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Mucoadhesive buccal disks for novel nalbuphine prodrug controlled delivery: effect of formulation variables on drug release and mucoadhesive performance

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Abstract

The objective of this work was to assess the effects of drug solubility and loading percent, as well as Carbopol 934/hydroxypropylcellulose (CP/HPC) ratio, on drug release and mucoadhesive performance of the nalbuphine prodrug loaded buccal disks. Drug release rates for the disks were found to be a function of drug solubility, with higher drug release rates for disks loaded with more hydrophilic prodrugs and an increased amount of β-cyclodextrin. The drug release rates increased with loading percents for nalbuphine hydrochloride, whereas an opposite drug release trend was observed for disks loaded with nalbuphine enanthate, which can be explained by the diffusional drug release mechanism. The CP/HPC ratio affected release rates of nalbuphine enanthate, whereas the ratio had no impact on the release of nalbuphine hydrochloride. Within the 2 days of experiment time, all formulations attached well to the porcine buccal tissues, indicating those formulation variables had no influence on the mucoadhesive performance of CP/HPC-based buccal disks.

Keywords: Controlled release; Buccal disk; Nalbuphine prodrug; Drug release; Mucoadhesion

1. Introduction

The buccal mucosa has been investigated for local and systemic delivery of therapeutic agents (Ishida et al., 1981; Rathbone, 1991; Cassidy et al., 1993; Guo, 1994; McQuinn et al., 1995). The attractive features of delivering drug via buccal route include excellent accessibility and significant robustness of mucosa (Merkle et al., 1991; Smart, 1993). The buccal mucosa also provides a delivery route to prevent premature drug degradation

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within the gastrointestinal tract, as well as drug loss due to first-pass hepatic metabolism.

To optimize drug delivery via buccal mucosa, the use of controlled release formulation with mucoadhesive properties is desirable. Several types of polymeric materials have been used in the design of such a system and most of them are hydrophilic macromolecules containing numerous hydrogen-bonding forming groups (Duchene et al., 1988; Merkle et al., 1991; Smart, 1993). For anionic polymers, Carbopol 934 (CP), sodium carboxymethylcellulose, sodium alginate and maleic anhydride copolymers are often used (Duchene et al., 1988; Anders and Merkle, 1989; Merkle et al., 1991; Smart, 1993). The non-ionic polymers used in such devices are hydroxypropylmethylcellulose, methylcellulose, hydroxypropylcellulose (HPC), polyethylene oxide and polyvinylalcohol; whereas chitosan and diethylaminoethyl dextrin are examples of cationic materials (Duchene et al., 1988; Anders and Merkle, 1989; Merkle et al., 1991; Smart, 1993). Among those bioadhesive polymers, CP is most extensively used and studied. The combination of a non-ionic polymer such as HPC with CP may provide the formulation with a constant drug release rate and desired mucoadhesive properties (Ishida et al., 1982; Nagai, 1986; Nagai and Konishi, 1987; Bottenberg et al., 1989; Smart, 1993). As a result, CP and HPC have been used in several buccal dosage forms to deliver various pharmaceutical agents. In order to adequately control drug release and mucoadhesion of the CP/HPC -based devices, the effects of several variables such as drug solubility and drug loading as well as CP/HPC ratio on drug release and mucoadhesion should be studied in a systematic way.

Nalbuphine is a narcotic analgesic often used in the treatment of both acute and chronic pain. It is a potent analgesic with relatively few side-effects. Owing to its short elimination half-life and low oral bioavailability, frequent injections are needed. It is obvious that patient compliance and therapeutic effectiveness may be improved by maintaining the plasma nalbuphine concentration. As a result, a series of nalbuphine prodrugs with various hydrophilicities have been synthesized, including nalbuphine propionate, nalbuphine pivalate, nalbuphine enanthate and nalbuphine decanoate (Wang, 1992). Various nalbuphine prodrug formulations such as biodegradable implant, suspension and microsphere have also been developed (Wang, 1992; Sung et al., 1998). The use of buccal devices incorporating these prodrugs may provide a constant drug release rate, resulting in both patient comfort and a reduced total amount of drug. The nalbuphine prodrugs may also be used as model compounds to study the effects of drug solubility, drug loading and polymer composition on drug release from the buccal delivery devices.

In the present study, three major goals are to be achieved. The first goal is to develop a series of nalbuphine hydrochloride and nalbuphine prodrug loaded buccal disks based on CP and HPC polymers. The second goal is to utilize a series of nalbuphine prodrug and various amounts of β-cyclodextrin to assess the effect of drug solubility on drug release and mucoadhesive performance of such devices. Finally, the influence of drug loading and CP/HPC ratio on drug release and mucoadhesion of the disks are also examined.

2. Materials and methods

2.1. Materials

HPC (1000–4000 cps, 2% in water) and ethylcellulose (100 cps) were obtained from TCI Chemicals (Japan) and Showa Chemicals (Japan), respectively. Carbopol 934 was pharmaceutical grade and purchased from BF Goodrich (Cleveland, OH, USA). The four nalbuphine prodrugs, including nalbuphine propionate, nalbuphine pivalate, nalbuphine enanthate and nalbuphine decanoate, were synthesized and supplied by the National Defense Medical Center (Taipei, Taiwan). All the other chemicals were purchased from Sigma Chemical (St Louis, MO, USA) and used as received.

2.2. Preparation of buccal disks

Various amounts of CP, HPC and drug were used in this study to prepare different formulations of buccal disks. The CP, HPC and drug were first sieved and mixed homogeneously before they were compressed by a manual single punch tablet machine (Chen-Tai Machinery Works, Taiwan). The compression pressure and time were 200 kg/cm^2 and 30 s, respectively. Approximately 500 μl of ethylcellulose solution (10% w/v in ethanol) was cast on one side of the disks as an impermeable backing layer. The diameter and thickness of the resulting disks were approximately 8 and 1 mm, respectively.

2.3. In vitro release study

The in vitro drug release studies were conducted by using Franz diffusion cells and were performed in phosphate buffer (pH 7.4). The volume of buffer in the receiver compartment was 18 ml. The stirring rate and temperature were kept at 300 rpm and 37°C, respectively. A polymer membrane with pore size of 0.2 μm was placed between cells to support the disks. The buffer samples were taken from cells on sampling times of 0.5, 1, 2, 4, 6, 8, 24 and 48 h. The medium removed from the cells were immediately replaced with fresh buffer. The samples were subjected to high-pressure liquid chromatography (HPLC) analysis.

2.4. HPLC assays

Nalbuphine and its prodrug concentrations were analyzed using HPLC (Wang, 1992; Ho et al., 1996; Sung et al., 1998). The chromatographic system consisted of a pump (HITACHI 655-A40), an autosampler (HITACHI L6000), a UV detector (HITACHI L4000) and an integrator (HITACHI D2500). A normal phase silica column (μ porasil, 3.9 mm × 300 mm, 10μm, Waters) was used for drug separation. An acetonitrile–pH 3.5 acetate buffer system (80:20) was used as the mobile phase. The flow rate and the UV wavelength were 1.5 ml/min and 210 nm, respectively. The injection volume was 10 μl. Under these chromatographic conditions, the retention times of nalbuphine hydrochloride, nalbuphine propionate, nalbuphine pivalate, nalbuphine enanthate and nalbuphine decanoate were approximately 9.8, 8.1, 7.4, 6.9 and 6.3 min, respectively. The formulation excipients were not found to interfere with the peaks of nalbuphine and its prodrugs. The drug concentrations were determined by measuring the peak area and comparing it with the peak area of known standards. More details concerning the validation of HPLC assays can be referred to elsewhere (Wang, 1992; Ho et al., 1996).

2.5. Mucoadhesion study

The mucoadhesive performances of the buccal disks were evaluated using porcine buccal tissues. In several previous studies, the detachment forces between formulations and biological tissues were measured (Ishida et al., 1981; Duchene et al., 1988); in the present study, the time for disks to detach from the porcine buccal tissue in a well stirred beaker were used to assess the mucoadhesive performance. The fresh-cut porcine buccal tissues were fixed on the side of the beaker with glue. Before addition of the buffer, the disks were attached to porcine buccal tissues by applying light force (approximately 0.5 N) with the finger tip for 20 s. The beaker was then filled with 800 ml phosphate buffer and was kept at 37°C. A stirring rate of 150 rpm were used to simulate buccal and saliva movement. The attachment of disks were monitored until 48 h (the drug release time). The time for the disk to detach from the porcine buccal tissue was recorded as the mucoadhesion time.

2.6. Disk hydration study

The hydration studies were also conducted in the Franz diffusion cells with phosphate buffer (pH 7.4). Periodically, the polymeric disks were withdrawn from the cell and weighed on an electronic balance (Mettler Model AE 240) after removal of surface water by light blotting with a laboratory tissue. The sampling times of hydration studies were 0.5, 1, 2, 4, 6, 8, 24 and 48 h. The hydration ratio of the disks was defined as:

$$\text{Hydration ratio} = \frac{(\text{partially hydrated disk weight} - \text{dry disk weight})}{(\text{dry disk weight})}$$

The hydration rate (hydration ratio/$h^{1/2}$) was calculated according to the model describing the absorption of liquid into polymeric matrices via diffusion (Vergnaud, 1993). Based on this model, the hydration rate (hydration ratio/$h^{1/2}$) in this study was obtained from the slope of the plot of hydration ratio versus square root of time.

3. Results and discussion

3.1. Effect of drug solubility

The influence of drug solubility on drug release from CP/HPC-based disks were assessed by using disks loaded with different nalbuphine prodrugs and disks loaded with various amounts of β-cyclodextrin. Due to the various ester side chains, the hydrophilicity and aqueous solubility of the prodrugs are different. Among those ester derivatives, nalbuphine propionate has the highest aqueous solubility, followed by nalbuphine pivalate, nalbuphine enanthate and nalbuphine decanoate (Sung et al., 1998). β-Cyclodextrin is often used as an enhancer to increase the solubility of a hydrophobic compound. As a result, both the nalbuphine prodrugs and β-cyclodextrin were utilized in this study to assess the influence of drug solubility on drug release from the CP/HPC-based disks. The effect of drug hydrophilicity on mucoadhesive performance of the disks was also evaluated.

Fig. 1 shows the drug release profiles of the CP/HPC-based disks loaded with various nalbuphine prodrugs. The drug loading was 30 mg and CP/HPC ratio was 90 mg/30 mg, respectively. According to Fig. 1, a greater drug release rate was observed for disks loaded with more hydrophilic prodrug, i.e. prodrug with higher aqueous solubility. For example, after 24 h, around 11.5, 9.9, 3.3 and 0.6% of drug have released from the disks loaded with nalbuphine propionate, nalbuphine pivalate, nalbuphine enanthate and nalbuphine decanoate, respectively. Moreover, within the 48 h of experiment time, those disks attached well to the porcine buccal tissues, indicating that the drug hydrophilicity had no significant influence on the mucoadhesive performance of the disks.

The effect of β-cyclodextrin on nalbuphine enanthate release from CP/HPC-based disks is shown in Fig. 2. The drug loading and CP/HPC ratio were also 30 mg and 90 mg/30 mg, respectively. The slowest drug release was observed for disks with no β-cyclodextrin, indicating that the drug release was significantly affected by incorporation of β-cyclodextrin. These results are consistent with a previous report that the release rates of buprenorphine (a narcotic analgesic) from buccal patches were increased by incorporation of β-cyclodextrin (Guo, 1995). Fig. 2 also demonstrates that the drug release rate increased with the amount of β-cyclodextrin in these disks. For example, at 24 h, around 3.3, 4.9, 5.3 and 5.9% of drug have released from the disks with 0, 15, 30, 60 mg of β-cyclodextrin, respectively. Statistical comparison using one way analysis of variance shows that the release rates (% release/$h^{1/2}$) of those profiles were not the same, suggesting that a

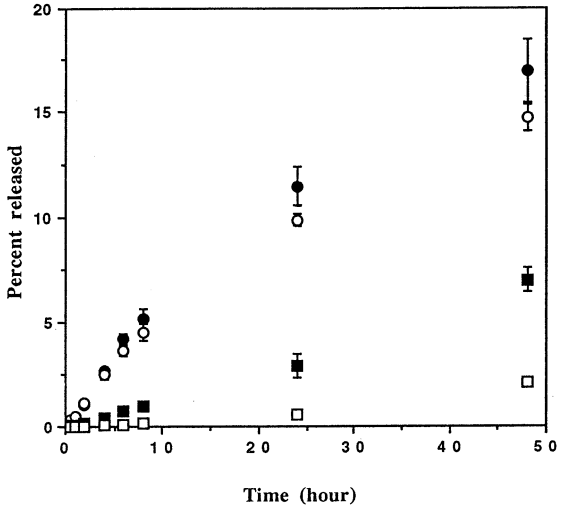

Fig. 1. The percent drug released vs time profiles for disks loaded with various prodrugs: (●) nalbuphine propionate; (○) nalbuphine pivalate; (■) nalbuphine enanthate; (□) nalbuphine decanoate. Mean ± standard error presented ($n = 3$).

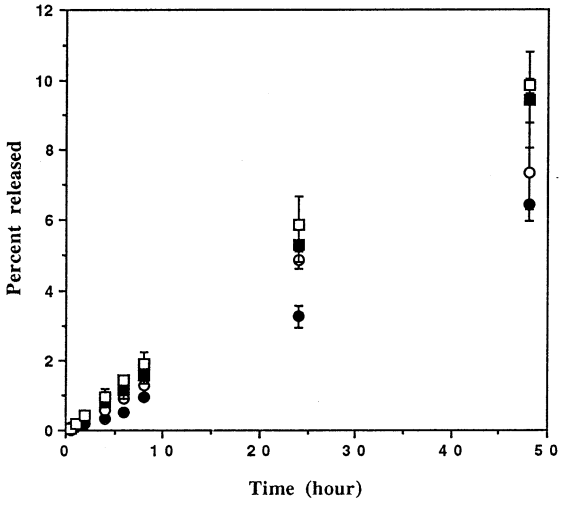

Fig. 2. The percent drug released vs time profiles for disks loaded with various amounts of β-cyclodextrin: (●) 0 mg; (○) 15 mg; (■) 30 mg and (□) 60 mg. Mean ± standard error presented ($n = 3$).

difference in the release rates can be observed for disks loaded with various amounts of β-cyclodextrin. However, the subsequent multiple comparison (LSD test) indicates that the release rates for disks loaded with 30 and 60 mg of β-cyclodextrin were not significantly different. Both Fig. 2 and statistical results show that the incorporation of various amounts of β-cyclodextrin in those disks can have effects on drug release rates, even though in some cases, the differences in release rates were not statistically significant.

For a drug incorporated in a polymeric matrix, the Higuchi expression describing Fickian drug release from a single face of a non-swelling tablet is frequently used to describe the drug release profiles of matrix extended release dosage forms. This model has also been used to describe the release profiles of several swellable and erodible systems (Doelker, 1987; Hogan, 1989), such as the hydroxypropylmethylcellulose-based matrices (Hogan, 1989; Sung et al., 1996). According to this model, a straight line is expected for the percent drug release versus square root of time plot if drug release is based on a diffusion mechanism. Table 1 shows the slopes (Higuchi rate constants) of the square root of time plots and the r values (correlation coefficients) for the formulations loaded with various prodrugs. It is notable that the r values of the linear regressions were greater than 0.98 and the residuals were randomly distributed for all the formulations studied, indicating that the data fit the Higuchi model well. This simple analysis of the drug release data, within the limitations of the model, demonstrates that the release of nalbuphine prodrug from those disks was consistent with a diffusion mechanism. The initial release of less soluble prodrugs such as nalbuphine enanthate and nalbuphine decanoate may be attributed to the slow dissolution of drug from the surface layer of disks; however, the release has gradually become diffusion controlled as the relaxation and swelling of surface polymer proceed. The above data analysis may also help to explain the results in Figs. 1 and 2: the incorporation of more soluble drug and loading with more solubility enhancer may increase the drug concentration (i.e. the diffusional driving force) inside the hydrated polymeric environment and, thus, the drug release rate is increased (Guo, 1995). By varying the drug hydrophilicity and the amount of solubility enhancer inside the disks, the above results clearly demonstrate that drug solubility is an important factor in controlling drug release from the CP/HPC-based disks, and it can also be used to produce a wide range of drug release rates.

3.2. Effect of drug loading

The effect of drug loading on drug release from CP/HPC-based disks was evaluated using nalbuphine hydrochloride and nalbuphine enanthate. In this study, nalbuphine hydrochloride was used

Table 1
The Higuchi rate constants (percent released/$h^{1/2}$) and r values of disks loaded with various prodrugs

Prodrug	Higuchi rate constant	r value
Nalbuphine propionate	2.80	0.997
Nalbuphine pivalate	2.40	0.998
Nalbuphine enanthate	1.07	0.981
Nalbuphine decanoate	0.042	0.981

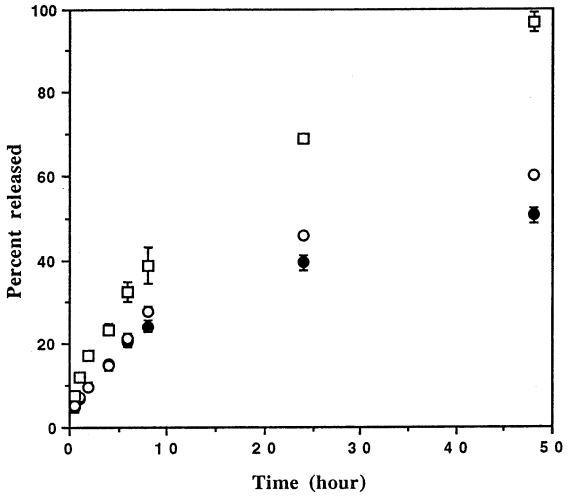

Fig. 3. The percent drug released vs time profiles for disks loaded with various amounts of nalbuphine hydrochloride: (●) 15 mg; (○) 30 mg and (□) 60 mg. Mean ± standard error presented ($n = 3$).

as a water-soluble model compound, whereas nalbuphine enanthate was used as a model compound with low aqueous solubility (3 μg/ml). Fig. 3 shows the release profiles for disks with various loadings of nalbuphine hydrochloride. The CP/HPC ratio was fixed at 90 mg/30 mg. A greater drug release rate was observed for disks with higher loading of nalbuphine hydrochloride. For example, at 24 h, around 39.5, 46.2 and 68.9% of drug have released from the disks with drug loadings of 15, 30 and 60 mg, respectively.

The release profiles for disks with various loadings of nalbuphine enanthate are shown in Fig. 4. On comparison with Fig. 3, Fig. 4 shows an opposite release trend: the percent drug release increased as drug loading decreased. For example, at 24 h, around 6.7, 3.3 and 1.4% of drug have released from the disks with drug loadings of 15, 30 and 60 mg, respectively.

For those disks with various drug loadings, all disks attached well to the porcine buccal tissues within the 48 h of experiment time, demonstrating that the drug loading had no effect on the mucoadhesive performance of the CP/HPC-based disks.

The above-mentioned release studies clearly demonstrate that increasing the loading of nalbuphine hydrochloride may increase the drug release rate (on a percent basis), whereas increasing the loading of nalbuphine enanthate may decrease the drug release rate. This phenomenon may be explained well by the drug release mechanism. For drug particles dispersed in polymeric matrices, two steps are involved in drug release: the drug has to dissolve inside the hydrated polymeric matrices and then release into the medium via diffusion. For nalbuphine hydrochloride (a water-soluble drug), it can dissolve easily in the hydrated polymeric environment. Therefore, as the loading of nalbuphine hydrochloride increased, an increased amount of drug would dissolve inside the hydrated matrices, resulting in higher diffusional driving force and faster drug release. For nalbuphine enanthate, due to its low aqueous solubility, only a limited amount of drug may dissolve inside the hydrated polymeric matrices. In this case, the concentration of nalbuphine enanthate inside the hydrated polymeric environment should be similar regardless of the drug loading. That is, the diffusional driving force and thus the amount of drug released would be independent of drug loading. Indeed, Fig. 5 shows that the amount of nalbuphine enanthate released versus time plots for disks with various drug

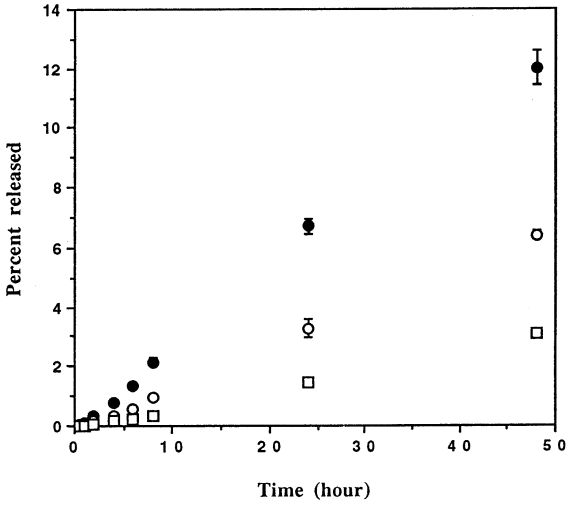

Fig. 4. The percent drug released vs time profiles for disks loaded with various amounts of nalbuphine enanthate: (●) 15 mg; (○) 30 mg and (□) 60 mg. Mean ± standard error presented ($n = 3$).

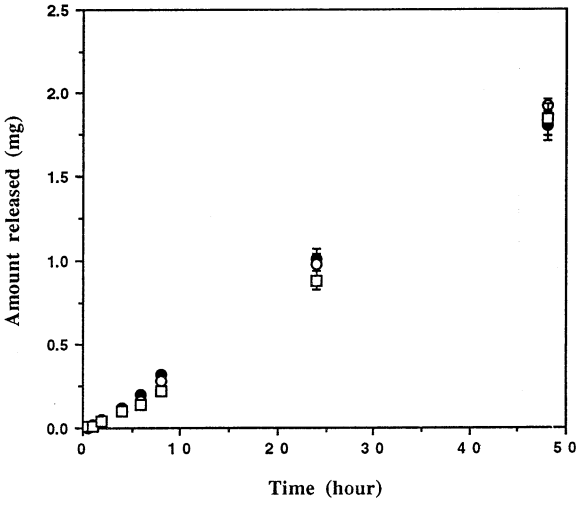

Fig. 5. The drug released amount (mg) vs time profiles for disks with various loadings of nalbuphine enanthate: (●) 15 mg; (○) 30 mg and (□) 60 mg. Mean ± standard error presented ($n = 3$).

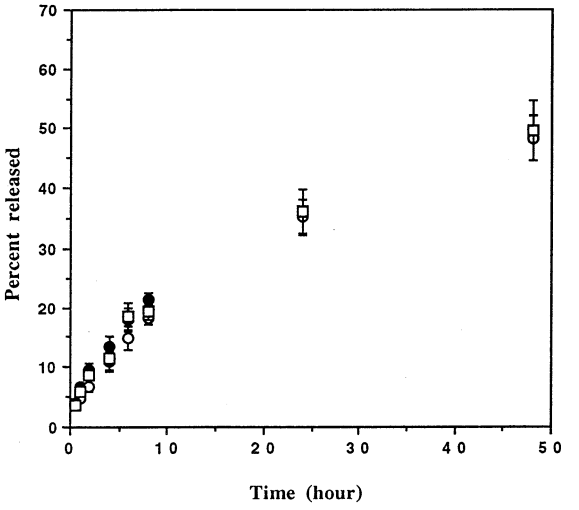

Fig. 6. The percent nalbuphine hydrochloride released vs time profiles for disks with various CP/HPC ratios: (●) 90/30; (○) 60/60 and (□) 30/90. Mean ± standard error presented ($n = 3$).

loadings are superimposible, indicating the previous inference can be used to explain the opposite drug release trends between nalbuphine hydrochloride and nalbuphine enanthate. Accordingly, as the loading of nalbuphine enanthate increased, the drug dissolution (on a percent basis) in the hydrated environment would be slower than the one with lower drug loading.

3.3. Effect of CP/HPC ratio

The effects of CP/HPC ratio on nalbuphine hydrochloride and nalbuphine enanthate release from the disks are shown in Figs. 6 and 7, respectively. The drug loading was 30 mg. The overlapped release profiles in Fig. 6 indicate that the CP/HPC ratio has no effect on the release of nalbuphine hydrochloride (a soluble drug) from the disks. However, the release of nalbuphine enanthate (a less soluble drug) from the delivery system was a function of CP/HPC ratio (Fig. 7): a greater drug release rate was observed for disks with higher CP/HPC ratio. The mucoadhesive performance for those disks with various CP/HPC ratios were similar, i.e. no disks dropped from the porcine buccal tissue within the 48 h of experiment time.

The effects of CP/HPC ratio on nalbuphine enanthate release can be attributed to drug solubility and polymer hydration. As stated earlier, for the release of nalbuphine enanthate from disks, its release rate was affected by two rate steps: dissolution of drug into the hydrated polymeric environment and diffusion of the dissolved

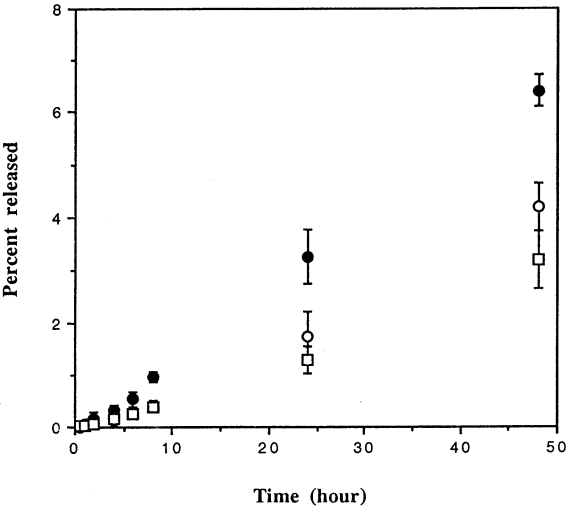

Fig. 7. The percent nalbuphine enanthate released vs time profiles for disks with various CP/HPC ratios: (●) 90/30; (○) 60/60 and (□) 30/90. Mean ± standard error presented ($n = 3$).

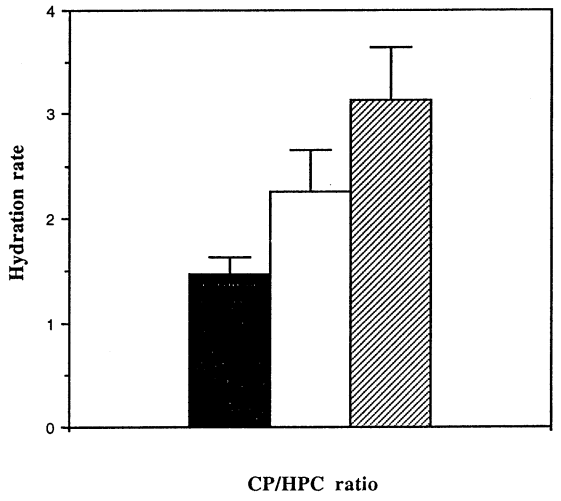

Fig. 8. The hydration rates (hydration ratio/$h^{1/2}$) for disks with various CP/HPC ratios: (■) 90/30; (□) 60/60 and (▨) 30/90. Mean ± standard error presented ($n = 3$).

drug molecules into the medium. The predominant rate step on drug release could be either dissolution or diffusion depending on their relative rates. The Yasuda's free volume theory indicates that higher polymer hydration may result in higher drug diffusivity in the hydrated polymeric environment (Yasuda and Lamaze, 1971). For the disks with faster hydration, due to the higher drug diffusivity and slow dissolution rate of nalbuphine enanthate, the diffusion step may become less important and both dissolution as well as the diffusion step can have effects on drug release. Accordingly, for those fast-hydrated disks, since the dissolution of nalbuphine enanthate was slow, the diffusional driving force and drug release rate are relatively lower in comparison with those disks with slower hydration. Faster matrix hydration may also result in longer diffusional pathlength and slower drug release (Gao et al., 1996). Fig. 8 shows the hydration rates (hydration/$h^{1/2}$) for disks with various CP/HPC ratios. Indeed, by comparing Figs. 7 and 8, the two graphs clearly show that the formulations with higher CP/HPC ratio correspond to lower hydration rates and higher drug release rates. These data demonstrate that both the dissolution rate of nalbuphine enanthate and disk hydration rate contributed to different nalbuphine enanthate release rates for the disks with various CP/HPC ratios.

In summary, the effect of drug solubility, loading percent and CP/HPC ratio on drug release and mucoadhesive performance of CP/HPC-based buccal disks were evaluated. The release rates were significantly affected by drug solubility, with higher drug release rates for disks loaded with more hydrophilic prodrug and an increased amount of β-cyclodextrin. Drug release from the disks with CP/HPC ratio of 90 mg/30 mg was consistent with a diffusion mechanism. The influence of loading percents on drug release were different for nalbuphine hydrochloride and nalbuphine enanthate, which could be due to their various aqueous solubility. The CP/HPC ratio affected the release rate of nalbuphine enanthate, whereas it had no impact on the release of nalbuphine hydrochloride. All formulations attached well to the porcine buccal tissues within the 2 days of experiment time, indicating those formulation variables had no influence on the mucoadhesive performance of the CP/HPC-based disks.

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