EXPERT OPINION

Colon: a gateway for chronotherapeutic drug delivery systems

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Colon-specific delivery systems have attracted considerable attention from the scientific community. One of the distinctions of this site-specific delivery system is its effectiveness in carrying a variety of medicinal agents (required for both localized diseases and systemic therapy). It has been proposed that the biological rhythm of the body may affect the normal physiological as well as biological functions. Diseases such as nocturnal asthma, angina pectoris, inflammation, rheumatoid arthritis, hypertension or cardiac arrhythmia, has been found to follow biological rhythm of the body. For the treatment of these diseases, development of a chronotherapeutic drug delivery system (CrDDS), which delivers a defined dose, at a selected time and chosen rate, and to a targeted site is required. Several CrDDSs have been developed by using various strategies (pH-, time-, microflora-triggered and pressure-controlled systems) with the aim of achieving colon-specific drug delivery. This *Editorial* article aims to highlight some of the recent advancements that have emerged in the field of colon-targeted drug delivery systems pertaining to the chronotherapy of certain disease conditions.

Keywords: biological clock, biological rhythm, chronobiology, chronopharmaceutics, circadian rhythm, colon targeting, pre-programmed delivery

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1. Introduction

"Targeted drug delivery systems are useful for selective and efficient delivery of pharmacologically active compounds to the predetermined targets in therapeutic concentration along with minimizing side effects of the drug" [1]. As far as oral delivery of drugs is concerned, colon-targeted drug delivery systems (CoDDS) have been one of the most preferred field for researchers since past two decades. Colonic delivery deals with the targeted delivery of active agents into the lower part of the gastrointestinal tract (GIT), that is, the large intestine. It can be accomplished either by using the oral route or by rectal administration of drugs. The main hindrances which must be overcome for attaining efficacious delivery of drugs to the colonic region via the oral route are the absorption and degradation of drug in the upper part of the GIT. Further, CoDDS is not only useful for the treatment of diseases (colon cancer, infection, inflammatory bowel disease and irritable bowel syndrome) which requires localized delivery of drugs in the colonic region but it is also useful for the delivery of those molecules which are likely to degrade in the upper part of GIT (e.g., proteins, peptides and vaccines) [2].

Since past two decades, a new type of drug delivery system *viz*. chronopharmaceuticals has attracted tremendous interest among pharmaceutical research community. It comprises the nitty-gritties and investigation of various features of chronopharmacology, chronopharmacokinetics, chronopathology, chronopharmacodynamics, chronotherapeutics, chronotoxicology, chronophysiology and

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chronogenetics. Generally, it brings together the concepts of chronobiology and pharmaceutics. Chronobiology is related with the learning of biological rhythms and mechanisms in living organisms [3]. Basically there are three types of biological rhythms in human body *viz*. circadian, ultradian and infradian. Circardian is originated from Latin terminology '*Circa*' means 'about' and '*dies*' means 'day'. Ultradian means alternation of shorter interval (> 1 cycle per day), whereas infradian means alternation extended for > 24 h (< 1 cycle per day) [4]. Ultradian and infradian rhythms are not as useful for chronotherapeutic drug delivery, as they have either > 1 cycle per day or < 1 cycle per day, respectively. On the contrary, many bodily functions have been regulated by circadian rhythm *viz*. sleep pattern, metabolism, hormone production, physiological behavior, and so on. Chronobiology is based on the principle that the biological processes and functions in all existing creatures demonstrate predictable erraticism over time [5]. On the other hand, pharmaceutics deals with the technological aspects of dosage form designing and manufacturing in order to ensure the safety, efficacy and quality of medicaments. Hence, chronopharmaceutics can be defined as a division of pharmaceutics, which is dedicated to the design, development and evaluation of the drug delivery system, that releases the drug at a pre-programmed pattern (rhythm) in synchronization with the biological clock (certain times of day or night) for the given disease therapy in order to increase the effectiveness and reduce the side effects [3]. As the onset of diseases such as arthritis, asthma, cardiac arrhythmias, hypertension or inflammation is at night time or early in the morning, chronotherapy can be utilized for the treatment of these diseased conditions. Moreover, as chronotherapy is based on the fact that the circardian rhythm should be matched with the drug release profile, it is desirable to have a delayed release delivery system that can provide nocturnal release of a drug. Further, it has been well documented that CoDDS can be useful for achieving such delayed onset of drug release [1]. This Editorial article is not envisioned to offer a comprehensive review on CoDDS, but to highlight some of the recent advancements that emerged in the field of CoDDS pertaining to the chronotherapy of certain disease conditions.

2. Conventional versus chronotherapy

Since many decades, conventional dosage forms have been extensively used for the treatment of various diseased conditions. They provide immediate or quick release of drug, which results into frequent administration, in order to maintain the therapeutic concentration of drug. These further result into poor patient compliance, reduced drug efficiency and increased episodes of side effects. Additionally, these types of dosage forms do not find their application in the treatment of diseases which present their symptoms during the night or early morning. Hence, to overcome the drawbacks associated with conventional dosage forms, modified drug release systems have been recommended. These systems were able to deliver the drug at a constant rate over a prolonged period of time which results into improved patient compliance and drug efficiency, and reduction in frequency of drug administration and subsequent side effects. However, apart from these merits, numerous modified release systems offers several difficulties *viz*. development of resistance and/or drug tolerance (because of continuous delivery of drug), and unavailability of additional amount of drug at the time when the symptoms are aggravated [3].

Recently, it has been proposed that the biological rhythm of the body may affect the normal physiological functions *viz*. Gastric-acid secretion, motility of GIT, blood flow in GIT, hepatic circulation, cardiac output, renal circulation, enzymatic activity in liver, drug–protein binding and urinary pH; and biological functions such as blood pressure, heart rate, platelet aggregation, body temperature, blood-plasma concentration, stroke volume and intraocular pressure [6]. Further, the functions of most of the organs varies as the day passes, specifically when rhythmic and temporal patterns are expressed in a given disease state. Diseases such as nocturnal asthma, angina pectoris, inflammation, rheumatoid arthritis, hypertension or cardiac arrhythmias have been found to follow biological rhythm of the body [3]. Thus, for the treatment of these diseases, development of chronotherapeutic drug delivery system (CrDDS) which delivers a defined dose, at a selected time and a chosen rate and to a targeted site is the need of the hour. The advantages offered by CrDDS is shown in (**Figure 1A**) [3,4].

3. Strategies for attaining CoDDS

CrDDS is envisioned to deliver a quick, or ephemeral, and quantified amount of drug molecule at a pre-programmed time in a predetermined region of GIT [3,4]. Development of CrDDS assists in achieving maximum efficacy of drug molecule against the targeted disease condition, thereby augmenting therapeutic efficiency and improving patient compliance. Further, the lag time for drug release from CrDDS primarily depends on the design aspects of the formulation [3]. The necessities which led to the development of CrDDS is shown in (**Figure 1B**) [3,4].

Over the past many years, several tactics have been used for achieving CrDDS of drugs by applying the concept of CoDDS. The principle strategies were development of pH-dependent systems, time-dependent systems, microbially and/or enzymatically driven drug delivery systems (comprising of biodegradable polymers [polysaccharides] and prodrugs-based CoDDS) and pressure-controlled-based systems [1,2].

3.1 pH-dependent systems

The concept of pH-dependent strategy is based on the principle that the pH of the GIT rises gradually from the stomach to the small intestine to the distal ileum. Enteric polymers

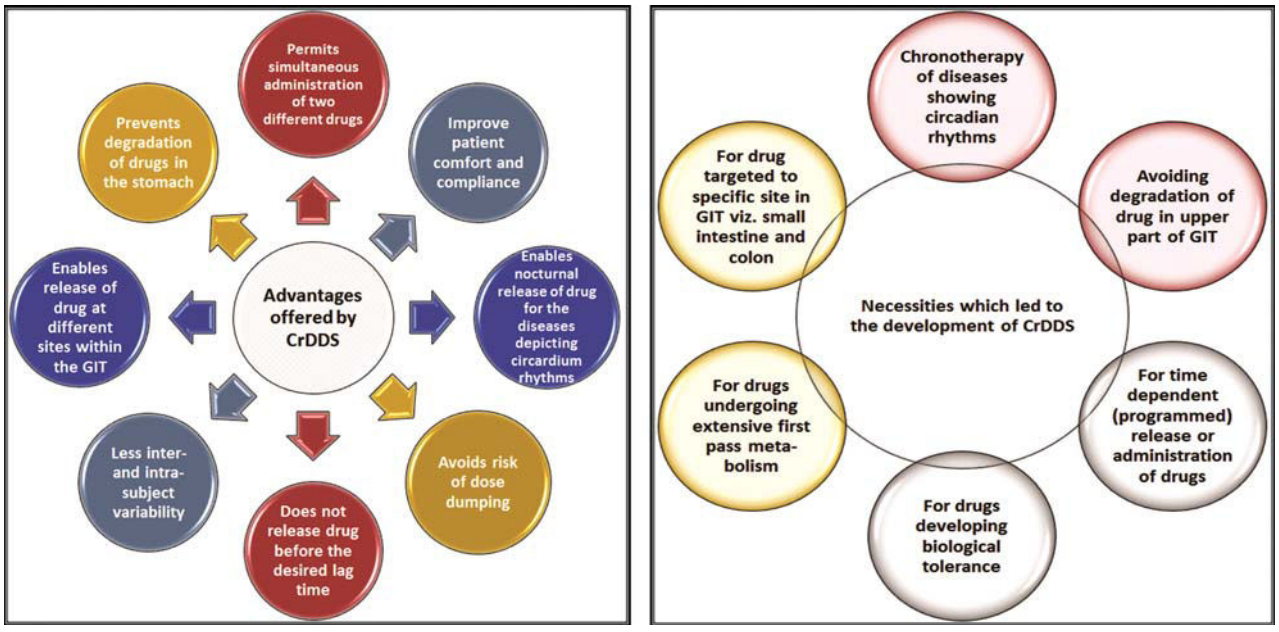

Figure 1. (**A**) Advantages offered by CrDDS, and (**B**) necessities which led to the development of CrDDS.

used for the preparation of these systems tend to prevent dissolution of drug in the upper part of GIT (as they are insoluble in acidic pH). Depending on their chemical composition, these polymers dissolve in the pH range of 5.0 – 7.5, thus preventing release of drug in stomach and providing a delayed release profile. Single-unit (tablets) and multi-unit (pellets) systems are most commonly preferred for enteric coating, as they are easy to manufacture at a comparatively low cost than that of complex systems. Most commonly used enteric polymers are the methacrylic acid copolymers (Eudragit® polymers). Other polymers that can be used for imparting enteric effects are hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, cellulose acetate trimelliate and polyvinyl acetate phthalate [1,2]. As far as commercial aspect is concerned pH-dependent systems are most extensively used [7]. Regardless of its extensive commercial applicability for achieving CoDDS, there always exists a controversy about their effectiveness for colon targeting [7]. This may be due to high erraticism in pH of GIT (both inter-individual and intra-individual) and dearth of an appropriate coating polymer, which dissolves at preferred pH of the colonic region. It has been well documented that the systems enclosed within pH-dependent polymers lack in providing site-specific release of drug to the colonic region, and they may either tend to provide an early release of medicament in small intestine or there will be no release of medicament in the colonic region [7,8].

3.2 Time-dependent systems

These systems are based on the concept of delaying the release of drug until they reach to the target site, that is, colon. The principle of this scheme is based on resisting the release of drug in acidic milieu of stomach, and providing a lag time of a pre-programmed duration of time, after which the drug release occurs in the colonic region. Here, lag times refers to the time required for transiting from the oral cavity to the colonic region [1,2]. In case of time-dependent drug delivery systems, the site for the initial release of drug largely depends on transit time of GIT. Although the small intestinal transit time is relatively constant (3 – 4 h), a large deviation in gastric evacuation time may tend to either an early release of medicament in small intestine or deferred release of drug way down in descending colon [9-11].

3.3 Microbially and/or enzymatically driven drug delivery systems

Microbially and/or enzymatically driven systems are reported to have greater supremacy over other approaches as far targeting of drugs to the colon is concerned. These systems retain the integrity of the dosage form until it reaches to the colonic region. The drug release in the colonic region is triggered as a result of degradation effect instigated due to the interaction between the microflora and/or enzymes present in the colonic region and the biodegradable polymers (polysaccharides) and prodrugs [1]. Naturally occurring polysaccharides are the most commonly used carriers which are specifically hydrolyzed by the microflora of colonic region. Unfortunately, due to the hydrophilic nature of majority of natural polysaccharides, controlling the release of drug from these material possess a key challenge.

As, as discussed, no single system is found to be precise and accurate enough to deliver active moiety into the colonic region, recently, a novel concept of using the di-dependent drug delivery system has been proposed. In these systems,

Table 1. Recently developed CrDDS for achieving CoDDS.

Approach	Type of dosage form	Description	Drug candidate evaluated	Ref.
Time-dependent systems	Capsule	A modified pulsincap system for chronotherapeutic delivery of ibuprofen was developed. It consists of a hard gelatin capsule body (insoluble), filled with ibuprofen surface solid dispersions, which is further sealed with guar gum hydrogel plug. The outer surface of the capsule was coated with ethyl cellulose in order to overcome the drawbacks of gastric emptying and to achieve CoDDS. Natural polymers *viz*. Guar gum, Hupu gum and Xanthan gum were used to prepare surface solid dispersions of ibuprofen by using the solvent evaporation method. *In vitro* evaluation revealed that guar gum provides suitable lag time for drug release and hence was used as material for hydrogel plug formation. Further, it was also observed that among different natural polymers evaluated, the surface solid dispersions prepared using Hupu gum showed highest drug release for a period of 12 h with Higuchi type release kinetics.	Ibuprofen	[15]
pH and time-di-dependent systems	Tablets	A "delayed-onset controlled-release colon-targeted system" of theophylline was prepared for chronotherapy of nocturnal asthma. The system comprised of a core tablet matrixed using HPMC (release retardant) and coated with a mixture of Eudragit S100:ethyl cellulose polymers (delayed release agents). *In vitro* evaluation revealed that the developed system prevents release of drug for 5 h and no release of drug was observed in the upper region of GIT. *In vivo* evaluations (both pharmacokinetic and roentgenography studies) in rabbits showed that the developed system remained intact until it reaches to the colonic region and the release of drug began only after a delay of 5 h.	Theophylline	[7]
	Multiparticulate systems (pellets)	A pulsatile drug delivery system consisting of theophylline loaded fast release pellets has been prepared which were further coated with pH (Eudragit S100) and time (Eudragit RL100) dependent polymers. *In vitro* evaluation in simulated gastric, intestinal, and colonic fluid revealed that the lag time for drug release depends on the amount of Eudragit RL100 in polymer mixture and the % level of coating. *In vivo* evaluation in New Zealand rabbits revealed that the developed system delivered a substantial lag time of 5 h.	Theophylline	[16]
Microbially and/or enzymatically driven drug delivery systems	Tablets	A compression coated CoDDS of theophylline was prepared for the treatment of nocturnal asthma. The core tablets of theophylline was compression coated with granulated chitosan containing 10% PVP K30. *In vitro* evaluation revealed that the coat applied can withstand the diverse conditions in the GIT. *In vivo* studies in beagle dogs depicts higher mean plasma concentration of the developed system compared to that of marketed products, revealing the potential of the developed system for chronotherapy of nocturnal asthma.	Theophylline	[17]
	Prodrug	Dextran-flufenamic acid (Dex-FFA) ester prodrug was prepared for the chronotherapy of arthritis. It was observed that the prodrug remains stable at pH 1.2 and 6.8. *In vitro* evaluation revealed that Dex-FFA with degree of substitution of 13 or 20 released flufenamic acid up to 70 or 20 one percentage of the dose, respectively, in the presence of 10% cecal contents (24 h-incubation). *In vivo* evaluation in rats revealed that Dex-FFA (degree of substitution thirteen, 20 mg equivalent of flufenamic acid/kg) delayed the release of flufenamic acid about 6 h compared to that of free flufenamic acid. Thus from the above results it can be concluded that the developed prodrug could be a useful tool for achieving a chronotherapeutic treatment of arthritis.	Flufenamic acid	[18]
pH and microflora-activated di-dependent systems	Microspheres	Pectin-based CoDDS loaded with aceclofenac was prepared for the treatment of rheumatoid arthritis. The microspheres were prepared by emulsion dehydration method which were further covered with Eudragit S-100 using solvent evaporation technique. *In vitro* drug evaluation revealed that the uncoated microspheres demonstrated 5 – 40% of drug release in the upper region of GIT. Further, the release of drug increases in the presence of rat cecal contents with maximum release at the 8^{th} h. *In vivo* evaluation revealed that the developed system can maintain the therapeutic concentration of drug for 24 h with significant anti-inflammatory effect.	Aceclofenac	[19]
	Microspheres	Guar gum-based CoDDS system loaded with theophylline was prepared for the treatment of nocturnal asthma. The microspheres were prepared by the emulsification technique which were further coated with a mixture of Eudragit S100 and Eudragit L100 (1:1) through solvent evaporation method (oil-in-oil). *In vitro* evaluation revealed that the coated system does not allow any early release of drug in upper region of GIT revealing the potential of the developed systems for colon targeting.	Theophylline	[20]

Table 1. Recently developed CrDDS for achieving CoDDS (continued).

Approach	Type of dosage form	Description	Drug candidate evaluated	Ref.
	Microspheres	A CoDDS consisting of chitosan microspheres loaded with diltiazem hydrochloride has been prepared which were further coated with Eudragit S100. Different variables *viz*. drug to polymer ratio, stirring speed and concentration of emulsifier were optimized with respect to the particle size and encapsulation parameters (encapsulation efficiency, % drug loading and % yield). *In vitro* drug release studies revealed that uncoated chitosan microspheres exhibited burst release (in the first hour) in simulated gastric fluid, whereas coated microspheres showed controlled release pattern with Higuchi type of release kinetics.	Diltiazem hydrochloride	[21]
Pressure controlled system	Capsule	A pressure-controlled CoDDS comprising theophylline dispersion in a lipid matrix (Gelucire 33/01 and surfactants (1 – 10%)) was developed as a CrDDS. The drug containing lipid dispersion was filled in hard gelatin capsule which was further coated with Eudragit S100. The *in vitro* evaluation of the prepared PCDC revealed that the coated capsules can withstand both acidic as well as alkaline conditions of stomach (pH 1.2) and small intestine (pH 6.8), respectively. *In vivo* evaluation in Beagle dogs revealed that the prepared system provides extended lag time with respect to the marketed formulation followed by an abrupt rise in drug plasma levels. Thus, it can be concluded that the developed system could be a useful tool for the chronotherapeutic treatment of nocturnal asthma.	Theophylline	[22]

two factors, that is, pH and time, and pH and microflora of the colon control the release of drug [1].

3.4 Pressure-controlled-based systems

Drug targeting to the colonic region using GI pressure has been proposed as one of the tool for achieving CoDDS. Contractions of muscular intestinal walls (for churning and propulsion of luminal contents) lead to establishment of this luminal pressure, which diverges throughout the GIT with respect to its strength and extent. The highest pressure is being generated by the colonic luminal region as a result of haustral contractions and viscous milieu [12]. There were many methods proposed for the development of these systems *viz*. by dipping method, by applying ethylcellulose coat on inner surface of gelatin capsule or by forming a coat on capsule-structured portions of suppository base at reduced temperature [13]. The application of GI pressure offers a state-of-the-art strategy for targeting drugs to various sites in GIT. However, there are inadequate data pertaining to the intestinal pressures in different parts of GIT, and these may either have an inter- and intra-subject variability as in the case of pH and transit time. Hence, it is a matter of time which will ascertain whether the pressure-controlled based systems will signify itself as a feasible means for CoDDS [12].

Oral delayed release systems envisioned for achieving chronotherapy for the treatment of diseases *viz*. nocturnal asthma, angina pectoris, inflammation, rheumatoid arthritis, hypertension or cardiac arrhythmias, when provided with an outer enteric coating (in order to overcome erratic gastric evacuation time), offer a remarkable potential for delivering drug to the colonic region. As the onset of these diseases is early in the morning or at night time, it is obligatory to have a delayed release system which can offer a nocturnal release of drug, which in turn offers a substantial respite to the patient during resting [2,7]. Taking into consideration the advantages and limitations of various approaches, using a di-dependent approach, one can ensure that there is delayed release of the drug. Further, the pharmacokinetic studies will provide proof of concept that the drug is absorbed and therapeutic concentrations are achieved, which will give an idea that the drug binds to the receptor and produces the effect. **Table 1** reveals several examples related to various strategies for achieving chronotherapy of different disease conditions using the CoDDS approach. Additionally, a detailed schematic diagram of some of the platform technologies developed and their functioning is portrayed in (**Figure 2**) [14].

4. Expert opinion

Since past 20 years, the pharmaceutical literatures have been deluged with several investigational methodologies for achieving CrDDS through oral route. Regardless of such a colossal volume of investigation being carried out by pharmaceutical researchers for developing CrDDS, very few of them

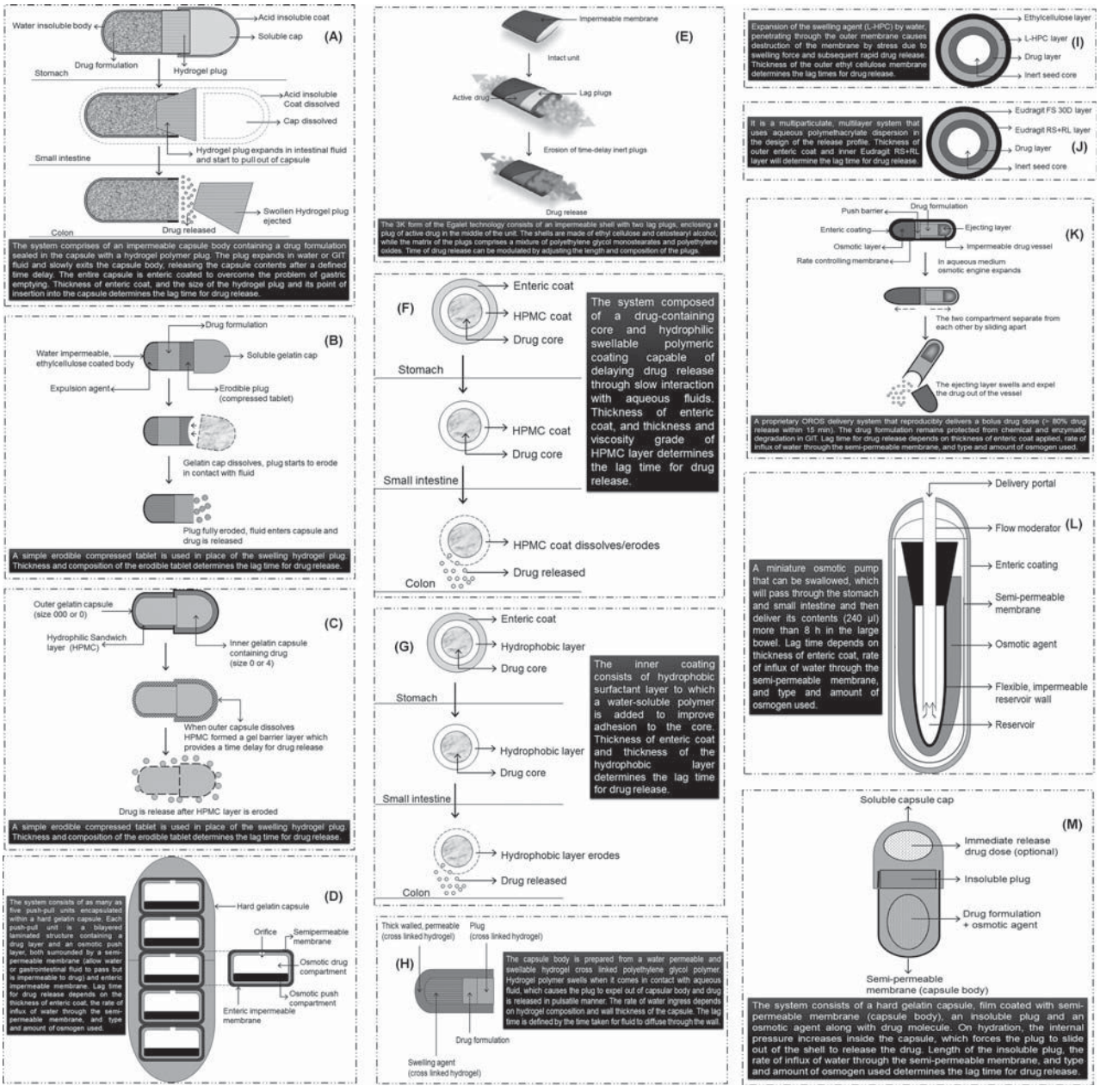

Figure 2. Schematic diagram of **(A)** Pulsincap®, **(B)** Erodible plug time-delayed capsule, **(C)** Hydrophilic sandwich capsule, **(D)** OROS®-CT, **(E)** Egalet®, **(F)** Chronotopic® system, **(G)** Time Clock® system, **(H)** Pulsatile hydrogel capsule, **(I)** Time controlled explosion system, **(J)** Eudracol®, **(K)** Chronset™, **(L)** Osmet™, **(M)** PORT® system.
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prospered in reaching the doors of clinical phase (the details of which have been discussed elsewhere) [3,5,14]. This may be attributed to some of the facts such as lack of industrial applicability, scale-up difficulties, limited availability of resources (materials), and overall cost of dosage forms development. This points out that much attention needs to be focused on these aspects. Further, development of more refined technologies for the large-scale implementation of these systems is the need of an hour.

An enormous variety of oral CrDDS reported in the literature depicts the interest of formulation scientist in this specific arena of pharmaceutics. As circadian rhythms have been described extensively for numerous diseases, a continual rise in the demand for the development of CrDDS has been forecasted. This leads to the increase in the attempts being made by the scientific community for the development of drug delivery system according to patient requirements, both with respect to compliance and therapeutic efficacy. CrDDS is

such a delivery system that makes the drug available at right place, at precise time and in accurate quantity. Moreover, as the understanding regarding the number of diseases following biological rhythm of the body increases, the research in the field of CrDDS will be strengthened to a greater extent, leading to a better treatment and patient compliance.

The regulatory aspects should be taken in consideration right from the early stage of CrDDS development. Implementation of Quality by Design element in product development and increment in the availability of advanced technology for formulation development and processability will help in overcoming the hurdles associated with the development of CrDDS.

Declaration of interest

The author state no conflict of interest and has received no payment in preparation of this manuscript.

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