DESIGN OF DIFFUSION CONTROLLED DRUG DELIVERY SYSTEMS

by

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ABSTRACT

Pharmaceutical controlled release systems, generally constructed from polymers, are defined as the systems which delivers a drug at a predetermined and constant rate for a specified period of time. Such systems exist in many forms, including injectable microspheres, specially designed tablets, implants and transdermal patches. Diffusion, degradation and dissolution are the most important mechanisms that control the drug release from these controlled release systems. However, diffusion controlled drug delivery system is the most widely used drug delivery systems. Diffusion control is particularly important to transdermal drug delivery where degradation and dissolution are nonviable mechanisms to control the release rates. Generally, in diffusion controlled release systems where a drug to be released is uniformly dissolved through a polymer, the release shows initially high rate followed by a rapidly declining rate. Various approaches have been employed over the last two decades to overcome this undesired burst effect and to obtain the desired dose of a drug. The present optimization study, however, concerns the optimal initial concentration distribution of a drug in the delivery device to eliminate the burst effect and obtain a zero-order release.

A commonly used objective function for the optimization is the standard of deviation between the instantaneous dose and the desired dose. The numerical value of the objective function provides a little insight from a therapeutic viewpoint. This work describes a novel and systematic approach to the design of transdermal or implanted delivery systems based on medically relevant specifications of maximum allowable dose rate, minimum effective dose rate, time to achieve the effective dose rate, and the design life of the patch. The delivery system is a three layer patch consisting of two drug containing layers of equal thickness and one barrier layer laminated together to form a matrix with a non-uniform initial concentration distribution.

This device allows drug release behavior conforming to the medically relevant specifications while maximizing utilization of the drug, *i.e.* the depletion of the drug from the patch. The thickness of the barrier layer and the relative concentrations in the two drug containing layers are the key design parameters. Optimization studies show little advantage from using variable thicknesses of the two drug containing zones or of using more than two drug containing zones. The application of the design approach is further extended to design a patch considering the skin as a barrier.

The last part of the thesis addresses the issue of the particle size distribution of a dispersed drug. It is known that the particle size of a dispersed drug plays a significant role in the release behavior. Compositional quenching, previously used in the manufacture of impact modified conventional polymer blends and biocatalytic composites is applied to disperse a model protein in the natural biopolymer. The green fluorescent protein and chitosan are used as a model protein and polymer, respectively. The manufacture of chitosan composites by solvent evaporation and compositional quenching process is investigated. The chitosan-protein composite manufactured by compositional quenching showed particle size distribution of dispersed protein of the superior quality compared to the solvent evaporation technique.