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Research paper

Enhanced permeation of triamcinolone acetonide through the buccal mucosa

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Abstract

To develop new formulations that have suitable bioadhesive force and provide sustained release in buccal area for an extended period of time, bioadhesive gels containing triamcinolone acetonide were prepared using two polymers, carbopol 934 and poloxamer 407 which were selected for their bioadhesiveness and gelling property, respectively. The drug release profiles from the gels were studied as a function of drug concentration and temperature. Different enhancers such as bile salts, glycols and non-ionic surfactants were used for the enhancement of its permeation through buccal mucosa. Among the enhancers used, sodium deoxycholate showed the best enhancing effects.

Keywords: Triamcinolone acetonide; Permeation; Buccal mucosa; Bioadhesive; Carbopol; Poloxamer

1. Introduction

Triamcinolone acetonide, a long-acting synthetic glucocorticoid, has been used for the treatment of inflammatory disease. Of the many drug delivery systems, buccal drug delivery has some advantages such as the abundant blood supply in the buccal area, bypassing the hepatic first pass effect, excellent accessibility, etc. It is very difficult to apply ointments, solutions, creams and lotions etc. onto the oral mucosa, and expect that their effects persist for a significant period of time, because they are very easily removed by salivation, temperature, tongue movement and swallowing. Therefore, the new formulations that have suitable adhesion or adhesive time and show sustained release for a period of time are needed. But, the major limitation to buccal delivery is the low permeation through the tissue resulting in a low bioavailability. The use of penetration enhancers is a logical approach to increase the drug permeation across the epithelium. The effect of various classes of transmucosal penetration enhancers such as bile salts, surfactants, fatty acids and derivatives, and chelators have been studied [1,2].

Poloxamer 407, polyoxyethylene–polyoxypropylene–polyoxyethylene type block copolymer consisting of 70% polyoxyethylene units is a non-ionic surfactant with an average molecular weight of 12 600. Aqueous solutions of 20–30% (w/w) poloxamer 407 have the interesting characteristic of reverse thermal gelation, that is, they are liquid at refrigerated temperature, but gel upon warming to ambient levels [3,4]. Carbopols are highly hydrophilic polyacrylic acid polymers and have been used to prepare gel formulations for topical administration due to high viscosity and good bioadhesiveness at low concentrations. In the present study, carbopol and poloxamer were used as the bioadhesive and gel-forming agent.

In our previous work [5], the mucoadhesive and physicochemical characteristics of carbopol-poloxamer gels containing triamcinolone acetonide was studied. The objective of this study was to determine the feasibility of buccal delivery of triamcinolone acetonide by studying its in vitro release characteristics. The present work was performed to determine the amounts of triamcinolone acetonide released from carbopol-poloxamer gels and to evaluate the mechanism of drug release from the carbopol-poloxamer gels. To improve the permeability through buccal mucosa, various enhancers were used, including bile salts, glycols, and non-ionic surfactants. The effects of drug concentration, temperature, and of various enhancers on drug release were evaluated.

2. Materials and methods

2.1. Materials

Carbopol 934 was obtained from BF Goodrich (USA) and poloxamer 407 was from BASF Korea (Seoul, South

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Korea). Triamcinolone acetonide was a gift from Shinpoong Pharm. Co. (Seoul, South Korea). Sodium deoxycholate, sodium taurodeoxycholate, sodium cholate, polyoxyethylene 2-stearyl ether, polyoxyethylene 2-oleyl ether, polyoxyethylene 23-lauryl ether, tetraethylene glycol (TEG), diethylene glycol (DEG) were from Sigma Chemical Co. Synthetic cellulose membrane was Spectra/Por membrane discs (MWCO: 14 000) from the Spectrum Medical Ind. Inc., (USA). All reagents were of analytical grade and used without further purification.

2.2. Preparation of carbopol-poloxamer gels of triamcinolone acetonide containing enhancer

Carbopol-poloxamer gels of 0.1% triamcinolone acetonide containing 5% enhancer was prepared with 1% carbopol and 20% poloxamer by cold method [6]. Poloxamer 407 was added into water with gentle stirring at about 5°C and the solution was left overnight in a refrigerator to complete polymer desolvation. Carbopol 934 was stirred into this solution under magnetic stirring and neutralized to pH 6 using NaOH solution [5]. Triamcinolone acetonide and enhancer were added with stirring to the above polymer solution.

2.3. Solubility

The solubility of triamcinolone acetonide was measured in propylene glycol/phosphate buffer (pH 7.4) mixture as a function of PPG content. An excess amount of triamcinolone acetonide was added into the mixture of various ratios of the propylene glycol/phosphate-buffered saline (PPG/PBS) solution. The mixture was shaken at 37°C for 24 h and filtered (NALGENE® syringe, 0.45 μm, 25 mm) and assayed by UV/VIS spectrophotometer at 242 nm after appropriate dilution.

2.4. Release of triamcinolone acetonide from the carbopol-poloxamer gels in vitro

Two grams of the carbopol-poloxamer gels containing triamcinolone acetonide were used for release test with 40% PPG/PBS solution at 37°C through the cellulose membrane using the modified Keshary–Chien diffusion cell (surface area of 0.79 cm^2). The effect of drug concentration was studied from 0.05 to 0.4%(w/w) and the effect of temperature on drug release was studied at 28, 32, 37 and 45°C for carbopol-poloxamer gel containing 0.1% TA. The total samples were taken from the receptor compartment at predetermined intervals, replaced by an equal volume of fresh medium. The samples were analyzed using HPLC. A μ Bondapak C18 column was utilized for drug separation, while methanol:water (6:4) was used as the mobile phase. The injection volume was 20μl and the flow rate and the UV wavelength were 1.0 ml/min and 242 nm, respectively.

2.5. Permeation of triamcinolone acetonide through the buccal mucosa in vitro

The freshly excised buccal tissue obtained from pigs weighing between 7 and 10 kg was used within 2 h of removal. Most of the underlying tissue was removed from the mucosa with surgical scissors, making sure that the basal membrane was still present [7]. The prepared buccal mucosa was mounted in a Valia–Chien diffusion cell. The donor compartment (mucosal) was filled with PBS solution containing 0.1% triamcinolone acetonide and 5% enhancer such as bile salts, glycols or non-ionic surfactants, respectively. The permeation studies were undertaken at 37 ± 0.5°C with stirring. The total samples were taken from the receptor compartment at predetermined intervals, replaced with the same volume of fresh medium and subsequently assayed by an HPLC method.

The cumulative amount of the permeated drug from mucosal side to serosal side was plotted versus time, and the flux was calculated from the steady-state of the curve. The efficacy of the different enhancers was determined by comparing the permeation rate of triamcinolone acetonide in the presence and absence of enhancer. It was defined as the enhancement factor (EF) which was calculated using the following equation:

$$EF = \frac{\text{TA permeation rate at steady state in the presence of enhancer}}{\text{TA permeation rate at steady state in the absence of enhancer}}$$

3. Results and discussion

3.1. Solubility and permeation of triamcinolone acetonide in PPG/PBS

The solubility of sparingly soluble triamcinolone acetonide was greatly increased by adding propylene glycol and reached a peak at 80% propylene glycol in PBS (Fig. 1). The permeation of triamcinolone acetonide from the gel formulations through cellulose membranes for 24 h is shown in Fig. 2. Even though the highest drug solubility was observed with the 80% PPG/PBS preparation, the greatest permeation of triamcinolone acetonide was reached with 40% propylene glycol. It might be due to high viscosity and increased hydrophobicity at 80% PPG/PBS solution. Therefore, 40% PPG/PBS mixture was chosen due to the highest permeation and increased solubility.

3.2. Effect of drug concentration on in vitro drug release

The effect of drug concentration on the release of triamcinolone acetonide from the prepared carbopol-poloxamer gels was studied through cellulose membrane at 37 ± 0.5°C. The concentrations tested were 0.05, 0.1, 0.2, and 0.4%, respectively. Fig. 2 shows a plot of released amount of TA vs. concentration of TA in the gel formulation containing 1% carbopol and 20% poloxamer 407. The permeation

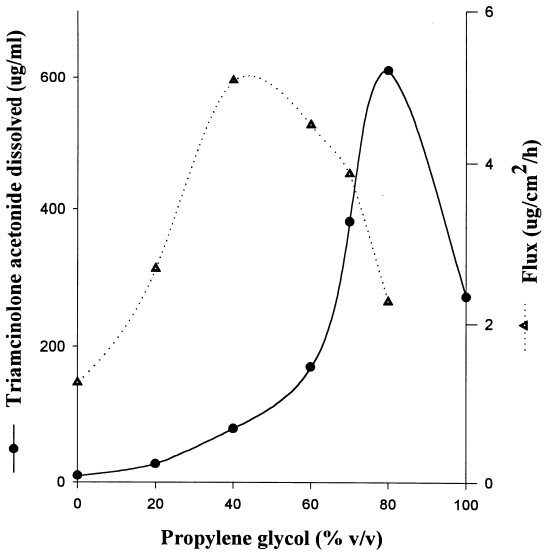

Fig. 1. Solubility and permeation of triamcinolone acetonide in various concentration of propylene glycol/phosphate buffer at 37°C.

rate of TA from the 0.1% formulation was about 85% higher than from the 0.05% formulation. However, the permeation rate from the 0.4% formulation was only about 25% higher than from the 0.2% formulation.

As the concentration of triamcinolone acetonide in the gels increased, the release increased. Based on the visual observation of the gel formulation, 0.2% seemed to be below the saturation and 0.4% slightly over saturation. Therefore, it can be expected that the permeation rate increases with increasing concentration of TA in the formulation up to 0.2%.

3.3. Effect of temperature on in vitro drug release

Poloxamer 407 and carbopol 934 can be used as a reservoir from which a drug is released when topically applied, since it forms a soft bioadhesive gel at body temperature [8].

The effect of temperature on the release of triamcinolone acetonide from the gel formulations containing 0.1% TA through cellulose membrane was evaluated at 28, 32, 37, and 45°C. The apparent permeation coefficient of triamcinolone acetonide increased with temperature (Fig. 3). Permeation of drug through membranes require an energy of activation for the small molecules to move through the barrier material. This fact is expressed in the Arrhenius equation.

The relationship between the permeation coefficient and the temperature is given by the following equation:

$$P = P_o e^{-E_a/RT}$$

When the logarithm of permeation coefficient is plotted as a function of the reciprocal of temperature, a linear relationship was observed with a correlation coefficient of 0.971 (Fig. 3). The slope was used to calculate the activation energy for drug permeation of 2.23 kcal/mol. Since poloxamer gel exhibits reverse thermal behavior, its viscosity increases as the temperature increased. According to the Stokes–Einstein

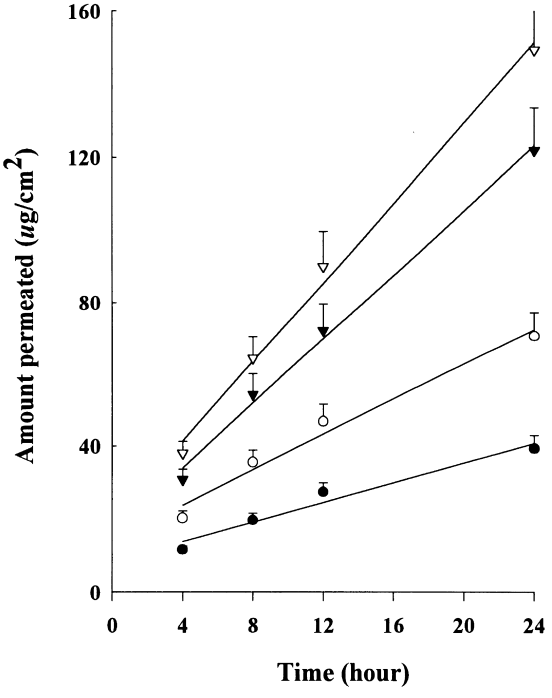

Fig. 2. Effects of drug concentration on the permeation of triamcinolone acetonide from the carbopol-poloxamer gels through cellulose membrane ($n = 5$). ●, 0.05%; ○, 0.1%; ▼, 0.2%; □, 0.4%.

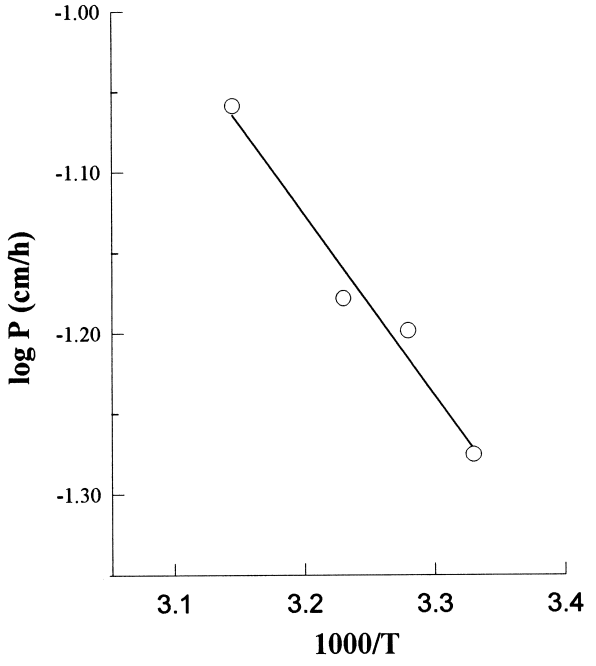

Fig. 3. Effect of temperature on drug permeation from carbopol-poloxamer gels containing 0.1% triamcinolone acetonide ($n = 5$).

Table 1
Enhancement factor of various enhancers

Enhancer	Permeation rate ($\mu g/cm^2$ per h)	Enhancement factor
Control	14.70 ± 1.3	1.00
Sodium cholate	20.98 ± 2.0	1.48
Sodium taurodeoxycholate	21.85 ± 2.2	1.57
Sodium deoxycholate	25.21 ± 2.6	1.74
Tetraethylene glycol	17.16 ± 1.4	1.18
Diethylene glycol	18.61 ± 1.7	1.34
Polyoxyethylene 2-stearyl ether	20.50 ± 2.1	1.35
Polyoxyethylene 23-lauryl ether	17.44 ± 1.5	1.13
Polyoxyethylene 2-oleyl ether	22.60 ± 2.3	1.56

equation, it is expected that the apparent diffusion coefficient should decrease with increasing viscosity [9]. However, the apparent permeation coefficient of TA increased with increasing temperature. These results indicate that the permeation of TA from the poloxamer gel formulation is largely dependent on the micro-viscosity of the water channel rather than the macro-viscosity of the gel [10].

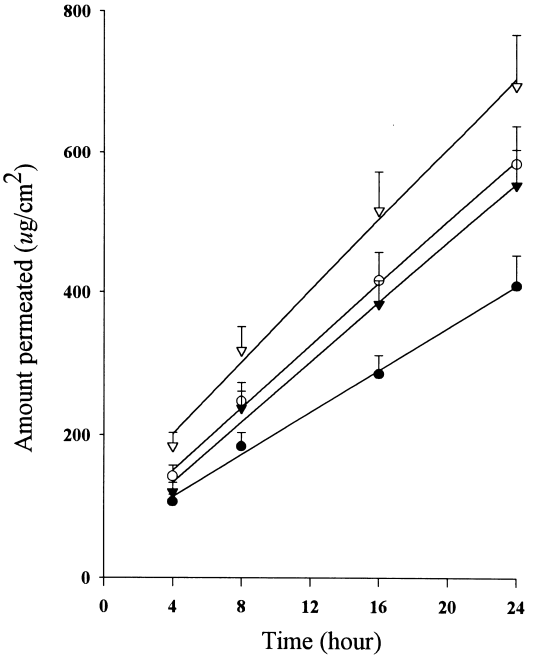

Fig. 4. Effect of bile salts on the permeation of triamcinolone acetonide from the carbopol-poloxamer gels through porcine buccal mucosa ($n = 4$). ●, control; ○, sodium taurocholate; ▼, sodium cholate; □, sodium deoxycholate.

3.4. Effects of enhancers on drug permeation

Effects of various permeation enhancers on the permeation of triamcinolone acetonide through the porcine buccal mucosa were investigated. The enhancers such as bile salts, glycols and non-ionic surfactants were used at a concentration of 5%. Permeation enhancer efficacy was evaluated by the determination of the enhancement factor as described in 2.5. The effect of the different enhancers is presented in Table 1. The glycols, such as diethylene glycol and tetraethylene glycol, increased only slightly the permeation rate of the drug. Non-ionic surfactants and bile salts showed some enhancing effects (Fig. 4). Among all the permeation enhancers tested, sodium deoxycholate showed the best enhancing effect with the enhancement ratio of 1.74. Permeation of triamcinolone acetonide from the carbopol-poloxamer gels could be enhanced through the buccal mucosa using various enhancers.

Acknowledgements

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