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AAPS PharmSciTech® Highlights

AAPS PharmSciTech (**http://www.pharmscitech.com**) closed its first year having published nearly 50 articles of original research focusing on pharmaceutical technology. Some of the highlights from Volume 1 are featured below:

Prediction of Adsorption from Multicomponent Solutions by Activated Carbon Using Single Solute Parameters

Dale Eric Wurster, Khouloud A. Alkhamis, and Lloyd E. Matheson

The adsorption of 3 barbiturates¾ phenobarbital, mephobarbital, and primidone¾ from simulated intestinal fluid (SIF), without pancreatin, by activated carbon was studied using the rotating bottle method. The concentrations of each drug remaining in solution at equilibrium were determined with the aid of a high-performance liquid chromatography (HPLC) system employing a reversed-phase column. The competitive Langmuir-like model, the modified competitive Langmuir-like model, and the LeVan-Vermeulen model were each fit to the data. Excellent agreement was obtained between the experimental and predicted data using the modified competitive Langmuir-like model and the LeVan-Vermeulen model. The agreement obtained from the original competitive Langmuir-like model was less satisfactory. These observations are not surprising because the competitive Langmuir-like model assumes that the capacities of the adsorbates are equal, while the other 2 models take into account the differences in the capacities of the components.

The results of these studies indicate that the adsorbates employed are competing for the same binding sites on the activated carbon surface. The results also demonstrate that it is possible to accurately predict multicomponent adsorption isotherms using only single-solute isotherm parameters. Such prediction is likely to be useful for improving in vivo/in vitro correlations.

Evaluation of Orntide Microspheres in a Rat Animal Model and Correlation to In Vitro Release Profiles

Janusz W. Kostanski, Bhas A. Dani, George-Ann Reynolds, Cyril Y. Bowers, and Patrick P. DeLuca

ABSTRACT Orntide acetate, a novel luteinizing hormone-releasing hormone (LHRH) antagonist, was prepared and evaluated in vivo in 30-day and 120-day sustained delivery formulations using a rat animal model. Orntide poly(d,l-lactide-co-glycolide) (PLGA) and poly(d,l- lactide) (PLA) microspheres were prepared by a dispersion method and administered subcutaneously in a liquid vehicle to rats at 2.2 mg Orntide/kg of body weight (30-day forms) or 8.8 mg Orntide/kg (120-day forms). Serum levels of Orntide and testosterone were monitored by radioimmunoassays, and a dose-response study at 4 doses (3, 2.25, 1.5, and 1.75 mg Orntide/kg) was conducted to determine the effective dose of Orntide. Microspheres with diameters between 3.9 and 14 µ were prepared. The onset and duration of testosterone suppression varied for different microsphere formulations and were influenced both by polymer properties and by microsphere characteristics. Microspheres prepared with 50:50 and 75:25 copolymers effectively sustained peptide release for 14 to 28 days, whereas an 85:15 copolymer and the PLA microspheres extended the pharmacological response for more than 120 days. Increase in drug load generally accelerated peptide release from the microspheres, resulting in higher initial serum levels of Orntide and shorter duration of the release. In general, apparent release was faster in vivo than under in vitro conditions. Orntide microspheres effectively suppressed testosterone in rats, providing rapid onset of release and extended periods of chemical castration. Testosterone suppression occurred immediately after microsphere administration without the initial elevation seen with LHRH superagonists.

Formulation and In Vitro Transfection Efficiency of Poly (D, L-lactide-co-glycolide) Microspheres Containing Plasmid DNA for Gene Delivery

Sisay Gebrekidan, Byung H. Woo, and Patrick P. DeLuca

ABSTRACT The stability, in vitro release, and in vitro cell transfection efficiency of plasmid DNA (pDNA) poly (D,L-lactide-co-glycolide) (PLGA) microsphere formulations were investigated. PLGA microspheres containing free and polylysine (PLL)-complexed pDNA were prepared by a water-oil-water solvent extraction/evaporation technique. Encapsulation enhanced the retention of the supercoiled structure of pDNA as determined by gel electrophoresis. PLL complexation of pDNA prior to encapsulation increased both the stability of the supercoiled form and the encapsulation efficiency. Free pDNA was completely degraded after exposure to DNase, while encapsulation protected the pDNA from enzymatic degradation. Rapid initial in vitro release of pDNA was obtained from microspheres containing free pDNA, while the release from microspheres containing PLL-complexed pDNA was sustained for more than 42 days. Bioactivity of encapsulated pDNA determined by in vitro cell transfection using Chinese hamster ovary cells (CHO) showed that the bioactivity of encapsulated pDNA was retained in both formulations but to a greater extent with PLL-complexed pDNA microspheres. These results demonstrated that PLGA microspheres could be used to formulate a controlled-release delivery system for pDNA that can protect the pDNA from DNase degradation without loss of functional activity.

A Bioresorbable, Polylactide Reservoir for Diffusional and Osmotically Controlled Drug Delivery

Sriramakamal Jonnalagadda and Dennis H. Robinson.

ABSTRACT The purpose of this study was to design and characterize a zero-order bioresorbable reservoir delivery system (BRDS) for diffusional or osmotically controlled delivery of model drugs including macromolecules. The BRDS was manufactured by casting hollow cylindrical poly (lactic acid) (PLA): polyethylene glycol (PEG) membranes (10 x 1.6 mm) on a stainless steel mold. Physical properties of the PLA:PEG membranes were characterized by solid-state thermal analysis. After filling with drug (5 fluorouracil [5FU] or fluorescein isothiocyanate [FITC]-dextran:mannitol, 5:95 wt/wt mixture) and sealing with viscous PLA solution, cumulative in vitro

dissolution studies were performed and drug release monitored by ultraviolet (UV) or florescence spectroscopy. Statistical analysis was performed using Minitab®(Version 12). Differential scanning calorimetry thermograms of PLA:PEG membranes dried at 25°C lacked the crystallization exotherms, dual endothermal melting peaks, and endothermal glass transition observed in PLA membranes dried at -25°C. In vitro release studies demonstrated zero-order release of 5FU for up to 6 weeks from BRDS manufactured with 50% wt/wt PEG (drying temperature, 25°C). The release of FITC dextrans of molecular weights 4400, 42 000, 148 000, and 464 000 followed zero-order kinetics that were independent of the dextran molecular weight. When monitored under different concentrations of urea in the dissolution medium, the release rate of FITC dextran 42 000 showed a linear correlation with the calculated osmotic gradient ($\Delta\pi$). This study concludes that PEG inclusion at 25°C enables manufacture of uniform, cylindrical PLA membranes of controlled permeability. The absence of molecular weight effects and a linear dependence of FITC-dextran release rate onDp confirm that the BRDS can be modified to release model macromolecules by an osmotically controlled mechanism.

Novel Mathematical Method for Quantitative Expression of Deviation from the Higuchi Model

Mukesh C. Gohel, Maulik K. Panchal, and Viral V. Jogani.

ABSTRACT A simple mathematical method to express the deviation in release profile of a test product following Higuchi's kinetics from an ideal Higuchi release profile was developed. The method is based on calculation of area under the curve (AUC) by using the trapezoidal rule. The precision of prediction depends on the number of data points. The method is exemplified for 2 dosage forms (tablets of diltiazem HCl and microspheres of diclofenac sodium) that are designed to release the drug over a 12-hour period. The method can be adopted for the formulations where drug release is incomplete (<100%) or complete (100%) at last sampling time. To describe the kinetics of drug release from the test formulation, zero-order, first-order, Higuchi's, Hixson-Crowell's, and Weibull's models were used. The criterion for selecting the most appropriate model was based on the goodness-of-fit test. The release kinetics of the tablets and microspheres were explained by the Higuchi model. The release profiles of the test batches were slightly below the ideal Higuchi release profile. For the test products, observed percentage deviation from an ideal Higuchi profile is less than 16% for tablets and less than 11% for microspheres. The proposed method can be extended to the modified release formulations that are designed to release a drug over 6, 18, or 24 hours. If the data points are not evenly separated, the ideal drug release profile and AUC are calculated according to the specific sampling time. The proposed method may be used for comparing formulated products during the research and development stage, for quality control of the products, or for promoting products by comparing performance of the test product with that of the innovator's product.

Development and Evaluation of Oral Multiple-unit and Single-unit Hydrophilic Controlled-release Systems

Manuel Efentakis, Antonios Koutlis, and Marilena Vlachou

ABSTRACT This study compared the release behavior of single-unit (tablets, capsules) and multiple-unit (minitablets in capsules) controlled-release systems of furosemide. The swelling and erosion behaviors of these systems, which contained the swellable hydrophilic polymers sodium alginate (high viscosity) and Carbopol 974P, were compared.

Swelling and erosion experiments showed a high degree of swelling and limited erosion for the Carbopol preparations, whereas less swelling but greater erosion was observed for the sodium alginate preparations. The sodium alginate preparations were eroded in 6 hours, while Carbopol preparations exhibited limited erosion within this period of time. These results appear to be attributed to the physicochemical characteristics of the polymers used in this study. Polymer characteristics greatly influenced the release of furosemide (model drug) from the formulations prepared and tested. Sodium alginate had a less pronounced sustained release effect compared with Carbopol (ie, in 8 hours all 3 sodium alginate dosage forms displayed complete release of furosemide, while only 30% of the drug was released from Carbopol dosage forms). Finally, all 3 Carbopol dosage forms (single- and multiple-unit) displayed similar release behavior while sodium alginate dosage forms displayed a different and more distinctive behavior. Minitablets and tablets showed a greater sustained release effect compared with capsules. Evaluation of the release data indicates that the release mechanism for sodium alginate formulations may be attributed to erosion/dissolution, while for Carbopol it may be attributed mainly to polymer relaxation and diffusion of the drug from the polymer surface.

Formulation Variables Affecting Drug Release From Xanthan Gum Matrices at Laboratory Scale and Pilot Scale

Nashiru Billa and Kah-Hay Yuen

The purpose of this research was to study processing variables at the laboratory and pilot scales that can affect hydration rates of xanthan gum matrices containing diclofenac sodium and the rate of drug release. Tablets from the laboratory scale and pilot scale proceedings were made by wet granulation. Swelling indices of xanthan gum formulations prepared with different amounts of water were measured in water under a magnifying lens. Granules were thermally treated in an oven at 60°C, 70 °C, and 80°C to studythe effects of elevated temperatures on drug release from xanthan gum matrices. Granules from the pilot scale formulations were bulkier compared to their laboratory scale counterparts, resulting in more porous, softer tablets. Drug release was linear from xanthan gum matrices prepared at the laboratory scale and pilot scales; however, release was faster from the pilot scales. Thermal treatment of the granules did not affect the swelling index and rate of drug release from tablets in both the pilot and laboratory scale proceedings. On the other hand, the release from both proceedings was affected by the amount of water used for granulation and the speed of the impeller during granulation. The data suggest that processing variables that affect the degree of wetness during granulation, such as increase in impeller speed and increase in amount of water used for granulation, also may affect the swelling index of xanthan gum matrices and therefore the rate of drug release.