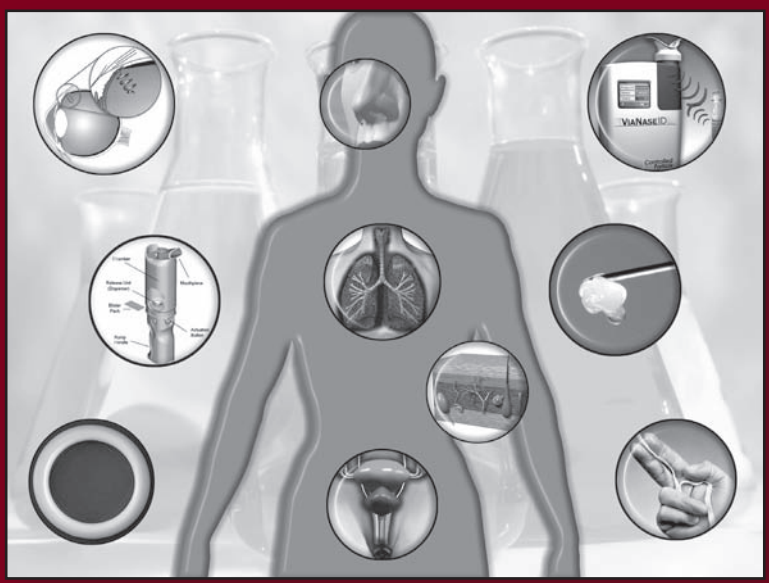
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 184

Modified-Release Drug Delivery Technology

Second Edition

Volume 2



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Modified-Release Drug Delivery Technology

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Modified-Release Drug Delivery Technology

Second Edition

Volume 2

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CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Version Date: 20150226

International Standard Book Number-13: 978-1-4200-4526-0 (eBook - PDF)

To my son Benjamin

—Michael J. Rathbone

Preface

Over the last few decades, rapid developments have occurred in the area of modified-release drug delivery technology, and significant research and development has occurred in all routes of drug delivery. This is an ever-expanding area of pharmaceutical research, and so we decided to update and expand *Modified-Release Drug Delivery Technology* to achieve a more comprehensive compilation of information.

To this end, the Second Edition is divided into two volumes. Volume 1 addresses modified-release drug delivery technologies developed for the oral mucosal and gastrointestinal routes. Volume 2 addresses modified-release drug delivery technologies for the parenteral, dermal, pulmonary, nasal, vaginal, and ocular routes. Both volumes assume that the reader is already familiar with fundamental controlled-release theories. The volumes are divided into discrete parts, each of which is defined by the route for drug delivery. Individual parts begin with an overview, written by the leaders in the respective fields. They cover the anatomical, physiological, and pharmaceutical challenges inherent in formulating a modified-release drug delivery technology for a particular route of drug delivery. Each overview is followed by chapters that provide specific examples of the different approaches that have been taken to design and develop an innovative modified-release drug delivery system for those routes (written by experts in that specific technology).

Modified-Release Drug Delivery Technology, *Second Edition*, aims to describe as many examples of modified-release drug delivery technologies as possible. Ultimately, however, inclusion of a given technology in this book was based on author availability, rather than the desire to include a particular technology or to select or reject a particular technology based on its relative merits. We hope that the selection is representative of each field.

The first part of Volume 2, edited by Stephen Perrett and Michael J. Rathbone, contains chapters that provide an overview of the modified drug release landscape as observed from the commercial (Perrett) and academic (Siepmann) viewpoints. An evaluation of the role of modified-release formulations to address patient and doctors' needs (Anelli), and a viewpoint on investors' requirements (Walton) are also discussed in this part. These chapters provide an interesting insight into how these different disciples view this area of research. In Part II, Robert Gurny and colleagues provide an overview of currently available and emerging modified-release ophthalmic drug

delivery systems. Most of these systems are in the developmental stage, but several technologies that have reached commercialization are described in depth. Part III addresses implant and injection technologies. In their introduction section leaders Majella Lane, Franklin Okumu, and Palani Balausubramanian offer a comprehensive overview of this evolving and challenging area of drug delivery. They complement their overview with chapters that cover a diverse range of implant and injection technologies. Section leaders for Part IV, Jonathan Hadgraft, Majella Lane, and Adam Watkinson, have written a thorough overview of the dermal and transdermal area and have organized a series of chapters that cover a wide range of diverse technologies, from wound dressings, through nail delivery, to propulsion of solid drug particles into the skin by means of a high-speed gas flow. Patches that deliver drugs via diffusion, iontophoresis, sonophoresis, or microprojections are also covered.

The nasal route is covered in Part V. Section leader Ashim Mitra offers an instructive overview into this interesting route of drug delivery that highlights how difficult drug delivery can be for this route of administration. David Woolfson (Part VI leader, vaginal route) presents a comprehensive account of the biological and pharmaceutical challenges to the vaginal route of drug delivery, which is restricted to 50 percent of the population and is limited by cultural and societal constraints. The chapters associated with this section provide an insight into the different approaches that can be employed to deliver drugs via the vaginal mucosa. In the final section of this book (Part VII) section leader Paul Myrdal provides an informative overview of the unique challenges associated with delivering drugs via the pulmonary tract. The chapters in Part VII describe the various systems, devices, formulations, and methods of drug delivery to the lung. The focus of pulmonary drug delivery systems tends not to be on the control of medicament release from the formulations in which they are presented, but rather on inhalation systems that deliver drugs practically instantaneously to the target organ (which is the "release" part for therapeutic activity for many of the currently approved products for inhalation). Numerous different technological approaches are described in the chapters associated with this section, each of which provides descriptive comments on the complexity of this route of drug delivery.

We would like to express our thanks to each of the section leaders, who spent a great deal of time identifying technologies, writing informative overviews, and editing the chapters associated with the routes of drug delivery in which they are expert. We would also like to thank all of the authors who contributed chapters to this book, whose individual innovative research activities have contributed so much to the current modified-release drug delivery technology portfolio that exists today. We thank them for taking the time to share their experiences and work.

Michael J. Rathbone
Jonathan Hadgraft
Michael S. Roberts
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PART III: INJECTION AND IMPLANT TECHNOLOGIES

PART IV: DERMAL AND TRANSDERMAL TECHNOLOGIES

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Part I: Using Modified-Release Formulations to Maintain and Develop Markets

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The Modified-Release Drug Delivery Landscape

The Commercial Perspective

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The life cycle management of pharmaceutical products through reformulation is an established practice in the industry and, historically, many commentators have recognized the opportunity that reformulation can represent for specialist companies and technology-focused innovators. The 1990s saw an increasing number of companies being created that based business models on the development of established therapeutic compounds as this offered pharmaceutical product development which was faster, cost less, and had a large part of the therapeutic risk removed. The estimated size of market represented by reformulation varies between commentators and relies upon the definition of drug delivery, but figures from Datamonitor estimate it to be currently worth in the region of $114 billion. If one also considers that on average between 2002 and 2005, 39% of all new product launches by the top 50 manufacturers were reformulations of existing drugs (MIDAS prescribing insights: IMS Health March 2006) and that IMS placed the global Pharmaceutical Market in 2006 at $643 billion, then the monetary value of reformulation is clearly significant.

COMMERCIAL DRIVERS OF REFORMULATION

The goal and driver for product reformulation is the generation of a positive return on the investment made to develop and launch a reformulated product and both innovators and companies specializing in reformulation must

carefully consider the financial implications in deciding whether or not to adopt this strategy for a given compound as although reformulating a product may improve it, it may not ultimately be worth it. Reformulation strategies generally seek to expand the market for a compound, to defend the market of a compound or to create a new market for a compound. There is inevitably some crossover in the strategies used and the approach taken is also a function of the competitiveness of the compound as it is and the actions of competitors.

In seeking to expand a market innovators are looking to take a compound into new areas through label expansion, this generally involves new clinical studies, it may also involve the concurrent production of dosage forms that are more friendly to a particular patient group—such as orally disintegrating tablets (ODTs) or suspension formulations.

In defending their markets, innovators are seeking to make their products more competitive by, e.g., launching once a day formulations into a therapeutic area where competing products are dosed multiple times per day. The most common form of market defense, however, is defense against generic launch and innovators seek to extend the life cycle of the brand by making it non-substitutable by a generic product, this means that formulation changes need not necessarily improve product performance, although this would be a desired outcome.

The final reformulation approach is to seek to create a new market for an already generic compound and, when they are not partnered with innovators, this is where specialist reformulation companies operate. This is not just the preserve of specialist companies and innovators will also play in this space if they see an opportunity. The strategic driver of reformulation depends on the position of a compound in the life cycle of a brand. The weights that are given to differentiation, in the sense of just being different, and true therapeutic differentiation vary greatly at different points in the life cycle. As discussed below, differentiation for generic defense need only mean that the product is different from the product used in an abbreviated new drug application (ANDA) filing, whereas a reformulation launched into an already generic market must represent a significant therapeutic improvement over the now commoditized product.

GENERIC DEFENSE

Differentiation from Generic Products

The goal of reformulation as a means of generic defense is clear: to prevent the substitution of the branded product by generics on patent expiry. To do this it is sufficient to alter the branded product only to the extent that it is no longer the same as the product that the generic companies are using as the reference for their registrations. This prevents pharmacies substituting generic product for the reformulated branded product which will not have been used as a

reference formulation. It is essential that the brand holder switch their patients to the new formulation prior to generic launch and the timing of the launch of the new formulation is crucial. If it is launched too soon then the generics will simply use the new formulation as the reference, if it is launched too late then the market for the brand will have already been lost to the generics.

One of the clearest and most successful instances of this has been the successive reformulations of fenofibrate by Fournier (now Solvay), who have succeeded in defending Tricor® (Abbott) through changing the dosage strength or the form of the product. The first product iteration was a 300-mg capsule containing particulate drug; the second, a capsule containing 200 mg of finely milled drug; the third a 160-mg tablet containing finely milled drug and surfactant; the fourth a 145-mg tablet containing nanoparticulate drug—all of these formulations are bioequivalent to one another. Progressive size reduction resulted in more than a two-fold increase in bioavailability, but all were bioequivalent to one another and essentially directly substitutable formulations from a medical perspective: however, they are not directly substitutable from a regulatory perspective. This means that scrips written for Tricor® cannot be substituted in the pharmacy and this is true even if the dosage from is changed from a capsule to a tablet. That said, the final nanoparticulate formulation did enable Abbot to remove the food requirement for dosing from the label.

It is debatable whether any of these changes represented anything other than a repackaging of the same ingredient; however, through the use of successive periods of market exclusivity associated with the new dosages the brand has been able to avoid substitution by generics, thus preserving its value through three successive expirations of market exclusivity, as the innovator was able to switch patients to the new formulation prior to this. The great advantage to this approach was that it was a relatively inexpensive series of progressions from the perspective of the clinical registration requirement in that no efficacy studies were required for formulations that aimed only at bioequivalence.

That it is the brand that drives value is further illustrated in the case of this drug by Scieles nanoparticulate product of fenofibrate licensed from Skyepharma, which is a low-dose small-particle formulation. The Sciele product was largely similar to Tricor® and had a similar label, including the lack of a food requirement, yet it was reported by Sciele to have only 1.8% of total prescriptions at the end of the first quarter 2007. That sales are a tiny fraction of those of the Tricor® brand may seem predictable, but it is perhaps salutary to those who might think that the pharmaceutical market differs substantially from any other.

While the market considerations driving Tricor® seem to have been paramount, there are other reformulation examples that more readily retain a link between product improvement and market defense. Pfizer's Procardia XL®, which used the Alza [now Johnson & Johnson; (J&J)] Oros® sustained

release tablet technology, changed the dosage form from a capsule to a tablet, changed the divided dosage form to a once daily dosage form which also provided for a zero-order drug release. Despite the fact that pharmacokinetic profile of this formulation was eventually duplicated, the proprietary nature of the formulation and its differentiated release characteristics were enough to prevent direct generic substitution of the brand for over 10 years.

Timing of Reformulation

As mentioned above, timing is of crucial in optimizing the commercial returns from a compound through its product life cycle and innovators must launch at the right time, to launch too soon is to squander the 3 years of market exclusivity offered by the FDA on the basis of new clinical studies, to launch too late is not only to have missed this, but to launch into a market in which reference pricing will have seriously eroded.

As an illustration, GlaxoSmithKline's (GSK's) Paxil CR®, a reformulation of GSK's paroxetine obtained U.S. marketing approval for the controlled-release form based on SkyePharma's Geomatrix® technology in February 1999; however, the product was not launched until three years later in 2002. This allowed Paxil® to progress further in its life cycle as no generic entry was anticipated prior to 2003, thereby allowing GSK to switch patients to the new dosage form at an appropriate time and not prematurely. Generic attack of the CR form will now only began in June 2007 when Mylan's ANDA filing for a controlled release dosage form received approval on the expiry of pediatric exclusivity related to a patent covering the crystalline form of the active pharmaceutical ingredient (API). This also illustrates an interesting point regarding reformulation; the new formulation uses a proprietary technology with patent coverage until 2012, yet it is not this that has prevented a generic from entering the market. This is worth mentioning because, although formulation patents provide a significant barrier, does not have the same defensive power as patents covering the compound itself.

It is also worth recalling at this point that Paxil was a compound that was dosed once-a-day; the CR form did not change that. In circumstances where the brand was not available or where the market was already generic reformulation in this way would not have been a viable option. The therapeutic benefits of the reformulation are arguably minimal, as we saw previously with Tricor, but the submission of new clinical studies qualifies the product for 3 years regulatory exclusivity and renders it nonsubstitutable by generic Paxil.

The D2/D3 agonists ropinirole (Requip®) from GSK and pramipexole (Mirapex®) and their use in the treatment of Parkinson's disease are also illustrative of timing as a driver for the development launch of reformulated products. GSK have again chosen to defend this brand against generic

attack and to extend its life cycle with an extended-release formulation using the Geomatrix® technology—Requip CR®. In this case, however, there is the bonus of a less frequent dosing schedule, which is welcome for this patient group. GSK originally filed for approval with the FDA in April 2006 in anticipation of patent term expiry in May 2008; however, administrative problems with the submission meant that the FDA only finally accepted the filing in April 2007. This means that GSK will struggle to switch their Parkinson's patients to the new formulation, before generic appearance in the United States should they receive approval before May 2008, if they receive approval after this date then they may be entering a reduced value generic market. It is therefore fortunate that there is a clearly defined difference between the two products.

Mirapex (pramipexole) has an estimated patent constraint date of 2011, although Barr now has final approval for a generic version, Pfizer hold patents to an extended-release dosage form, but as yet there are no reports on the development of such a formulation, despite the fact that this would be a better dosage form. To launch, at this stage in the product life cycle would be to waste 3 years of regulatory exclusivity. That the development of Requip CR® has not caused Pfizer to move may be due to the fact that the revenue that might be lost to during the 2 to 3 year period that it will exist alongside Mirapex, would be as great as the 2 to 3 years' of revenue that would be lost to generics after 2011, if a CR formulation were brought forward now. Mirapex easily outsold Requip in 2005, $254 as opposed to $159 (IMS data) and one assumes that it is perception as a better drug will to some extent counter the convenience of Requip CR. Certainly of greater importance at this time is the registration of Mirapex for the treatment of restless legs syndrome as this is a new market in which Requip is currently unopposed. Since its approval in this indication in June 2005, U. S. sales have increased from $159 in 2005 to $315 in 2006 (IMS data).

This speculated timing of the launch of a Mirapex CR can be contrasted with Pfizer's reformulation of Detrol® to Detrol LA®. This reformulation occurred early on in the product life cycle in response to the appearance of Ditropan XL®, as the market began its move to once-a-day therapy. At this stage it was not possible to allow the competition to erode the revenue expectation of Detrol over an extended period. In this case, the potential loss over the remaining life span of the product would likely be much greater than would have been recouped through the delay of generic entry for a period of 2 to 3 years.

Defensibility and Value of Reformulation

Extended-release technology for oral drug delivery is a mature technology. Approaches that are able to also build features that go beyond converting multiple dose schedules to once-a-day are likely to fare best.

An interesting modification of the extended release angle was used in Pfizer's Azithromycin Zmax® azithromycin suspension. Azithromycin has a long half-life and dosing of Zithromax® was already once daily. By combining a high dose (2 g) with a sustained release technology, Pfizer was able to establish that a complete course of treatment was possible with a single dose. It is unclear as to whether the high dose or the formulation technology is the more important factor, but by using both, more defensibility can be built into the formulation.

That the dose of the formulation may be the technology is very well illustrated by Merck's alendronate, where the 70-mg dose can now be dosed once per week rather than being taken daily. This truly is a therapeutic benefit to patients and, as a result, it created a very competitive product. This has proven more difficult to defend from a patent viewpoint, but not entirely due to the fact that the dosing schedule is harder to defend per se.

The best technology patents look like new chemical entity (NCE) patents and in some cases they are. The recent launch of GSK's extended release Coreg® was based on Flamel's Micropump® technology: however, this product owes much to the phosphate salt of carvedilol used in the formulation. Carvedilol is poorly soluble at neutral and alkaline pH, meaning that absorption of the immediate release formulation occurs primarily in the upper part of the GI tract. A sustained release formulation would need either to be based on upper GI retention and/or the use of a bioavailability enhancement technology suited to insoluble drugs for the delayed-release portion of the dose. Through consideration of Flamel and GSK's patent application (1) a key mechanistic part of the formulation is linked to the increased solubility of the phosphate salt in combination with acidic excipients in the delayed release fraction of the formulation. The contribution of the Micropump technology is unclear, but should this patent proceed to grant substitution of the formulation becomes much less straightforward, being based more upon the chemistry of salt forms and combinations of chemical species in a particular dosage construct it becomes a more difficult task to duplicate without encroaching on the patents covering the product.

The move to use the phosphate salt and switch to a capsule from a tablet also resets the competitive clock of technology-focused developers, such as Biovail and Egalet, that were developing sustained elease carvedilol formulations. The substitution of the sustained release formulation that GSK had in development may not have been an express aim of their program, but now it is no longer an option. Controlled release formulations for substitution will need to be based on the phosphate form and on a capsule.

If one pursues this theme, the very best of all defense strategies would be new chemical entities, and one can reasonably say that Shire have taken

such an approach to the life cycle management of Adderall XR®. The recent settlements between Shire and Barr and Shire and Impax will allow Barr to market generic versions of Adderall XR in the United States on April 1, 2009 and Impax to market generic versions of Adderall XR in the United States 181 days following Barr's launch. Through a $2.3 billion acquisition of New River, Shire have obtained lisdexamphetamine, Vyvanse®, a dexamphetamine pro-drug, something that can be looked upon as a molecular sustained release technology. Vyvanse is also claimed to have less abuse potential and to be safer that its active moiety, but its biggest commercial advantage is the fact that it is a NCE and consequently entitled to 5 years of NCE exclusivity as well as benefiting from patents covering the compound itself.

We should not leave this area of life cycle management without considering the relatively recent phenomenon of reformulations through the separation of the active isomers from drugs that were previously marketed as the raecemate. This approach has been largely pioneered by the specialty pharmaceutical company Sepracor, who were among the first to recognize this business opportunity. Through the purification and selection of the most active isomer from a previously mixed product, medications with equivalent efficacy can be made using a lower dose of API, thus qualifying for market exclusivity in much the same way as we saw above for Tricor fenofibrate: however, in this case the protection is much more robust. The compound is also an NCE and may be eligible for much longer term patent protection. The weakness of this approach is that medical benefits, if present, are difficult to tease out. Despite this, Astra Zeneca's rebranding of raecemic omeprazole, Prilosec®, to the single isomer esomeprazole Nexium® has been successful—the clinical benefits being generated largely through what is effectively a dose increase.

A second example is Forest/Lundbeck's citalopram (Celexa®), whose franchise has been protected through the registration and launch of escitalopram with patent coverage now extending to March 2012 following a U.S. District Court ruling in July 2006 in Lundbeck/Forest's favor (2).

This launch was not as successful as it might have been as Lexapro is subject to more generic competition than anticipated due to Forest's failure to switch patients quickly enough from Celexa to Lexapro® before generic Celexa entered the U.S. market; with 29% of Forest's depression prescriptions still being written for Celexa on that date.

While there is price pressure from payers where the raecemic generic is available, and the very close similarities between the two products are self-evident, the fact that this strategy works (and that it works to the extent that it does) illustrates once again the power of marketing structures and the brand.

We have considered a series of formulation approaches with varying degrees of complexity and have seen that a simple reformation does not generally buy any more time from generic competition than is offered by the three years of exclusivity for the new dosage form given by the regulatory authorities. In many ways, the more challenging or suboptimal the formulation is in the original product, the greater are the possibilities for the innovator to retain control as improvements are sequentially added.

MARKET EXPANSION

There is a disincentive to add new formulations, such as extended release formulations, at points other than the late phases of the life cycle as this is to forgo the extension of life cycle as a means of generic defense. There is also a second disincentive: the cannibalization of the existing product. This will inevitably occur, making this a questionable move in terms of return on investment. Unless competitive products are gaining market share owing to a better dosing regimen, innovators will not move in this direction until the appropriate point in the life cycle.

At the approximate midpoint of a product life cycle, an appropriate means to grow sales of the product, as it is within any market, is to enter new markets. The expansion into new geographies is part of the normal progression of the product. In addition, the product progresses into new therapeutic areas through the performance of new clinical trials to add new indications to the product label. These can be incremental or moves into unrelated therapeutic areas or even the characterization of new disease states, such as restless legs syndrome, which has become an important market for Requip with sales almost doubling since approval.

Combination Products

The reformulation strategies used around the midpoint or a little beyond are, therefore, designed to add value through expanding the market reach of the compound, in these cases the original formulation will continue to exist with the new. Examples of this type of approach are found in combination products such as Novartis's Exforge®, a fixed dose combination of valsatran and amlodipine, and Lotrel, a fixed dose combination of amlodipine and benazepril. Other examples include Pfizer's Caduet®, a fixed dose combination of atorovastatin and amlodipine and Merck's Vytorin®, a fixed dose combination of simvastatin and ezetimibe. The Caduet® and Vytorin® products are interesting as they are arguably good and bad examples of the combination formulation approach, from a commercial perspective.

Caduet was intended to be the first combination therapy to target both dyslipidemia and hypertension. Although there is a strong correlation between the disease states the cross-risk factors and the titration schemes make the product difficult to use and the message of greater convenience is lost in a cumbersome prescribing regimen that involves 11 different formulations. Conversely, Vytorin®, a combination of two cholesterol-lowering drugs, is available in only 4 dosage combinations. The marketing message—that it is superior to monotherapies in lowering cholesterol—is clear and its prescribing is simple. This joint venture between Schering Plough and Merck has been very effective in extending the life cycle of Zocor® even though generic simvastatin is now readily available.

These reformulation strategies may not make as much use of the formulation scientists' art as controlled release formulations, but there are examples where technically innovative approaches are found in combination product or in products that coexist with the original dosage forms. Abbott's Kaletra®, a fixed dose combination of lopinavir and ritonavir, in which a liquid product requiring refrigeration dosed as a liquid or six soft shells was replaced by four tablets not requiring refrigeration. This was achieved using Abbott's Soliqs® technology and was approved by the FDA in October 2005 and in the European Union (EU) in July 2006.

The now abandoned combination of atorvastatin and torcetrapib, a product aimed to raise HDL levels while lowering LDL, which was under development by Pfizer as part of the management of the life cycle of Lipitor®, also incorporated a solubility enhancement technology to increase the absorption of torcetrapib (3). This added formulation complexity and, of course, enhances defensibility.

One of the most successful combination products has occurred in pulmonary medicine, and although there may be less opportunity for this delivery route, some reformulated products have been strikingly successful. Advair®, in which the combination of two drugs, salmeterol and fluticasone, which were previously separately available and remain so, has enabled GSK to create product with over $6 billion in sales. This was the first fixed dose combination of a bronchodilator and a steroid and accounted for 56% of new scrips after its launch in 2004.

This field has also seen one truly innovative product reach the market through the development of Exubera®, inhaled insulin, which represents a true breakthrough in the delivery of large molecules. Unfortunately, this has not led to commercial success.

Other noteworthy examples in this space are the development of a dry powder inhalation of the antimicrobial tombramycin for the treatment of bacterial lung infections in patients with cystic fibrosis. The present formulation is an air-jet nebulized delivery of a solution with an inhalation time of at least 15 minutes, which is bulky and not portable. The new formulation under development by Nektar and Novartis promises to be rapid and easily

portable. In this patient group, who are the subjects of a high pharmaceutical burden, reduction in treatment times or treatment approaches that contribute to an increase in their freedom is very welcome.

New Routes of Administration

The extended release formulations of J&J's risperidone, Risperdal Consta® is an injectable formulation based on the Medisorb® biodegradable microsphere technology of Alkermes, with a single injection providing therapeutic coverage for a two-week period. The oral form, Risperdal® was launched in the United States in 1994 and in the EU in 1997. Consta® was launched in the United States in 2003 and in the EU in 2002. It is the only injected antipsychotic and it could reasonably be said that it has 100% of the market represented by those patients who are unwilling to comply with oral therapy; in 2006 worldwide sales of Risperdal Consta® were $870 M (IMS data). It should be noted that worldwide sales of the tablet form were $3.6 billion (IMS data) and it has been suggested that there would have been more take up of Risperdal Consta if pricing had not been at such variance to the tablet—the difference being approximately five-fold in the United States.

J&J have chosen to manage the life cycle of Risperdal® with an NCE paliperidone, which is an active metabolite of risperidone. Invega® (paliperidone) was launched in the United States in January 2007 using J&J's Oros® sustained release tablet technology. The fact that the product is an NCE is currently providing the only means of U.S. defense for this product as it qualifies for five years NCE exclusivity from the FDA, giving it exclusivity until December 2011. The only Orange Book listed patent, which is specific to the NCE, expires in October 2009. Despite this less than ideal situation, which should be qualified by saying that this type of regulatory exclusivity is watertight, the technology does offer advantages that will help to drive the switching strategy, the Oros formulation of paliperidone is a true once-a-day, which is not always the case with Risperdal. The formulation also removes the need for titration at the onset of therapy; the complement long-acting injectable formulation of paliperidone palmitate has a longer period of action and can be injected less frequently, about six weeks. The injectable form also uses Elan's nanoparticle technology, creating a further entry barrier.

On the negative side, the product does face its stiffest competition from generic risperidone. There may be enough to prevent the product from being seen as purely created for the purposes of patent extension by physicians and payers, but the pricing pressure exerted by a generic product which is essentially therapeutically equivalent will be significant. Although the medical advance offered by this reformulation is more incremental, there is probably enough differentiation in the package for J&J to switch patients to the new forms with appropriate pricing.

The reformulation of products that were always injectables has also provided a successful means to expand markets. They have added the most in terms of the use of biodegradeable polymers to extend the efficacy of LHRH agonists, which has been continued to the point where formulations will provide coverage for several months and even as long as one year if the Viadur® titanium implant from Alza (now J&J) is used. One of the advantages of this type of technology is that duplication is not a simple task. The only real alternative is the Atrigel® implant technology from QLT.

There are also approaches in the injectable arena that employ a technology to sustain therapeutic effect through modifying the molecule itself. Pegylated interferon has largely replaced the nonconjugated parent molecule as a drug product. Frequent injections are both unpleasant and time-consuming and products that alleviate this do well. Other reformulations of injectable products have sought to decrease the toxicity of certain products, most notably paclitaxel. Also, the removal of the surfactant Cremophore® from Taxol® was seen to be desirable for the reduction in premedication that this would bring, as the delivery vehicle itself was pyrogenic and contributed to the dose-limiting toxicity of the medication. This proved considerably more challenging than would-be formulators of next generation Taxol imagined. But the eventual launch of Abraxane®, in which insoluble paclitaxel is absorbed to the surface of albumin particles, promises to be both a safer and more efficacious therapy.

New Dosage Forms

Successful formulation-based approaches aimed at expanding markets need not involve a switch to a different route of administration. The production of more convenient dosage forms or dosage forms suited to a particular type of patient are also used to expand the market reach of products and to enhance the competitive profile of the brand. The production of more convenient dosage forms, such as ODTs and suspension formulations, are popular means of doing this. The development of such formulations may also qualify for extension of patent terms of six months if directed toward pediatrics.

The suspension formulation is particularly suited to pediatrics as it can be easily titrated and is suited to all ages. The ODT is a relatively recent development tablet and early formulations were brought to the market by Cima (now Cephalon), Yamanouchi, Lafon (now Cephalon) and Ethypharm. These early formulations were rather fragile, required special packaging, and were not well-suited to high drug doses of active. Second-generation technologies such as Eurand's Advatab® and Cephalon's Durasolv® have characteristics that are similar to conventional tablets, while still possessing the ability to disintegrate very rapidly in the oral cavity.

The ODT dosage form has proven useful, not only for pediatric and geriatric dosage forms, but also for particular types of patients and disease

states. In cases where symptom onset is sudden and unpredictable, such as migraine or acute pain, the ODT is useful as it can be taken immediately by the patient, without the need for water, e.g., Zomig®, and Fentora® (fentanyl). In cases such as psychiatric disease, where the patient may not wish others to be aware that they are taking medication or where they may avoid taking it by holding conventional pills in their cheek or under the tongue, the ODT is useful. Examples of such products in include Risperdal ODT, Remeron® ODT, and Zyprexa® ODT.

A particular problem that has been encountered in formulating tablets that are designed to disintegrate in the oral cavity is that many drugs have an unpleasant taste and an additional technology of taste-masking is required to overcome this. This involves coating the drug particles so that a polymer barrier exists between the drug particle and the tongue. This ideally has to be achieved without delaying the release of the drug. This is particularly relevant to drugs that need to act rapidly, such as those for the relief of acute pain such as migraine and the 3-hour T_{max} of zolmitriptan in ODT form as opposed to the 2-hour T_{max} (Zomig® prescribing information) of the conventional tablet form is clearly a move in the wrong direction for a drug designed to bring rapid pain relief.

Other applications where the ODT dosage form is used are those in which the patient is extremely nauseas and would prefer not to contemplate swallowing water. ODT dosage forms are found in Zofran® (ondansetron), which is used for the prevention of nausea and vomiting during chemotherapy. It is also found in other applications where GI symptoms may also be a concern, such as the Prevacid® ODT form.

It is thus necessary to have both a sophisticated ODT technology and a sophisticated taste-masking technology to create successful products. Companies, such as Eurand, that are able to combine a diversity and experience in particle coating with advanced ODT technology are well positioned to further expand the use of the ODTs as a means to extend the market reach of products.

USING FORMULATION TO CREATE NEW PRODUCTS

The final area where reformulation can represent a commercial opportunity is in the reformulation of drugs whose patent has already expired. In this area, specialist companies need not partner with the innovator and brand owner; brand owners may also be opportunistic and attack markets created by others.

A well-publicized and illustrative example of this is the reformulation of methylphenidate by J&J into a once-a-day formulation using the Oros® technology it acquired from Alza, to both revitalize a market with a superior product and to take this market from the original franchise holder. J&J did not have a methylphendidate franchise prior to their launch of Concerta®, a

once-a-day Oros formulation, in 2000. Methylphenidate (Ritalin®), a Novartis compound, had already endured four years of patent expiry and sales had largely stagnated in the attention-deficit/hyperactivity disorder (ADHD) market. The patient group is primarily school children and the drug is a controlled substance. This had meant that the original twice-a-day dosing schedule required that the drug be dispensed under the supervision of a school nurse, making those on medication conspicuous with consequent embarrassment.

The ability to dose methylphenidate once daily for ADHD offers particular advantages, so despite a lack of a methyliphendiate franchise, J&J were able to step in and not only transform the ADHD market, but to take the ADHD market from the original franchisee through possession of a formulation technology and foresight. There were also thought to be additional advantages linked the Oros release kinetic, as ascending dose is thought to be a more effective way for the drug to enter the body. Concerta® soon dominated the market for methylphenidate-based drugs. Following the introduction of Concerta, between 2001 and 2003, the market exhibited a compound annual growth rate of 28% reaching $852 million in 2003. Concerta almost exclusively drove this growth, with 74% of all methylphenidate sales in 2003 (IMS data). In 2006 J&J reported sales growth of 20.2% and sales of approximately $900 million. This product has not been substituted in a now highly genericized market and still retains Orange Book exclusivities until 2008.

J&J were not alone in exploiting the particular advantages offered by once-a-day formulations in this market. Shire's Adderall XR®, a sustained release formulation of mixed amphetamine salts, was approved by the FDA on October 12, 2001. Although it was launched only six months prior to the market entry of Barr's generic, strong patient switching from Adderall to Adderall XR was achieved. In its first quarter on the market, Adderall XR accounted for 21% of total Adderall franchise sales. The momentum of uptake of the new formulation was maintained following the launch of further amphetamine generics from Eon and Ranbaxy in 2002. After three companies had launched generics, the XR reformulation still represented 83% of franchise sales and 68% of total molecule sales. That Shire has been able to regularly increase the price of Adderall XR, is entirely due to the fact that it is such a highly differentiated product.

The effect of both Concerta and Adderall XR has been to transform a generic market with products that have profiles similar to those of new entrants rather than the follow-on profiles of reformulations associated with generic defense that we considered earlier. These two products and their market illustrate well the ability of reformulation to drive growth and alter market structure. Further, the conception of these two approaches also illustrates two distinct drivers for reformulation. In the case of Adderall XR,

the defense against generic attack and in the case of Concerta the opportunistic conquest of an existing market with a superior product.

This is worth comparing with the reformulation of Xanax®. After patent expiry by Pfizer (Pharmacia and Upjohn), the extended-release formulation was approved in the United States in January 2003, nine years after patent expiry. This product offered a more convenient dosage scheme, but that was all that it offered. It did not overcome a particular problem in the way that Concerta did and could not claim any particular advantages associated with the technology used or offer any patent protection, and after regulatory exclusivity expired it was rapidly substituted by generics. In the three years before generic substitution occurred, revenues increased by approximately $48 million (Datamonitor), but the combination of clinical and launch costs probably make this a marginal product in terms of return on investment. Xanax XR® was never able to gain the momentum of Concerta, and although this strategy would have worked well for life cycle extension it did not work well as a means to revitalize the market for this compound.

There are a limited number of examples where reformulation has delivered a benefit to therapy to the extent that Concerta and Adderal XR have and these were more associated to the particular problems associated with the disease demographic than any unusual property of the formulation itself.

The reformulation of fentanyl has provided examples where the innovation associated with the formulation has also contributed in a large part to the success of the product. Fentanyl was originally developed by J&J in 1962. It is a highly potent opioid analgesic, with a potency approximately 100-fold that of morphine, and it is an important molecule in the management of severe and chronic pain.

In collaboration with Alza, which J&J subsequently acquired, J&J developed the Duragesic® patch, which has a number of important advantages over the injectable or oral means of delivery that had been used. Patients were exposed to a smooth flow of drug, without the need for infusion, over a long period (up to 72 hours). This was a better and more convenient therapy than those offered by generics allowing Duragesic to easily out-compete alternatives. At its peak, Duragesic represented a $1.6 billion market and worldwide sales have only just begun to decline 15 years post-launch with the appearance of generics in 2005: Duragesic sales reported by J&J for 2006 were $1.295 billion.

The approach that Anesta (now Cephalon) took with fentanyl was to enter a new market with a formulation designed to meet the needs of patients in that market. Actiq® was specifically targeted to break through cancer pain, which is a condition in which cancer sufferers experience acute, unpredictable spikes of severe pain that overcome their pain therapy. Actiq is a lollipop formulation of fentanyl, which patients place into their mouths

when they experience an episode of breakthrough pain. The very high potency of fentanyl together with its ability to cross the buccal mucosa means that pain relief is achieved very rapidly without the need for injection, furthermore patients can optimize dosing by removing the lollipop once the pain has abated. From 200 to 2003 U.S. sales of Actiq grew from $14 to $245 million in 2003 giving Actiq a 16% of the fentanyl market (Datamonitor). In that time the price of Actiq almost doubled. Sales of Actiq reported by Cephalon for 2006 totaled $572.1 million, representing a year-on-year growth of 39%. Cephalon has managed the life cycle of this franchise through the launch in October 2006 of Fentora®, an ODT tablet for buccal absorption based on the Oravescent® technology acquired from Cima.

A very recent example of an innovative formulation of an old drug to produce a differentiated product is provided by the launch in June 2006 of Vivitrol®, a sustained release injectable formulation of naltrexone licensed from Alkermes. Following subcutaneous or intramuscular administration a steady release rate of naltrexone release into the bloodstream is sustained for up to 1 month.

Naltrexone is an opioid receptor antagonist and was approved for the treatment of alcohol dependence in 1994 and for opioid dependence a decade prior to that. Naltrexone acts at μ, δ, and κ opioid receptors, each of which is implicated in at least one aspect of alcohol and opiate dependence. The blockade of the μ opioid receptor in particular inhibits the reward received from opioids or alcohol and is linked with diminished dependence. The value of oral naltrexone in the long-term treatment of alcohol or opiate dependence has been greatly undermined by the failure of the substance abusers to adhere to the daily dosing schedule. There is an absence of suitable alternative products in this arena, with only Disulfiram and Acamaprosate available. Disulfuram relies on the severe aversive effect produced by inhibition of acetaldehyde dehydrogenase during the metabolism of ethanol, but the adverse side effects associated with this can be severe and even fatal. Acamprosate is thought to act on γ-aminobutyric acid and glutaminergic receptors, but it is administered orally requiring a total dose of 2 g to be administered in three divided doses.

Market uptake to date has been slow, partly due to the fact that this is a difficult market to define and manage. It will be interesting to see how this product will progress. It has solved an important therapeutic drawback associated with naltrexone and entered an area of unmet therapeutic need. The challenge for this product will be to convince doctors and patients alike that pharmacotherapy is an effective treatment for alcohol dependency. Unlike methylphenidate or fentanyl, naltrexone is not a gold standard for the treatment of the condition which the improved formulation addresses.

CONCLUSION

The great majority of drug reformulations are driven by the life cycle of the product and must occur in the right sequence and at the right time if the value of the product is to be fully realized. With efficient planning, this would be built into the life cycle management plans prior to product launch. Timing is crucial, particularly toward the end of product life cycles, at which time it is very difficult to recover from prior delays. The therapeutic advance offered by a reformulation need not be great and may even be minimal if it is allied to the brand. In this case, it is sufficient that it differentiates the new product from its predecessor only to the extent that it can enjoy an extended period of regulatory exclusivity or patent protection. In addition, a reformulation that improves the competitive profile of a compound only to the extent that it takes sales from the previous formulation would be a pointless exercise.

Reformulations that occur beyond the product life cycle face a much higher bar, the benefits offered by reformulation in this case must be akin to those features possessed by new products: they must offer a clear therapeutic advantage and they must be robustly defensible if their life cycle is to last beyond the three years of exclusivity offered by Waxman Hatch. Only a handful of these more independent products created by formulation have emerged, and these have been successful as they have solved special inconveniences present in their therapeutic area or have allowed the treatment of a previously poorly or untreated condition.

In considering the target of reformulation, during the course of the product life cycle this will be heavily biased to market need. It is only after the completion of life cycle that priority can be given to therapeutic need. This is not to give the impression that brands somehow do not respect therapeutic need, it is the therapeutic compound that is leading the response to this challenge in the earlier parts of the life cycle, priorities shift after this goal has been met and the market is given up to generics.

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2

The Modified-Release Drug Delivery Landscape

Academic Viewpoint

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INTRODUCTION

Two types of modified (or controlled) drug delivery systems can be distinguished: (*i*) devices that *de*crease the release rate of the drug compared to conventional dosage forms, often during prolonged periods of time (e.g., several hours, days, or months) (1–3), and (*ii*) systems that *in*crease the release rate compared to conventional dosage forms (e.g., in the case of poorly water-soluble drugs) (4,5). Both types of systems can be very helpful to improve the therapeutic efficacy of many pharmaco-treatments.

The steadily increasing practical importance of modified drug delivery systems can be attributed to the major advantages they can offer over conventional dosage forms, including:

- The possibility to optimize the resulting drug concentration time profiles at the site of action in the human body over prolonged periods of time (1,2,6). Every drug is characterized by its "minimal effective concentration" (MEC) (below which no therapeutic effect occurs), and its "minimal toxic concentration" (MTC) (above which undesired side effects occur) (Fig. 1, dotted lines). The range in-between the MEC and MTC is called "therapeutic range," or "therapeutic window." Depending on the type of drug, this concentration range can be more or less narrow. If a highly potent

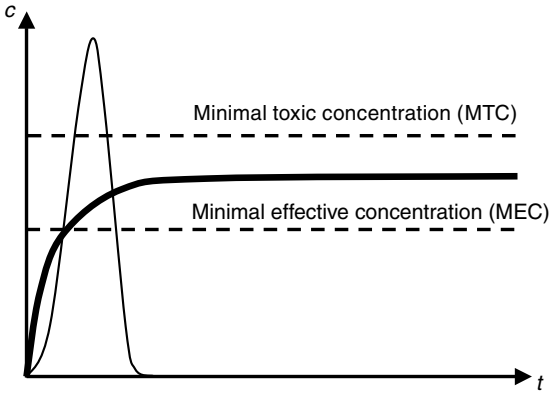

Figure 1 Schematic presentation of the "therapeutic window" of a drug and possible drug concentration time profiles upon administration of oral immediate (*thin curve*) and controlled release dosage forms (*bold curve*). (*c*) denotes the drug concentration at the site of action in the human body, *t* the time after administration.

drug with narrow therapeutic window (e.g., anticancer drug) is administered using a conventional dosage form, the entire drug dose is generally rapidly released. In the case of oral administration, the drug is subsequently absorbed into the blood stream, distributed throughout the human body and reaches the site of action. Depending on the administered dose and therapeutic range of the drug, the risk can be considerable that toxic concentrations are achieved. In addition, as there is no further drug supply (the entire dose is rapidly released) and as the human body eliminates the drug, its concentration at the site of action decreases again. In many cases, therapeutic drug concentrations are attained only during short periods of time (Fig. 1, thin curve). To overcome this restriction, the first step, the release of the drug out of the dosage form can be time–controlled. For example, a constant drug supply can be provided, compensating the drug elimination out of the human body and, thus, resulting in about constant concentrations within the therapeutic range at the site of action during prolonged periods of time (Fig. 1, bold curve). Consequently, toxic side effects and time periods with sub-therapeutic drug concentrations can be minimized.

- The possibility to reduce the administration frequency of drugs exhibiting short half-lives in vivo. For example, three times daily oral administration might be replaced by once daily administration only. This is particularly important for elderly patients with multiple drug treatments. Also, required daily injections of drugs (that need to be administered parenterally and are rapidly eliminated out of the human body) might be replaced by injections of depot systems twice a year only. Obviously, this very much facilitated administration schedule allows to

significantly improve patient compliance and, thus, the therapeutic efficacy of the treatments.

- The possibility to *enable* new pharmacotherapies. For example, the treatment of brain diseases is particularly difficult due to the blood–brain barrier (BBB), which effectively hinders the transport of most drugs from the blood stream into the central nervous system (CNS). Generally, only small, lipid-soluble molecules and a few nutrients can cross this barrier to a significant extent, either by passive diffusion or using active transport mechanisms (7,8). One possibility to overcome this restriction is to directly inject the drug into the brain tissue (intracranial administration). However, due to the generally short half-lives of the drugs within the CNS, frequent administration would be required over long periods of time for the treatment of many brain malignancies. For instance, brain tumors and neurodegenerative diseases (e.g., Alzheimer's and Parkinson's disease's) require therapeutic drug concentrations at the site of action during several weeks/months/years. As each intracranial administration implies a significant risk to provoke severe CNS infections, this type of treatment method is not feasible. Modified release microparticles or implants can help to overcome this restriction: Ideally, one single injection/implantation is sufficient to provide therapeutic drug concentrations at the site of action during prolonged periods of time.
- The possibility to simulate night time dosing. For the treatment of certain diseases (e.g., asthma) it is important that the drug is available at the site of action in the very early morning. Thus, the patient should take a conventional dosage (e.g., standard tablet) during the night to allow for drug absorption into the blood stream and appearance at the site of action in the very early morning. Alternatively, so-called "pulsatile" drug delivery systems can be administered in the late evening (Fig. 2). During the first couple of hours, no drug is released. Then, after a predetermined lag time (e.g., 4 hr), the entire drug dose is rapidly released without the need for the patient to wake up. An example for a pulsatile drug delivery system is a polymer coated pellet, with a rupturable coating that is poorly permeable for the drug as long as it is intact (Fig. 2). Upon contact with aqueous body fluids, water penetrates into the pellet and builds up a steadily increasing hydrostatic pressure within the core, which acts against the polymeric film. As soon as a critical threshold value is attained, the coating ruptures and the drug is rapidly released through water-filled pores/channels (Fig. 2).
- The possibility to simulate multiple dosing with one or several drugs. Combining different types of pulsatile drug delivery systems with various lag-times (e.g., different types of polymer coated pellets, filled into hard gelatin capsules or compressed into tablets), several drug doses can be released at pre-determined time points upon one single administration.

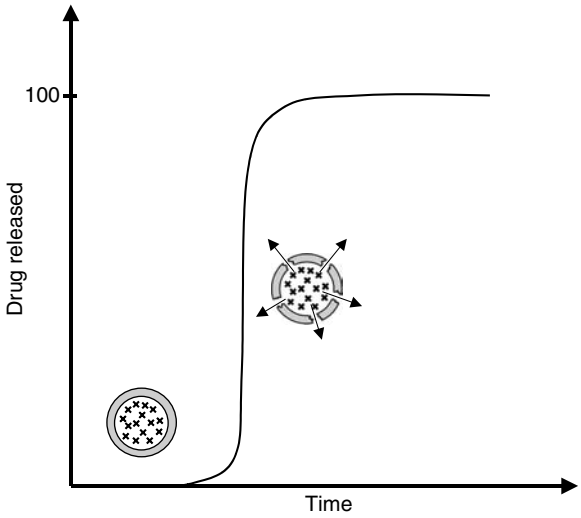

Figure 2 Schematic presentation of a pulsatile drug release profile: negligible release at early time points, followed by rapid and complete drug release after a predetermined lag-phase. A polymer-coated pellet is illustrated as an example: The intact macromolecular membrane effectively suppresses drug release until the monotonically increasing hydrostatic pressure within the pellet core reaches a threshold value at which crack formation within the coating sets on, resulting in rapid drug release through water-filled pores/channels.

This can substantially facilitate the administration schedule for many elderly patients.

To be able to control the rate at which a drug leaves its dosage form, the active agent is generally embedded within a matrix former. Often polymers are used for this purpose (9–11). For parenteral administration the polymer should ideally be biodegradable to avoid the necessity to remove empty remnants after drug exhaust. Depending on the type of drug, type of polymer, composition and geometry of the device, preparation technique and release conditions [e.g., contents of the gastrointestinal tract (GIT) versus muscle tissue], different physico-chemical processes can be involved in the control of the resulting drug release rate. This might include e.g., water diffusion, polymer chain relaxation, glassy to rubbery state transitions, polymer degradation, diffusion of degradation products, drug dissolution and diffusion, polymer dissolution, creation of acidic microenvironments, autocatalytic effects, crystallization of degradation products, re-dissolution of the latter, drug degradation, a decrease or increase in system size, an increase in polymer chain mobility as well as drug polymer interactions. If several of these phenomena are simultaneously involved and of importance for the resulting drug release kinetics, it is generally difficult

to optimize the system, because effects of formulation and processing parameters on the resulting drug release kinetics are not straightforward and device development is often based on series of time-consuming trial and error experiments. However, in some systems only one or two mechanisms are dominant (12–14). If for example, several processes take place in sequence and one of them is significantly slower then the others, this process determines the overall drug release rate. In the following section, the most important drug release rate controlling mechanisms are briefly described.

INVOLVED MASS TRANSPORT PHENOMENA

Diffusion

Diffusional mass transport is occurring in almost all modified drug delivery systems. Different species can be diffusing, including water, drug, soluble polymer chains, drug and polymer degradation products, additional excipients present in the modified release system, as well as substances dissolved within body fluids the device is exposed to. In practice, often the diffusion of the drug through a polymeric network is the rate limiting step for drug release.

Diffusional processes can best be described using Fick's first and second law of diffusion (15,16). Depending on the structure of the device and solubility of the drug within the release rate controlling excipient(s) [generally polymer(s)], different types of diffusion controlled drug delivery systems can be distinguished (Fig. 3):

- *Reservoir devices with a core-shell structure*. The drug is located at the center of the system (e.g., pellet or tablet). The shell consists of the release rate controlling polymer. Generally, drug diffusion through the coating barrier controls the release rate. Depending on the drug solubility within the core upon water penetration and on the drug loading, two types of reservoir systems can be distinguished:
  - Devices with a *non-constant activity source*. In this case, only dissolved drug exists within the system's core upon water penetration (Fig. 3). Thus, drug molecules that diffuse out of the device are not replaced and the drug concentration at the inner membrane's surface decreases with time. If the system does not swell, perfect sink conditions (negligible drug concentrations in the release medium; no hindrance of further drug release by already released drug) are maintained, and if the membrane's properties do not change with time, first order release kinetics (exponentially decreasing release rates) are observed with this type of modified drug delivery system, irrespective of the geometry of the device.
  - Devices with a *constant activity source*: In this case, the initial drug loading is much higher than the amount of drug that is soluble

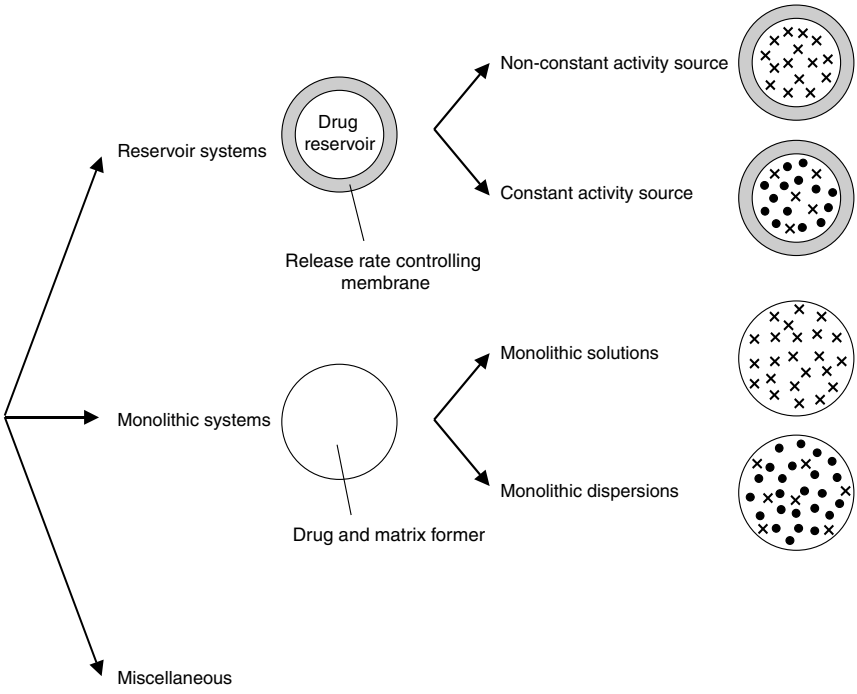

Figure 3 Classification system for primarily diffusion-controlled drug delivery systems.

within the wetted core. Thus, dissolved and non-dissolved drug coexist during major parts of the release period (Fig. 3). Importantly, drug molecules that diffuse through the polymeric barrier out of the device are replaced by the partial dissolution of the excess amount of drug. Consequently, a saturated drug solution is provided at the inner membrane's surface over prolonged periods of time (as long as non-dissolved drug exists). If the system does not swell, perfect sink conditions are maintained and the membrane's properties do not change with time, this leads to constant drug concentration gradients (being the driving forces for diffusion). In this case, the resulting drug release rate is constant as long as drug excess is provided in the system's core, irrespective of the geometry of the device (zero order release kinetics).

- *Monolithic devices*. The drug is distributed (generally homogeneously) throughout the system. This type of devices is also called "mono-bloc" system. Again, depending on the drug solubility within the wetted device and on the drug loading, two types of monolithic systems can be distinguished:

- Monolithic *solutions*, in which the drug is molecularly dispersed within the wetted matrix former (Fig. 3). In case of the simple geometry of thin films that do not swell, dissolve or degrade and under perfect sink conditions, a square root of time relation can be used to describe the first 60 % of drug release (17). This mathematical description should not be confused with the famous square root of time relationship introduced by Takeru Higuchi for thin ointment films with very high initial drug loadings in relation to drug solubility (18). In the case of poorly water-soluble drugs, monolithic solutions can be used to increase the resulting drug release rate in the human body compared to conventional dosage forms. As the drug is molecularly dispersed, no crystals or amorphous aggregates need to be destroyed prior to drug dissolution. In this case, a rapidly hydrating polymer should be chosen as matrix former, and drug release should not significantly be hindered by the macromolecular network. A major challenge during the development of this type of modified drug delivery system can be to provide long-term stability during storage, avoiding, e.g., the formation of thermodynamically more advantageous crystalline structures.
- Monolithic *dispersions*, in which the drug is partially molecularly dispersed and partially non-dissolved within the wetted device (Fig. 3). For the simple geometry of thin films, significant initial drug excess (drug concentration >> drug solubility), perfect sink conditions and a matrix former that does not swell, dissolve or degrade, Takeru Higuchi derived the famous square root of time relationship (18). Unfortunately, it is often misused and applied to drug delivery systems that do not fulfill one or more assumptions the Higuchi equation is based on.

- *Miscellaneous systems*. This can, for instance, be a coated pellet or tablet containing the drug not only in the core, but also in the film coating, or a device that consists of a monolithic drug polymer core and an additional polymer coating, with the core and coating controlling the resulting drug release rate.

Swelling

Depending on the physicochemical properties of the matrix former, polymer swelling can be of major importance (19,20). For example, hydroxypropyl methylcellulose (HPMC)-based matrix tablets can significantly swell (17). The two most important consequences of polymer swelling are:

1. The increase in the length of the diffusion pathways (increase in volume of the systems). This can lead to decreasing drug concentration gradients and, thus, decreasing drug release rates.

2. The increase in the polymer molecular mobility. This can lead to significantly increasing drug mobility within the polymeric network and, thus, increasing drug release rates. For example, in dry tablets, diffusion is generally negligible (the diffusion coefficients approach zero). In contrast, in a fully swollen polymer matrix drug diffusivities can be of the same order of magnitude as in aqueous solutions (17).

Depending on the type of polymer and type of drug, one of these effects can dominate, resulting in decreasing or increasing drug release rates.

Figure 4 schematically illustrates the phenomena which can be involved in the control of drug release from a swellable delivery system. This can for instance be a cross section through half of a matrix tablet which is exposed to an aqueous bulk fluid in radial direction. On the right-hand side, the tablet is still dry and non-swollen, on the left-hand side the bulk fluid is located. Due to concentration gradients, water diffuses into the drug delivery system. With increasing water content, the mobility of the polymer chains and drug molecules increases. At a certain, polymer-specific water concentration, the macromolecular mobility steeply increases ("polymer chain relaxation"). The front at which this phenomenon occurs is called "swelling front," separating the swollen from non-swollen matrix. Importantly, this is not a stationary boundary, but a moving one. If the initial drug concentration in the system is higher than the solubility of the drug in the swollen matrix, dissolved and non-dissolved drug co-exist within

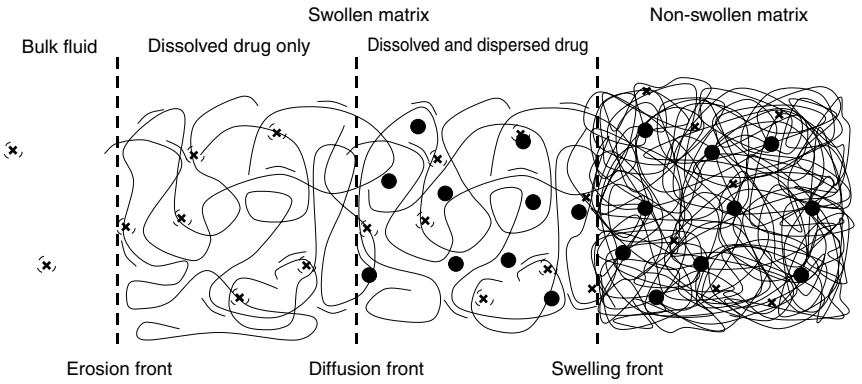

Figure 4 Schematic presentation of a swelling, controlled drug delivery system containing dissolved and dispersed drug (crosses and black circles, respectively), exhibiting the following moving boundaries: (*i*) an "erosion front," separating the bulk fluid from the delivery system; (*ii*) a "diffusion front," separating the swollen matrix containing dissolved drug only and the swollen matrix containing dissolved and dispersed drug; and (*iii*) a "swelling front," separating the swollen and non-swollen matrix.

the matrix directly next to the swelling front. Due to concentration gradients and the significantly increased mobility, dissolved drug molecules diffuse out into the bulk fluid. As long as a non-dissolved excess of drug exists, the concentration of dissolved drug in this part of the matrix is constant (released drug molecules are replaced by the partial dissolution of non-dissolved drug, providing a saturated drug solution). But as soon as all excess drug is dissolved, the drug concentration within the swollen matrix decreases. The front that separates the swollen matrix containing only dissolved drug from the swollen matrix that contains both, dissolved and non-dissolved drug, is called "diffusion front" (Fig. 4) (21,22). Importantly, also this front is not stationary. Furthermore, a third front can be distinguished, which separates the drug delivery system from the bulk fluid: the "erosion front," which is also moving.

Dissolution

Various species can dissolve during drug release and contribute to the overall control of the release rate, including the drug itself, the matrix former and potential further excipients present in the delivery system. To quantify the rate at which a *low* molecular weight substance dissolves, generally the Noyes-Whitney equation can be used (23). To describe the dissolution of a *high* molecular weight material, the so-called "reptation theory" can be applied (24,25). In the case of water-soluble, swellable polymeric matrix formers, the initially dry system consists of highly entangled macromolecules (Fig. 4, right-hand side). Upon water penetration the polymer swells, resulting in decreasing polymer concentrations and increasing macromolecule mobility (as discussed above). On a molecular level, the snake-like motions of the polymer chains ("reptation") permanently change the structure of the network. Entangled chains can either disentangle or modify their entanglement configuration, and disentangled chains can entangle or remain disentangled. At high and moderate polymer concentrations, the resulting macrostructure of the system is approximately time-invariant. However, below a certain polymer concentration, the number of disentangling polymer chains exceeds the number of newly entangled macromolecules, resulting in a destruction of the polymer network. Once the macromolecules are disentangled at the device's surface, they diffuse through the unstirred layer surrounding the system (not shown in Fig. 4), which is characterized by a distinct polymer concentration gradient. Then, convection leads to a homogeneous distribution of the polymer chains within the bulk fluid.

Erosion/Degradation

Unfortunately, different definitions of the terms "erosion" and "degradation" are used in the literature (26). In this chapter, polymer degradation is understood as the chain scission process by which polymer chains are

cleaved into oligomers and finally monomers. In contrast, erosion is understood as the process of material loss from the polymer bulk. Such materials can be monomers, oligomers, parts of the polymer backbone or even parts of the polymer bulk.

Two polymer erosion mechanisms can be distinguished: (*i*) surface (= heterogeneous) erosion; and (*ii*) bulk (= homogeneous erosion) (27–29). The basic principles of these two mechanisms are illustrated in Figure 5. In the case of surface eroding drug delivery systems, polymer degradation is much faster than water penetration into the polymer bulk. Thus, degradation occurs primarily in the outermost polymer layers. Consequently, erosion affects only the surface and not the inner parts of the system (heterogeneous process) (Fig. 5A). The inner structure of the systems remains unaltered, but the device shrinks. Drug molecules that are embedded within the polymer matrix are predominantly released by the disappearance of the surrounding macromolecular network. In contrast, polymer chain cleavage is slow compared to water penetration in the case of

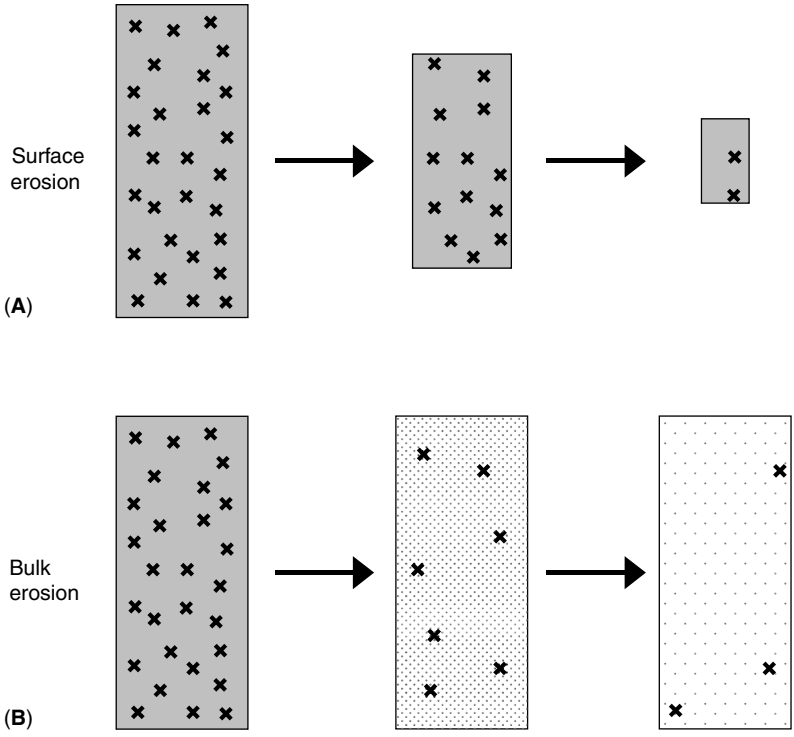

Figure 5 Schematic presentation of: (**A**) Surface eroding drug delivery systems, and (**B**) bulk eroding drug delivery systems. The crosses represent drug molecules.

bulk eroding drug delivery systems (Fig. 5B). In this case, the entire device is rapidly hydrated and the polymer chains are cleaved throughout the system. Consequently, erosion is not restricted to the polymer surface (homogeneous process). The outer dimensions of the drug delivery systems remain unaltered, while the average polymer molecular weight decreases, leading to an increased macromolecular mobility. Due to the release of polymer degradation products into the bulk fluid, the density of the macromolecular network decreases and the porosity increases. Thus, embedded drug molecules become more and more mobile within the device and diffuse out into the release medium.

As a basic rule, polymers that are built from very reactive functional groups tend to degrade fast and to undergo surface erosion, whereas polymers containing less reactive functional groups tend to be bulk eroding. Polyanhydrides are examples for predominantly surface eroding polymers, while poly(lactic acid) and poly(lactic-co-glycolic acid) (PLGA) are examples for predominantly bulk eroding materials. However, it has to be kept in mind that the ratio polymer chain cleavage rate/system wetting rate determines whether the device is surface or bulk eroding, and the system wetting rate also depends on the dimensions of the device (e.g., nanoparticles are much more rapidly completely wetted than large implants). Consequently, drug delivery systems based on the same polymer can be primarily surface or bulk eroding depending on their size. von Burkersroda et al. (30) introduced a critical device dimension ($L_{critical}$). If a drug delivery system is larger than $L_{critical}$, it undergoes surface erosion, while bulk erosion predominates if the device is smaller than this polymer-specific threshold value. For polyanhydrides the $L_{critical}$ value is in the order of 100 μm, for poly(α-hydroxy esters) (e.g., PLGA) it is in the order of 10 cm. However, it has to be pointed out that in the vicinity of the $L_{critical}$ values, both, surface as well as bulk erosion are of importance and the overall erosion behavior of the system shows characteristics of both types of erosion.

Miscellaneous

In practice, a combination of two or more of the above described physicochemical phenomena might be simultaneously involved in the control of drug release from a specific delivery system (31,32). For example, HPMC-based matrix tablets (being generally the first choice for an oral controlled drug delivery system) are can be governed by a combination of three different phenomena (33–36) (Fig. 6):

1. *Diffusion*: At least three species can be diffusing: water, drug, and disentangled polymer chains. As soon as the tablet comes into contact with aqueous fluids, water molecules (represented as diamonds) diffuse into the system (due to concentration gradients). Then, dissolved drug

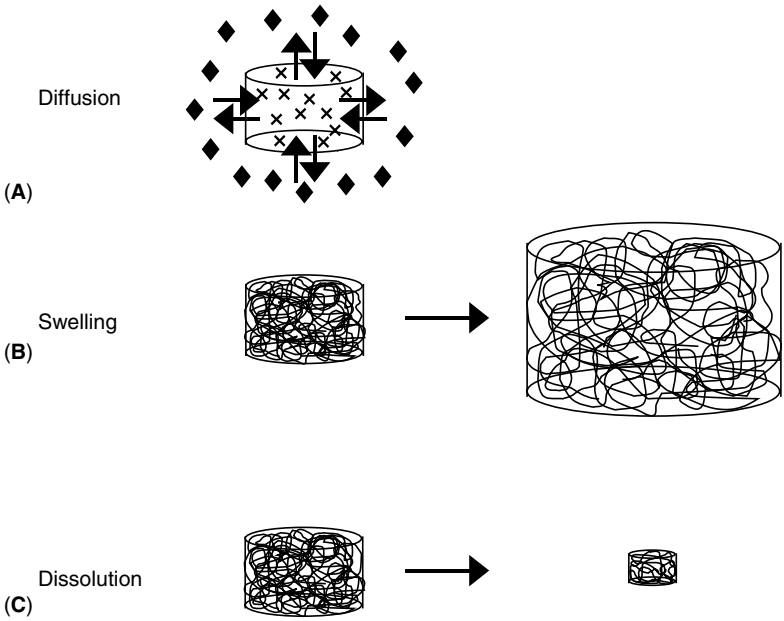

Figure 6 Schematic presentation of the most important physical and chemical phenomena involved in the control of drug release from HPMC-based matrix tablets: (**A**) Diffusion, (**B**) swelling, and (**C**) dissolution. The crosses and diamonds represent drug and water molecules, respectively. *Abbreviation*: HPMC, hydroxypropyl methylcellulose.

molecules (crosses) diffuse out of the device. Thirdly, polymer chains that have disentangled from the macromolecular network diffuse through the liquid unstirred layer surrounding the tablet (not shown) into the bulk fluid.

2. *Polymer swelling*: The increase in volume of HPMC-based matrix tablets and increase in macromolecular mobility can be considerable. This leads to a drastic increase in the length of the diffusion pathways and mobility of the drug molecules (as discussed above).
3. *Polymer dissolution*: HPMC is water-soluble. Depending on the average polymer molecular weight and degree of substitution, the macromolecules more or less rapidly disentangle from the polymeric network and diffuse into the surrounding bulk fluid.

If a poorly water-soluble drug is incorporated within the tablets, also drug dissolution can significantly contribute to the overall control of drug release. Due to the complexity of the underlying drug release mechanisms it is not straightforward to mathematically describe the resulting drug release

kinetics and to make quantitative predictions of the effects of formulation and processing parameters on the system's properties (17,36).

PLGA-based microparticles are generally the first choice for controlled *parenteral* drug delivery (37,38). Unfortunately, also in these systems generally not only one of the above described physico-chemical phenomena is solely controlling the resulting drug release rate. As water penetration into the microparticles is much faster than the subsequent polymer chain cleavage (ester hydrolysis), the system undergoes bulk erosion. Consequently, shorter chain acids are generated throughout the device (Fig. 7). Due to concentration gradients, monomeric and oligomeric acids diffuse out into the surrounding bulk fluid, where they are neutralized. In addition, bases from the surrounding liquid diffuse into the microparticles and neutralize the generated acids. However, diffusional mass transport is relatively slowly and the rate at which the acids are generated can be higher than the rate at which they are neutralized. Consequently, the micro-environmental pH within the system (in particular at the center of the

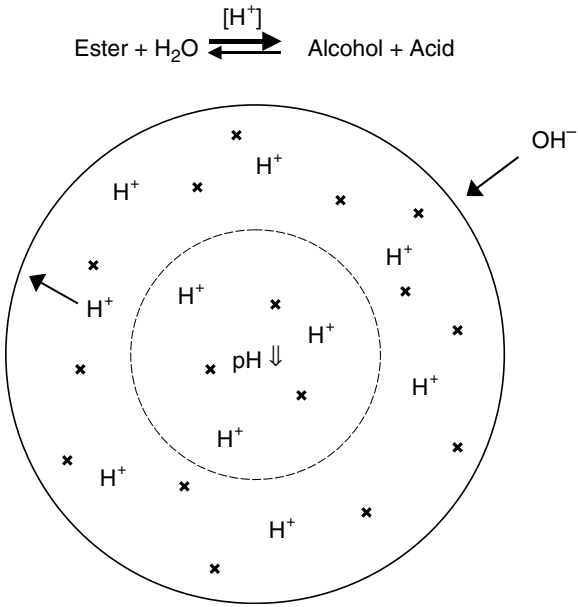

Figure 7 Scheme of a bulk eroding PLGA-based microparticle: Generated shorter chain acids diffuse out of the system, while bases from the surrounding bulk fluid diffuse in. Depending on the relative acid neutralization and acid generation rate, the micro-environmental pH within the system (in particular at the center of the microparticle) can significantly drop and cause drug degradation and autocatalysis: the hydrolytic ester bond cleavage is catalyzed by protons. *Abbreviation*: PLGA, poly(lactic-co-glycolic acid).

microparticles) can drop significantly (39–41). This can lead to drug inactivation (e.g., of protein-based drugs) and accelerated polymer degradation: hydrolytic ester bond cleavage is catalyzed by protons (42). Thus, also drug release can be accelerated (43,44). The two most critical parameters determining the relative importance of such autocatalytic effects are: (*i*) the microparticle size (determining the length of the diffusion pathways), and (*ii*) the microparticle porosity (determining the mobility of the diffusing acids and bases). As in the case of HPMC-based matrix tablets, the complexity of the underlying drug release mechanisms render the optimization of this type of controlled drug delivery systems challenging (45).

FUTURE OUTLOOK

Major challenges in the future development of modified drug delivery systems include (from an academic viewpoint):

1. The development of novel polymeric carrier materials: A serious restriction for the administration of highly promising novel protein-based drugs is the lack of appropriate pharmaceutical dosage forms. Due to the significant advances in biotechnology, numerous proteins can now be made available in sufficient quantities and at relatively low costs. Due to their limited half-lives in the human body, modified drug delivery systems will be required to allow for efficient therapies. Nowadays, proteins are generally administrated parenterally. Unfortunately, the standard parenteral controlled drug delivery system (PLGA-based microparticles) often leads to the loss of bioactivity of encapsulated proteins, due to the creation of acid micro-environments (as discussed earlier). The establishment of novel polymeric materials offering less aggressive environments for protein drugs would represent a major breakthrough for many future therapies. For instance, new dextran-based hydrogels might offer non-acidic, aqueous microclimates and be able to appropriately control the resulting protein release rates (46–48).
2. The possibility to allow for more convenient administration routes for the patient. Nowadays, the necessity to frequently administer drugs parenterally still presents a major practical limitation for many pharmaco-treatments. The use of long term releasing parenteral delivery systems can be of significant help, but obviously the complete circumvention of parenteral administration would be of even greater benefit in the future. Alternative routes might include pulmonary administration (e.g., an inhalable insulin product has recently been commercialized), nasal administration as well as the oral route. Major research efforts are ongoing to allow for oral administration of proteins (49,50). For example, muco-adhesive devices that protect the drug against enzymatic degradation and aggressive pH values within the GIT are under

investigation. The simultaneous release of substances that temporarily enhance drug absorption across the GIT mucosa might be of great practical importance. Obviously, it will be crucial to appropriately control the release of the drug as well as of absorption enhancers from such systems. Thus, modified drug delivery systems can be expected to play a central role in these novel treatment strategies.

3. The possibility to allow for overcoming the BBB in order to effectively treat brain diseases (51–53). Malignancies of the CNS will be of steadily increasing practical importance, especially in the industrial countries. The increasing life expectancy leads to a rising number of patients suffering from Alzheimer's and Parkinson's diseases. The consequences of these disorders (not only for the patients, but also for their family members) will be of fundamental importance in the future. Modified drug delivery systems might significantly contribute to the development of novel CNS treatment strategies (54,55).
4. The development of "intelligent" drug delivery systems: In the very long run, the ideal modified drug delivery system should be able to release the drug(s) "on demand." The device should, thus, be able to precisely detect how much drug is needed and be able to release exactly this amount. As an example, the delivery of insulin should be coupled to the plasma glucose level for the treatment of diabetes. Drugs regulating the blood pressure should be released from delivery systems that are sensitive to this parameter. Novel microchip-based technologies might be very useful to fulfill these advanced tasks (56,57).

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3

The Modified-Release Drug Delivery Landscape

Advantages and Issues for Physicians and Patients

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INTRODUCTION

The field of modified-release drug delivery (MDD) has recently expanded from the first marketed "depot injections" of several decades ago to include new types of oral delivery systems, transdermal drug systems, intrauterine devices, and implantable pumps to name a few.

As we mentioned, the first MDD formulations to enter clinical practice were probably the so-called depot injections used to deliver antibiotics or central nervous system drugs.

Today, there are at least four major classes of MDD formulations, these include:

1. Enteral (oral) MDD formulations:
   - monolithic forms
   - multiparticulate forms

2. Parenteral MDD formulations:
   - subcutaneous
   - intramuscular
   - intravenous
   - intraperitoneal

3. Implantable MDD formulations:
   - diffusion MDD formulations
   - externally activated MDD formulations

4. Transdermal MDD formulations:
   - membrane moderated formulations
   - diffusion controlled formulations
   - matrix type formulations
   - reservoir formulations

In this chapter we focus mainly on oral MDD formulations, even though the majority of the concepts that are described apply also to the other forms. A detailed description of the development all the types of MDD formulations and of their characteristics can be found in the comprehensive textbook edited by Robinson and Lee (1).

MODIFIED-RELEASE SYSTEMS: WHY?

The main objective to formulate an active pharmaceutical ingredient (API) in an MDD system is related to pharmacokinetics (PK).

In fact, an appropriate formulation can make the absorption, distribution, metabolism, and excretion (ADME) profile of a drug much more favorable. This change of the ADME paradigm to MDD–ADME (Fig. 1) can have a profound impact on many aspects of the clinical use of a drug, from patient compliance and convenience to its very efficacy, tolerability, and safety parameters.

MDD FORMULATIONS: CLINICAL USES

The main areas where oral MDD formulations are involved are:

- gastroprotection
- taste masking
- improvement of PK characteristics
- targeting
- chronotherapeutics
- life extension

Gastroprotection

Many drugs (most proton pump inhibitors, or pancreatic enzymes, just to name two categories) are not stable in an acidic environment and would be rapidly inactivated by the hydrochloric acid in the gastric juice.

Enteric-coated or gastroprotected forms are usually obtained by covering the whole tablet or capsule (or the single "particles" in case of multiparticulate forms) with a layer of polymers such as Eudragit or HP-55,

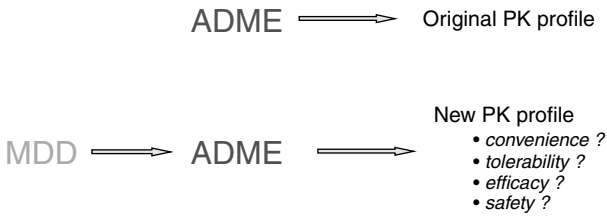

Figure 1 The change of ADME paradigm to MDD-ADME. *Abbreviations*: ADME, absorption, distribution, metabolism, and excretion; MDD, modified-release drug delivery.

which are stable for a very long time at low pH, but dissolve very rapidly once the pH has reached values around 5. The result obtained with this modification is that the drug is isolated from the environment in the stomach and then is rapidly released once the partially digested food is emptied into the duodenum and the contents have been buffered by the bile salts and the pancreatic juice.

Taste Masking

Several APIs have a pungent or unpleasant taste. Ibuprofen—one of the most widely used analgesics—is an example. The problem of unpleasantness is particularly important in pediatric or veterinary formulations, where the oral administration of a bad-tasting medicine could be very difficult or even impossible.

Taste masking is quite relevant also in orally dispersible formulations, also known as fast-melting tablets, which are formulations that can be dissolved in the mouth before swallowing and are usually taken without the need for water.

The masking of the organoleptic characteristics of a compound is usually obtained by covering the whole tablet—or the single particle—with layer or layers of substances, which are stable at the pH of the oral cavity and dissolve rapidly in the stomach. Flavoring agents may also be added. Mixing the right excipients in the right proportions is almost an "art" and also the evaluation of the acceptability of a taste masked formulation is not an exact science and usually involves tasting panels, composed of trained or untrained subjects.

Improvement of PK Characteristics

As we mentioned earlier, an appropriate MDD formulation can change radically the PK profile of a given API. The objectives of these types of formulations are usually to increase the time between two doses as well as to reduce the fluctuation of drug blood levels. The reduction from 3–4 times a day administrations to twice or even once daily, greatly increases patient compliance and

reduces the potential for dosing errors, especially in those categories of patients (e.g., the elderly) who routinely assume several preparations. The reduction in the frequency of administration can also have a favorable impact on the cost of care in those situations (long-term care centers, hospitals, etc.) where licensed personnel administered the drugs to the patient.

For the majority of drugs, a constant therapeutic blood level is one of the goals of treatment. Wide fluctuations, in fact, can be the cause of therapeutic failure or of an undesirable toxic effect. This is especially true, for example, in the case of antibiotics, where the blood and tissue levels must be maintained constantly above the minimum inhibiting concentrations of the susceptible germs, in order to avoid the selection of resistant strains.

As shown in Figure 2, the immediate-release formulation of a hypothetical drug (in its native form) could grant 12 hours of coverage at a certain risk of toxicity, since its C_{max} is slightly above the toxicity threshold.

On the other hand, the same drug—administered in a MDD formulation—could eliminate the risk of toxicity and offer longer therapeutic coverage, which may be close to 24 hours.

Targeting

Drug targeting, which is the delivery of a drug only at the site where it is most active and needed, has been the "Holy Grail" of all drug delivery researchers. Despite some remarkable successes, it remains an area that needs to be explored, especially in the field of parenteral administration. A very good description of parenteral drug targeting techniques and issue, with special

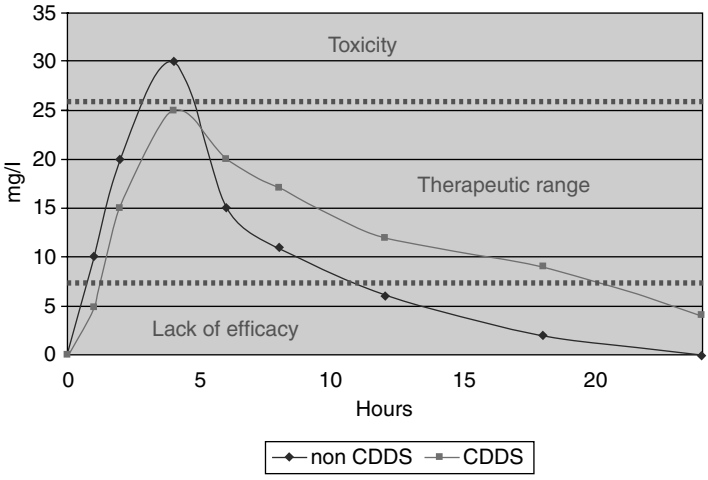

Figure 2 The formulation in a CDDS can reduce the risk of toxicity and extended coverage. *Abbreviation*: CDDS, controlled drug delivery system.

relation to its main field of interest: oncology can be found in the recent textbook edited by Pagé (2). Oral drug targeting may have a less dramatic relevance, but the combination of delayed and prolonged/extended-release techniques allows, just to give an example, to deliver exogenous pancreatic enzymes where they are needed most to promote assimilation of macro and micronutrients (duodenum and upper part of the jejunum). In many cases, such as in cystic fibrosis, where the endogenous pancreatic function is practically nonexistent from birth, this administration is a real life saver.

Another example of successful drug targeting is the administration of 5-aminosalycilic acid directly to the colon, where it is directly active on the lesions of inflammatory bowel disease, avoiding as much as possible its release in the small bowel where it is not needed and, if absorbed, could cause untoward systemic effects.

Chronotherapeutics

Chronotherapeutics can be considered the present frontier of MDD formulations. It is an established fact that many physiological and pathological parameters follow a circadian (that is, "around the day") pattern. For example, the pain and stiffness in arthritic joints are more pronounced in the morning. Similarly, the blood pressure is highest in the early hours of the morning (when the majority of heart attacks and CV accidents occur) and declines during the day. For this reason, it would seem appropriate to deliver an analgesic/antiinflammatory or an antihypertensive when it is needed most. Coverage at the moment of awakening is one of the rationales behind the common practice of prescribing NSAIDs at bedtime on a full stomach, to exploit the intrinsic retardant effect of food.

A recent example of chronotherapy is verapamil controlled onset extended release (COER), a special formulation of verapamil where a prolonged-release formulation of the calcium channel blocker is covered with a polymer layer meant to dissolve—and therefore start the release of the API—a few hours after ingestion.

Even though this approach makes a lot of sense, the clinical advantages of chronotherapeutics have not yet been scientifically proven (or not proven). In fact, controlled onset verapamil investigation of clinical endpoints (CONVINCE): a very large trial on the effect on the administration of verapamil COER versus standard therapy on the number of cardiovascular events in high risk hypertensive patients (3), was stopped for logistical reasons before any statistical significance was reached which may have yielded some scientific evidence. While a final word on the validity of chronotherapeutics might come from smaller studies presently ongoing in the field of endocrinology, the administration of exogenous hormones (cortisol, growth hormone, etc.) in a way that mimics the physiological secretory peaks may allow a more effective treatment of some patient populations.

Life Extension

Finally, a reason why many APIs undergo reformulation in a new MDD formulation is not scientific, but essentially related to marketing and assets protection. When the patent of a successful drug expires, its owner usually faces a significant drop in revenues (in some cases up to 90%) caused by the competition of generic drugs manufacturers. For this reason, the launch of a new formulation of a well-known brand, with some additional claims of improved convenience, safety and/or efficacy, could considerably extend the "commercial life" of a drug, especially if the technology used to produce the MDD formulation is in itself patentable.

WHICH DRUGS ARE SUITABLE FOR MDD FORMULATION?

The extent of fluctuation in drug concentration at steady state is determined by the relative magnitude of the elimination half-life and the dosing interval. For example, if a drug is given at an interval equal to the elimination half-life, then there is a twofold difference between the maximum and minimum concentrations at steady state.

For drugs with short half-lives and with a clear relationship between concentration and response, it will therefore be necessary to dose at regular, frequent intervals in order to maintain the concentration within the therapeutic range. Higher doses at less frequent intervals, in fact, will result in higher peak concentrations, with the possibility of toxicity.

For some drugs with wide margins of safety, this approach may be satisfactory, e.g., amoxicillin has a half-life of approximately 1 hour, but a dosage frequency of 8 hours. This means that very large fluctuations will occur within a dosing interval, but, in view of the low toxicity of this drug, no difficulty with this approach is encountered provided the concentrations are always above the minimum effective concentration during the dosing interval. On the contrary, clinical efficacy may be enhanced by the transiently high bactericidal concentration of some antibiotics e.g., beta-lactams.

Conversely, drugs with long half-lives can be given at less frequent intervals. There is generally no advantage in formulating these drugs as extended-release formulations unless a rapid rate of change of concentration during the absorptive phase is responsible for transient adverse effects, as it may be the case with antihypertensive drugs.

It must be noted, however, that the pharmacological effect of some drugs with short half-lives can be much more prolonged than their PK would suggest. This happens in cases such as the following:

- The drug binds to the tissues, e.g., tissue-bound ACE inhibitors. For these drugs, less frequent dosing is needed even though the drug may have a short half-life.

- The drugs have irreversible effects, e.g., the acetylation of platelet cyclooxygenase by aspirin.
- The relationship between response and plasma/blood concentrations is relatively flat or if the given dose results in concentrations which are in the plateau region of the dose–response relationship, e.g., thiazides in hypertension.
- The drug is metabolized to pharmacologically active metabolite(s), which are more slowly cleared than the parent drug, e.g., quinapril, trandolapril, and venlafaxine.

Therefore, even though a good percentage of drugs could benefit from some tweaking of their PK characteristics, not all APIs are suitable for formulation in a MDD formulation.

MONOLITHIC VS. MULTIPARTICULATE FORMS

Whenever the formulation in a MDD approach is involved, a very important distinction to be made is between monolithic and multiparticulate formulations. A tablet obtained by compression is an example of monolithic form, while a capsule filled with drug beads or granules is an example of multiparticulate. There are also hybrid formulations, such as granules compressed into a tablet, or mini- or microtablets (obtained by compression, but only 1–2 mm in size) put into a capsule. Monolithic and multiparticulate forms tend to have slightly different behaviors in vivo.

POTENTIAL ISSUES WITH MDD FORMULATIONS

Unfortunately, even though the potential benefits of an appropriate MDD formulation are many, the development (and the use) of these formulations have to face some hurdles. Sometimes, in fact, a modified, extended or prolonged release form can actually represent a serious disadvantage from the point of view of the patient or of the clinician. The potential issues that need to be taken into consideration when dealing with MDD formulations relate to: GI transit time (TT), regional absorption, first pass, dose dumping, and food effect.

Gastrointestinal Transit Time

The GI/TT is the time an undigested particle takes to travel from the mouth to the anus. According to the various techniques and the diagnostic needs, different—or segmental TTs—may be measured (i.e., gastro-duodenal, gastro-colic, gastro-cecal, etc.). Subject or population variability in TT may affect drug PKs, notably absorption. This is likely to be of limited relevance for immediate-release formulations, which release all their content in a

matter of minutes, but may have greater importance for modified-release (delayed-release, sustained-release) formulations and even more for chronotherapeutic agents. In these cases, in fact, a shorter time may result in a more limited exposure to the drug and viceversa. According to published evidence, TT shows variability among different ethnic groups and/or geographic areas and in particular, major difference exists between Indian people and Caucasians. The mechanism of ethnic difference in TT is not yet ascertained, although various causes have been hypothesized. It is a fact, however, that the intestinal TT of Indians, in fact, is shorter, and their stool weight larger than that of Caucasians.

According to published studies, the possible reasons for this are dietary habits—fiber or spice diet content—and/or genetic factors. A greater fiber intake is widely considered as a likely cause for shorter TT in Indian people, compared to Caucasians, but there is not complete agreement on this issue. Even in studies supporting the importance of a greater fiber intake, in fact, the latter does not completely account for the shorter TT observed in Indian people (4–7). Although the involvement of genetic factors in determining the shorter TT reported in Indian people cannot be excluded, no specific data are available in the published literature.

Other ethnic groups, such as the Chinese and peoples of Africa, also have variability in GI TT. The oro-cecal TT of Chinese people, in fact, is longer than that of Caucasians and the cause may lie again in different environmental factors, data is unavailable on this issue (8).

On the other hand, the intestinal TT of some African peoples, is again shorter than that of Caucasians which speculates that environmental factors may be involved, notably the high fiber consumption, even though genetic factors cannot be ruled out (9,10).

Regional Absorption

The absorption pattern of a given drug in the different parts of the GI tract may be very different and examples will be provided to give the reader insight into some of these differences.

This is the case, e.g., of some beta-blockers, such as atenolol, which show a definite absorption window in the upper tract of the small bowel. The variations in the absorption pattern (especially from jejunum, ileum, and colon) can be due to the differences in the epithelium of the three tracts mentioned above and/or in their content (food in different stages of digestion, pH, water percentage, etc.).

For these reasons, the formulation of some drugs in a delayed or even in an extended/prolonged release formulation, could cause a dramatic reduction in the total bioavailability, as it can be seen from Figure 3, where a delay in the release of the drug—formulated to assure an extended release—versus the immediate release formulation results in a marked reduction of both C_{max}