滲透壓活化膨脹形成釋藥口型藥物傳遞系統之探討

Drug Delivery System by In-Situ Formation of Orifice Via Osmotic Pressure Activated Swelling

中文摘要

本研究目的爲探討滲透壓活化膨脹形成釋藥口型之藥物傳遞系統（drug delivery system by in-situ formation of orifice via osmotic pressure activated swelling）的處方因子對藥物溶離特質之影響性。錠蕊部分由具有滲透壓性物質（osmogent）的無水乳糖（anhydrous lactose）與膨脹型材質的羥丙基甲基纖維素（hydroxypropylmethylcellulose, HPMC）所組成，外面包覆一層以 Pharmacoat 606 塑化而具有半透膜性的乙基纖維素（ethylcellulose）爲滲透壓控釋膜衣，並選擇 doxazosin mesylate 作爲模式藥物。蕊錠是採用直接壓錠的方式製備，而控釋膜衣的包覆是以噴灑方式於傳統的梨型包覆鍋內進行。體外溶離試驗在不同的溶離液（pH 1.2、pH 6.8 緩衝液、蒸餾水以及 NaCl 溶液），以及不同的轉速（75rpm 、100rpm 以及 150rpm ）條件下，比較藥物的釋放特性。並透過臨床人體預試驗觀察此設計於體內的藥動學特質。此外，藉由水份吸收試驗進一步了解藥物的釋放機轉。之後再以動態機械分析儀 (dynamic mechanical analyzer, DMA)以及掃瞄式電子顯微鏡（scanning electron microscopy, SEM）探討不同組成膜衣的機械性質以及結構上的差異。

結果顯示，在此劑型設計中，滲透壓控釋膜衣經過一段延遲時間（lag time）後被內部所產生的滲透壓脹破進而達到藥物之釋放；延遲時間不受溶離液 pH 值以及轉速的影響。延遲時間會隨著包覆程度（coating level）的提升而延長；隨著包覆溶液中水可溶性 Pharmacoat 606 加入 以及水分添加量增加而縮短。延遲時間也會隨著溶液中 NaCl濃度的提升而延長。與體內藥動學試驗結果比較顯示，體外的溶離試驗必須在高轉速和添加 NaCl溶液的條件下，才能反映出在體內的藥物血中濃度變化。水分吸收速率會隨著包覆溶液中水分含量的增加而加快，此外，也會受到錠蕊中不同特性羥丙基甲基纖維素的影響。另外，隨著包覆溶液中 Pharmacoat 606 的增加以及水分含量的提升會使得膜衣機械性質降低且結構上也會較具孔洞性。

英文摘要

The objective of this study was to develop a drug delivery system by in-situ formation of orifice via osmotic pressure activated swelling. This system consisted of a controlling membrane coated tablets containing osmogent and swellable agents. Doxazosin mesylate selected as a model drug were prepared by direct compression with anhydrous lactose and different viscosity grades of hydroxypropyl methylcellulose. Ethylcellulose plasticized by Pharmacoat 606 were applied as the semi-permeable outer coat. Drug release behaviors were investigated by dissolution test using the CHPⅤ apparatusⅡ at rotation speed of 75, 100, and 150rpm in four media of pH 1.2, pH 6.8 buffer, distilled water and NaCl solution.

Pilot studies of in vivo pharmacokinetic were conducted as well for comparison with in vitro results. Water uptake was measured to further elucidate the mechanism of drug release. Mechanical properties and construction of films with varying compositions were observed by dynamic mechanical analyzer and scanning electron microscopy.

The results showed that controlling membrane was ruptured by osmotic pressure to activate drug release with a delay time. The lag time was not influenced by pH value of release medium and rotation speeds. The lag time increased with a higher coating level, but decreased with the addition of hydrophilic pore former, Pharmacoat 606, and water amount in coating solution. The lag time also increased with the higher concentration of NaCl in the medium. The results of dissolution study under higher rotation speeds and NaCl solution were found to correlate well with in vivo performance revealed by those in vivo pilot studies. The rates of water uptake increased with higher water amount in coating solution and would be affected by the characteristics of hydroxypropylmethylcellulose in the core tablets. Addition of Pharmacoat 606 and water amount to the coating solution reduced the mechanical properties of films and increased the porosity in membranes.