口服間質性控釋錠片之研發

Development of oral controlled release matrix tablets

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.