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Crosslinked Poly(Methyl Vinyl Ether-Co-Maleic Anhydride) as Topical Vehicles for Hydrophilic and Lipophilic Drugs

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Poly(methyl vinyl ether-co-maleic anhydride) crosslinked with ethylene glycol (GZ-ET), 1,4-butanediol (GZ-BUT), 1,6-exandiol (GZ-EX), 1,8-octanediol (GZ-OCT), 1,10-decanediol (GZ-DEC) or 1,12-dodecanediol (GZ-DOD) was prepared and employed as a supporting material for aqueous topical gels containing pyridoxine hydrochloride (PYCL) chosen as a hydrophilic model molecule or for O/A emulsion containing β-carotene chosen as a hydrophobic model molecule. We analyzed the effect of the nature of the crosslinker on the permeation of hydrophilic and lipophilic vitamins through porcine skin by in vitro permeation studies. The vehicles formed by crosslinked poly(methyl vinyl ether-co-maleic anhydride) showed enhanced vitamins permeation with respect to the same vehicles formed by noncrosslinked poly(methyl vinyl ether-co-maleic anhydride) (GZ). The decrease in the crosslinker acyl chain length provides vehicles accelerating the drug permeability through the skin.

Keywords β-Carotene, Poly(Methyl Vinyl Ether-Co-Maleic Anhydride), Pyridoxine Hydrochloride, Skin Permeation, Topical, Vitamin

The barrier function of skin (Scheuplein 1971) often limits the efficacy of topical formulations. In transcutaneous formulations, selection of a suitable vehicle is very important as it can affect both drug release and percutaneous absorption. Factors that contributed to the selection of a suitable vehicle are the solubility of the drug in the vehicle, the release of the drug from the vehicle into the skin, and the enhancement of drug penetration to the stratum corneum. Methods for improving transcutaneous delivery (Guy 1996) rely either on the use of chemical penetration enhancers (Fuhrman Jr. et al. 1997; Xu and Chen 1991), microemulsions (Gasco 1997; Yun-Seok et al. 2001), and liposomes (Mezei 1991; Kirjavainen et al. 1999) or novel polymeric-based delivery systems (Orienti, Luppi, and Zecchi 1999; Orienti et al. 2000). These systems can enhance skin permeation by different strategies such as increasing the degree of drug saturation in the formulation (Lippold and Schneemann 1984), increasing drug solubility in the skin (Moghimi, Williams, and Barry 1998), or increasing drug diffusivity in the skin (Williams and Barry 1991).

The aim of our study was to prepare vehicles able to increase pyridoxine hydrochloride (selected as a hydrophilic molecule model) and β-carotene (selected as a lipophilic molecule model) transcutaneous absorption. Due to its high bioadhesive performance (Esposito, Colombo, and Lovrecich 1994) and the possibility for substitution through chemical linkage to its anhydridic groups, poly(methyl vinyl ether-co-maleic anhydride), a synthetic copolymer widely used for pharmaceutical purposes (Mortada et al. 1988; Arbós et al. 2002) as a thickening and suspending agent, denture adhesive, and adjuvant for transdermal patches (Sharma et al. 1999), was selected as a starting material for the synthesis of hydrophilic crosslinked polymers. Ethylene glycol, 1,4-butanediol, 1,6-exandiol, 1,8-octanediol, 1,10-decanediol, or 1,12-dodecanediol were used as crosslinking agents.

The present study suggests that crosslinked poly(methyl vinyl ether-co-maleic anhydride) may be used as a potential vehicle in the transcutaneous delivery of pyridoxine hydrochloride and β-carotene. In particular, we evaluated the correlations between the nature of the crosslinker and the functional properties of 2 vehicles prepared with the aim of determining the conditions favoring vitamin permeation through the skin.

MATERIALS AND METHODS

Materials

Poly(methyl vinyl ether-co-maleic anhydride) (Gantrez® AN-119, Mw = 216000) was a kind gift of ISP (Milan, Italy). Pyridoxine hydrochloride, β-carotene, ethylene glycol, 1,4-butanediol, 1,6-exandiol, 1,8-octanediol, 1,10-decanediol, 1,12-dodecanediol, gum arabic, and Tween 85 were purchased from Fluka (Milan, Italy). Acetone was from Carlo Erba (Milan, Italy) and

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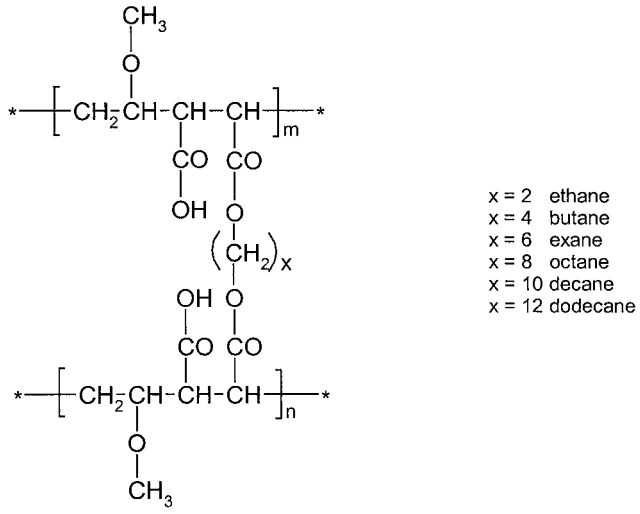

FIG. 1. Chemical structure of crosslinked GZ.

acetonitrile (HPLC grade) was from Romil Pure Chemistry. Phenomenex Luna C 18(2) column was obtained from Chemtek Analitica (Bologna, Italy). Other organic and inorganic chemicals were commercially available and used without further purification.

Synthesis of Crosslinked GZ

Crosslinked GZ (Figure 1) were prepared adding ethylene glycol (0.89 ml; 16.04 mmoles), 1,4-butanediol (1.42 ml; 16.04 mmoles), 1,6-exandiol (1.98 g; 16.04 mmoles), 1,8-octanediol (2.34 g; 16.04 mmoles), 1,10-decanediol (2.79 g; 16.04 mmoles) or 1,12-dodecanediol (3.24 g; 16.04 mmoles) in a GZ solution (2.00 g; 32.08 mmoles of dimer) in 60 ml of acetone to obtain a 50% molar ratio (diol: dimer). The solution was stirred (200 rpm) at room temperature for 48 hr, TLC (stationary phase: silica gel; mobile phase: toluene/acetone, 7/3) indicating maximum conversion (absence of the 3 crosslinker's spot). Subsequently the substituted polymer was separated by precipitation with diethyl ether (100 ml). The precipitate obtained was dissolved in 50 ml acetone and reprecipitated with diethyl ether (100 ml) and finally dissolved in 200 ml water/acetone (3/1) mixture and spray dried: a fine white powder was obtained.

FT-IR of Crosslinked GZ

Infrared spectra of the crosslinked polymers were taken with a Jasco FT-IR-410 spectrophotometer. KBr disks were prepared by mixing the polymer and dry KBr in a weight ratio of 1:9 and subsequently compressing this physical mixture by a punch press working at 7 ton cm^{-2}.

^{1}H-NMR of Crosslinked GZ

The degree of substitution of the crosslinked polymers was determined by ^{1}H-NMR using a Gemini 300 instrument and recording the spectra in $(CD_3)_2SO$ to assign nonexchangeable coupled protons.

Preparation of Pyridoxine Hydrochloride Gels

The gels of crosslinked GZ (5%, w/w) were prepared by dispersing 1 g of polymer in 20 g of water. The pH of each gel was adjusted to 5.5 by means of a NaOH 10% aqueous solution. Then, 4 g of each gel were supplemented with 600 mg of PYCL. As a comparison the same gel was prepared with noncrosslinked GZ. These gels were used for in vitro percutaneous studies through the skin.

Preparation of β-Carotene Emulsions

First, 50 mg of β-carotene were added to 5 g of mineral oil (internal phase) and then emulsionated with 95 ml of an aqueous solution containing 1.25 g of gum arabic and 1 g of Tween 85 (external phase). Next, 0.6 ml of this emulsion were added to 4 g of the gels previously described. As a comparison the same emulsion was added to the gel prepared with noncrosslinked GZ. These vehicles were used for in vitro percutaneous studies through the skin.

Viscosity Tests

The viscosity of all the GZ vehicles were measured at 37°C, before and after supplementing 600 mg of PYCL or β-carotene emulsion, by a rotational viscosimeter (Visco Star-R, Fungilab-Spain). The operative conditions were spindle TR8, spindle velocity 200 rpm.

In Vitro Percutaneous Studies of Pyridoxine Hydrochloride

Porcine ears were obtained from a local slaughterhouse. Circular skin segments were separated and hydrated in phosphate buffer solution (0.1 M PBS at pH 7.4) at 4 ± 1°C for 24 hr. The thickness of the hydrated segments was determined for each sample with a gauge. Only the skin segments with thickness 1.00 ± 0.05 mm were used for this study. The permeation studies were conducted in a Franz-type permeation cell with a diffusional area of 10.7 cm^2. Skin samples were mounted horizontally between donor and receptor compartments of the cell and clamped with the dermal side in contact with the receptor medium. To avoid drying the donor sample, the donor compartment was closed with a glass stopper. At time zero, the gel samples were placed on the skin in the donor compartment. The receiver phase (100 ml of PBS, maintained at 37°C by means of a surrounding jacket) was stirred constantly and at predetermined time intervals was withdrawn and replaced with blank buffer to maintain "sink conditions." The amount of PYCL in the receiving phase was analyzed spectrophotometrically ($\lambda = 324$ nm) using the same gel without vitamin as blank. Five parallel experiments were conducted with each gel and in

each experiment skin of different ears was used to evaluate the deviation of the data on several ears. The studies were carried on for 6 hr.

In Vitro Percutaneous Studies of β-Carotene

Direct measurements of β-carotene in the skin were taken. The skin, treated as previously described, was mounted in a Franz-type permeation cell and the different vehicles were placed on it. Then 3 or 6 hr after the application of the vehicles, the skin segment was rinsed with water and gently dried with a cotton swab. Following the addition of 10 ml acetone, the skin sample was subjected to ultraturrax (10000 rev/min, 5 min) and the suspension obtained was centrifuged at 15000 rev/min (ALC 4239R, Milano, Italy). Then 5 ml from the supernatant was dessicated by vacuum rotation and the remainder was resolved in 0.5 ml acetone. β-carotene was finally determined by HPLC as described in the following section. To establish the recovery of β-carotene, three experiments were conducted without removing the excess of vehicle applied: in this case the amount of β-carotene applied on skin surface corresponded to 0.300 mg. The mean recovery (%) for three independent experiments was β-carotene 97.2%.

Chromatographic Conditions for Determination of β-Carotene

Chromatographic separations were performed using a Shimadzu (model LC-10AT$_{VP}$) liquid chromatograph connected to a UV-Vis detector (model SPD-10A$_{VP}$) and to a ChromatoPlus computerized integration system (Shimadzu, Kyoto, Japan). Manual injections were made using a Rheodyne 7125 injector with a 20 μl sample loop. A C18 Phenomenex Luna (3 μm, 150 × 4.60 mm i.d.) (Chemtek Analitica) column was utilized with acetonitrile as mobile phase at a flow rate of 1.0 ml/min. Ultra violet detection was at 425 nm and the retention time was 13.5 min. The calibration graph for β-carotene was constructed by plotting the peak area of β-carotene against the corresponding drug concentration. Satisfactory linearity was obtained in the range of 0.1–4.0 μg/ml. The limit of detection (signal to noise ratio 3:1) was 56.0 ng/ml β-carotene. Reproducibility was 1.9%.

Statistical Analysis

All data are the arithmetic means of results from three experiments ±S.D. Statistical data were analysed using Student's t-test, with $p \leq 0.05$ as minimum level of significance.

RESULTS AND DISCUSSION

FT-IR of Crosslinked GZ

The infrared spectra of the crosslinked GZ showed the absorption band of the ester carbonyl at 1730 cm^{-1} resulting from the linkage of GZ with the crosslinker and the absorption band of the carboxylic group at 1800 cm^{-1} resulting from the opened maleic anhydride (data not reported).

^{1}H-NMR of Crosslinked GZ

Figure 2 shows ^{1}H-NMR spectra of GZ-ET. Proton assignments for GZ-ET in $(CD_3)_2SO$ (relative to dimethylsulphoxide δ 2.50): δ 12.37 ppm = OH (a), δ 3.27 ppm = O─CH_3 (b), and δ 4.03 ppm = O─CH_2 (c). The degree of substitution was 48.3%. This datum was obtained by comparing the signal of O─CH_2 (δ 4.03 ppm) protons of the substituent to O─CH_3 (δ 3.27 ppm) protons present at 100% in the GZ. The same analysis was conducted for all the crosslinked GZ. The degrees of substitution obtained for the other polymers were GZ-BUT 49.0%, GZ-EX 45.9%, GZ-OCT 47.9%, GZ-DEC 46.2%, and GZ-DOD 43.5%.

Viscosity Tests

The vehicles analyzed present a wide range of viscosities (Table 1). In particular, increasing the crosslinker chain length, increased the viscosity. Moreover, the addition of pyridoxine hydrochloride decreased the viscosity of all the gels analyzed, whereas the addition of β-carotene emulsion to the GZ gels did not.

In Vitro Percutaneous Studies of Pyridoxine Hydrochloride

The in vitro permeation of pyridoxine hydrochloride from the crosslinked GZ gels was higher than that from the corresponding noncrosslinked GZ. Moreover, it increased in the presence of the lower chain length of the crosslinker (Figure 3).

TABLE 1
Viscosities (cPs ± S.D.; $n = 3$) of GZ gels

Vehicle	GZ	GZ-ET	GZ-BUT	GZ-EX	GZ-OCT	GZ-DEC	GZ-DOD
Unloaded gels	1900 ± 100	2900 ± 100	4900 ± 200	7500 ± 200	12900 ± 300	20200 ± 200	25000 ± 100
+ Pyridoxine hydrochloride	1200 ± 100	2000 ± 100	4300 ± 100	6900 ± 100	11000 ± 300	17800 ± 300	22400 ± 200
+β-carotene emulsion	1900 ± 200	2800 ± 200	5100 ± 200	6700 ± 100	12400 ± 300	17900 ± 200	24600 ± 300

TABLE 2
Permeation parameters (±S.D.; $n = 3$) of pyridoxine hydrochloride (PYCL) from GZ gels through porcine skin

Vehicle	GZ	GZ-ET	GZ-BUT	GZ-EX	GZ-OCT	GZ-DEC	GZ-DOD
Flux (mg/h cm^2)	1.29 ± 0.12	5.83 ± 0.22	4.91 ± 0.14	4.32 ± 0.10	3.82 ± 0.09	3.25 ± 0.11	2.42 ± 0.12
D (cm^2/h)	0.13 ± 0.01	0.88 ± 0.05	0.76 ± 0.03	0.32 ± 0.03	0.21 ± 0.03	0.18 ± 0.02	0.15 ± 0.03

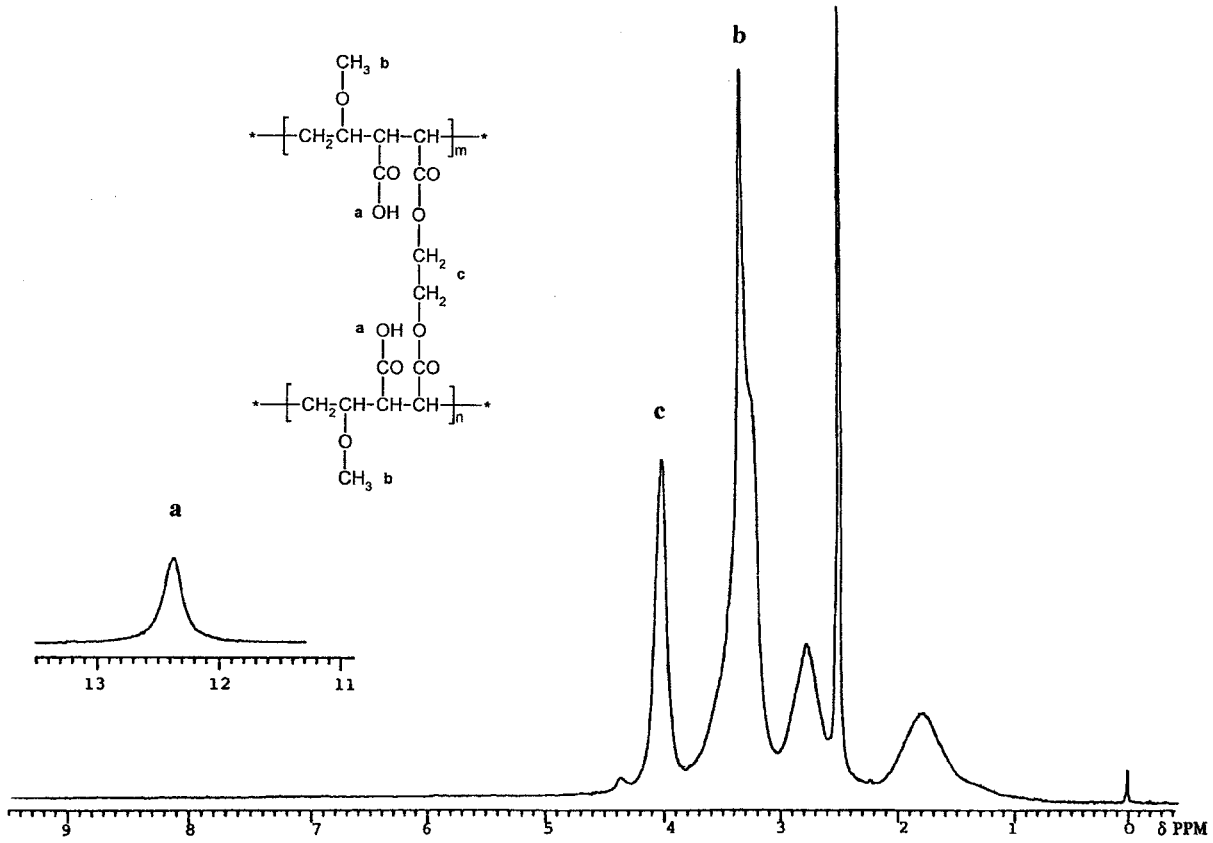

FIG. 2. ^{1}H-NMR spectra of GZ-ET.

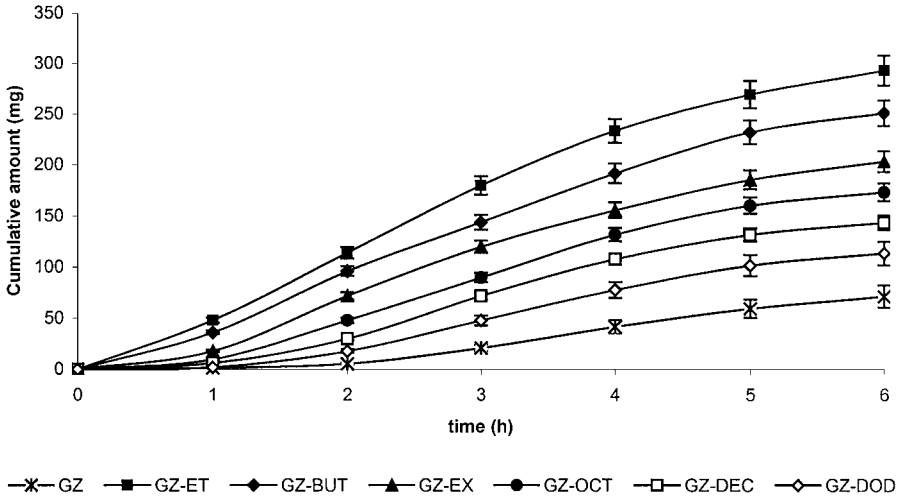

FIG. 3. In vitro permeation profiles of pyridoxine hydrochloride through porcine skin from GZ gels. All data were means of 3 experiments ± S.D.

TABLE 3
Percent absorption of β-carotene [(mg β-carotene/g skin) $\times$ 100] in the skin 3 or 6 hr after application of different vehicles

Vehicle	GZ	GZ-ET	GZ-BUT	GZ-EX	GZ-OCT	GZ-DEC	GZ-DOD
After 3 hr	0.0 ± 0.0	48.6 ± 0.3	42.0 ± 0.1	35.0 ± 0.1	25.0 ± 0.6	8.0 ± 1.0	3.0 ± 0.3
After 6 hr	1.9 ± 0.1	79.8 ± 0.2	65.0 ± 0.5	60.2 ± 0.4	39.5 ± 0.6	12.0 ± 1.3	5.3 ± 0.4

All the data were means of three experiments $\pm$S.D.

The flux was evaluated from the following equation (Buri et al. 1985; Higuchi 1960):

$$dM/dt = ADC/h$$

where dM/dt is the flux of the drug through the skin from an unsaturated vehicle thus in nonsteady-state conditions, A—the skin surface, h—the skin thickness, D—the drug diffusion coefficient through the skin and, C—the concentration of the drug in the skin in equilibrium with the concentration of the drug in the vehicle.

The flux was determined by the slopes of the linear portions of the permeation profiles. The fluxes obtained from the crosslinked GZ were higher than that from the noncrosslinked GZ. Moreover, decreasing the crosslinker chain length increases the fluxes (Table 2). This behavior can be explained by the favorable effect of the vehicle in enhancing the diffusion coefficient D of pyridoxine hydrochloride in the skin. In fact, at the examined formulative concentration, the crosslinked GZ raised the flux with respect to the noncrosslinked GZ by increasing the diffusibility of the vitamin in the skin (Table 2). This could be due to the ability of the vehicle to partially solubilized in the upper part of the stratum corneum due to amphyphilic properties conferred by the concomitant presence of the hydrophilic (acrylic chain) and lipophilic (crosslinking chain) portions on the polymeric network (Chien and Lee 1987).

The higher crosslinked GZ viscosities with respect to noncrosslinked GZ, did not represent a limit to vitamin absorption, whereas, among the crosslinked GZ, the vehicle viscosity decreased pyridoxine hydrochloride partition ability from the vehicle to the skin. In particular, increasing crosslinker acyl chain and viscosity, lag time increased and flux decreased.

In Vitro Percutaneous Studies of β-Carotene

The amount of β-carotene in the skin increased over time and was higher after the application of the crosslinked GZ than the noncrosslinked GZ (Table 3). Moreover, it increased in the presence of the lower chain length of the crosslinker. This behavior confirmed the ability of the crosslinked GZ to enhance the vitamin diffusivity in the skin. The crosslinked GZ viscosities also can represent a limit to β-carotene partition from the vehicle to the skin. In particular, increasing crosslinker acyl chain, the amount of vitamin recovered in the skin decreased.

CONCLUSION

Poly(methyl vinyl ether-co-maleic anhydride) crosslinked with ethandiol, butandiol, exanediol, octanediol, decanediol, and dodecanediol provided vehicles able to increase the skin permeation of pyridoxine hydrochloride and β-carotene with respect to noncrosslinked GZ. This effect seems to be linked to an increased vitamin solubility in the skin probably produced by the interaction of the polymer with the stratum corneum. The maximum enhancement of drug permeation was observed in the presence of the lower length of the crosslinker acyl chain.

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