嘉南藥理科技大學專題研究計畫成果報告

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Narcotics 類止痛劑長效劑型之研究

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計畫類別：整合型計畫

計畫編號：CNPH94-04

執行期間：94 年　1 月　01 日至　94 年　12 月 31 日

計畫主持人：宋國峻教授

計畫參與人員：

執行單位：嘉南藥理科技大學藥學系

中　華　民　國　95　年　1　月　31 日

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Tramadol 口服長效間質劑型藥物釋放之研究

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.之參考資料。

中文摘要

本研究之主要目的乃是對不同控釋機轉及不同製程之 Tramadol 長效製劑之一系列研究。Tramadol 為一 Narcotics 類之口服止痛劑，常用於各種急性或慢性疼痛之病人。然欲達到治療之血中濃度，其每天給藥次數較為頻繁，每天至少須給藥 3-4 次。由此，為增加病人使用此藥物之有效性、安定性及方便性，Tramadol 口服長效製劑之基礎研究即成為重要之課題。由於控釋製劑的控釋機轉及製程改變均會對藥物之釋放及吸收造成影響，進而間接影響藥物在血中濃度及治療效果，因此本研究將針對 Tramadol 以 cellulose derivative 及 fatty acid ester 為基質之控釋製劑作一系列釋放及控釋機轉之研究。本研究不但能探討 Narcotics 類藥物於類似製劑之釋放效果，所得到之訊息也可作為工業界未來發展 Tramadol 長效口服製劑

Results and discussion

Tramadol, a narcotics often used in treatment of chronic pain, was used as a water soluble model drug. The various systems studied including hydrophobic matrix, hydrophilic matrix and matrix-film coating systems. The drug release from hydrophobic matrix using various manufacture processes, including wet granulation method and fusion-granulation method, was also evaluated. The results indicate that prolonged tramadol release can be observed by incorporation of drug into both hydrophobic and hydrophilic matrix systems. Drug release from those systems followed a Higuchi release model, suggesting a diffusional release mechanism. The release rate of tramadol was further decreased by coating a rate controlling membrane on top of matrix and the results suggest both matrix as well as coating membrane controlled the release rate. Moreover, the fusion-granulation method provided a better sustaining effect compared to the wet granulation method. Those studies indicate that, by changing the manufacture process and adding rate controlling membrane, an *in vitro* prolonged release of tramadol up to 24

hours can be obtained.

Fig 1: Release profiles of formulation G and H

Formulation G:40% HPMC

Formulation H:40% HPMC+5% coating

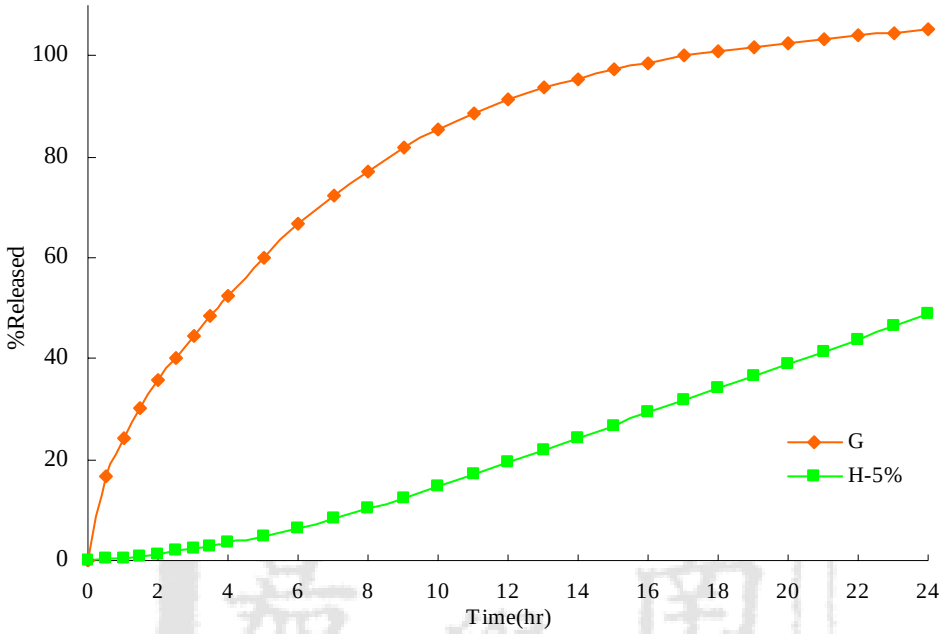
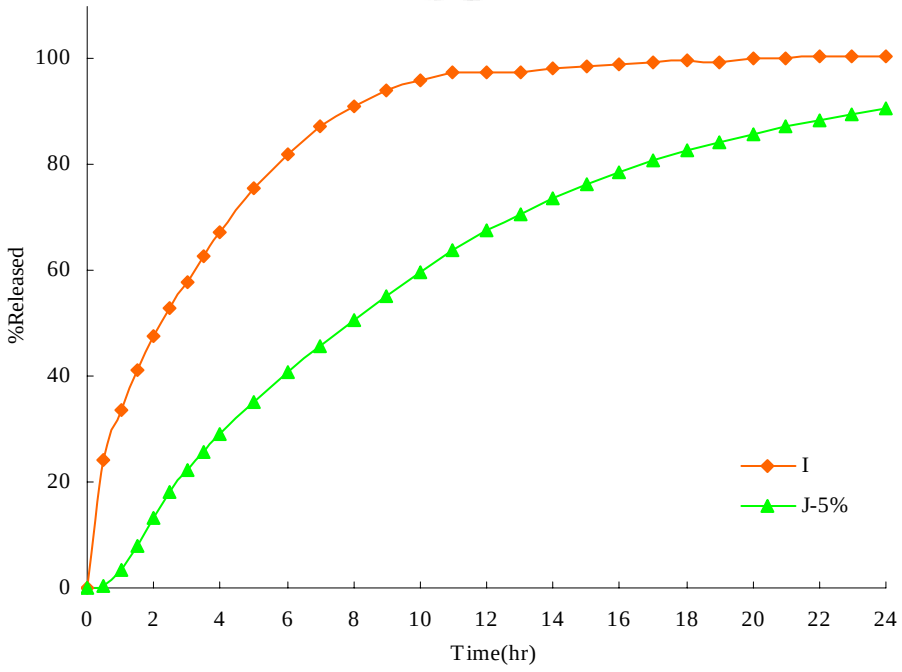


Fig 2: Release profiles of formulation I and J

Formulation I: 30% EC

Formulation J: 30% EC+5% coating



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Morphine 前驅藥凝膠劑型經皮吸收之研究

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計畫類別：整合型計畫

計畫編號：CNPH94-04

執行期間：94 年　1 月　01 日至　94 年　12 月 31 日

計畫主持人：韓若怡助理教授

共同主持人：宋國峻教授

計畫參與人員：

執行單位：嘉南藥理科技大學藥學系

中　華　民　國　95　年　1　月　31 日

嘉南藥理科技大學專題研究計畫成果報告

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主持人：韓若怡　嘉南藥理科技大學藥學系

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體內經皮吸收之依據。.

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, 10μm, 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

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2. S.T. Ho eta 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

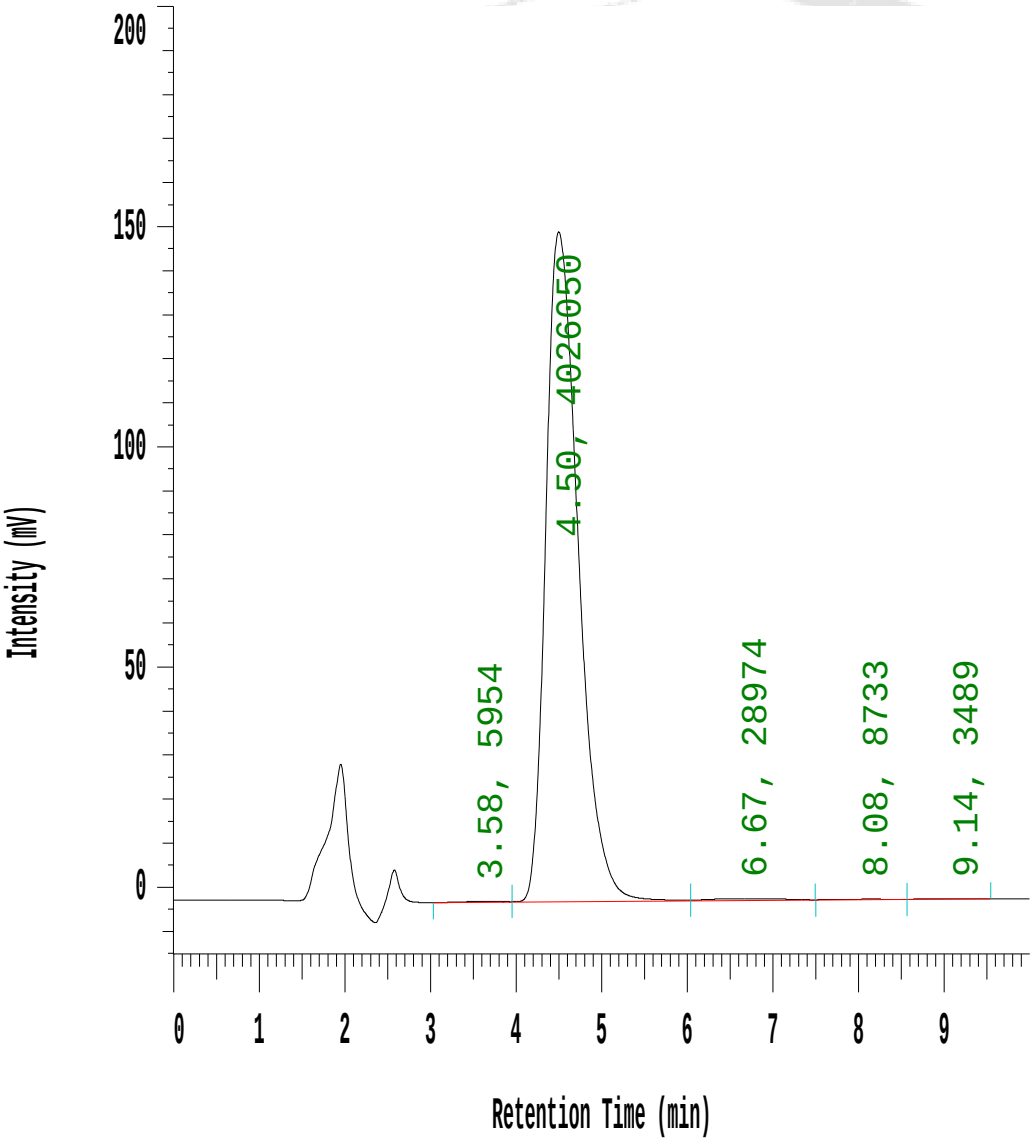
flow rate: 1ml/min

stock so'ln: 1mg/ml

soluble solvent: methanol

injection conc.: 100ug/ml

retention time: 4.5min ; AUC: 4026050



- Morphine propinate

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

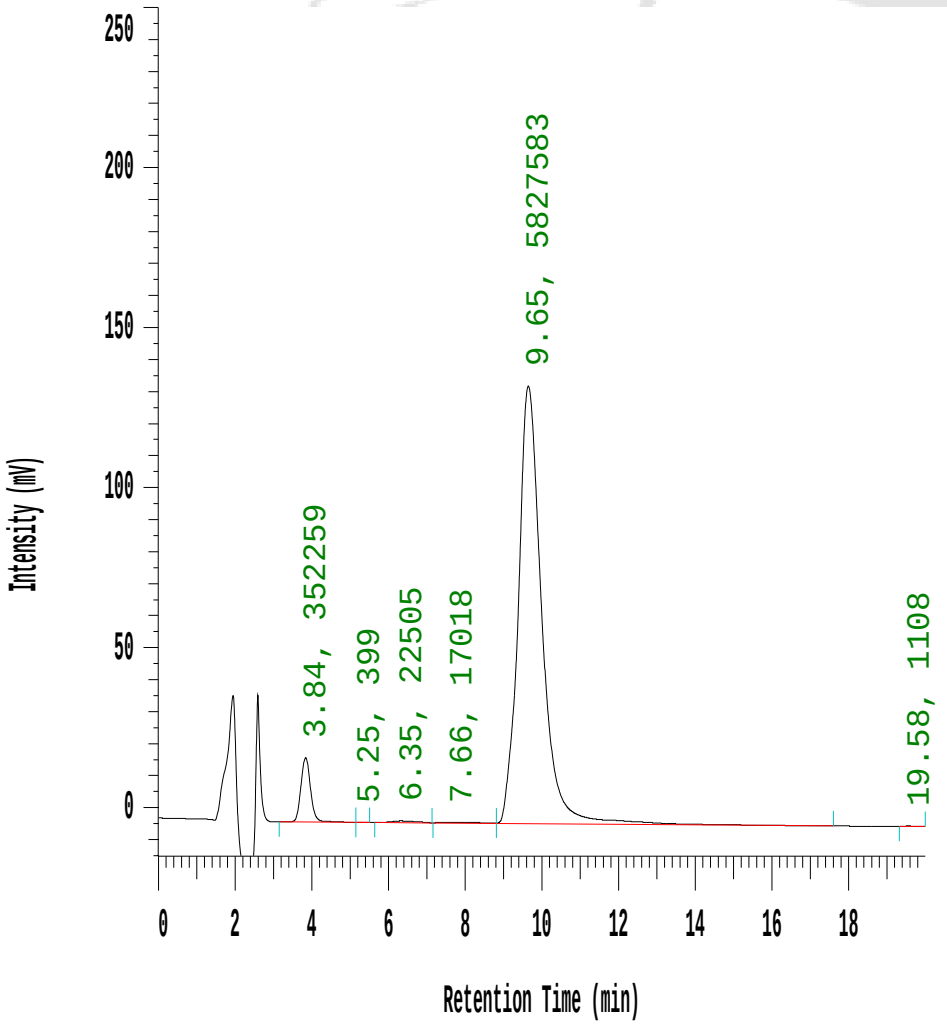
flow rate: 1ml/min

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

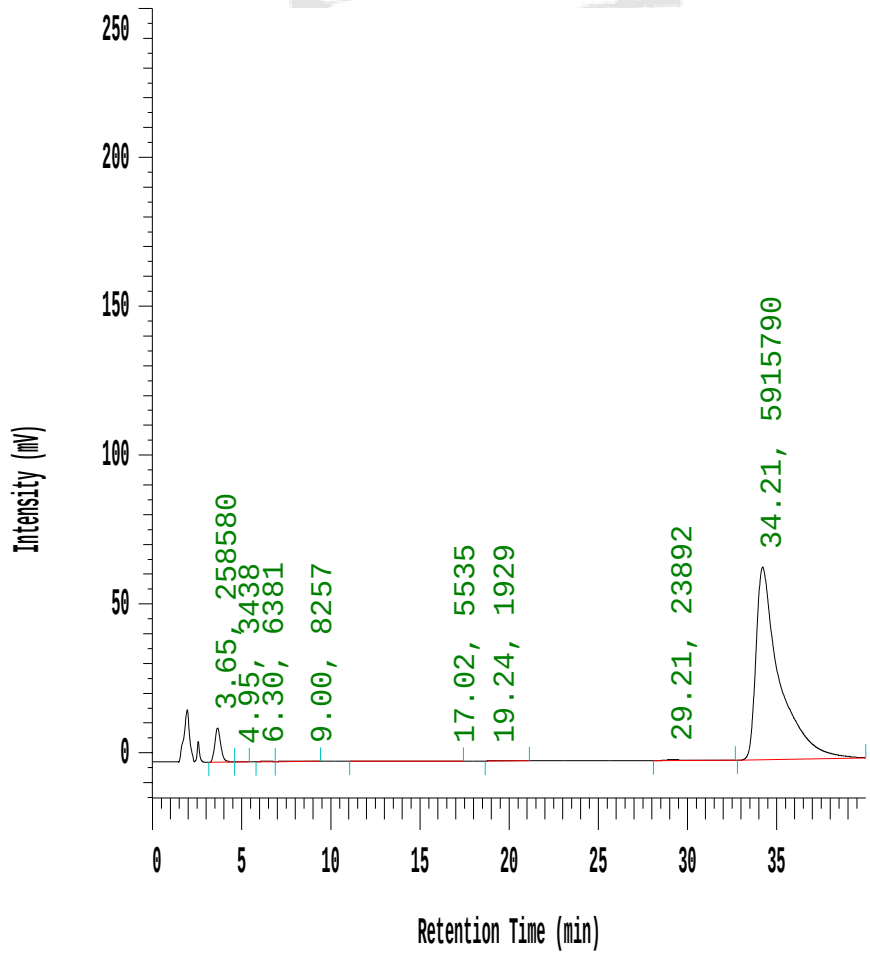
flow rate: 1ml/min

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

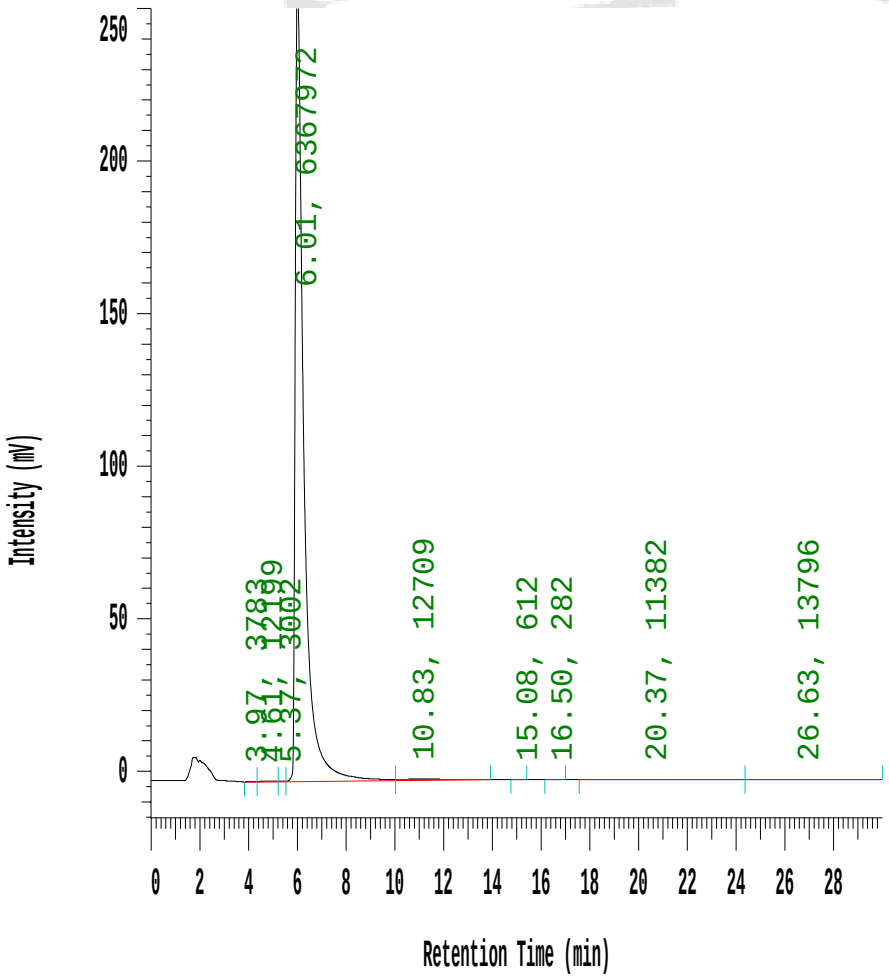
flow rate: 1ml/min

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

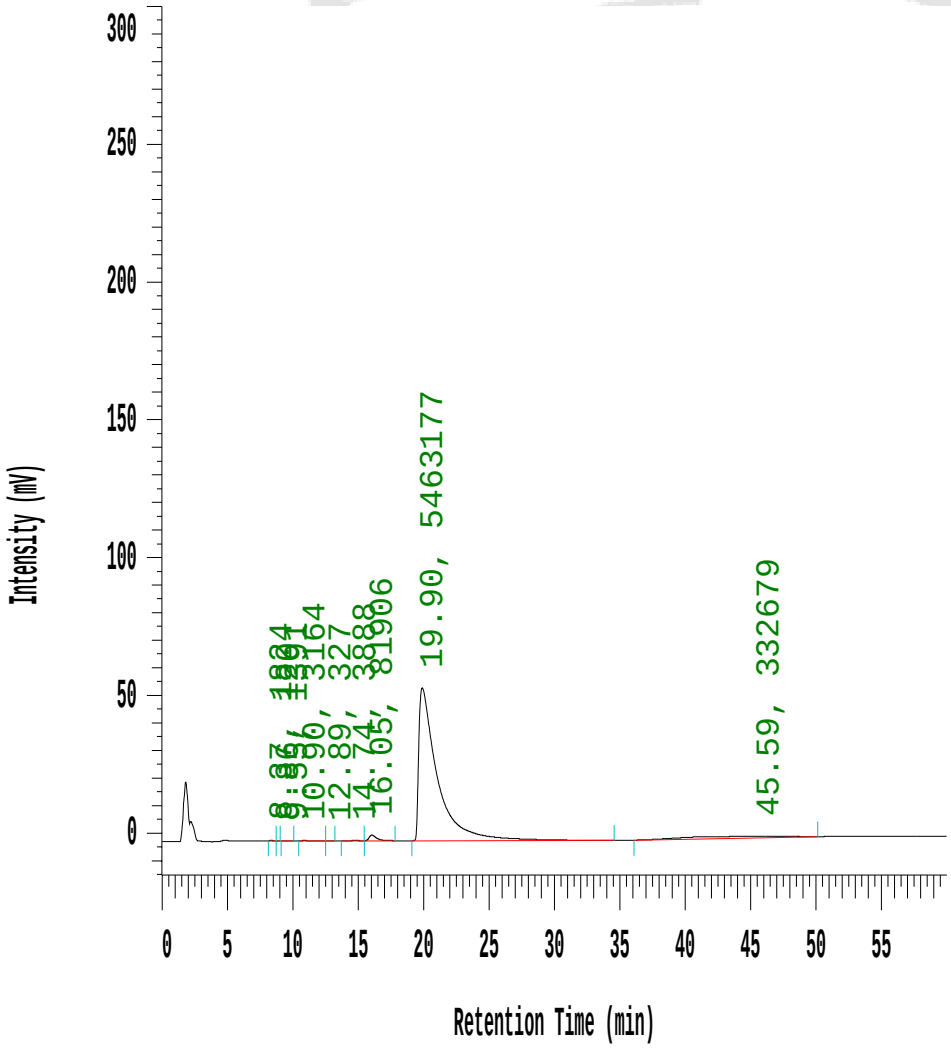
flow rate: 1ml/min

stock so'ln: 1mg/ml

soluble solvent: methanol

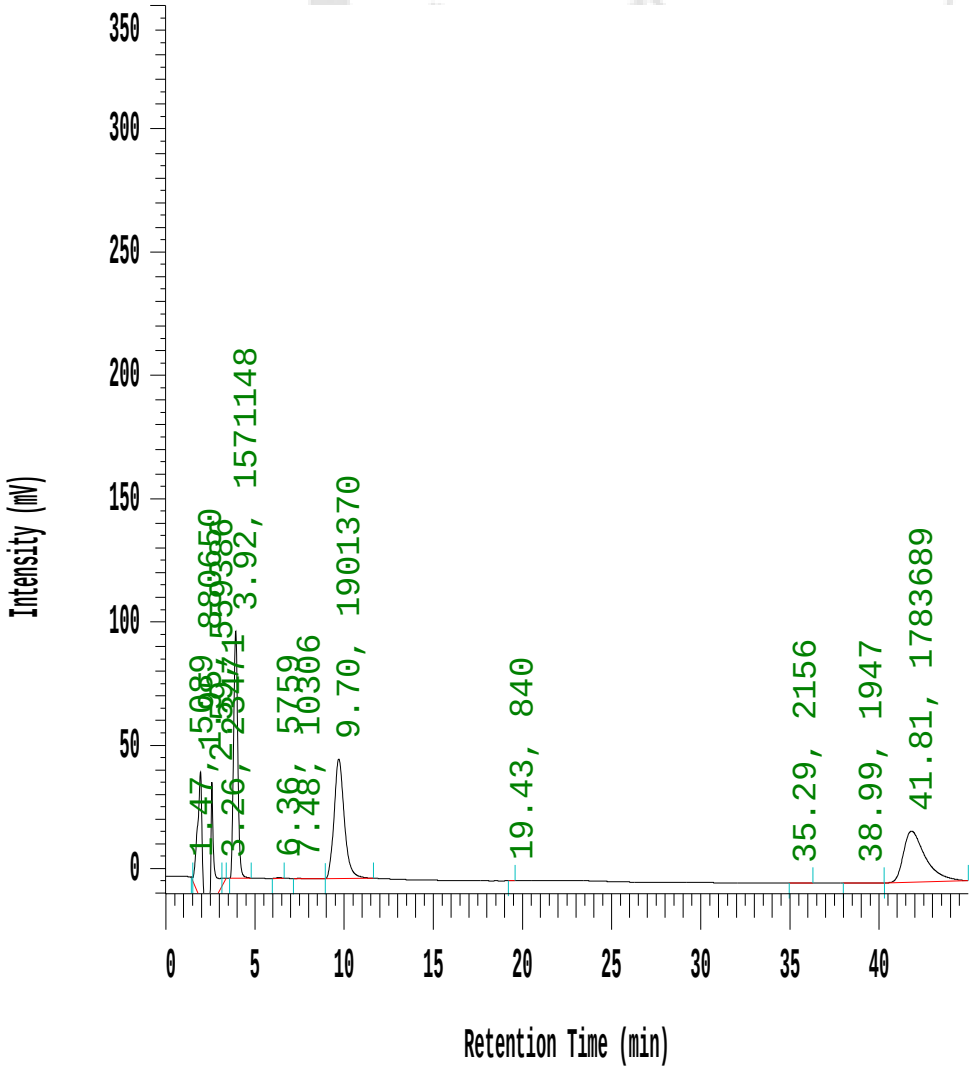
injection conc.: 100ug/ml

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



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