嘉南藥理科技大學專題研究計畫成果報告

減肥藥物之凝膠型耐米微粒藥物輸移系統

Investigation of hydrogel nanoparticles delivery systems for anti-obesity **drug**

計畫編號：CNPH-92-06
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一、中文摘要

本研究採用含無數奈米微粒之懸液來改善難溶性藥物 phenylpropanolamine (PPA)之溶解度。奈米微粒包覆 PPA HCl 是以固態凝膠研磨技術來完成，負載 PPA HCl 之親水膠體奈米微粒以雷射粒徑分析儀與掃瞄式電子顯微鏡來檢測其粒子大小，懸液之流體特性是以 Cone and Plate 黏度計來評估，此外，藥物與膠體聚合物間之交互作用則是以熱卡式分析儀來檢視。結果顯示，以固態凝膠研磨技術所獲得的 PPA HCl 親水膠體奈米微粒其平均粒徑是介於 40 到 800 奈米之間，基於體外藥物釋離圖形，PPA HCl 於最初突釋 40%至 50%後，其釋離可維持 24 小時的持續釋放，而且，當負載藥物奈米微粒之懸液其酸鹼值上揚超過 3 時，也未有不溶性藥物明確的凝結物生成；經由熱分析的觀察得知，不論是製造或是凍晶乾燥粉體加水還原之過程，各組成分間均未有明顯的化學交互作用發生。綜合上述之實驗結果，將有助於協助發展其他難溶性藥物之輸移系統。

關鍵詞：phenylpropanolamine，水不溶，奈米微粒，親水膠體

Abstract

Suspensions composed of numberless nanoparticles were used for improved solubilization of phenylpropanolamine (PPA). Nanoparticles encapsulating PPA HCl were prepared using the solid jelly pulverization technique. The size of the PPA HCl - hydrogel nanoparticles was assessed using a LS particle size analyzer and scanning electron microscopy（SEM）. The rheological properties of suspensions are characterized by Cone and Plate Viscometer. In addition, any drug-polymer interactions were assessed using a differential scanning calorimeter (DSC). The results show that solid jelly pulverization technique yielded PPA HCl hydrogel nanoparticles with a mean diameter of 40 nm to 800 nm. Based on our release profiles, following an initial burst release of 40% to 50% PPA HCl, the release was sustained over the 24-hours

study period. Moreover, while pH value of PPA HCl – loaded nanoparticles suspension increased over 3, no significant agglomeration of insoluble drug were grown. The DSC measurements indicated that the chemical interaction does not occur among the components during manufacturing processes and reconstituting lyophilized powder. The above results will be helpful to possible development of the other water-insoluble drug delivery systems.

Keywords: Phenylpropanolamine, Water-insoluble, Nanoparticles, Hydrogel

二、Introduction

Obesity is rapidly becoming a worldwide epidemic, with significant consequences in terms of clinical burden and economic costs in treating its complications, [1-3] so effective new drugs used for weight reduction are urgently needed. Phenylpropanolamine （PPA）[4], a synthetic phenylisopropanolamine sympathomimetic agent and an over-the-counter drug, is approved for treating obesity [5]. PPA is a weak base. It had appreciable aqueous solubility only at pH values less than 2, usually administered as the HCl salt. The dissolution of PPA HCl at pH values greater than 3 was practically zero. The drug instantaneously formed oily globules. Thus, bioavailability of PPA is dependent upon pH and particle size, and problems of generic inequivalence have therefore arisen.

To avoid the particle size increased due to agglomeration of insoluble drug, a number of studies have provided efficient dosage forms and methods, such as inclusion complexes [6,7], solid dispersion [8] and micelles [9] etc.

Recently, we found that hydrogel nanoparticles could be carried out by solid jelly pulverization technique. We have developed drug-loaded nanoparticles to minimize tissue irritation which was caused by free drug. In the work, we attempt to investigate hydrogel nanoparticles as a novel delivery system for improved solubilization of water-insoluble drugs using PPA as a model drug.

三、Results and discussion

PPA is a water-insoluble drug and a significant amount of the drug formed oily globules at pH values greater than 3. In an attempt to minimize the drug precipitation and aggregation during the pH value variation, the dissolved PPA was

encapsulated into hydrogel nanoparticles. Scanning electron microscopy analysis shows in Fig. 1, it is possible to obtain spherically shaped and nonaggregated nanoparticles. At a drug : jelly weight ratio of 1:10000 yielded a mean particle size ranging from 40 nm to 800 nm is shown in Fig. 2. The efficiency of encapsulation was around 40-50% and did not change when the water was replaced by phosphate buffer（ pH=3 ） solution in preparing jelly. The rheological properties of suspensions including a high concentration of small hydrogel nanoparticles are characterized as shown in Fig 3. The viscosity increases with increase in shear rate and time. The time-dependent behaviour of ointments is referred to as dilatant flow and exhibit shear thickening. The *in vitro* release of PPA HCl from the hydrogel nanoparticles was carried out in the 15-ml vertical Franz diffusion assembly and shown in Fig. 4. Based on our release profiles and Higuchi plots, it appears that PPA HCl is trapped in the hydrogel matrix. Following an initial burst release of 40% to 50% PPA HCl, the release was sustained over the 24-hours study period. Moreover, while pH value of PPA HCl – loaded nanoparticles suspension increased over 3, no significant agglomeration of insoluble drug were grown.

Differential scanning calorimeter (DSC) was used to establish physical-chemical properties of hydrogel nanoparticles is shown in Fig. 5. The DSC measurements indicated that the chemical interaction does not occur among the components during manufacturing processes and reconstituting lyophilized powder.

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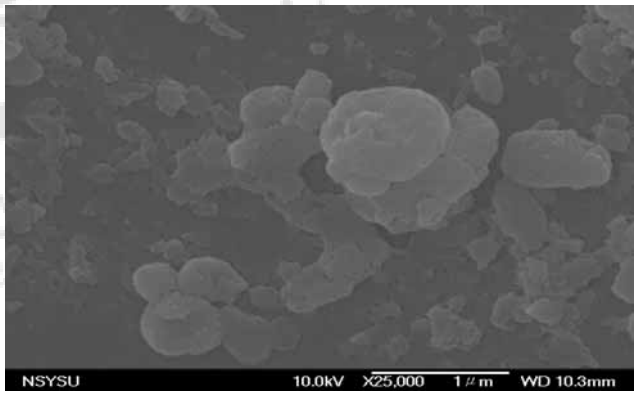

Fig. 1. SEM photographs of PPA HCl – hydrogel nanoparticles

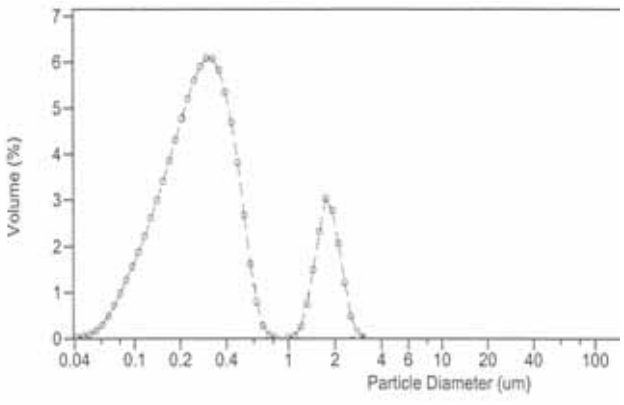

Fig. 2. Particle distribution of PPA HCl – hydrogel nanoparticles were prepared by solid jelly pulverization technique.

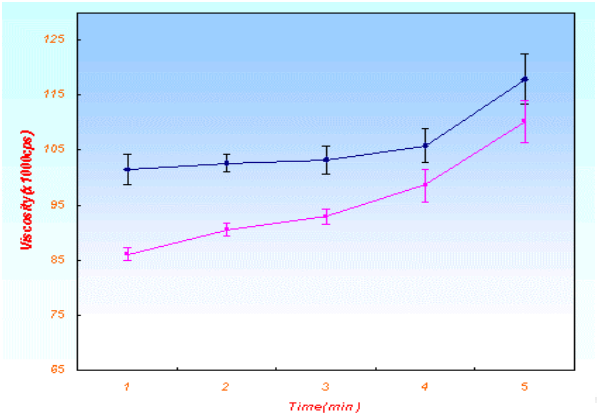

Fig. 3. Rheological properties of suspensions containing PPA HCl – hydrogel nanoparticles (—▲—: formulae No.3; —■—: formulae No.1)

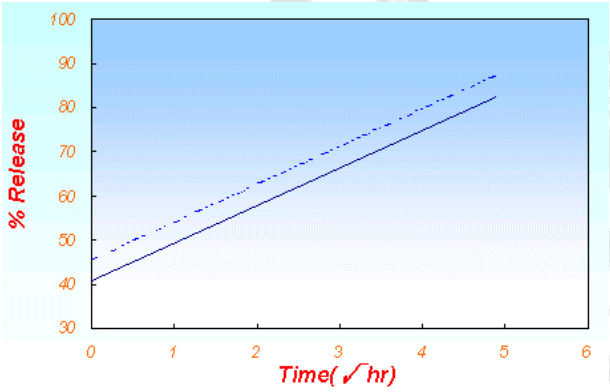

Fig. 4. Release profile of PPA HCl from hydrogel nanoparticles. (------: formulae No.1; ——: formulae No.3)

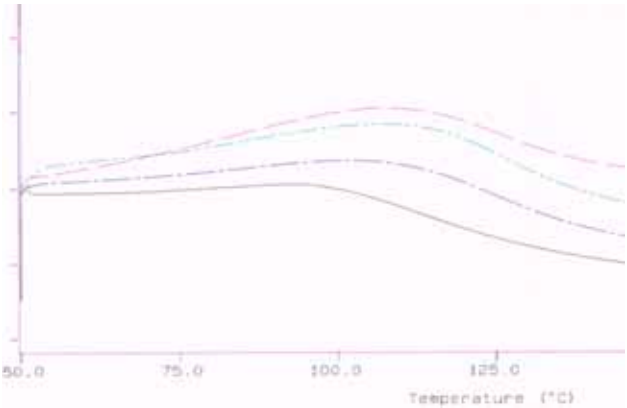

Fig. 5. DSC thermograms of PPA HCl - hydrogel nanoparticles. (---) formulae No.1; (-• •-) agar jelly alone and prepared with phosphate buffer; (-•-) formulae No.3; (——) agar jelly alone and prepared with water

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