Long-term stability and pharmacodynamic effects of PGE1 in urethral injection for erectile dysfunction

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Prostaglandin E1(PGE1), a potent peripheral vasodilator, is used in erectile dysfunction treatment, but very unstable in aqueous conditions due to degradation mechanism by dehydration. It is well known that PGE1 readily undergoes dehydration in both acidic and basic aqueous solutions to produce prostaglandin A1(PGA1) which further isomerizes to prostaglandin B1(PGB1) in alkaline conditions. In this study, long-term stability of PGE1 over 12 months was evaluated and the major degradation products of PGA1 and PGB1 was identified with standards.
The amounts of degradation product, PGA1, was increased, but no trace amount of PGB1 was found at 4℃, the shelf storage condition of 4℃. Semilog plots of residual PGE1 were tried for the stability assessment of urethral injections and temperature dependences of degradation were analysed by Arrhenius plot. Pharmacodynamic effects, including intracavernous pressure(ICP), penile length and duration of erctile response of urethral injection were studied also with cats. The effects were similar to those of intracavernosal injection as control.

[PE1-22] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

Characterization of Salmon Calcitonin in Microsphere by Capillary Electrophoresis with Off-Line Mass Spectrometry

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The potential of capillary electrophoresis (CE) with off-line matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-TOF MS) has been demonstrated for stability and chemical changes of peptides in microspheres during in vitro release test. In this study, PLGA microsphere containing salmon calcitonin (sCT) was prepared using a solvent extraction/evaporation method. CE profiles of sCTs extracted from microspheres during in vitro release test showed the presence of an additional peak in addition to the native sCT. As the time goes on, the additional peak was increased, whereas native sCT was reduced. Using the photodiode array detection of CE, the similarity index of two peaks was 0.921, indicating the additional peak is the derivative of sCT. The fractions of two peaks were then collected for the determination of MALDI-TOF MS. MALDI-TOF mass spectrum of first peak fraction was corresponded to the mass of the native sCT (3436.46 m/z), while the second peak fraction showed two peaks (3494.15 and 3552.16 m/z). These two peaks are consistent with the mass of the complex between sCT and polymer fragments. These results indicate that some interaction between peptide and polymer within the microsphere occurs during the in vitro release test. The combination of CE and MALDI-TOF MS could be applied as a powerful tool for the characterization of peptide in the microsphere with the advantages of speed, high resolution, and small sample consumption.

[PE1-23] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

Comparison of Salmon Calcitonin Release Properties Between Hydrophilic and Hydrophobic PLGA Microspheres

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The purpose of incorporating peptide drugs into a polymer matrix is to improve the therapeutic efficacy, suitable for parenteral administration to maintain the pharmacological activity for a prolonged period. Many studies have also been attempted to evaluate the polymer matrices. In this study, PLGA microspheres containing salmon calcitonin (sCT) using hydrophilic polymer (RG503H) was much faster compared to hydrophobic polymer (RG503) were prepared by a solvent extraction/evaporation method. Using capillary electrophoresis (CE) and matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-TOF MS), the in vitro release rates of sCT from two different microspheres were determined, and demonstrated that the polymer properties affected the sCT release pattern from biodegradable PLGA microspheres. Degradation of microsphere and drug release occurred much faster in RG503H polymer than in RG503 polymer. Also, the complex peak between sCT and polymer fragments was detected and increased with the time during the release test. The sCT in RG503 polymer also demonstrated stronger interaction between sCT and polymer units than in RG503H indicating that the hydrophobicity of polymers might be the important factor for the interaction with peptides.

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In Vitro Stability of Peptides in Poly(Lactic-co-Glycolic Acid) Microspheres

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One of the critical aspects in the development of peptide/protein-loaded microspheres is the investigation of release characteristics of peptide/protein from microsphere matrix. The stability and chemical changes of peptides in microspheres during in vitro release test were investigated by using capillary electrophoresis (CE) and matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-TOF MS). Leuprolide and human parathyroid hormone (1-34) (hPTH1-34) were employed as model systems. In the CE electropherogram of two peptides extracted from microspheres after incubation for 3 days at 37oC, the leuprolide microsphere showed no degradation product, while hPTH1-34 microspheres showed the extra peak in addition to the intact peptide. MALDI-TOF mass spectrum of hPTH1-34 extracted from microsphere showed three peaks, including hPTH1-34 (4114.91 m/z) and two peaks (4172.96 and 4228.84 m/z), whereas the leuprolide showed only the mass corresponding to the intact peptide (1208.95 m/z), showing the different stabilities within the microspheres. The two peaks from hPTH1-34 microsphere are corresponded to the association product of hPTH1-34 and polymer fragments. The in vitro release profiles of leuprolide and hPTH1-34 microspheres also showed different patterns. These results indicate that the interaction of peptide to polymer affects the release profiles from the microsphere.

[PE1-25] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

Non-invasive method to encapsulate basic proteins into porous poly(DL-lactide-co-glycolide) microspheres

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Non-invasive method to encapsulate protein into PLGA microspheres has been tried by soaking blank porous PLGA microspheres into protein solution. The incorporation mechanism was systematically studied by varying incorporation parameters such as pH, salt and temperature using five model proteins with different physical properties such as molecular weight and pI. With including NaCl as a porosigen in the primary water phase, porous PLGA microspheres were prepared by W/O/W double emulsion solvent evaporation method using hydrophilic 50:50 PLGA polymer (RG502H, Boehringer Ingelheim) which contains free carboxyl end group. At neutral pH, 37°C, for 24hr, basic proteins, such as lysozyme and ribonulease A were incorporated more than 10% (weight