Controlled-Release of Oral Dosage Forms

Nandita G. Das and Sudip K. Das

The development of controlled-release formulations continues to be a big success for the pharmaceutical industry. The success of any technology relies on the ease of its manufacturing process and its reproducibility of desirable biopharmaceutical properties.

Nandita G. Das, PhD, is assistant professor of pharmaceutics, ndas@pharmacy.isu.edu and Sudip K. Das, PhD, is associate professor of pharmaceutics, das@pharmacy.isu.edu, at Idaho State University, College of Pharmacy, Pocatello, ID.

The technologies behind oral drug delivery have emerged from the mainstream pharmaceutical industry and have become influential forces in their own right, as evidenced by the burgeoning "drug delivery companies" that are at the forefront of innovation and hold their own niche market.

Drug delivery companies and their pharmaceutical industry partners are poised to reap the rewards of the multibillion-dollar drug delivery market, which is forecast to grow to about $70 billion by 2005 (1). The market for oral controlled drug delivery alone is expected to grow at 9% or more every year through 2007. The driving forces behind this booming market can be divided into two main groups: patient-related factors (see Table I and Figure 1) and market-driven factors.

Market factors drive development

Drug delivery is a valuable drug lifecycle management tool. The most important force driving growth and viability of the pharmaceutical industry, the regular introduction of new molecular entities (NME),

Table I: Benefit characteristics of oral controlled-release drug delivery systems.

Benefit	Reason
Therapeutic advantage	Reduction in drug plasma level fluctuations; maintenance of a steady plasma level of the drug over a prolonged time period, ideally simulating an intravenous infusion of a drug
Reduction in adverse side effects and improvement in tolerability	Drug plasma levels are maintained within a narrow window with no sharp peaks and with AUC of plasma concentration versus time curve comparable with total AUC from multiple dosing with immediate release dosage forms. This greatly reduces the possibility of side effects (see Figure 1), as the scale of side effects increase as we approach the MSC.
Patient comfort and compliance	Oral drug delivery is the most common and convenient for patients, and a reduction in dosing frequency enhances compliance.
Reduction in healthcare cost	The total cost of therapy of the controlled release product could be comparable or lower than the immediate-release product. With reduction in side effects, the overall expense in disease management also would be reduced.

is currently weak. Expenses accrued from drug development are hitting the roof, and true innovation is at an all-time low. Moreover, FDA's more-cautious review process and demand for a greater number of complex clinical trials are increasing time to market. In addition, compliance with 21 *CFR* Part 11 and the new Health Insurance Portability and Accountability Act (HIPAA) is affecting the clinical trial process.

In 1996, FDA approved 53 NMEs; this figure dropped to 27 in 2000 and is expected to be even lower in 2003. In the next five years, at least 20 blockbuster products with combined sales of nearly $40 billion will lose patent protection. This prevalence of patent expiration has hit pharmaceutical companies drastically. Hence the emergence of

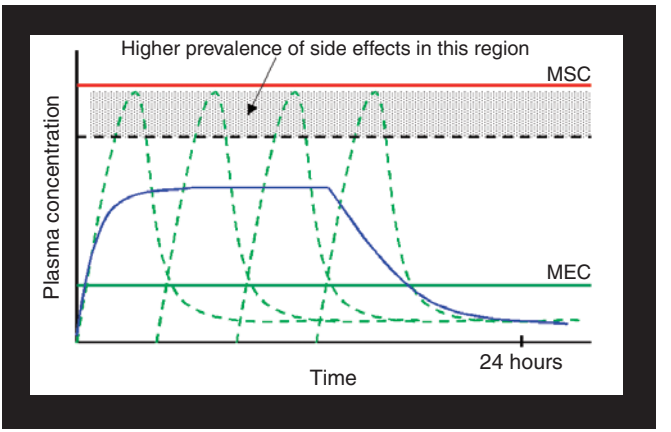

Figure 1. Plasma drug concentration profiles for conventional tablet or capsule formulation (– –) and a zero-order controlled-release formulation (___). MEC = Minimum Effective Concentration; MSC = Maximum Safe Concentration.

repatentability, achieved by the introduction of controlled-release formulations of existing immediate-release products, as an attractive financial option for pharmaceutical companies, in addition to seeking new therapeutic indications for these "new" products. The recent market introduction of two products, Augmentin XR (GlaxoSmithKline) and Cipro XR (Bayer), are harbingers of this option becoming a trend.

Early oral controlled-release drugs

Controlled-release technology evolved with matrix technology. Several articles in the 1950s and 1960s reported simple matrix tablets or monolithic granules. In 1952, Smith Kline & French introduced the Spansule, a timed-release formulation that launched a widespread search for other applications in the design of dosage forms (2).

The goal behind the development of oral controlled-release formulations at that time was the achievement of a constant release rate of the entrapped drug. On the basis of that concept, the zero-order osmotic delivery system used in Procardia XL became one of the top 10 bestselling medicines in the past century.

From that point in time, the industry has seen a number of innovative oral controlled-release dosage forms patented at a rapid pace, but the main drawback of these technologies continues to be the lack of in vitro–in vivo correlation. Ideally, oral controlled-release systems are reliant upon the dosage form to control the rate of drug release with little or no effect from the intrinsic properties of the drug or the conditions prevailing within the gastro intestinal (GI) tract. Realistic drug candidates exhibit high permeability across the GI epithelium (Class I & II drugs according to the Biopharmaceutics Classification

System) such that their absorption rate is controlled exclusively by the rate of release from the dosage form (3). It is only under these conditions that in vitro dissolution rates can possibly be used to predict in vivo absorption rates and guide formulation development.

Currently marketed oral controlled-release systems

Advances in oral controlled-release technology are attributed to the development of novel biocompatible polymers and machineries that allow preparation of novel-design dosage forms in a reproducible manner. The main oral drug-delivery approaches that have survived through the ages are as follows:

- Coating technology using various polymers for coating tablets, nonpareil sugar beads, and granules
- Matrix systems made of swellable or nonswellable polymers
- Slowly eroding devices
- Osmotically controlled devices.

Conventional tablet formulations are still popular in the design of single-unit, matrix-type controlled-release dosage forms. The advancement of granulation technology and the array of polymers available with various physicochemical properties (such as modified cellulose or starch derivatives) have made the development of novel oral controlled-release systems possible.

Matrix devices made with cellulose or acrylic acid derivatives, which release the homogeneously dispersed drug based on the penetration of water through the matrix, have gained steady popularity because of their simplicity in design. The drawback of matrix-type delivery systems is their first-order drug delivery mechanism caused by changing surface area and drug diffusional path length with time. This drawback has been addressed by osmotic delivery systems, which maintain a zero-order drug release irrespective of the pH and hydrodynamics of the GI tract. Multiparticulate systems are gaining favor over single-unit dosage forms because of their desirable distribution characteristics, reproducible transit time, and reduced chance of gastric irritation owing to the localization of drug delivery.

Although several technologies for the production of microparticulate systems have been designed, thus far the mainstream technologies are still based on spray-drying, spheronization, and film-coating technology. Textbook references mention reservoir-type devices; however, because of the technical hurdles in manufacturing reproducibility and lack of safety and efficacy, true reservoir devices have not yet succeeded.

FDA regulation of oral controlled-release drugs

In the 1980s, FDA introduced rigorous regulations governing bioequivalence and in vitro–in vivo correlations for controlled-release products. Required pharmacokinetic evaluations involve

- relative bioavailability following single dose
- relative bioavailability following multiple doses

- effect of food
- dose proportionality
- unit dosage strength proportionality
- singe-dose bioequivalence study (experimental versus marketed formulations at various strengths)
- in vivo–in vitro correlation
- pharmacokinetic/pharmacodynamic (PK/PD) relationship.

In general, for drugs in which the exposure–response relationship has not been established or is unknown, applications for changing the formulation from immediate release to controlled release requires demonstration of the safety and efficacy of the product in the target patient population. When an NME is developed as a controlled-release dosage form, additional studies to characterize its absorption, distribution, metabolism, and excretion (ADME) characteristics are recommended.

The future

The future of controlled-release products is promising, especially in the following areas that present high promise and acceptability:

- Particulate systems: The microparticle and nanoparticle approach that involves biodegradable polymers and is aimed at the uptake of intact drug-loaded particles via the Peyer's patches in the small intestine could be useful for delivery of peptide drugs that cannot, in general, be given orally.
- Chronopharmacokinetic systems: Oral controlled drug delivery with a pulsatile release regimen could effectively deliver drugs where need exists to counter naturally occurring processes such as bacterial/parasitical growth patterns (e.g., the once-daily oral Pulsys system introduced by Advancis Pharmaceutical Corp., which could potentially inhibit the emergence of resistant strains of microorganisms).
- Targeted drug delivery: Oral controlled drug delivery that targets regions in the GI tract and releases drugs only upon reaching that site could offer effective treatment for certain disease states (e.g. colon-targeted delivery of antineoplastics in the treatment of coloncancer).
- Mucoadhesive delivery: This is a promising technique for buccal and sublingual drug delivery, which can offer rapid onset of action and superior bioavailability compared with simple oral delivery because it bypasses first-pass metabolism in the liver.

References

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