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Chronopharmaceutical drug delivery systems: Hurdles, hype or hope?☆

Bi-Botti C. Youan

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

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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 drug 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 and modeling, perhaps using system biology and (iii) regulatory guidance.

Contents

1. Introduction . . . 898
2. Overview of the current status of chronopharmaceutical drug delivery . . . 899
3. Hurdles in chonopharmaceutical drug research and development . . . 899
   3.1. Rhythmic biomaterials and system design hurdles . . . 899
   3.2. Rhythm engineering and modeling hurdles . . . 900
   3.3. Regulatory hurdles . . . 901
4. Conclusions and perspectives . . . 902
Acknowledgments . . . 902
References . . . 902

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 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, and rhythm therapy) and pharmacological (lithium, antidepressants, and 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] have also been demonstrated. Therefore, a plethora of data both from studies ranging from basic chronobiology to clinical applications (chronotherapy) have been recently compiled

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E-mail address: youanb@umkc.edu.

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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 cases such as asthma, cancer and heart diseases for novel chronopharmaceutical drug products either for therapy or prevention. Such novel drug dosage forms should be effective, safe, robust (predictable drug release rate in biological systems) 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, Synchromed™, Rhythmic™) and controlled release microchip strategies. Examples of technologies intended for oral administration include Contin™, Chronset™, Codas™, Ceform™, Diffucaps™, TIMERx®, Chronotopic™, Egalet™, GeoClock™, Port™, Three-dimensional printing (3DP)™, methods involving physicochemical 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 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 chonopharmaceutical 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 drug