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CHRONOTHERAPEUTIC SYSTEMS: NOVEL SYSTEMS OF DRUG DELIVERY

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ABSTRACT: Chronotherapeutic systems are meant for the treatment of most of the diseases that occurred and found till date, which are proved to be in association with the biological/circadian rhythms of our body with respect to disease symptoms and their severity. Such diseases use this treatment as it involves *in-vivo* drug availability with distinctive release patterns so as to match the rhythms of disease and achieve optimized therapeutic outcomes with minimized side effects. The specific time at which patients take their medications is taken into consideration as it is the main reason for the treatment success. There is a synchronization of pharmacodynamics and pharmacologic activity of drugs with that of the biological clock, so variations in disease state and plasma drug concentration are taken into consideration during the development of this drug delivery system. Various novel technologies are employed in developing Chronotherapeutic devices and dosage forms, some are available in the market already, and many others are yet to arrive. The main objective of this review is to explore the current status of Chronotherapeutic technologies and also to provide a view on various variations in dosage forms that contribute for chronotherapy.

INTRODUCTION: The goal of drug research has always been involving the development of a formulation that is related only to a particular pathological condition. Of all the routes of drug delivery oral route is considered as the most favoured and user-friendly means as it has the highest degree of patient compliance and also provides reproducible and effective in-vivo plasma concentration [1]. Oral drug delivery systems only focuses on drug output with minimization of drug concentration peaks in the body. Oral drug delivery can be classified into three categories:

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A. Immediate release dosage forms for the immediate release of drug for rapid absorption.

B. Sustained release dosage forms designed on the basis of spansule technology for extended absorption.

C. Controlled and targeted drug delivery system- which offers more pharmaceutical and clinical superiority over conventional immediate release pharmaceutical products.

Another category *i.e.,* modified release dosage forms, are developed that have control over the release of drug in a predetermined fashion. These dosage forms provide numerous advantages such as reduced dosage and frequency, least side effects, and better-improved patient compliance, but these also still show stable plasma concentrations [2]. Certain disease conditions require drug release after

a lag time *i.e.;* they need periodical variations in plasma concentrations. It is also reported that some medications may work better if their administration is made to coordinate with day-night patterns and biological rhythms. These all drawbacks of various dosage forms and varied requirements of disease condition led to the development of "Chronotherapeutic Drug Delivery Systems," which include learning about chrono-therapeutics, chronopharamceutics and chrono-biology [3, 4]. Chronotherapeutics is defined as a treatment that employs a distinctive *in-vivo* drug release pattern of drug that's timed to match rhythms of disease symptoms so as get optimized therapeutic outcomes and minimized side effects5, 6. Its main goal involves the management or reversal of acute or chronic disease conditions existing and delivery of drugs to the right site in the body, at the right time, in an optimal dose.

Chronotherapeutic drug delivery systems show specific transient release of drug in a bust at circadian timings that are correlated with the pathological disorder after a predetermined off-release period. The specific time at which patients take their medications is taken into consideration as it is the main reason for treatment success. There is the synchronization of pharmacodynamics and pharmacologic activity of drugs with the biological clock.

Thus these systems provide time-specific and site-specific drug delivery system in order to achieve the maximum effect of drug with increased patient compliance and hence are gaining a lot of interest [7-11]. Chronopharmaceutics is framed mainly using two words: "Chronobiology" and "Pharmaceutics". Chronobiology is defined as the study of biological rhythms and their respective mechanisms [12, 13].

Biological Rhythms: They are of three types

1. Circadian Rhythms: The term "circadian" is derived from Latin words "circa" which means 'about' and "dies" that means 'day'. It is defined as an oscillation in our body that is completed in 24 h.

2. Ultradian Rhythms: It is defined as an oscillation in our body that is completed in <24 h.

3. Infradian Rhythms: It is defined as the oscillation that is completed in more than 24 h [12, 13].

Circadian Time Structure: The circadian time structure in humans is used to interpret the peak time of 24 h. **Fig. 1** shows the peak time for a selected number of human circadian rhythms that are related to the synchronized routine of most human being's parameters through the figure; the information clearly illustrates that physiology and biochemistry of every human being are not constant, vary with time [14].

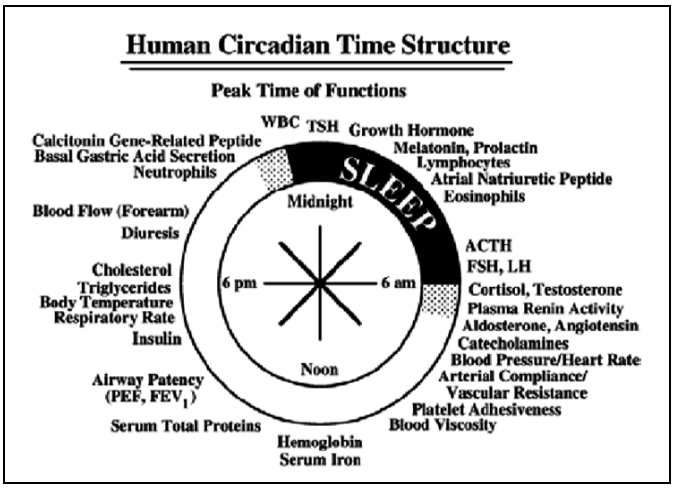

FIG. 1: CIRCADIAN TIME STRUCTURE

Mechanism of Biological Timekeeping: The circadian rhythm of our body is under the control of suprachiasmatic nuclei situated in the hypothalamus and pineal gland.

The rhythmic activity of clock genes (per 1, per 2, and per 3) and the nocturnal secretion of melatonin from pineal gland are mainly responsible for the central timekeeping mechanism.

This so-called master clock controls the duration and phase of the multitude of circadian clocks which are present in the cells, tissues, and organ system [15, 16].

Biological timekeeping is mainly an adaptation that is being evolved with time due to the cyclic phenomenonal changes that are being displayed in the environment.

Hence they ensure the peak functioning of the all humans during the day, and restoration and repair during the night. It is also in helpful from all these years by making adjustments with different seasons of the year. These variations in a day are shown in **Fig. 2** [17-20].

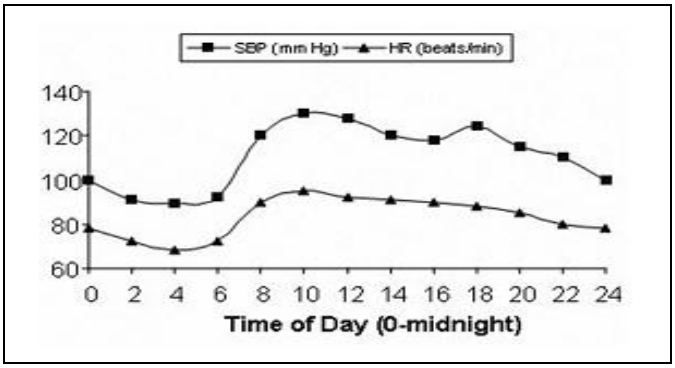

FIG. 2: CIRCADIAN VARIATION IN SYSTOLIC BLOOD PRESSURE AND HEART RATE

Biological rhythms at the cellular and subcellular levels can give rise to significant dosing-time differences in the pharmacodynamics of medications unrelated to their pharmacokinetics [21]. This phenomenon is termed 'chronesthesy'.

Circadian Rhythms Association with Disease:

1. Bronchial Asthma: Airway resistance, bronco-constriction, and exacerbation symptoms increase progressively at night in asthmatic patients. The risk of an asthma attack is greater during nighttime sleep than during daytime activity [22-24].

2. Pain: The pain threshold doesn't follow the same regular pattern in all tissues. Circadian rhythms with respect to acute pain are recorded in cases such as dental surgery, with a high morning peak during the first postoperative day [25].

3. Arthritis: Patients with osteoarthritis show less pain in the morning and more at night, but for those with rheumatoid arthritis, they have pain in peaks at the morning and decreases throughout the day [26].

4. Cardiovascular Diseases: Several cardiovascular functions like BP, heart rate, stroke volume, cardiac output, blood flow vary with circadian rhythms. Various studies show an increase in the occurrence of early-morning myocardial infarction, sudden cardiac death, stroke, and episodes of ischemia, marked rise in blood pressure ('the morning surge') [27].

5. Hypercholesterolemia: A circadian rhythm occurs during hepatic cholesterol synthesis, which is generally higher during the night, but in many individuals, it is opposite; therefore, it is synthesized during the night as well as during the day, but the maximum production occurs early in the morning [28].

6. Diabetes: Studies show clear circadian variation occurs in the blood glucose levels which are low in the morning and high at evening and midnight, while insulin levels are lower in the afternoon and night [29].

7. Epileptic Seizure: The brain area which contains the highest concentration of noradrenergic nerve terminals and adrenergic nerve terminals and noradrenaline (NA) have a circadian rhythm [30].

8. Cerebrovascular Accidents: The cerebro-vascular accidents mostly occur in the first hours of the morning between 10 am and 12 noon, and declines steadily during the evening and midnight [31].

9. Myocardial Infarction: The onset of myocardial infarction is more frequent in the morning, with almost 34% of events occurring between 6 am and noon because of the release of catecholamines, cortisol, increase in the platelet aggregation, and vascular tone [32].

10. Peptic Ulcer Disease: Patients with peptic ulcer disease often experience the greatest degree of pain near the time that they go to bed is because the stomach acid secretion and perforation of gastric and duodenal ulcers are more at night rather than in day [33].

11. Parkinson's Disease: The existence of circadian rhythm in this disease is not evaluated. Though clinical data shows daily fluctuations of motor activity patterns, the effect of the phase of the disease and their subsequent roles of drugs are difficult to estimate [34].

12. Allergic Rhinitis: There are two phases of allergic rhinitis, *i.e.*, early phase due to release of histamine, prostaglandins, cytokines, TNF-α, chemotactic factors that result in sneezing, nasal itch, rhinorrhea, and late phase, which is due to elaboration, adhesion, and infiltration of circulating leukocytes, T cells and eosinophils that results in nasal congestion, inflammation of the nasal, sinus and other tissue of the upper airway [35].

13. Sleep disorder: The time of sleep required by each person is usually constant, but still, there is a wide variation among individuals. Sleep consists of a circadian combination of the changes in

physiological, biochemical, and psychological processes [36].

Need for of Pulsatile/ Chronotherapeutic Drug Delivery Systems: The shift of usage from conventional sustained release technique to the modern pulsatile delivery system is due to the following reasons4:

1. First Pass Metabolism: Some drugs like beta-blockers, and salicylamide, undergo extensive first-pass metabolism and thus require fast drug input to saturate metabolizing enzymes for minimization of pre- systemic metabolism. Thus, a constant/sustained oral method of delivery would result in reduced oral bioavailability.

2. Biological Tolerance: Continuous release drug into plasma are often accompanied by a decrease in the pharmacotherapeutic effect of the drug, *e.g.*, biological tolerance of transdermal nitro-glycerine.

3. Local Therapeutic Need: local disorders such as inflammatory bowel disease require the delivery of compounds to the site of inflammation with no loss as it is absorbed into the small intestine and is highly desirable to achieve the therapeutic effect and to minimize side effects.

4. Drug Absorption Differences in Various Gastrointestinal Segments: In general, drug absorption is slow in the stomach, rapid in the small intestine, and sharply declining in the large intestine. Compensation for changing absorption characteristics in the gastrointestinal tract may be important for some drugs.

For example, it is rational for a delivery system to pump out the drug much faster when the system reaches the distal segment of the intestine to avoid the entombment of the drug in the faeces.

5. Gastric irritation or Drug Instability in Gastric Fluid: For compounds with gastric irritation or with chemical instability in gastric fluid, the use of a sustained-release preparation may exacerbate gastric irritation and chemical instability in gastric fluid.

Classification: Classified into following [37, 38]

a. Time Controlled Pulsatile Release:
i. Single Unit System:

1. Capsular system

2. Port system

3. Delivery by solubility modulation

4. Delivery by reservoir systems

ii. Multi-particulate System:

1. Pulsatile system based on rupturable coating (Time controlled expulsion system)

2. Sigmoidal release system

3. Low density floating multiparticulate pulsatile systems

b. Stimuli Induced:
i. Internal Stimuli Induced Pulsatile System:

1. Temperature-induced system

2. Chemical stimuli induced system

3. pH-sensitive drug delivery system

ii. External Stimuli Induced System:

1. Electrically stimulated Pulsatile system

2. Magnetically stimulated Pulsatile system

3. Ultrasonically stimulated Pulsatile system

Pulsicap System: It consists of a water-insoluble capsular body that has a filling of drug and a cross-linked hydrogel plug that swells upon contact with the dissolution medium or gastrointestinal fluids thereby pushing drug out of the capsules, which is clearly shown in **Fig. 3**.

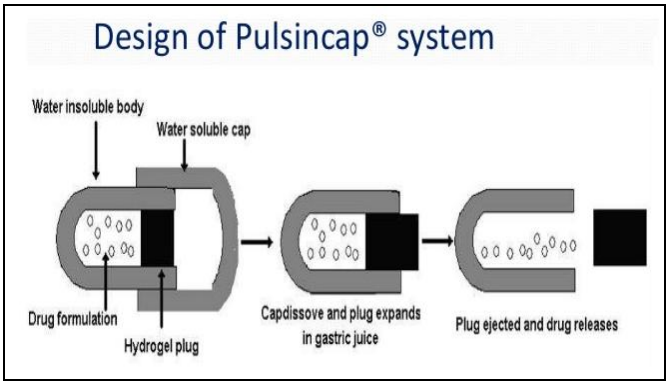

FIG. 3: PULSICAP SYSTEM

Port Systems: It consists of a gelatine capsule in a cellulose acetate semi-permeable membrane with an inside insoluble plug and osmotically active ingredient along with the drug. When this system

absorbs the gastric fluids, it leads to increased inner pressure that ejects the plug after a lag time. **Fig. 4** gives a picture of port systems.

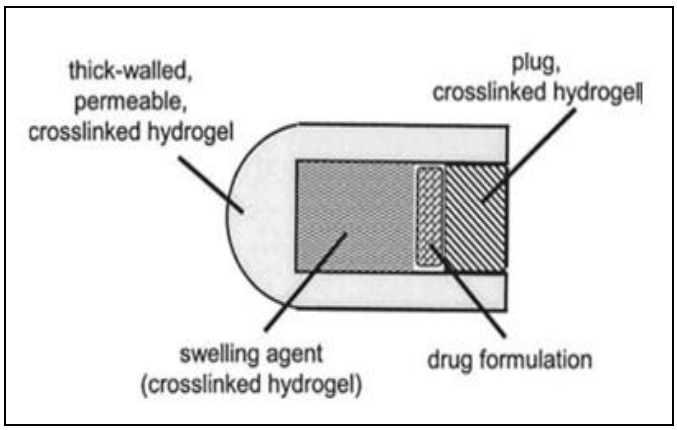

FIG. 4: PORT SYSTEMS

Delivery by Solubility Modulation: They contain a solubility modulator (solid organic acid, inorganic salt, or organic salt) for pulsatile delivery of a variety of drugs. The compositions contain a drug, a modulating agent, sodium chloride.

The amount of NaCl used is such that it is less than the amount that is needed to maintain saturation in a fluid that enters the osmotic device. The pulsed delivery is based on drug solubility.

Delivery by Reservoir System with Erodible/Soluble Barrier Coatings: Barrier layer is coated upon the reservoir device wherein the barrier erodes/dissolves after a specific lag time enabling the drug release rapidly from the reservoir as shown in **Fig. 5**.

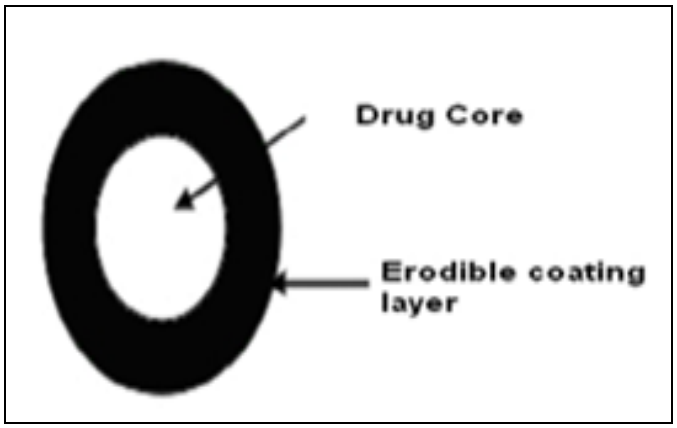

FIG. 5: SYSTEMS WITH ERODIBLE COATINGS

Multiparticulate System: Drug release depends on the type of coating, pH-dependent coating, insoluble coating, which influence the solubility changes in G.I. tract in all physiological conditions and thereby facilitating slow erosion.

Time Controlled Explosion System: These systems employ the incorporation of Super-disintegrants as swelling agents that facilitate timed burst release upon ingress of water.

The drug is coated upon non-peril seeds initially, followed by a swellable layer and an insoluble top layer coating. This is shown in **Fig. 6**.

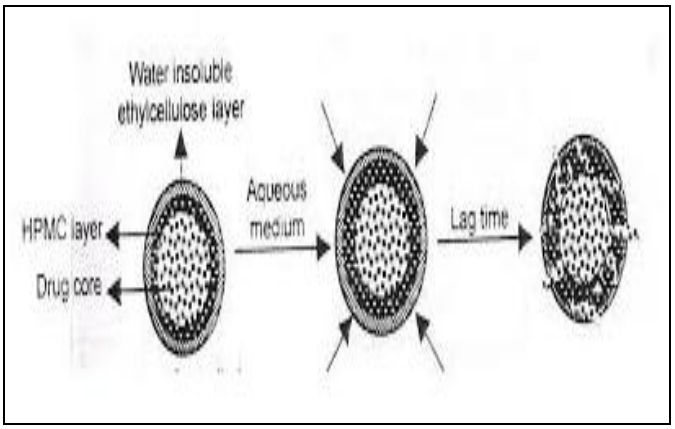

FIG. 6: TES SYSTEM

Sigmoidal Release Systems: It is made up of pellets that comprise different acids such as succinic acid, acetic acid, glutamic acid, malic acid, citric acid that are coated with ammonia methacrylate copolymer.

Water influx turns the drug core into an acidic solution that increases the hydrated polymer film permeation.

Low Density Floating Systems: For the drugs which have an absorption window in the stomach, low density floating micro particle pulsatile dosage forms are helpful by retaining the drug in the stomach for a longer period without influencing by the pH fluctuations and gastric emptying, as shown in **Fig. 7**.

Thermoresponsive Pulsatile Release: Hydrogels at their respective transient temperatures undergo reversible volume changes with response to change in temperature.

Among the various polymers, N-isopropyl acrylamide is most extensively used. This is shown in **Fig. 8**.

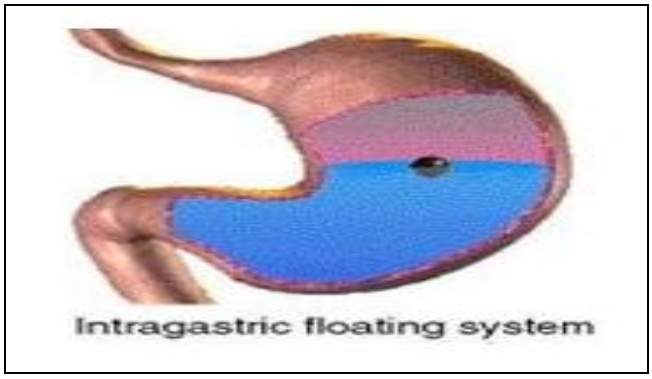

FIG. 7: LOW DENSITY FLOATING SYSTEMS

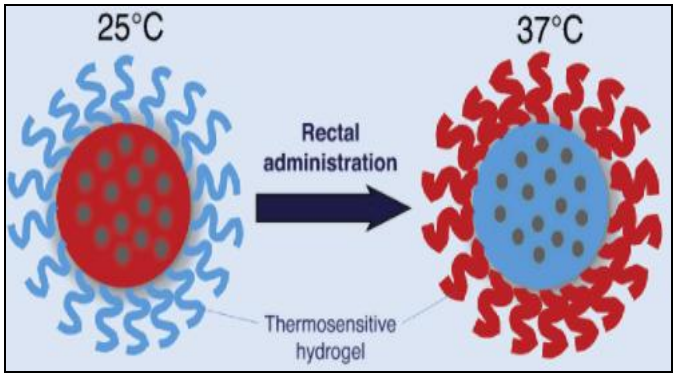

FIG. 8: THERMORESPONSIVE SYSTEMS

Chemical Stimuli Induced Pulsatile Release: These systems release the drug in the presence of enzymes or any other chemical stimuli.

PH Sensitive Drug Delivery Systems: pH-dependent polymers enable the drug release only in a desired pH range such as eudragit, pthallates, carboxymethylcellulose, methacryllic acid especially polymers like eudragit L and S favour colon targeting of which one example is explained by **Fig. 9**.

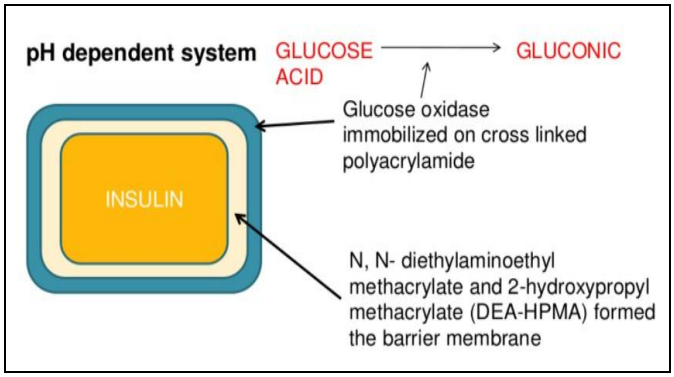

FIG. 9: PH SENSITIVE SYSTEMS

Electro responsive pulsatile release: Drug release is facilitated by the action of applied electric field on the rate-controlling membrane that contains polyelectrolytes, as shown in **Fig. 10**.

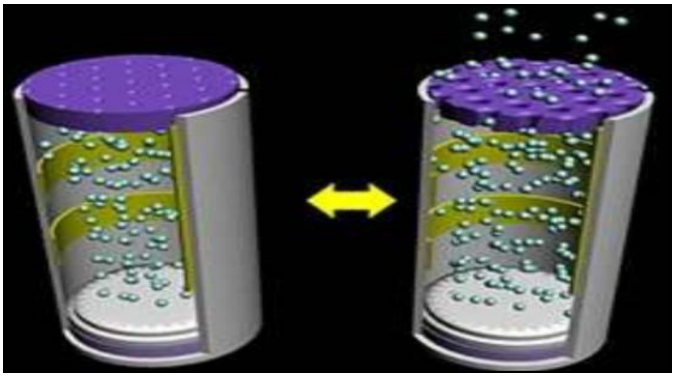

FIG. 10: ELECTRO RESPONSIVE SYSTEMS

Magnetically Induced Pulsatile System: In these systems, there is the incorporation of magnetic materials such as magnetite, iron and nickel, cobalt into the capsule or tablets by the external influence of the magnetic field. Using this, we can position the drug at a specific place or slow down its access to unwanted sites, thereby changing the time/extent of drug absorption into the stomach or intestine, as shown in **Fig. 11**.

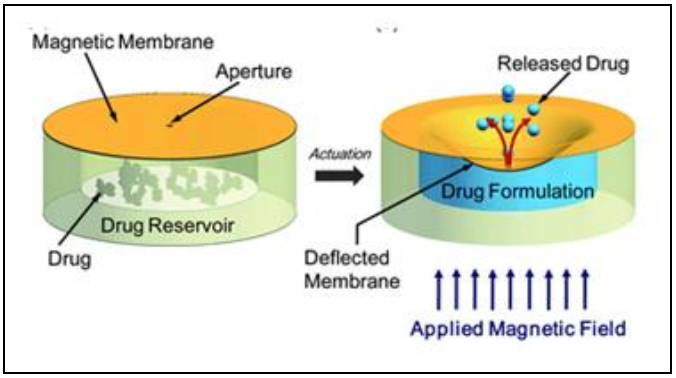

FIG. 11: MAGNETICALLY INDUCED SYSTEMS

Ultrasonically Stimulated Systems: Ultrasound interaction with that of biological tissues improves the drug permeation through biological barriers such as skin. The Mechanism involved here is the absorption of ultrasonic energy by the fluids or tissues. This is shown in **Fig. 12**.

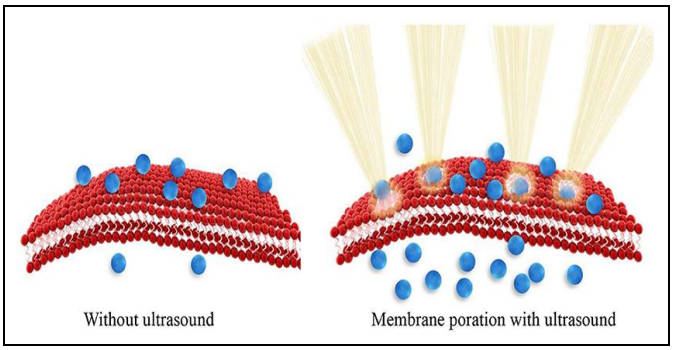

FIG. 12: ULTRASONICALLY STIMULATED SYSTEMS

MARKETED TECHNOLOGIES OF ChrDDS

S. no.	Type	Information
1	Enteric-coated systems[39]	Used to prevent release in stomach eg- Chronotropic®
2	Layered systems[39]	3 layered tablet systems with biphasic release eg- Geomatrix, Qtrol™ coating technology, Geminex TM technology, ACCU- Break.
3	Press coated systems[39]	Direct compression of coat and core with immediate-release drug
4	Contin® Technology[39]	molecular complexes are formed by solvating the cellulose polymer and reacting it with a non-polar solid aliphatic alcohol
5	Physicochemical modification of the API[17]	Properties of API are modified by introducing new substituents to the original structure
6	OROS® technology[17]	API and osmotically active agents are kept in a reservoir surrounded by a semipermeable membrane layer. Eg- COER-24, Chronset™.
7	CODAS® technology[17]	Multiparticulate type containing a nonenteric coating on the drug-loaded beads.
8	CEFORM® technology[17]	It contains uniformly sized, shaped, coated or combined microspheres produced by 'melt-spinning' Eg- Cardizem R LA
9	Diffucaps® Technology[39]	Multiparticulate populations of drug-containing particles like beads, pellets, granules. Eg:- Propranolol-containing innopranr xl for the management of hypertension
10	Chronomodulating Infusion Pumps[39]	These systems contain a core having drug and disintegrant that is coated with cellulose acetate polymer. Eg - melodies®, programmable synchromed®, panomat®v5infusion, and the rhythmic® pumps
11	TIMERx® technology[17]	controlled release hydrogel technology that combines xanthan and locust bean gums mixed with dextrose forming a strong binding gel
12	Pulsys[39]	Consists of three components i.e., one immediate release pulse and two delayed-release pulses of dosage. Eg - Moxatag tablet
13	Egalet Technology[39]	Consists of impermeable shell made of slowly biodegradable polymer and plasticizer
14	3-D printing[39]	used in fabrication of complex oral dosage delivery basing on solid freeform fabrication methods
15	Controlled-release microchip[17]	This is a solid-state silicon microchip, an alternate for microfabrication technique, that is similar to micrometer scale pumps, valves, and flow channels,
16	Controlled-Release Erodible Polymers[39]	Erodible polymers are designed in different forms (e.g. Tablets, capsules, microparticles) for chrdds
17	Eurand's pulsatile and chrono release System[40]	This system provides one/more rapid release of pulsed doses with predetermined lag times at specific sites of absorption
18	SODA's technology[40]	production of uniform spherical beads of 1-2 mm in diameter containing drug plus excipients and coated with product specific controlled release polymers
19	PRODAS Technology[40]	Presented as a number of minitablets combined in a hard gelatin capsule.
20	DMDS Technology[40]	Allows tablet to be broken down in half so that each respective portion of the tablet will achieve exactly the same release profile as the whole tablet.
21	PMDS Technology[40]	the multiphasic delivery of any active ingredient in a more controlled fashion
22	Magnetic Nanocomposite Hydrogel[40]	Magnetic nanocomposite of temperature-responsive hydrogel was used as remote-controlled pulsatile drug delivery
23	Banner's Versetrol Technology[40]	the drug is incorporated in lipophilic or hydrophilic matrix, and that is then incorporated in the soft gelatin capsule shell
24	OSDrC Technology[40]	Allows placement of any number of cores of any shape into the tablet just where they need to be positioned for optimum delivery of active pharmaceutical ingredients.
25	IPDAS Technology[40]	composed of numerous high density controlled release beads, which are compressed into a tablet form

CONCLUSION: Sustained and controlled delivery systems that are available traditionally for several years gained a lot of success and application in the field of medication. These are helpful as they keep the in vivo drug concentration at the therapeutic level for a prolonged period of time. Though it is essential, they are not sufficient to treat diseases associated with circadian rhythms with respect to symptoms and severity. Therefore, there develops a need to comprehend the effect of the biological environment on release patterns so that a successful design with expected *in-vivo* performance can be developed [41-43]. Recently the research that is done in Chrono-pharmaceutics demonstrated the

importance of biological rhythms in drug therapy and led to the development of a new approach for drug delivery systems. It is proved that optimum clinical outcome is not achieved if drug plasma concentrations are constant. As symptoms of a disease are showing circadian variation, drug release should also vary with time. Hence different technologies are applied to develop time-controlled, pulsed, triggered, and programmed drug delivery devices in recent years as the timing of drug administration in disease therapy has a significant impact upon treatment success. Therefore chronotherapeutics remains an important area for continuing research [44, 45].

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