

Controlled Release Technologies for Oral Drug Delivery: Comparative Advantages, Market Trends and Available Technologies

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Introduction

Over the past two decades, the pharmaceutical market has demonstrated an increasing preference for modified oral dosage forms that allow for controlled release (CR) rather than immediate-release (IR). Increased patient compliance, patent extension, product differentiation, heightened safety and efficacy, and a greater rate of return represent significant motivations for the application of CR formulations to new and existing drugs. Several general techniques of CR oral drug delivery have been developed to accommodate the administration of therapeutics with specific pharmacokinetic and biopharmaceutic properties: enteric-coated or delayed release, bi-phasic or pulsed, and extended or sustained release; these techniques may be combined to produce general first-order, bi-phasic, or near zero-order pharmacokinetic profiles, or unique profiles specific to a given compound. The major types of oral CR delivery systems – coated-bead or multiparticulate, reservoir devices, and diffusion-based systems such as physical-geometric, simple matrix and hydrogel matrix systems – each possess certain advantages toward achieving a given pharmacokinetic release profile.

Advantages of Controlled Release Formulations

Much of the industry's preference for CR formulations lays in their fundamental ability to reduce the number of doses required over a period of time for those drugs which must be administered multiple times on conventional IR dosing schedules. Through the combination of a reduction in dosing frequency and an optimisation of the amount of drug entering systemic circulation, a CR formulation may increase the efficacy of the compound and may improve patient compliance as the dosing frequency is reduced.

The object of many controlled release technologies is to minimise the time the concentration of active drug is above or below the therapeutic window, while extending the duration the active agent exists within the efficacious range of concentration. Maintaining drug concentration within this therapeutic window may be complicated by many factors including receptor saturation, site-specific or reduced bioavailability of the drug within the gastrointestinal (GI) tract, plasma protein binding, and alterations in the number and concentration of drug

metabolites. Concentrations above this range may result in toxicity, and concentrations below this range may result in decreased efficacy, manifested by breakthrough symptoms. Those readily bioavailable compounds possessing short-elimination half lives (<8 hours) often produce a large fluctuation between the maximum (C_{max}) and minimum (C_{min}) concentrations of drug in circulation, (Ritschel, 1989), which are themselves above and below the therapeutic window. This "peak and trough" effect may result in the patient experiencing dramatic onset and withdrawal of the drug's effects in addition to side effects or being without therapeutic benefit until the next dose. Alternatively, those compounds with a narrow therapeutic index whose half-lives are >20 hours may benefit from CR formulations through the suppression of plasma levels approaching C_{max} and the associated increased risk of toxicity (Pillay and Fassih, 1999; Pillay, 2000).

The optimal dosing regimen for many drugs is once- or twice-per-day such that steady-state concentrations of the drug are present in systemic circulation, or plasma concentrations peak during a particular time of day. This is often the case with cardiac drugs such as diltiazem and metoprolol that must provide continued therapeutic efficacy during early morning, (often hours after the dose is administered), and anti-hyperlipidaemics, which achieve maximum efficacy at night during periods of peak cholesterol production.

The Economics of Oral CR Drug Delivery

In 2000, half of all pharmaceuticals employing any type of drug delivery system were orally administered, and delivery technologies were incorporated into 40% of the US\$55 B oral pharmaceuticals market in the US. Of the US\$22 B oral drug delivery market, CR formulations comprise more than 90% of the total demand, amounting to nearly US\$20 B. This market has consistently grown 8-9% per year in recent years and is expected to rise to approximately US\$29 B in 2005, and to US\$40 B in 2010 (Datamonitor, Inc.). While the increase in application of CR delivery systems is driven by their comparative advantage over IR systems, the increase in patient populations requiring pharmacological therapy for chronic conditions and the utilisation of CR formulations as a means of pharmaceutical product life cycle management will also contribute to this significant growth. The expected increase in the penetration of CR

formulations into the chronic therapeutic market over the next 10 years – from 13% in 2000 to almost 19% in 2010 – reflects both of these trends.

The general market distribution of delivery system types is not expected to change dramatically in coming years, with multi-particulate or coated-bead technology retaining 46-47%, reservoir devices growing slightly to 14-15%, and diffusion devices of various types (including hydrogel matrices, simple matrices and physical-geometric devices) at approximately 38% of the total oral CR market (Freedonia Group, 2001). The market distribution among therapeutic categories will reflect current trends in both technology and life cycle management, with cardiovascular oral CR formulations remaining a mainstay for all three delivery technologies – reservoir devices and multiparticulate systems commanding roughly twice the demand as diffusion-based systems – while central nervous system and respiratory oral CR formulations are almost exclusively diffusion and multi-particulate systems, anti-infectives are primarily formulated in diffusion-based systems, and gastrointestinal therapies largely employ multi-particulates. While the domination of any one broad therapeutic category by a given delivery system type is not expected to be reversed, significant shifts are occurring in the respective demand for these delivery systems relative to their respective portions of the market: multi-particulate and diffusion-based technologies will increase their presence among CNS compounds but rely less heavily on respiratory (asthma) and cardiovascular therapies; and diffusion-based and reservoir-device technologies will see dramatic increases in the number of hormone and diabetes oral CR formulations (Freedonia Group, 2001). The historical dependence of the drug delivery market on developments within therapeutic categories (as opposed to developments in drug delivery technology) will continue. The de-emphasis of the respiratory and cardiovascular markets as the primary sources of revenue for oral CR therapies will also continue as more ethical pharmaceuticals go off-patent and new developments in CNS (multiple sclerosis, antidepressants), diabetes and oncology therapies emerge (Datamonitor, 2001).

Traditional and Novel Drug Delivery Technologies

The significant presence of a given delivery system type within a therapeutic category is largely a function of both the strengths of the delivery technology itself and the relative familiarity of formulators with a given technology in their portfolio. Thus, the dominance of coated-bead systems among gastrointestinal therapies reflects their ability to offer good distribution and quick transit time through the upper GI while providing protection from gastric pH; diffusion matrices among CNS therapies because of their extended release capacity and high large drug loads; and reservoir devices among cardiovascular therapies that often require zero-order release profiles.

Coated-bead and multi-particulate systems often employ pH-sensitive, enteric or sustained release coatings

upon aggregate or non-pareil granules of the API. These granules may then be packaged in a capsule or compressed with additional excipients to form a tablet. The API may also be blended or granulated with polymers before coating to provide an additional level of control; these systems may also appear as a blend of coated-beads with differing release rates for extended release or pulsatile release formulations. The complexity of production of coated bead systems – large numbers of excipients, use of solvents and multiple manufacturing steps – have allowed companies such as **Andrx**, **Biovail** and **Elan** to become specialised providers of the technology.

Reservoir devices usually consist of a semi-permeable barrier that is involved in the release of the API from a core site within the tablet. Some devices such as **ALZA's** OROS® push-pull osmotic system employ multiple compartments, one containing a swellable osmotic agent and another containing drug that is pushed out of one or more orifices as the hydrophilic agent pulls water into the dosage form. Other technologies employ additives to aid in solubilisation, further control release through polymers that further limit the influx of fluid, or utilise pore-forming membranes instead of orifices to facilitate drug diffusion. Although capable of producing a linear release pattern, factors such as the complexity of design and access to specialised equipment necessary for the manufacturing processes may result in limited applicability for many products.

Geometrical-physical systems incorporate the active ingredient into a layer or core, which is then formed into a pellet and altered by physical means to effect and control the rate of erosion or dissolution of the dosage form. Surface-area modifications are often employed to retard the burst release of highly soluble actives or increase the extent of the release of actives from tablet cores that possess diffusion limitations. The physically-altered pellet may then be incorporated alone or in combination with other modified pellets and excipients into a capsule or tablet. These systems can be quite simple, such as an enteric-coated tablet, or highly complex, such as the modified-core tablet systems of Procise™, developed by **GlaxoSmithKline**, and Smatrix™, developed by **Smatrix Technologies**. Many of the physical-geometric delivery system designs are intentionally complex so as to remain distinctive and proprietary while also providing a significant degree of flexibility in formulation and a wide range of available release profiles. As the rate and extent of release is dependent upon how the physical alteration to the tablet is affected *in vivo*, variations in the coatings or barriers dramatically affect the release of the active ingredient, may result in a high degree of *in vivo* release variability.

Simple matrix systems such as pore-forming waxes incorporate the API into an insoluble base and rely upon the rate of erosion to control the release of the drug. The API and a water soluble excipient (such as a polymer or salt) are introduced into a wax or wax-like compound (such as paraffin) and then placed in an aqueous environment in order to allow the water soluble polymer to dissolve out of the wax, resulting in the formation of pores. Upon

contact with the gastrointestinal fluid, the pores facilitate erosion of the wax and the subsequent release of the active ingredient. This erosion is often non-linear – the accuracy and efficacy of the resulting rate of release is often of insufficient precision for many pharmaceutical products – and is rarely capable of controlling drug release in a near-linear fashion over 24 hours, because the high volume of controlling excipient required for such a duration often results in a significant portion of the drug remaining trapped in the wax matrix.

Diffusion systems rely on hydrophilic polymer swelling for control of drug release, and may then be coated with diffusion barriers to further control drug release. These systems often employ granulation steps to incorporate the drug in a single polymer such as polyethylene oxide or hydroxypropyl methylcellulose; the diffusion barriers are often formed from film-forming polymers such as acrylic resins or ethyl cellulose. These granulation and coating processes add extra processing steps, variability and cost to manufacturing. While such diffusion systems have yielded acceptable sustained release patterns for short durations, it is difficult to produce a linear release over 12 to 24 hours.

A unique alternative to diffusion matrices which rely upon granulation and coating are **SCOLR**'s self-correcting hydrogel matrices. This "self-correcting" characteristic refers to the ability to correct changes in surface area, gel viscosity and diffusional pathlength which occur during hydration and swelling required to achieve first-order, bi-phasic, or near zero-order release kinetics over 24 hours. By employing excipients capable of inducing inter-gel pH after hydration while simultaneously controlling the influx of water, erosion of the tablet and diffusion of the drug, these hydrogel diffusion systems are capable of producing release profiles comparable in performance with multi-particulate, reservoir or physical-geometric systems at the cost of more rudimentary diffusion matrix systems. As the controlling excipients are only activated *in situ*, the manufacturing process is limited to either two-step dry-blend and direct-compression, or granulation of the active and subsequent dry-blend and direct compression.

Conclusion

The comparative advantages of oral CR delivery technologies over IR technologies are significant: reduced dosing frequency, increased efficacy, flexible pharmacokinetic profiles and improved patient compliance. The market for oral CR therapies is very strong, expected to double by 2010 and diversify significantly with expansion of diabetes, oncology and CNS therapies. Numerous traditional and novel methods of achieving CR with oral formulations are available, each with differing degrees of flexibility in terms of *in vivo* performance and complexities of manufacture.

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