J. Cosmet. Sci., 64, 273–286 (July/August 2013)

Lauroyl/Palmitoyl glycol chitosan gels enhance skin delivery of magnesium ascorbyl phosphate

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Accepted for publication October 4, 2012.

Synopsis

Palmitoyl glycol chitosan (GCP) hydrogel has been reported as erodible controlled-release systems for the delivery of both hydrophilic and hydrophobic molecules. In this study we prepared lauroyl/palmitoyl glycol chitosan (GCL/GCP) in gel form and evaluated their application for skin delivery of the hydrophilic compound, magnesium ascorbyl phosphate (MAP), which is widely used in cosmetic formulations. Release of MAP from the polymer gels was significantly decreased with increasing concentration of GCL/GCP in the formulations in comparison with glycol chitosan (GC). In both aqueous and 10% ethanol vehicles, MAP flux was increased 1.58- to 3.96-fold of 1% GC from 1% GCL/GCP. Increase in MAP flux was correlated to the increase in GCL/GCP concentration prepared in 10% ethanol vehicle. GCL/GCP, in either water or 10% ethanol vehicles, increased the skin penetration and skin deposition of MAP in comparison with GC, hydroxypropylmethylcellulose, and carbopol, while sustaining its release from the polymer gels. Both the enhancement in skin penetration/deposition and sustained release of MAP were depended on polymer concentration. Also, with increase in polymer concentration, epidermal to dermal drug deposition ratio tended to increase, which will be beneficial to its activity in the epidermis, such as inhibition of tyrosinase and protection from UV damage. These data suggested both GCL and GCP can be applied as delivery vehicles to improve percutaneous absorption of MAP.

INTRODUCTION

Magnesium ascorbyl phosphate is a derivative of L-ascorbic acid (Vitamin C) that is known to be stable in the light, air or heat. After entering the human or animal body, it is converted into L-ascorbic acid through the enzymolysis of phosphatase, and maintains the same physiological function and biological efficacy as L-ascorbic acid. MAP is a key constituent of skin moisturizer intended for effective inhibition of tyrosinase activity in skin and facilitation of collagen synthesis. MAP also resists the damage caused on the

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skin due to the UV light, smog, and other environmental effects and hence has been widely used in cosmetics (1–3). In addition, it is known that MAP may stimulate growth of human dermal fibroblast cells (4,5). It is also shown that MAP stimulates growth of dermal papilla cells *in vitro* and early conversion from telogen phase to anagen phase in mice (6). Furthermore, MAP treatment resulted in significant elongation of hair shafts in isolated hair follicles. It has been suggested that the responsible mechanisms include its proliferative and antiapoptotic effects on dermal papilla cells (6).

Chitosan, a polysaccharide comprising copolymers of glucosamine and *N*-acetylglucosamine, is derived by deacetylation of chitin, the second abundant polysaccharide present in nature (7). It has been regarded as biocompatible, biodegradable, nontoxic, and non-immunogenic, and is an interesting biomaterial because of its ability as a cosmetic carrying materials and ease of modification (8). Despite its superiority as a biomaterial, chitosan is only soluble in acidic solutions, which limits its application (9). Water-soluble glycol chitosan (GC) is derived from chitosan, and is emerging as novel carriers of drugs (10). To improve its pharmaceutical acceptability, GC was modified with hydrophobic groups (fatty acids) to form a noncovalently cross-linked amphiphilic hydrogels (11,12). GCP hydrogel has been shown as erodible controlled-release systems for the delivery of both hydrophilic macromolecules and hydrophobic drugs (13,14). In this work, we describe the use of lauroyl/palmitoyl glycol chitosan (GCL/GCP) in the form of gel as supporting material for skin absorption of hydrophilic molecules using MAP as model compound. The use of an amphiphilic polymer (GCL/GCP) to prepare gels may add the potential advantage of improving skin delivery of MAP for cosmetic applications.

EXPERIMENT

MATERIALS

GC (Mw 128 kDa; degree of polymerization ≥400), palmitic acid *N*-hydroxysuccinimide (PNS), lauric acid *N*-hydroxysuccinimide (LNS), hydroxypropylmethylcellulose (HPMC), L-Ascorbic acid 2-phosphate sesquimagnesium salt hydrate, phosphate buffered saline (PBS), and sodium bicarbonate were purchased from Sigma chemical Co. (St. Louis, MO). Carbopol 940 was obtained from ACROS Organics (Morris Plains, NJ). Chloral hydrate was purchased from Tokyo Chemical Inc. (Tokyo, Japan). Absolute ethanol was purchased from Panreac Quimica (Barcelona, Spain). Acetone and diethyl ether were obtained from Merck Co. (Darmstadt, Germany). Dialysis tubing of molecular weight cut-off (MWCO) 12–14 kDa was obtained from Millipore Co. (Billerica, MA).

SYNTHESIS OF GCL/GCP

The synthesis of GCL/GCP was carried out according to the methods described in Noble *et al*. (11) and Cerchiara *et al*. (12). Briefly, GC (100 mg) was dissolved in Milli-Q water (20 ml), to which sodium bicarbonate (76 mg) and absolute ethanol (10 ml) were added. A solution of LNS (133 mg) or PNS (158 mg) in absolute ethanol (10 ml) was added dropwise to the alkaline solution of GC over 1-h period. After 72 h of stirring protected from light, acetone (20 ml) was added to the reaction mixture and the resulting solution

was evaporated under reduced pressure at 45°C to remove organic solvents. The residual mixture was extracted with diethyl ether (40 ml) and subjected to exhaustive dialysis within dialysis tubing for 24 h with six changes of water, and were centrifuged at 4,500 rpm for 10 min at 4°C and then freeze-dried.

PHYSICOCHEMICAL CHARACTERIZATION OF GCL/GCP

Scanning electron microscopy (SEM) images of the specimens were recorded using a JSM-6700F microscope. FTIR spectra of the specimens were obtained with a Nicolet Magna 560 Spectrometer. Samples of GCL/GCP were ground into a powder form, mixed with KBr (1:100), and pressed into a disk and analyzed. Molecular weights of GCL/GCP were determined by gel permeation chromatography (GPC) run at 40°C in 0.05M $NaNO_3$–NaN_3 water (15) (at a flow rate of 0.5 ml/min) on a Waters 510 HPLC pump with an Ultrahydrogel™500 column using a RI-detector (Perkin Elmer, Norwalk, CT). The injection volume was 150 µl of a 0.48% w/w polymer in 10% ethanol. Molecular weight calculations were based on a linear calibration curve obtained using molecular weight standards Pullulan (Shodex standard WAT034207). Viscosity of 1–3% polymer gels prepared in Milli-Q water and 10% ethanol was analyzed by VISCO Star-R (Fungilab, Spain) at 37°C for 30 min.

^{1}H NUCLEAR MAGNETIC RESONANCE (NMR) SPECTRA STUDY

^{1}H nuclear magnetic resonance (NMR) correlation spectroscopy experiments (Bruker AV-500 NMR spectrometer, Darmstadt, Germany) were performed on solutions of GC and GCL/GCP in CF_3COOD to assign non-exchangeable coupled protons (11). Levels of lauroylation/palmitoylation in mol% of GC were estimated by the ratio given below.

GCL/GCP lauroyl/palmitoyl methyl proton (δ 0.85–0.93 ppm)/acetyl proton (δ 1.83 ppm)

IN VITRO RELEASE/SKIN PERMEATION APPARATUS

Both release and skin permeation experiments were performed using vertical type flow-through diffusion cells (Laboratory Glass Apparatus, Berkeley, CA) with an effective diffusion area of 1 cm^2 and a receiver volume of 3.6 ml, and maintained at a constant temperature with a 37°C-circulating water bath. Buffers were pumped through the receiver compartment at a flow rate of 3–4 ml/h with a peristaltic pump (Ismatec, Glattbrug-Zürich, Switzerland), and the fluid in the receptor phase was stirred continuously at 700 rpm.

PREPARATION OF MAP-CONTAINING GCL/GCP GELS

At least three batches of synthesized polymers were mixed for the preparation of MAP formulations. Appropriate amounts of polymers were mixed with 3% MAP solution in Milli-Q water or 10% ethanol, and equilibrated in an orbital shaker overnight to form 1–3% gel.

IN VITRO RELEASE STUDIES

The release membrane (Spectra/por® MWCO 1,000 Dalton) was clamped between the donor and receptor phases of the diffusion cells with the receptor phase filled with normal saline (0.9% sodium chloride), which has been adjusted to pH 6.0 by acetic acid. 500 µl of 3% MAP gels were dosed onto the membrane surface. Receiver solutions were collected every hour for 6 h and analyzed by HPLC.

IN VITRO SKIN PERMEATION STUDIES

Full-thickness dorsal skin from ICR nude mice (Nar1: ICR-Foxn1nu, National Laboratory Animal Center, Taiwan) was used for all the permeation experiments. The skins were mounted between the donor and receptor phase of the diffusion cells with the receptor phase filled with PBS having pH 7.4. As much as 500 µl of MAP gels were applied to the skin surface, and then occluded with parafilm. The receiver solution was collected at 1-h intervals for 6 h. At the end of 6 h, the skin segment was dismounted from the diffusion cells, rinsed with Milli-Q water for three times, and gently dried with Kimwipes® to remove the residual gels. The skin was placed on glass disc and heat-separated into epidermis and dermis at 60°C water bath for 1.5 min. Both the separated epidermis and dermis were weighed and homogenized in 1 ml phosphate buffer (pH 5.0) using a Polytron PT210 homogenizer. The homogenates were centrifuged at 14,500 rpm for 20 min. MAP concentrations in the supernatants and receiver fractions were determined by HPLC.

HPLC ASSAY OF MAP

The HPLC system consists of a Waters 510 pump (Milford, MA), an autosampler (Waters 717), a UV detector (Waters 486), and a workstation (SISC 32, Taipei, Taiwan). The column was a C18 reversed-phase column (Purospher® star, 4.6 × 150 mm, 5 µm), eluted with a mobile phase of acetonitrile: 50 mM NaH_2PO_4 with 2 mM cetyltrimethylammonium bromide (adjusted with H_3PO_4 to pH 5) (5:6 v/v) at a flow rate of 0.7 ml/min. The detection wavelength was set at 255 nm, and MAP was detected at a retention time of 8 min. The assay was linear in the concentration range of 0.2–20.0 µg/ml. The inter- and intra-day assay accuracy (% error) and precision (% CV) were between −2.0% and 9.0%. No interference from the GCL/GCP gels or skin tissue was observed.

DATA ANALYSIS

Both the release and skin permeation experiments for each preparation were repeated three to six times and data were expressed as the mean value ± S.D. Release rate and skin flux were calculated from slope of the linear part of the cumulative amount of MAP released/penetrated vs. time curve. Statistical analyses were performed using one-way ANOVA test. A p value <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

CHARACTERIZATION OF SYNTHESIZED GCP/GCL

Both the freeze-dried GCL/GCP appeared to be a spongy, porous white solid. SEM images revealed the gels to have an extremely porous structure (Figure 1). GCL and GCP analyzed using FTIR showed absorption bands characteristic of amide I and II bands around 1650 and 1550 cm^{-1}. The 2860–2930 cm^{-1} aliphatic C–H stretching bands of GCL/GCP were attenuated in comparison with lauric and palmitic acids, but were stronger than GC. The FTIR spectra confirmed the attachment of aliphatic group to GC to form GCL (Supplementary Figure 1)/GCP (Supplementary Figure 2). The relative molecular weights of GCL and GCP were 124 and 140 kDa as determined by GPC, respectively. The level of lauroylation in GCL and palmitoylation in GCP estimated by ^{1}H NMR spectroscopy was found to be 16.3 ± 2.5 ($n = 10$) and 13.4 ± 1.8 ($n = 7$) mole %, respectively. The viscosity of 1% GC, GCL, and GCP prepared in either Milli-Q water or 10% ethanol was comparable; however, viscosity of GCP was slightly higher than GCL, and Milli-Q water gel was more viscous than 10% ethanol gel (Table I). When GCL/GCP concentration in the gel was increased from 1% to 3%, the viscosity was also increased less than proportionally. The presence of 3% MAP in the gels did not change the viscosity significantly (data not shown).

The physicochemical properties of the synthesized GCL/GCP were similar to those previously reported (11,12). It is known that properties of polymers are directly related to the structure of the cross-link network. The higher level of lauroylation in GCL may be explained by the greater reactivity of shorter chain length fatty acid, as inferred from the report by Dey (16), molar cross-link density of polymer network increased with decreasing fatty acid chain length for the preparation of vinyl ester resins containing methacrylated fatty acid comonomer. Lower cross-link density of GCP may result in a more porous network structure, as suggested by Raj Singh *et al*. (17). The slight difference in gel viscosity may be due to higher molecular weight of GCP than GCL, as indicated by Zlatanić *et al*. (18) that viscosity was significantly influenced by molecular weight of the polymer. Viscosity of polymers containing both hydrophobic and hydrophilic structures is dependent on polymer composition and concentration, but solvent also plays an important role (19). It was shown that incorporation of ethanol in aqueous solutions of polyvinyl alcohol and methylcellulose improves their salvation and inhibit gelation, and addition of alcohol to cellulose acetate and acidic chitosan solutions reduces the viscosity and increases the homogeneity (20,21).

MAP RELEASE TEST

MAP release profiles from GCL/GCP gels as a function of time were shown in Figure 2, and their release rates were summarized in Figure 3 and Table I. Release rate of MAP from 1% GC aqueous gel was similar to aqueous solution, whereas that from 1% GCL and GCP gels was significantly reduced to 65% and 70% of aqueous solution. Release rate was further slightly reduced when the concentration of GCL/GCP was increased from 1% to 3%. When prepared in 10% ethanol, MAP release from 1% GC was 19.5% higher than from 10% ethanol solution, but that from 1% GCL and 1% GCP was comparable to from 10% ethanol solution, and were 13.2% and 24.4% lower than from 1% GC, all

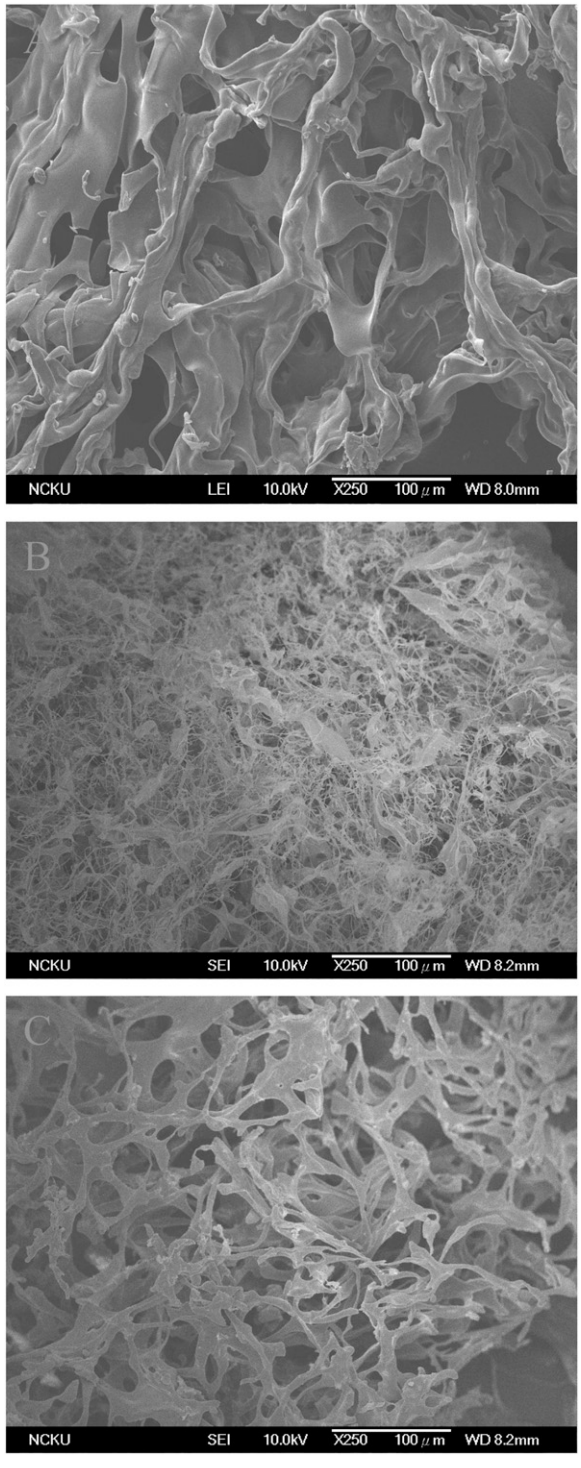

Figure 1. SEM images showing (A) the structure of GC, (B) GCL, and (C) GCP.

Table I
Release rate and skin flux of 3% MAP from various formulations

	Release Rate ($\mu g/h/cm^2$)	Skin Flux ($\mu g/h/cm^2$)	Epidermis ($\mu g/g$)	Dermis ($\mu g/g$)	Viscosity (cps)
Aq. solution	1533.5 ± 30.3	2.32 ± 1.4	12.9 ± 2.4	43.7 ± 3.5	ND
1% GC	1517.9 ± 103.1	2.38 ± 1.5	5.0 ± 2.0	6.5 ± 1.5	945 ± 215
1% GCL	995.0 ± 83.8	6.82 ± 2.3	33.8 ± 9.9	5.2 ± 2.7	675 ± 98
3% GCL	915.4 ± 82.4	ND	ND	ND	1082 ± 196
1% GCP	1074.5 ± 32.9	3.77 ± 1.9	27.2 ± 8.3	20.6 ± 2.3	1075 ± 192
3% GCP	806.6 ± 178.2	ND	ND	ND	2485 ± 246
10% ethanol	1292.1 ± 87.1	3.43 ± 2.0	93.1 ± 23.2	82.9 ± 29.2	ND
1% GC	1544.5 ± 67.5	0.83 ± 0.6	27.8 ± 11.6	47.5 ± 22.3	809 ± 20
1% GCL	1340.9 ± 38.2	3.29 ± 1.3	42.6 ± 29.7	89.6 ± 58.9	299 ± 4
2% GCL	1235.5 ± 61.6	6.95 ± 4.5	64.9 ± 56.7	21.6 ± 17.8	ND
3% GCL	1024.2 ± 37.5	11.66 ± 3.2	228.1 ± 92.5	89.4 ± 39.3	512 ± 107
1% GCP	1168.2 ± 114.0	2.69 ± 1.6	26.8 ± 15.4	24.3 ± 18.6	629 ± 88
2% GCP	965.5 ± 91.5	7.32 ± 2.4	186.6 ± 73.8	70.6 ± 48.0	ND
3% GCP	888.7 ± 76.3	10.80 ± 4.7	292.8 ± 99.4	91.8 ± 84.2	1039 ± 86
1% Carbopol	ND	0.48 ± 0.1	21.2 ± 10.8	10.1 ± 2.9	12440 ± 219
1% HPMC	ND	0.76 ± 0.6	17.2 ± 10.1	20.2 ± 4.0	2520 ± 219

ND: not determined.

without statistically significant differences. Similar to Milli-Q solution, release rate was further decreased with increasing GCL/GCP concentration in 10% ethanol, and was inversely correlated to the polymer concentration in the range of 1–3% ($p = 0.009$ for GCL, and $p = 0.079$ for GCP). As with a diffusion-controlled release mechanism of gel matrix, it is expected that the greater the gel viscosity the more resistant the gel to drug diffusion, and hence drug release from the matrices would be retarded (22). For all the MAP preparation tested, there was no statistically significant difference in their release rates between two vehicle bases. Although no statistically significant difference was observed between the two polymers, there was a trend shown in 10% ethanol that GCL released more MAP than GCP did. It is likely that the smaller fatty acid chains (lauroyl) can be built more completely into the polymeric chains, thus increasing the free volume holes in the polymer resulting in higher permeability for drug release (23).

IN VITRO SKIN PERMEATION AND DEPOSITION OF MAP

Skin permeation of MAP from different formulations as a function of time was shown in Figure 4, and their permeation rates were summarized in Figure 5 and Table I. MAP flux through nude mouse skin from aqueous solution was similar to that from 1% GC, while skin flux was significantly increased 2.86- and 1.58-fold from 1% GCL and GCP, respectively, as compared to 1% GC. In 10% ethanol vehicle, MAP flux from 10% ethanol solution, 1% GCL, and 1% GCP was 4.13-, 3.96-, and 3.24-fold of 1% GC, respectively. Increase in GCL/GCP concentration has further increased the MAP flux to 8.38 (2%

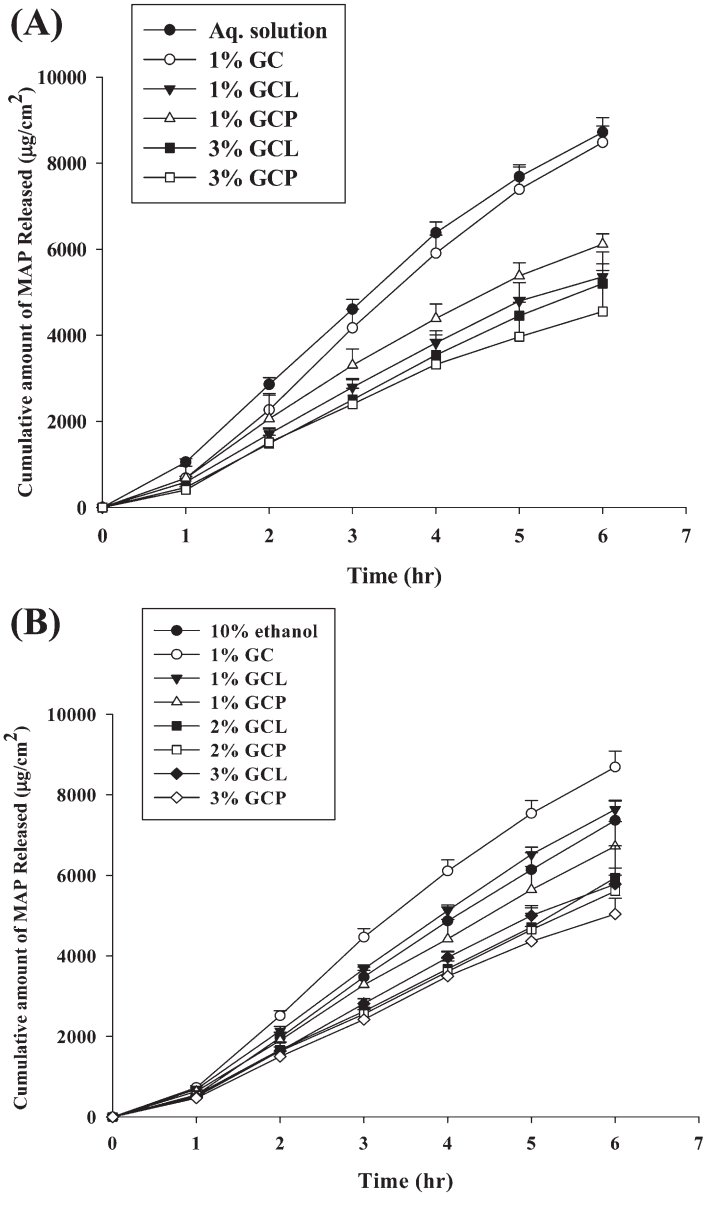

Figure 2. MAP release as a function of time from GC, GCL, and GCP gels in water and 10% ethanol vehicles.

GCL), 14.04 (3% GCL), 8.82 (2% GCP), and 13.01 (3% GCP) fold of 1% GC. Increase in MAP flux was correlated to the increase in GCL/GCP concentration prepared in 10% ethanol vehicle ($p < 0.05$ for both GCL and GCP).

Skin deposition of MAP after 6 h application of 3% MAP preparations in aqueous vehicle onto nude mouse skin is summarized in Table I and depicted in Figure 6. MAP deposition in the epidermis was the greatest from 1% GCL, followed by 1% GCP, aqueous solution, and 1% GC, whereas in dermis, MAP deposition decreased in the order of aqueous

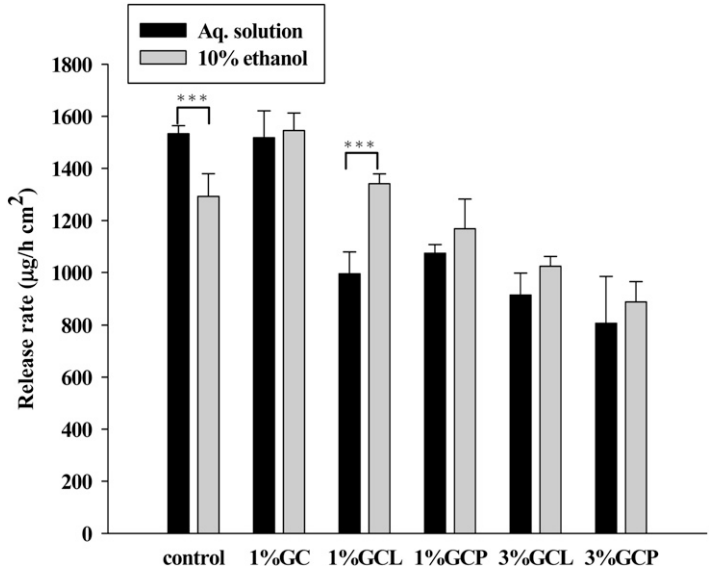

Figure 3. MAP release rates from GC, GCL, and GCP gels in water and 10% ethanol vehicles. (***$p < 0.005$)

solution, 1% GCP, 1% GC, and 1% GCL. In 10% ethanol vehicle, solution deposited more MAP into epidermis than the three polymer gels, while dermal deposition was comparable between 1% GCL and control solution, followed by 1% GC and 1% GCP. In addition, epidermal deposition of MAP was increased with GCL/GCP concentration in 10% ethanol. While the dermal deposition of MAP from 1% to 3% GCP showed similar trend, deposition from 2% GCL appeared to be less than 1% and 3%. There was no significant difference in epidermal deposition of MAP between the two polymers in either vehicle.

Fatty acids have been widely used to improve transdermal delivery of both lipophilic and hydrophilic molecules (24). In general, saturated alkyl chain length of C_{10}–C_{12} are more potent enhancers than the others, as a result of interacting and modifying the lipid domain of the stratum corneum. However, when the fatty acids are grafted onto polymers such as GC, their penetration into the stratum corneum, and hence the interaction with lipids may be limited. Cerchiara *et al*. (12) have shown that the amphiphilic chitosan cross-linked with fatty acids increased hydrophilic drug solubility and hence skin penetration, and proposed polymer interaction with stratum corneum was the likely mechanism. The maximal effect was observed with the shorter cross-linker chain length. Our skin deposition data also showed strong concentration-dependent interaction of GCL/GCP with the skin in comparison with GC, although we were not able to differentiate the effect between the two amphiphilic polymers.

COMPARISON WITH CARBOPOL AND HPMC GELS

MAP skin flux and skin deposition were also compared with the commercially available gels (Figure 5B and Table I). HPMC and 1% carbopol delivered only 14–28% skin flux of GCL/GCP gels at the same polymer concentration in 10% ethanol vehicle, and less

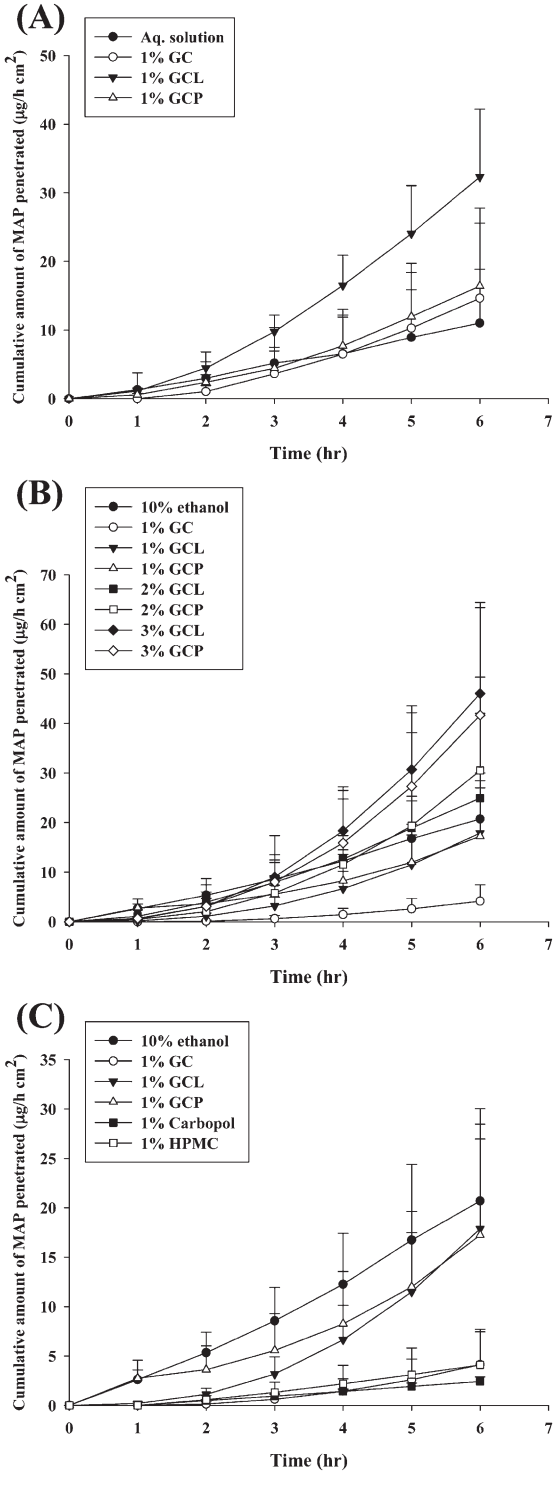

Figure 4. Skin permeation of MAP as a function of time from various polymer gels.

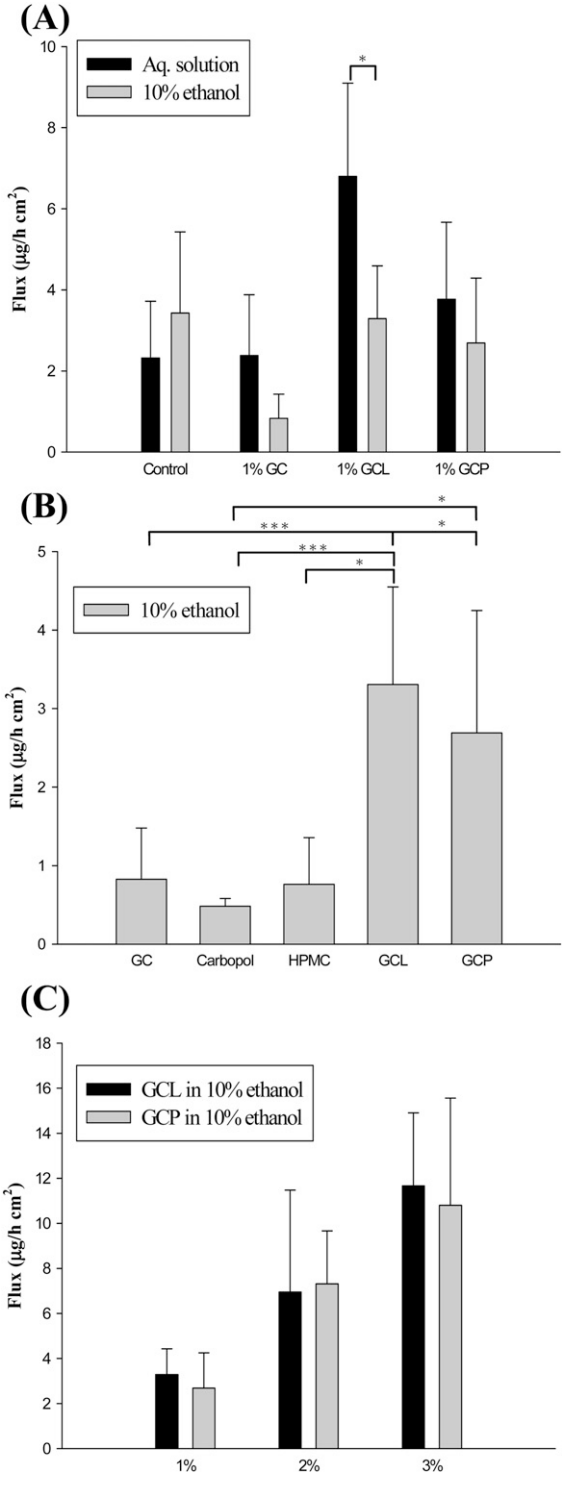

Figure 5. MAP flux through skin from various polymer gels. (*$p < 0.05$, **$p < 0.01$, ***$p < 0.005$)

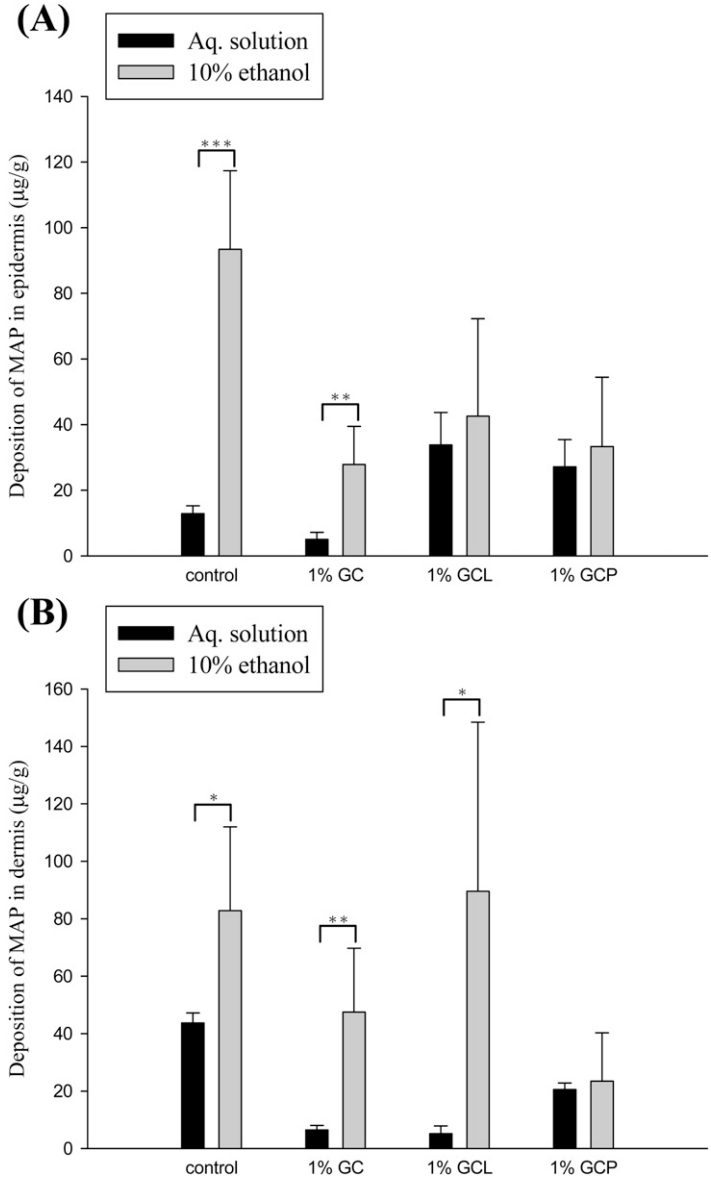

Figure 6. MAP deposition in the (A) epidermis and (B) dermis from 1% GC, GCL, and GCP in water and 10% ethanol vehicles. (*$p < 0.05$, **$p < 0.01$, ***$p < 0.005$)

amounts of MAP were deposited in both epidermis and dermis strata, presumably due to the higher viscosity of both gels.

CONCLUSIONS

GCP hydrogel has been reported as erodible controlled-release systems for the delivery of both hydrophilic and hydrophobic molecules (13,14). In this study, we showed that

GCL/GCP can also be applied for skin delivery of MAP in the form of gels. GCL/GCP gels prepared in either water or 10% ethanol vehicles increased the skin penetration and skin deposition of MAP in comparison with GC, HPMC, and carbopol, while sustained its release from the polymer gels. The reduction in MAP release was attributed to its viscosity resulting from cross-link structure, whereas increase in skin penetration and deposition may be result of polymer interaction with stratum corneum. Both the enhancement in skin penetration/deposition and sustained release of MAP were dependent on polymer concentration. Also, with increase in polymer concentration, epidermal to dermal MAP deposition ratio tended to increase, which will be beneficial to its activity in the epidermis, such as inhibition of tyrosinase and protection from UV damage. The data suggested both GCL and GCP gels can be applied as skin delivery vehicles to improve percutaneous absorption of MAP for cosmetic purposes.

ACKNOWLEDGMENTS

This work was supported by grants from the National Science Council of Taiwan (NSC 98-2320-B-006-015).

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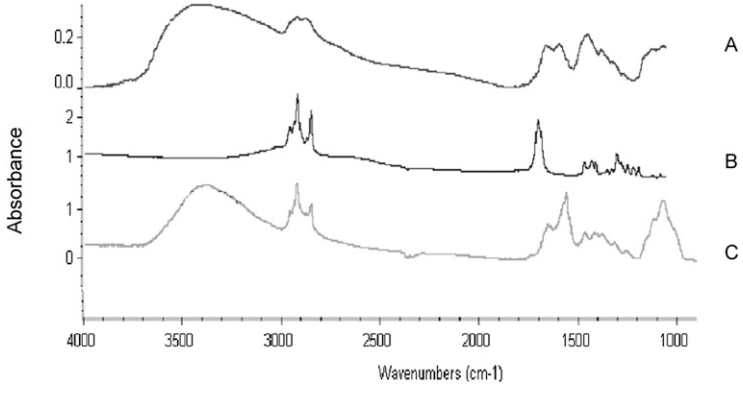
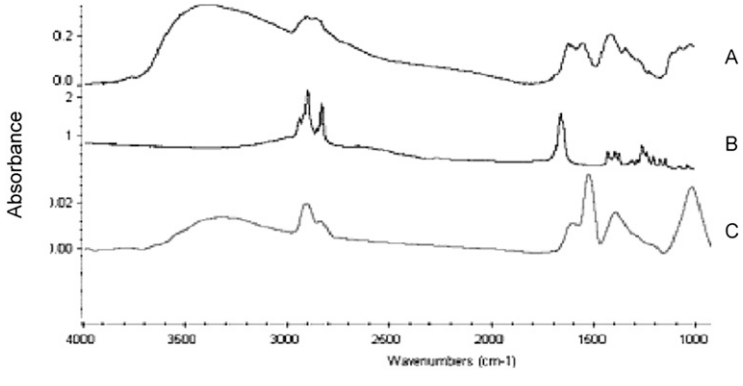


Supplementary Figure 1.



Supplementary Figure 2.