Published in final edited form as:

Adv Drug Deliv Rev. 2010 July 31; 62(9-10): 898–903. doi:10.1016/j.addr.2010.04.010.

Chronopharmaceutical Drug Delivery Systems: Hurdles, Hype or Hope?®

Bi-Botti C. Youan^{a,*}

^aLaboratory of Future Nanomedicines and Theoretical Chronopharmaceutics, Division of Pharmaceutical Sciences, School of Pharmacy, University of Missouri Kansas City, 2464 Charlotte, Kansas City, MO 64108

Abstract

The current advances in chronobiology and the knowledge gained from chronotherapy of selected diseases strongly suggest that “the one size fits all at all times” approach to drug delivery is no longer substantiated, at least for selected bioactive agents and disease therapy or prevention. Thus, there is a critical and urgent need for chronopharmaceutical research (e.g., design and evaluation of robust, spatially and temporally controlled drug delivery systems that would be clinically intended for chronotherapy by different routes of administration). This review provides a brief overview of current delivery system intended for chronotherapy. In theory, such an ideal “magic pill” preferably with affordable cost, would improve the safety, efficacy and patient compliance of old and new drugs. However, currently, there are three major hurdles for the successful transition of such system from laboratory to patient bedside. These include the challenges to identify adequate (i) rhythmic biomaterials and systems, (ii) rhythm engineering modeling, perhaps using system biology and (iii) regulatory guidance.

Keywords

Chronopharmaceutics; delivery systems; chronotherapy; rhythmic biomaterials; modeling; regulations

1. Introduction

It has been reported that approximately 100,000 deaths and more than 2 million hospitalizations annually in the United States are due to properly prescribed medications [1;2]. These adverse drug reactions could be related to multiple factors (e.g. disease determinants, environment, and genetics). However, in drug delivery in biology of living species, time is a fundamental dimension that has been long overlooked in drug design and delivery. It is now documented that cycles of different scales exist in biological activities ranging from very short (ultradian) rhythms to rhythms with a period of approximately one day (circadian) and rhythms with longer cycles, of a week, a month, a season, or even

®This review is part of the Advanced Drug Delivery Reviews theme issue on “Chrono-drug-delivery focused on biological clock: Intra- and inter-individual variability of molecular clock”.

© 2010 Elsevier B.V. All rights reserved

*Corresponding author. Tel.: +1-(816) 235-2410; fax: +1-(816) 235-5779. youanb@umkc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

longer. Instead of being a passive response to external changes, these rhythms are generated by endogenous biological clocks, i.e., time-keeping structures. In mammals, the central pacemaker is the suprachiasmatic nucleus (SCN) [3]. For example, it has been reported that non-pharmacological (light therapy, sleep deprivation, rhythm therapy) and pharmacological (lithium, antidepressants, agomelatine) therapies of affective disorders influence circadian rhythms [3]. Beside familial advanced sleep-phase syndrome [4], the importance of the biological rhythm in drug dosing [5], metabolic syndromes [6] has also been demonstrated. Therefore, a plethora of data both from studies ranging from basic chronobiology to clinical applications (chronotherapy) have been recently compiled for readers interested in comprehensive background information on this emerging and promising research topic [7].

The foregoing facts suggest that it is now known that in drug dosage forms design, the notion that “one size fits all at all times” is not correct. Among strategies to address this concern, traditionally, patients and health care providers attempted better controlled over the administration of conventional dosage forms with respect to time (a proven concept referred to as chronotherapy [8]). Additionally, a promising strategy to improve the efficacy and safety of old and new drugs is to revisit our current drug discovery and formulation approaches based on knowledge gained from chronobiology for future chronotheranostics of human diseases whenever a clinical or therapeutic advantage can be proven. Clearly, there is a critical and urgent need at least in such cases such as asthma, cancer and heart diseases for novel chronopharmaceutical drug product either for therapy or prevention. Such novel drug dosage forms should be effective, safe, robust (predictable with biological release rate) and clinically justified, with spatial and temporal control ability after administration by different routes. Theoretically, such ideal drug delivery system (preferably a noninvasive system with affordable cost) would potentially improve the safety, efficacy and patient compliance of old and new drugs. This ideal goal of the “magic pill” remains elusive due to several hurdles or bottlenecks. After a brief overview of the current status of chronopharmaceutical drug delivery, this review focuses on the three major hurdles that should be overcome for the chronopharmaceutical drug formulation concept to transition from hype to real hope in future clinical practice.

2. Overview of the current status of chronopharmaceutical drug delivery

The chronopharmaceutical technologies based on physical and/or chemical activation for controlled drug release that is intended for different route of administration have been described in detail elsewhere [7;9;10]. Examples of technologies that may be used for parenteral routes in chronotherapy include chronomodulating infusion pumps (i.e. Melodie™, Panomat™ V5, Synchroned™, Rhythmic™) and controlled-release microchip strategies. Examples of technologies intended for oral administration include Contin™, Chronset™, Codash™, Ceform™, Diffucaps™, TIMERx®, Chronotopic™, Egalet™, GeoClock™, Port™, Three-dimensional printing (3DP)™, methods involving physico-chemical modification of the active pharmaceutical ingredient and/or the use of controlled-release erodible polymer [7;9]. Recently, a novel floating pulsatile system using high internal phase emulsion based porous material intended for chronotherapy have been reported [11]. In this floating system, drug loading using a porous carrier, synthesized by high internal phase emulsion technique using styrene and divinylbenzene, was achieved via solvent evaporation method. The lack of chemical agent as release modifiers made this delivery system distinct from other technologies for chronotherapy. Overall, the concept of low density floating multiparticulate pulsed-release dosage forms have been extensively explored [12]. Moreover, the combination of floating and pulsatile principles to develop drug delivery system for chronotherapy in nocturnal acid breakthrough has been demonstrated by using a programmed delivery of ranitidine hydrochloride from a floating tablet with time-lagged coating [13]. It is important to underscore that the clinical relevance

or advantage of chronopharmaceutical formulation or delivery remains to be proven on case by case basis perhaps depending on the type of patient population, disease and/or bioactive agent. For example, the bioavailability of the extended-release tramadol (opioid analgesic) capsules for once daily administration was not affected by the time-point of administration in pain management. The total and maximum exposure of the product was bioequivalent after intake in the morning and at night suggesting that the time-point of administration may be adjusted to the patient's needs without any significant change in the *in vivo* performance [14]. However, a recent clinical trial investigated the administration-time dependent antihypertensive efficacy of the slow-release, once-a-day nifedipine gastrointestinal-therapeutic-system formulation. In this study, The blood pressure (BP) reduction after treatment and the number of patients with controlled ambulatory BP were significantly larger bedtime than morning treatment. Moreover, the morning surge of BP (a risk factor for stroke) was also significantly reduced only after bedtime administration of nifedipine. Therefore, the increased efficacy on ambulatory BP as well as the significantly reduced prevalence of edema after bedtime as compared to morning ingestion of this drug should be taken into account when not only during the design of novel delivery system for this application but also when prescribing such cardiovascular medication for patients with essential hypertension [15]. Moreover, in resistant hypertension, it has also been shown that the time of treatment may be more important for BP control and for the proper modeling of the circadian BP pattern than just changing the drug combination [16].

The development of transdermal drug delivery system for chronopharmaceutical applications was recently reviewed [7;17]. Examples of such systems include ChronoDose™, crystal reservoir [18] and thermoresponsive membrane systems [19]. For rectal routes, a novel chronopharmaceutical and rectal aminophylline delivery system for asthma therapy has been reported [20]. It consisted of a sustained-release hollow-type (SR-HT) suppositories using sodium alginate, sodium polyacrylate or polyacrylate-PANa (PA-PANa) co-polymer as gelling polymers/gel agent. The SR-HT suppository, particularly using PA-PANa as a gel agent, may be useful against nocturnal symptoms of asthma, thus providing (besides transdermal strategies), potentially an alternative method for chronotherapy for patients that are unable to take oral medications.

Recently novel drug loaded nanocarriers have also been investigated in chronotherapy. The chrono-administration of drug containing nanoformulation appears to be a new therapeutic strategy that can increase for example breast cancer curability with no added side effects, costs, and risks for the patients. For example, based on the fact that the periodical sex hormones during menstrual cycle regulate the cyclic expression of VEGF in breast cancer and modulate the cancer vascular permeability and since the expression of cancer VEGF varies considerably at different menstrual cycle stages, it was conceivable that the variation between the highest and lowest cancer vascular permeabilities during menstrual cycle was significant. Thus, it was shown that nanoformulations (i.e. Caelyx and/or Abraxane) given at the proper menstrual stage with predicted highest VEGF expression and cancer vascular permeability could allow significantly increased drug retention in breast cancer, and thus leading to the maximal cancer growth control and minimal cancer metastatic spread. Caelyx/ Doxil is a pegylated liposomal doxorubicin and Abraxane is a nanoformulation of paclitaxel using albumin molecules forming nano-size particles (130 nm). [21]. These data further suggest that the efficacy and/or targeting ability of novel nanomedicines could be enhanced by taking into account the biological rhythm as well. Future research in this field should also embody the design of novel systems not only for improved therapy but also for the chronoprevention of diseases with potential application in markers-guided chronotheranostics (integration of diagnostic and chronotherapeutic products) and vaccination / immunization strategies [7].

3. Hurdles in chronopharmaceutical drug research and development

The current hurdles in chronopharmaceutical drug development include advances in (i) rhythmic biomaterials and system design, (ii) rhythm engineering and modeling (iii) regulatory guidance related to these types of modified dosage forms.

3.1. Rhythmic biomaterials and system design hurdles

The first major hurdle to the development of chronopharmaceutical drug product is the lack of safe and rhythmic biomaterials with reversible properties and systems. Although there have been some efforts to develop drug products intended for chronotherapy [7;9], the true breakthrough in this field will only be possible with smarter biomaterials. In the past decades, significant efforts have been made in the area of designing smart biomaterials [22;23]. However, there are still major challenges in the design of rhythmic biomaterials that are not only biodegradable and / or biocompatible but also reversibly responsive to specific biomarkers in an ultrafast and rhythmic manner in biological systems following the specific biological rhythm under consideration. Current efforts toward that ultimate goal involved the use of chemical oscillators (e.g., pH oscillations to drive rhythmic drug delivery) [24] and stimuli-sensitive polymers [25;26]. For example, the availability of such materials would be useful in the treatment of hypopituitary dwarfism. It has been reported that the administration of human growth-hormone-releasing hormone (GHRH) is more effective when GHRH is administered in a pulsatile manner that exhibits a period characteristic of the patient's circadian rhythm [25].

Based on the lessons from nature, several biomaterials that respond to external stimuli such as temperature, pH, light, electric field, chemicals and ionic strength[23] have been designed. These responses are basically dramatic changes in one of the following: shape, surface characteristics, solubility, and formation of an intricate molecular self-assembly or a sol-to-gel transition. Some of the biomaterials even direct specific cellular behaviors, or respond to specific cellular signals [22]. In addition to these materials with responsive bulk properties to light, temperature, pH, shape-memory [23], materials with smart surfaces that can reversibly switch between hydrophilic and hydrophobic in response to an electric potential have been investigated [23]. The latter may be perhaps used one day for light induced chronopharmaceutical delivery system. Advances in microfabrication have also provided new approaches for developing microchips based drug delivery system [27]. The co-entrapment of bioactive agents and biosensors into computer-controlled microchips may lead to responsive, fully automated chronotherapy in the future. Finally, nanofabrication techniques, if well harnessed, may provide some future solution in chronotherapy. In recent years, efforts have been made to control linear and rotary motion in such molecular systems towards the construction of synthetic machines that can perform useful functions [28].

Overall, regardless of the methods and materials involved in the design of rhythmic biomaterials and systems, the concepts of robustness in controlling complex systems [29] and reversibility in response are critical for the future successful application of these biomaterials and systems in disease therapy and prevention.

3.2. Rhythm engineering and modeling hurdles

The second major hurdle to chronopharmaceutical drug formulation is our ability to engineer rhythm and use reliable models, not only to predict the complex physicochemical properties of these novel delivery systems but also their biological responses. Models are also necessary to comprehend the transition from simple to complex oscillatory behavior and to elucidate the conditions under which they arise [30]. In general rhythmic processes, like many physical phenomena, have been modeled using differential equations.

On more theoretical standpoint, an age-structured partial differential equation (PDE) with time-periodic coefficients was used to compare the growth rate of the model controlled by a time-periodic control on its coefficients with the growth rate of stationary models of the same nature, but with averaged coefficients. The authors firstly derived a delay PDE with solutions illustrated by numerical simulations which allowed them to prove several inequalities and equalities on the growth rates and discussed the necessity to take into account the structure of the cell division cycle for chronotherapy modeling [31]. The Rössler model (a system of three non-linear ordinary differential equations exhibiting very rich dynamics, including both spiral and funnel chaos) was recently proposed for chronotherapy modeling [32]. These authors represented chronotherapy as a periodic forcing (sine function) and illustrate numerically that one can move among chaotic and periodic windows by manipulating the amplitude and frequency of the forcing. Unfortunately, purely theoretical manuscripts such as these have limited application because they have are not yet supported by empirical and biomedical/clinical observations. However, they provide some excellent insight in modeling directions of rhythmic processes. For example, the work with the Rössler model suggested that there is no need to return the parameters back to their original values to restore health. Instead, the system under consideration simply has to enter a region in which it exhibits “proper” (non pathological) behavior which could be quite large in design space. Therefore, an accurate understanding of the bifurcation structure of the system is needed with insight from detailed physiological/clinical and/or physicochemical characterization and standardization of the disease and drug delivery system under consideration.

With respect to effort to elucidate rhythmic phenomena in physicochemical processes, a phase models and array of electrochemical reactions were used to describe and tune complex dynamic structures to desired states, thus demonstrating the power of mild model-engineered feedback to achieve a desired response [33]. So, the notion that rhythm phenomena as uncontrollable and unpredictable is now challenged. Moreover, recently a numerical algorithm was used to compute the swelling dynamics of chemoresponsive polyelectrolyte gels. A prediction was possible for a piece of hydrogel that swells/shrinks as a function of pH and can exhibit spontaneous mechanical and chemical oscillations. This study illustrates ongoing effort to elucidate the nonlinear dynamics related to polymeric systems [34].

With respect to effort to elucidate rhythmic processes in biological systems, the future challenge in this area includes engineering rhythmic responses in biological system from the molecular response (from the rhythmic translation of mRNA to protein) to cellular, organ, tissue and, whole organism levels. The protein production process involves translation and subsequent processing steps such as phosphorylation, dimerization, transport and nuclear entry. To achieve this goal, new mathematical, statistical and numerical analysis methods are needed. As initial steps toward that goal, several efforts have now been made.

At cellular level, recently, detailed systems design with experimental analyses and mathematical modeling, allowed to monitor oscillating concentrations of green fluorescent protein with tunable frequency and amplitude by time-lapse microscopy in real time in individual Chinese hamster ovary cells [35]. An excellent predictive mathematical model was also evaluated against the experimentally observed cell-autonomous circadian phenotypes of gene knockouts, particularly retention of rhythmicity and changes in expression level of molecular clock components [36].

A statistical model for mapping and characterizing specific genes or quantitative trait loci (QTL) that affect variations in rhythmic responses have been presented [37]. This model integrated a system of coupled differential equations (to describe circadian behavior of the

intracellular oscillator of given messenger RNA and its translated protein) into the framework for functional mapping, allowing hypotheses about the interplay between genetic actions and periodic rhythms to be tested. The model assumed that the protein production cascade and the negative feedback are nonlinear processes in the reaction loop with a time delay between protein production and subsequent processing. A simulation approach based on sustained circadian oscillations of the clock proteins and their mRNAs has been designed to test the statistical properties of the model. The model has significant implications for probing the molecular genetics mechanism of rhythmic oscillations through the detection of the clock QTL throughout the genome. It may further be integrated in the system biology approach to elucidate and predict biological rhythm.

To understand chronobiology at the system level, it is critical to examine the structure and dynamics of cellular and organism function, rather than the characteristics of isolated parts of a cell or organism. Properties of systems, such as robustness, emerge as central issues, and understanding these properties may have an impact on the future of medicine [38]. Hence, systems biology appears to be a natural extension of molecular biology and can be defined as biology after identification of key gene(s). Using mammalian circadian clocks as a model system, some systems-biological approaches were described, including the identification of clock-controlled genes, clock-controlled cis elements, and clock transcriptional circuits driven by functional genomics. As perspective for systems-biological investigations, the system-level dynamical questions related to the core of clocks, were also introduced [39]. The rationale integration of time from gene to system levels would be critical for design of safe and effective of future chronopharmaceutical drug products.

Toward a system-level understanding of this transcriptional circuitry, clock-controlled elements have been identified on 16 clock and clock-controlled genes in a comprehensive surveillance of evolutionarily conserved cis elements and measurement of their transcriptional dynamics [40]. For example, in mammals, the SCN-evoked time generated by specific genes localized to the SCN is converted to neuronal (time signals) and hormonal (e.g. glucocorticoids) signals and synchronizes the clocks in the whole body through the central parasympathetic and sympathetic nuclei [41]. Clinical trials and systems-biology approaches in cancer chronotherapeutics raise novel issues to be addressed experimentally in the field of biological clocks. The challenge ahead is to therapeutically harness the circadian timing system to concurrently improve quality of life and down-regulate malignant growth [42]. These include for each gene of therapeutics interest, a precise estimate of the time underlying the molecular events of biological rhythms and any potential synergistic and antagonist effect between and their future clinical significance. Moreover, a cell cycle automaton (CCA) model describing the transitions through the successive phases of the cell cycle for chemotherapy has been proposed. The CCA model is not based on molecular details but provides a simple representation of the cell cycle in terms of transitions between sequential states corresponding to the successive phases of the cell cycle. A probabilistic exit occurs from the cell with the incorporation of a chemotherapeutic agent in the system depending on the agent concentration. To account for the variability of transitions between cell cycle phases in a proliferating cell population, a random component is considered as well. In addition to circadian control, the CCA can readily be used to investigate the impacts of different temporal patterns of drug administration. For example, the model indicated that the cytotoxic effect of 5-fluorouracil (5-FU) was minimum for the circadian delivery peaking at 4 a.m., and maximum for the continuous infusion or the circadian pattern peaking at 4 p.m. [43]. CCA has also allowed showing how circadian changes in oxaliplatin (I-OHP) cytotoxicity may arise from circadian variations in the levels of plasma thiols and glutathione. Consistent with experimental and clinical data, the simulations of this model account for the observation that the temporal profiles minimizing I-OHP cytotoxicity are in antiphase with those minimizing cytotoxicity for 5-FU [44]. Mathematical models further

show that the therapeutic index of chemotherapeutic drugs can be optimized through distinct delivery profiles, depending on the initial host/tumor status and variability in circadian entrainment and/or cell cycle length [43].

At purely organism level, a computer controlled infusion pump based on Dirac impulse function and a convolution operator for regulation of target tissue concentration of radioactive compounds was recently developed and validated using [¹¹C]flumazenil administered to Sprague-Dawley rats and microPET-scanner [45]. Based on these study, it is reasonable to approximate the time-dependent targeted drug tissue concentration (C) using equation 1.

$$C(t) = S(t) * R(t) \quad (1)$$

Where t represent the time, S, the drug delivery function and R the drug delivery rate. S is an impulse response related to biological responses and the hypothetical drug delivery system properties. The symbol * is the convolution operator. By definition, the convolution of S and R is a particular kind integral transform of the product of the two functions after one is reversed and shifted. A deconvolution, an algorithm-based process, may be used to reverse the effects of convolution on recorded data. For extremely short drug delivery time t (say, t = ε second) in physiologically relevant media, the Dirac impulse “function” (δ(t)) could allow to approximate S(t) before its use for C(t) estimation according to equation equation 2.

$$C_{\epsilon}(t) = S(t) * \delta(t) = S(t) \quad (2)$$

Where δ(t) represents an infinitely sharp peak bounding unit area: δ(t) has the value zero everywhere on x-axis except at t = 0 where its value is infinitely large in such a way that its total integral is 1.

Future investigations in this field may be inspired by the use of such modeling approaches in future chronopharmaceutical drug development strategies with detailed considerations including the specific period for S(t) and/or R(t) functions based on the biologic rhythm being studied. Collectively, these models may useful to rationalize and predict biological rhythm and potential chronopharmaceutical product performance in the future. However, additional research efforts are needed to clarify in this direction considering the vast amount of information to be handled from molecular, cellular to system level.

3.3. Regulatory hurdles

In every human activity, it is always wiser to begin with the end in mind. If a chronopharmaceutical product would be launched on the market and widely used in clinical practice, one has to keep in mind the current regulatory hurdles [7]. Although the scientists in pharmaceutical industry usually keep these regulatory concerns in mind, this is not always the case for those working in academia who are mostly fascinated by proof of concepts that may never reach the patient bedside without regulatory considerations. The regulatory hurdles include pre and post-approval considerations.

In preapproval phase, it is sometimes difficult to demonstrate chronotherapeutic advantage of **controlled release** (CR) or modified release (MR) formulations in clinical setting. This is partly related to the first two hurdles lacked of truly rhythmic biomaterials and system and rhythm engineering and better prediction tools. CR or MR including chronopharmaceutical drug formulation provide several advantages over the conventional immediate release formulation (IR) of the same drug, such as (i) a reduced dosing frequency, (ii) a decreased

incidence and or intensity of side effects, (iii) a greater selectivity of pharmacological activity and (iv) a better control over drug plasma concentration fluctuation leading to optimal therapeutic outcome. Since MR formulations provide unique challenges from a formulation and manufacturing point of view, they require specific studies to characterize the controlled release nature of their drug delivery [46]. Due to the specificity of these studies, in many cases, the pharmaceutical innovators worked closely with the Federal Agency, educating them and making sure that relevant/critical process parameters are appropriately selected/controlled. The bioavailability requirements for CR products are covered in the US Code of Federal Regulations under 21 CFR 320.25[47]. The basic principle in an *in vivo* bioavailability study is that no unnecessary human research should be done. The regulations of application with already approved IR formulation of the same drug ingredient or active moiety, are covered under 21 CFR 314.54[48].

In post-approval phase, beside the challenge of assuring product quality [46], it is important to note that designer drugs and high content modified release formulations have been exploited both in casual recreational drug abuse as well as, on a much larger scale, by the criminal diversion of these products for profit [49]. The challenges before manufacturers and regulators as they approach the problem of abuse potential of these new drug products and some of the solutions specifically designed to counteract abuse have been provided. Briefly, both the regulator and drug sponsor should consider factors that might render the drug substance “abuse-ready” so that appropriate risk management strategies can be implemented post-approval [49]. An alternative to declining to approve a product when there is the perception that the product may present excessive risk to the population is approval with restrictions to assure safe use, or “restricted distribution” under the provisions of the regulations in 21 CFR 314.520[50]. Risk management strategies have been a modern supplement to the approval of drugs with known abuse potential. The FDA has relied heavily on the development and implementation of Risk Management Programs (MAP) as a strategy to allow an approval of a drug to go forward while exercising some restrictions [49].

Overall, with advances in drug delivery system, there will be a critical need for elucidating critical manufacturing variables that affect drug release characteristics and devise strategies to better control these variables and to assure quality of the product post approval [46]. Pharmacovigilance or phase IV clinical studies may also become very critical with these novel drug formulations. Moreover, novel analytical noninvasive methods (e.g. with low limit of detection, ultrafast and real time *in vivo* responses), and novel process analytical technologies (that accurately relate the key product attributes to their intended functionality such as drug release kinetics to ensure robustness and batch to batch reproducibility) are also needed. It also remains to be seen how a given drug or disease affects the normal biological rhythm in different conditions.

4. Conclusions and perspectives

There are numerous scientific evidences from basic chronogenetic/chronobiological and clinical studies strongly suggesting that there is a critical and urgent need to revisit the formulation of both new and old drugs at least for selected diseases. Among other limitations in the fulfillment of this clinical demand, there are three major hurdles to widespread production and use of chronopharmaceutical drug products. These hurdles include advances needed in rhythmic biomaterials and system design, engineering processes and regulatory guidance. We should learn from nature and elucidate the structure-property for successful future development and rational design of new functional smart materials [26]. Nanotechnologies, an expression of the human ability to control and manipulate matter on a very small scale, seems promising for disease therapy and prevention but there are

some ethical issues concerning biomedical applications and ongoing discussion on related guidelines and regulations [51]. Novel mathematical, statistical and numerical methods are required to be able to predict dynamic and rhythmic processes both in physicochemical and biological processes. Considering the considerable number possible variations in the estimated 24,000 genes in the human genome, it would be useful to have standard criteria for databases of variation [52] before effective use of system biology in this field. Moreover, many breakthroughs in experimental devices, advanced software, and analytical methods are required before systems biology can live up to potential such as chronotherapy applications [38]. Because these endeavors involve novel materials and products, new validation methods are needed and there should be constant interactions with regulatory agency to substantiate their need and to ensure public health. Let us imagine or dream about a “true magic pill” or an advanced bioactive agent delivery systems composed of nanometre-sized components that is a self-controlled molecular machine where complex and responsive and reversible processes operate with accuracy, precision and, reproducibility; where translational and rotational motions are directed in four dimensions (width, length, height, and time) with precision and ultrafast response based on demand based on need for molecular function (DNA repair, insulin release, etc.); a nano-container triggered by specific/targeted elements (e.g., disease biomarker, light, etc...) with specific active targeting ability when administered by a given route. The image that comes to mind is the Space Shuttle landing on planet Mars. It appears that we are currently able to design and manipulate robots at macroscale and several million miles distance away: launching unmanned mission to invisible location to perform detailed function. But unfortunately, we are not currently able to do similar work perhaps because we are too big to manipulate the nanostucture or perhaps, we have not invested the similar level of resources and motivation. So, ironically, we are not yet able to manipulate complex nanosystems to cure diseases that can affect us. For example, the Phoenix (launched on August 4, 2007), was only the first Mars lander properly equipped to do detailed identification and analysis since the 1976 Viking mission. Phoenix landed on Mars on May 25, 2008, after a 422 million mile journey. Phoenix has fully functional robotic arms and even a brain. The robotic arms can dig collect soil samples. These arms have a camera to capture detailed images of soil before and after it has been scooped up. The Mars lander also carries a stereoscopic imager to capture full panoramas; electrical, chemical, and microscopy tools to analyze samples; and temperature and pressure sensors for meteorological observation. Phoenix's brain is a radiation-hardened computer. Actually, Phoenix dug, scooped, baked, sniffed and tasted the Red Planet's soil and already returned more than 25,000 pictures. The next mission to the planet was scheduled to be launched in September 2009 and to land on Mars in July-September 2010 (<http://www.nasa.gov>). How effective could we be in disease diagnosis, treatment and prevention if we were able to have similar nanoscale robot able to perform such detailed function and molecular repair after a journey inside the human body? Perhaps, to achieve this daunting mission, we should also learn from the earlier challenges in airplane design. Airplanes can now fly without the exact anatomy and physiology of a bird. Perhaps, this dream of human body exploration with the “magic pill” in future medicine will become true with more time, perseverance, enthusiasm/motivation, and availability of resources (human, financial and technology). For this dream to become true, we would need not only interdisciplinary work at the interfaces between microtechnology, nanotechnology and biochemistry[53] but also with advances in chronogenetics and evidence based medicine[7;54].

Acknowledgments

As relatively new investigator in this field, the author sincerely acknowledge partial support from the following national awards: New Therapy Grant (the Epilepsy Research Foundation of America), Award number GM 069397-01A2 from the National Institutes of General Medical Sciences and Award Number R21AI083092 from the

National Institute of Allergy and Infectious Disease. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute Of Allergy And Infectious Diseases or the National Institutes of Health of USA.”

References

- [1]. Shastry BS. Genetic diversity and new therapeutic concepts. *J. Hum. Genet.* 2005; 50:321–8. [PubMed: 16041496]
- [2]. Shastry BS. Pharmacogenetics and the concept of individualized medicine. *Pharmacogenomics J.* 2006; 6:16–21. [PubMed: 16302022]
- [3]. Schulz P, Steimer T. Neurobiology of circadian systems. *CNS Drugs.* 2009; 23(Suppl 2):3–13. [PubMed: 19708721]
- [4]. Jones CR, Campbell SS, Zone SE, Cooper F, DeSano A, Murphy PJ, Jones B, Czajkowski L, Ptacek LJ. Familial advanced sleep-phase syndrome: A short-period circadian rhythm variant in humans. *Nat. Med.* 1999; 5:1062–5. [PubMed: 10470086]
- [5]. Ohdo S, Koyanagi S, Suyama H, Higuchi S, Aramaki H. Changing the dosing schedule minimizes the disruptive effects of interferon on clock function. *Nat. Med.* 2001; 7:356–60. [PubMed: 11231636]
- [6]. Staels B. When the Clock stops ticking, metabolic syndrome explodes. *Nat. Med.* 2006; 12:54–5. discussion 55. [PubMed: 16397568]
- [7]. Youan, BBC., editor. *Chronopharmaceutics: Science and Technology for Biological Rhythm Guided Therapy and Prevention of Diseases.* John Wiley & Sons; Hoboken, NJ, USA: 2009.
- [8]. Oren DA, Wehr TA. Hypernyctohemeral syndrome after chronotherapy for delayed sleep phase syndrome. *N. Engl. J. Med.* 1992; 327:1762. [PubMed: 1435929]
- [9]. Youan BB. Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery. *J. Control. Release.* 2004; 98:337–353. [PubMed: 15312991]
- [10]. Khan Z, Pillay V, Choonara YE, du Toit LC. Drug delivery technologies for chronotherapeutic applications. *Pharm. Dev. Technol.* 2009; 14:602–12. [PubMed: 19883249]
- [11]. Sher P, Ingavle G, Ponrathnam S, Benson JR, Li NH, Pawar AP. Novel/conceptual floating pulsatile system using high internal phase emulsion based porous material intended for chronotherapy. *AAPS PharmSciTech.* 2009; 10:1368–80. [PubMed: 19936939]
- [12]. Roy P, Shahiwal A. Multiparticulate formulation approach to pulsatile drug delivery: current perspectives. *J. Control. Release.* 2009; 134:74–80. [PubMed: 19105973]
- [13]. Roy P, Shahiwal A. Statistical optimization of ranitidine HCl floating pulsatile delivery system for chronotherapy of nocturnal acid breakthrough. *Eur. J. Pharm. Sci.* 2009; 37:363–9. [PubMed: 19491027]
- [14]. Warnke A, Schug B, Vanderbist F, Erbist, Blume H. Significance of the biopharmaceutical properties of tramadol sustained-release formulations for chronopharmacologically optimized treatment of pain from various sources. *Int. J. Clin. Pharmacol. Ther.* 2009; 47:405–12. [PubMed: 19473603]
- [15]. Hermida RC, Ayala DE, Mojon A, Fernandez JR. Chronotherapy with nifedipine GITS in hypertensive patients: improved efficacy and safety with bedtime dosing. *Am. J. Hypertens.* 2008; 21:948–54. [PubMed: 18600215]
- [16]. Hermida RC, Ayala DE, Fernandez JR, Calvo C. Chronotherapy improves blood pressure control and reverts the nondipper pattern in patients with resistant hypertension. *Hypertension.* 2008; 51:69–76. [PubMed: 17968001]
- [17]. Hradetzky D. Transdermal drug delivery devices for chronotherapy. *Med. Device Technol.* 2008; 19:45–7. [PubMed: 18557410]
- [18]. Kato H, Nagata O, Yamazaki M, Suzuki T, Nakano Y. Development of transdermal formulation of tulobuterol for the treatment of bronchial asthma. *Yakugaku Zasshi.* 2002; 122:57–69. [PubMed: 11828751]

- [19]. Lin SY, Ho CJ, Li MJ. Precision and reproducibility of temperature response of a thermo-responsive membrane embedded by binary liquid crystals for drug delivery. *J. Control. Release.* 2001; 73:293–301. [PubMed: 11516506]
- [20]. Shiohira H, Fujii M, Koizumi N, Kondoh M, Watanabe Y. Novel chronotherapeutic rectal aminophylline delivery system for therapy of asthma. *Int. J. Pharm.* 2009; 379:119–24. [PubMed: 19555748]
- [21]. You S, Li W. Administration of nanodrugs in proper menstrual stage for maximal drug retention in breast cancer. *Med. Hypotheses.* 2008; 71:141–7. [PubMed: 18299174]
- [22]. Langer R, Tirrell DA. Designing materials for biology and medicine. *Nature.* 2004; 428:487–92. [PubMed: 15057821]
- [23]. Anderson DG, Burdick JA, Langer R. Materials science. Smart biomaterials. *Science.* 2004; 305:1923–4. [PubMed: 15448260]
- [24]. Siegel, RA. Autonomous Rhythmic Drug Delivery Systems Based on Chemical and Biochemical Oscillators. *Chemomechanical Instabilities in Responsive Materials.* Borckmans, P.; Metens, S.; DeKepper, P., editors. Springer Verlag; 2009. p. 175–201.
- [25]. Peppas NA, Leobandung W. Stimuli-sensitive hydrogels: ideal carriers for chronobiology and chronotherapy. *J. Biomater. Sci. Polym. Ed.* 2004; 15:125–44. [PubMed: 15109093]
- [26]. Jeong B, Gutowska A. Lessons from nature: stimuli-responsive polymers and their biomedical applications. *Trends Biotechnol.* 2002; 20:305–11. [PubMed: 12062976]
- [27]. Santini JT Jr, Cima MJ, Langer R. A controlled-release microchip. *Nature.* 1999; 397:335–8. [PubMed: 9988626]
- [28]. Wesley RB, Feringa BL. Making molecular machines work. *Nature Nanotechnol.* 2006; 1:25–35. [PubMed: 18654138]
- [29]. Kitano H. A robustness-based approach to systems-oriented drug design. *Nat. Rev. Drug Discov.* 2007; 6:202–10. [PubMed: 17318209]
- [30]. Goldbeter A. Computational approaches to cellular rhythms. *Nature.* 2002; 420:238–45. [PubMed: 12432409]
- [31]. Clairambault J, Gaubert S, Lepoutre T. Comparison of Perron and Floquet eigenvalues in age structured cell division cycle models. *Math. Model. Nat. Phenom.* 2009; 4:183–209.
- [32]. Betancourt-Mar JA, Nieto-Villar JM. Theoretical models for chronotherapy: periodic perturbations in funnel chaos type. *Math. Biosci. Eng.* 2007; 4:177–86. [PubMed: 17658922]
- [33]. Kiss IZ, Rusin CG, Kori H, Hudson JL. Engineering complex dynamical structures: sequential patterns and desynchronization. *Science.* 2007; 316:1886–9. [PubMed: 17525302]
- [34]. Boissanade J. Oscillatory dynamics induced in polyelectrolyte gels by a non-oscillatory reactions: a model. *Eur. Phys. J.* 2009; 28:337–346.
- [35]. Tigges M, Marquez-Lago TT, Stelling J, Fussenegger M. A tunable synthetic mammalian oscillator. *Nature.* 2009; 457:309–12. [PubMed: 19148099]
- [36]. Mirsky HP, Liu AC, Welsh DK, Kay SA, Doyle FJ 3rd. A model of the cell-autonomous mammalian circadian clock. *Proc. Natl. Acad. Sci. U S A.* 2009; 106:11107–12. [PubMed: 19549830]
- [37]. Liu T, Liu X, Chen Y, Wu R. A computational model for functional mapping of genes that regulate intra-cellular circadian rhythms. *Theor. Biol. Med. Model.* 2007; 4:5. [PubMed: 17261199]
- [38]. Kitano H. Systems biology: a brief overview. *Science.* 2002; 295:1662–4. [PubMed: 11872829]
- [39]. Ueda HR. Systems biology of mammalian circadian clocks. *Cold Spring Harb Symp. Quant. Biol.* 2007; 72:365–80. [PubMed: 18419294]
- [40]. Ueda HR, Hayashi S, Chen W, Sano M, Machida M, Shigeyoshi Y, Iino M, Hashimoto S. System-level identification of transcriptional circuits underlying mammalian circadian clocks. *Nat. Genet.* 2005; 37:187–92. [PubMed: 15665827]
- [41]. Okamura H. Suprachiasmatic nucleus clock time in the mammalian circadian system. *Cold Spring Harb. Symp. Quant. Biol.* 2007; 72:551–6. [PubMed: 18419314]

- [42]. Levi F, Filipski E, Iurisci I, Li XM, Innominato P. Cross-talks between circadian timing system and cell division cycle determine cancer biology and therapeutics. *Cold Spring Harb. Symp. Quant. Biol.* 2007; 72:465–75. [PubMed: 18419306]
- [43]. Altinok A, Levi F, Goldbeter A. A cell cycle automaton model for probing circadian patterns of anticancer drug delivery. *Adv. Drug Deliv. Rev.* 2007; 59:1036–53. [PubMed: 17692993]
- [44]. Altinok A, Levi F, Goldbeter A. Identifying mechanisms of chronotolerance and chronoefficacy for the anticancer drugs 5-fluorouracil and oxaliplatin by computational modeling. *Eur. J. Pharm. Sci.* 2009; 36:20–38. [PubMed: 19041394]
- [45]. Eriksson O, Wallberg A, Syvanen S, Josephsson R, Langstrom B, Bergstrom M. A computerized Infusion Pump for control of tissue tracer concentration during Positron Emission Tomography in vivo Pharmacokinetic/Pharmacodynamic measurements. *BMC. Med. Phys.* 2008; 8:2. [PubMed: 18513382]
- [46]. Marroum P. Development and evaluation of controlled release products with emerging technologies. *Amer. Pharm. Rev.* September/October.2009 :147–149.
- [47]. FDA. 21 CFR 320.25. 2009. Guidelines for the conduct of an vivo bioavailability study.
- [48]. FDA. 21 CFR 314.54. 2009. Procedure for submission of an application requiring investigations for approval of a new indication for, or other change from, a listed drug.
- [49]. McCormick CG. Regulatory challenges for new formulations of controlled substances in today's environment. *Drug Alcohol Depend.* 2006; 83(Suppl 1):S63–7. [PubMed: 16567060]
- [50]. FDA. 21 CFR314.520. 2009. Approval with restrictions to assure safe use.
- [51]. Spagnolo AG, Daloiso V. Outlining ethical issues in nanotechnologies. *Bioethics.* 2009; 23:394–402. [PubMed: 19673855]
- [52]. Cotton RG, Appelbe W, Auerbach AD, Becker K, Bodmer W, Boone DJ, Boulyjenkov V, Brahmachari S, Brody L, Brookes A, et al. Recommendations of the 2006 Human Variome Project meeting. *Nat Genet.* 2007; 39:433–6. [PubMed: 17392799]
- [53]. LaVan DA, Lynn DM, Langer R. Moving smaller in drug discovery and delivery. *Nat. Rev. Drug Discov.* 2002; 1:77–84. [PubMed: 12119612]
- [54]. Youan BB. Impact of nanoscience and nanotechnology on controlled drug delivery. *Nanomed.* 2008; 3:401–6.