International Journal of Medicine and Pharmaceutical Research

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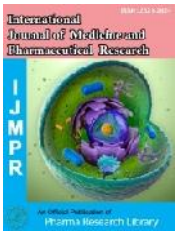

Review Article Open Access

Pulsatile Drug Delivery System: An Approach for Control Drug Delivery

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A B S T R A C T

Pulsatile drug delivery systems (PDDS) are gaining importance in the field of pharmaceutical technology as these systems deliver the right dose at specific time at a specific site. These systems are designed according to the circadian rhythm of the body. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired. The release of the drug as a pulse after a lag time has to be designed in such a way that a complete and rapid drug release follows the lag time. These systems are beneficial for the drugs having chronopharmacological behaviour where night time dosing is required and for the drugs having high first-pass effect and having specific site of absorption in GIT. Some of the disease conditions wherein PDDS are promising include duodenal ulcer, cardiovascular diseases, arthritis, asthma, diabetes, neurological disorder, cancer, hypertension and hypercholesterolemia.

Keywords: Pulsatile drug delivery systems, circadian rhythm, zero-order, lag time and chronopharmacological.

A R T I C L E I N F O

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Article History: Received 19 October 2016, **Accepted** 17 November 2016, **Available Online** 10 December 2016

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Manuscript ID: IJMPR3232

PAPER-QR CODE

Citation: S. B. Krishna Moorthy, *et al.* Pulsatile Drug Delivery System: An Approach for Control Drug Delivery. *Int. J. Med. Pharm. Res.*, 2016, 4(6): 366-374.

1. Introduction

Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. The release of the drug as a pulse after a lag time has to be designed in such a way that a complete and rapid drug release follows the lag time. These systems are designed according to the circadian rhythm of the body. The principle rationale for the use of

pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired. To understand the concept of pulsatile drug delivery, it is necessary to define the following terms.

Chronobiology: Chronobiology is the science concerned with the biological mechanism of the diseases according to a time structure. "*Chrono* pertains to time and —*biology* pertains to the study, or science, of life.

Chronopharmacology:

Chronopharmacology is the science concerned with the variations in the pharmacological actions of various drugs over a period of time of the day.

Chronopharmacokinetics:

Chronopharmacokinetics involves study of temporal changes in drug absorption, distribution, metabolism and excretion. Pharmacokinetic parameters, which are conventionally considered to be constant in time, are influenced by different physiological functions displaying circadian rhythm. Circadian changes in gastric acid secretion, gastrointestinal motility, gastrointestinal blood flow, drug protein binding, liver enzyme activity, renal blood flow and urinary pH can play role in time dependent variation of drug plasma concentrations.

Chronotherapy:

Co-ordination of biological rhythms and medical treatment is called chronotherapy.

Chronotherapeutics:

Chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. It is becoming increasingly moreevident that the specific time that patients take their medication may be even more significant than was recognized in the past.

Biological Rhythms

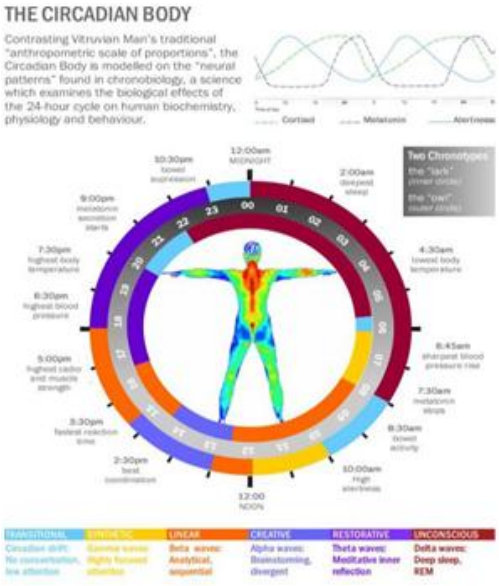

Figure 1

a) Circadian: "Circa" means about and "dies" means day. E.g. sleeping and waking patterns.

b) Ultradian: Oscillation of shorter duration is termed as Ultradian (more than 1 cycle per 24 hrs). E.g. Milliseconds take for a neuron to fire or a 90- minute Sleep cycle.

c) Infradian: Oscillations those are longer than 24 h (less than one cycle per day).

d) Seasonal:

Seasonal affective disorder (SAD), which causes depression in susceptible people during the short days of winter.

Advantages [10, 11, 12]

1. Used for the effective treatment of inflammatory bowel diseases like ulcerative colitis, crohn's disease, etc.
2. Decreases the side effects in the treatment of colon diseases.
3. Prevents gastric irritation resulting due to the administration of NSAIDs.
4. Minimizes first pass metabolism.
5. Provides suitable environment for proteins and peptides that are sensitive to gastric fluid and digestive enzymes.
6. Increased patient compliance.
7. Decreased frequency of administration. Hence decreased cost of drugs.
8. High retention time thus increasing the bioavailability of poorly absorbable drugs.

Limitation [13, 14]

1. Lack of manufacturing reproducibility and efficacy.
2. Large number of process variables.
3. Multiple manufacturing steps in case of Multiparticulate drug delivery system.
4. Higher cost of production.
5. Need of advanced technology.
6. Trained/ skilled personal needed for manufacturing.

2. Necessities of Pulsatile DDS [15, 16]

1. First pass metabolism:

Some drugs, such as beta blockers,and salicylamide, undergo extensive first passmetabolism and require fast drug input tosaturatemetabolizing enzymes in order tominimize pre-systemic metabolism. Thus, aconstant /sustained oral method of deliverywould result in reduced oral bioavailability.

2. Biological tolerance:

Drug plasma profiles are oftenaccompanied by a decline in thepharmacotherapeutic effect of the drug, e.g.,biological tolerance of transdermalnitroglycerin, salbutamol sulphate.

3. Special chronopharmacological needs:

Circadian rhythms in certainphysiological functions are well established. Ithas been recognized that many symptomsand onset of disease occur during specifictime periods of the 24 hour day, e.g., asthmaand angina pectoris attacks are mostfrequently in the morning hours.

4. Local therapeutic need:

For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption inthe small intestine is highly desirable toachieve the therapeutic effect and to minimizeside effects.

5. Gastric irritation or drug instability in gastric fluid:

Protection from gastric environment is essential for the drugs that undergo degradation in gastric acidic medium (eg, peptide drugs), irritate the gastric mucosa (NSAIDS) or induce nausea and vomiting.

3. Approaches for Pulsatile DDS [17]

PDDS has been gaining the importance as good oral controlled release dosage forms because conventional systems with a continuous release are not ideal for certain disorders as these systems release drug within therapeutic window for prolonged period of time. In this paper an attempt was made to review various approaches available for the development of PDDS.

Currently Reported Systems [18, 19]

Pulsatile systems are basically time controlled drug delivery systems in which the system controls the lagtime independent of environmental factors like pH, enzymes, gastro-intestinal motility. These time controlled systems can be classified as

- Single unit (e.g., tablet or capsule) or
- Multiple unit (e.g., pellets, beads) systems.

Single-Unit Systems:

- ❖ Capsular Systems
- ❖ Capsular System Based on Osmosis
- ❖ Pulsatile system with erodible or Soluble barrier coating
- ❖ Pulsatile system with Rupturable

Multiple-Unit Systems

- ❖ Pulsatile System Based on Rupturable Coating
- ❖ Osmotic-Based Rupturable Coating Systems
- ❖ Pulsatile system delivery by change in membrane permeability

3. Capsular system [19]

Different single-unit capsular pulsatile drug delivery systems have been developed. A general structure of such system consists of an insoluble capsule body housing a drug and a plug. The plug is removed aftera predetermined lag time owing to swelling, erosion or dissolution. The Pulsincap® system shown in **fig.** (Scherer DDS, Ltd) is an example of such a system hat is made up of a water-insoluble capsule body filled with drug formulation. The body is closed atthe open end with a swellable hydrogel plug. Uponcontact with dissolution medium or gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a lag time. This is followed by a rapiddrug release. The lag time can be controlled by manipulating the dimension and the position of theplug. For water-insoluble drugs, a rapid release canbe ensured by inclusion of effervescent agents ordisintegrants.

The plug material consists of insoluble but permeable and swellable polymers (e.g., polymethacrylates), erodible compressed polymers (e.g., hydroxypropyl methyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate), and enzymatically controlled erodible polymer (e.g., pectin). These formulations were well tolerated in animals and healthy volunteers, and there were no reports of gastrointestinal irritation. However, there was a potentialproblem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine.

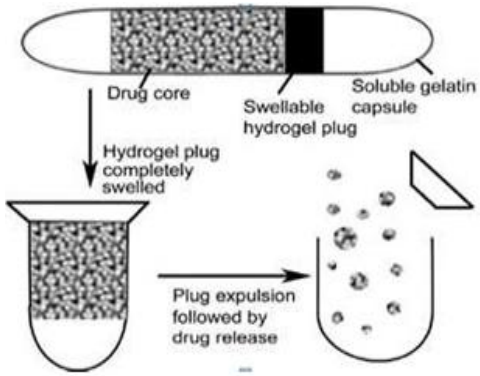

Figure 2

Osmotic systems (20)

It consists of capsule coated with asemipermiable membrane. An insoluble drug consisting of the osmotically active agents and drug formulations are incorporated inside the capsule. When this capsule comes in contact with dissolution fluid, the semipermiable membrane allows the entry of water, which causes development of pressure and the insoluble plug expels after a lag time. Such systems are utilized to deliver methylphenidate.

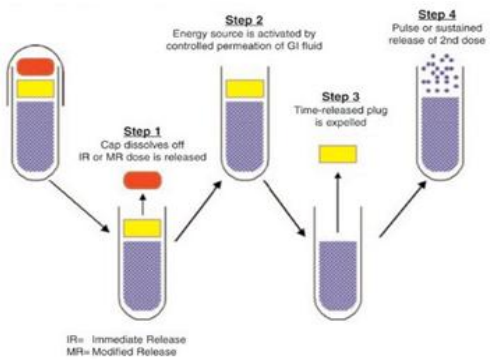

Figure 3

Drug delivery system with eroding or soluble barrier coating [21]: These systems are based upon a drug reservoir surrounded with a soluble barrier layer that dissolves with time and the drug releases at once after this lag time. Chronotropic® system consists of a core containing drug reservoir coated by ahydrophilic polymer HPMC. An additional enteric-coated film is given outside this layer to overcome intra-subject variability ingastric emptying rates. The lag time and the onset of action are controlled by the thickness and the viscosity grade of HPMC. The time clock system is a delivery device based on solid dosage form that is coated by an aqueous dispersion. This coating is ahydrophobic-surfactant layer to which a water-soluble polymeris added to improve adhesion to the core. Once in contact with the dissolution fluid, the dispersion rehydrates and redisperses. The lag time could be controlled by varying the thickness of thefilm. After the lag time, i.e., the time required for

rehydration, the core immediately releases the drug. This system has shown reproducible results *in vitro* and *in vivo*. The effect of lowcalorie and high calorie meal on the lag time was studied using gamma scintigraphy. The mean lag time of drug release was 345and 333 min, respectively. A drug delivery device with readily adjustable intervals between drug delivery pulses. This could be accomplished by providing for a constant driving force against multiple layers contained in an impervious compartment having an opening away from the constant driving force. The design of the multiple layers was such that the drug layer was adjacent to an expansion layer with an inert and impervious spacer layer alternating with the adjacent drug layer and so on. Two factors affected the duration between pulses, viz., the rate of constant driving force and the thickness of the spacer layer and the multiple layers (drug or combined drug/expansion layer). A thicker layer exhibited a longer duration between pulses of drug since it tooka long time for thicker spacer layer to completely traverse theopening.

Delivery systems with rupturable coating layer [22]

In this system, outer release controlling water insoluble but permeable coating and based on mechanically induced rupture phenomenon. In recent times different systems based on hardgelatin capsules and tablet core were illustrated, all coated by outer rupturable layer and innerswellable. The film rupture may be attained by swelling, osmotic or effervescent additives in the reservoir. By optimizing the system, drug release can be obtained at specific time Interval. Sungthongjeen et al developed a tablet system consisting of core coated withtwo layers of swelling and rupturable coatings where in they used spray dried lactose andmicrocrystalline cellulose in drug core and then core was coated with swelling polymer croscarmellose sodium and an outer rupturable layer of ethyl cellulose

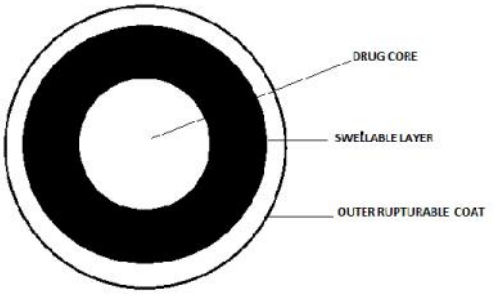

Figure 4

4. Recent Advances in Oral Pulsatile Delivery Technology [23, 24, 25]

1. ACCU-BREAK Technology
2. SODAS Technology
3. IPDAS Technology
4. CODAS Technology
5. GEOCLOCK Technology
6. Eurand's pulsatile and chrono release system
7. PULSYS Technology
8. Diffutab Technology
9. PRODAS Technology
10. Versetrol Technology
11. OSDrC Technology
12. PMDS Technology
13. TMDS Technology
14. Eurand's Diffucaps multi particulate system
15. GEOMATRIX Technology
16. Intelli Matrix Technology
17. Orbexa Technology
18. Eurand's Minitabs Technology
19. DMDS Technology

1. ACCU-Break Technology (25)

ACCU-BREAK tablets are designed to provide physicians and patients with easily divisible tablets that when divided, result in exact smaller doses, thus facilitating ease of dosage adjustment. In ACCU-T-CR Trilayer tablets, the controlled release technology is used to further enhance treatment options. Tablet contains a controlled-release (CR) medication at either end separated by a drug-free break layer, allowing the CR dose to be divided into exact half doses. Additionally, an immediate release (IR) component can be added to CR tablets to add even more treatment options and potential product capabilities.

2. SODAS Technology [25]

Spheroidal Oral Drug Absorption System is Elan's Multi particulate drug delivery system. This technology enables production of customized dosage forms that respond directly to individual drug candidate needs. The drug is released in pulsatile bursts throughout the day. The system consists of uniform spheroidal beads of 1-2mm in diameter containing drug & excipients and is coated with product specific controlled release polymers.

3. IPDAS Technology (intestinal protective drug absorption system) [26]

In this, the beads with high density drug are compressed to form controlled release tablets. It isparticularly suitable for tablet that cause gastro irritation and disintegrates rapidly. The release iscontrolled by the nature of the drug-containing bead matrix or its semi-permeable membrane coating. It is extruded and spheronised Multiparticulate based technology. Initially, it was developed for a proprietary formulation of naproxen with fast onsetof action to relief pain over a 24-hour period which ismarketed in the US and Canada under the tradename Naprelan.

4. CODAS® Technology [27]

Chronotherapeutics Oral Drug Absorption System (CODAS) technology is a multiparticulate system designed for bedtime dosing. Here a nonenteric coating is applied on the drug-loaded beads to delay the release of the drug, up to five hours. Here release controlling contains a mixture of both water-soluble and water-insoluble polymers. When this dosage form comes in contact with the GI fluid, the water-soluble polymer gets dissolved slowly and pores are formed on the coating layer. Drug diffuses through these resulting pores. The water-insoluble polymer, acting as a barrier, maintains the controlled, fashion-like release of Verapamil. The rate of release is independent of pH, posture, and food.

5. GEOCLOCK® Technology [28]

Geoclock® tablets have an active drug inside an outertablet layer consisting of a mixture of hydrophobic wax and brittlematerial in order to obtain a pH-independent lag time prior to coredrug delivery at a predetermined release rate.

This dry coating approach is designed to allow the timed release of both slowrelease and fast release active cores by releasing the inner tabletfirst after which the surrounding outer shell gradually disintegrates. Skye Pharma has used this novel technology to develop Lodotra™, a rheumatoid arthritis drug, which delivers the active pharmaceutical ingredient at the most suitable time of day to treatthe disease condition.

6. EURANDs Pulsatile and chrono release System[(28)]

This system is capable of providing one or more rapidrelease pulses at predetermined times lag. They can help tooptimize efficacy or minimize side-effects of a drug substance. Forexample, Eurand has created a circadian rhythm release (CRR)dosage form for a cardiovascular drug, Propranolol hydrochloride,with a four-hour delay in release after oral administration. Whenadministered at bedtime, Propranolol is released after the initialdelay such that maximum plasma level occurs in the early morninghours, when the patient is mostly at risk.

7. PULSYSTM [29]

MiddleBrook Pharmaceuticals, Inc. has developed a delivery technology called PULSYS, which enables pulsatile delivery or delivery in rapid bursts of certain drugs. The technology provides the prolonged release and absorption of a drug. The company's PULSYS product MOXATAG (amoxicillin extended-release) tablets, 775 mg are used for the treatment of pharyngitis/tonsillitis secondary to *Streptococcus pyogenes*, commonly known as strep throat, for adults and pediatric patients age 12 and older. MOXATAG's once-daily extended-release tablet consists of three components: one immediate release and two delayed-release components. The three components are combined in a specific ratio using its PULSYS technology to prolong the release of amoxicillin from MOXATAG compared with immediate-release amoxicillin

8. DIFFUTAB® Technology [29, 30]

Multiparticulate drug dosage forms are composed of small beads, each small bead further composed of many layers. Some layers contain drug substance; others are rate controlling polymers. With Eurand's Diffucap® multiparticulate system, customized drug release profiles are created by first layering active drug onto an inert core (such as a cellulose sphere), then applying one or more rate controlling, functional polymers, to produce spherical, multilayered particles. The drug layering process can be conducted either from aqueous or solvent based drug solutions. Diffutab® technology work on same principle as given below.

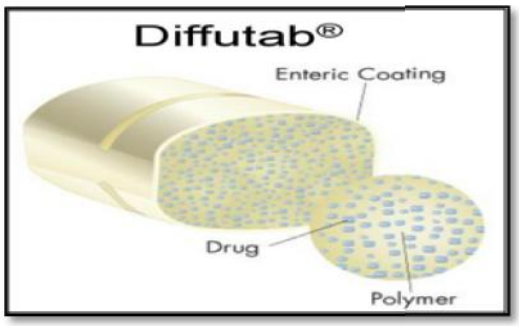

Figure 5

Diffutab® technology

Diffutab® technology for sustained release profiles and targeted delivery of pharmaceutical products. This technology incorporates a blend of hydrophilic polymers that control drug release via diffusion through, and erosion of, a matrix tablet. The Diffutab technology is particularly useful for the development of high dosage products and is an effective way to develop sustained release, once a day dosage forms.

Advantages:

- Matrix tablet utilizes a combination of water soluble particles and active drug
- Suitable for high drug loading
- Supports sustained release, once a day dosing

9. PRODAS® Technology [30, 33]

Programmable Oral Drug Absorption System (PRODAS Technology) is a multi particulatetechnology, which is unique in that it combinesthe benefits of tabletting technology within acapsule.The PRODAS delivery system is presented asa number of minitablets combined in a hardgelatin capsule. Very flexible, the PRODAStechnology can be used to pre-program therelease rate of a drug. It is possible toincorporate many different minitablets, eachone formulated individually and programmedto release drug at different sites within thegastro-intestinal tract. It is also possible toincorporate minitablets of different sizes sothat high drug loading is possible. PRODAS technology, by incorporating minitablets with different release rates, can display thecharacteristics of a number of differentconventional dosage forms:

- Immediate release component will mimic the conventional formulation. ensuring that the once daily formulation is as fast acting
- Delayed release can provide site / regional release and food resistance
- Sustained release component provides additional controlled release/protection

Figure 6: PRODAS® Technology

10. Banner's Versetrol™ Technology [30]

Banner is a global polymer based drug delivery and specialty pharmaceutical company. Versetrol™ Technology is novel innovative technology that provides time controlled release for wide range of drug. In this technology drug is incorporated in lipophillic or hydrophilic matrix and that is than incorporated in soft gelatin capsule shell. This technology is versatile because depending on physiochemical properties of drug either emulsion or suspension can be developed. For lipophilic drugs

suspension formulation is preferred while for hydrophilic drugs emulsion form is utilized. By applying combination of lipophilic and hydrophilic matrices desire release profile can be achieved. The utility of the Versetrol™ technology is greatly enhanced because it combines a versatile controlled release technology with the benefits of a customer preferred dosage form.

Versetrol controlled release softgels combine the qualities of a consumer preferred dosage form with the ability to control the release rate of active ingredients. Versetrol offers the flexibility to develop almost any release profile by simply tailoring the formulation variables, resulting in a more predictable release profile. Versetrol™ is a unique oral controlled release technology for the pharmaceutical market place. When combined with softgels, controlled release technology provides a consumer preferred dosage form with the ability to tailor release profiles for a wide variety of drugs. Versetrol™ offers controlled release formulations with the benefits of greater effectiveness in the treatment of chronic conditions by reducing side effects through minimizing peak plasma concentrations, and greater convenience leading to higher levels of patient compliance due to a simplified dosage schedule. Versetrol™ technology can be applied early on in pharmaceutical product development, leading to the parallel development of immediate release and controlled release for mutations to maximize market exposure.

Features:

- Unique, proprietary technology
- Novel,innovative controlled releasetechnology system
- Depending onthe physicochemical properties of the compound, an emulsion or suspension is chosen as the formulation
- Varying proportions of hydrophilic and hydrophobic components can be added to the formulation matrix to provide a tailored release profile including a dual release profile
- Good option for moisture sensitive drugs, due to inherent hydrophobic environment in the fill
- Ability to engineer to almost any desired release profile
- Unique matrix formulations for both lipophilic and hydrophilic compounds
- Compatible with EnteriCare® enteric softgels and absorption enhancement techniques
- Consumer preferred dosage form

Benefits:

- Provides first to market opportunity for lifecycle extension and brand building
- Provides market protection for new products
- Versetrol™ technology may be applied to difficult to solubilize compounds

11. OSDrC® Technology [30]

OSDrC® means one step dry coating Technology. This Technology opens the door to new world of pharmaceutical tablet manufacturing. The key word in this new world is “unique”, “High quality”, “low cost” and “Innovative”. OSDrC® optimized dose delivery technology enables the design of single or multi-core tablets, with a practically endless variety of core numbers, shapes, sizes, and placement within the tablet. This flexible-core capability offers the broadest available range of controlled release designs for drug formulators, providing the potential for optimal dosing, therapeutic product profiles, and plasma release profiles to meet patient needs in a high quality, one step manufacturing process.

Advantages of this technology:

Accurate & Flexible Control Technology: OSDrC® technology 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 (API). Misaligned cores are a thing of the past. This paves the way for high value-added drug formulation development, such as divided tablets with two cores, pulsatile tablets with three cores, and combination products.

Poor-Compressibility Encasing Technology:

OSDrC® technology allows incorporation of core ingredients with poor compressibility, such as magnesium stearate. OSDrC® tablets with pellets as their core can replace conventional capsules. OSDrC® paves the way for development of various novel drug formulations, such as new oral rapid disintegration tablets.

OSDrC® Provides Controlled Release:

Precise OSDrC® positioning technology enables product development scientists to control the release of the API by altering the thickness of the outer coating. The ability to precisely position multiple cores allows the creation of tablet products with a variety of pulsatile drug release profiles.

One-Step Dry-Coating Technology:

The OSDrC® rotary tableting machine, with its variable double-punch configuration, supports single-step manufacturing of pharmaceutical products. In addition to the commercial-scale production of conventional cored (tablet-within-a-tablet) tablets, this machine is ideal for manufacturing a variety of high-quality drug products at low cost. This innovative technology can also replace conventional sugar- and film-coated tablets.

12. PMDS® Technology [30]

PMDS® (Programmed Multiple action Delivery System) technology is designed to provide for the multiphasic delivery of any active ingredient in a more controlled fashion as compared to typical controlled release technologies. This system controls release rates for multiple ingredients within a single table in a programmed manner. Our TMDS technology allows for the release of more than one active ingredient in a single tablet formulation to be released in multiple profiles over time. PMDS technology is designed to allow for the release of the active ingredient at predetermined time intervals and desired levels on a consistent basis. This technology allows us to overcome one of the technical challenges in the development of multi-particulate dosage forms achieving acceptable uniformity and reproducibility of a product with a variety of release rates. It is designed to provide greater dosing flexibility that improves product efficacy and may reduce side effects.

13. TMDS Technology [30]

TMDS (Time Multiple Action Delivery system) Technology provide control release rate of multiple ingredient within single tablet in programme manner. TMDS Technology allows for more than one active ingredient in a single tablet formulation provide multiple release profile over extended period of time. Similar to CMDS, this system controls release rates for multiple ingredients within a single table in a programmed manner. Our TMDS technology allows for the release of more than one active ingredient in a single tablet formulation to be released in multiple profiles over time.

14. Eurand's Diffucaps® Multiparticulate System [30]

Diffucaps technology facilitates the development and commercialization of novel, controlled release delivery systems for once or twice daily dosing of single drugs or drug combinations that exhibit extreme pH dependent solubility profiles and/or are poorly soluble in physiological fluids. This multiparticulate system can provide dosage strength flexibility, and required pK profile and optimal release profiles for single drugs and drug combinations. The Diffucaps® drug release system can also be used in combination with other proprietary technologies to enhance drug solubility in the GI tract. Diffucaps is a multiparticulate bead system comprised of multiple layers of drug, excipients, and release controlling polymers. The beads contain a layer of organic acid or alkaline buffer to control the solubility of a drug by creating an optimal pH microenvironment for drugs that exhibit poor solubility in intestinal pH, in environments with pH greater than 8.0, or in physiological fluids. Alternatively, the beads can contain a solid solution of drug and crystallization inhibitor to enhance bioavailability by maintaining the drug in its amorphous state.

Diffucaps technology is especially suitable for drugs that traditionally require multiple daily doses or drugs needing customized release formulations. Each Diffucaps bead has an inert core surrounded by drug and coated with a functional polymer membrane to control the rate of drug release.

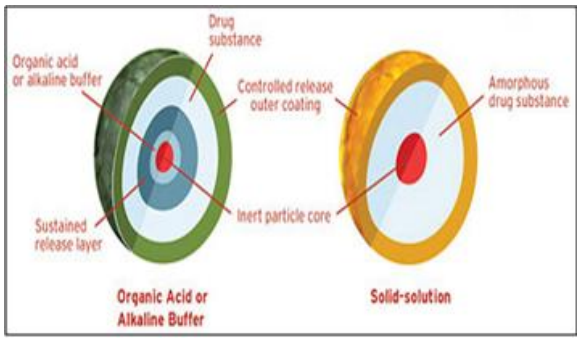

Figure 7: Eurand's Diffucaps technology

Advantages of Diffucaps

- Ideal for drugs exhibiting poor solubility in lower intestinal pH, in environments with pH above 8.0, or in physiological fluids
- Can combine multiple drugs and/or multiple release profiles in the same dosage form
- Simple formulation of dose proportional strengths.
- Can minimize food effect

15. GEOMATRIX™ Technology [30]

The Geomatrix™ technology is applied to achieve customised levels of controlled release of specific drugs and can achieve simultaneous release of two different drugs and different rates from a single tablet. The controlled release is achieved by constructing a multilayered tablet made of two basic key components. A. Hydrophilic polymers such as hydroxy propyl methylcellulose (HPMC) andB. Surface controlling barrier layers. Active loaded core surface that is available for drug release when exposed to the fluid is controlled by barrier layers. The combination of layers, each with different rates of swelling, gelling and erosion, is responsible for the rate of drug release within the body. When first swallowed, for example, the drug concentration is high but the surface area low. As time progresses the core swells and the surface area increases to compensate for the decrease in drug concentration. One of the major benefits of the Geomatrix™ technology is its ability to be easily incorporated into the production line. The Geomatrix™ tablets can be manufactured by readily available equipment that can be integrated into widely used pharmaceutical processes, thus giving firms more control over their own production activities.

Advantages

- Reproducibility
- Efficacy
- Versatility of release control mechanisms
- Controlled release of poorly soluble drugs
- Timed release of drugs
- Biphasic release of drugs
- Release of 2 or more drugs at different rates
- Pulsed release of drugs

16. Intellimatrix™ Technology [30]

Intelli Pharmaceutical is a pharmaceutical technology development company with a suite of proprietary tablet technologies. This Company have developed Novel oral Time controlled Release Matrix tablet Known as IntelliMatrixTM tablet. IntelliMatrixTM drug delivery platform is unique composition of several different 'intelligent' polymers such as hydroxy ethylcellulose and a channel former as Lactose. IntelliMatrixTM system is at the heart of proprietary drug delivery. Proprietary modelling enables precise profile control and site specific drug delivery.

18. ORBEXA® Technology [30]

Orbexa® technology is a multiparticulate system that enables high drug loading and provides a formulation choice for products that require granulation. This technology produces beads that are of controlled size and density - and suitable for formulation as controlled release multiparticulates - using granulation, Spheronization and extrusion techniques. The resultant beads can be coated with functional polymer membranes for additional release rate control and may be filled into capsules or provided in sachet form. This process allows for high drug concentrations within each bead. The technology is suited for use with sensitive drugs such as proteins.

Advantages:

- Aqueous or solvent based granulation
- High speed process is well suited for sensitive molecules like proteins
- Suitable for high drug loading

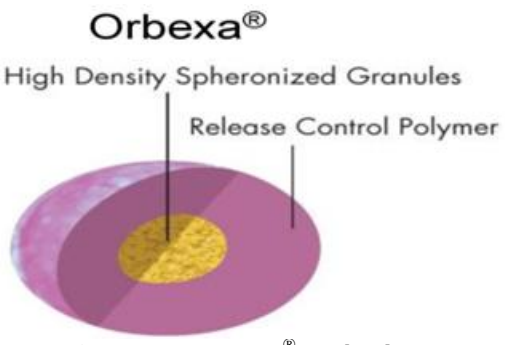

Figure 8: ORBEXA® T*echnology*

18. Eurand Minitabs® Technology [30,]

Eurand Minitabs® technology combines the simplicity of tablet formulation with the sophisticated drug release control offered by multiparticulate drug forms. Eurand Minitabs are tiny, approximately 2 mm in diameter, cylindrical tablets. Functional membranes may be applied to the tablets to further control release rate. Eurand Minitabs offer high drug loading, a wide range of release rate designs, and fine tuning of these release rates. Capsules containing the Eurand Minitabs can be opened and the contents used as a "sprinkle" formulation.

Figure 9

19. DMDS Technology

DMDS (Dividable Multiple Action Delivery System) is designed to provide greater dosing flexibility that improve product efficacy and reduces side effects. Traditional controlled release tablet often lose their controlled release mechanism of delivery once it broken. But DMDS technology allows tablet to be broken down in half so that each respective portion of the tablet will achieve exactly thesame release profile as the whole tablet. This allows the patient and physician to adjust the dosing regimen according to the clinical needs without compromising efficacy.

Table 1: Diseases Requiring PDDS [6, 7, 8, 9]

S.No	Diseases	Chronopharmacological Behavior	Drugs used
1	Peptic ulcer	Acid secretion is high in afternoon and in night	H2 blockers
2	Asthma	Precipitation of attacks during night or at early morning hour	B2 agonist, Antihistaminic
3	Cardiovascular diseases	Blood pressure is at its lowest during the sleep and rises steeply during the early morning awakening period	Nitroglycerin, Calcium channel blockers, ACE inhibitors
4	Arthritis	Pain in the morning and more pain at night	NSAIDs, Glucocorticoids
5	Diabetes mellitus	Increase in blood sugar level after Meal	Sulfonylurea, Insulin, Biguanide
6	Attention deficit syndrome	Increase in DOPA level in Afternoon	Methyl phenidate
7	Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during day time	HMG CoA reductase Inhibitors.

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