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Design and Evaluation of Progesterone Microparticles Using Biodegradable Polymers

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***Abstract**: Progesterone microparticle for injection were prepared by the solvent evaporation method. An aerosol method was used to prepare microparticles with a mean diameter of 23 μm. Due to low yields produced by the spinning top aerosol generator, an aerosol method was used to prepare microparticles with a mean diameter of 12μm. This decision was made to avoid excessive loss of isotope. It was observed that the drug/polymer matrix formulated in the form of microparticles for intramuscular injection can provide long-term drug release. It supports the concept that parenteral controlled release of the drug from the polymer/drug preparation was a viable procedure for the delivery of drugs*

***Keywords:** Progesterone, Microparticles, Matrix Diffusion, Biodegradable polymers of PLA, Controlled release*

I. Introduction

Administration of Drug by injection has been accepted as a convenient and effective method. Enormous potential exists for the utilization of biodegradable polymers of PLA in the controlled release of drug formulated as microparticles for the parenteral drug administration. The use of an injection system of microparticles containing calculated proportions of a range of mean size diameter microparticles is likely to provide drug plasma levels suitable for the control of certain conditions. The surface area factor will influence both the drug release rate and the polymer biodegradation. The aim being the design of drug loaded microparticles from biodegradable PLA polymers, copolymers, mixtures of different molecular weight homopolymers etc. having different biodegradation rates after injection. In this study, three microparticle systems were prepared from [^{14}C]-PLLA and [^{3}H] progesterone. The purpose of using dual labelling was to monitor both the drug release rate from the polymer, and to determine the extent of polymer erosion. It was envisaged that polymer erosion would begin at some stage during the study period. The influence of particle size on drug release and or polymer erosion was expected to have a leading role in the observed differences in drug release rates from the three microparticle systems.

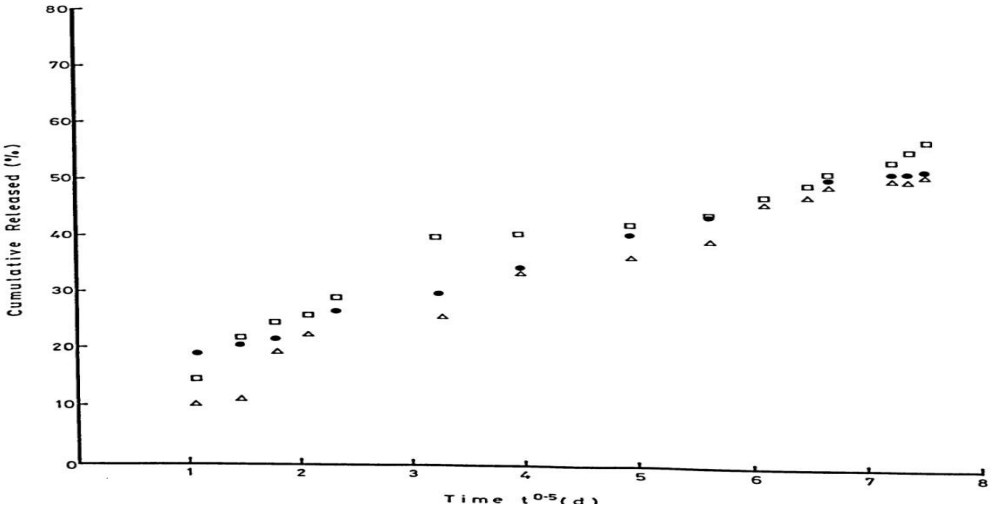
Materials and Method: Progesterone; the purities reported by the manufacturer for the drug were 95.3 and 98 per cent respectively. The specific activities were 402 m Ci mg^{-1} (14.9 GB q mg^{-1}) for [^{3}H] and 177 m Ci mg^{-1} (6.55 MBq mg^{-1}) for [^{14}C].

Laboratory synthesized [^{14}C]-PLLA had an intrisic viscosity of 1.3 (Mv = 42,350 and a specific activity of 1.2 μ Ci g^{-1}.Methanol, absolute alcohol, all of AR grade and hydrogen peroxide 30 per cent of special grade.

II. Methods

Microparticles with a mean diameter of 53 μm, and a nominal progesterone content of 22 per cent were prepared by the solvent evaporation method. An aerosol method was used to prepare microparticles with a mean diameter of 23 μm. Due to low yields produced by the spinning top aerosol generator, an aerosol method was used to prepare microparticles with a mean diameter of 12μm. This decision was made to avoid excessive loss of isotope. In an attempt to improve drug loading level in microparticles prepared by the solvent evaporation techniques the initial proportions of progesterone was increased to 22 per cent, and the interrupted solvent evaporation technique was employed (270). With this procedure, stirring was stopped at some stage after the emulsion was formed and before methylene chloride evaporation was complete. The partially hardened microparticles were allowed to settle and the aqueous supernatant phase containing the FVA decanted, and

replaced with deionized water. After washing off the dispersing agent, microparticles were re-suspended in deionized water, stirred and methylene chloride allowed to evaporate to completion. Removal of the aqueous PVA dispersing agent before solvent evaporation was completed, minimized the formation of free drug crystals in the aqueous phase or on the surface of the microparticles (74).The drug/polymer solutions for the production of labeled microparticles were prepared by pipetting tritiated progesterone solution in toluene into a 20 ml glass vial and the solvent evaporated under a gentle flow of nitrogen gas. A weighed amount of cold progesterone was added to the dried labelled drug and a solution in methylene chloride formed. Weighed amounts of [^{14}C]- PLLA were added to the mixed drugs and dissolved. The solvent was evaporated under nitrogen and duplicate dried powder samples removed for analysis to determine the new specific activities for the polymer and drug. A final solution was made in methylene chloride for the production of microparticles.



In vitro drug release from microparticles with meandiameters of (o) 53 µm ; (0) 23 µm ; and (a) 12 µm

III. Evaluation Of Microparticles

In vitro dissolution studies

Microparticles were evaluated for their drug content and for in vitro drug release. Progesterone loaded microparticles (5 mg) were dissolved in 1 ml of methylene chloride. The formed solution 100μl was transferred into a 20 ml scintillation vial and 15 ml of the cocktail fluor added prior to counting.The in vitro drug release from microparticles was monitored by suspending a calculated weight of microparticles containing progesterone, the concentration of which did not exceed 10 per cent of the aqueous solubility at 37°C. Dissolution studies were carried out using a modified Levy beaker method USP (271). The assembly consisted of a covered, 1L round-bottom flask, an immersion magnetic stirrer and a PTFE covered magnetic bar (2.4 cm long). The powder was first suspended in a small quantity of water and sonicated in an immersion sonicator (cavitator ultrasonic cleaner, Mettler Electronics Corp. Scientific Industries International Inc (UK) Ltd) for 30 s to disperse agglomerated particles. The suspension was added with stirring to the thermostated dissolution medium. The stoppered flask was maintained at 37°C, and stirred at a constant rate to keep the microparticles suspended. Samples of dissolution medium were removed periodically and immediately filtered using a syringe fitted with 0.45 μm millipore filter. The dissolution medium was maintained at constant volume by adding to the flask the equivalent volume of dissolution medium withdrawn. This was previously used for rinsing the filter membrane. In this way, microparticles removed during sampling were returned to the dissolution vessel. The drug concentration in the filtrate was determined by scintillation counting.

IV. Results And Discussion

(a) In vitro drug release

A total weight of 8.0 mg of microparticles from each size group was used to determine the in vitro drug release. The amount of drug contained in each microparticle series was 1.58; 1.47 and 1.57 mg for microparticles with mean diameters of 53, 23 and 12 µm respectively. The in vitro drug release profiles displayed an initial rapid and irregular pattern over the first 5 days of the study. This phase was followed by a more regular release pattern, which exhibited a gradual decline over a prolonged period of time. To test whether the matrix diffusion controlled release was followed, the Higuchi model (72) was used by applying the drug-release-square root of time relationship to the in vitro release data. Although reasonable linear behaviour for the

entire release period seemed to hold (r = 0.998, 0.992, 0.979 and for AB and C respectively) these values were not absolute evidence that conformity with the Higuchi model was being followed. Hadgraft (280) has suggested that normally the linear region is seen only up to 30 per cent of drug release from microspheres beyond which deviation from linearity becomes apparent. The slopes (k) of the lines (Figure 5.1) taken as drug release rates revealed that a faster release rate was provided by microparticles with a larger mean diameter (53 µm), which had a k value of 3.36 µg $d^{-0.5}$ respectively. The corresponding intercept values, taken to be a measure of the burst effect from the microparticles were 1.73; 12.13 and 15.66 per cent for microparticle systems with diameters of 53; 23 and 12µm respectively. The higher value shown by microparticles with the smallest mean diameter probably shows the influence of the surface area which was in contact with the dissolution medium. The higher and irregular release pattern produced by the three microparticle systems during this early phase of drug release was probably due to surface crystalline progesterone.The results have shown that the drug/polymer matrix formulated in the form of microparticles for intramuscular injection can provide long-term drug release. It supports the concept that parenteral controlled release of the drug from the polymer/drug preparation was a viable procedure for the delivery of drugs. Although the influence of microparticle size on drug release rate was overshadowed by the method of manufacture, there was a useful indication that each microparticle system must have a specifically developed individual preparation method that influences drug release.

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