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Status of Oral Chronopharmaceuticals Drug Delivery System, Latest Technologies, and Hurdles

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Abstract
Conventional drug delivery systems are designed based on homeostatic theory, which assumes that all biological functions are in a constant state over time. In later logical discoveries, it was accepted that the idea of body homeostatic balance is never again evident. Consequently, researchers consider employing the concept of circadian rhyme in developing a new approach for drug delivery (chronotherapeutics) that will bring about new treatment modalities (Chronotherapy). Until this point, no drug delivery system can fulfill all the prerequisites of chronotherapeutics along these lines, However, further studies are still needed to diversify its applications to chemoprevention of diseases, potentiate maker guided chronotheranostics and vaccination
Aim: *The current study reviewed the technologies and hurdles in chronotherapeutics for oral drug delivery.*
Methodology: *The investigation evaluated the articles published by different journals over the past 20years, as well as the various reports and textbooks were overviewed accordingly.*
Conclusion: *The search for novel drug delivery systems that can enhance the quality of life through individualized therapy is of high excess. Therefore, extensive research in the field of chronotherapy is a world necessity and the need to agglomerate all available innovative drug delivery system that time to time can be improved and communicated to the regulatory agency to pathway for clinical trials could provide synergy among researchers and policy formulator*
Keywords: *homeostatic balance, circadian rhythm, chronotherapy, chronopharmaceuticals.*

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I. INTRODUCTION

The expression "Drug Delivery" covers an exceptionally broad scope of techniques used to convey therapeutic agents into the human body. Drugs administered to cure certain diseases.(1)Among the assorted routes of drug delivery, the oral route is most popular. However, conventional dosage form shows some limitations of poor patient compliance, multiple dosing, and fluctuation of the therapeutic vary range that would be overcome by modifying these drug delivery systems to sustainable and controlled drug delivery systems.(2)Previously, conventional drug delivery system designed on the bases of homeostatic theory, which assumes that all biological functions are in a constant state over time. (3)It was later understood that, diseases manifestation and likewise the blood plasma concentration shows circadian variations over time. Therefore, researchers realized the need for employing the concept of circadian rhyme in developing a novel approach for drug delivery (chronotherapeutics) that will bring about new treatment modalities (Chronotherapy). (4)However, further studies are still needed to diversify its applications to Chronoprevention of diseases, potentiate maker guided chronotheranostics and vaccination.(5)

CHRONOTHERAPEUTICAL DRUG DOSAGE FORMS

Various types of machinery to develop time-controlled paroral drug delivery systems have been extensively studied in recent decades.

1. A tablet in capsule device: A novel drug delivery system based on a “tablet in capsule device” produces three pulses of drug release (65). Three steps, are involved in designation which are; coating of hard gelatin capsule shell (#0) with Eudragit S100, preparation of first-pulse granules and second-pulse matrix tablets, encapsulating all pulses in coated hard gelatin capsule result in “tablet in capsule system” (TICS). (6)The device comprises a water-soluble cap, an impermeable capsule body, and two multi-layered tablets, encapsulated and sealed with a water-soluble cap.Lactose is usedin filling the capsule that modulate barrier layer. The rainproof capsule includes ethylcellulose (EC), while the fast release layer comprises cross povidone

and lactose. HPMC, sodium alginate, carbopol and carboxymethylcellulose were evaluated for use as the modulating the barrier, with alginate and HPMC displaying the best results. (65)

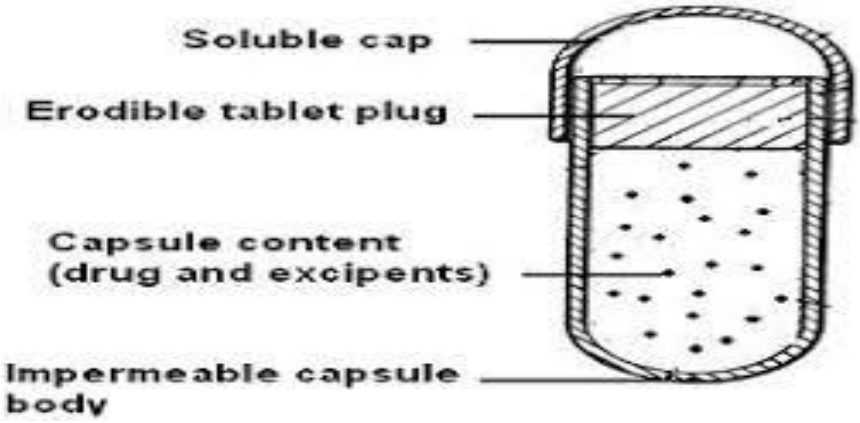

Figure 1: ***A tablet in capsule device***

2. Core-in-cup tablet technology: Efentakis et al. developed a drug delivery system based on core-in-cup technology. (7)The core-in-cup design where the medication containing dynamic center encompassed by an impermeable cup made of hydrophobic material that goes about as a hindrance and permits sedate discharge from a solitary uncovered surface. (8) An active sustained-release plate molded network center containing the dynamic fixing is pressure covered on the base just as an outline to shape a cup around the center. (9)The top layer contained a dissolvable polymer, for example, sodium carboxymethylcellulose, sodium alginate, and PEO. Upon contact with disintegration media, the top spread ingests liquid and swells making a hindrance between the disintegration media and the inward medication-containing center. The time taken for the swollen layer to dissolve decides the slack time. Once the top layer has disintegrated, drug release occurs.(7)

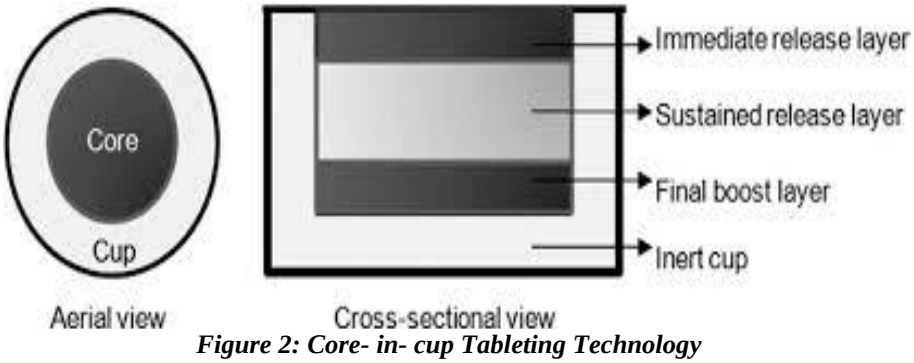

Figure 2: Core- in- cup Tableting Technology

3. Coated drug-core tablet matrix: Lee et al. developed a hydroxypropylmethylcellulose tablet matrix comprising an inner drug core and an outer drug coating. The inner drug core was prepared using direct compression of the drug and polymer. The core was then coated with a drug containing aqueous-based polymeric Eudragit® RS30D dispersion. The tablet was able to provide a biphasic release profile with an initial zero-order release followed by a second phase of drug release.(10)

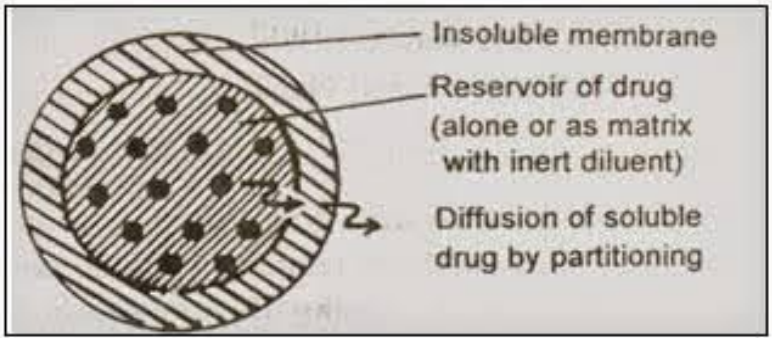

Figure 3: coated drug-core tablet matrix

4. A bi-layered tablet: A study by Karavas et al. involved the development of a bi-layered tablet that gave a slack stage followed by medicate discharge. The bi-layered tablet utilizes felodipine and PVP as a medication center and an HPMC/PVP mix encompassing the center. The mix of HPMC and PVP served to improve the mucoadhesive properties of the tablet. Upon introduction to disintegration media, the external layer broke down presenting the center to the gastric substance and in this way permitting drug discharge. Slack time was subject to the expanding/disintegration of the HPMC/PVP network. Fluctuating the proportion of the HPMC to PVP likewise influenced the slack time.(11)A quick/ slow-release system gives an underlying eruption of medication discharge followed by a consistent rate (in a perfect world) of discharge over a characterized period. (12)

CHRONOTHERAPEUTIC DRUG DELIVERY TECHNOLOGY

1. CONTIN®: Technology (Purdue Pharma, Pickering, Ontario, Canada), involving dynamic medicament and hydrophilic polymer followed by particular hydration with a polar solvent and obsession through a higher alcohol liquor. A molecular coordination complex-shaped betweena cellulose polymer and a subbed alcoholic liquor, the product is a complex that could be used for controlled drug release. The complex product has a uniform porosity that might change. (13) This technology is used in the long-acting bronchodilator Uniphyl® (Theophylline).

2. Chronotopic®: Chronotopic® is a technology delivery system that contains a functioning medication loaded center covered with hydroxyl propyl methylcellulose (HPMC) polymer (a swellable hydrophilic). The HPMC covering experiences polished rubbery progress when in contact with watery liquids. The dynamic medication is then discharged over the gel-layer by either dissemination or disintegration. The beginning of medication discharge and slack time are constrained by the thickness and consistency evaluation of the HPMC coat utilized during the formulation. (14)Moreover, the utilization of a gastro-resistant film onto the polymer-coated center of the system beats the fluctuation in gastric transit time and takes into consideration colon explicit drug discharge (15). The film permits the system to remain unchanged until arriving at the digestive tract where it in the end disintegrates and uncovered the HPMC layer to the intestinal liquid in this way permitting the system to be pH-responsive. The tablet matrix is set up right off the bat, grinding the medication with a scope of excipients, which is compared. A blend of HPMC and PEG arrangements is then spray coated onto the core and permitted to dry. From that point, a coating of Eudragit® is applied onto the external surface of the tablet lattice. (16)

3. Pulsincaps®: Pulsincaps® technology (Catalent Pharma Solutions, Somerset, New Jersey, USA) consists of a water-insoluble drug-loaded capsule. (17)The capsule is sealed with a swellable hydrogel plug comprising polymers such as the poly (methacrylates), hydroxypropylmethylcellulose, polyvinyl alcohol, polyvinyl acetate, polyethylene oxide, saturated polyglycolic d-glycerides, glycerylmonooleate or pectin(18). The capsule is then coated with an enteric layer that dissolves after arriving at the small digestive tract where the polymeric attachment starts to grow to bring about a slack stage preceding medication discharge. (14)The attachment at that point grows and is pushed outward to influence medicate release. The variety in measurements of the fitting and its point/profundity of inclusion into the case decides the slack time created preceding drug release.(19) Pulsincaps® technology has the versatility of allowing one or more mini-tablets, coated tablets, solutions, or multiple particulates to be stacked inside the container for the conveyance of medications in a chronotherapeutic way.(17)

4. CEFORM®: CEFORM® technology (Biovail Corporation, Mississauga, Ontario, Canada) involves the production of microspheres that are uniform in shape and size. The diameter of microspheres lies between 150–180 μm with a high drug-loading capacity that can be applicable in many drug delivery systems including capsules, suspensions, tablets, effervescent tablets and sachets.(20), (19), (21)the technology involves exposing biodegradable polymers or bioactive agents to a mixture of thermal gradients, mechanical forces, and flow-rates during processing. CEFORM® technology employed in the development of chronopharmaceutical Cardizem® LA which contains Diltiazem as an active pharmaceutical ingredient, the drug prescribes to be taken once daily(20)

5. TIMERx®: TIMERx® is a multipurpose hydrogel base control-release technology developed by Penwest Pharmaceuticals (Danbury, Connecticut, USA). It can be designed to convey different release kinetic (like zero-order, CR, pulsatile release et al.) simply be manipulation of molecular interaction. (22) TIMERx® delivers drug to gastrointestinal tract at programmed rate that coincide with circadian rhythm. (14)As the tablet moves along the gastrointestinal tract through the pylorus into the duodenum, the outer swellable coating undergoes erosion. After approximately 3.5hours, erosion of the coating is complete, exposing the drug-loaded core to the intestinal environment where drug is released. The inclusion of a surfactant into the drug-loaded core confers immediate drug release capabilities.(22)

6. OROS®*:* An OROS® osmotic pump patented by the DURECTCorporation (Cupertino, California, USA) that makes use of an osmotic mechanism to deliverthe predetermined, controlled drug. The technology

involves three compartments namely, drug-loaded compartment, a push compartment, and semi-permeable membrane. The drug compartment comprised drug and polyethylene oxide (PEO) grated with a solution of poly vinyl pyrolidine (PVP). The push compartment comprises PEO, hydroxypropylmethylcellulose (HPMC), sodium chloride and black ferric oxide granulated with HPMC. Both the drug compartment and the push compartment were later compressed into a bi-layered core. The entire core, or otherwise only the drug compartment,is sub-coated with a 95% hydroxyethylcellulose (HEC) and 5% poly(ethylene glycol) (PEG) solution that aids a drug-free interval of 2–5 hours. From there on, the sub-coated medication core is covered with a semi-permeable film including 60% cellulose acetic acid derivation, 35% hydroxypropyl cellulose (HPC) and 5% PEG. The hole is then penetrated into the external and inward core to connect the medication layer with the outside of the drug delivery system. Finally, the osmotic pump is dried for 96 hours to evacuate leftover dissolvable and a further 2 hours to take out any abundance moisture, drug release occurs due to the influx of fluid across the semi-permeable membrane into the push compartment. (23)

1. **CODAS®:** CODAS® Elan Corporation (Florida, USA) mass-produced multi particulate drug delivery system that delivers drugs in a controlled manner, bringing about a coincided release of circadian rhythms.(24)The technology consists of a drug-loaded core and a multilayered membrane surrounding the core containing water-soluble and water-insoluble polymers. If the product is exposed to water, the hydrophilic polymers dissolve and the drug diffuses through the pores present in the coating, while hydrophobic polymers act as a barrier and maintain the release of the drug (5).Verelan® PM (verapamil) was designed to be administered at bedtime, aiming to release the drug within 4–5 hours after ingestion to overcome the surge in morning blood pressure. (25)

1. **Diffucaps®:** Eurand Pharmaceuticals (Pennsylvania, USA) manufactured multiple particulate-based drug formulations capable of delivering the drug in coincidence with circadian rhythms. The medication layered onto a nonpartisan center that may include an inert particle such as sugar spheres, crystals or granules. The latent coating utilized to tie the medication particles to the inner core then the drug particles suspend in a 5–10% solution of a binder. Later the drug-loaded core is coated with a plasticized enteric-coated and from that point covered with a blend of water-insoluble and enteric polymers.(26)

1. **Egalet®:** Egalet® (Egalet a/s, Copenhagen, Denmark) technology uses erosion techniques.The technology encompasses an impermeable shell with two lag plugs enclosing a drug-loaded core. (27)The lag-phase is reliant onthe composition as well as the length of the plugs. The impermeable shell comprises ethylcellulose and cetostearyl alcohol, whereas the plug consists of PEG and PEO.(27)The matrix is intended to disintegrate upon contact with the gastrointestinal liquid, however gastric liquid ought not to diffuse in the framework until the purpose of medication discharge. This decreases hydrolysis and luminal enzymatic action. In a perfect world, parity should exist between disintegration and dissemination with the end goal that the surface territory presented to the disintegration media is consistent guaranteeing. (27)The plan likewise takes into consideration that more than one medication can be consolidated in a solitary drug delivery system. Furthermore, by changing the outer fitting, distinctive discharge profiles might be acquired.

HURDLES IN CHRONOPHARMACEUTICAL

Current hurdles in chronopharmaceutical drug development are three, they includes:

1. **Rhythmic biomaterial and system design**: Biomaterial and system design: the first obstacle approaches the designation of chronotherapeutics is the lack of ideal rhythmic biomaterials that are biocompatible, biodegradable and reversible that respond to specific biomarkers in ultra-fast rhythmic patterns in a biological system.(28)Efforts were made to overcome this hindrance for decades, but the latest technology introduced the designation of dosage forms that use chemical oscillators like PH oscillators as well as stimuli-sensitive polymers. Some studies reveal that chronotherapeutical administration of GHRH in the treatment of hypopituitary dwarfism is more effective.(5) In recent trends some of these biomarkers have been designed, they respond to external stimuli such as PH, temperature, light, electric field and ionic strength et al. this response resulted from changes in solubility, shape, surface characteristics, and formation of complex molecular self-assembly or sol - to -gel transition.(29)In the latest advancements, knowledge of microfabrication was employed to develop microchips based drug delivery systems. Robotic microchips forecast to be designed by co-entrapment of bioactive agents and biosensors into computer-controlled microchips and adoption nano microchips may optimize chronotherapy and stand as the lasting solution to this hurdle.(30)

1. **Rhythm engineering and modeling hurdles**:Coming-up with models that will be able to rationalize and predict biological rhythm stand as the second gigantic challenge in design chronopharmaceutical product.

(31)Besides the ability of the model to predict, physicochemical properties of these novel drug delivery systems analog with their biological responses, it also necessary to comprehend the transition of complex oscillatory behavior and to elucidate the condition under which they arise.

In an attempt to upper solution to this hurdle, several authors first demonstrate in-vivo experiment on the growth rate by solutions illustrated by numerical simulation using a delay partial differential equation (PDE), in

which they provide the necessity of taking the structures of 'cell division circle' into account for chronotherapy modeling.(32)Moreover, the Rössler model, three non-linear differential equations systems were proposed for chronotherapy modeling. Despite limited applications of the aforementioned models, they gave insight in modeling the direction of the rhythmic process.

(33)Concerning the effort attributes to elucidate the rhythmic processes in biological systems, the future challenge in this area includes engineering rhythmic responses in the biological system from the molecular response (rhythmic translation of mRNA to protein) to cellular, organ, tissue and, whole organ system. The protein synthesis process comprises transcription (transfer of genetic information from DNA to mRNA), translation (genetic codes of mRNA to protein) and their subsequent processing steps. To realize this goal a new mathematical, statistical and numerical analytical method is required to put in place. Though several unflinching efforts have been made to make it possible, amongst a Cell Circle Automation (CCA) model has been proposed, the model described transition through sequential phases of the cell cycle for chemotherapy. Besides the regulation of circadian, the Cell Circle Automation (CCA) can further be employed to investigate the role of different temporal patterns (a segment of signals that recur frequently) of drug administration.

. control infusion pump, it's logical to approximate the time dependent targeted drug tissue concentration ——(1) (34)$C(t) = S(t) * R(t)$ _____(1)

where 't' stand for a time, S, for drug delivery function and R for drug delivery rate. For extremely short drug delivery time t (say, $t = \varepsilon$ second) in physiologically relevant media, the Dirac impulse "function" ($\delta(t)$) could allow approximating S(t) before its use for C(t) estimation according to equation 2.

$C\varepsilon(t) = S(t) * \delta(t) = S(t)$_____(2) (33)

However, due to wide-ranging of Importation and complex processes to be elucidated from molecular up to the system level, a lot of researches need to be conducted for future prospective.. (33)

1. **Regulatory hurdles:** Regulatory hurdles include pre and post-approval considerations. In the pre-approval phase, it is believed to have partial relation with first and second hurdles because it is somehow difficult to evidence chronotherapeutic advantage of **controlled-release** (CR) or modified release (MR) formulations in clinically. Considering the control release nature of MR/CR formulations, they require specific considerations and regulation before conventional delivery formulations. (33)This is why pharmaceutical innovators use to educate the Federal Agency on the importance of putting these products under control. The US Code of Federal Regulations under 21 CFR 320.25 provides the bioavailability requirements for CR products.(35)The regulations of application with already approved IR formulation of the same drug ingredient or active moiety were covered under 21 CFR 314.54(36)Post-approval phase: Possibility of abusing these new drug products is the major obstacle encountered by manufacturers and regulators, fortunately, some solutions to counteract this problem were set aside. Both the regulator and manufacturers should consider all possible factors that could lead to drug "abuse-ready" so that proper risk management policies for implementation of post-approval,(37)as harnessed by FDA under it is initiated Programs called (MAP), which happen to be a strategy to allow approval of a drug to move on while making use ofsome restrictions.(38)

II. CONCLUSION

The search for novel drug delivery systems that can enhance the quality of life through individualized therapy is of high excess. Therefore, extensive research in the field of chronotherapy is a world necessity and the need to agglomerate all available innovative drug delivery systems that time to time can be improved and communicated to a regulatory agency to pave-way for clinical trials could provide synergy among researchers and policy formulator. However, in drug delivery in the biology of living species, time is a fundamental aspect that was long overlooked in drug design and delivery hence the need to conceptualize chronotherapy.

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