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## COMMUNICATIONS

# BIOADHESIVE POLYMER BUCCAL PATCHES FOR BUPRENORPHINE CONTROLLED DELIVERY: SOLUBILITY CONSIDERATION

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## ABSTRACT

By using a two-roll milling method, a new bioadhesive polymer patch formulation for buprenorphine controlled delivery and consisting of polyisobutylene, polyisoprene, and Carbopol® 934P was prepared. Since solubility of drug in the polymer patches is the first factor which should be considered before to modify the feasibility of delivering drug through the buccal mucosa, the effects of α-cyclodextrin, β-cyclodextrin, sodium taurocholate, and sodium glycodeoxycholate on the solubility of buprenorphine were investigated, and β-cyclodextrin was found the strongest solubility enhancer of them. The drug release profiles were significantly affected by the drug loading and the existence of β-cyclodextrin. Increasing the drug loading and solubility enhancer would increase the drug release from the buccal polymer patches. The pH value change in the microenviroment of polymer patches during the hydration of Carbopol® 934P could even release 20% of drug from the polymer patches which didn't contain any solubility enhancer.

## INTRODUCTION

Recently the buccal mucosa has been studied as a potential site for delivery of drug, because of its accessibility and low enzymatic activity. The buccal mucosa may offer alternate route of delivery for drugs including those that are metabolically unstable (1). The buccal mucosa was investigated as a potential site for drug delivery several decades ago and interest in this area for transmucosal drug administration is still growing (1-3).

Buprenorphine is a partial $\mu$ agonist opioid analgesic that is well absorbed by both the intramuscular and sublingual routes and is 25-50 times more potent than morphine (4). The drug's onset of action occurs rapidly, with maximum blood drug levels attained within five minutes of intramuscular injection. The duration of action of buprenorphine can be extended from the 4-5 hours obtained with a single intramuscular dose to 5-6 hours with the use of sublingual administration. The latter route is already being developed as an alternative to the injectable formulation (5).

The in-vitro characterization of a newly developed bioadhesive patch for controlled drug delivery via the buccal mucosa was investigated by Guo (6-7) and Scherrer, et al (8). The effects of different ratios of Carbopol® 934P, polyisobutylene, and polyisoprene on the surface properties, adhesion, and swelling of buccal patches were investigated. They had developed patches composed of Carbopol® 934P, polyisobutylene, and polyisoprene having physical properties that are required for the buccal controlled drug delivery.

Solubility of drug in the polymer patches is the first factor which should be considered before to modify the feasibility of delivering drug through the buccal mucosa. This paper describes the factors which would affect the solubility of buprenorphine, a partial $\mu$ agonist opioid analgesic, via the buccal mucosa, in the polymer patches, and the effects on the release of buprenorphine from those patches would be discussed as well.

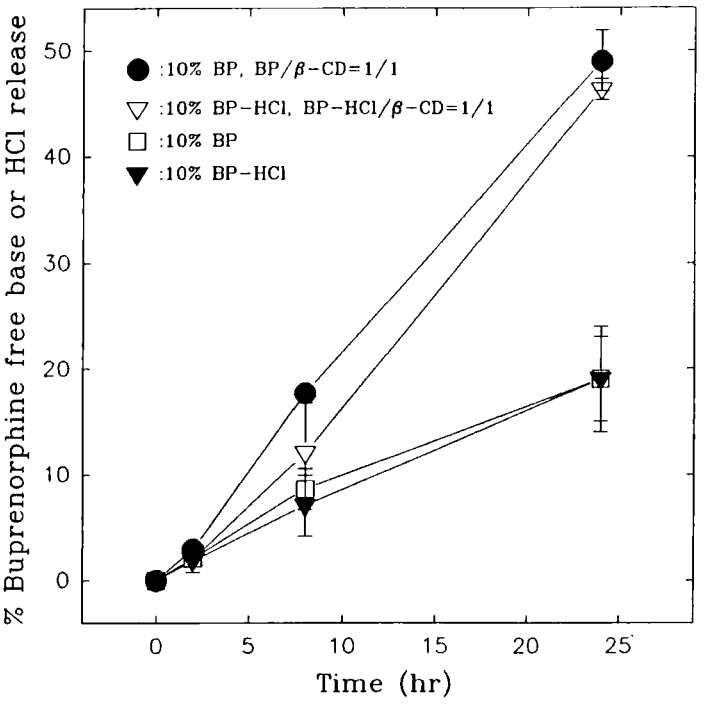


FIGURE 1

The effect of β-cyclodextrin on the buprenorphine release from the CP/PIB/PIP=60/35/5 buccal patches.

## MATERIALS AND METHODS

Preparation of polymer patches was as follows: a desired ratio of bioadhesive polymer Carbopol® (934P grade, BF Goodrich, Cleveland, OH) (CP), polyisobutylene (LMMH grade, EXXON Chemical Co., Houston, TX) (PIB), and polyisoprene (GoodYear Chemical Co., Akron, OH) (PIP) were mixed homogeneously with buprenorphine (Diosyngy, NJ) and additive (α-cyclodextrin, β-cyclodextrin, sodium taurocholate, or sodium glycodeoxycholate) (Sigma, MO) by a two-roll mill. The elastomer polymer

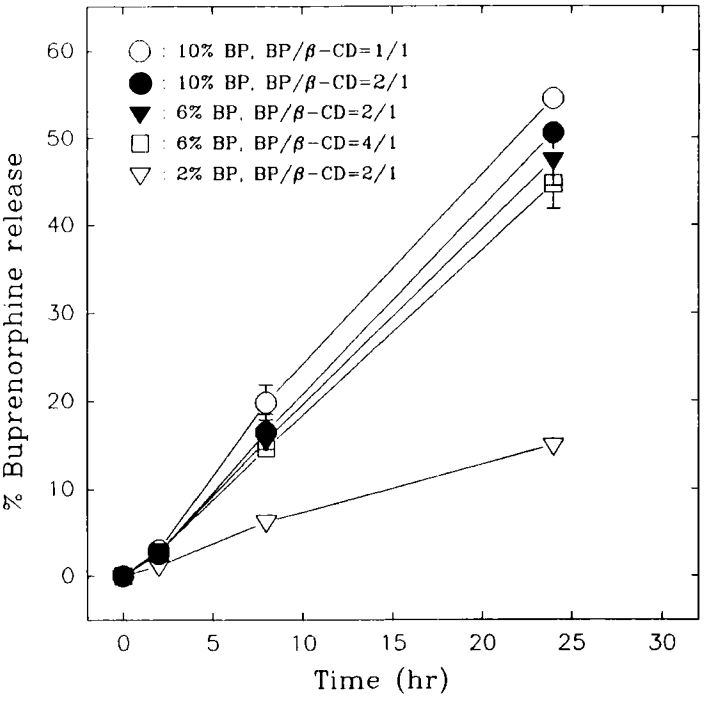


FIGURE 2

The effect of -cyclodextrin and drug loading on the burprenorphine release from the CP/PIB/PIP=50/43.75/6.25 buccal patches.

mixture was compressed in a predetermined thickness, and appropriate sizes were punched out for in-vitro testing (6-7).

The in-vitro drug release through the hydrated polyvinyl pyrrolidone/cellulose acetate hydrogel film was conducted by using diffusion cells and were performed in phosphate buffer (pH=7) at 37°C. Aliquots were taken at various times up to 24 hours and assayed for buprenorphine free base or HCl salt by high-pressure liquid chromatography. The gradient system used in this study consisted of mobile phase, $CH_3CN$/16.6 mM $CH_3(CH_2)_5SO_3Na$ aqueos solution/$CH_3COOH$, 70%/30%/1%, (v/v/v) at flow rate 1.5 ml/min.

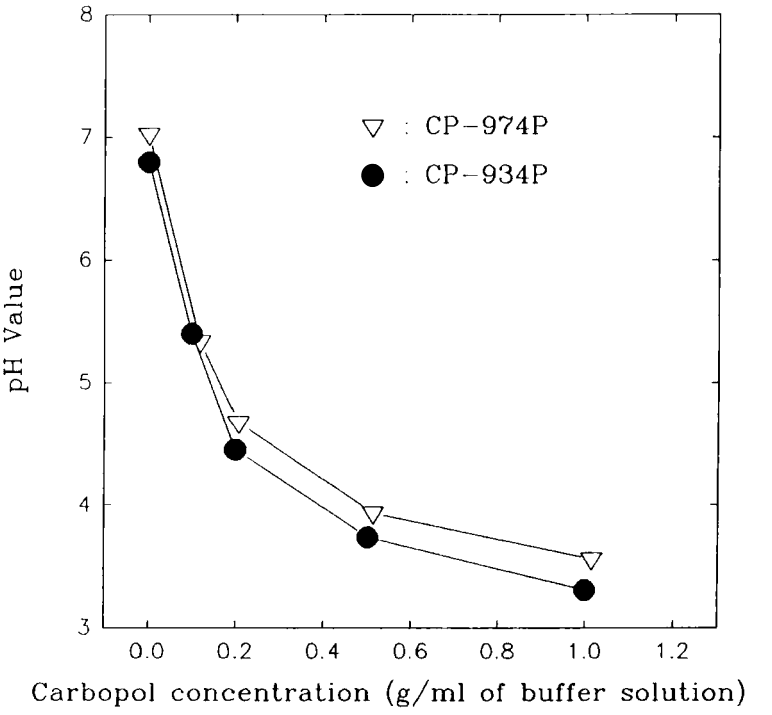


FIGURE 3

The pH values of different CP-934P or CP-974P concentrations (at pH 7 Phosphate Buffer).

## RESULTS AND DISCUSSION

The effects of α-cyclodextrin, β-cyclodextrin, sodium taurocholate, and sodium glycodeoxycholate on the solubility of buprenorphine free base or HCl salt were investigated. β-cyclodextrin was found the strongest solubility enhancer of buprenorphine free base and HCl salt (β-cyclodextrin > α-cyclodextrin > sodium taurocholate > sodium glycodeoxycholate). The effects of β-cyclodextrin and drug loading on the buprenorphine free base or HCl salt release profiles from CP/PIB/PIP = 60/35/5 and CP/PIB/PIP = 50/43.75/6.25 formulations are demonstrated in Figures 1 and 2, respectively.

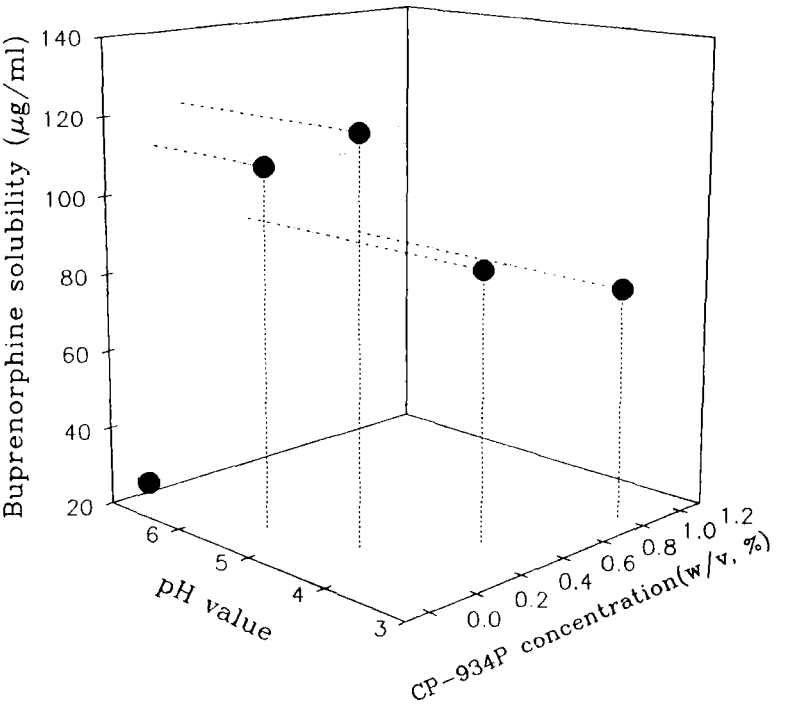


FIGURE 4

The solubilities of buprenorphine in the CP-934P solutions.

The drug release profiles were significantly affected by the drug loading and the existence of β-cyclodextrin. Increasing the drug loading and solubility enhancer would increase the drug release from the buccal polymer patches, since increasing the amount of β-cyclodextrin and drug loading would increase the driving force of drug in the polymer patches. However, as shown in Figure 1, even 20% of drug released from the polymer patches which didn't contain the β-cyclodextrin. This phenomenon could be explained by the pH value change in the microenviroment of polymer patches during the hydration of CP.

The pH values of different concentrations of CP 934P and 974P solutions (dissolved in pH 7 buffer solution) were indicated in Figure 3. Increasing the

CP concentration would decrease the pH value of the CP solution. The decrease of pH value of CP solution was accompanied by the increase of buprenorphine solubility in this solution (Figure 4). Therefore, it can explain that even 20% of drug could release from the polymer patches which didn't include the β-cyclodextrin. However, the buprenorphine solubility decreased slightly at higher CP concentration solution, because the CP solution became more viscous at higher CP concentration and entrapped some of buprenorphine.

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