Non-Higuchi Drug Release Mechanism and the Controlling Variables

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Introduction: The Higuchi Equation has been used to predict the release of a drug from an insoluble matrix where the drug is dispersed as individual particles[1]. Drug elution from the sample into external media is composed of two separate processes: dissolving of drug particles into the matrix as free molecules and diffusion of the free drug molecules out of matrix into external media. The basic assumption behind the Higuchi Equation is that the rate at which the drug particles dissolve into matrix is much faster than the rate of drug molecules diffusion and the molecular concentration of the drug in the matrix is kept at its saturation limit. This assumption works for a lot of drug-polymer systems. However, if the rate of drug dissolution into matrix is slower than its molecular diffusion rate in the matrix, Higuchi equation does not work. In such a case, the dissolution rate of drug particles into matrix limits the overall drug elution from the sample. If the total amount of drug in matrix is constant, the dissolving rate of the drug particles is proportional to their total surface area which is the reciprocal to their particle size. Then, it should be expected that the overall drug elution rate would increase as the particle size decreases. In the Higuchi mechanism, drug elution rate is independent on its particle size. In this abstract, we report a series of experiments to demonstrate non-Higuchi drug release mechanism where the drug release rate is controlled by particle size. The drug used here is clonidine HCl and the polymer used is a poly(D,L-lactide-co-glycolide). The samples were made into short fibers with typical diameter being 0.5 to 1 mm.

Materials: Clonidine HCl was purchased from Spectrum Chemicals. Poly(D, L Lactide-co-glycolide) (PLGA) was purchased from Lakeshore Biomaterials.

Methods: Spray Drying – Clonidine HCl was dissolved in methanol at 12% (w/w) and spray dried with a Buchi Mini Spray Dryer. PLGA and clonidine HCl were co-dissolved in acetone / methanol mixture at a 10:1 weight ratio respectively and a 2% (w/w) overall solution.

Extrusion – Formulations of drug and polymer were dry mixed and fed into a Haake Mini-Lab extruder. Formulations were melt extruded at 130C and hand pulled out a cylindrical die to desired diameters.

In-Vitro Elution – Strands were cut to desired lengths, weighed and placed in scintillation vials with phosphate buffered saline pH 7.4 for drug elution testing. At pre-selected times, the elution media was completely removed, measured with a UV-Vis spectrophotometer and the vials filled with fresh elution media.

Microscopy Analysis – Drug particle distribution was determined by analyzing cut ends of the formulations with either the TOF-SIMS instrument or Scanning electron microscope.

Results: Figure 1 showed the drug release rate from 3 different formulations which differ in the size of the clonidine HCl particle embedded within the PLGA rod of the same drug loading. Figure 2 shows the TOF-SIMS image capturing the differing particle sizes and proves the drug has far exceeded the solubility limit of the polymer. The co-spray dried formulation of clonidine HCl and PLGA had the smallest particle size of ~1-3 micrometers, the spray dried clonidine HCl formulation had the middle size of ~20 micrometers, and the clonidine HCl used directly from the manufacturer had the largest size of ~10-100 micrometers.

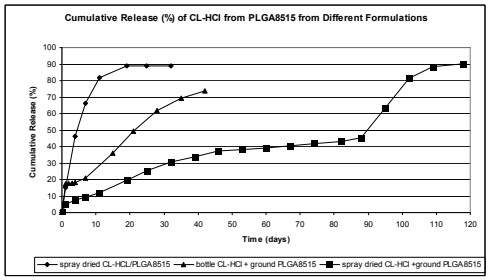

Figure 1. Cumulative % Release of Clonidine HCl from Different Particle Sizes

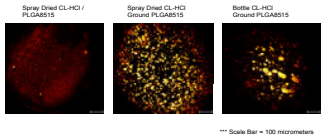

Figure 2. TOF-SIMS Image of Formulations in Figure 1

The slowest drug release was from the middle sized group (20 micrometers) while the faster drug release was from the smallest drug particles. The results illustrate the small drug particles dissolve much faster into the polymer matrix due to the larger surface area to volume ratio and the diffusion of the drug molecules is very fast from the polymer matrix. The largest particle size has multiple mechanisms controlling the release. A high burst caused by large surface drug particles, a lag phase caused by drug particles dissolving, and finally a release rate caused by drug molecule diffusion. Also, the large voids left behind from the very large particles caused a faster release rate than a smaller drug particle void. The best particle size for a long duration drug release is ~20 micrometers. The drug particle size controlled the dissolving of the drug into the polymer matrix and the drug particle size was the right overall size compared to the diameter of the rod tested.

Conclusions: A non-Higuchi release mechanism was demonstrated in this abstract. The drug elution rate was controlled by the drug particle sizes; the samples with smaller particles sizes had faster drug release but smaller initial burst. Mathematical equations are needed to quantitatively predict the drug elution behavior.

Reference:

1. Higuchi, T., J. Pharm. Sci., 1961, 50:874-875.