口服脈衝式藥物傳遞系統之處方研發與評估

Development and Evaluation of Formulation for Oral Pulsatile Drug Delivery System

中文摘要

本實驗以開發單室錠劑(甲磺酸多薩坐辛)與圓粒(鹽酸普潘奈)劑型之脈衝式藥物傳遞系統爲目的。單室錠劑系統之製備，係以不同黏度之羥丙基甲基纖維素(HPMC)製備三種錠片(A：HPMC 50+4000 cps, B: E10M 和 C: K100M)再以羥丙基甲基纖維素(黏度值 6)塑化之乙基纖維素半透膜衣，來包覆而成不同膜衣厚度。進而評估添加水量影響羥丙基甲基纖維素溶解程度。以槳式溶離裝置，分別於 75、100 與 150 轉速及使用四種不同溶離液(酸鹼值 1.2、6.8 緩衝溶液、去離子水和氯化鈉溶液)進行評估藥物溶離釋出情形。依藥物溶離實驗結果顯示，三種不同黏度之錠劑置於去離子水溶液中，當轉槳轉速增加而藥物釋出量亦增加；若羥丙基甲基纖維素黏度增加則釋出減緩。又藥物在三種不同離子強度的 NaCl 溶離液中相較於去離子溶離液中藥物釋出量明顯地提升。以核心 A 與核心 B 在酸鹼值 1.2 之藥物溶離率皆慢些。但在酸鹼值 6.8 時之藥物溶離率較在去離子水溶液時快些。然而，核心 C 在以上三種溶離液中，下藥物釋出速率相近且慢於核心 A 與核心 B 錠片。包覆膜衣錠片之藥物溶離率顯示，控釋膜衣受滲透壓和膨脹作用造成膜衣破裂，則藥物釋出前之滯後時間，並不受溶離液酸鹼值與轉槳轉速之影響。滯後時間，隨包覆膜衣量之增加而延長卻因添加親水性羥丙基甲基纖維素塑化劑與添加水量於膜衣溶液而縮短；而滯後時間增加隨氯化鈉濃度之增加。此外，在滯後時間藥物之釋出速率受到羥丙基甲基纖維素凝膠化程度與溶離液離子強度影響。在單室圓粒系統部分，本研究試圖開發具有降低藥物通過胃腸道時間與酸鹼值影響性之及時控釋劑型。以鹽酸普潘奈爲模式藥物與 Innopran® XL 爲對照商品，並將藥物直接包覆於糖蕊或以間質型材料添加滲透劑利用擠出搓圓法製備藥物圓粒，乃選用水不溶性乙基纖維素與速率控制非酸鹼值依賴性 Eudragit® RS 之聚合物材料作爲控釋膜衣並包覆於藥物圓粒上。其特點是對於脈衝式釋放曲線之釋放速率與滯後時間在模擬胃腸道緩衝液中，其酸鹼值改變不具依賴性。實驗結果顯示，於 Eudragit® RS 添加 30%檸檬酸三乙酯且包覆量爲 20%時，其滯後時間與對照商品接近但其釋放速率較慢些。然而，利用乙基纖維素作爲控釋膜衣添加羥丙基甲基纖維素作爲塑化劑，雖未觀察到藥物圓粒有滯後時間，但其與對照商品有相似之釋放曲線。換言之，以包覆不同量之 Eudragit® RS 作爲控釋膜衣之間質型藥物圓粒，可調節脈衝式預期釋藥的滯後時間，並達成不受酸鹼值改變之及時控釋作用。然而，基於此滯後時間只在 5 小時範圍之內，並無法滿足臨床使用上之需求性。若添加滲透劑(氯化鈉或乳糖)於間質型藥物圓粒，並利用 Eudragit® RS 包覆不同量之膜衣，則能有效地延長脈衝式預期之釋藥曲線滯後時間達 15 小時且具有不受酸鹼值改變之及時控釋作用。預期在臨床

上可滿足實際需要並降低藥物通過胃腸道時間與酸鹼值之影響性。

英文摘要

This study attempted to develop the single-unit reservoir systems of tablet (doxazosin mesylate) and pellet (propranolol hydrochloride) dosage form with pulsatile–release patterm. In single unit tablet system, this study attempted to characterize the influence of core and coating formulations on the release profiles for a pulsatile drug delivery system activated by membrane rupture based on three core tablet formulations (A-core: HPMC 50+4000 cps, B-core: E10M, and C-core: K100M) coated with various thicknesses of a semipermeable ethylcellulose membrane plasticized with HPMC 606 (Pharmacoat 606) at different ratios with/without adding various amounts of water to dissolve it in the coating solution. Drug release behaviors were investigated using apparatus II in four media of pH 1.2 solution, pH 6.8 buffer, deionized water, and a NaCl solution rotated at 75, 100, and 150 rpm. Pilot studies of the in vivo pharmacokinetics were conducted as well for comparison with the in vitro results. Results demonstrated that drug release from the three kinds of core tablets in deionized water increased with an increasing stirring rate, and decreased with an increasing viscosity grade of HPMC used in the core formulations. A significant promotion of drug release from core tablets was observed for the three levels of NaCl media in comparison with that in deionized water. Results further demonstrated that a slightly slower release rate in pH 1.2 solution and a faster release rate in pH 6.8 buffer than that in deionized water were observed for the A-core and B-core tablets, with the former being slower than the latter. However, similar release rates in the three kinds of media were observed for C-core tablets, but they were slower than those for the A- and B-core tablets. Dissolution of coated tablets showed that the controlling membrane was ruptured by osmotic pressure and swelling which activated drug release with a lag time. The lag time was not influenced by the pH value of the release medium or by the rotation speeds. The lag time increased with a higher coating level, but decreased with the addition of the hydrophilic plasticizer, Pharmacoat 606, and of the water amount in the coating solution. The lag time also increased with a higher concentration of NaCl in the medium. The release rate after the lag time was determined by the extent of retardation of gelation of HPMC in the core tablet based on the ionic strength of the medium. In single unit pellet system, this study attempts to develop a timely controlled release dosage form with minimization of transit time and pH effects of gastrointestinal tract. Using the release profiles of propranolol from Innopran XL as the reference, two water-insoluble and pH-independent rate-controlling polymeric materials of ethylcellulose and Eudragit RS selected as the controlling membrane for drug-layering non-pareil seeds (NP) or extrusion-spheronized pellets incorporated with matrix materials or osmogents were characterized in the SGF and the pH change medium for the pH-independency of the release rate and the lag time and their pulsatile patterns. Results demonstrate that when propranolol was layered on NP, Eudragit RS membrane plasticized with 30% TEC coated at an amount of 15% is able to adjust a lag time close to that for reference product but with a slower release rate after then, while EC membrane plasticized with HPMC was not able to delay release of drug at a lag time closely similar to the reference product. Furthermore, the controlling membrane of EC incorporated with lactose coated on the pellets manufactured by extrusion-spheronization method is able to adjust the lag time pattern by coating with different level, but resulting in a release rate correspondingly decreasing with increasing lag time, of which the lag time was shorter and the release rate was slower than that for the reference product. On the other hand, coating Eudragit RS on matrix pellets as the controlling membrane at different coating level is able to adjust a lag time of desire with a pulsatile release pattern to accomplish the timely controlled release independent of the pH change. However, the lag time could be adjusted was only within a 5 hour range that would be not so practical to meet the clinical needs. Finally, coating Eudragit RS on matrix pellets that containing various ratio of osmogent, NaCl or lactose, as the controlling membrane at different coating level are able to effectively adjust a lag time of desire as long as 15 hr with a pulsatile release pattern to accomplish the timely controlled release independent of the pH change that could meet the practical need in clinics with the minimization of the pH and transit effects of GI tract.