel on 4 days after surgery (left : control, right : SF loaded PVA hydrogel)

Over all result suggested that this system could be a novel approach in wound care.

4. Acknowledgements

This work was supported by grant No. RTI04-01-04 from the Regional Technology Innovation Program of the Ministry of Commerce, Industry, and Energy (MOCIE).

5. References

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