

嘉南藥理科技大學專題研究計畫成果報告

Morphine 前驅藥凝膠劑型經皮吸收之研究

計畫編號：CNPH94-04

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主持人：韓若怡 嘉南藥理科技大學藥學系
體內經皮吸收之依據。

中文摘要

Morphine 為一種臨床上常使用之 opiate 類之止痛劑。在藥物動力學方面 morphine 之體內半衰期並不長，且一般靜脈或肌肉注射投藥頻率一天須 3 甚至 4 次，且口服後有相當明顯之肝臟首渡效應。由此，有一系列的 morphine prodrugs 已被合成以改善上述 morphine 在生物藥劑學上使用不便之問題。另外，由上述之資訊也可得知 morphine 及其 prodrugs 合適以經皮輸藥系統方式投與以避免肝臟首渡效應 (first-pass effect) 的發生並達到控制釋出 (controlled release) 的目的以減少投藥頻率。藥物以經皮輸藥方式給予時其載體 (carriers; vehicles) 之不同會明顯影響其經皮吸收能力，若藥物將來擬應用於臨床上則固體或半固體劑型較溶液製劑更為適當，一般而言現今臨床上使用之劑型以貼片型式及軟膏製劑較常被應用，今擬以 morphine 及其 prodrugs 為模式藥物，設計其水性凝膠半固體劑型從事生體外經皮吸收研究。本計畫將著重於生體外 morphine prodrug HPLC 分析及可行性評估部份，在體外評估方面最主要是以人工 cellulose 膜及裸鼠全皮為主要滲透障壁，經由選擇生體外試驗較適宜之處方以便未來進行生

Materials and methods

HPLC analysis

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 reverse phase silica column (Lichrospher RP-18, 3.9mm*250mm, 10 μ m, Merck) was utilized for drug separation, while an acetonitrile-pH 2.2 phosphate buffer system was used as the mobile phase. The flow rate and UV wavelength were 1 ml/min and 212 nm, respectively. The detailed chromatographic condition can be referred to the following result section.

Results and discussion

Figure 1 to Figure 6 show the HPLC condition as well as HPLC chromatograms of morphine and morphine prodrugs. The results clearly demonstrate that those chromatographic conditions can be utilized for further permeation studies.

References

1. Banga, A.K., Bose, S., Ghosh, T.K. (1999). *Int. J. Pharm.* **179**: 1-19
2. S.T. Ho et al., *J. Chromatogr. B*,

678(1996)289-296.

3. R. C. Etches et al., *Anesthesiology*,
75(1991) 9-14.
4. Tyle, P. (1986) *Pharm. Res.* **3**: 318-326



Morphine & Morphine prodrug HPLC

- Morphine

column type: Merck ; Lichrospher RP-18 (25cm long)

mobile phase: Acetonitrile / 20 mM phosphate buffer pH 2.2 (contain 1 mM SDS)
=35 / 65

UV wavelength: 212nm

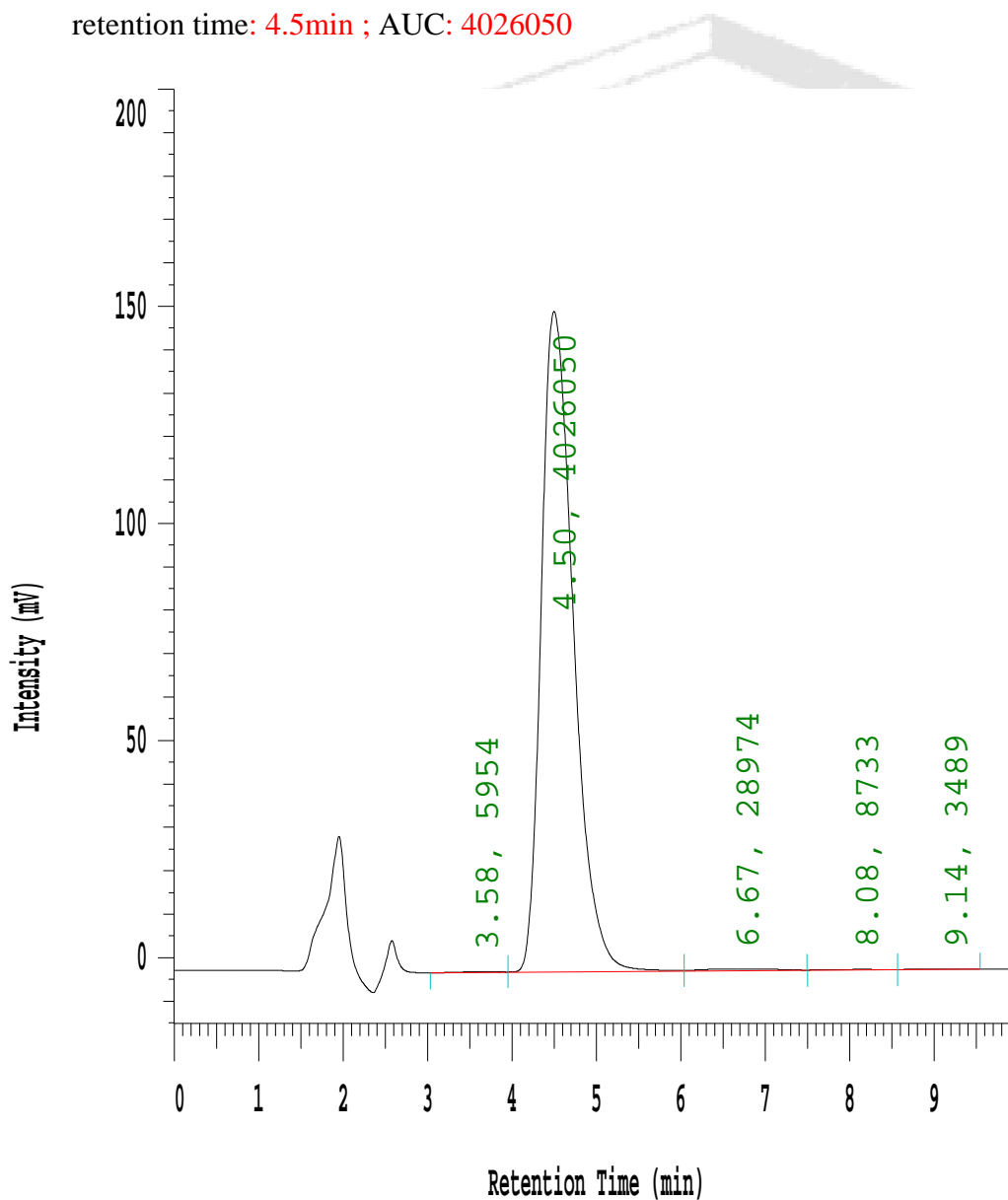
flow rate: 1ml/min

stock so'ln: 1mg/ml

soluble solvent: methanol

injection conc.: 100ug/ml

retention time: 4.5min ; **AUC:** 4026050



● Morphine propionate

column type: Merck ; Lichrospher RP-18 (25cm long)

mobile phase: Acetonitrile / 20 mM phosphate buffer pH 2.2 (contain 1 mM SDS)
=35 / 65

UV wavelength: 212nm

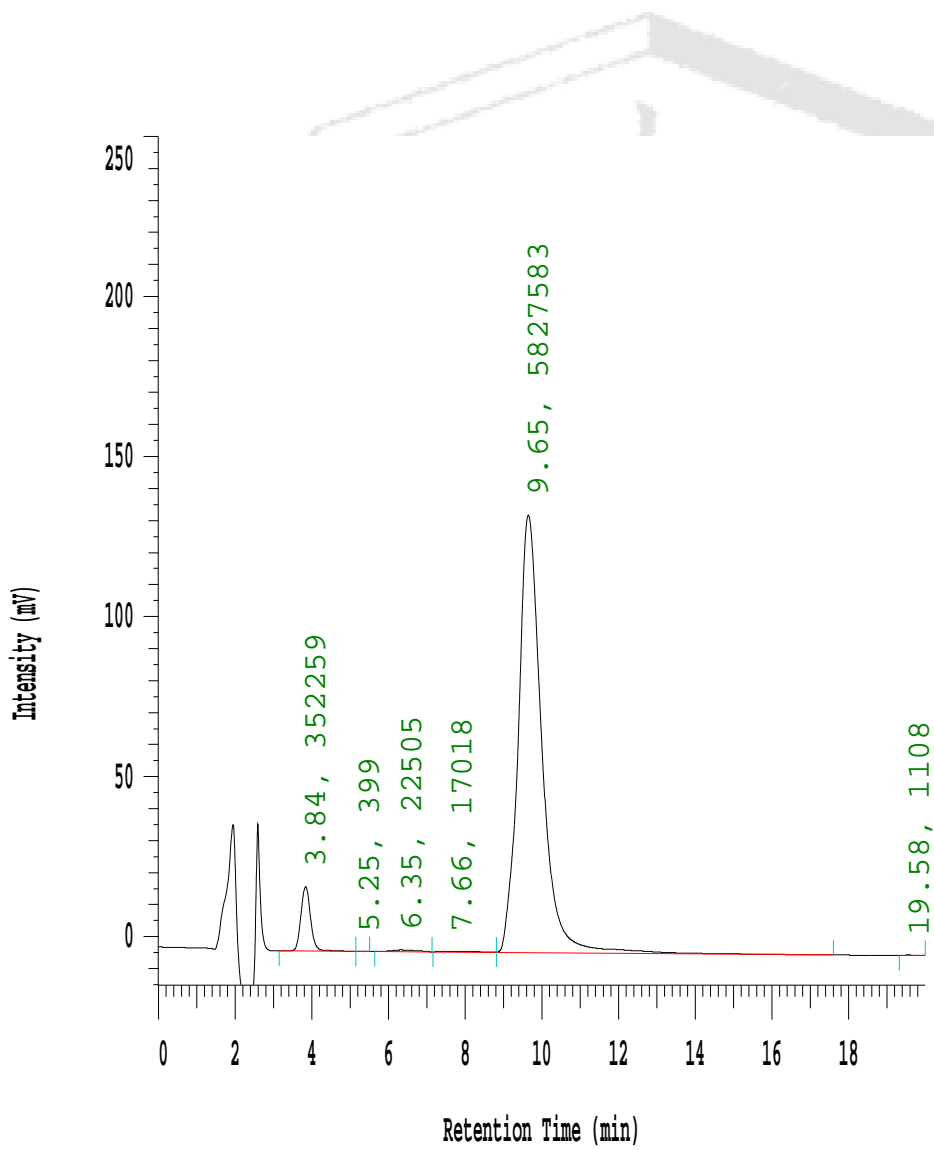
flow rate: 1ml/min

stock so'ln: 1mg/ml

soluble solvent: methanol

injection conc.: 100ug/ml

retention time: 9.65min ; AUC: 5827583



● Morphine valerate

column type: Merck ; Lichrospher RP-18 (25cm long)

mobile phase: Acetonitrile / 20 mM phosphate buffer pH 2.2 (contain 1 mM SDS)

=35 / 65

UV wavelength: 212nm

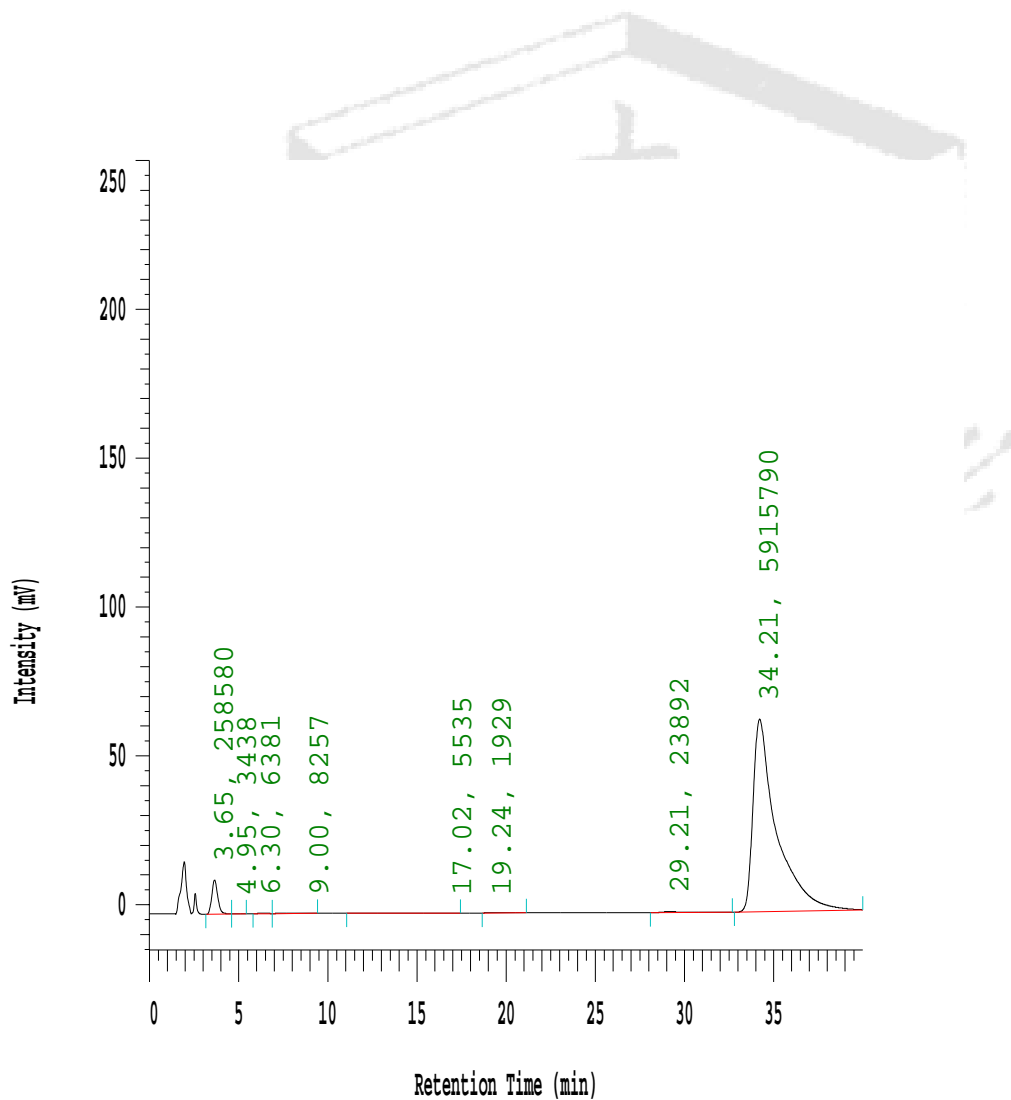
flow rate: 1ml/min

stock so'ln: 1mg/ml

soluble solvent: methanol

injection conc.: 100ug/ml

retention time: 34.21 ; **AUC:** 5915790



● Morphine enanthate

column type: Merck ; Lichrospher RP-18 (25cm long)

mobile phase: Acetonitrile / 20 mM phosphate buffer pH 2.2 (contain 1 mM SDS)

=55 / 45

UV wavelength: 212nm

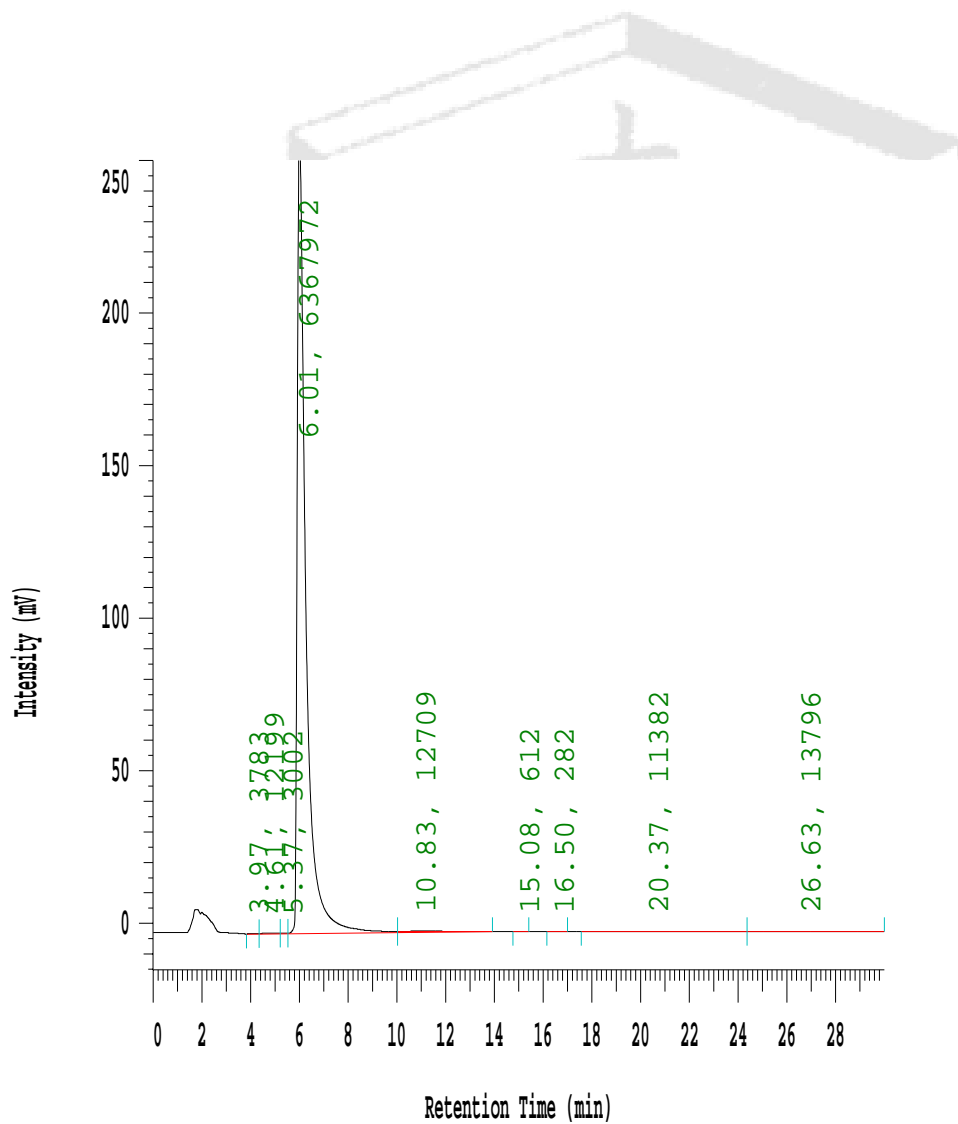
flow rate: 1ml/min

stock so'ln: 1mg/ml

soluble solvent: methanol

injection conc.: 100ug/ml

retention time: 6.01 ; **AUC:** 6367972



● Morphine decanoate

column type: Merck ; Lichrospher RP-18 (25cm long)

mobile phase: Acetonitrile / 20 mM phosphate buffer pH 2.2 (contain 1 mM SDS)
=55 / 45

UV wavelength: 212nm

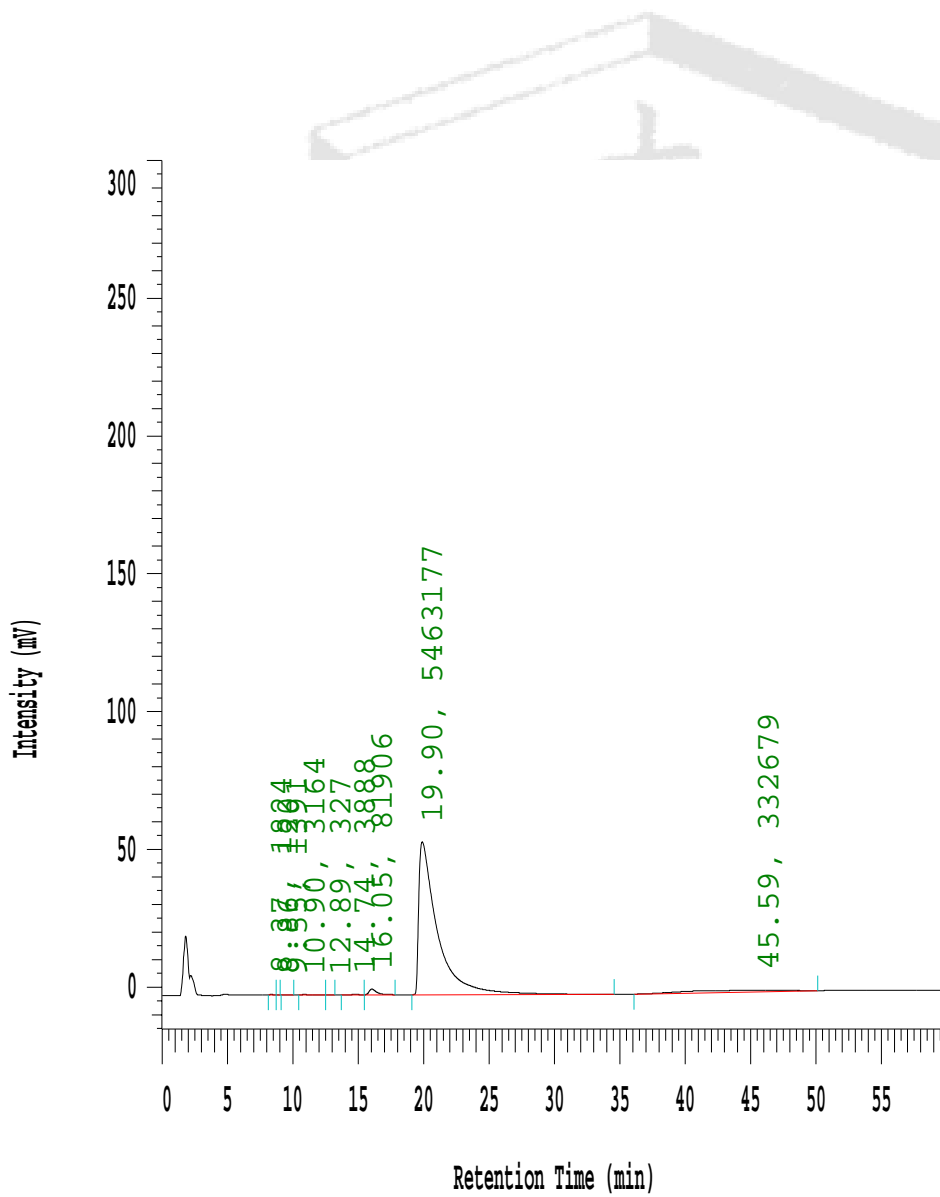
flow rate: 1ml/min

stock so'ln: 1mg/ml

soluble solvent: methanol

injection conc.: 100ug/ml

retention time: 19.90 ; AUC:5463177



- Morphine+Morphine propionate+Morphine valerate

column type: Merck ; Lichrospher RP-18 (25cm long)

mobile phase: Acetonitrile / 20 mM phosphate buffer pH 2.2 (contain 1 mM SDS)
=35 / 65

UV wavelength: 212nm

flow rate: 1ml/min

stock so'ln: 1mg/ml

soluble solvent: methanol

injection conc.: 100ug/ml

morphine: 3.92, 1571148

morphine propionate: 9.70 , 1901370

morphine valerate :41.81,1783689

