Expert Opinion

Multiple-pulse drug delivery systems: setting a new paradigm for infectious disease therapy

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Background: Pulsatile drug delivery of actives based on the body's biological rhythms came into sight as a novel and emerging concept in the field of drug delivery. The concept of late has given birth to another field of research worth exploring: multiple-pulse drug delivery. *Objective*: Delivering a drug in multiple pulses has been applied to antibiotics for effective and patient compliant drug delivery. Delivering antibiotics in divided pulses results in better annihilation of microbes, as it prevents them going into a resistant/dormant stage and developing biological tolerance. The concept appears to have potential, and on 16 March 2009 MiddleBrook™ Pharmaceuticals, Inc. will launch the first of such once-daily product based on their proprietary pulsatile drug delivery technology, PULSYS™. *Methods*: This review focuses on the rationale, possible strategies and technologies employed for multiple-pulse delivery, as well as current status and future trends. *Conclusion*: The concept is in its infancy and promises great potential in the fight against microbial resistance; many approved formulations based on similar approaches with new and improved therapeutic paradigms are anticipated in the near future.

Keywords: biological tolerance, chronotherapeutics, coating, delayed release, drug fractions, Eudragits, lag time, multiple pulse delivery, pellets, PULSYS™, single pulse

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1. Introduction

Oral drug delivery undoubtedly remains the most popular, convenient and patient-compliant mode of drug administration. Over the past three decades, we have seen oral drug formulations increase in complexity from formulations that released drug immediately after administration to a range of more complex formulation technologies capable of affording controlled and sustained release. Early in the 1990s, the concept of chronotherapy emerged based on the fact that physiological parameters in the body are variable and do not remain constant over a period of time. Following this, pharmaceutical scientists were inspired by the challenge to develop novel drug delivery systems, which after ingestion could release the drug after a well-defined interval – at a time when the drug is most needed, based on the symptoms manifested by a particular disease.

The concept of delivering drugs after lag is being further explored with a view to offsetting the most serious and pressing topic of drug research: bacterial resistance to antibiotics, also known as 'biological tolerance'. Over the decades since the discovery of penicillin in 1929, antibiotics have been critical in the fight against infectious disease caused by bacteria and other microbes. Antimicrobial chemotherapy is among the key reasons for the dramatic rise of average life expectancy in the twentieth century. However, disease-causing microbes that have become resistant to antibiotic drug therapy are an increasing public health problem. From the

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outset of the antibiotic era, resistance was recognized and reported as a problem. Resistance has followed the introduction of all the major classes of antibiotics, typically within a period of 5 years [1].

The development of biological tolerance in microbes can be defined in terms of Darwin's theory of evolution, in which he proposed the fundamental principles of variation (there is variation in every population), competition (organisms compete for limited resources), genetics (organisms pass genetic traits on to their offspring), and survival of the fittest (species adapt and change by natural selection, with the best suited mutations becoming dominant). Competition for survival leads to the death of some individuals in a population, while others survive. Individuals having advantageous variations are more likely to survive and reproduce than those without the advantageous variations [2,3]. Microbes have developed this exceptional resilience against the anti-infectives, and have passed this trait on.

One part of the problem is that bacteria and other microbes that cause infections are remarkably resilient and have developed several ways [4] to resist antibiotics and other antimicrobial drugs. Another part of the problem is increasing use, and misuse, of existing antibiotics in human and veterinary medicine and in agriculture. Improper waste management in the bulk drug industry leaves high concentrations of antibiotics in the waterways, allowing resident microbes to develop resistance. Unless antibiotic resistance problems are detected as they emerge, and action is taken immediately to contain them, society could be faced with previously treatable diseases that have once again become untreatable, as in the days before antibiotics were developed [5].

The development of microbial resistance, along with economic incentives, has resulted in research and development in the search for new antibiotics in order to maintain a pool of effective drugs at all times [5]. The development of new antibiotic strains is not a daily process; a more rational approach for dealing with this serious predicament is required. More recently in the search to combat bacterial antibiotic resistance, scientists have discovered the potential for delivering antibiotics in concomitant pulses. This pulsed delivery of antibiotics offers greater advantage in effectively killing the microbes at a dose almost half that of conventional therapy.

One reason for increasing resistance to antibiotics is the development of spores resulting in an impregnable dormant phase. The vulnerable microbes are killed when the drug is administered and the one capable of forming spores hibernates and again becomes active in the division phase when no drug is available in the body [6]. Delivering antibiotics in a pulsed fashion concomitantly assures the execution of microbes in the division phase, leading to a more effective therapy. Fractioning the antibiotic dose and its administration in a pulsatile manner may expose the target bacteria to higher concentration of antibiotic with appropriate lag time, affecting the various phases of the bacterial cell growth and attacking the most vulnerable one in the overall population. The exact status of bacterial cells when the drug is taken is unknown: some may be in growth/division phase, while others may be in dormant phase (spore formation). Exposure of the bacteria to antibiotic may encourage dormancy; the period of growth resumption is the post-antibiotic effect, and the next pulse will effectively kill the bacteria [7]. Therefore, the overall efficacy of antibiotic increases and mitigates the issues of resistance. Pulsatile drug delivery systems are presented as a potential solution to the issue of biological tolerance. Other than overcoming this snag of biological tolerance and improving bactericidal activity, multiple-pulse drug delivery systems offer additional advantages such as decreased emergence of resistance bacteria and lower drug concentration, as well as a reduced dose-related side effects profile and shorter duration of therapy, which improve overall patient compliance [8]. The pulsatile dosing is not only poised to change antibiotic therapy, but could also impact upon antiviral and antifungal dosage regimens [9]. Pulsatile delivery may also be developed for combination products with superior efficacy over either product alone [10-12].

2. Pulsed delivery systems

For expediency and for the scope of this review, we are dividing the systems involving pulses into 'single-pulse' and 'multiple-pulse' drug delivery systems. The review will focus more on the multiple-pulse delivery aspects – its current status, the different approaches and technologies available to formulate such systems; and the key issues involved in the large-scale execution of such delivery systems.

2.1 Single-pulse drug delivery systems

Single-pulse drug delivery systems are those that release a drug after a well-defined time period, ideally in the form of a conventional immediate-release dose. This releases the entire drug in a single pulse to provide maximum concentration of the drug at the time when the body most needs it, depending on the circadian response of the body to the ailment. Much research has been devoted to this concept in the last two decades, and we have fortunately come up with formulations that can correspond to the physiological transformations that take place in the body with occurrence of an ailment. Some formulations have found a place on the pharmacist's shelf, while others are regarded as poten tial delivery devices in the near future with the development of technologies that can assure large-scale realization of the concepts.

A few technologies worth mentioning that release the drug after a well-defined delay include OROS (Alza Corporation, CA, USA, 1988 [13]), with technology based on gellable barrier layers using hydrophilic polymers (Gazziranga *et al*, 1993 [14,15]). Others include Geomatrix technology based on press coating (Skyepharma, London, UK, 1997 [16-18]); time clock formulation (Pozzi *et al*, 1994 [19]); time-delayed drug release from a rupturable tablet (Held *et al*, 1990 [20]); coated pellet

delivery system with a sigmoidal release profile (Stevens *et al*, 1992 [21,22]); time-controlled explosion system (TES), describing the bursting pellet technology for the first time (Ueda *et al*, 1994 [23]); alternative pulsatile pellet system (Chen, 1993 [24]); pulsatile hydrogel capsule system (Rashid, 1990 [25]); PORT capsule system (Crison *et al*, 1995 [26]); Pulsincap capsule system (McNeill *et al*, Scherrer DDS Ltd., 1993 [27]); Chronset technology (Wong *et al*, 1994, Alza Corporation, CA, USA [28]); erodible plug, time-delayed capsule system (Strathclyde University, Glasgow, Scotland [29]); pressure controlled systems (Niwa *et al*, 1995 [30]); and hydrophilic sandwich capsule system (Stevens *et al.*, 2000 [31]).

The above-mentioned technologies are either 'time-controlled' or 'site-specific' chronotherapeutic drug delivery systems, and offer complete drug release in a single pulse in either a conventional immediate-release or the controlled-release manner after a well-defined lag period.

2.2 Multiple-pulse drug delivery systems

Multiple-pulse delivery systems follow the basic principles of single-pulse chronotherapeutic drug delivery systems, delivering the drugs after a well-defined lag in a pulse. The difference lies in the number of pulses delivered concomitantly with corresponding number of lags. The number of lags is usually one minus the number of pulses, as most of the formulations have an immediate-release fraction without any barrier or coating that will release immediately following ingestion. The basic ideology behind multiple-pulse systems is to fractionate the drug dose into various components and to coat the fractions accordingly with swellable, erodible or pH-dependent polymers acting as a barrier layer of different weight depending on the physical and chemical properties of the polymers. The fractions may be in the form of drug-impregnated beads prepared by an extrusion-spheronization process, or drug-layered sugar spheres or minitablets; or they may be tablets prepared with multi-tip tooling. The differently layered fractions of minitablets or beads may be encased in a capsule shell, or the coated pellets may be compressed into a tablet. The layering over the different fractions is optimized such that each fraction will release at specific locations in the gastrointestinal (GI) tract after a well-defined lag time. The system may have two, three or more pulses, depending on the intended formulation and the duration of therapy.

2.2.1 *Formulation strategies for achieving multiple pulses*

Depending upon the manner in which the drug fractions are divided in the dosage form for optimal effectiveness, the different types of pulses in a multiple-pulse delivery system may be classified as follows.

2.2.1.1 *First pulse*

Immediate-release pulse may be defined as any pulse from a dosage form that begins to dissolve in the stomach when given orally. Exposure to the liquid content in the stomach will cause the fraction to begin releasing the active constituent immediately. The release of active constituent from immediate-release pulse will be substantially free of any modified-release characteristics designed to impart a lag time of > 15 min or to extend the release for more than about 45 min. Immediate-release pulse may be obtained from uncoated minitablets or drug-loaded beads. Immediate release from a tablet can be achieved by compressing the active agent with immediate-release tableting agents that are collectively known as processing techniques such as direct compression, roller compaction, slugging, wet granulation and fluid granulation [32,33].

2.2.1.2 *Second pulse*

These types of pulse are designed to provide a lag time followed by rapid release, and are commonly known as delayed-release pulses. The most common example of this type of pulse is the enteric-coated dosage form designed to release the drug in the upper part of the small intestine such as the proximal or distal jejunum, having a pH of 6.5 and 6.8, respectively [34]. Enteric coating provides a pH-dependent release from an acid-insoluble coating such that no release occurs in the stomach, but is effected upon entering into the small intestine. The time and position of release in the body is controlled by the nature of the enteric polymer (i.e., the pH at which the polymer will dissolve and the thickness of coating). Polymethyl methacrylates or Eudragits such as L-100, L-30 D55 dispersion may be employed for coating to release the drug in the upper part of the small intestine.

An enteric dosage form does not provide pulsing from the stomach, but must first exit the stomach to reach a pH that is high enough to dissolve the acid-resistant polymer. The process of exiting the stomach causes the phenomenon known as 'pulse collapse'. In order to provide a lag and a delayed-release pulse from the stomach, a pH-independent or time-dependent mechanism is required. In addition to this requirement, the fraction of the dosage form providing such a pulse must be retained within the stomach: that is, gastric retention is necessary to obtain the desired lag time, after which a rapid release can be achieved. After initiation of the release, the released drug is free to travel to more distal regions of the GI tract for absorption. Therefore, it can be seen that without fulfilling time-dependent release and gastric retention, a delayed-release pulse that initiates from within the confines of the stomach cannot occur [32].

2.2.1.3 *Third pulse*

This is another delayed-release pulse in which the fraction of the drug-loaded spheres or minitabs may be coated with a polymer with properties of dissolving at higher pH such as that of the proximal (pH 7.2) or distal ileum (pH 7.5) [34]. A thicker polymer coating of Eudragit L, or using a mixture of Eudragit L and S, may serve this purpose, as the coating given will take time to dissolve and will release the drug later in the desired location.

If the dosage form is a three-pulse system, in place of the enteric polymers, sustained or controlled-release agents may be substituted, depending on the solubility of the drug or the dissolution properties of the core. Suitable agents for slowing the release include high-molecular-weight hydrophilic polymers like hydroxypropyl cellulose, hydroxypropyl methylcellulose (HPMC), high-molecular-weight polyoxyethylene, carboxyvinyl polymers, polyacrylic polymers, sucrose stearate, and others that form a semipermeable film through which the active release rate is controlled by a form of diffusion kinetics [32]. Use of low-viscosity swelling agents such as HPMC 3 – 5 cps inside the core coated with water-insoluble polymers such as ethyl cellulose (EC) may give a prominent lag, as the slow entry of solvent into the core and corresponding swelling of the inside polymer may rupture the outer EC coating and release the drug. Normally such polymers may give a prominent lag, but an abrupt release may not always be possible as the drug may start to diffuse out of the polymer matrix slowly in a sustained-release manner. This may not suit the purpose – certainly of bacterial annihilation, which requires instant pulsed exposure of the drug to microbes.

US6531152 [35] provides an excellent solution to this. The inventors have used a coating of ethyl cellulose with a hydrophilic but water-insoluble pore-former such as calcium pectinate, sodium alginate or microcrystalline cellulose over a core containing drug, disintegrant and similar polymers. The hydrophilic polymers in the coat imbibe water-forming channels while maintaining the integrity of the coat (being water-insoluble), and the inside core after solvent entry ruptures the outer coating to release the drug instantly. The concept described in this patent is currently used for single-pulse systems, but may be extended to multiple-pulse systems.

2.2.1.4 *Subsequent pulses*

The colon is a site where both local and systemic drug delivery can take place. Normally pulsed fraction is designed to release the drug in the terminal part of the GI tract – such as the transverse, ascending and descending colon – in which the fraction may retain for as long as 360 ± 240 min; however, the pH of this section of the GI tract is highly variable, in the range of 6.5 – 8 [34]. A thicker coating of the polymers used in the third pulse or a coating of Eudragit FS 30 D may provide release precisely in this area [36,37]. Drug-layered pellets have been coated with an inner layer of a combination of two pH-independent polymers, Eudragit RL and RS (2:8), with an outer layer of Eudragit FS. There was no drug release for 12 h at pH 6.5. There was a sustained release of drug (5-ASA) for > 12 h at both pH 7.0 and pH 7.5 (after a lag time at pH 7.0, and with no lag time at pH 7.5). The release rate was faster at pH 7.5 than at pH 7.0. The delivery system demonstrated its potential for colonic delivery by resisting drug release until pH 6.5, and the combination of Eudragit RL and RS with an overcoating of Eudragit FS proved successful for the sustained delivery of drug at the expected pH of the colon [38].

2.2.2 *Basic designs of a multiple-pulse delivery system*

2.2.2.1 *Three 'pulse-release' drug-release system based on 'tablet in capsule' devices*

Such a system would have three minitablets within a capsule shell, with equal distribution of drug and with different coating levels. One of the three tablets may be an uncoated core for providing an immediate pulse of drug, while another is coated with swellable polymer, releasing the second pulse of the drug after a well-defined lag time. The final fraction of the drug will be released by the third tablet, which is coated with a higher-weight build-up or an enteric polymer coat. The tablet can be coated using a pan-coating machine or by a fluidized bed-coater (air-suspension coating or Glatt coating).

2.2.2.2 *Three-pulse drug release system with three fractions of beads in a capsule device*

A similar drug delivery device consists of three bead fractions with equal drug distribution, one of which may be an immediate-release fraction and the other two being delayed-release or enteric-release fractions. The beads can be drug-layered nonpareil sugar sphere/seeds (NPS) and further coated with sustained/delayed/enteric-release polymer by Wurster coating/Glatt process. The drug-saturated spherical beads may also be prepared by marumerization process and further coated by an air-suspension process.

2.2.2.3 *Two-pulse system based on a Geomatrix system design*

The drug dose may be divided into two parts, one of which may be used in preparing a core tablet coated with swellable/erodible or biodegradable polymers, while another drug fraction may be compression-coated or spray-coated, depending upon the drug load or dose fraction to be coated. The drug-coated fraction will provide the first immediate pulse, and the polymer-coated core will release the drug as a second pulse after a predetermined lag time provided by the polymer swelling/erosion.

2.3 Multiple-pulse endeavors

The concept of multiple-pulse drug delivery is in its infancy, and we can anticipate many related designs and strategies in the near future. This is evident from the fact that so far only one such delivery system has been approved by the US FDA to enter the market. This success has been realized by MiddleBrook™ (previously Advancis) Pharmaceuticals, Inc. in developing a multiple-pulse version using amoxicillin as a drug candidate, and we can expect the formulation on the market very soon. Being the first and only successful endeavor, a special attention is given to this delivery system later in the review; recent similar efforts to develop such systems are summarized below.

2.3.1

Kastra and colleagues (1998, 1999) utilized a three-dimensional printing technology (Therics, Inc., Ohio, USA) as a novel approach for the development of programmable release.

Liquid binder and drug were deposited onto excipient material using a computer-controlled printer to build up two-dimensional layers, one at a time. Excipient layers were built up using mechanical techniques until a three-dimensional structure was achieved. *In vitro* release profiles showing successive release of different drug layers were reported [39,40].

2.3.2

An impermeable capsule body contained two multilayered tablets with a water-soluble cap to give a programmed drug release. The system, proposed by Li and co-workers, contained sodium alginate and hydroxyl-propyl methyl cellulose (HPMC E5) as the candidate modulating barrier material. Lag time between the first two pulsatile releases was optimized by adjusting the ratio of sodium alginate and lactose. By adjusting the ratio of HPMC E5/lactose, the lag time between the second and third pulse was successfully modulated. A separating layer was kept between the third and the modulating barrier to improve the drug-release rate of the second pulsatile dose in the three-layered tablet. The results from testing this design revealed that programmed drug delivery to achieve pulsatile drug release three times daily can be achieved [41,42].

2.3.3

El-Malah and Nazzal (2008) studied the possibility of controlling lag time by manipulating weight gain of the Eudragit-coated beads and the concentration of Eudragit® NE 30D in the blend [43]. The dissolution behavior of beads coated with the Eudragit® NE 30D/Eudragit® L 30D-55 polymer blends (in different ratios) up to 120% weight gain was studied. Cast films were evaluated by texture analysis and differential scanning calorimetry. Evaluation of films by DSC revealed increased miscibility, softness, and decreased stiffness of the films with increasing Eudragit® NE 30D concentrations. SEM analysis demonstrated that the size of the pores formed after the dissolution of Eudragit® L 30D-55 at pH 6.8 was dependent on the miscibility of the Eudragit® blend. For the 75:25 and 80:20 blends, a linear increase in lag time up to 7 h was observed with an increase in coat weight gain from 15 – 120%. At 60% weight gain, the 80:20 blend delayed drug release by approximately 7 h, whereas the less miscible 75:25 blend delayed drug release by only 3.5 h.

2.3.4

Ibrahim and colleagues (2004) established that metronidazole administered in standard, pulse-dosing fashion was highly active against both susceptible and resistant strains of *Bacteroides* spp [44]. A comparison of the standard thrice-daily dosing and pulse-dosing of metronidazole against *Bacteroides* spp. was carried out in an *in vitro* model. Two American-type culture collection *Bacteroides fragilis* isolates (metronidazole MIC for each organism = 1 mg/l) were exposed to metronidazole for 48 or 96 h. A metronidazole-resistant *B. fragilis* strain was also exposed to both dosing regimens and, additionally, to a regimen of 1500 mg administered once daily. Thrice daily, pulsed-dose and once-daily dosing regimens all exhibited bactericidal activity.

2.3.5

US5162117 described a two-pulse tablet of flutamide for the treatment of prostate cancer. The first pulse was contained in an immediate-release layer while the second pulse was obtained from a core that contained a solid dispersion of the flutamide in a carrier. The pulses were separated by a film layer of an enteric coating at 4 – 15% weight of the core. The enteric coating slowly dissolved after the delivery of the first pulse of drug, which then allowed release of the second pulse. However, there are certain disadvantages to the enteric coated systems, such as the possibility of variability and potential for inaccurate time modulation. Colonic pH (6.5) is slightly acidic, which could cause the enteric coating to stop dissolving upon colon entry and may cause the second dose to be undelivered if the delay time between pulses is longer than the time of transit through the small intestine. The delay to the second pulse would be limited to about 3 – 4 h if the first dose were to be limited to delivery to the small intestine rather than to the stomach, which magnifies the existing disadvantage [45].

2.3.6

A capsule containing several types of pellets with varying delay time to drug release has been described in US5260069. The delay time to drug delivery of the pellets was controlled by the pellets containing a swelling polymer and the drug being surrounded by a membrane that contained a water-insoluble film and a water-soluble film. The water-soluble component of the film dissolved slowly, thereby weakening the membrane. The weakened membrane ruptured as a result of water entry into the pellets and their consequent swelling [46].

2.3.7

WO 99/18938 described an immediate-release gastrointestinal drug delivery system. It was composed of a drug-containing core surrounded by a hydrophobic polymer material into which hydrophilic but water-insoluble particulates are embedded. Upon exposure to the gastrointestinal environment, the insoluble hydrophilic particles swell, forming channels that serve as conduits for the controlled entry of liquid into the drug core. The swelling of the core did impart pressure on the coat, which resulted in the bursting of the coat; the drug was released from the core at a predetermined time [47].

The solubility of the drug and the dose may be factors governing the rupture of the coat and may be carefully considered while optimizing the core. Some water-soluble excipients with a high rate of solubilization – such as mannitol – may be granulated, with the drug having low dose and low solubility to achieve an instant release following the lag. To facilitate

the swelling and rupture of the core, some low-viscosity hydrophilic swellable and erodible polymers (such as HPMC 3 – 5 cps) may be incorporated. However, this would have a direct impact on slowing down the release to some extent after the lag phase [47].

2.3.8

In 2003, Eurand Pharmaceuticals first demonstrated the general application of a delivery system with a time-controlled series of pulses that did not specifically stress antibiotics as the drug candidate. This concept was later explored by Advancis Pharmaceuticals in developing PULSYS™.

The formulation design was to provide time-controlled pulses occurring several hours after oral administration, with or without an immediate-release pulse. The invention was a multicoated particulate dosage form with an active core, having a first membrane of an enteric polymer and a second membrane of a mixture of water-insoluble and enteric polymers. An organic acid-containing membrane was provided between the first and second membrane layers referred to above to provide for time-separated pulses. While the membranes can be applied in any order, the enteric polymer membrane was applied as the innermost membrane [48].

2.3.9

Drug levels in the plasma are often required during the daytime. Methylphenidate hydrochloride, a mild central nervous system stimulant, is indicated for the treatment of children with attention deficit hyperactivity disorder (ADHD). Élan Pharmaceuticals (Dublin, Ireland) applied this concept to a product of Novartis Pharmaceuticals (Basel, Switzerland) which was Ritalin® containing methylphenidate for the treatment of ADHD [49]. The new product, Metadate® CD, maintains plasma drug levels in children during school hours; in some cases, the plasma drug levels decrease after school hours, to avoid the side effects of appetite suppression and insomnia. The dosage form is to be taken 30 – 45 min before breakfast. Metadate® CD releases the methylphenidate in two concomitant pulses separated by a delay. It is a bimodal, multiparticulate capsule formulation of methylphenidate comprising both IR and SR beads designed to deliver a portion of the dose for rapid onset of action and the other portion of the dose in a controlled manner for approximately 12 h. The formulation is to be administered at breakfast, to avoid the need for midday dosing of a scheduled drug product in the school.

2.3.10

In 1989, Conte and co-workers described a biphasic release formulation of the NSAID, ibuprofen. This consisted of an immediately available drug layer that was separated from a second drug compartment by means of a barrier formed by hydrophilic polymeric material. The second layer of drug and barrier layer were encased in an impermeable layer that prevented fluid access to the second drug layer until the removal of the first drug layer and the barrier material [50]. A pictorial representation of the two-pulse concept is given in **Figure 1**, and the anticipated release profile is given in **Figure 2**.

However, this kind of tablet design requires the manufacture of a tri-layered tablet over which a compression coating of the impermeable layer will be given. Moreover, the drug dose must be equally divided between the upper and lower layer of the encased tablet.

3. PULSYS™: biggest breakthrough in anti-infective therapy

PULSYS™ technology, pioneered by MiddleBrook™ (previously Advancis) Pharmaceuticals, Inc., could be considered a significant step forward in improving current antibiotics treatment regimens. From the very start, the company faced numerous setbacks and challenges before its once-daily amoxicillin (775 mg) product, Moxatag, based on PULSYS™ technology, was approved by the US FDA on 24 January 2008; it is set to enter the market on 16 March 2009 [51]. Moxatag is an extended-release tablet for the treatment of adults and pediatric patients aged ≥ 12 years with pharyngitis and/or tonsillitis secondary to *Streptococcus pyogenes* (commonly referred to as 'strep throat') [52,53]. With this approval, US physicians at last had the option of an FDA-approved once-daily amoxicillin therapy to treat their adolescent and adult patients with pharyngitis/tonsillitis. This should ensure better first-line therapy compliance with a penicillin class of antibiotic [54,55].

The PULSYS™ technology of delivering drug in parallel concomitant pulses corrected the flaws in traditional anti-infective therapy, which relied on single, strong and immediate drug doses that – rather than killing microbes – tend to trigger defensive dormancy in bacteria; studies have shown that antibiotics are most effective against actively growing bacteria. However, traditional anti-infective therapy methods, which focus on immediate-release doses, prompt bacteria to enter a dormant state, in which they may survive the drug. Exposing the bacteria to rapid antibiotic pulses within the first hours of initial dosing was found to have the potential to cripple the natural defense mechanisms of bacteria, eliminating them more efficiently and effectively than conventional anti-infective therapy regimens [56,57].

3.1 Selection of drug for PULSYS

The drugs that may be suitable for PULSYS™ adaptation are mainly broad-spectrum blockbuster antibiotic molecules under the class of penicillins and cephalosporins, and are prescribed as a first-line therapy for common infections. Advancis's targeting of amoxicillin when developing the first version of the PULSYS™ system is evident from the fact that approximately 60 million prescriptions for amoxicillin were written in 2006, with total retail sales of more than $650 million. For pediatricians, amoxicillin is the most prescribed drug among all therapeutic classes. Among family physicians, amoxicillin is the twelfth most prescribed drug among all therapeutic classes [58].

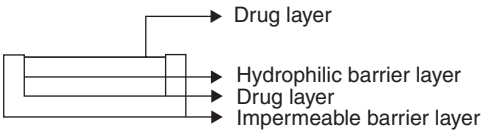

Figure 1. Two-pulse system [50].

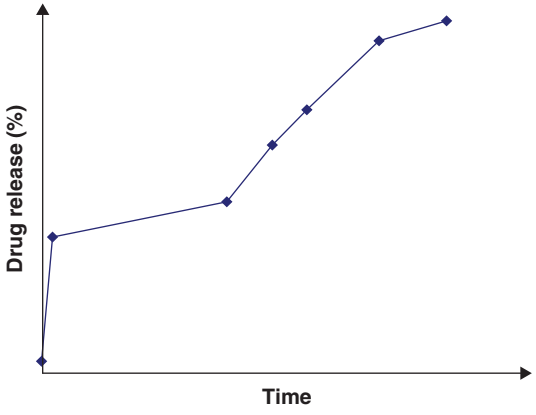

Figure 2. Biphasic release from partially coated tablet.

To develop the PULSYS™ delivery system for antibiotics, evaluation of the properties of antibiotics and selection of those best suited for antibiotic functional enhancement via the PULSYS™ drug delivery technology is necessary to create unique timing and composition profiles. However closely the time of drug release can be controlled in such systems, one consequence of pulsatile drug delivery strategies is that the drug will be released in spurts at a range of sites in the GI tract. Where it is known that the drug is effectively absorbed from the entire length of the GI tract, this will not be a problem. However, any drug that should be variably absorbed depending on the GI tract site may not be a good candidate for multiple-pulse drug delivery. Amoxicillin is a candidate that is known to be absorbed along the entire length of the GI tract. MiddleBrook™ is developing PULSYS™ adaptation of a broad portfolio of drugs with characteristics that are favorable for pulsatile drug delivery. A prime example of this is cefalexin, marketed as Keflex, a PULSYS™ version of which would open the path for MiddleBrook™ having PULSYS™ versions of two of the top five most-prescribed antibiotics in the United States [58,59]. MiddleBrook™ has identified additional product candidates that could be developed for delivery in a pulsatile manner. The timing of further development work on these candidates depends on the commercial potential of the products. We may see PULSYS™ technology extended to the creation of antibiotic product candidates that target some of the most common use of antibiotics. These uses include: sinusitis, chronic bronchitis, acute otitis media, urinary tract infections, and community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) [60]. Another criterion for selecting the drug may be the history of developed and increasing biological tolerance of microbes against a particular drug.

3.2 Preclinical studies

Preclinical trials have demonstrated that pulsatile dosing of certain antibiotics not only kills more bacteria and prevents the development of resistant strains, but does so at significantly lower drug concentrations. Antibacterial action for amoxicillin was demonstrated for *Streptococcus pneumoniae* when dosed by PULSYS™, even at drug concentrations that are not expected to inhibit growth [61]. It was also found that penicillin intermediate-resistant *S. pneumoniae* became resistant after once- or twice-daily dosing of amoxicillin, but not when dosed by PULSYS [62,63].

3.3 Clinical studies

The approval of Moxatag was based on MiddleBrook's Phase III clinical study of > 600 adults and pediatric patients aged ≥ 12 years in a double-blind, double-dummy, randomized, parallel-group, 50-center noninferiority trial. The company compared its Moxatag tablet for the treatment of pharyngitis/tonsillitis due to *Streptococcus pyogenes* (group A streptococcus) delivered in a once-daily, 775 mg tablet for a period of 10 days to 250 mg of penicillin dosed four times daily, for a total of 1 g/day, for 10 days [64].

Bacteriological eradication at the post-therapy test-of-cure visit in the per-protocol population was 85.0% (198/233) of patients with Moxatag and 83.4% (191/229) with penicillin. These results demonstrated statistical noninferiority (95% confidence interval, -5.1 – 8.2). Moxatag therapy demonstrated statistical noninferiority to the comparator therapy in all primary and secondary end points [65,66].

MiddleBrook will also conduct a pediatric study of an amoxicillin extended-release formulation for the treatment of tonsillitis and/or pharyngitis secondary to *S. pyogenes* in pediatric patients aged 2 – 12 years; the final report is expected on 31 March 2013 [66].

3.4 PULSYS™ technology

Conventional dosing regimens of amoxicillin may be twice daily (b.i.d.), whereby the composition is administered every 12 h; three times daily (t.i.d.), whereby the composition is administered every 8 h; four times daily (q.i.d.), whereby the composition is administered every 6 h; or such dosing regimens may even conceive of dosing the composition in excess of four administrations per day. The most commonly prescribed treatment for the management of group A streptococcal pharyngitis is 500 mg of amoxicillin dosed three times daily for a period of 10 days [67,68].

The typical PULSYS drug delivery format is a once-daily tablet containing multiple pellets with different release profiles. The pellets are formulated in a proportion that delivers optimal antibiotic levels. Moxatag is a once-daily extended-release

formulation of amoxicillin for oral administration consisting of at least three components or fractions: one immediate-release and two or more delayed-release components. The components are combined in a specific ratio to prolong the release of amoxicillin from Moxatag compared with immediate-release amoxicillin.

US20080132478 described an amoxicillin tablet that incorporated an immediate-release component (pulse 1), a first delayed-release component (pulse 2), and a second delayed-release component (pulse 3). The multiple-pulse 775-mg amoxicillin tablet is a three-pulse dosage form. Tablets were manufactured by combining the immediate-release granulation (pulse 1, 45%) with two functionally coated delayed-release pellets (pulse 2, 30% and pulse 3, 25%). The amoxicillin product may include 200 – 2500 mg of amoxicillin, depending on the form of product, which can otherwise contain 475, 775, 1250, 1550 or 2325 mg of amoxicillin [69].

The immediate-release component is designed so that release of the amoxicillin is not substantially delayed after administration. The second and third of the (at least three) components are delayed-release components, whereby drug release is delayed until after initiation of release of the amoxicillin from the immediate-release component. With respect to delayed release, the time of release can be controlled by a variety of mechanisms such as pH trigger point, coating thickness, choice of polymer, choice of plasticizer, osmotic pressure, physical swelling pressure, or combinations of these [68,70].

The amoxicillin released from the second component achieves a C_{max} at a time after the amoxicillin released from the first component achieves a C_{max} in the plasma, and the amoxicillin released from the third component achieves a C_{max} in the plasma after the C_{max} of amoxicillin released from the second component [68].

Each of the components may be used either as a pellet or a particle, with a pellet or particle then being formed into a unitary pharmaceutical composition – for example, in a capsule, embedded in a tablet, as a sprinkle, or suspended in a liquid for oral administration. The tablet may be a rapidly disintegrating tablet, whereby the various components of the product are released upon ingestion for further transport into the intestine in the form of either pellets or granules. The pictorial representation of the working of PULSYS™ is given in the company's website [71] and the resulting plasma drug concentration–time profile is shown in **Figure 3**.

Each of the fractions of the composition may also be formulated as a tablet, with each tablet being put into a capsule to produce a unitary amoxicillin product. Thus, a three-component amoxicillin product may include a first component in the form of a tablet that is an immediate-release tablet, and may also include two or more additional tablets, each of which provides for a delayed release or a sustained release of the amoxicillin.

The amoxicillin product may also be in the form of a sprinkle product, the various components of which be placed as pellets in a sachet, capsule or other form that can be used to administer the components simultaneously in particulate form [67].

US6541014 issued to Advancis (now MiddleBrook™ Pharmaceuticals, Inc., MD, USA) has also explained the application of this technology extended to antiviral treatment regimens. The patent describes a similar once-daily dosage unit comprising at least three antiviral dosage form fractions. These are formulated so that each of the dosage forms has a different release profile, such that each of the dosage forms starts the release of the antiviral at different times after administration. The three fractions comprise an immediate-release component, a non-pH-sensitive delayed-release component and a pH-sensitive (enteric) delayed-release component, in accordance with the PULSYS™ concept. Applicants found that a single-dose antiviral product of at least three antiviral dosage forms, each having a different release profile, was an improvement over a single-dose antiviral product consisting of an antiviral dosage form with a single-release profile [72].

The multiple pellets with different release profiles are combined in such a way that a constant escalation in plasma drug levels during the first few hours of the once-daily dosing is provided. Studies at MiddleBrook revealed that as the pellets travel along the lumen wall of the small intestine, they afford a more consistent GI transit than other solid dosage forms such as sustained-release tablets [73].

MiddleBrook currently has a total of 26 US-issued patents and two foreign-issued patents covering its PULSYS™ technology [69,70]. Patents specifically relating to Moxatag run to 2020.

4. Conclusion

Chronotherapy and pulsatile drug delivery systems have come a long way over the past decade; a lot of work has been done, and continues to be done, in this area. However, a remarkable finding by MiddleBrook may provide a solution to the crucial issue of microbial tolerance against anti-infectives. The technology, affectionately known as PULSYS™, involves fractionating the drug and delivering it in the form of multiple concomitant pulses that do not allow the microbes to go into the resistant dormant phase. The work, supported by clinical findings, has been approved by the US FDA, and we can expect the first of this type of formulation in the market very soon – following which a plethora of multiple-pulse versions of anti-infectives (including antibiotics, antiviral and antifungal drug molecules) is likely to become available.

5. Expert opinion

The term 'pulsatile drug delivery' has often been used as a synonym for chronotherapeutic drug delivery. This is not entirely appropriate, as each drug delivery system addresses very different patient needs and was formulated for a very different purpose. Chronotherapeutic systems are based on the circadian

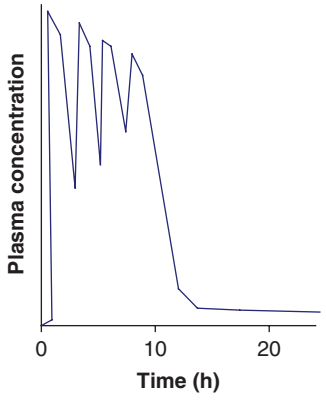

Figure 3. Plasma drug concentration–time profile showing sequential bursts of drug.

rhythms of the body and the need for a drug to be in its maximum concentrations at a particular time of the day, as evidenced by an endless list of ailments that manifest certain symptoms at a particular time of the day. Chronotherapeutic drug delivery systems are mostly single-pulse systems after a single lag phase, whereas pulsatile systems are driven by multiple pulses with a hiatus in between, and are seldom designed with circadian rhythms in mind. An ideal pulsatile system is one that delivers the drug in variable pulses with troughs in the release profile.

Some researchers find no differences among site-specific chronotherapeutic systems and the basic and more conventional intestinal or colon-targeted systems due to the formulation approach, mechanism and intended landing site of the drug being similar despite the different intentions on the part of the formulator. Colon-targeted systems are designed either for local action in the intestine (e.g., mesalazine for inflammatory bowel disease) or to enable variability in the drug's absorption and address stability-related issues in the upper GI tract (e.g., omeprazole). Drugs in a site-specific chronotherapeutic system are also destined for absorption in the lower GI tract, but the purpose is to provide a delay in release due to the biological rhythms associated with the ailment, as discussed earlier in this review.

The attempt to offset biological tolerance by administration of drugs in concomitant multiple pulses is based on clear clinical evidence, and the concept promises to bring a new revolution in anti-infective therapy. However, though PULSYS™ technology has a verifiable scientific foundation, the notion of using gastroresistant enteric coating polymers to perform predictably in multiple-pulse products remains somewhat alien. The enteric coat has been found effective in protecting the tablets from disintegration in the stomach, but disintegration following exit from the stomach is extremely variable in terms of both time and intestinal site of release. This reduces the usefulness of enteric polymers in supplying reproducible time-delayed drug delivery. Moreover, the three small intestinal sites shown in the picture on the company's website [71], in which the drug is expected to release after the first pulse release in the stomach, are very close; some variability relating to pH levels is inevitable.

From a technological viewpoint, the more pulses delivered, the more complex the formulation, which correspondingly introduces the chance of variation. PULSYS™ involves a multistep procedure involving distinct stages such as preparation of the pellets, fractionating and layering with drug (as per the dose division), followed by air-suspension polymer coating over the pellet fractions in different concentrations or ratios, and finally compression of the coated pellets. The pellets may be replaced with minitablets of 1 – 3 mm. Multi-tip tablet tooling is available, which can produce about 10 – 12 minitablets with a single rotation; these tablets, divided in fractions, can easily be coated in a conventional pan-coating machine. The technology involved in the preparation of a two-pulse system may also be developed to be given in twice-daily dosing, which may involve fewer steps and thus prove more cost-effective. This may be suitable, for example, for an antibiotic dose divided into two parts, one part of which could be prepared as a core tablet coated with delayed-release polymers while the other dose fraction is compression-coated with compressible soluble excipients or disintegrants to provide the immediate pulse. Compression coating, unlike pan coating, may facilitate higher amounts of drug load over the coated core. Such a tablet given twice a day would offer four pulses in a single day.

In conclusion, the field of multiple-pulse drug delivery is still in its infancy; we await with interest the work that will emerge in this field as the concept moves from adolescence to adulthood. This novel approach of targeting microbial infections will undoubtedly attract competition, encouraging generic drug manufacturers to improve upon the formulations and technologies used in anti-infective therapy. Given the important role of advances in technology, many companies may be vying for similar products: with innovator patents being valid until 2020, Para IV filings and related litigation may be seen in the near future. This will eventually benefit the consumer by making available quality medications at a cheaper price.

Nevertheless, the promise of this novel drug delivery system should not distract us from making every effort to avoid unnecessary prescribing of antibiotic medications, which remains a crucial strategy in slowing the development of microbial resistance.

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