

Drug Development

Timing Drug Availability With Therapeutic Need

By: Troy M. Harmon, MS, MBA, Senior Director, Business Development, Eurand, Inc.

Introduction

The Specialty Pharmaceutical marketplace continues to expand across many fronts: Companies specializing in developing products for specific patient populations, such as pediatrics or geriatrics; companies focusing in niche therapeutic areas; and drug delivery companies utilizing proprietary technology bases to create unique pipelines. The success of the Specialty Pharma industry segment is evidenced by the steady increase in the number of Specialty Pharmaceutical products that have been brought to market. There are significantly more new drug products approved compared to the approval of new chemical entities (NCEs) (Figure 1); two-thirds of NDAs are for line-extensions and/or new formulations of already marketed drugs. Likewise, the number of Specialty Pharma “blockbuster” products with >\$500 million in annual sales is on the rise — a 250% increase in the past 7 years to more than 50 such products last year (Figure 2).

In many cases, Specialty Pharma companies are taking advantage of the risk/reward benefits of reformulation of already approved drugs with known safety profiles and shorter development cycles. The bread-and-butter of Specialty Pharmaceutical product development relies on minimizing

the risk of drug product development. Big Pharma needs NCEs to drive growth and keep generic competition from destroying brand value; however, small and mid-size companies can reap significant reward from reformulation projects that provide for an unmet need — greater convenience, fewer side-effects, innovative use of off-patent drugs in new indications or in combination products. Frequently, Specialty Pharma will turn to drug delivery technology companies to provide creative approaches to developing their new products — needless injection, transdermal patches, nasal and lingual sprays. In the oral drug delivery field alone, there are companies offering technologies for gastroretention (when the absorption window is a concern) or lipid-based formulations to enhance bioavailability or pulsatile release to create custom pharmacokinetic profiles.

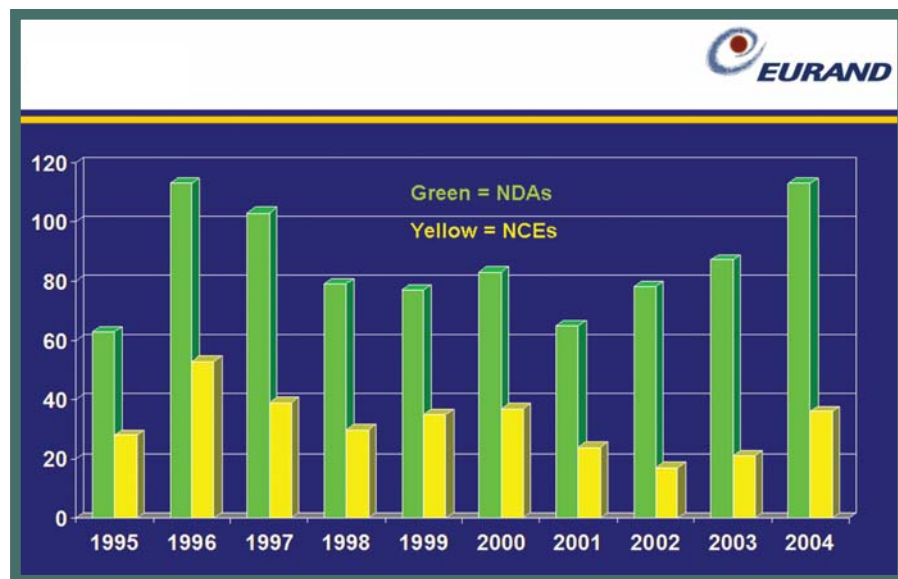


Figure 1

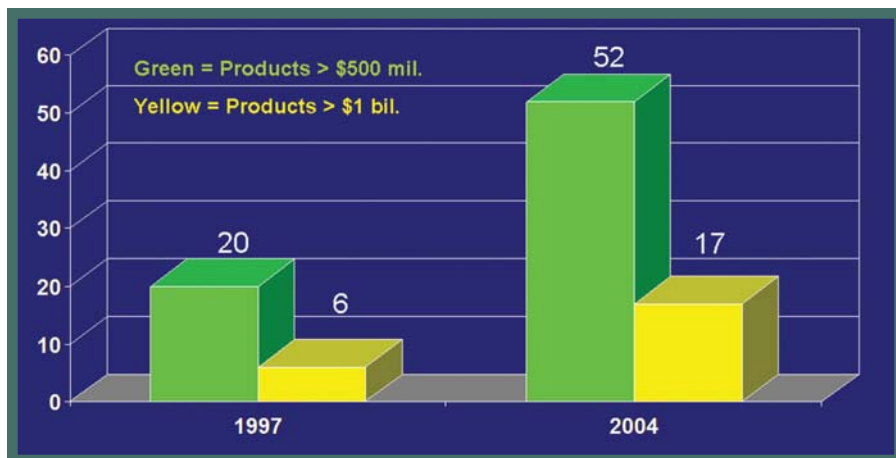


Figure 2

However, the gold standard for route of administration remains oral delivery, preferably once-a-day administration, and pulsatile and/or delayed-release technologies can be used to enable qd dosing for challenging drug substances. Specifically, with regard to delayed or pulsatile drug delivery, there is an opportunity to develop specialized “chronotherapeutic” products to time the release of drug at the optimal time-of-day.

Chronotherapy

Most physiological, biochemical, and molecular processes in healthy organisms display robust, predictable changes on a 24-hour schedule. Chronotherapeutic products can synchronize drug delivery with circadian rhythms in order to optimize efficacy and/or minimize side-effects. This is one avenue to extend the useful life of a drug substance and create new brands for Specialty Pharma — a less expensive development proposition with potentially higher returns given the time to develop a product based on an NCE or even a combination product for a new indication.

The outdated western theory of “homeostasis” taught that the probability of risk or intensity of disease was equal throughout a specific period. However, chronobiology (the quantitative study of the rhythmic temporal relationships of biologic phenomena) has quite clearly been proven across many biological functions:

- **Intraocular Pressure (IOP)** — in glaucoma patients IOP peaks at 4 AM and has a trough in the afternoon, opposite that of people with normal IOP;
- **Hormone Secretion** — growth hormone and melatonin are produced at night; testosterone and cortisol in the early morning hours;
- **Allergic Response** — skin tests produce a 3X greater result when given at night;
- **Gastric Motility** — slower at night, which can impact controlled-release product design;
- **Seasonal Affective Disorder (SAD)** — affects 1% to 3% of adults; increased sleep and appetite are a well-known phenomena in winter;

- **Atrial Fibrillation** — hospital admissions peak in April with a trough in August;
- **Blood Coagulation** — even with constant heparin infusion rate, thromboplastin time and risk of bleeding vary significantly during the day;
- **Cholesterol Production** — statins dosed in evening have been shown to be more effective;
- **Asthma Treatment** — evening dosing can improve lung function during sleep; and
- **Cancer Drug Administration** — treatment timing can significantly reduce side-effects.

For diseases ranging from asthma to arthritis, the cure may be dictated by the timing of drug administration. Hence the emergence of chronotherapy — coordination of medical treatment with biological rhythms is especially useful for disease states with known circadian patterns. Chronotherapy has been appreciated in the principles of eastern medicine for a long time, but drug development is just now catching up. By taking advantage of known biological patterns in disease manifestation, the goal of developing chronotherapeutic products to optimize the desired effects of a drug and minimize its undesired ones, can be achieved in certain disease states. For

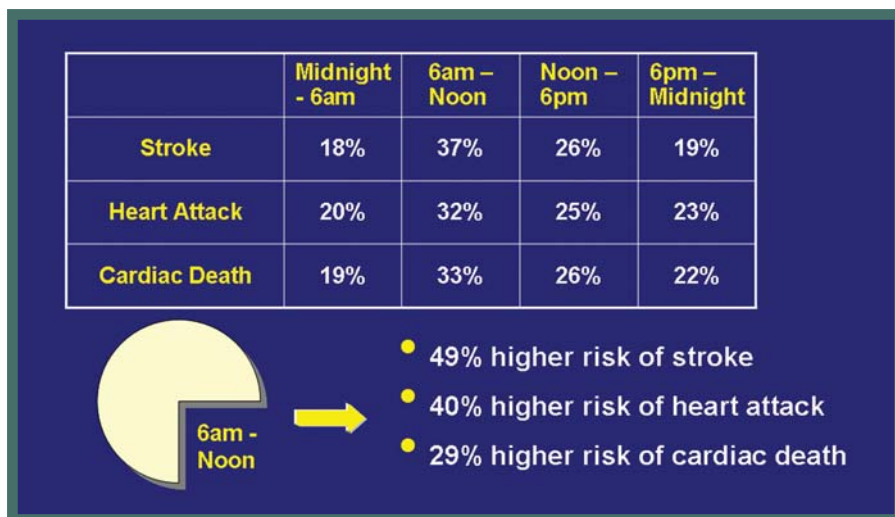


Figure 3

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example, the benefits of chronotherapy are well established in the treatment of cancer, and the timing of chemotherapy drug administration can improve treatment tolerability and permit higher, more efficacious dosing. The survival rate in ovarian cancer may be quadrupled when doxorubicin is given in the morning and cisplatin in the evening.

Furthermore, there is a high incidence of disease symptoms and adverse events in the morning hours, so ensuring that adequate plasma levels of a drug are present in the morning can be critical to effective treatment of many diseases, including cardiovascular disease (Figure 3). This is also true for pain management — pain in the morning is greatest for some conditions, but evening pain is more common in other conditions. In addition, the more narrow the therapeutic window of the active, the more important the implication of circadian variation in plasma levels. Development of suitable chronotherapeutic oral dosage forms can be achieved using delayed- and/or pulsatile-release technologies.

Pulsatile Drug Delivery

Oral drug delivery technology has been used to enable a number of chronotherapeutic drug products. In the treatment of attention-deficit disorder, it is important to maintain adequate plasma levels during school hours, and, in some cases, have the plasma levels decrease after school hours so that the side-effects of appetite suppression and

insomnia are not manifested. There are a couple of methylphenidate products on the market that achieve this goal, including MetaDate CD[®], which releases the methylphenidate in two pulses separated by a delay.

Chronotherapy is important in the GI area — treatment of ulcers and heartburn throughout the day can be improved by timing drug availability before meals as gastric acid secretion increases after a meal. Also, some patients suffer from night-time gastro-esophageal reflux disease (GERD), and a pulsed drug product has been developed to minimize acid secretion during the night. Delayed-release medications for hypertension are prescribed for evening dosing so that adequate plasma levels are available in the morning hours

when cardiovascular events are more likely. Covera HS[®], Verelan PM[®], and InnoPran XL[®] (Figure 4) are examples of marketed products utilizing this approach.

There are a variety of oral dosage form technologies suitable for achieving pulsatile drug delivery: Osmotic-pump systems, erosion-based monolithic tablets, and multiparticulate-containing capsules to name a few. In particular, there are numerous advantages of multiparticulate systems for achieving flexible and accurate pulsatile drug delivery. Multiparticulate dosage forms are composed of small beads, with each bead composed of many layers. Some of the layers contain drug substance, and other layers are rate-controlling polymers (Figure 5).

The beads are typically ≤ 1 mm in diameter and readily disperse in the stomach. Unlike larger tablets, these small beads exit the stomach in a more consistent fashion, thus pharmacokinetic variability is decreased. Also, adjustment of dose strength and creation of dose-proportional products is quite facile with a multiparticulate system. Combination drug products can also be formulated without drug-drug compatibility issues. The range of drug-release profiles is not limited with multiparticulate dosage

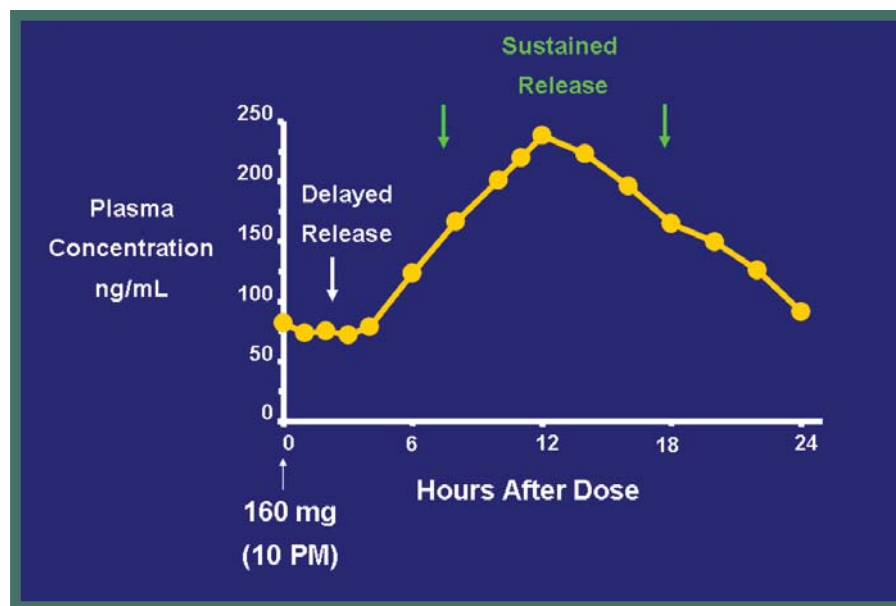


Figure 4

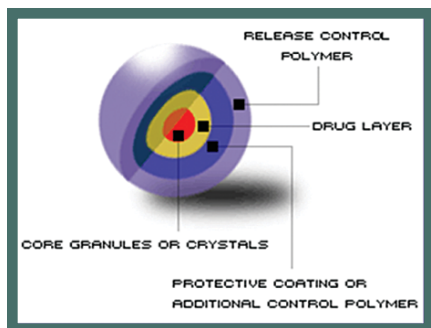


Figure 5

forms; the dose can be spread over different amounts in two or three pulses, and lag times between pulses can be varied from 1 hour to up to 8 hours. In Figure 6, the drug load is split into two equal parts with the first pulse delivered after the beads have exited the stomach, and the second pulse delivered after a lag time of 6 hours.

Summary

There are several technical challenges that must be overcome to develop chronotherapeutic medicines using pulsatile delivery technology. Ensuring that the drug has an adequate absorption in the lower GI tract is an important

consideration. In some cases, it is necessary to conduct *in vivo* intubation studies before a formulation can be developed. Also, a growing number of drug candidates demonstrate pH-dependent solubility, especially poor solubility at the higher pHs of the lower gastrointestinal tract. By careful choice of the polymer film composition of the bead layers, solubility hurdles often can be overcome. Correlating the pharmacokinetic profile with the pharmacodynamic response is instrumental in designing the ideal release profile, and whether or not there is significant activity, and circulating plasma half-life, from any metabolites of the active.

Finally, from the regulatory perspective, proof that treatment efficacy is improved by a customized dosing regimen is needed to receive a strong label claim and to get intellectual property protection for an improved formulation. All of this makes development of chronotherapeutic, pulsatile-release products particularly challenging; however, getting the right drug to the right place at the right time can provide competitive differentiation in an increasingly crowded marketplace, where many companies are increasingly developing new formulations of the same drug.

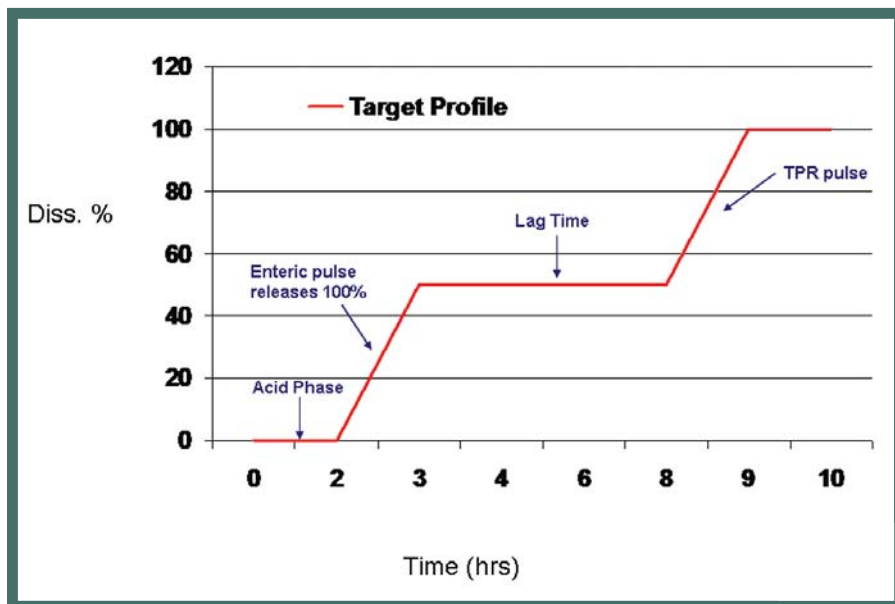


Figure 6



TROY M. HARMON, MS, MBA

Senior Director,
Business
Development,
Eurand, Inc.

Mr. Troy Harmon is currently a Sr. Director, Business Development for Eurand, Inc., a Specialty Pharmaceutical company focused on the development of novel drug delivery technologies and products. Mr. Harmon joined Eurand in 2002, and his responsibilities include business development, marketing, and licensing efforts for Eurand in North America. Prior to joining Eurand, Mr. Harmon was Director, Business Development at Delsys Pharmaceutical in Princeton, NJ, where he was responsible for marketing and partnering the company's electrostatic powder deposition technologies worldwide. In addition, Mr. Harmon has served as Director, Business and Product Development at FEI Technologies, a company specializing in implantable drug delivery systems, and as Sr. Scientist at Summit Technology, an innovator in laser vision correction procedures. Mr. Harmon earned his BS from the University of Kentucky, where he was elected to Phi Beta Kappa and received the University's first prize for undergraduate academic research. Mr. Harmon also earned an MS in Physical Chemistry from Cornell University, and an MBA from Villanova University.