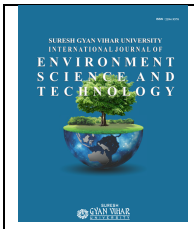

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Review Article

A Review on Chronopharmaceutical Drug Delivery Systems: Rhythmic Difficulties and Regulatory Challenges

Bhagyesh U. Janugade* and Neelam Singla

School of Pharmacy, Suresh Gyan Vihar University, Jaipur- 302025, Rajasthan, India.

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Abstract

Advances in the field of chronobiology and chronotherapy have unveiled the limitations of the conventional approach to drug delivery called "one size fits all" for certain bioactive agents and disease treatments. Hence, a crucial need has emerged for cutting-edge research in chronopharmaceuticals. The ultimate goal is to create an "ideal magic pill," economically accessible, which could significantly enhance safety, efficacy, and patient adherence to both existing and novel drugs. Despite the promising prospects, presently three foremost obstacles are preventing the seamless translation of these systems from the laboratory to the patient's bedside. The first challenge involves identifying suitable rhythmic biomaterials and systems that can synchronize with the body's internal clock and circadian rhythms. Secondly, the development of rhythm engineering models, possibly utilizing systems biology, is essential to better comprehend and predict the dynamics of drug action and response over time. Lastly, the regulatory landscape presents its own set of hurdles that must be overcome to ensure that these innovative chronopharmaceuticals meet the required safety as well as efficacy standards.

*Corresponding author's e-mail addresses: bjanugade@gmail.com

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1. Introduction

Reports indicate significant number of deaths and hospitalizations in the United States, nearly 100 thousand deaths and hospitalizations over 2 million annually, are attributed to correctly prescribed medications (Shastry, 2005; Shastry, 2006), and these adverse effects to drugs could be influenced by various aspects like disease factors, genetics, and the environment. In the realm of drug delivery within living organisms, the dimension of time has long been neglected in drug design and administration. It is now well-documented that biological activities follow cycles of different durations, from very short ultradian rhythms to daily circadian rhythms, as well as longer cycles spanning weeks, months, or even seasons. These rhythms aren't mere responses to external changes; they stem from internal biological clocks, the structures that keep time. For mammals, suprachiasmatic nucleus (SCN) is the central pacemaker (Schulz & Steimer, 2009). For example, therapies aimed at affective imbalances- whether non-pharmacological interventions like sleep deprivation, light and rhythm therapy or the pharmacological like antidepressants, lithium and agomelatine cast a ripple upon the body's natural rhythm section (Schulz & Steimer, 2009).

The relevance of biological rhythms in areas like metabolic syndromes (Staels, 2006) and drug dosing (Ohdo et al., 2001) has been demonstrated, and wealth of data extending from basic chronobiology to the clinical applications (chronotherapy) has been compiled for those keen on delving into this burgeoning research area (Youan, 2009). All these findings collectively show that the assumption of a universal, constant approach "one size fits all" is flawed. Amid solutions to address this, the conventional approach has been to refine the controlled administration of the conventional dosage forms in accordance with time (Oren & Wehr, 1992). Another hopeful tactic to enhance effectiveness as well as safety of both new and existing drugs is to re-evaluate the prevailing formulation methods and drug discovery methods using insights from chronobiology, shaping the future of chronotheranostics for human ailments when clinical or therapeutic benefits are apparent.

Notably, there's a pressing need, particularly in cases like cancer, heart diseases and asthma for novel chronopharmaceutical products meant for prevention or therapy, and these innovative drug formulations should exhibit effectiveness, safety, and reliability (predictable release rate in biological settings), while being clinically substantiated and allowing spatial and temporal control post-administration via diverse routes. Theoretically such ideal drug delivery system (noninvasive and cost-effective) could enhance the safety, efficacy, and patient adherence to both established and novel drugs. However, the concept of this "magic pill" stays challenging owing to multiple obstacles.

Consequently, present piece of writing focuses on key challenges to be surmounted to elevate concept of chronopharmaceutical formulation of drug from being a buzz to becoming a tangible beacon of hope in upcoming clinical practices. The present piece of writing includes current status of chronopharmaceutical drug delivery system (CDDS), recent advancements and regulatory challenges related to CDDS.

2. Current status of CDDS

Reports have extensively detailed chronopharmaceutical technologies that rely on chemical and/or physical triggers for controlled drug release across various administration routes (Youan, 2004; Khan et al., 2009). These technologies encompass a range of applications, from parenteral routes with methods like infusion pumps (chronomodulating) such as Panomat™ V5, Rhythmic™, Melodie™ and Synchromed™ to innovative strategies like controlled-release microchips. Similarly, technologies geared towards oral administration are Ceform™, Contin™, Diffucaps™, Chronset™, TIMERx®, Codas™, Chronotopic™, Port™, GeoClock™ and Egalet™, three-dimensional printing (3DP)™, approaches relating to physico-chemical modification of drugs and utilization of erodible controlled-release polymers (Youan, 2009; Youan, 2004). Recent innovation for chronotherapy has introduced novel floating pulsatile system employing high internal phase emulsion-based porous material (Sher et al., 2009), wherein loading of drug through porous carrier, synthesized by using divinylbenzene and styrene via high internal phase emulsion, had been achieved through solvent evaporation. What distinguishes this developed system is the absence of chemical agents as release modifiers, setting it apart from supplementary chronotherapy advancements. Concept of low-density multiparticulate floating pulsed-release dosage forms has been explored extensively (Roy & Shahiwala, 2009). Additionally, a blend of pulsatile and floating principles resulted in a drug delivery system targeting nocturnal acid breakthrough, achieved by employing floating tablet with time-lagged coating for programmed delivery of ranitidine hydrochloride (Roy & Shahiwala, 2009).

It's imperative to emphasize that clinical significance and benefits of chronopharmaceutical formulations require case-specific validation, contingent on patient demographics, disease type, and bioactive agents. For instance, extended-release capsules of tramadol for once-a-day administration demonstrated unchanged bioavailability across different administration times in pain management. This suggests that administration times can be adjusted based on patient needs without substantial *in vivo* performance alterations (Warnke et al., 2009). Conversely, current clinical trial examined antihypertensive efficacy of slow-release once-a-day gastrointestinal therapeutic system of nifedipine, revealing significantly greater blood pressure reduction and

controlled ambulatory blood pressure during bedtime treatment. Furthermore, morning surge of blood pressure and stroke risk factor was abridged exclusively post bedtime after nifedipine administration. This data underscores importance of considering augmented efficacy and reduced side effects when designing novel drug delivery systems for essential hypertension prescribing cardiovascular medication (Hermida et al., 2008). Additionally, in cases of resistant hypertension, timing of treatment had shown to play a pivotal role in blood pressure control and modeling circadian blood pressure patterns, surpassing mere changes in drug combinations (Hermida et al., 2008). Recent studies have explored transdermal delivery systems tailored for chronopharmaceutical applications (Hradetzky, 2008), and examples encompass thermoresponsive membrane systems (Lin et al., 2001), crystal reservoir and ChronoDose™ (Kato et al., 2002).

Novel aminophylline delivery system for chronopharmaceutical and rectal application, targeting asthma therapy and featuring sustained-release hollow-type suppositories has been introduced by utilizing sodium polyacrylate, sodium alginate or polyacrylate-PANa co-polymers as gelling agents (Shiohira et al., 2009). This system could serve as an alternative chronotherapy method for patients unable to take oral medications. Additionally, emerging research has probed the potential of novel drug-loaded nanocarriers in chronotherapy. Administering drug-containing nanoformulations in a chrono-administrative manner appears as a novel therapeutic approach with the potential to enhance curability of conditions like breast cancer without additional side effects, costs, or patient risks. One example highlights cyclic expression of VEGF in case of breast cancer, regulated by periodic sex hormones during the menstrual cycle. Nanoformulations, such as Caelyx and Abraxane, administered during peak VEGF expression stages, demonstrated increased drug retention, leading to heightened cancer growth control and reduced metastasis (You & Li, 2008). These findings underline the prospect of harnessing biological rhythms to enhance targeting ability along with the effectiveness of novel nanomedicines. In essence, the landscape of chronopharmaceutical technologies spans various methods and routes of administration, holding potential to optimize drug delivery based on patient-specific needs and biological rhythms.

2.1. CDDS for cancer management

To enhance effectiveness of cancer treatment, patients often receive the maximum tolerable dose of chemotherapy drugs, even if sometimes it can lead to harmful side effects. To address this, researchers have explored the idea of synchronizing the administration of chemotherapy with the body's natural circadian rhythms. Several studies have demonstrated the potential benefits of aligning drug dosing with the body's internal clock to reduce toxicity associated with

chemotherapy. For instance, Ravichandiran et al. have reported on the influence of circadian dosing schedules in mitigating the cytotoxic effects of anti-cancer drugs wherein they observed that the timing of chemotherapy administration in relation to the body's circadian rhythm could play a significant role in reducing drug-induced toxicity (Ravichandiran et al., 2009). Furthermore, Levi et al. conducted research on mice and found platinum-based chemotherapy drugs were best tolerated when administered during the nocturnal activity phase. They also noted when these drugs were given 12 hours after the administration of 5-fluorouracil, the latter drug was better tolerated (Levi et al., 2007). Additionally, patients with variety of cancers were studied, including acute lymphoblastic leukemia, ovarian cancer, endometrial uterine cancer, metastatic colorectal cancer, metastatic transitional cell carcinoma, bladder cancer, progressive metastatic renal cell carcinoma, breast carcinoma, lung carcinoma, hormone-refractory metastatic prostate cancer, and genitourinary tract cancer. In this research, patients who received chemotherapy treatments synchronized with their circadian rhythms consistently experienced positive outcomes (Vogt et al., 2017). Consequently, the concept of chronotherapy, which involves aligning the timing of chemotherapy with the body's internal clock, has shown promise in reducing chemotherapy-induced toxicity and improving treatment outcomes for a range of cancer types. This approach offers a potential avenue for enhancing the efficacy of cancer treatments while minimizing the negative side effects.

2.2. CDDS for asthma management

In a survey conducted by Turner-Warwick, it was revealed that 74% of the asthmatic patients included in the study experienced awakening with breathing difficulties (Burkioka et al., 2002; Sutherland, 2005). A separate study investigated the effectiveness of inhaled corticosteroids administered once daily at 15:00 hours, and it yielded results equivalent to those of four times daily dosing of the same drug (Mastiholimath et al., 2007). Another study found that a single daily dose at 17:30 hours also produced comparable results to the four times daily dosing regimen (Gwen, 2002). Furthermore, the use of Desloratadine, a non-sedating oral antihistamine, was explored as a potential treatment for asthma in a study conducted by Geha and Meltzer in 2001.

2.3. CDDS for hypertension management

Research findings have illuminated the dynamics of blood pressure and heart rate, both in normotensive (normal blood pressure) and hypertensive (high blood pressure) patients, highlighting a noticeable surge during the morning hours, specifically from 6:00 to 12:00. This phenomenon is attributed to heightened sympathetic stimulation, involving an increased release of adrenaline and noradrenaline in the morning (Lemmer, 2006; Douglas, 2002). Conversely, during the nighttime hours when individuals are asleep, there is a significant reduction in

sympathetic output, ranging from 10% to 20%, as reported by Gherghel et al. (2004). These fluctuations in sympathetic activity play a significant role in the elevated risk of cardiovascular diseases, including myocardial infarctions, strokes, and angina, particularly during the morning hours (Smith, 2001). Douglas has summarized a study suggesting that the morning hours are associated with a higher risk of stroke, up to 49%, an increased risk of heart attack, up to 40%, and a rise in the risk of cardiac death by up to 29% in patients with heart conditions (Douglas, 2002). Furthermore, the "MAPEC study," a prospective investigation, was specifically designed to evaluate the hypothesis that administering one or more hypertension medications at bedtime, as opposed to the conventional morning intake, can effectively control blood pressure and reduce the risk of cardiovascular diseases (Hermida et al., 2010).

2.4. CDDS for osteoarthritis management

The circadian rhythm is closely linked to disorders affecting the skeletal system. Patients afflicted with osteoarthritis often find their pain symptoms to be more pronounced in the morning, whereas those with rheumatoid arthritis tend to experience heightened pain during the morning hours compared to the rest of the day. These symptoms are contingent upon the levels of interleukin-6 and C-reactive protein, both of which follow a circadian pattern (Cutolo, 2003). Researchers have conveyed that a larger dose of nonsteroidal anti-inflammatory drugs, when taken twice daily, proves to be more efficacious than spreading the same total dose across four smaller doses, provided that one of the doses is administered at night (Sher, 2007). This approach can be effectively managed through medications grounded in the principles of chronotherapeutics. Furthermore, Kadiyam and Muzib have introduced a colon-specific drug delivery formulation of tramadol hydrochloride for the treatment of arthritis, employing a chronotherapeutic delivery system. In addition, the use of long-acting nonsteroidal anti-inflammatory drugs (NSAIDs) such as flurbiprofen, ketoprofen, and indomethacin in once-a-day forms can optimize their therapeutic effects while minimizing or preventing adverse side effects (Kadiyam and Muzib, 2015). This approach offers potential benefits in the management of these conditions.

3. Recent advancements in CDDS

The strategy behind creating drug delivery systems aligned with CDDS hinges on the fundamental principle that medications should be administered precisely when they are most essential.

3.1. 3D printing

Emerging technologies, like the utilization of 3D printing methods, find extensive application in the realm of chronotherapy. They are instrumental in producing medical implants, surgical models, and prosthetic limbs (Kovatchev et al., 2016).

3.2. Eurand's system

Eurand's innovative time-regulated pulsatile release device is designed to deliver one or more rapid-release pulses at predefined intervals and specific locations within the gastrointestinal (GI) tract, aligning with the principles of Chronotherapy. This capability proves valuable in optimizing the effectiveness and potential side effects of medication substances. For instance, Eurand has pioneered the development of a circadian rhythm release (CRR) system (Jain et al., 2011). One notable application of this technology is in the formulation of a dosage form for the cardiovascular drug, Propranolol hydrochloride. With a deliberate four-hour delay in release following oral administration, when Propranolol is administered at bedtime, it ensures that the drug is released after the initial delay, thereby achieving peak plasma concentration (Portaluppi and Lemmer, 2007). This innovative approach holds promise in enhancing therapeutic outcomes and minimizing potential adverse effects.

3.3. CODAS technology

Elan Drug Technology has introduced the CODAS® technology, a groundbreaking innovation tailored to achieve extended-release intervals. This technology offers a multitude of advantages, including a delivery profile finely tuned to harmonize with circadian rhythms, a controlled and gradual onset of action, an extended-release mechanism, release rate that remains largely unaffected by factors such as pH, body position, or food consumption, the convenience of "sprinkle" dosing by opening the capsule and dispersing its contents on food, a reduction in the effective daily dose and overall drug exposure, precise targeting within the gastrointestinal tract for localized effects, and the reduction of systemic exposure to attain a desired drug profile (Abbasi et al., 2020). This versatile approach offers numerous benefits in optimizing drug therapies.

3.4. PRODAS® technology

This technology facilitates the pre-programming of drug release rates, offering the ability to integrate multiple distinct mini tablets. Each of these mini tablets can be meticulously formulated and programmed to release the drug at various locations within the gastrointestinal tract. Additionally, the incorporation of mini tablets of varying sizes allows for the achievement of high drug loading, a capability made possible through the utilization of PRODAS Technology (Rewar et al., 2014). This approach opens the door to tailored drug delivery strategies with enhanced precision and effectiveness.

3.5. Gel-CapTM technology

Gel-CapTM technology relies on the use of a highly viscous substance known as sucrose acetate isobutyrate (SAIB). This material is insoluble in water but dissolves readily in alcohol. SAIB-

based formulations possess exceptional resistance to crushing, breaking, freezing, or misuse through inhalation due to their high viscosity. Furthermore, the insolubility of SAIB in water makes it challenging to extract the drug from the dosage form. Upon oral administration of a Gel-CapTM formulation, the gelatin capsule and the associated solvents dissolve, allowing the drug to be methodically released from the adhesive SAIB matrix (Webster, 2007). This approach ensures controlled drug release and prevents potential abuse or tampering with the medication.

4. Difficulties in system design and rhythmic biomaterials

Primary challenge hindering the progress involving chronopharmaceutical drug products is absence of dependable and reversible biomaterials that are both safe and responsive to biological rhythms. While attempts have been made to formulate chronotherapy drug products (Youan, 2009; Youan, 2004), genuine breakthroughs in this domain hinge on the development of more sophisticated biomaterials. The past decades have seen substantial endeavors in the realm of intelligent biomaterial design (Langer & Tirrell, 2004; Anderson et al., 2004). However, designing rhythmic biomaterials that meet the criteria of biodegradability, biocompatibility, and reversible responsiveness to specific biomarkers in rapid alignment with biological rhythms remains a significant hurdle. Ongoing endeavors in pursuit of this decisive aim encompass utilization of chemical oscillators such as pH oscillations (Siegel, 2009) and stimuli-sensitive polymers (Peppas & Leobandung, 2004; Jeong & Gutowska, 2002). These advancements could prove invaluable, as evidenced by their potential application in addressing hypopituitary dwarfism. Notably, the effectiveness of human growth hormone-releasing hormone (GHRH) administration is heightened when it follows a pulsatile pattern synchronized with patient's circadian rhythm (Peppas & Leobandung, 2004). Biomaterials, reacting to external triggers like pH, electric fields, temperature, light, ionic strength and chemicals, have been designed (Anderson et al., 2004) wherein these responses typically manifest as significant changes in surface characteristics, shape, intricate molecular self-assembly, solubility or even a switch from a sol-to-gel state. Certain biomaterials can even react to or direct specific cellular responses towards distinct cellular signals (Langer & Tirrell, 2004).

Advancements extend beyond bulk properties, encompassing smart surfaces capable of reversible transitions between hydrophilic and hydrophobic states under electric potential stimulation (Anderson et al., 2004). These surfaces might hold promise for future light-triggered chronopharmaceutical delivery systems. The field of microfabrication has introduced novel avenues, particularly in the development of microchip-based drug delivery systems (Santini, 1999). Co-embedding of biosensors and bioactive agents within computer-controlled microchips has the potential to pave the way for responsive, fully automated chronotherapy. Additionally,

nanofabrication techniques offer a prospective solution for chronotherapy. Recent strides have been taken in controlling rotary and linear motion within molecular systems, thereby constructing synthetic machines with utilitarian functions (Wesley & Feringa, 2006). Regardless of the techniques and materials employed to devise rhythmic biomaterials and systems, principles of robust control over intricate systems (Kitano, 2007) and the ability to reverse responses remain pivotal for their effective application in disease therapy and prevention in the future.

5. Regulatory challenges

A fundamental premise underlying therapeutic innovations is the aspiration to enhance the quality of healthcare. This principle serves as a pivotal theme in all regulatory discussions. Moreover, the common objective shared by both the pharmaceutical industry and regulatory bodies is the development of medications that are not only safe and effective but also well-tolerated and acceptable to patients. Over the past decade, there has been a notable surge in the introduction of novel formulations designed to achieve several key objectives. These innovations aim to enhance bioavailability through various administration routes, reduce dosing frequency, mitigate unwanted or intolerable side effects, improve taste, and minimize the intrusiveness of medication management in chronic diseases.

Despite the shared goals between regulators and the pharmaceutical industry, the standards for obtaining marketing approval for these products are exacting. When a groundbreaking formulation, designed to address significant health issues such as pain or narcolepsy, also happens to involve substances with potential for abuse, the regulatory framework becomes considerably more complex. The widespread distribution of substances with potential for misuse or financial gain carries significant public health implications. Consequently, the regulatory path to approval in such cases extends beyond the customary demonstration of safety and efficacy. While the precise details of this regulatory path may not have been entirely articulated by the US Food and Drug Administration (FDA), evolving standards are set to enhance the management of risks associated with these innovative, high-content formulations and designer drugs. It is imperative to acknowledge that the new requirements being imposed on the pharmaceutical industry carry substantial weight and significance (McCormick CG, 2006).

In any endeavor, it's prudent to start with the end goal in mind. When considering the launch and widespread adoption of a chronopharmaceutical product in clinical practice, it's crucial to navigate the existing regulatory challenges (Youan, 2009). While pharmaceutical industry scientists typically factor these regulatory aspects into their work, this isn't always the case for academics who might be more focused on proving concepts that might not translate to patient care without regulatory compliance. These regulatory challenges span the pre- and post-approval

phases. During the pre-approval phase, demonstrating the chronotherapeutic advantage of modified or controlled release formulations in clinical context can be challenging. This is partially due to initial barriers of lacking truly rhythmic biomaterials and systems, along with the need for improved prediction tools.

Modified and controlled release formulations, including chronopharmaceutical designs, offer distinct benefits over immediate release formulations of same drug. These advantages encompass reduced dosing frequency, diminished side effects, enhanced pharmacological selectivity, and more controlled plasma concentration fluctuations for optimized therapeutic outcomes. MR formulations, given their unique formulation and manufacturing complexities, demand dedicated studies to characterize their controlled release profiles (Marroum, 2009). Given the specifics of these studies, pharmaceutical innovators often collaborate closely with regulatory bodies, ensuring the pertinent process parameters are suitably chosen and controlled. 21 CFR 320.25 (FDA 21CFR 320.25, 2009) outlines bioavailability requirements for controlled release products in *in vivo* bioavailability studies. These regulations often entail comparing the controlled release product's performance with an already approved immediate release formulation of same drug, as covered under 21 CFR 314.54 (FDA 21 CFR 314.54, 2009).

In post-approval phase, beyond the challenges of maintaining quality of the product (Marroum, 2009), it is noteworthy that designer drugs as well as high-content modified release formulations, have been subject to both larger-scale criminal diversion and casual recreational abuse for profit (McCormick, 2006). Addressing abuse potential becomes a shared challenge for manufacturers and regulators. Approaches to counteract abuse potential have been explored, emphasizing risk management strategies. Both drug sponsors and regulators should assess factors that might render a drug substance prone to abuse, enabling the implementation of risk mitigation measures post-approval (McCormick, 2006). An alternative to outright non-approval is granting approval with restrictions, ensuring safe usage via "restricted distribution" under 21 CFR 314.520 (FDA 21 CFR 314.520, 2009). Risk management strategies, like Risk Management Programs (MAP), have gained prominence, enabled drug approval while applied certain restrictions (McCormick, 2006). Ultimately, as drug delivery systems advance, a crucial aspect will be deciphering manufacturing variables influencing drug release characteristics and devising strategies for enhanced control, ensuring product quality after approval (Marroum, 2009).

Pharmacovigilance and phase IV clinical studies will also play a pivotal role with these novel drug formulations. Furthermore, there's a demand for innovative noninvasive analytical methods with ultra-sensitive and real-time *in vivo* responses, along with innovative process analytical technologies linking the key product attributes with intended functionality, ensuring batch-to-

batch reproducibility and robustness. Moreover, the impact of given drug or disease on normal biological rhythm across various conditions remains an area for exploration. The fundamental principle underpinning therapeutic advancements that enhance healthcare quality is a key theme in all regulatory discussions. Additionally, the common objective shared by both industry and regulators is the development of medications that are not only safe and effective but are also well-tolerated and acceptable to patients. Over the past decade, there has been a noticeable surge in the introduction of novel formulations engineered to enhance bioavailability through various administration routes. These innovations aim to reduce dosing frequency, mitigate undesirable or intolerable side effects, improve taste, and lessen the intrusiveness of medication in chronic disease management.

Despite the alignment of goals between regulators and the regulated pharmaceutical industry, the requirements for obtaining marketing approval for such products are stringent. When a groundbreaking formulation designed to treat significant health conditions like pain or narcolepsy also possesses the potential for abuse, the regulatory landscape becomes considerably more intricate. The widespread distribution of substances that could be diverted for non-medical use or financial gain carries substantial public health implications. Consequently, the path to regulatory approval in such cases extends beyond the typical demonstration of safety and efficacy. While the USFDA may not have explicitly outlined this regulatory pathway, standards are evolving to enhance the management of risks associated with these novel high-content formulations and designer drugs. The new demands placed on the pharmaceutical industry are not insignificant.

6. Future perspectives

The preceding information underscores the recognition that the concept of a universally applicable, one-size-fits-all approach in drug dosage form design is inherently flawed. In addressing this issue, the conventional approach has involved patients and healthcare providers striving to exert better control over the timing of administration of traditional dosage forms, a concept well-established in the field of chronotherapy. Moreover, a promising avenue for enhancing the effectiveness and safety of both existing and novel medications is the reevaluation of current drug discovery and formulation methodologies, guided by insights from chronobiology. This approach holds promise for the future of chronotheranostics, aiming to optimize the treatment of various human diseases whenever there is a clear clinical or therapeutic advantage.

In the contemporary landscape, pulsatile drug delivery is emerging as a notably favored approach. The key advantage of this drug delivery method lies in its ability to release the

medication precisely when it is most needed. Consequently, risk of developing drug resistance, a concern often associated with conventional and sustained release formulations, can be mitigated. Moreover, certain anticancer drugs are notorious for their high toxicity levels, which can pose noteworthy challenges in conventional and sustained release therapies. Fortunately, there is growing availability of FDA-approved chronotherapeutic drugs in the market, offering a promising alternative to address these issues and enhance the effectiveness of drug treatments.

Evidently, there is a pressing and immediate need, particularly in cases like asthma, cancer, and heart diseases, for innovative chronopharmaceutical drug products designed for both therapeutic and preventive purposes. These novel drug dosage forms should demonstrate effectiveness, safety, predictability in terms of biological release rates, and clinical justification. They should also possess the ability to control spatial and temporal drug release after administration through various routes. In theory, such drug delivery system, ideally noninvasive and cost-effective, has the potential to significantly enhance the safety, efficacy, and patient compliance of both established and emerging medications (Mandal et al., 2010).

7. Conclusion

A wealth of scientific evidence emerging from both foundational studies in chronogenetics/chronobiology and clinical investigations is compellingly indicating an immediate and crucial necessity to reevaluate the formulation of both established and novel drugs, especially for specific ailments. Amid various obstacles that impede the realization of this clinical imperative, three significant challenges stand out, hindering the widespread development and adoption of chronopharmaceutical drug products. These challenges encompass the requisite advancements in the domain of system design and rhythmic biomaterials, the refinement of engineering processes, and the formulation of comprehensive regulatory guidelines. By drawing inspiration from nature's mechanisms, we can delve into the structural characteristics that underpin successful future endeavors in the design and development of innovative functional smart materials. The exploration of nanotechnologies, which epitomize humanity's prowess in manipulating and governing matter on a minute scale, holds considerable promise for both disease prevention and therapy. This avenue offers a beacon of hope, paving the way for transformative advancements in the medical landscape.

Conflicts of Interest

Authors declare no conflicts of interest. All authors have contributed equally.

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