行政院國家科學委員會專題研究計畫成果報告

Nalbuphine 前驅藥微球粒劑型生體外及生體內的評估研究

In-Vitro and In-Vivo Evaluation of Biodegradable Microsphere for Nalbuphine Prodrug Controlled Delivery

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摘要:

本計畫主要目的在於開發一系列止痛藥物 Nalbuphine 前驅藥之 poly(lactide/glycolide)長效微球粒劑型及其生體外和生體內藥物釋放之評估研究。於生體外之藥物釋放實驗顯示不同比例之 lactide/glycolide 高分子及不同親水性之前驅藥均對藥物釋放動力學有所影響。於體內之藥物動力學研究則顯示當 Nalbuphine 前驅藥親水性增加時其釋放速率將較快並較完全。對此系列 Nalbuphine 前驅藥而言，其微球粒製劑之生體外及生體內藥物釋放具有很好的相關性。

關鍵詞：Nalbuphine 前驅藥、微球粒劑型、藥物釋放

Abstract

The major purpose of this project is to develop and in vitro- in vivo evaluation of poly(lactide/glycolide) based microsphere for nalbuphine prodrug controlled delivery .The in vitro release studies showed that the different poly(lactide/glycolide) ratios and the different hydrophilic prodrugs both affect the kinetics of drug release. The in vivo release studies showed that the release of more hydrophilic prodrug is faster and more complete. A good correlation can be observed from the in vivo and in vitro release studies.

Keywords : Nalbuphine prodrug, Microsphere, Drug release

Introduction

Nalbuphine is a relatively new morphine-like drug with partial agonist activity at the κ-opiate receptor and antagonist activity at the μ-opiate receptor[1,2].As an analgesic agent, it is almost as potent as morphine and has been widely used in the treatment of acute and chronic pain[1-3]. Due to its short elimination half-life and low oral bioavailability, frequent injections are 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, nalbupine enathate and nalbuphine decanoate have been synthesized[4]. Various nalbuphine prodrug formuiations such as biodegradable implant, and oily suspension and microsphere have also been developed [4,5].

In the present study, two major goals are to be achieved. The first goal is

to develop a series of nalbuphine prodrug loaded microsphere based on poly(lactide/glycolide).The second goal is to evaluate the kinetics of drug release from those microspheres both in vitro and in vivo. The information obtained can thus be utilized to develop the optimum poly(lactide/glycolide) microspheres for nalbuphine prodrug controlled delivery.

Results and discussion

Preparation of drug loaded microsphere

Nalbuphine prodrug-loaded microspheres were prepared by the wellkown emulsion-solvent evaporation process. The 2% drug and 2% polymer were dissolved in CH_2Cl_2 and drop in aqueous phase contain 7mM SLS and 1M NaCl. The microdroplets were then solidified by the slow evaporation of the organic solvent with ice bath.

The nalbuphine prodrugs used in the present study were nalbuphine enathate and nalbuphine decanoate . The poly(lactide/glycolide) used in the study were poly(lactide/glycolide) 75/25 and 50/50. Three various types microspheres were used in this study: nalbuphine enathate loaded microsphere (75/25), nalbuphine enathate loaded microsphere (50/50) and nalbuphine deanoate loaded microsphere(50/50). Under the examination of SEM, these microspheres looked spherical and fairly uniform in size. The diameter of the microspheres was approximately 25 μ m. The drug loading precentages were 32.7% ,31.38%, 25.05%, respectively.

In vitro release study

The influence of prodrug hydrophilicity and copolymer composition on drug release from microspheres were evaluated using various nalbuphine prodrugs and polymers with various lactide/glycolide ratios. The nalbuphine prodrugs used in the present study were nalbuphine enathate and nalbuphine decanoate. The polymer used in the study were poly(lactide/glycolide) 75/25 and 50/50.

Figure 1 shows the in vitro release profiles of the different poly(lactide/glycolide) ratio microspheres loaded with nalbuphine enathate. According to Figure 1, a greater drug release was observed for the more hydrophilic poly(lactide/glycolide) i.e., copolymer with lower lactide/glycolide ratio. For example, after 96 hours, around 49.3%, 66.02% of drug have released from the microsphere with poly(lactide/glycolide) 75/25 and 50/50, respectively.

Figure 2 shows in vitro release profiles for the poly(lactide/glycolide) microspheres (50/50) loaded with various nalbuphine prodrugs. According to Figure 2, a greater drug release was observed for microspheres load with more hydrophilic prodrug, i.e., prodrug with higher aqueous solubility. After 96 hours, around 66.02%, 26.37% of drug have released from the microsphere loaded with nalbuphine enathate, nalbuphine decanoate, respectively.

In vivo release study

The effect of prodrug hydrophilicity on in vivo drug release from microspheres were examined using nalbuphine enathate, nalbuphine decanoate. The copolymer used was poly(lactide/glycolide) (50/50).

After intravenous administration of nalbuphine hydrochloride in rabbits, the plasma nalbuphine concentration profiles were shown in Figure 3. The application of pharmacokinetic model on drug concentration profiles of the three rabbits revealed that nalbuphine followed a two-compartment model with one distribution phase and one elimination phase. Table 1 shows that the elimination half life, elimination constant(k) and AUC were 83.8± 18.4 minutes ,8.5± 1.84 x 10^{-3}, 4101 ± 429(ng/ml)*hr, respectively. (n=3,± s.d.)

After subcutaneous aministration of nalbuphine enathate microspheres in rabbits, the highest plasma nalbuphine concentration (117.5± 25.3 ng/ml) (n=3,± s.d.) were observed at 12 hours post administration, then the plasma concentrations decreased rapidly afterwards on the first day (24 hours) and slowly decreased until day 4 (96 hours) (Figure 4). The AUC and absolute bioavailability were calculated to be 2602± 133 (ng/ml)*hr and 63.4± 3.2 %, respectively.(n=3,± s.d.) (Table 2).

After subcutaneous administration of nalbuphine decanoate microsphere in rabbits, the highest plasma concentrations (44.5± 33 ng/ml) (n=3,± s.d.) were measured at 1 hours post administration, the concentration then slowly decreased until day 4 (96 h)(Figure 4). The AUC and absolute bioavailability were calculated to be 1669 ± 1152(ng/ml)*hr and 40.7 ± 28 %, respectively.(n=3,± s.d.) (Table 3).

The in vitro nalbuphine prodrug release profiles suggest that the nalbuphine enathate may release faster and more complete in vivo. Indeed, Figure 4 and Table 2-3 demonstrate that a significant higher AUC and bioavailability were obtained for the release of nalbuphine enathate in vivo. The results clear demonstrate that a good correlation can be observed between the in vitro and in vivo nalbuphine prodrug release from poly(lactide/glycolide) based microsperes.

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(Table 1). The pharmacokinetics of nalbuphine hydrochloride after intravenous administration in rabbits(n=3).

N	K	T ½(minutes)	AUC (ng/ml)*hr
1	6.5×10^{-3}	106.1	4195
2	0.011	60.98	4573
3	8.2×10^{-3}	84.46	3538
Mean± S.D.	$8.5\pm 1.84 \times 10^{-3}$	83.8± 1.84	4101± 429

(Table 2). The pharmacokinetics of nalbuphine after subcutaneous administration of nalbuphine enathate loaded microsphere in rabbits(n=3).

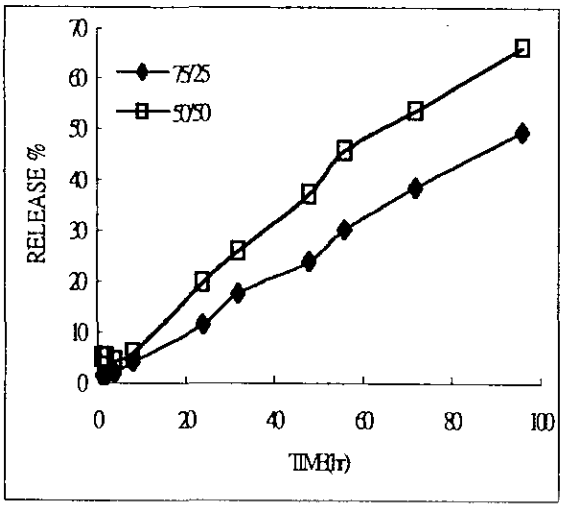
N	AUC (ng/ml)*hr	Absolute bioavailability (F)
1	2746	66.9%
2	2634	64.2%
3	2425	59.1%
Mean± S.D.	2602± 133	63.4± 3.2 %

(Table 3). The pharmacokinetics of nalbuphine after subcutaneous administration of nalbuphine decanoate loaded microsphere in rabbits(n=3).

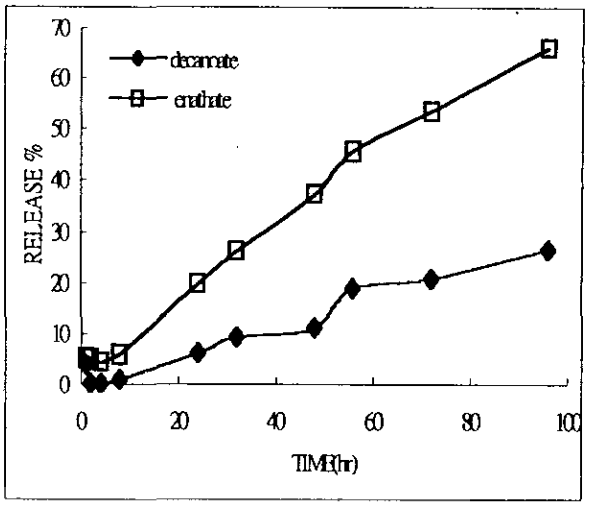
N	AUC (ng/ml)*hr	Absolute bioavailability (F)
1	3155	76.9%
2	347	8.46%
3	1506	36.7%
Mean± S.D.	1669± 1152	40.7± 28 %

Comments

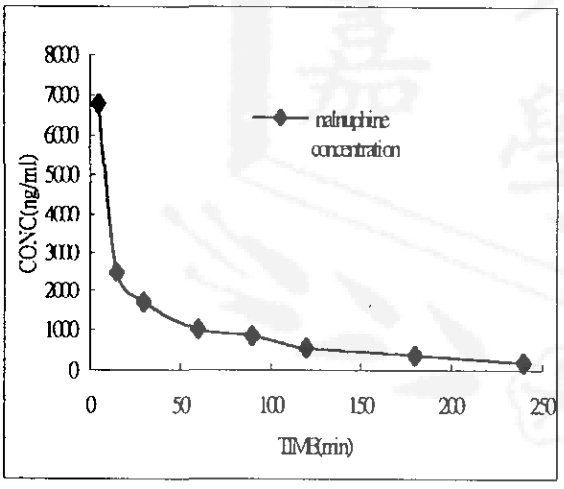
Most of the content in this study are in accordance with the proposal , although two prodrugs were not incorporated due to the supply of drug and evolution of this project. This study has been written in a paper format and prepared to be sent for publication in a scientific journal.



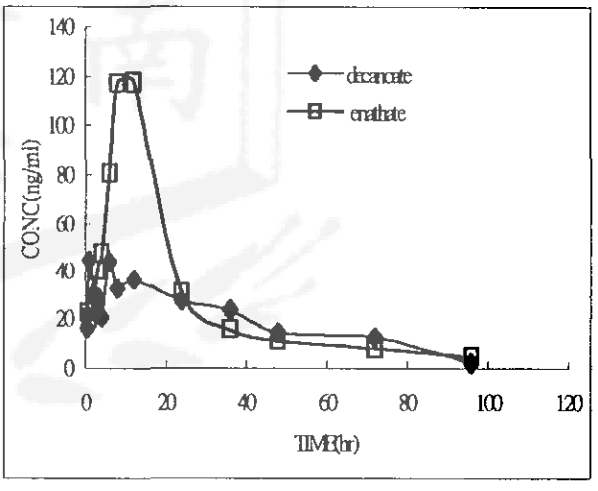
(Figure 1). The in vitro release profiles for the poly(lactide/glycolide) 75/25 and 50/50 microsphere loaded with nalbuphine enathate. (n=3).



(Figure 2). The in vitro release profiles for the poly(lactide/glycolide) 50/50 microsphere loaded with nalbuphine enathate and nalbuphine decanoate.(n=3).



(Figure 3). The nalbuphine concentration-time profile after intravenous administration of nalbuphine hydrochloride in rabbits. (n=3).



(Figure 4). The plasma concentration-time profiles of nalbuphine after subcutaneous administration of nalbuphine enathate and nalbuphine decanoate. loaded microsphere in rabbits. (n=3).