行政院國家科學委員會專題研究計畫 成果報告

新型 morphine 前驅藥相轉變控釋劑型之研究
研究成果報告(精簡版)

計 畫 類 別 ：個別型
計 畫 編 號 ：NSC 95-2320-B-041-004-
執 行 期 間 ：95 年 08 月 01 日至 96 年 07 月 31 日
執 行 單 位 ：嘉南藥理科技大學藥物科技研究所

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行政院國家科學委員會補助專題研究計畫

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執行單位：嘉南藥理科技大學藥物科技研究所

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Abstract

The major purpose of this project is to deliver morphine and its novel morphine prodrug using phase change systems. By utilizing the phase change systems, the phase transition from solution to gel or from solution to solid may occur and drug release can be sustained by the formation of gel or solid. The project is a continuous effort of our laboratory in exploring appropriate dosage forms on newly synthesized narcotic prodrugs for pain management. The obtained information from this study may contribute to the design of novel dosage forms for various narcotics.

The phase change system used in the present study is carbopol/pluronic polymer solution system. Its rheological behavior in 0.3% carbopol/14%pluronic concentration ratio was characterized. The shear stress at pH 7.4, 37^0C (physiological condition) obtained were much higher than those at pH 4.0, 25^0C medium (non-physiological condition), suggesting the occurrence of phase transition between these two condition for the polymer system studied.

Morphine propionate, an ester prodrug of morphine was synthesized and its release from phase change system was evaluated. A retarding effect was observed by incorporating morphine and its prodrug in the system. Due to higher lipophilicity of morphine propionate, drug release was slower comparing that to morphine.

Key words: Phase-transition, morphine, prodrug, controlled release

中文摘要

本計畫主要目的乃是利用具相轉變特性之高分子載體來控制輸送 morphine 及新合成之 morphine 前驅藥。希望藉由此些具相轉變性質之載體使製劑在施用藥品時為溶液態，而在注射入生體環境下可轉變成凝膠態或固態之特性以便利此一系列藥物之輸送，並有控制釋放速率之效果。此研究乃是延續近年來計畫主持人對相轉變系統及 narcotics 類前驅藥劑型之一系列研究。經由本計畫之執行，將對 narcotics 類止痛藥品新型製劑之研究探討及開發均將有所助益。

本計畫所使用之相轉變高分子系統乃是利用 carbopol/pluronic 高分子溶液系統。所使用之模式藥物為 morphine 及 morphine propionate。結果顯示 0.3% carbopol / 14% pluronic 高分子系統在 pH4.0 及 25℃下其黏度值顯著小於在 pH7.4 及 37℃下，顯示此高分子系統由非生理條件下至生理條件下具相轉變特性。由藥物釋放實驗中顯示 morphine 及 morphine propionate 於模擬生理條件(pH7.4，37℃)下由高分子系統中釋出可因此高分子系統在模擬生理條件下產生由溶液至凝膠之相轉變而具有延遲釋放之效果。

關鍵詞：相轉變，嗎啡，前驅藥，控制釋放

Introduction

The major purpose of this project is to deliver morphine and its novel morphine prodrug using phase change system. By utilizing the phase change systems, the in situ phase transition from solution to gel or from solution to solid may occur and drug release can be sustained by the formation of gel or solid. The project is a continuous effort of our laboratory in exploring appropriate dosage forms on newly synthesized narcotic prodrugs for pain management. The obtained information from this study may contribute to the design of novel dosage forms for various narcotics.

The phase change system used in the present study is carbopol/pluronic solution system. Its rheological behavior in fix carbopol/pluronic concentration ratio was characterized. Morphine propionate, an ester prodrug of morphine was synthesized and its release from phase change system was evaluated.

Materials and methods

Preparation of prodrug

Ten grams of morphine HCl was added in 300 mL of flask. Added 141 mL of Dichloromethane into the flask under Ar gas. Add 8.62 mL of TEA into the flask and then stir continuously. Slowly dropped approximately 7 mL of acid chloride and stir continuously for overnight. The acyl chlorides added were propionyl chloride.

In the purification step, first to dry the DCM using rotorvapor, then added appropriate amount of ethylacetate into the separation funnel. Use 5% of NaHCO3 to wash two to three times and then wash with MilliQ water for two to three times, collect the organic layer. Use rotorvapor to dry the ethyl acetate. The resultant compound was then added into silica gel column and for further purification. The solvent system for eluting the prodrug incluing NH4OH, methanol and dichlomethane. The eluting solution was then dried with vacuum pump.

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 (35/65) was used as the mobile phase. The flow rate and UV wavelength were 1 ml/min and 212 nm, respectively. By using the chromatographic condition, the retention times of morphine and morphine propionate can be obtained approximately at 4.50 min and 9.65 min, respectively.

Rheological Studies

The rheological studies were carried out on a cone (4°) and plate geometry viscometer (Brookfield RVCP DV-III). The viscosity

and shear stress of the sample solutions were measured at various shear rates at physiological (pH 7.4, 37^0C) and non-physiological conditions (pH 4.0, 25^0C) , respectively.

In vitro Release Studies

The *in vitro* drug release from various polymer solutions was first carried out by filling drug-containing polymer solution into small, circular plastic containers and placing each container in a 1000 mL beaker. The beaker was then filled with 1000 mL pH 7.4 buffer and placed in a circulating water bath equipped with stirring rods to stir the release medium. The temperature and stirring rate were maintained at 37℃ and 75 rpm, respectively. Aliquots (1mL) were withdrawn from the release mediums at each sampling time. The samples were subjected to HPLC analysis to determine drug concentrations.

Results and discussion

Figure 1 shows the stress versus shear rate flow curves of 0.3%carbopol/ 14%pluronic solution systems measured under pH 4.0, 25^0C (non-physiological condition) and pH 7.4, 37^0C (physiological condition). The flow curve of 0.3% carbopol/14%pluronic solution system shows a Newtonian flow behavior under pH 4.0, 25^0C medium, whereas a non-Newtonian flow behavior (pseudoplastic flow behavior) was observed for the polymer system under pH 7.4, 37^0C medium. The shear stress at pH 7.4, 37^0C (physiological condition) were much higher than those at pH 4.0, 25^0C medium (non-physiological condition), suggesting the occurrence of phase transition between these two condition for the polymer system studied.

Figure 2 shows morphine release from aqueous buffer solution and from phase change polymer solution into pH 7.4, 37^0C medium. Without incorporated in polymer solution, morphine released very fast and reached plateau immediately. The phase change system was able to retard morphine release, indicating thatthe system can be used to prolong the release time of morphine. Figure 3 compares the release profiles of morphine and its propionate produg from phase change systems. Both profiles indicate drug release was retarded by the polymer system. Due to higher lipophilicity of morphine propionate, drug release was slower comparing to morphine release.

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Assessment of progress

The results indicate that a phase change system is successful developed to prolong drug release under physiological condition. More time will be spent to study rheological and drug release behaviors of PLGA/benzyl benzoate/benzyl alcohol phase change system.

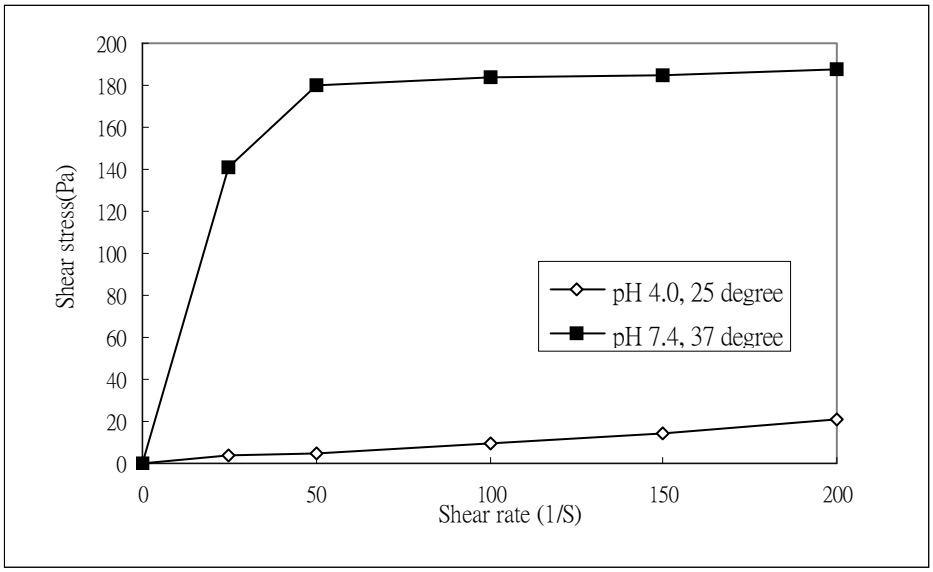

Figure 1

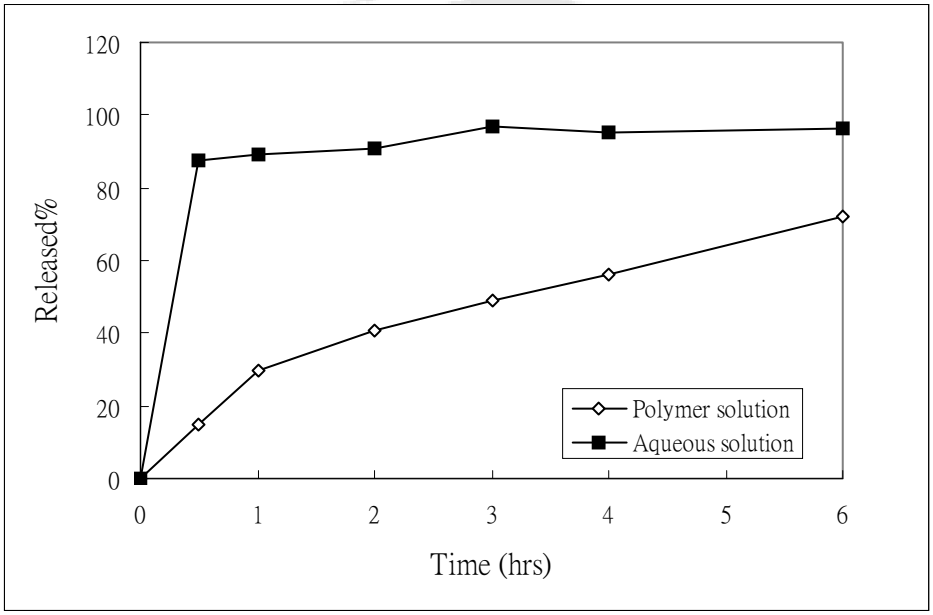

Figure 2

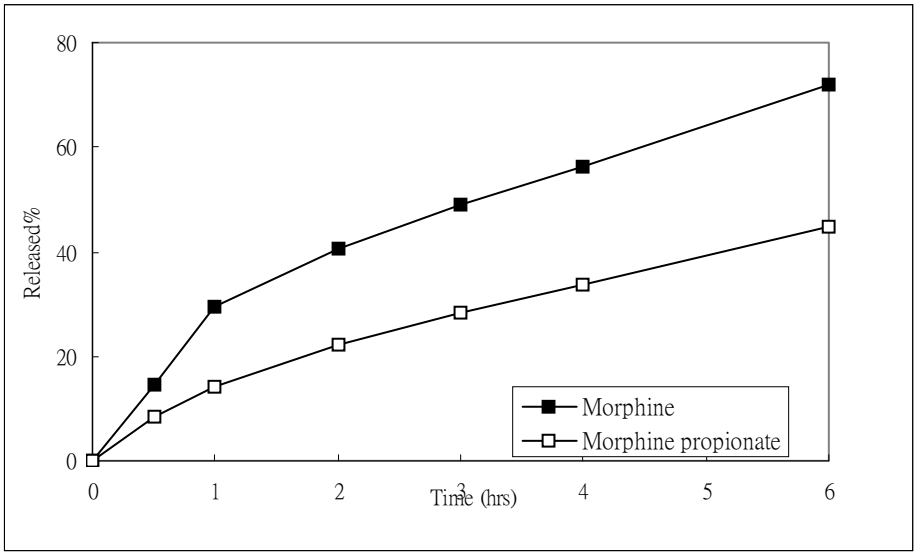

Figure 3