利用羥乙基纖維素和幾丁聚醣開發 Losartan 之胃滯留藥物傳遞系統

Development of Gastroretentive Drug Delivery System for Losartan Based on Hydroxyethylcellulose and Chitosan

中文摘要

本實驗目的爲開發新穎的胃滯留藥物傳遞系統，主要是以具有膨脹特性的聚合物羥乙基纖維素和不同黏度之幾丁聚醣以不同比例混合，再依不同的打錠壓力製錠，評估錠片於體外模擬胃液及去離子水中的膨脹特性和懸浮特性(懸浮作用延遲時間和懸浮作用持續時間)。爲進一步縮短達到懸浮的作用所需要的時間，加入能產生氣體的碳酸氫鈉來評估其增進懸浮能力的效果。最後將模式藥物 Losartan 與設計之處方混合，進行體外溶離試驗，探討整體的胃滯留與藥物釋放特性之影響。

當打錠壓力爲 0.25 噸時，錠片能於極短時間內懸浮至模擬胃液上方；而打錠壓力爲 0.5 噸時，大部分處方皆可於 15 分鐘內達到懸浮作用；但打錠壓力爲 1 噸時，錠片皆無法產生懸浮的效果。因此確認 0.5 噸的打錠壓力在考量懸浮特性而言是最爲恰當。

實驗結果顯示，隨著 chitosan 比例增加，懸浮延遲時間越短，而使用低黏度的 chitosan 時，達到懸浮作用所需要的時間也較短。當 HEC 與 chitosan 的混合比例爲 9:1 時，其達到懸浮作用所需的時間及懸浮作用維持時間比其他混合比例時更短。但當 HEC 與 chitosan 的混合比例爲 5:5 時，懸浮延遲時間不但縮短，且懸浮作用維持時間能超過 8 小時以上。而添加 20 公絲和 40 公絲碳酸氫鈉後，可以縮短懸浮作用延遲時間在 1 分鐘內，且使錠片在模擬胃液中懸浮 16 到 24 小時以上延長胃滯留時間。

羥乙基纖維素和不同黏度之幾丁聚醣混合後在模擬胃液中經 6 到 12 小時後，錠片可達到直徑大於 2 公分而具有胃滯留效果，在去離子水中有些處方雖然也能產生膨脹，但效果並不佳，其膨脹能力隨幾丁聚醣所佔比例增加而下降，當羥乙基纖維素和低黏度幾丁聚醣混合比例爲 3:7 時，錠片甚至會快速崩散。

在體外溶離試驗結果顯示，當羥乙基纖維素和幾丁聚醣之混合比率爲 5:5 時，錠片在模擬胃液中可以延緩模式藥物 Lorsartan 之釋放。

而以 HEC 250HHX 和 Chitosan 混合比率爲 5:5 之膨脹基質適合做爲胃滯留劑型之配方，且具有控釋藥物之效能。

總結，在體外溶離試驗結果顯示，當羥乙基纖維素(HEC 250HHX) 和幾丁聚醣(Chitosan) 之混合比率爲 5:5 時，錠片膨脹形成的膠體基質具有胃滯留之效果，且具有控釋藥物之效能。在模擬胃液中可以延緩模式藥物 Lorsartan 之釋放。

在進行交聯反應（crosslink reaction）的部分雖然進行交聯反應後幾丁聚醣-羥乙基纖維素親水性凝膠在模擬胃液中能產生膨脹，但是卻無法控制藥物的釋放。

英文摘要

The aim of this study was to develop a novel gastroretentive drug delivery system (GRDDS) for administering Losartan. Swellable and floatable GRDDS tablets combining hydroxyethylcellulose 250HHX (HEC 250HHX) and Chitosan of different viscosity grade were prepared at various compression pressures for evaluating swelling characteristics and floating capacity (floating lag time and floating duration) in simulated gastric fluid (SGF) and de-ionized water (DIW). Then sodium bicarbonate used as a gas-generating agent was incorporated in the tablet to evaluate the potential improvement of floating capacity. Losartan was thus incorporated into optimized formulations for drug dissolution characterization.

Tablets floated in a short time when used 0.25 ton compression pressure. Most of them floated within 15 minute when used 0.5 ton compression pressure. All of them were unable to float when used 1 ton compression pressures. As a result, the optimal compression pressure was 0.5 ton.

Results demonstrate that the floating lag time was declined while the content of chitosan increased. Floating lag time was shorter when used low viscosity chitosan than high viscosity chitosan. When the proportion of HEC 250HHX and Chitosan were 9:1, the floating lag time and floating duration was shorter than other proportion. When the combination of HEC 250HHX and chitosan were 5:5, exhibited shorter floating lag time and the floating duration was longer than 8 hour. Incorporating 20 mg and 40 mg sodium bicarbonate into formulations exhibited a short floating lag time(less than 1 min) and increased floating duration had prolonged GRT for 16 to 24 hour in SGF.

The matrix of HEC 250HHX and Chitosan of different viscosity grade swelled to 2cm after 6 to12 hour immersed in SGF. The diameter of those tablets were larger than 2 cm, result in the gastroretentive effect. Although some formulations swelled in DIW, the swelling ratio was less than that in SGF. The swelling ability was declined while the content of chitosan increased. When the proportion of HEC 250HHX and low viscosity chitosan were 3:7, the tablet disintegrated immediately.

The results of the in vitro dissolution test demonstrate that the combination of HEC 250HHX and chitosan in the ratio of 5:5 exhibited the best swelling capacity, and Losartan sustained release from this matrix.

In conclusion, the developed gastroretentive dosage form composed of HEC and chitosan in the ratio of 5:5 possessed significantly swelling potential for longer gastric retention with sustained drug release characteristics.

Although crosslinked Chitosan-HEC hydrogel swelled in SGF, it was not able to control the drug release.