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Review papers

AN OVER VIEW OF CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEMS BASED ON FLOATING PULSATILE CONCEPT

Abstract

In the modern era of pharmaceutical research much attention has been focussed on patients' health by improving their therapeutic efficacy and minimising adverse effects. The tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24-hour period, may be changing as researchers' report that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms. All these conditions pushed the formulation scientists to develop chronotherapeutic drug delivery system. This article focuses on role of circadian rhythms in major risk occurring disorders like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, diabetes, attention deficit syndrome, hypercholesterolemia, and hypertension and their treatment by conventional and novel pulsatile drug delivery systems.

Keywords: Chronotherapeutic, Floating Pulsatile, Multiparticulate and Drug Delivery

1.0 INTRODUCTION

In the modern era of pharmaceutical research much attention has been focussed on patients' health by improving their therapeutic efficacy and minimising adverse effects. The tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24-hour period, may be changing as researchers report that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms[1] The term "chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time[2] Researchers have concluded that all living organisms are composites of rhythms with varying frequencies that may range from seconds to seasons. Perhaps the best known and studied chronobiologic frequency is the circadian rhythm which

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approximates the earth's 24-hour rotation around the sun. Researchers have recently concluded that both disease states and drug therapy are affected by a multitude of rhythmic changes that occur within the human body[1]

Biological rhythm

A biological rhythm is a self-sustaining process inside the human body. It is defined as the process that occurs periodically in an organism in conjugation with and often in response to periodic changes in environmental condition. Our bodies' rhythm, also known as our biological clock, and the rhythm of the solar system that change night to day and lead one season into another. Our internal clocks are also dictated by our genetic makeup[3].

There are 4 types of rhythms in our body

1. Ultradian: Which are cycles shorter than a day

   E.g. Milliseconds take for a neuron to fire or a 90- minute sleep cycle.

2. Circadian: Which last about 24 hours

   E.g. sleeping and walking patterns.

3. Infradian: It is referring to cycles longer than 24 hours. E.g. Menstrual cycle
4. Seasonal: Seasonal affective disorder (SAD), which causes depression in susceptible people during the short days of winter.

1.1 Circadian rhythm

Biological rhythm within a single day is termed as circadian rhythm. Here, the oscillation time is 24 hours. Human circadian rhythm is based on sleep -activity cycle, is influenced by our genetic makeup and hence, affects the body's function day and night (24-Hrs period).[4] The dependence of body's functions in certain disease states on circadian rhythm is well known. Chronobiological studies have established circadian rhythm for almost all body functions, e.g. Heart rate, blood pressure, body temperature, plasma concentration of various hormones, gastric pH and renal function[5]

1.1.1 Generation of circadian rhythm

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The circadian rhythm is first coined by Halberg and Stephens in 1959[6]. The human circadian time structure represents peak of actions directly related to the daily routine of most human beings. As human physiology and biochemistry predictably vary during 24 hour period. It is easy to understand that some medical conditions present prevalence at certain periods of the day.

Figure 1: Generation of circadian rhythm

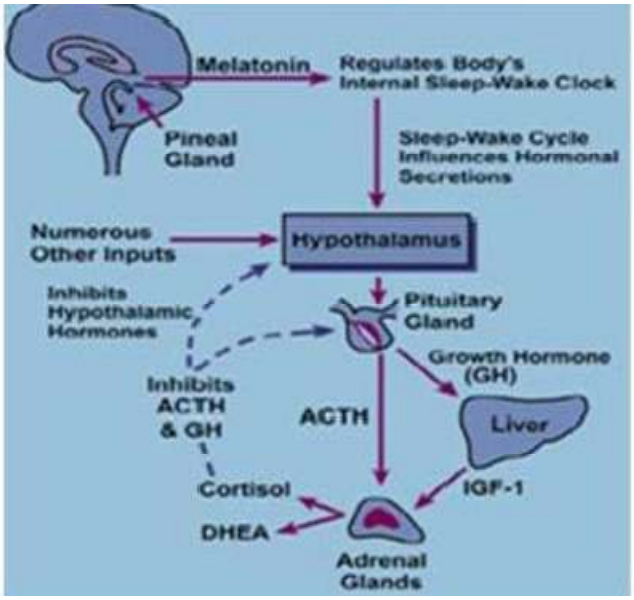

Figure 1 represents suprachiasmatic nucleus present in brain (SCN). It acts as biological clock and generates biological rhythm by control of clock genes. The rhythm cycle is generated by SCN and it calibrated by tarnation of dark and brightness both through melatonin secretion through penal gland. Secretion of various hormones like aldosterone, rennin, and cortisol is fluctuated in bloodlevels[7].

1.1.2 Circadian time structure

The results of numerous biological rhythm studies help to define the temporal organization of human beings. One means of illustrating the human circadian time structure is to depict the peak time of 24-h rhythms on a clock-like diagram like that shown in Fig. 2.This figure shows the peak time of a select number of human circadian rhythms in relation to the typical synchronizer routine of most human beings-sleep in darkness from 10.30 P.M to 6.30 A.M and activity during the light of the day between 6.30 A.M and 10.30 P.M. The peak gastric acid secretion, white blood cells count (WBC), calcitonin gene related protein, and atrial natriuretic peptide occurs late at night or early in sleep. Growth and thyroid stimulating

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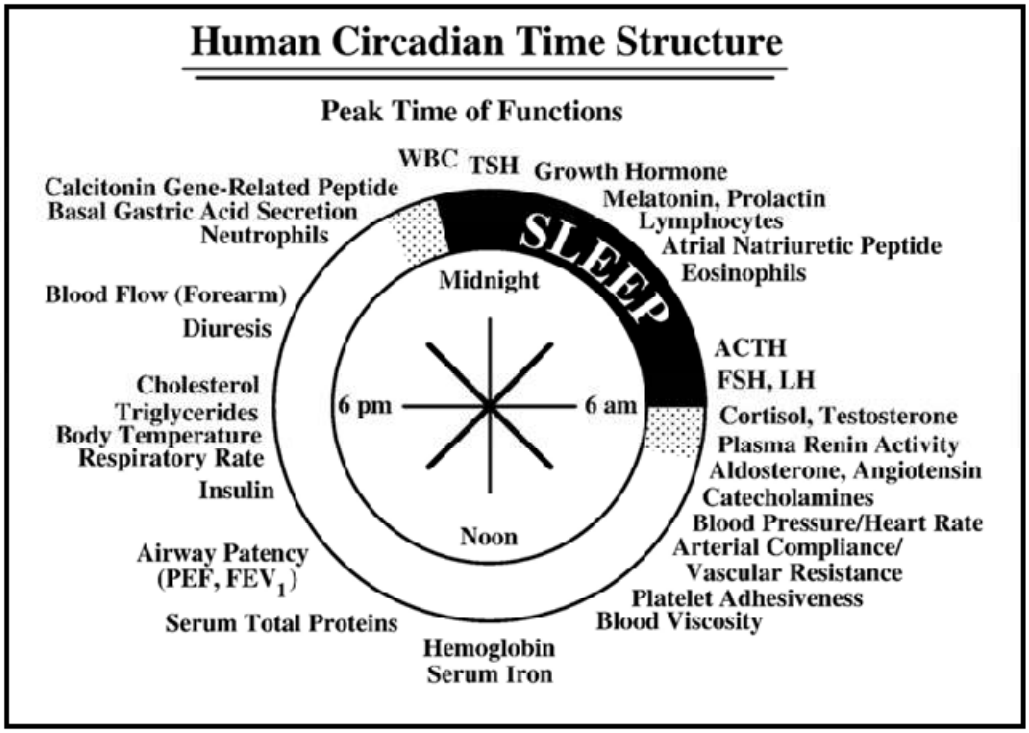
hormone (TSH), blood lymphocyte and eosinophil number, and plasma melatonin and prolactin crest during sleep as do the adrenocorticotropic (ACTH), follicle stimulating (FSH), and luteinizing (LH) hormones. Plasma cortisol, renin activity, angiotensin, and aldosterone peak in the morning as do arterial compliance, vascular resistance, platelet aggregation, and blood viscosity. Haemoglobin and insulin concentrations peak at noon and in the afternoon, as do the spirometric measures of airways caliber FEV1 (forced expiratory volume in 1 s) and PEF (peak expiratory flow rate).

The circadian rhythms of serum cholesterol and triglycerides and urinary diuresis crest early in the evening. The information conveyed in this figure clearly illustrates that the biochemistry and physiology of human beings are not constant; rather, they are variable in a predictable and coordinated manner during the 24h[8].

Figure 2: Human circadian time structure.



The above figure represents the approximate peak time of circadian (24-h) rhythms of selected biological variables in persons adhering to a normal routine of daytime activity (~6–7 a.m. to 10–11 p.m.) alternating with night time sleep[9 - 11]

2.0 Concepts of chrono therapeutics, depends on the following concepts[12]

2.1 Chrono biology

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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.

2.2 Chrono pharmacology

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

2.3 Chrono pharmacokinetics

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, gastro intestinal 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.

2.4 Chronotherapy:

Coordination of biological rhythms with medical treatment is called *Chronotherapy*. Chronotherapeutics refers to a treatment method in which in vivo drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. It is based on the observation that there is an interdependent relationship between the peak-trough rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity and pharmacokinetics of many drugs

2.5 Need of chronotherapeutic drug delivery systems[13-14]

2.5.1 Many body functions follow circadian rhythm, i.e., their activity increases or decreases with time. A number of hormones like rennin, aldosterone, and cortisol show daily as well as timely fluctuations in their blood levels. Circadian effects are also observed in case of pH and acid secretion in stomach, gastric emptying, and gastro-intestinal blood transfusion.

2.5.2 Acid secretion, gastric emptying, cholesterol synthesis, and gastrointestinal blood transfusion may alter with circadian rhythm.

2.5.3 Chrono pharmacotherapy of diseases which shows circadian rhythms in their path physiology like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension.

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2.5.4 Lag time is essential for those drugs undergo acidic degradation (e.g. peptide drugs) that irritate the gastric mucosa or induce nausea and vomiting.

2.5.5 Targeting a drug to distal organs of gastro-intestinal tract (GIT) like the colon the drug release should be prevented in the upper two-third portion of the GIT.

2.5.6 Drugs which undergo extensive first pass metabolism are easily given by pulsatile drug delivery system.

2.5.7 Drugs that produce biological tolerance due to continuous exposure of drug

2.6 Advantages of Chronotherapy

2.6.1 Chronotherapy is drug-free

2.6.2 Chronotherapy is more effective when a person sleeps for several hours.

2.6.3 While Chronotherapy patients often fall asleep this improves their condition and confidence as well.

2.6.4 Chronotherapy is different from other treatments because it got the beginning, middle, and an end. So one can predict easily the point at which it will work.

2.6.5 It gives you a new schedule like getting up and sleeping early which will be quite unusual for some days but it will give you a period to adjust psychologically

2.6.6 Improved stability

2.6.7 No risk of dose dumping[15]

2.7 Disadvantages of Chronotherapy

2.7.1 It develops a non 24 hours sleep wake syndrome after the treatment as the person sleeps or over 24 hours during the treatment.

2.7.2 Person become less productive during Chronotherapy and staying awake till the other schedule will be a bit uncomfortable.

2.7.3 Medical supervision is mandatory for this therapy.

2.7.4 Large number of process variables.

2.7.5 Trained /skilled person is needed for manufacturing[16]

3.0 Diseases of known pathogenesis associated with oscillatory changes of body

Before designing a chronotropic or pulsatile drug delivery system, understanding of a disease and role of circadian rhythm in its pathophysiology is required. Diseases that are currently targeted by chronotropic systems are those for which there is enough scientific background to justify their need for chronotropic systems as compared to conventional drug delivery systems. Particular rhythms in the onset and extent of symptoms were observed in

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diseases such as bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, diabetes, attention deficit syndrome, hypercholestemia and hypertension. Table 1 enumerates various diseases and their chronological behaviour.

In case of asthma, aggravation of attacks occur in early morning or after midnight, the reason is low lung function is promoted by circadian changes at that time (due to release of nor epinephrine and epinephrine). Also in case of cardiovascular diseases several functions of heart (blood pressure, heart rate, stroke volume, cardiac output, and blood flow) get affected according to circadian changes leading to angina, hypertension, myocardial infarction, stroke etc. Circadian variations of glucose and insulin in diabetes have been extensively studied. Furthermore circadian changes also contribute in lipid metabolism in patients as well as in normal subjects, leading to complication in cholesterol synthesis in patients[17]. Plasma concentration of C - reactive protein and interleukin-6 increases in rheumatic patients during morning hours due to circadian changes.

TABLE 1: Circadian rhythm and the manifestation of clinical disease

Disease	**Chronological behavior**	**Drugs**
Asthma	Exacerbation more common during the sleep period & attacks after midnight or at early morning hours	β2 agonist, Antihistamines
Allergic rhinitis	Worse in the morning/upon rising	Antihistamines
Hormone secretion	Growth hormone and melatonin produced at night testosterone and cortisol in morning hr.	Corticosteroids
Rheumatoid arthritis	Pain in the morning and more pain at night	NSAIDs, Glucocorticoids
Osteoarthritis	Symptoms worse in the middle/later portion of the day	NSAIDs
Angina Pectoris	Chest pain and ECG changes more common in early morning	Anti anginal drugs
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than day time	HMG CoA reductase inhibitors
Myocardial Infraction	Incidence higher in the early morning	Cardiovascular agents
Stroke	Incidence higher in the morning	Cardiovascular agents
Sudden cardiac death	Incidence higher in the	Cardiovascular agents

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	morning after awakening	
Diabetes mellitus	Increased blood sugar level after meal	Sulfonylurea, Insulin
Peptic ulcer disease	Acid secretion high in afternoon and at night	H2 blockers

4.0 Chronotherapeutic Drug Delivery Systems

Chronotherapeutics refers to the clinical practice of synchronizing drug delivery in a manner consistent with the body's circadian rhythm to produce maximum therapeutic activity and minimum side effects by determining the best biological time for drug dosing. The basic concept for new drug delivery systems for safety and efficacy of the drug by coordinating the peak plasma concentration of the drug with the circadian rhythm of the body is to synchronize drug release with the circadian rhythm of the body. Several techniques have been developed and applied to design chronopharmaceutic delivery systems for desired drug release.

These techniques are broadly classified into following three major categories:

1. Time controlled chronotropic systems.
2. Stimuli induced pulsatile drug delivery systems
3. Externally regulated pulsatile drug delivery systems

5.0 Novel Approach to PDDS : Floating Pulsatile Drug Delivery System

Nowadays, chronotherapeutic formulations are developed, specifically to time-controlled release dosage forms, in order to achieve the maximum drug concentration in the plasma at the peak time of the symptomatology. To follow this principle, dosage form ought to be taken at the convenient time before sleep, providing maximum drug release in the morning. The major disadvantage of these systems reclines in achieving long residence time which is desired for diseases needing morning medication. With conventional pulsatile release dosage forms, the highly variable nature of gastric emptying process can result *in vivo* variability and bioavailability problems.[18]To overcome this novel approach term as floating pulsatile drug delivery system was developed.

A combination of floating and pulsatile principles of drug delivery system would have the advantage that a drug can be released in upper GI tract after a defined time period of no drug release.[19] A pulsatile drug delivery that can be administered at bed time but releases drug in early morning would be a promising chronotherapeutic system.

5.1 The potential benefits of floating pulsatile drug delivery system

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5.1.1 Retention of drug delivery system in stomach prolongs overall.

5.1.2 Acidic substance like aspirin cause irritation on the stomach wall when come into contact with it hence floating pulsatile formulation may be useful for administration of aspirin and other similar drugs.

5.1.3 It has application also local drug delivery to the stomach and proximal small intestine e.g., ranitidine for nocturnal acid breakthrough.

5.1.4 No risk of dose dumping.[20]

5.1.5 The formulation is to be taken after meal, where immediate release dose will provide from acid secretion in response to the meal; while time controlled floating pulsatile tablet with delay "burst" release will attenuate midnight acidity. This will provide an ideal therapeutic regimen with enhanced patient compliance.

5.1.6 Floating pulsatile drug delivery system for obtaining no drug release during floating and rapid drug release in distal small intestine to achieve chronotherapeutic release e.g. indomethacin. Floating with no drug release in acidic medium by pulse drug release in basic medium.

5.1.7 When there is vigorous intestine movement and short transit time as might occur in certain type of diarrhoea, poor absorption is expected. Under such circumstances, it may be advantageous to keep the drug in floating condition in stomach to get relative better response.

5.1.8 Floating pulsatile drug delivery increase drug bioavaibility; predictable, reproducible, and improved generally short gastric residence time; no risk of dose dumping; local drug action; and the flexibility to blend dosage form with different composition and release pattern.

5.2 Disadvantages

5.2.1 Drug which are irritant to gastric mucosa is not desirable or suitable

5.2.2 The dosage form should be administered with full glass of water (200-250ml)

5.2.3 Manufacturing this type of dosage form requires multiple formulation steps, higher cost of production, need of advance technology, and trained or skilled person.

5.3 List of polymers used for floating pulsatile drug delivery systems

5.3.1 Polymers used for buoyancy layer

Carbopol 934p, Methocel, Hydrogenated Castor oil, low methoxy pectin, HPMC K 100M and Sodium bicarbonate, PVP K-30, Cellulose acetate or HPMC, Polyethylene glycol 4000,anhydrous citric acid, Sodium bicarbonate, Glycerol behenate (compritol 888), Methocel E5.

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5.3.2 Polymers used for pulsatile release:

Methocel E 15,Ethocel 45P,low methoxy pectin, Eudragit S100,Eudragit L 100, Eudragit RS 100 and RL 100, Cellulose acetate, Ethyl cellulose, Eudragit NE 30D.

5.3.3 Recently porous carriers has been used in floating pulsatile systems:

Porous calcium silicate, Poly propylene foam powder, Magnesium Alumino Meta silicate, porous ceramic and porous silicon dioxide

6.0 Design of floating pulsatile drug delivery systems

The purpose of designing by which the drug is released from dosage form depends on the type of coating; insoluble coating under all physiological conditions, pH-dependent coating whose solubility changes dramatically at some point in GI tract, and slowly erodible coating. The method of application and processing conditions may influence the porosity of the coating and consequently the release mechanism.

Less obvious but also important to the kinetics of release are the influences of the core formulation, in terms of both physical properties and amounts of the drug and excipient materials present, and physiological environment to which the drug is released.

In multi particulate pulsatile delivery systems, the swelling and rupturing; dissolution or erosion; and changed permeability of the coating membrane are primarily involved in the control of release. The development of low-density floating multi particulate pulsed release dosage forms possessing gastric retention capabilities has also been addressed with increasing focus on the upcoming multi particulate-pulsatile technologies being exploited on an industrial scale.

6.1 Time controlled floating pulsatile drug delivery system

Time-dependent dosage forms are formulated to release their drug load after a predetermined lag time. The release mechanisms employed include bulk erosion of the polymer, in which drug by diffusion is restricted, surface erosion of layered devices composed of altering drug-containing and drug-free layers, and osmotically controlled erosion coating layer

6.2 Different Mechanisms:

6.2.1 Reservoir System with Eroding Polymer or Soluble Barrier Coating:

A pulsatile-floating drug delivery system consists of three different parts, a core tablet, containing the active ingredient; an erodible outer shell; and a top cover buoyant layer, as shown in [Figure 3]. One layer is for buoyancy and the other for drug pulsatile release

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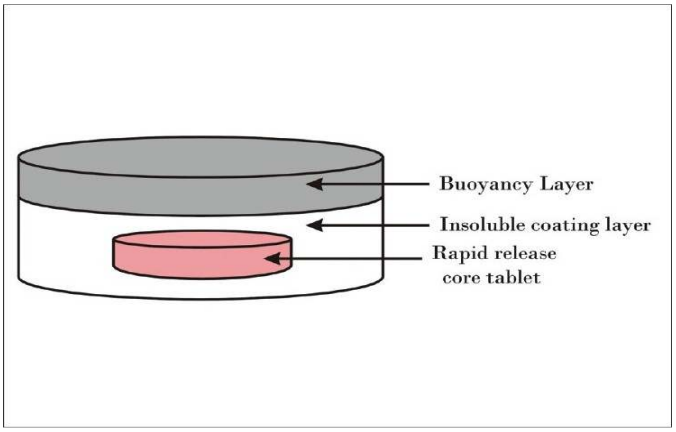
Fig: 3



The pulsatile release system with various lag times was prepared by compression with different erodible polymeric layers. Combined usage of hydroxypropyl methylcellulose (HPMC) and carbomer in a gastric floating or mucoadhesive drug delivery system has been reported[19-20] to improve the floating properties or mucoadhesiveness of the combined system. The novel system could result in[1] a floating dosage form with a prolonged gastric residence time and in[2] a pulsatile dosage form, in which the drug is released rapidly in a time-controlled manner after rupturing of the coating. Floating-pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release[21].

6.2.2 Reservoir System with Rupturable Coating:

Reservoir-type delivery systems based on the expansion of the core have been evaluated for both floating delivery systems having a lower density than GI fluids, and for pulsatile systems in which the core expansion causes rupturing of the coating to allow rapid drug release[22].

The major challenge was to develop a tablet which can float and also provide a burst release once the outer time-lagged coating ruptures[23]. Therefore, we have incorporating low-density material like wax and other excipients like super disintegrants and/or low-viscosity grade swelling polymers which allows high water penetration into the core, pulsatile release profile from a time-lagged coating using a combination of rupturable and erodible, are required. A blend of floating and pulsatile principles of drug delivery system seems to present the advantage that a drug can be release in the upper GI tract after a definite time period of no drug release, intended for chronotherapy in nocturnal acid breakthrough. This pattern was achieved by using a programmed delivery of ranitidine hydrochloride from a floating tablet with time-lagged coating. The functionality of the outer polymer coating i.e. percentage weight ratio of ethyl cellulose

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(EC) to HPMC in the coating formulation and coating level (% weight gain) used to predict lag time and drug release. The proposed mathematical model is found to be robust and accurate for optimization of time-lagged coating formulations for programmable pulsatile release of ranitidine hydrochloride, consistent with the demands of nocturnal acid breakthrough. Krogel and Bodmeier developed floating and pulsatile drug delivery systems based on a reservoir system consisting of a drug-containing effervescent core and a polymeric coating.[24]Studies identified important core and coating properties for the two systems. For the floating system, a polymer coating with a high elongation value and high water- and low CO_2 permeabilities was selected (Eudragit® RL: acetyl tributyl citrate) in order to initiate the effervescent reaction and the floating process rapidly, whereas for the pulsatile drug delivery system, a weak, semipermeable film which ruptured after a certain lag time was best (EC: dibutyl sebacate). With the floating system, the polymeric coating did not retard the drug release. A polymer (cellulose acetate or HPMC) was added to the core to control the drug release. The time to float could be controlled by the composition (type of filler, concentration of effervescent agents) and hardness of the tablet core and the composition (type of polymer and plasticizer) and thickness of the coating. For the pulsatile system, a quick releasing core was formulated in order to obtain a rapid drug release after the rupture of the polymer coating. The lag time prior to the rapid drug release phase increased with increasing core hardness and coating level. Floating multilayer coated tablets were designed based on gas formation. The system consists of a drug-containing core tablet coated with a protective layer (HPMC), a gas-forming layer (sodium bicarbonate), and a gas-entrapped membrane, respectively.[25]The mechanical properties of acrylic polymers (Eudragit® RL 30D, RS 30D, NE 30D) and EC were characterized. Eudragit® RL 30D was chosen as Gas-entrapped membrane due to its high flexibility and high water permeability. The obtained tablets enabled to float due to the CO_2 gas formation and the gas entrapment by polymeric membrane. The effect of formulation variables on floating properties and drug release was investigated. The floating tablets using direct-compressed cores had shorter time to float and faster drug release than those using wet granulated cores. The increased amount of a gas-forming agent did not affect time to float but increased the drug release from the floating tablets, while increasing coating level of gas-entrapped membrane increased time to float and slightly retarded drug release. These floating tablets seem to be a promising gastro retentive drug delivery system.

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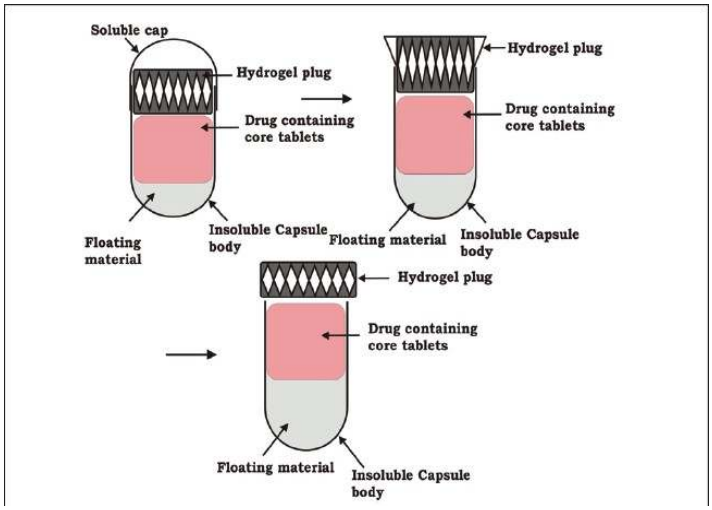
6.2.3 Capsule Shape System Provided With Release Controlling Plug

This novel system consists of a drug tablet placed within an impermeable polymeric cylinder closed with an erodible drug-free plug and floating material filled at the bottom as shown in Figure 4. When in contact with the aqueous fluids, the erodible drug-free plug is responsible for a lag phase preceding the onset of release and the floating material filled at the bottom is responsible for buoyancy properties of the formulation

Fig: 4



A blend of floating and pulsatile principles of drug delivery system seems to present the advantage that a drug can be released in the upper GI tract after a definite time period of no drug release[26] System was to develop and evaluate a floating and pulsatile drug delivery system based on an impermeable cylinder. Pulsatile capsule was prepared by sealing the drug tablet and the buoyant material filler inside the impermeable capsule body with erodible plug. The drug delivery system showed typical floating and pulsatile release profile, with a lag time followed by a rapid release phase. The lag time prior to the pulsatile drug release correlated well with the erosion properties of plugs and the composition of the plug could be controlled by the weight of the plug. The buoyancy of the whole system depended on the bulk density of the dosage form. Gamma-scintigraphic evaluation in human beings was used to establish methodology capable of showing the subsequent *in vivo* performance of the floating and pulsatile release capsule. The pulsatile release capsule prepared could achieve a rapid release after lag time *in vivo*, which was longer than that *in vitro*.

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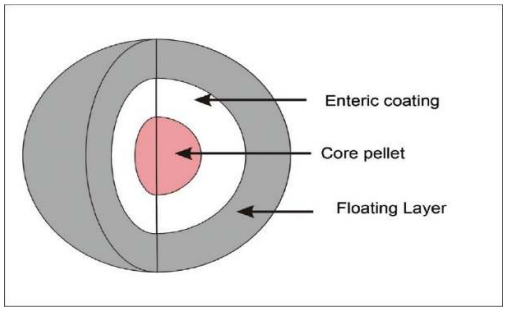
The scintigraphic evaluation could confirm qualitatively that the system with *in vitro* lag time of 4.0 hours provided, with relatively high reproducibility, a pulsatile release occurred around 5.0 hours after administration.

A multifunctional drug delivery system based on HPMC-matrices (tablets) placed within an impermeable polymeric cylinder[27]was developed. Depending on the configuration of the device, extended release, floating or pulsatile drug delivery systems could be obtained. The release behavior of the different devices was investigated as a function of its viscosity grade, HPMC content, type of drug (chlorpheniramine maleate or ibuprofen), matrix weight, position of the matrix within the polymeric cylinder, addition of various fillers (lactose, dibasic calcium phosphate, or microcrystalline cellulose), and agitation rate of the release medium. The release was fairly independent of the agitation rate, the position of the tablet within the polymeric cylinder, and the length of the cylinder. With the pulsatile device, the lag time prior to the drug release could be controlled through the erosion rate of the matrix (matrix weight and composition).

6.2.4 Multiparticulate Drug Delivery System

Functional membranes (referred to as lag-time coating) are formed of a typical pellet or bead in a multiparticulate system with bi-modal pulse. It comprises of an external water-insoluble polymer (e.g., EC) or enteric polymer (e.g., hypromellose phthalate) over an immediate release drug layer, followed by a release control polymer over the timed pulsatile release drug layer applied on core granules. Multiparticulate systems are made by using this type of methods as systems based upon change in membrane permeability, systems with soluble or eroding polymer coatings, and systems based upon rupturable coating.

Figure 5



Multiparticulate pulsatile release dosage forms like Reservoir systems with rupturable polymeric coatings, soluble or eroding polymer coatings and changed membrane permeability are having longer residence time in the GI tract and due to highly variable

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nature of gastric emptying process, may result in poor and bioavailability problems *in vitro/in vivo* relationship. In contrary, floating multiparticulate pulsatile dosage forms reside in stomach only and are not affected by variability of pH, local environment, or gastric emptying rate. These dosage forms are also specifically advantageous for drugs either absorbed from the stomach, requiring local action, or distal part of small intestine. Overall, these considerations led to the development of multiparticulate pulsatile release dosage forms possessing gastric retention capabilities. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release.

Shaji and Patole developed a multiple-unit, floating-pulsatile drug delivery system (FPDDS) for obtaining no drug release during floating and in the proximal small intestine followed by pulsed, rapid drug release to achieve chronotherapeutic release of indomethacin.[28] The system developed consists of drug-containing core pellets prepared by extrusion-spheronization process, which were coated with an inner pH-dependent layer of Eudragit S100 and outer effervescent layer of sodium bicarbonate and HPMC K100M. Pellets showed instantaneous floating with no drug release in acidic medium followed by pulsed drug release. The system showed excellent lag phase followed by burst release, which gives site- and time-specific delivery of indomethacin acting as per chronotherapy of rheumatoid arthritis.

Polysaccharides are widely used in oral drug delivery systems because of the simplicity to obtain the desired drug delivery system and drug release profile, by the control of cross-linking, insolubility of cross-linked beads in gastric environment, and broad regulatory acceptance. Badve *et al.* developed hollow calcium pectinate beads for floating-pulsatile release of diclofenac sodium or aceclofenac intended for chronopharmacotherapy.[29]To overcome limitations of various approaches for imparting buoyancy, hollow/porous bead[30]were prepared by simple process of acid-base reaction during ionotropic crosslinking. *In vivo* studies by gamma scintigraphy determined on rabbits showed gastroretention of beads up to 5 hours. The floating beads provided expected two-phase release pattern with initial lag time during floating in acidic medium followed by rapid pulse release in phosphate buffer. This approach suggested the use of hollow calcium pectinate microparticles as promising FPDDS for site- and time-specific release of drugs acting as per chronotherapy of diseases.

Sharma and Pawar reported that a blend of floating and pulsatile principles of drug delivery system would have the advantage that a drug can be released in the upper GI

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tract after a definite time period of no drug release. A multiparticulate FPDDS was developed using porous calcium silicate (Florite RE® [FLR]) and sodium alginate, for time- and site-specific drug release of meloxicam for chronopharmacotherapy of rheumatoid arthritis.[31] Meloxicam was adsorbed on the FLR by fast evaporation of solvent from drug solution containing dispersed FLR. Drug adsorbed FLR powder was used to prepare calcium alginate beads by ionotropic gelation method.

Floating time was controlled by density of beads and hydrophobic character of drug Sher et. al. was to design a novel/conceptual delivery system using ibuprofen, anticipated for chronotherapy in arthritis with porous[32]material to overcome the formulation limits (multiple steps, polymers, excipients) and drug loading for a desired release profile suitable for *in vitro* investigations. This delivery system lies in the availability of maximum drug amount for absorption in the wee hours as recommended. Drug loading on porous carrier, synthesized by high internal phase emulsion technique using styrene and divinylbenzene, was done through solvent evaporation using methanol (M) and dichloromethane (DCM). This uniqueness helped in achieving the least drug release an ideal one, without using any release modifiers, making it distinct from other approaches/technologies for time-controlled release and for chronotherapy. Chronotherapy, a new approach for treating pathological conditions, is based on circadian rhythm. Present work conceptualizes a specific technology has been conceptualized, based on combining floating and pulsatile principles to develop drug delivery system,[33] intended for chronotherapy in arthritis. This approach was achieved by using low-density microporous polypropylene, Accurel MP 1000®, as a multiparticulate carrier along with drug of choice Ibuprofen. Carrier amount and solvent volume was kept invariant in designing this simple system by adsorbing drug through melting or solvent evaporation using different carrier: drug ratios. In solvent evaporation, M and DCM were used. Drug-loaded multiparticulate system was subjected to various characterization and evaluation parameters showing influence of adsorption process. Present drug delivery system devoid of any additives/excipients influencing drug release shows distinct behaviour from other approaches/technologies in chronotherapy by (a) observing desired low drug release (11%) in acidic medium, (b) overcoming the limitations of process variables caused by multiple formulation steps, (c) reducing time consumption due to single step process, and (d) can be extended to controlled release also.

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A novel multiparticulate gastro retentive drug delivery system has been developed.[34]Floating microparticles consisting of (i) polypropylene foam powder; (ii) verapamil HCl as model drug; and (iii) Eudragit RS, EC or polymethyl methacrylate as polymers were prepared with an O/W solvent evaporation method. The effect of various formulation and processing parameters on the internal and external particle morphology, drug loading, *in vitro* floating behaviour, *in vitro* drug release kinetics, particle size distribution, and physical state of the incorporated drug was studied. The size of the microparticles was almost independent of the drug loading, but strongly depended on the amount of polymer. The drug was partly dissolved and partly in the amorphous form, distributed throughout the system.

7.0 In Vitro evaluation parameters for single Unit FPPDS: (Tablet)[35]

1. Drug excipient compatability study

(i) FTIR
(ii) DSC
(iii) XRPD

2. Uniformity of weight
3. Hardness
4. Thickness and Diameter
5. Friability
6. Content uniformity
7. Buoyancy study
8. Floating lag time
9. Swelling index
10. Pulsatile lag time
11. Dissolution study

8.0 In vitro evaluation parmeters for Multi particulate FPDDS:[31]

1. Drug excipient compatability study
   (i) FTIR
   (ii) DSC
   (iii) XRPD
2. Particle size analysis
3. Percent yield
4. Entrapment efficiency
5. Surface topography

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6. Buoyancy study
7. Floating lag time
8. Pulsatile lag time
9. Dissolution study

9.0 In vivo evaluation parameters:[36]

1. X –Ray Study
2. Gamma Scinitigraphy
3. Ultrasonography
4. Alternating current biosusceptometry
5. Magnetic resonance imaging

Conclusion:

This review emphasizes on chronotherapeutic drug delivery based on novel concept which is a blend of floating pulsatile principles. With conventional pulsatile release dosage forms, the highly variable nature of gastric emptying process can result *in vivo* variability and bioavailability problems. To overcome this, novel approach floating pulsatile drug delivery system was developed. This novel floating pulsatile drug delivery system plays a vital role in the treatment of various diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, diabetes, attention deficit syndrome, hypercholesterolemia, and hypertension that rely on circadian rhythms which is genetically present in human beings.

Different methods of FPDDS are time-controlled FPDDS which includes delivery systems with rupturable coating layer or with erodible coating layers or with release controlling plug and multiparticulate system. These considerations, coupled with the potential therapeutic benefits of FPDDS, should ensure that the current high level of interest in this area would extend well into future and result in the betterment of quality of life.

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