Current Research in Pharmacology and Drug Discovery 2 (2021) 100015

Contents lists available at ScienceDirect

Current Research in Pharmacology and Drug Discovery

journal homepage: www.journals.elsevier.com/current-research-in-pharmacology-and-drug-discovery

Application of coating technology to chronotherapeutic drug delivery systems: Recent publications and patents

Buduru Gowthami [a,*], S.V. Gopala Krishna [b], D. Subba Rao [c]

[a] Faculty of Pharmaceutical Sciences, J.N.T.U.A Ananthapuramu, 515002, Andhra Pradesh, India
[b] Vagdevi College of Pharmacy and Research Centre, Brahmadevam, Nellore, 524001, Andhra Pradesh, India
[c] Dept. of Chemical Engineering, J.N.T.U.A Ananthapuramu, 515002, Andhra Pradesh, India

ARTICLE INFO

Keywords:
Chronotherapeutics
Coating
Scientific prospection
Patents

ABSTRACT

In general, extended release systems have the ability to maintain the drug concentration with in therapeutic range for prolonged period of time, but this may not be the primary requisite for circadian rhythm diseases like asthma, hypertension and rheumatoid arthritis, etc. They require prompt release of drug as per the disease condition, which can be achieved by programmed lag time. Chronotherapeutic drug delivery systems (CDDS) can be achieved by several methods, coating is one amongst them. Though the coating process is complex in terms of methodology, solubility issues and difficulty in achieving the uniform coating, many researchers were successfully employed in development of CDDS. A scientific prospection was made from 2010 to 2020 using PubMed database. Apart from exploration of publication data, we attempt to brief about classification of patents and concordance. The scrutiny also highlights the patents filed on chronotherapeutic systems, focusing particularly on coating technologies. The review is concluded the successful application of coating technology to develop CDDS, as evident from vast number of publications and patents filed.

1. Introduction

Many surveys conducted throughout the world have confirmed that numerous deaths and hospitalizations occur due to the untimely release of unquantified drugs (Youan, 2010). In the 1700s, Jean Jacques noted the occurrence of 24 h patterns, which were later designated as circadian rhythms by Stephens and Halberg (Khan et al., 2009). Circadian rhythms can direct most of the regular bodily functions, thereby influencing the pharmacokinetic profile of a drug dosage administered in a specific form (Ohdo, 2007; Lemmer, 1991; Lemmer, 1996). Several biological functions and hormones are known to follow circadian rhythms. Thus, understanding chronobiology may facilitate the development of innovative techniques for optimizing drug delivery (Bi-Botti, 2010). Chronobiology affects a large number of common diseases, such as angina pectoris (Portaluppi and Lemmer, 2007), asthma (Smolensky et al., 2007, Martin and Banks-Schlegel, 1998), rheumatoid arthritis (Bruguerolle and Labrecque, 2007), and hypertension. Many recent studies have focused on the development of chronotherapeutic drug delivery systems (CDDSs) that are capable of releasing the required amount of drug at the appropriate site of action and at an accurate time according to chronobiology and inherent mechanisms. Drug release from these systems is irrespective of the conditions and circadian rhythms. CDDSs are mainly designed for administration at bedtime because diseases affected by circadian rhythms are generally worse in the middle of the night or the early morning. Drug release by these systems follows a sigmoid release profile with a specific lag time appropriate to the disease conditions. Sustained or prolonged formulations may even release the drug in the lag time, which can result in unwanted effects. CDDSs can be “time controlled” or “site specific” (Ali et al., 2010), but most pulsatile systems are typically time controlled. Various approaches used for CDDSs and different drugs affected by circadian rhythms are shown in Fig. 1. Among the time-controlled approaches, systems based on an erodible coating layer are most widely employed, where bulk erosion can occur due to the rapid ingress of water compared with the degradation rate of the polymer. In another approach, a reservoir device is coated with an erodible or soluble layer, which dissolves over time to release the drug after a specific or programmed lag time. Effervescent excipients, swelling agents, or osmogens are used to generate the pressure required to rupture the coating layer when designing a CDDS with a rupturable coating layer system. Several of the approaches mentioned above can be applied to design pulse-in-cap systems, where the lag time is maintained by a plug that is lost by swelling or erosion to release the drug. In stimuli-induced

* Corresponding author.
E-mail address: gowthu.buduru@gmail.com (B. Gowthami).

https://doi.org/10.1016/j.crphar.2021.100015
Received 18 September 2020; Received in revised form 19 January 2021; Accepted 19 January 2021

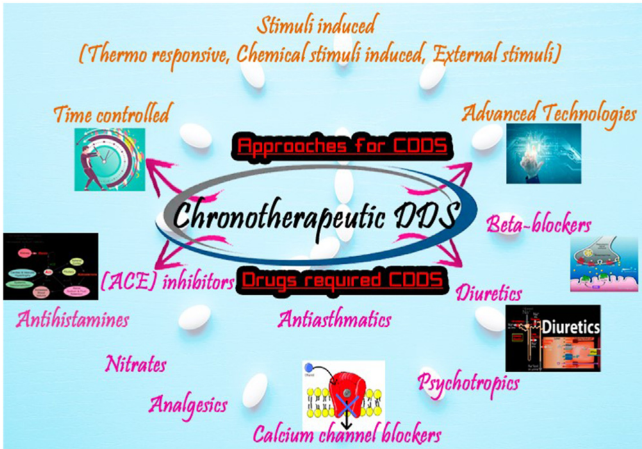

Fig. 1. Approaches and drugs required based on CDDSs.

systems, the drug is released in response to biological stimuli, such as temperature changes (thermoresponsive), biological factors, including the pH changes, enzymes and other chemicals (chemical stimuli), or external stimuli (electroresponsive, ultrasonication, or magnetically induced).

Advanced CDDS technologies include CONTIN® (Purdue Pharma, Pickering, Ontario, Canada), Chronotropic® and Pulsincaps® (Catalent Pharma Solutions, Somerset, New Jersey, USA), CEFORM® (Biovail Corporation, Mississauga, Ontario, Canada), TIMERx® (Penwest Pharmaceutical Company, Danbury, Connecticut, USA), OROS® (DURECT Corporation, Cupertino, California, USA), CODAS® (Elan Corporation, Gainesville, Florida, USA), Egalet® (Egalet a/s, Værløse, Copenhagen, Denmark) and Diffucaps® (Eurand Pharmaceuticals, Yardley, Pennsylvania, USA). Several marketed products are available based on these novel approaches (Jain et al., 2011).

Among the various approaches available, coating technology is used most widely to optimize the required release timing for a drug. Initially, film coating was the most widespread approach used to address the many issues encountered during various stages of product development. However, liquid coating technology may have several drawbacks, because it can be time consuming, while the drugs produced may be unstable due to their lability and hydrolysis under heating, as well as causing environmental pollution. Hence, alternative coating techniques that use less or no solvents are used to overcome these limitations, such as compression or press coating. Many studies have applied coating technology to develop optimum therapeutics for various diseases. Film coating, press coating, and compression coating are generally used to develop drug delivery systems, such as tabs in cap, pulse cap, erodible, and multiparticulate systems.

2. Coating strategies

Tablet coating involves the application or formation of a dry, outer layer of coating material on a core material in order to obtain specific benefits. In recent decades, tablet coating has evolved into a technically advanced process that conforms to good manufacturing practices. Several coating strategies have been applied to obtain various pharmaceutical drug dosage forms. In the present review, we focus on film and compression coatings because they are applied widely to develop CDDSs.

2.1. Film coating

Film coating involves the formation of a very thin polymeric film (with a thickness of approximately 25–100 μm) on different solid surface substrates such as tablets, granules, or capsules in order to: (i) alter the drug release rate, (ii) protect the drug from various environmental/physiological factors, (iii) enhance the physical and chemical properties of the substrate, (iv) mask unpleasant tastes and odors, and (v) avoid interactions with various incompatible substances. The film formation mechanism in coating process is shown in Fig. 2.

Functional coatings such as modified release, osmotic pressure-controlled drug delivery system, and enteric coatings can be employed in advanced drug delivery systems. The film coating process ensures batch-to-batch uniformity and good reproducibility.

The film coating process is a successful strategy because of the following advantages:

a) Minimum weight increase (2–3% of the core weight);
b) Considerable reduction in the processing time;
c) Enhanced process efficiency and outcomes;
d) Flexibility when selecting polymers and solvents;
e) Increased resistance to chipping by the final product.

2.2. Compression coating

Compression coating is also referred to as press coating or dry coating. In this process, fine dry granules are compressed onto a core drug tablet (Fig. 3) generally by using a specially designed tablet press, such as a Drycota (Manesty) or Prescota (Killian) system. Compression coating is essentially a dry process and it may be suitable for coating tablets containing heat and moisture labile drugs such as aspirin and penicillin. This coating process has also been used to separate two incompatible active pharmaceutical ingredients, where one is present in the tablet core and the other in the coating. Repeat action and sustained action tablets can be produced using this coating method (Vemula, 2015). Compression coating is traditionally a less popular process but it has attracted increased interest in recent years as a method for producing specialized modified-release products.

3. Application of coating to chronotherapeutics

A survey was conducted regarding chronotherapeutics and the application of coatings over the period from 2010 to 2020 by using the PubMed database with the following two search queries: (i) “Chronotherapeutic in Title/Abstract” and (ii) “Chronotherapeutic [Title/Abstract] and Coating [Title/Abstract]," and the results are represented in Fig. 4. In total, 208 publications were retrieved regarding chronotherapeutics and 23 described the use of coating technology. The number of publications increased from 2010 to 2015, thereby confirming the growing interest in CDDSs, but the number stabilized during 2016–2019 in both cases, possibly because some publications did not mention the keywords “chronotherapeutic and/or coating” in the title/abstract. Detailed descriptions of studies that investigated the development of CDDSs using coatings are presented in Table 1.

Most studies that described coatings used capsule shells and dry coating techniques. Tabs in cap systems have been successfully fabricated for valsartan, losartan, and theophylline to allow biphasic pulsed release. The capsule bodies are coated with enteric polymers or impermeable materials using dip coating or pan coating, and the cap remains uncoated. This system was applied to immediate release formulations and spacer/erodible tablets (without drugs) for sustained release formulations. Erodible tablets are used to achieve the required lag time between the pulsed release of two drugs. In immediate release formulations, the first pulse drug is released immediately after the capsule cap dissolves. The lag time can be maintained between 3 and 6 h depending on the chronobiology, before the second pulse in sustained release (SR) or conventional formulations. This approach was shown to be efficient in terms of the bioavailability in both in vitro and in vivo correlation studies. A multiparticulate system with salbutamol sulfate was prepared by using pH-independent and pH-dependent coating polymers comprising Eudragit RSPO and Eudragit L100, respectively, where the coating was applied to the core pellets using a solution layering technique. In vitro drug release analysis confirmed that the lag time was 3.5–4 h for the

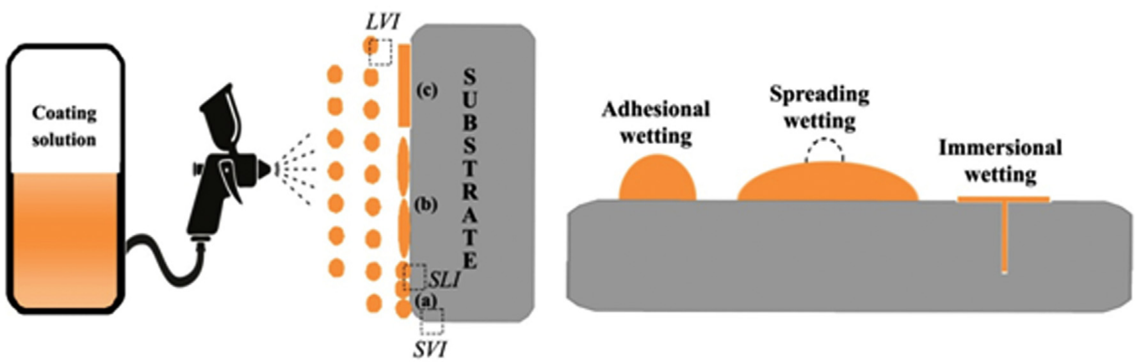

Fig. 2. Film coating method (adapted from the study by Kurakula et al., 2020) comprising (a) contact, (b) spreading and solvent evaporation, and (c) film formation with various types of wetting (LVI: liquid–vapor interface; SLI, solid–liquid interface; SVI: solid–vapor interface).

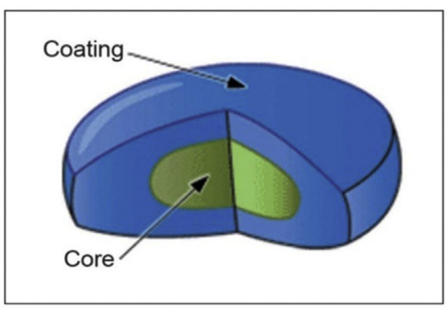

Fig. 3. Cross section of a compression-coated tablet.

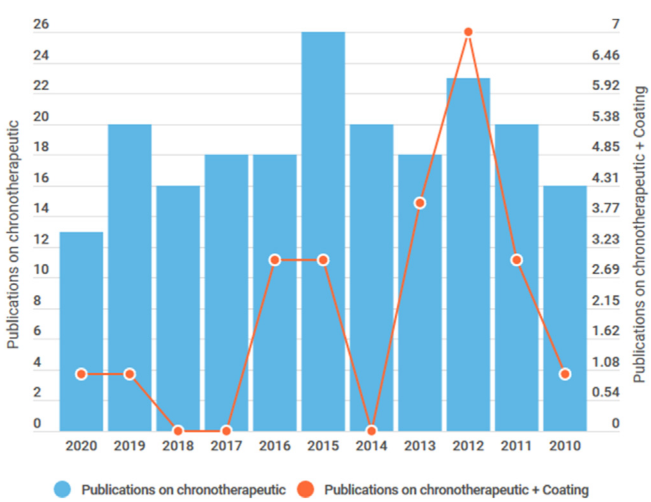

Fig. 4. Numbers of publications that investigated chronotherapeutics and chronotherapeutics plus coatings.

chronotherapeutic release system. Another floating pulsatile system was developed by Zou et al. to meet the requirements of chronopharmacotherapy (Zou et al., 2008), where the core tablet was dry coated with a hydrophilic erodible polymer to obtain the lag phase. Gastric retention of the dosage form was improved by adding Methocel K4M, sodium bicarbonate, and Carbopol 934 P. Gamma scintigraphy and in vivo studies demonstrated that the programmed lag time was achieved and the gastric residence of the system was enhanced. Barakat et al. developed a novel pressure-controlled colon delivery capsule to treat nocturnal asthma by using Eudragit S 100 polymer as the film coating on a hard gelatin capsule enclosed for drug–lipid dispersion, and in vivo studies of Beagle dogs confirmed biphasic drug delivery with the required lag time, as well as significant increases in C_{max} and T_{max} compared with the marketed formulation (Nahla et al., 2011). Another programmable drug delivery system was designed for valsartan to prevent the early morning surge in blood pressure, where swellable polymers (L-HPC, PEO, etc.) and erodible tablet formulations were assembled in a pre-coated capsule. The optimized formulation obtained a lag time of 6 h followed by continuous drug release according to everted rat intestinal dissolution analysis. The critical effects of lubricants, hydrophilic additives, glidants, and the molecular weights of HPMCs on the lag times of press-coated tablets were investigated by Patadia et al., 2015a,b), who concluded that hydrophilic additives had extreme effects, whereas glidants and lubricants were found to have highly minimal impacts on the lag time. Low molecular weight HPMCs were shown to be more effective than high molecular weight HPMCs for designing press-coated tablets (Agarwal and Bansal, 2013; Agarwal and Bansal, 2013).

4. Technological development

Patent related information was collected regarding chronotherapeutics and chronotherapeutics + polymer by using “The Lens” free and open patent and scholarly search portal with the following search terms: (a) Title: Chronotherapeutic (Abstract: Chronotherapeutic OR Claims: Chronotherapeutic) and Filters: Publication Date (January 1, 2001 to August 1, 2020); and (b) [Title: Chronotherapeutic OR (Abstract: Chronotherapeutic OR Claims: Chronotherapeutic)] AND [Title: Coating OR (Abstract: Coating OR Claims: biomedical)] and Filters: Publication Date (January 1, 2001 to August 1, 2020) (Fig. 2) (Kurakula and Naveen Raghavendra, 2020). The total number of patent documents related to chronotherapeutics increased greatly up to 2004, before reaching a plateau up to 2007 and then following a fluctuating pattern (Figs. 5 and 6). The number of patents related to chronotherapeutics + coating increased rapidly up to 2009, before then following the same pattern as those related to chronotherapeutics. Negative slopes were observed after 2017. The total numbers of patents retrieved between 2001 and 2020 regarding chronotherapeutics and chronotherapeutics + coating were 199 and 117, respectively. Unexpectedly, the total number of patent documents exceeded those of publications. Details of these patents are shown in Figs. 5 and 6. The USA ranked first with 49 patents related to chronotherapeutics and 39 related to chronotherapeutics + coating, followed by World Intellectual Property Organization (WIPO) with 33 and 22, respectively. According to the patent records, only 20.51% of the total patent applications were granted. Few ambiguous, amended, and limited patents were also observed.

4.1. *Classifications of patents*

Patents were classified and grouped according to their technical features and the patent information. Previously, each country used its own classification system, which could sometimes mislead developers.

Table 1
Recent studies of CDDSs developed using coating technology.

Title	Coating technology used	Core material	Coating composition	Drug	Ref
A novel system for three-pulse drug release based on "tablets in capsule" device	Solvent evaporation	Capsule body	Ethyl Cellulose EC, DMT	Diclofenac	Li et al., 2007
In vitro evaluation of once a day chronotherapeutic drug delivery system of *Gymnema sylvestre*	Spray coating and dip coating	Tablet and pellets	Hydroxypropyl methylcellulose (HPMC), polyethylene glycol (PEG) 600 and HPMC phthalate-50, PEG 600	*Gymnema sylvestre*	Jaina and Devi, (2016)
Formulation and pharmacokinetics of colon-specific double-compression coated mini-tablets: Chronopharmaceutical delivery of ketorolactromethamine	Double compression	Tablets	HPMC K100M, Eudragit S100	Ketorolactromethamine	Kunal et al., 2012
In-vitro/in-vivo correlation of pulsatile drug release from press-coated tablet formulations: A pharmacoscintigraphic study in the beagle dog	Press coating	Tablet	Glyceryl behenate, L-Hydroxy Propyl Cellulose (HPC)	Theophylline	Ghimire et al. (2007)
Utilizing guar gum for development of "tabs in cap' system of losartan potassium for chronotherapeutics	Dip coating	Capsule body	Ethyl cellulose, dibutyl phthalate (DP)	Losartan potassium	Gangwar et al. (2015)
A pharmacoscintigraphic study of three time-delayed capsule formulations in healthy male volunteers	Spray coating	Capsule body	Organic ethylcellulose (Ethocel 1; 100 premium grade), triacetin	Theophylline	McConville et al. (2009)
A novel core–shell chronotherapeutic system for the oral administration of ketoprofen	Dip coating followed by solvent evaporation	Beads	Eudragit S-100	Ketoprofen	Cerciello et al., 2016
Design and evaluation of a dry coated drug delivery system with floating–pulsatile release	Dry coating	Tablets	Methocel E15, Carbopol 934P, sodium bicarbonate	Verapamil hydrochloride	Zou et al. (2008)
A new pressure-controlled colon delivery capsule for chronotherapeutic treatment of nocturnal asthma	Spray coating	Capsule	Eudragit S100	Theophylline	Nahla et al., 2011
Chronotherapeutic drug delivery for early morning surge in blood pressure: A programmable delivery system	Pan coating	Capsule body	Ethyl cellulose, DP	Valsartan	Nayak et al. (2009)
Development and evaluation of a chronotherapeutic drug delivery system of torsemide	Compression coating	Tablets	Polyethylene Oxide (PEO) WSR 301 or PEO WSR 1105	Torsemide	Sunil et al. (2011)
Felodipine b-cyclodextrin complex as an active core for time delayed chronotherapeutic treatment of hypertension	Pan coating	Tablets	Ethyl cellulose, DP	Felodipine	Kunal et al. (2012)
A time-adjustable pulsatile release system for ketoprofen: In vitro and in vivo investigation in a pharmacokinetic study and an IVIVC evaluation	Spray coating	Tablets	Eudragit L100	Ketoprofen	Wang et al. (2017)
Investigating critical effects of variegated lubricants, glidants and hydrophilic additives on lag time of press coated ethylcellulose tablets	Compression coating	Tablets	EC	Prednisone	Patadia et al. (2015a)
Formulation and evaluation of multiparticulate system for chronotherapeutic delivery of salbutamol sulfate	Pan coating	Pellets	Eudragit RSPO, Eudragit L100	Salbutamol sulfate	Chaudhari and Chaudhari, 2012
Investigating effects of hydroxypropyl methylcellulose (HPMC) molecular weight grades on lag time of press-coated ethylcellulose tablets	Compression coating	Tablets	EC, HPMC	Prednisone	Patadia et al. (2015)
An in vitro and in vivo investigation into the suitability of compression coated tablets of indomethacin for the treatment of rheumatoid arthritis which follow circadian rhythms	Compression coating	Tablets	PEO WSR Coagulant	Indomethacin	Songa et al. (2013)
Formulation development and statistical optimization of chronotherapeutic tablets of indometacin	Compression coating	Tablets	HPMC	Indomethacin	Tinny et al. (2013)
Theophylline colon specific tablets for chronotherapeutic treatment of nocturnal asthma	Compression coating	Tablets	Chitosan granules	Theophylline	Yassi et al., 2012
Design and optimization of a chronotherapeutic dosage form for treatment of nocturnal acid breakthrough	–	Tablets	Tamarind gum, HPMC	Famotidine	Agarwal et al., 2012
Formulation and Evaluation of mini-tablets-filled pulsincap delivery of lornoxicam in the chronotherapeutic treatment of rheumatoid arthritis	–	Tablets	Celluloseacetate Pthalate (CAP), HPMC-K100M	Lornoxicam	Hadi et al. (2015)
Statistical optimization and fabrication of a press coated pulsatile dosage form to treat nocturnal acid breakthrough	–	Tablets	Mimosa gum, HPMC	Famotidine	Agarwal and Bansal, 2013

Thus, the Cooperative Patent Classification (CPC) and IPC International Patent Classification (IPC) systems were developed to consolidate patents. CPC was implemented from Q4 in 2010 as an extension of IPC and it is managed by the United States Patent and Trademark Office (USPTO) and European Patent Office (EPO). The CPC and IPC classifications are compared in Table 2.

According to the IPCR classification, the highest number of patents regarding chronotherapeutics + coating was assigned to class A61K. This class contains medical, dental, or toilet preparations, and devices that are specially designed to manufacture pharmaceutical products in different forms. The highest number of patents filed was 536 in the A61K class according to the IPCR classification. Similarly, most patents were assigned to the A61K class in the CPC classification, which also includes drugs or biological compositions for preventing, alleviating, treating, or curing pathological conditions of the living body. A small number of patents were included in class Y02A in the CPC classification, which covers technologies that allow adaptation to adverse conditions or climate change due to human and industrial activities. Drug, bio-affecting, and body treating compositions were granted patents under class 424 in the US classification (Fig. 7). Very low numbers of patents were included in classes 424 and 514 compared with the other classifications.

The citation frequencies were also investigated to assess the impacts

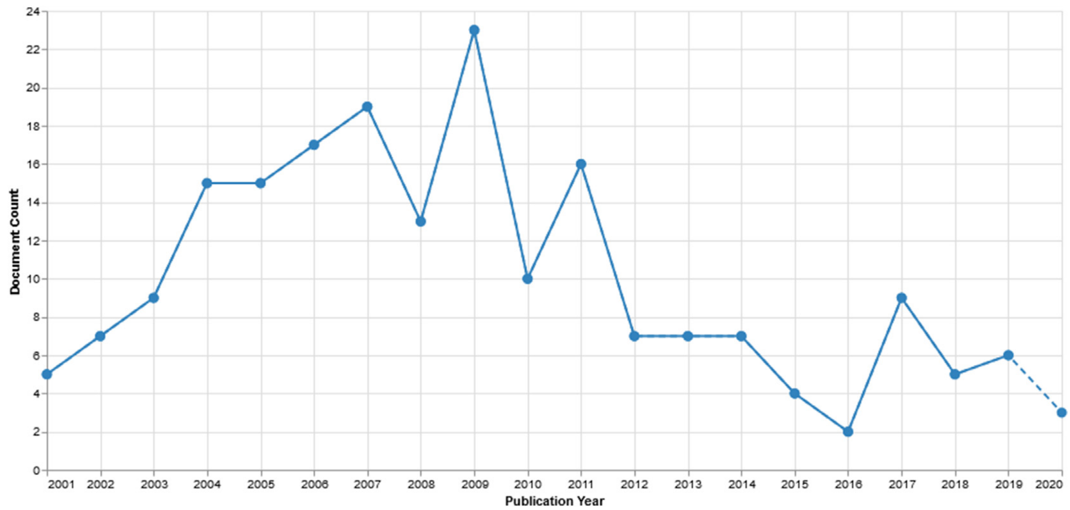

Fig. 5. Number of patent documents filed regarding chronotherapeutics during 2001–2020.

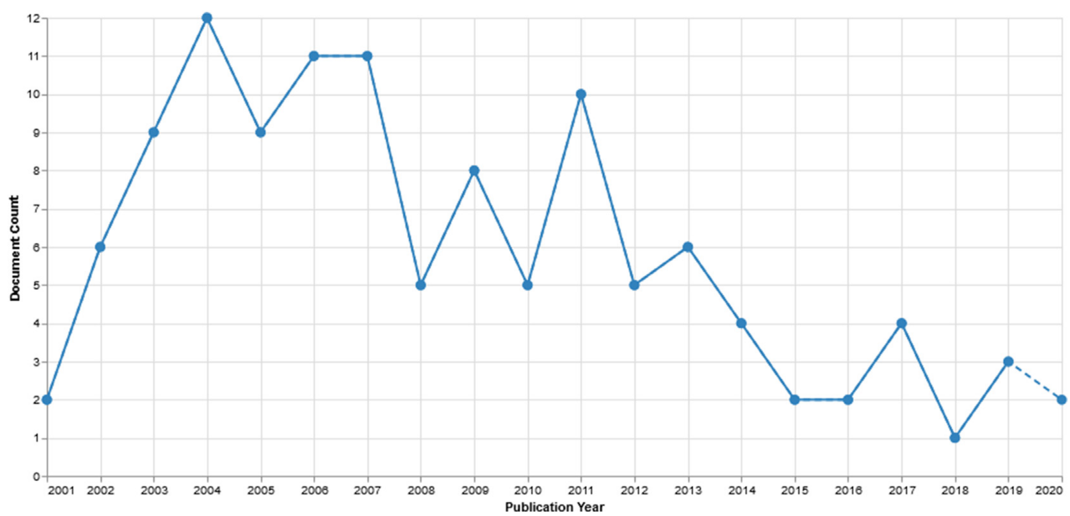

Fig. 6. Number of patent documents filed regarding chronotherapeutics + coating during 2001–2020.

Table 2
CPC and IPC patent classifications and entity details.

CPC Classification		IPC Classification
Section	Entity	Section
A	Human necessities	A
B	Performing operations transporting (notes & warnings)	B
C	Chemistry metallurgy (notes & warnings)	C
D	Textiles paper	D
E	Fixed constructions	E
F	Mechanical engineering lighting heating weapons blasting (notes & warnings)	F
G	Physics (notes & warnings)	G
H	Electricity (notes & warnings)	H
Y	Tagging of new technological developments	–

of patents. Fig. 8 shows scatter plots of the patent publication dates and their citation counts. Many patents were cited during 2006–10. The highest relevance was determined as 0.2 between 2007 and 2008 and the family size was close to 40. African Regional Intellectual Property Organization jurisdiction patents were highly cited compared with others.

5. Recent Patents

In recent years, several coating techniques and methods have received intellectual protection and patents, especially those developed for chronotherapeutic drug delivery. No previous review has comprehensively analyzed these methods. Thus, Table 3 summarizes patents granted (from 2000 to 2020) regarding the application of coating methods in chronotherapeutics.

Odidi developed a controlled release composition by using a transition coating to target pharmaceutical, biological, and chemical materials. The three coatings surrounding the tablet comprise polyvinyl acetate (PVA), EC, and methacrylate. The required controlled delivery and lag time were obtained with this triple coating. Baichwal was granted a formulation patent comprising a core material (active ingredient) and delayed release compression coating layer made of natural or synthetic gums. This formulation also contains an ionizable agent, surfactants, and hydrophobic material to satisfy the requirement of the drug delivery system. The lag time can be readily maintained between 2 and 18 h by changing the concentrations of the various components. In an invention, Boldhane described a chronotherapeutic formulation containing the active ingredient, a pH-dependent agent such as HPMC, HPC, or polyvinylpyrrolidone (PVP), and hydrophilic agents (natural gums or carboxymethyl cellulose (CMC), but mostly cellulose derivatives). The

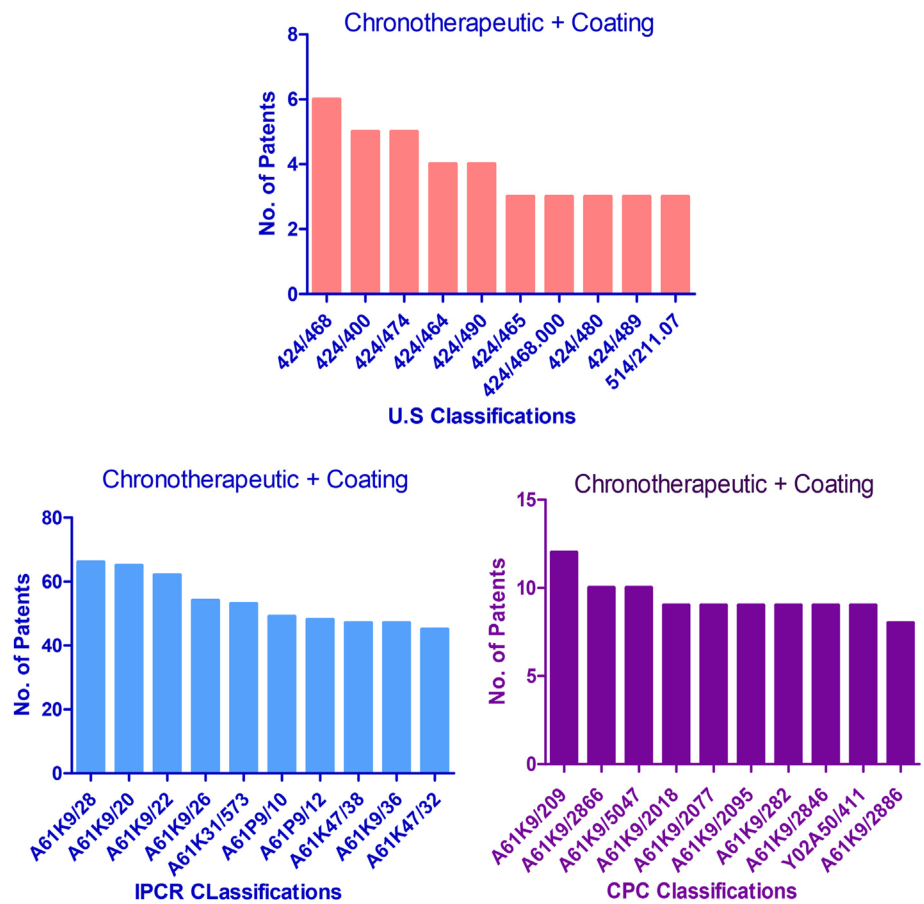

Fig. 7. Patents related to chronotherapeutics + coating applications according to the US, IPCR, and CPC classifications.

enteric coating is applied to the prepared tablets and the formulation satisfies the criteria for maintaining a lag time of 4–6 h followed by the prolonged release of the active ingredient for up to 24 h. Biovail Lab Int Srl was granted a patent for their controlled release galenical preparation of diltiazem containing a neutral acrylic polymer, acrylic methyl ester, and HPMC. This invention is also targeted by using an osmotic device containing diltiazem as the core material together with immediate release angiotensin-converting enzyme (ACE) inhibitors applied by spray coating as an external coat. This formulation can allow the delayed and controlled release of active ingredients. In another invention, the enteric coating comprises polyvinyl acetate phthalate (PVAP), methacrylic acid, or shellac, with calcium channel blockers and statins as active moieties. Fogarty invented a chronotherapeutic multiparticulate system for enalapril. Press-coated tablet formulations containing swellable materials such as NaCMC, PVP, and sodium alginate as core materials and hydrophilic materials (cellulose derivatives) or hydrophobic materials (glyceride stearic acid, hydrogenated vegetable oils, shellac) as coating materials were shown to be effective in dosage form because they could obtain the required lag time and desired drug release profiles.

6. Obstacles that hinder the development of CDDSs

The following problems hinder the further development of CDDSs and drug delivery optimization: (a) the development of rhythmic biomaterials, (b) rhythm engineering and modeling, and (c) regulatory guidelines.

The main issue related to CDDS development is the lack of safety of rhythmic materials due to their reversible properties. Some trials have aimed to overcome this issue but real breakthroughs can only be achieved by the application of smarter biomaterials. Significant efforts have been made to design smart systems but the main challenges are related to biodegradability, biocompatibility, and the responsive to specific biomarkers according to specific biological rhythms. Our ability to engineer rhythms and use reliable models is the next major problem. The model selected should be capable of predicting the physicochemical nature of a system and its biological response. Pharmaceutical industry researchers will usually consider all regulatory concerns, but this might not always apply to university researchers who are focused on proof-of-concept investigations that might never require regulatory considerations. In the pre-approval phase, it is sometimes difficult to demonstrate the chronotherapeutic advantages of modified release formulations in clinical settings, partly because of the first two issues discussed above. In the post-approval phase, several challenges need to be addressed by manufacturers and regulators due to the possible abuse of new formulations. Thus, both drug sponsors and drug regulators should consider the factors that might render a product “abuse ready” so appropriate risk management strategies can be implemented after approval.

7. Conclusion

Previous studies have confirmed the importance of chronobiology for treating several chronic diseases. Conventional or extended-release systems can maintain the drug concentration at the therapeutic level for a prolonged time, but this might not be appropriate for circadian rhythm-related diseases. This problem can be overcome by a programmed lag phase according to the changes in physiological conditions. The application of coating technologies to develop chronotherapeutic systems is limited compared with that of other techniques, probably due to the

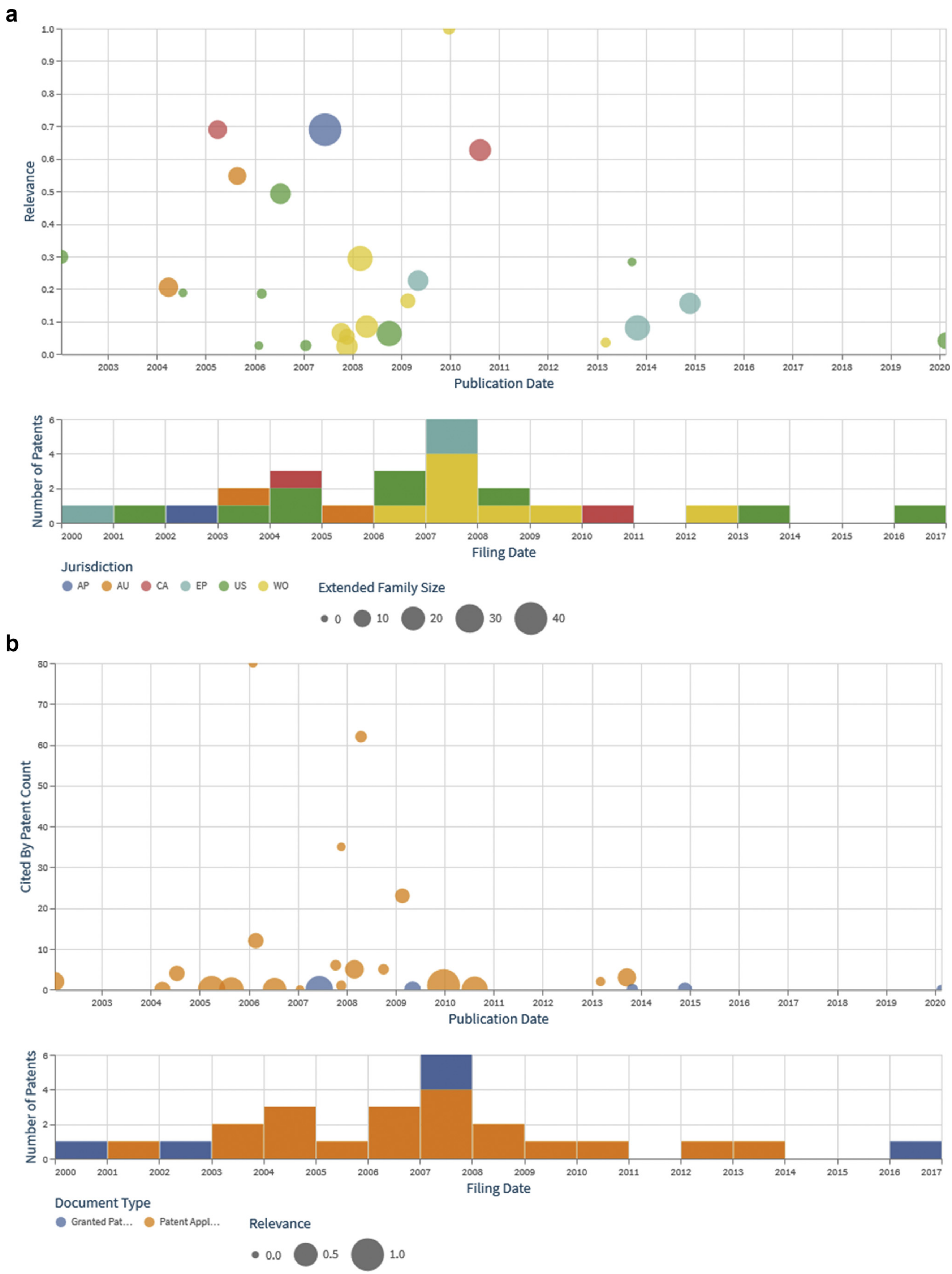

Fig. 8. Patent citations, publication dates, and jurisdictions.

Table 3
Patents granted regarding coating techniques for CDDS from January 2001 to August 2020 (Source: www.lens.org)..

Jurisdiction	Publication Number	Publication Year	Title	Applicant
US	US 10624858 B2	2020	Controlled Release Composition Using Transition Coating, and Method of Preparing Same	Odidi, I.
US	US 10561602 B2	2020	Controlled Extended Release Pregabalin	Odidi, I.
US	US 10314787 B2	2019	Controlled Release Delivery Device Comprising an Organosol Coat	Intellipharmaceutics Corp
US	US 2019 0083399 A9 20190321	2019	Drug Delivery Composition	Odidi, I.
US	US 2019/0076363 A1	2019	Controlled Release Delivery Device Comprising an Organosol Coat	Intellipharmaceutics Corp
US	US 10159649 B2	2018	Controlled Release Delivery Device Comprising an Organosol Coat	Intellipharmaceutics Corp
US	US 2017/0273896 A1	2017	Controlled Extended Release Pregabalin	Odidi, I.
KR	KR 101762453 B1	2017	Chronotherapeutic Pharmaceutical Composition	
US	US 2017/0112770 A1	2017	Controlled Release Delivery Device Comprising an Organosol Coat	Intellipharmaceutics Corp
US	US 9561188 B2	2017	Controlled Release Delivery Device Comprising an Organosol Coat	Odidi, I.
WO	WO 2016/187718 A1	2016	Controlled Extended Release Pregabalin	Odidi, I.
US	US 9278076 B2	2016	Chronotherapeutic Dosage Forms	Baichwal, A.R.
CN	CN 102316864 B	2015	Chronotherapeutic Pharmaceutical Composition	Abbott Healthcare Private Ltd
EP	EP 2007360 B1	2014	Controlled Release Delivery Device Comprising an Organosol Coat	Odidi, I.
EP	EP 1368005 B9 20140611	2014	Chronotherapeutic Dosage Forms	Endo Pharmaceuticals Inc
EP	EP 2389174 A4	2014	Chronotherapeutic Pharmaceutical Composition	Abbot Healthcare Private Ltd
ES	ES 2436523 T3	2014	Formas De Dosificación Terapéutica	Penwest Pharmaceuticals Co
EP	EP 2061437 B1	2013	Combined Pharmaceutical Formulation with Controlled-release Comprising Dihydropyridine Calcium Channel Blockers And HMG-CoA Reductase Inhibitors	Hanall Biopharma Co Ltd
US	US 2013/0243861 A1	2013	Press-coated Tablets of Prednisone	Cadila Healthcare Ltd
EP	EP 1368005 B1	2013	Chronotherapeutic Dosage Forms	Endo Pharmaceuticals Inc
JP	JP 5232062 B2	2013	JP 5232062 B2	
WO	WO 2013/030602 A1	2013	Solid Extended Release Composition for Oral Administration Comprising Substantially Amorphous Capecitabine	Beijnen, J.H.
US	US 2012/0070472 A1	2012	Chronotherapeutic Compositions and Methods of their Use	Devane, J.
US	US 2012/0015032 A1	2012	Combination Preparation Comprising Inhibitor of HMG-CoA Reductase and Aspirin and Method for Manufacturing the Same	Kim, S.W.
US	US 2011/0217336 A1	2011	Chronotherapeutic Dosage Forms and Methods of Treatment Using Chronotherapy	Baichwal, A.R.
IL	IL 214136 D0	2011	Chronotherapeutic Pharmaceutical Composition	Abbott Healthcare Private Ltd
US	US 2011/0195121 A1	2011	Chronotherapeutic Pharmaceutical Dosage Form	Sewlall, S.
AU	AU 2010/211985 A1	2011	Chronotherapeutic Pharmaceutical Composition	Abbott Healthcare Private Ltd
IL	IL 157633 A	2011	Chronotherapeutic Dosage Forms	Penwest Pharmaceuticals Company
US	US 7887841 B2	2011	Chronotherapeutic Dosage Forms and Methods of Treatment Using Chronotherapy	Baichwal, A.R.
WO	WO 2010/089772 A3	2010	Chronotherapeutic Pharmaceutical Composition	Piramal Healthcare Ltd
WO	WO 2010/089772 A2	2010	Chronotherapeutic Pharmaceutical Composition	Piramal Healthcare Ltd
CA	CA 2750611 A1	2010	Chronotherapeutic Pharmaceutical Composition	Abbott Healthcare Private Ltd
CA	CA 2440588 C	2010	Chronotherapeutic Dosage Forms	Penwest Pharmaceuticals Co
WO	WO 2009/153635 A1	2009	A Chronotherapeutic Pharmaceutical Dosage Form	University of Witwatersrand Johannesburg
US	US 2009/0304787 A1	2009	Drug Delivery Composition	Odidi, I.
US	US 2009/0220613 A1	2009	Controlled Release Delivery Device Comprising an Organosol Coat	Odidi, I.
JP	JP 2009149691 A	2009	Time Therapy (chronotherapeutic) Administration Form	Penwest Pharmaceuticals Co
US	US 2009/0169587 A1	2009	Chronotherapeutic Dosage Forms	Penwest Pharmaceuticals Co
US	US 2009/0118256 A1	2009	Chronotherapeutic Diltiazem Formulations and the Administration Thereof	Biovail Lab Int Srl
WO	WO 2009/022821 A2	2009	Combination Preparation Comprising Inhibitor of HMG-CoA Reductase and Aspirin and Method for Manufacturing the Same	Hanall Pharmaceutical Co Ltd
AU	AU 2008/229834 A1	2008	Chronotherapeutic Dosage Forms	Penwest Pharmaceuticals Co
US	US 7348028 B2	2008	Chronotherapeutic Diltiazem Formulations and the Administration Thereof	Albert, K.S.
WO	WO 2007/132293 A2	2007	Once-daily Administration of Central Nervous System Drugs	Circ Pharma Res And Dev Ltd
WO	WO 2007/131357 A1	2007	Pharmaceutical Composition Having Reduced Abuse Potential	Odidi, I.
WO	WO 2007/112581 A1	2007	Controlled Release Delivery Device Comprising an Organosol Coat	Odidi, I.
WO	WO 2007/112579 A1	2007	Drug Delivery Composition	Odidi, I.
US	US 2007/0104788 A1	2007	Once-daily Administration of Central Nervous System Drugs	Mulligan, S.
EA	EA 008224 B1	2007	Chronotherapeutic Dosage Forms	Penwest Pharmaceuticals Co
HU	HU 0501071 A2	2007	Chronotherapeutic Dosage Forms	Penwest Pharmaceutical Co
US	US 2007/0014858 A1	2007	Method for Controlling Lag Time of In-situ Passageway Formation in Osmotic Delivery System	Empax Pharma Inc
US	US 2006/0039976 A1	2006	Controlled Release Composition Using Transition Coating, and Method of Preparing Same	Odidi, I.
AU	AU 2002/244295 B2	2006	Chronotherapeutic Dosage Forms Containing Glucocorticosteroid	Penwest Pharmaceuticals Co
US	US 2006/0024361 A1	2006	Disintegrant Assisted Controlled Release Technology	Odidi, I.
US	US 2006/0003001 A1	2006	Chronotherapeutic Compositions and Methods of their Use	Devane, J.
US	US 2005/0276853 A1	2005	Chronotherapeutic Dosage Forms and Methods of Treatment Using Chronotherapy	Baichwal, A.R.
MX	MX PA03008292 A	2003	Chronotherapeutic Dosage Forms Containing Glucocorticosteroid	Penwest Pharmaceuticals Co

complexity of the coating process, solubility issues associated with coating materials, and the difficulty of achieving uniform coatings. Environmental and other safety-related issues may also increase the production cost, thereby failing to meet the requirements for large-scale production. In the future, these techniques can be replaced with techniques that require little or no solvent, such as three-dimensional printing, powder layering and injection molding, in order to bypass the drying steps that consume large amounts of time and energy. Several new approaches such as hydrogel and transdermal systems will certainly improve patient acceptance and optimize the management of circadian rhythm-associated diseases. Many achievements have been made but further developments in chronotherapeutics may facilitate the design of novel drug delivery systems.

Funding

This review did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Buduru Gowthami: Conceptualization, Resources, Writing - original draft, Formal analysis. **S.V. Gopala Krishna:** Conceptualization, Validation, Supervision, Writing - review & editing, Formal analysis, Project administration. **D. Subba Rao:** Conceptualization, Validation, Supervision, Writing - review & editing, Formal analysis, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Agarwal, Vaibhav, Bansal, Mayank, 2012. Design and optimization of a chronotherapeutic dosage form for treatment of nocturnal acid breakthrough. Curr Drug 9 (6), 608–616. https://doi.org/10.2174/156720112803529756.

Agarwal, Vaibhav, Bansal, Mayank, 2013. Statistical optimization and fabrication of a press coated pulsatile dosage form to treat nocturnal acid breakthrough. Curr. Drug Deliv. 10 (4), 444–452. https://doi.org/10.2174/1567201811310040009.

Ali, Javed, Baboota, Sanjula, Ahuja, Alka, Saigal, Nitin, 2010. Distinctive features of "chronotherapeutic" and "pulsatile" drug delivery systems negating the practice of their interchangeable terminology. J. Drug Target. 18 (6), 413–419. https://doi.org/10.3109/10611861003587250.

Bi-Botti, C., 2010 July 31. Youana chronopharmaceutical drug delivery systems: hurdles, hype or hope? Adv. Drug Deliv. Rev. 62 (9–10), 898–903. https://doi.org/10.1016/j.addr.2010.04.010.

Bruguerolle, B., Labrecque, G., 2007. Rhythmic pattern in pain and their chronotherapy. Adv. Drug Deliv. Rev. 59 (9–10), 883–895. https://doi.org/10.1016/j.addr.2006.06.001.

Cerciello, Andrea, Auriemma, Giulia, Del Gaudio, Pasquale, Sansone, Francesca, Aquino, Rita P., Russo, Paola, 2016. A novel core–shell chronotherapeutic system for the oral administration of ketoprofen. J. Drug Deliv. Sci. Technol. 32, 126–131. https://doi.org/10.1016/j.jddst.2015.07.017.

Chaudhari, M.P., Chaudhari, D.P., 2012. Formulation and evaluation of multiparticulate system for chronotherapeutic delivery of salbutamol sulphate. J Pharm Bioall Sci 4, 71–73. https://doi.org/10.4103/0975-7406.94144.

Gangwar, Guarav, Kumar, Anil, Pathak, Kamla, 2015. Utilizing guar gum for development of "tabs in cap' system of losartan potassium for chronotherapeutics. Int. J. Biol. Macromol. 72, 812–818. https://doi.org/10.1016/j.ijbiomac.2014.09.027.

Ghimire, Manish, McInnes, Fiona J., Watson, David G., Mullen, Alexander B., Stevens, Howard N.E., 2007. In-vitro/in-vivo correlation of pulsatile drug release from press-coated tablet formulations: a pharmacoscintigraphic study in the beagle dog. Eur. J. Pharm. Biopharm. 67 (2), 515–523. https://doi.org/10.1016/j.ejpb.2007.03.002.

Hadi, Mohd Abdul, Raghavendra Rao, Nidagurthi Guggilla, Rao, Avanapu Srinivasa, 2015. Formulation and evaluation of mini-tablets-filled-pulsincap delivery of lornoxicam in the chronotherapeutic treatment of rheumatoid arthritis. Pak. J. Pharm. Sci. 28 (1), 185–193.

Jain, Deepika, Raturi, Richa, Jain, Vikas, Bansal, Praveen, Singh, Ranjit, 2011. Recent technologies in pulsatile drug delivery systems. Biomatter 1 (1), 57–65. https://doi.org/10.4161/biom.1.1.17717.

Jaina, Nimisha, Devi, V. Kusum, 2016. In vitro evaluation of once a day chronotherapeutic drug delivery system of Gymnema sylvestre. Ind. Crop. Prod. 88, 58–64.

Khan, Zaheeda, Pillay, Viness, Choonara, Yahya E., du Toit, Lisa C., 2009. Drug delivery technologies for chronotherapeutic applications. Pharmaceut. Dev. Technol. 14 (6), 602–612. https://doi.org/10.3109/10837450902922736.

Kunal, P., Pagarpradeep, R., Vavia, 2012. Felodipine b-cyclodextrin complex as an active core for time delayed chronotherapeutic treatment of hypertension. Acta Pharm. 62, 395–410. https://doi.org/10.2478/v10007-012-0023-0.

Kurakula, Mallesh, Naveen Raghavendra, N., 2020. Prospection of recent chitosan biomedical trends: evidence from patent analysis (2009–2020). Int. J. Biol. Macromol. 165, 1924–1938.

Kurakula, M., Naveen, N.R., Yadav, K.S., 2020. Formulations for polymer coatings. Polymer Coatings 415–443. https://doi.org/10.1002/9781119655145.ch19.

Lemmer, B., 1991. Implications of chronopharmaco kinetics for drug delivery; antiasthmatics, H2-blockers and cardiovascular active drugs. Adv. Drug Deliv. Rev. 6 (1), 83–100. https://doi.org/10.1016/0169-409X(91)90033-9.

Lemmer, B., 1996. The clinical relevance of chronopharmacology in therapeutics. Pharmacol. Res. 33 (2), 107–115. https://doi.org/10.1006/phrs.1996.0016.

Li, Bin, Zhu, JiaBi, Zheng, ChunLi, Gong, Wen, 2007. A novel system for three pulse drug release based on "tablets in capsule" device. Int. J. Pharm. 352 (1–2), 159–164. https://doi.org/10.1016/j.ijpharm.2007.10.043.

Martin, R.J., Banks-Schlegel, S., 1998. Chronobiology of asthma. Am. J. Respir. Crit. Care Med. 158, 1002–1007.

McConville, Jason T., Hodges, Lee-Ann, Jones, Tamara, Band, Janet P., O'Mahony, Bridget, Lindsay, Blythe, Ross, Alistair C., Florence, Alastair J., Stanley, Adrian J., Humphrey, Michael J., Wilson, Clive G., Stevens, Howard N.E., 2009. A pharmacoscintigraphic study of three time-delayed capsule formulations in healthy male volunteers. J. Pharmacol. Sci. 98 (11), 4251–4263. https://doi.org/10.1002/jps.21739.

Nahla, S. Barakat, Al-Suwayeh, Saleh A., Taha, Ehab I., Yassin, Alaa Eldeen Bakry, 2011. A new pressure-controlled colon delivery capsule for chronotherapeutic treatment of nocturnal asthma. J. Drug Target. 19 (5), 365–372. https://doi.org/10.3109/1061186X.2010.504264.

Nayak, Usha Yogendra, Shavia, Gopal Venktesh, Nayak, Yogendra, Averinena, Ranjith Kumar, Mutalik, Srinivas, Reddy, Sreenivasa Meka, Gupta, Purshottam Das, Udupa, Nayanabhirama, 2009. Chronotherapeutic drug delivery for early morning surge in blood pressure: a programmable delivery system. J. Contr. Release 136, 125–131. https://doi.org/10.1016/j.jconrel.2009.02.008.

Ohdo, S., 2007. Chronopharmacology focused on biological clock. Drug Metabol. Pharmacokinet. 22 (1), 3–14. https://doi.org/10.2133/dmpk.22.3.

Patadia, Riddhish, Vora, Chintan, Mittal, Karan, Mashru, Rajashree, 2015a. Investigating critical effects of variegated lubricants, glidants and hydrophilic additives on lag time of press coated ethylcellulose tablets. Pharmaceut. Dev. Technol. 21 (3), 1–9. https://doi.org/10.3109/10837450.2014.999788.

Patadia, Riddhish, Vora, Chintan, Mittal, Karan, Mashru, Rajashree, 2015b. Investigating effects of hydroxypropyl methylcellulose (HPMC) molecular weight grades on lag time of press-coatedethyl cellulose tablets. Pharmaceut. Dev. Technol. 21 (7), 794–802. https://doi.org/10.3109/10837450.2015.1055767.

Portaluppi, F., Lemmer, B., 2007. Chronobiology and chronotherapy of ischemic heart disease. Adv. Drug Deliv. Rev. 59 (9–10), 952–965. https://doi.org/10.1016/j.addr.2006.07.029.

Smolensky, M.H., Lemmer, B., Reinberg, A.E., 2007. Chronobiology and chronotherapy of allergic rhinitis and bronchial asthma. Adv. Drug Deliv. Rev. 59 (9–10), 852–882. https://doi.org/10.1016/j.addr.2007.08.016.

Songa, Ambedkar Sunil, Meka, Venkata Srikanth, Nali, Sreenivasa Rao, Kolapalli, Venkata Ramana Murthy, 2013. An in vitro and in vivo investigation into the suitability of compression coated tablets of indomethacin for the treatment of rheumatoid arthritis which follow circadian rhythms. Drug Dev. Ind. Pharm. 39 (3), 447–456. https://doi.org/10.3109/03639045.2012.662509.

Sunil, Songa Ambedkar, Rao, Nali Sreenivasa, Srikanth, Meka Venkata, Uhumwangho, Michael Uwumagbe, Kumar, Kommana Srinivas Phani, Murthy, Kolaplli Venkata Ramana, 2011. Development and evaluation of a chronotherapeutic drug delivery system of torsemide. Braz. J. Pharm. Sci. 47, 3. https://doi.org/10.1590/S1984-82502011000300017.

Tinny, T., Chacko, A.J., Jose, S., 2013. Formulation development and statistical optimization of chronotherapeutic tablets of indometacin. Drug Dev. Ind. Pharm. 39 (9), 1357–1363. https://doi.org/10.3109/03639045.2012.715352.

Vemula, Sateesh Kumar, 2015. Formulation and pharmacokinetics of colon-specific double-compression coated mini-tablets: chronopharmaceutical delivery of ketorolac tromethamine. Int. J. Pharm. 491 (1–2), 35–41. https://doi.org/10.1016/j.ijpharm.2015.06.007.

Wang, Haiying, Cheng, Lizhen, Wen, Haoyang, Li, Caiyan, Li, Yuenan, Zhang, Xiaoyu, Wang, Yongfei, Wang, Yanyan, Wang, Tuanjie, Pan, Weisan, Yang, Xinggang, 2017. A time-adjustable pulsatile release system for ketoprofen: in vitro and in vivo investigation in a pharmacokinetic study and an IVIVC evaluation. Eur. J. Pharm. Biopharm. 119, 192–200. https://doi.org/10.1016/j.ejpb.2017.06.015.

Yassi, Alaa Eldeen B., Aodah, Alhassan H., Al-Suwayeh, Saleh, Taha, Ehab I., 2012. Theophylline colon specific tablets for chronotherapeutic treatment of nocturnal asthma. Pharmaceut. Dev. Technol. 17 (6), 712–718. https://doi.org/10.3109/10837450.2011.572896.

Youan, B.B., 2010. Chronopharmaceutical drug delivery systems: hurdles, hype or hope? Adv. Drug Deliv. Rev. 62, 898–903. https://doi.org/10.1016/j.addr.2010.04.010.

Zou, Hao, Jiang, Xuetao, Kong, Lingshan, Gao, Shen, 2008. Design and evaluation of a dry coated drug delivery system with floating pulsatile release. J. Pharmacol. Sci. 9, 263–273. https://doi.org/10.1002/jps.21083.