# 行政院國家科學委員會專題研究計畫成果報告

## Nalbuphine前驅藥口腔控釋貼劑之開發及評估研究

## Development and In-vitro Evaluation of Bioadhesive Buccal Patches for Nalbuphine Prodrug Controlled Delivery

計畫編號：NSC 86-2314-B-041-003
執行期限：85年8月1日至86年7月31日
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本計畫主要目的乃是開發一系列Nalbuphine前驅藥之口腔控釋貼劑以及評估貼劑中藥物溶解度，負載量和配方比例對藥物由貼劑釋放速率之影響。實驗結果顯示當藥物溶解度上升時藥物釋放速率即會加快。對溶解度好的藥物而言，增加貼劑中藥物負載量可上升藥物之釋放速率（以百分比計），而對溶解度較差的藥物而言，則有相反的表現。另外，貼劑中不同比例之Carbopol及Hydroxypropylcellulose對溶解度好的藥物由貼劑中釋放並無顯著影響；而對溶解度較差的藥品而言其釋放速率將隨著此比例的上升而加快。

關鍵詞：Nalbuphine前驅藥、口腔控釋貼劑、藥物釋放

**Abstract**

The major purpose of this project is to develop and evaluate a series of bioadhesive buccal devices for nalbuphine prodrug controlled delivery. Drug release from the disks were examined by varying three formulation variables, including drug solubility, drug loading and polymer ratio. Higher release rates were observed for the disks loaded with more soluble drugs and with more solubility enhancer. While loaded with a water soluble drug, the release rates from disks increased with loading and an opposite phenomenon was observed when loaded with a less soluble drug.The Carbopol/hydroxypropylcellulose ratio did not affect the release rates of a water soluble drug significantly; however, the ratio may affect the release rates of a less soluble drug.

**Keywords:** Nalbuphine prodrug, Bioadhesive buccal disk, Drug release

**Introduction**

The buccal mucosa has been investigated for local and systemic drug delivery of therapeutic agents [1-4]. The attractive feature of delivering drug via buccal mucosa included excellent accessibility, lower enzyme activity, and higher patient acceptance [2]. The buccal mucosa has provided a delivery route to prevent premature drug degradation within the GI tract as well as drug loss due to first pass hepatic metabolism [1,2].

To optimizing drug delivery via buccal mucosa, the use of a controlled-release formulation with buccal adhesive property is most desirable. Several types of buccal adhesive materials have been used in the design of such system and most of the buccal adhesive materials are hydrophilic macromolecules that containing numerous hydrogen bonding forming groups [1,2]. Among those buccal adhesive materials, Carbopol are most extensively used and studied. The combination of a rate retarding material such as hydroxypropylcellulose (HPC) with Carbopol may provide a formulation with a constant drug release rate and buccal adhesive properties. Nevertheless, in order to adequately control drug release from the Carbopol/HPC-based devices, several variables such as drug solubility, drug loading as well as Carbopol /HPC ratio should be studied in a systematic way.

Nalbuphine is a narcotic analgesics used effectively in the treatment of both acute and chronic pain. It has quite potent analgesic effects and relatively low side effects. Due to its short elimination half-life and low oral bioavailability, frequent injection is needed. It is obvious that the patient compliance and therapeutic effectiveness in pain management can be improved by maintaining the blood nalbuphine concentration. As a result, a

series of nalbuphine prodrug, including nalbuphine propionate, nalbuphine pivalate, nalbuphine enanthate and nalbuphine decanoate have been synthesized [5]. Various nalbuphine prodrug formulations such as biodegradable implant, suspension and microsphere have also been developed [5,6]. The use of buccal devices incorporating those prodrugs may provide a constant drug release rate, resulting in both patient comfort and a reduced total amount of analgesics. The series of nalbuphine prodrug may also be used as model compounds to study the effect of drug hydrophilicity on drug release from the buccal adhesive devices.

In the present study, three major goals are to be achieved. The first goal is to develop a series of nalbuphine and nalbuphine prodrug buccal delivery systems based on the Carbopol/HPC polymers. The second goal is to use a series of nalbuphine prodrugs and β-cyclodextrins to assess the effect of drug solubility on drug release from the disks. The final goal is to assess the effect of drug loading and Carbopol/HPC ratio on drug release from the Carbopol/HPC-based buccal adhesive disks.

## Results and discussion

### *Effect of drug solubility*

The influence of drug solubility on drug release from Carbopol/HPC-based buccal adhesive disks were evaluated using various nalbuphine prodrugs and various amounts of β-cyclodextrins. The nalbuphine prodrugs used in the present study are nalbuphine propionate, nalbuphine pivalate, nalbuphine enanthate and nalbuphine decanoate. Due to the various ester side chains, their aqueous solubility are different. β-cyclodextrin is often used as a solubility enhancer to increase the solubility of various compounds. As a result, both variables were utilized to examine the effect of drug solubility on drug release from the HPC/Carbopol-based disks.

Figure 1 shows the drug release profiles for the Carbopol/HPC-based disks loaded with various nalbuphine prodrugs. According to Figure 1, a greater drug release was observed for disks loaded with more hydrophilic prodrugs, i. e., prodrug with higher aqueous solubility. For example, after 24 hours, around 11.5, 9.9, 2.9 and 0.6 % of drug have released from the disks loaded with nalbuphine propionate, nalbuphine pivalate, nalbuphine enanthate and nalbuphine decanoate, respectively.

The effect of β-cyclodextrin on nalbuphine enanthate release from Carbopol/HPC-based disks is shown in Figure 2. The slowest drug release profile was observed for disks with no β-cyclodextrins, indicating drug release is significantly affected by the incorporation of the solubility enhancer. Figure 2 demonstrates that a greater drug release was observed for disks loaded with more β-cyclodextrins. For example, at 24 hours, around 2.9, 4.9, 5.3, and 5.9% of drug have released from the disks with 0, 15, 30, 60 mg of β-cyclodextrins, respectively. The above results demonstrate that the drug solubility is an important factor in controlling drug release from Carbopol/HPC-based polymeric buccal adhesive disks.

### *Effect of drug loading*

The effect of drug loading on drug release from Carbopol/HPC-based disks were examined using nalbuphine hydrochloride and nalbuphine enanthate. Nalbuphine hydrochloride was used as a soluble model compound whereas nalbuphine enanthate was used as a less soluble model compound. Figure 3a shows the release profiles of nalbuphine hydrochloride from Carbopol/HPC-based disks with various drug loading. The fastest drug release (on a percentage basis) was observed for the disks with highest drug loading, i.e., a greater drug release rate was observed for disks loaded with more nalbuphine hydrochloride. For example, at 24 hours, around 39.5, 46.2,

68.9 % of drug have released from the disks with drug loading of 15, 30 and 60 mg, respectively.

The release profiles of various loadings of nalbuphine enanthate from Carbopol/HPC-disks are shown in Figure 3b. The percent drug release of nalbuphine enanthate was significantly lower than that of nalbuphine hydrochloride. Comparing to Figure 3a, an opposite phenomenon was observed. The drug release rate increased as the loading decreased. For example, at 24 hours, around 6.7, 3.3 and 1.2 % of drug have released from the disks with drug loading of 15, 30, 60 mg, respectively. The above results demonstrate that increasing the loading of a soluble drug (nalbuphine hydrochloride) may increase the drug release rate whereas increasing the loading of a less soluble drug (nalbuphine enanthate) may decrease the release rate.

*Effect of Carbopol/HPC ratio*

The effects of Carbopol/HPC ratio on nalbuphine hydrochloride and nalbuphine enanthate release from the buccal delivery system are shown on Figure 4a and 4b, respectively. Figure 4a shows the release profiles of nalbuphine hydrochloride from disks with various Carbopol/HPC ratio. The overlapped release profiles indicating that Carbopol/HPC ratio did not affect the release rates of nalbuphine hydrochloride (a water soluble drug) from the disks. However, the release of nalbuphine enanthate (a less soluble drug) from the delivery systems were a function of Carbopol/HPC ratio (Figure 4b). A greater drug release rate was observed for disks with higher Carbopol/HPC ratio. These results indicates that Carbopol/HPC ratio may affect the release rate of low water-soluble drugs and may not have impact on the release rate of water-soluble drugs.

## Comments

The study has developed buccal adhesive disks for nalbuphine prodrugs and has evaluate different variables that may affect drug release from the Carbopol/HPC-based disks. Most of the content in this study are in accordance with the proposal, although minor changes still exists due to evolution of this project. This study has been written in a paper format and prepared to be sent for publication in a scientific journal.

## References


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Figure 1

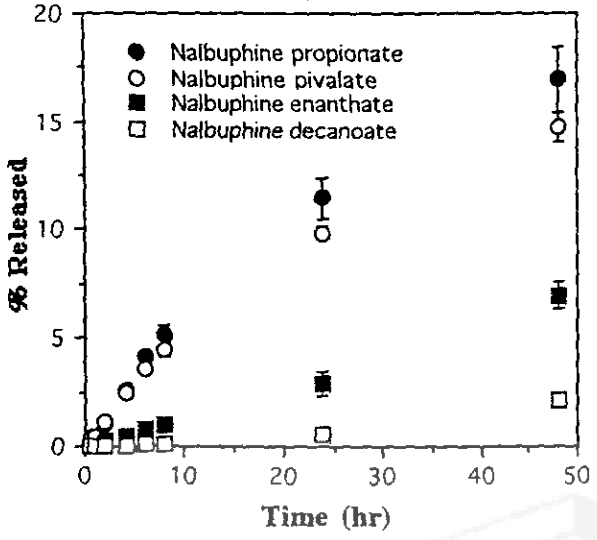


Figure 2

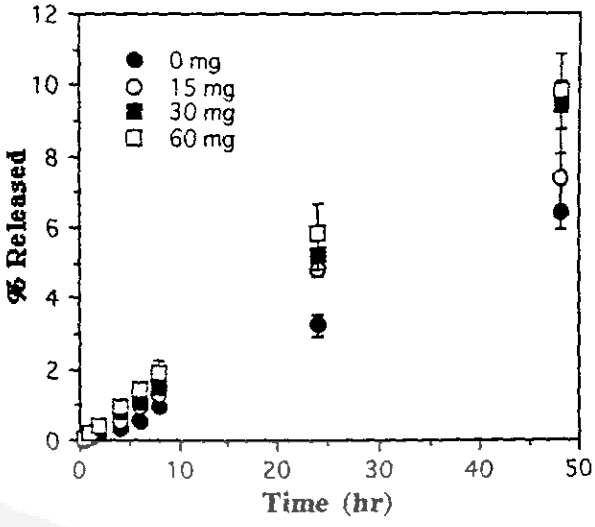


Figure 3a

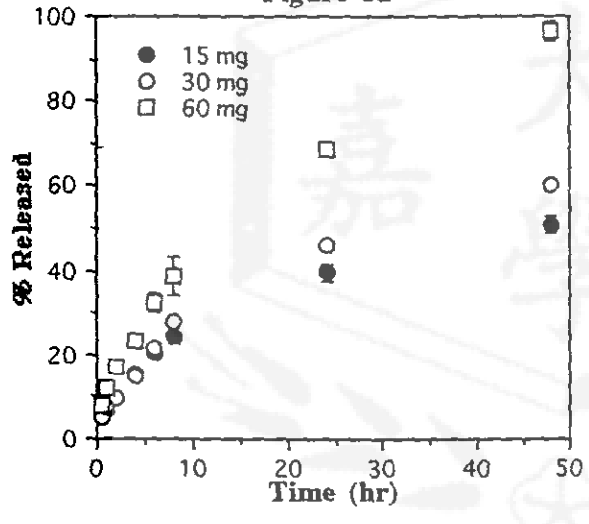


Figure 3b

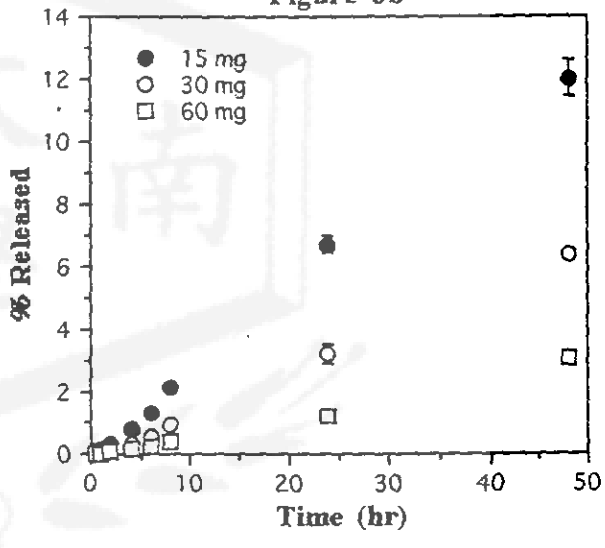


Figure 4a

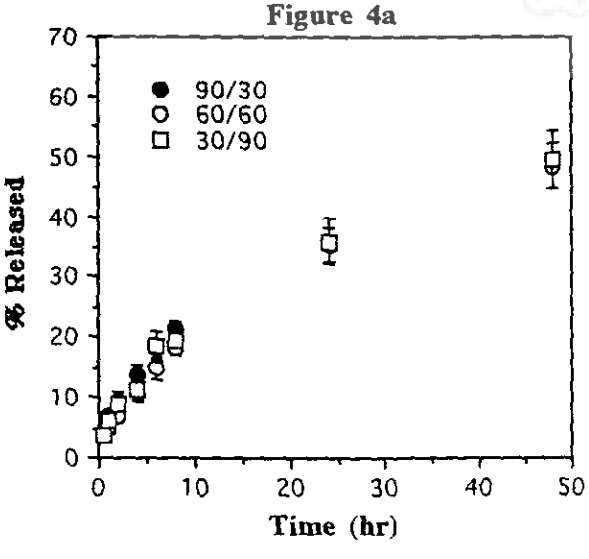


Figure 4b