Handbook of Pharmaceutical Controlled Release Technology

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Preface

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Research and Development Aspects of Oral Controlled-Release Dosage Forms

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I. INTRODUCTION

Controlled release may be defined as a technique or approach by which active chemicals are made available to a specified target at a rate and duration designed to accomplish an intended effect. More specifically, an oral controlled release drug delivery system is, in principle, a device or dosage form that controls drug release into the absorption site in the gastrointestinal (GI) tract. It controls the drug absorption rate to achieve the desired plasma profiles defined by the steady-state pharmacology (1). A typical controlled release system is designed to provide constant or nearly constant drug levels in plasma with reduced fluctuation via slow release of drug over an extended period of time. Controlled release systems are sometimes called extended release or sustained release systems. In practical terms, an oral controlled release should allow a reduction in dosing frequency as compared to that drug presented as a conventional dosage form (2).

Over the last two decades, controlled technology has received increasing attention from the pharmaceutical industry and academia. As new technologies emerge, they not only open up a wide range of new therapeutic opportunities, but also offer the benefits of product differentiation, market expansion, and patent extension. By 1998 over 70 chemical entities had been formulated into more than 90 oral controlled release products that were approved for marketing by the U.S. Food and Drug Administration (FDA) (3).

Controlled release technology may provide increased clinical value as well as extended product life. The advantages of an ideal controlled release dosage form over an immediate release product include improved patient compliance due to a reduced dosing frequency, a decreased incidence and/or intensity of the side effects, a greater selectivity of pharmacological activity, and a more constant or prolonged therapeutic effect, as well as an increase of cost effectiveness. A typical example is diltiazem hydrochloride, a calcium antagonist for the treatment of hypertension. To enhance drug therapy and competitiveness, this compound was formulated into three generations of dosage forms, including immediate release tablets (Cardizem) approved from 1982 to 1986, twice-daily controlled release capsules (Cardizem SR) approved in 1989, and once-daily controlled release capsules (Cardizem CD) approved from 1991 to 1992.

With the growing need for optimization of therapy, controlled release technologies providing programmable delivery rates other than immediate input have increasingly become more important, especially for drugs for chronic use or with a narrow therapeutic index. Thus, understanding and utilizing the fundamentals of controlled release technologies is essential to the successful formulation research and development of a controlled release product.

II. CONTROLLED RELEASE SYSTEMS FOR ORAL ADMINISTRATION

The basic concepts of controlled release have been reviewed thoroughly in the literature (1,4–6). Various physical and chemical approaches have been applied to produce a well-characterized dosage form that controls drug input into the body within the specifications of the desired release profile. In this section, commonly used methods based on application of physical and polymer chemistry to oral drug delivery systems will be briefly discussed with emphasis on polymeric systems.

A. Common Oral Polymeric Controlled Release Systems

The thrust of oral controlled release efforts has been focused mostly on the dosage forms with well-defined controlled release profiles. Almost all of the oral solid controlled release products on today's market are based on the designs of matrix, membrane-controlled, and osmotic systems (see Table 1). The application of polymeric systems to the oral controlled release dosage form designs and release-controlling mechanisms of these systems have been extensively investigated (1,7). The mechanisms of these controlled release dosage forms generally involve drug diffusion through a viscous gel layer, tortuous channels, or a barrier; drug dissolution via system erosion; and drug solution or suspension forced out of the device by osmotic pressure.

1. Matrix Systems

Both hydrophilic and hydrophobic polymeric matrix systems are widely used to provide controlled delivery of drug substances because of their versatility, effectiveness, and low cost. These types of systems are also suitable for in-house development since they are usually manufactured using conventional equipment and processing. In a matrix system, a drug is incorpo-

Table 1 Common Oral Controlled Release Polymeric Systems Feasible for Commercial Development

Matrix systems	Reservoir systems	Osmotic systems
Hydrophilic matrix	Coated beads or tablets	Elementary osmotic pump
• Swellable	Microencapsulation	Push-Pull system
• Swellable and erodible		Push-Layer system
Hydrophobic matrix		Push-Stick system
• Homogeneous (nonporous)		
• Heterogeneous (porous)		
1. Inert (monolithic)		
2. Erodible		
3. Degradable		

rated into the polymer matrix by either particle or molecular dispersion. The former is simply a suspension of drug particles homogeneously distributed in the polymer matrix, whereas the latter is a matrix with drug molecules dissolved in the polymer. Drug release occurs by diffusion and/or erosion of the matrix system.

In a hydrophilic matrix, there are two competing mechanisms involved in the drug release: Fickian diffusional release and relaxational release. Diffusion is not the only pathway by which a drug is released from the matrix; the erosion of the matrix following polymer relaxation also contributes to the overall release. The relative contribution of each component to the total release is primarily dependent on the properties of a given drug. For instance, the release of a sparingly soluble drug from hydrophilic matrices involves the simultaneous absorption of water and desorption of drug via a swelling-controlled diffusion mechanism. As water penetrates into a glassy polymeric matrix, the polymer swells and its glass transition temperature is lowered. At the same time, the dissolved drug diffuses through this swollen rubbery region into the external releasing medium. This type of diffusion and swelling generally does not follow a Fickian diffusion mechanism. A simple semiempirical equation was introduced to describe drug release behavior from hydrophilic matrix systems (8,9):

$$Q = kt^n \tag{1}$$

where Q is the fraction of drug released in time t, k is the rate constant incorporating characteristics of the macromolecular network system and the drug, and n is the diffusional exponent. It has been shown that the value of n is indicative of the drug release mechanism (10–14). For $n = 0.5$, drug release follows a Fickian diffusion mechanism that is driven by a chemical potential gradient. For $n = 1$, drug release occurs via the relaxational transport that is associated with stresses and phase transition in hydrated polymers. For $1 > n > 0.5$, non-Fickian diffusion behavior is often observed as a result of contributions from diffusion and polymer erosion (10).

In order to describe relaxational transport, Peppas and Sahlin derived the following equation by introducing a second term into Eq. 1 (12):

$$Q = k_1 t^n + k_2 t^{2n} \tag{2}$$

where k_1 and k_2 are constants reflecting the relative contributions of Fickian and relaxation mechanisms. In the case where surface area is fixed, the value of n should be 0.5. Thus, Eq. 2 becomes:

$$Q = k_1 t^{0.5} + k_2 t \tag{3}$$

where the first and second terms represents drug release due to diffusion and polymer erosion, respectively. This equation was later successfully applied to describe drug release from the hydrophilic matrices (14,15).

In a hydrophobic inert matrix system, the drug is dispersed throughout a matrix that involves essentially negligible movement of the device surface. For a homogeneous monolithic matrix system, the release behavior can be described by the Higuchi equation subject to the matrix boundary conditions (16):

$$M_t = [DC_s(2A - C_\sigma)t]^{1/2} \tag{4}$$

where M_t is the drug released per unit area at time t, A is the drug loading per unit volume, C_s is the solubility, and D is the diffusion coefficient in the matrix phase. Equation 4 was derived based on the assumptions that (a) a pseudo–steady state exists, (b) the drug particles are small compared to the average distance of diffusion, (c) diffusion coefficient is constant, (d) perfect sink conditions exist in the external media, (e) only the diffusion process occurs, (f) the drug

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