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An Over View of Chronotherapeutic Drug Delivery Systems Based on Floating Pulsatile Concept

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Authors' contributions

This work was carried out in collaboration among all authors. Author TV did the literature search and wrote the manuscript. Authors TEGKM and ASR proof read the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

In the modern era of pharmaceutical research much attention has been focussed on patients' health in terms of therapeutic efficacy and safety. 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 different drug delivery systems its advantages and disadvantages, role of circadian rhythms in major risk occurring disorders, like joint pains in case of rheumatoid arthritis, cardiovascular diseases like angina pectoris, hypertension, myocardial infarction, pulmonary disorder like asthma and their treatment by conventional and novel pulsatile drug delivery systems.

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1. INTRODUCTION

Oral dosage forms plays a vital role in treating diseases as these are easily acceptable by patients as there is no difficulty while taking these medications.

The objective of this article is to give brief description of different drug delivery systems, prerequisite conditions, advantages, disadvantages and case studies.

There are various types of oral drug delivery systems that have been developed with respect to drugs and disease conditions. These include

1.1 Sustained Drug Delivery

Sustained release dosage forms are defined as the dosage form that extends the therapeutic activity of the drug [1]. These dosage forms are being used in the treatment of acute and chronic disorders as they maintain plasma drug concentration within therapeutic window for prolong period of time [2].

Pre requisite characteristic features of drug suitable to design sustained release dosage form [3,4]
Drugs should have short half - life i.e. 2-8 hours. Eg: Tramodol HCl
Drugs must be absorbed through GIT. Eg: Ivabradine HCl, Nicorandil.
Drugs should have good soluble nature. Eg: Captopril.
Dose of the drug should be low, as large doses are incorporated in sustained release dosage form. Eg: Glimepiride.

1.1.1 Advantages of sustained drug delivery [5]

1. Local and systemic side effects were reduced.
2. Reduction in total amount of drug used, as the drug levels are maintained in plasma in steady state for prolong period of time
3. Reduction in dosing frequency
4. Improved patient compliance.
5. Fluctuations of drug level in plasma is not seen which is present in multiple dosing of conventional therapy for drugs with short half life.

1.1.2 Disadvantages of sustained drug delivery [6]

1. Dose dumping occurs as multiple doses are incorporated in a single dosage form.
2. Once sustained release dosage form is administered termination of therapy is difficult as many doses are administered in a single dosage form.
3. Costlier when compared to conventional dosage forms.
4. Patient should be educated while administering these dosage form i.e. they should not chew the tablet
5. Poor in vitro in vivo correlation.
6. Variations in gastric emptying time results in reduced efficacy of an administered dose because of incomplete drug release into absorption medium from device.

Table 1. Case studies on sustained release dosage forms

S. no	Drugs	Polymers + excipients	Results	Ref. no
1.	Tramadol HCL	Gum Kondagogu+ HPMC	Drug Release was sustained upto 10 hours and followed zero order kinetics. Mechanism by which drug released was found to be swelling, erosion and diffusion	[7]
2.	Ranitidine HCL	Eudragit RLPO+ Eudragit EPO	Combination of 10% Eudragit RLPO and 10% Eudragit EPO sustained the drug release upto 12 hours and moisture gain was found to be decreased.	[8]
3	Cefixime Trihydrate	Tamaring gum+ Carnuba wax+ HPMC	Tablets prepared with combination of HPMC and carnuba wax sustained the release for 112 hours and followed Higuchi model.	[9]

1.2 Floating Drug Delivery System (FDDS)

Floating drug delivery system has been developed in an attempt to increase the gastro retention time of dosage form there by targeting the drug release in specific area of the body. i.e. in the upper GIT for local / systemic treatment. These are low density systems that remained floating over gastric contents for prolonged period of time by maintaining buoyancy without affecting gastric emptying rate [10,11]

Drugs suitable to formulate FDDS:

1. Drugs which got local action in the stomach. Eg: Antacids, Misoprostol [12].
2. Drugs that is unstable in the lower part of GIT. Eg: Captopril, Ranitidine Hydrochloride [13].
3. Drugs with low solubility at high p^H Eg: Verapamil [14].
4. Drugs with narrow absorption window in GIT. Eg: Levodopa, Riboflavin [15,16].

Drugs unsuitable to formulate FDDS:

1. Drugs that are unstable in gastric region Eg: Erythromycin [15].
2. Drugs with limited acidic solubility Eg: Phenytoin [12,15,17]
3. Drugs with selective release in the colonic region Eg: Corticosteroids, 5 Aminisalicylic acid [12,15,17].

1.2.1 Advantages of FDDS

1. Drugs that shows it efficacy in stomach region Eg: Antacids [13]
2. Drugs with maximum absorption in stomach Eg: Ferrous salts, antacids, thiopental [18].
3. Site specific drug delivery [13].

1.2.2 Dis advantages of FDDS

1. These drug delivery systems requires to maintain fluid in stomach in a higher level; then only these dosage forms works effectively. So patients asked to take water for every 1 hour [12]
2. Drugs which have stability and solubility problems cannot be formulated as FDDS.

Drugs that cause irritation and lesions to gastric mucosa cannot be designed as FDDS.

1.3 Chronotherapeutic Drug Delivery

Chronotherapy got attention in designing of Novel drug delivery system for treating diseases that rely on circadian rhythm.

The custom of prescribing medication that maintains 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

Table 2. Case studies on FDDS

S. no	Drugs	Polymers + excipients	Results	Ref. no
1.	Ciprofloxacin	HPMC+PEO+ NaHCO3	Optimized formulation contained 22% NaHCO3 and 11% of total polymers in the ratio of (5:5) of HPMC 10K and PEO 1000 K exhibited floating lag time of less than 5s, total floating time > 8h and drug release was found to be more than 80% for 8 h.	[19]
2.	Nizatidine	HPMC+NaHCO3+citric acid	Optimized batch of tablets showed floating lag time of 10s and total floating time of 12 hrs with 99.46% of drug release	[20]
3	Capecitabine	HPMCK4M, Sodium alginate, carbomer 934 p, NaHCO3.	These formulations exhibited floating lag time from 30- 200s and floated for more than 24 hrs and the drug release was extended up to 24 hours.	[21]

biological rhythms [22]. The term "Chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time [23]. 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 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.

Human body contains biological rhythm/ biological clock. This rhythm occurs episodically in human body in accordance with systematic changes that takes place in environmental conditions. Genetic make up dictates the internal clocks [24].

Human body exhibits four rhythms [25].

1. Ultradian: cycles takes place for short interval
   Eg. sleep cycle that occurs with in 90 minutes.
2. Circadian: time duration for this rhythm is 24 hours.
   Eg. sleep wake cycle.
3. Infradian: Time interval for this type of rhythm is more than 24 hours
   Eg. Menstrual cycle
4. Seasonal: this type of rhythm occurs seasonally.
   Eg: Seasonal affective disorder.

1.4 Circadian Rhythm

Rhythm that occurs in body within 24 hours is referred to as circadian rhythm. It rely on sleep wake cycle which is prejudiced by genetic makeup in our body. This in turn reflects the physiological functions of human body [26]. Certain disease conditions like hepatic and renal impairment, lung and cardiovascular diseases rely on circadian rhythm, which was supported by chronobiological studies. These studies revealed that all body functions are in coherence with circadian rhythm [27].

1.5 Generation of Circadian Rhythm

Halberg and Stephens coined the term circadian rhythm in 1959 [28]. Habitual actions ie physiological and biochemical secretions are under the control of circadian rhythm in human body that vary in a day. Hence abnormalities in physiology also vary in a day.

Suprachiasmatic nucleus of brain produces circadian rhythm that is regulated by melatonin harmone of pineal gland. Fluctuations in secretion of hormones like rennin, cortisol and aldosterone in blood are seen as these are controlled by circadian rhythm [29].

1.6 Circadian Time Structure

The results of numerous biological rhythm studies help to define the temporal organization of human beings. 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 following table 3 shows metabolic hormones and/ secretions takes place at peak level in human body at various time intervals.

The physiological and bio chemical responses vary in synchronized way during the day and night [30].

2. CHRONOTHERAPY

Coordination of biological rhythms with medical treatment is called *Chrono therapy.* 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.

2.1 Need of Chrono Therapeutic Drug Delivery Systems [31,32]

2.1.1 Diseases like hypertension, angina pectoris, myocardial infarction bronchial asthma, ulcer, rheumatoid arthritis require chronotherapy as they shown crests and trough in their symptoms in 24 h cycle.

2.1.2 This delivery system is necessary for drugs that undergo degradation in acidic medium (e.g. peptide drugs), that cause irritation to mucosa of stomach region or provoke nausea and vomiting

Table 3. Peak levels of Hormonal and biochemical secretions in human body at various time intervals

Early morning	Afternoon	Evening	Night/ during sleep
Plasma cortisol, renin activity, angiotensin, and aldosterone peak in the morning and also arterial compliance, vascular resistance, platelet aggregation, and blood viscosity.	Haemoglobin and insulin concentrations rises drastically in the afternoon	Synthesis of cholesterol, triglycerides and diuresis are at peak level in the early evening.	Gastric acid secretion, white blood cells count (WBC), secretion of calcitonin gene related protein, and secretion of atrial natriuretic peptides are peak at late night or early in sleep. Growth and thyroid stimulating hormone (TSH), blood lymphocyte and eosinophil number, and plasma melatonin and prolactin show steep increase during sleep.

2.1.3 Targeted drug delivery system where drug release is confined to particular part of GIT Eg: colon targeted drug delivery system in which drug release is restricted in stomach and small intestine and drug is released in colon.

2.1.4 Drugs that undergo hepatic metabolism are formulated as pulsatile dosage form.

2.1.5 Drugs which can develop tolerance upon continuously exposing to body parts requires chronotherapeutic dosage forms .

2.2 Advantages of Chronotherapy

2.2.1 Chronotherapy is drug-free: In case of sustained release, the extra amount of doses has been incorporated for prolonging the drug release. Whereas in chronotheray the extra doses are not required as the drug is released when symptoms are at peak level.

2.2.2 This type of treatment becomes effective if person sleeps for long time.

2.2.3 This therapy is unlike from other therapies as one can envisage the time at which it works better as it has an initial, middle, and final phase;

2.2.4 Stability of drug is improved as lag phase is maintained where drug is not stable

2.2.5 Risk of dose dumping is controlled [33]

2.3 Disadvantages of Chronotherapy

2.3.1 Medical supervision is mandatory for this therapy.

2.3.2 Large number of process variables are required when compare to conventional process e.g pulsin cap technology vs. conventional tablet.

2.3.3 Trained /skilled person is needed for manufacturing [34]

3. 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 essential. Scientific background is required to justify the need for chronotropic systems as compared to conventional drug delivery systems. Particular rhythms in the onset and extent of symptoms are observed in diseases such as bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, diabetes, attention deficit syndrome, hypercholestemia and hypertension.

In case of asthma, aggravation of attacks often 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 [35]. Plasma concentration of C - reactive protein and interleukin-6 increases in rheumatic patients during morning hours due to circadian changes.

4. TYPES OF CHRONO THERAPEUTIC DRUG DELIVERY SYSTEMS

(i) Pulsatile drug delivery system
(ii) Floating pulsatile drug delivery system

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 chronotherapeutic delivery systems for desired drug release.

These techniques are broadly classified into following three major categories [25]:

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

4.1 Pulsatile Drug Delivery System (PDDS):

Certain disease like asthma, angina pectoris, hypertension rely on circadian rhythm where these disease shows peak symptoms at particular time in biological clock. To satisfy these conditions pulsatile drug delivery system was emerged where drug is released in a burst manner immediately after a pre determined lag phase. It is a time and site specific drug delivery system [36]

4.1.1 Prerequisite conditions for PDDS

1. Drugs which degrade in acidic medium of GIT requires lag phase.
   Eg: peptide drugs [37]
2. Colon targeting drugs where drug release is restricted in upper two third portion of git.
   Eg: Tramadol HCl. [37]
3. Drugs that exhibit first pass metabolism required to formulate as pulsatile dosage forms.otherwise it may result in reduction in bio availability of drug
   Eg: Ivabradine HCl. [37]
4. Diseases that rely on circadian rhythms:
   Eg: Myocardial infarction, angina pectoris, hypertension, rheumatoid arthritis, bronchial asthma [38].

4.1.2 Advantages of PDDS

1. Dose size, dosing frequency, cost has been reduced.
2. Adverse effects have been minimized
3. Local irritation can be reduced.
4. Targeting drug to particular site Eg: colon can be achieved.
5. Drug loss by extensive first pas metabolism can be prevented.

4.1.3 Disadvantages of PDDS

1. Lack of manufacturing reproducibility.
2. Skilled persons are required for developing these dosage forms.
3. Long residence time in stomach is not possible which results in *in vivo* variability and bio availability problems due to high variable nature of gastric emptying process.

4.2 Novel Approach to PDDS: (ii) Floating Pulsatile Drug Delivery System

Pulsatile drug delivery systems can maintain lag phase and releases the drug in burst manner but it could not retain the dosage form in stomach for longer period of time. As a result variation in process of gastric emptying occurs that causes *in vivo* variation and reduced bio availability [41]. To overcome this novel approach to PDDS termed as floating pulsatile drug delivery system was developed.

Table 5. Case studies on pulsatile drug delivery system (PDDS):

S. no	Drugs	Polymers + excipients	Results	Ref. no
1.	Ramipril	HPMCK100M, Ethyl cellulose, cross caramellose sodium.	The optimized batch showed lag time for 5 h. and exhibited 83.96% of drug release for 7 h.	[39]
2.	Nebivolol	L HPC, Ethyl cellulose	The optimized batch exhibited lag time for 5.25 h before burst release could occur.	[40]

In this approach combining the principles of floating and pulsatile would be advantageous, that drug can be retained in stomach for prolonged time as it floats in stomach and lag phase is maintained during floating, burst release is exhibited in small intestine after predetermined lag phase [42]. A pulsatile drug delivery that can be administered at bed time but releases drug in early morning would be a promising chronotherapeutic system.

4.2.1 Advantages of floating pulsatile dosageforms

1. Gastric residence time for these dosage forms has been increased.
2. Conventinal tablets of aspirin irritates gastric mucosa when comes in contact with it. Hence floating pulsatile approach may be suitable to formulate these type of drugs. In case of floating pulsatile, the lag phase (Period of no drug release) is maintained during floating in acidic medium i.e. in stomach. So aspirin will not be released in stomach and hence no irritation to GI tract.
3. It has application for local drug delivery to the stomach and proximal small intestine e.g., ranitidine for nocturnal acid breakthrough.
4. In sustained release multiple doses are required where as single dose is sufficient in floating pulsatile release. So dose dumping risk is less in the floating pulsatile release when compared to sustained release.
5. Time controlled floating pulsatile tablet with lag phase followed by “rapid” release would treat midnight acidity.
6. Floating pulsatile drug delivery increases drug bioavaibility; predictable, reproducible, and improved retention time of dosage form in stomach, risk of dose dumping is reduced;

4.2.2 Disadvantages

1. Full glass of water (200-250 ml) is required while administering these dosage forms.
2. Various formulations steps are involved while manufacturing these dosage forms hence production cost increases. Requires advanced technology, trained and skilled person.

4.2.3 Polymers used for floating pulsatile drug delivery systems

1. Polymers used for buoyancy layer Carbopol 934p, HPMC K_4M, HPMC $K_{15}M$, Hydrogenated Castor oil (Kolliwox HCO), 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.
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.
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.

5. DIFFERENT FLOATING PULSATILE DOSAGE FORMS

5.1 Time Controlled Floating Pulsatile Drug Delivery System

Time-dependent dosage forms are designed to deliver the drug after a predetermined lag time [43]. E g. Ivabradine HCl floating pulsatile microspheres.

5.2 Different Mechanisms

Reservoir System containing erodible Polymer or Barrier Coating with soluble nature:

A floating pulsatile dosage form contains three different parts, upper buoyancy layer, middle erodible layer, inner rapid release layer containing active pharmaceutical ingredient. In this dosage form buoyancy layer is suitable for prolonging gastric residence time .Lag time in pulsatile dosage forms was obtained by erodible polymers. Combination of HPMC and carbomer was used to improve floating or muco adhesiveness of drug delivery systems [44,45].

Table 6. Summary of previous works on floating pulsatile drug delivery systems

S. no	Drugs /Category	Dosage form	Polymers/ Excipients	Method	Reason/Result	Ref. no.
1	Meloxicam/NSAID .For treating rheumatoid arthritis	Tablet	Crosscaramellose sodium ,Crospovidone,MCC, HPMCE5,E15,E50, HPMCK15,NaHCO3	1.WET Granulation for rapid release core tablet (RRCT) 2.Dry coating of optimized RRCT by HPMC(E5,E15,E50)for obtaining pulsatile release tablet(PRT) 3.Optimized PRT was compressed along with HPMCK15 N aHCO3 for floating pulsatile release tablet(FPRT).	1. In RRCT 5%conc of crospovidone was optimized as it showed required hardness, content uniformity, lowest disintegration& highest drug release.so it is suitable to prepare PRT 2. The optimization of PRT was done based on lag time of 6 hrs during which drug was not released ,this was achieved by HPMCE50(280mg).This was further used to prepare FPRT by compressing this along with 120 mg of HPMCK15 & 10mg of NaHCO3 which gave satisfactory floating lag time of 4.6 min and more than 12 hrs of floating.	[51]
2	Ibuprofen/NSAID For treating rheumatoid arthritis	Micro beads	Cavilink(styrene &divinyl benzene copolymer made by HIPE technique)	Drug adsorption via solvent evaporation using porous carrier cavilink	More amount of drug got adsorbed by using DCM (97%)than with methanol (85%) 1.Methanol adsorbed micro beads had shown 1.3-52% of drug release in acidic medium whereas in DCM micro beads exhibited 0.98-2.84% of drug release. both type of beads had shown floating property for 6 hrs. 2.In basic medium both methanol and DCM micro beads exhibited burst release but vary in the % of release i.e 54.13-82.8% (methanol micro beads),71-87%(DCM microbeads).Hence DCM microbeads were optimized.	[52]
3	Aceclofenac/NSAID For treating rheumatoid arthritis	Floating Pulsatile microspheres	Eudragit S100,L 100	Emulsion solvent diffusion technique	These microspheres provided time and site specific drug release with initial lag phase during floating in acidic medium followed by burst release in basic medium.	[49]
4	Metoprolol Tartrate/Antihypertensive agent . For controlling B.P	Floating Pulsatile microspheres	Eudragit S100,L 100	Emulsion solvent diffusion technique	These microspheres provided time and site specific drug release with initial lag phase during floating in acidic medium followed by burst release in basic medium	[53]
5	Meloxicam/ NSAID For treating rheumatoid arthritis	Ca alginate beads containing drug adsorbed florite powder	Sodium alginate, porous calcium silicate(Florite RE)	Ionotropic gelation method	Beads had shown a lag time ranging from 1.9-7.8 hrs in acidic medium followed by rapid release of drug in intestinal fluid within 1 hr.	[54]

S. no	Drugs /Category	Dosage form	Polymers/ Excipients	Method	Reason/Result	Ref. no.
6	Ibuprofen/ NSAID For treating rheumatoid arthritis	Micro particles	Accurel MP 1000(polypropylene foam powder)	Adsorption of drug via melting or solvent evaporation.	1:3 (Accurel MP: drug) was optimized in both melting and solvent evaporation technique without much deviation in drug release.	[55]
7	Diclofenac sodium / NSAID For treating rheumatoid arthritis	Hollow calcium pectinate beads	Pectin	Acid base reaction during ionotropic crosslinking	Invivo studies conducted in rabbits have shown gastric retention of beads for 5 h followed by burst release which is a promising approach for time and site specific release for chronotherapy.	[56]
8	Indomethacin/ NSAID For treating rheumatoid arthritis	Pellets	Eudragit S100(ES100),HPMCK100M,NaHCO3	Extrusion Spheronjization process	Drug containing core pellets were coated with ES100,a PH dependent polymeras an inner layer & outer floating layer with NaHCO3 and HPMCK100M.These pellets showed excellent lag period followed by burst release.	[50]
9	Ranitidine Hcl/H2 receptor blocker for treating acidity	Tablet	MCC, Croscarmellose Na Ethyl cellulose (ECN10) ,HPMCE15,NaHCO3,Eudragit RL100(ERL100)	Direct compression method for rapid release core tablet (RRCT) which was further coated with ECN10, HPMCE15 for pulsatile release (PRT). For effervescence purpose this PRT is further coated with HPMCE15 and NaHCO3. Finally for effervescence entrapment it was coated with Eudragit RL 100	5% w/w of croscaremellose Na&50.15%w/w of MCC was optimized for obtaining RRCT. For pulsatile release (97.56%) with lag time of 3-3.5 hr was obtained withECN10:HPMCE15 (80:20%. Ratio of HPMCE15 & NaHCO3(1:4%w/w)gave satisfactory results for providing effervescence and floating lag time of 5 min.5%w/w of ERL100was found to be best as it increased tablet weight by 1%& floating lag time was found to be 5 min. Further increase in concentration increased floating lag time and obtained sustained release instead of pulsatile release.	[47]
10	Metoprolol Tartrate/Antihypertensive agent . For controlling B.P	Tablet	Crosscaramellose sodium ,Crospovidone,MCC, HPMCE5,E15,E50, HPMCK15,NaHCO3	1.WET Granulation for rapid release core tablet (RRCT) 2.Dry coating of optimized RRCT by HPMC(E5,E15,E50) for obtaining pulsatile release tablet(PRT) 3. Optimized PRT was compressed along with HPMCK15 NaHCO3 for floating pulsatile release tablet(FPRT).	1.In RRCT 5%conc of crospovidone was optimized as it showed required hardness, content uniformity, lowest disintegration& highest drug release.so it is suitable to prepare PRT 2. The optimization of PRT was done based on lag time of 6 hrs during which drug was not released ,this was achieved by HPMCE50(280mg).This was further used to prepare FPRT by compressing this along with 120 mg of HPMCK15 & 10mg of NaHCO3 which gave satisfactory floating lag time of 4.6 min and more than 12 hrs of floating.	[57]

S. no	Drugs /Category	Dosage form	Polymers/ Excipients	Method	Reason/Result	Ref. no.
11	Diclofenac sodium / NSAID For treating rheumatoid arthritis	Pellets	Eudragit S100(ES100),HPMCK100M,NaHCO3	Extrusion Spheronization process	Drug containing core pellets were coated with ES100,a PH dependent polymeras an inner layer&outer floating layer with NaHCO3 and HPMCK100M.These pellets showed excellent lag period followed by burst release.	[58]
12	Valsatran	Hollow Calcium alginate beads	Sodium alginate, potassium bicarbonate,CaCl2	Ionotropic gelation	Sodium alginate concentration to interpret lag phase and drug release was analysed statistically by response surface methodology for optimization. Floating beads were porous & have bulk density <1,floated for 11 hrs.It provided two phase release pattern with initial lag time of 6 hrs during floating in acidic medium followed by burst release in basic medium.	[59]
13	Aceclofenac/NSAID For treating rheumatoid arthritis	Hollow calcium pectinate beads	Pectin, CaCl2	Ionotropic gelation	These beads had shown two phase release pattern with initial lag phase during floating in acidic medium followed by burst release in basic medium.	[60]
14	Lornoxicam/Non selective COX2 inhibitor. For treating rheumatoid arthritis	Tablet	Crospovidone,PVPK-30,βcyclodextrin,MCC,Eudragit S100(ES100), HPMCK 100 M.HPMC E50,NaHCO3.	Wet granulation method for rapid release core tablet(RRCT) followed by coating withES100 solution for pulsatile release and finally compressed HPMCK 100 M. or HPMC E50,and NaHCO3 for obtaining floating property.	The optimized floating pulsatile release tablet had shown excellent floating property in acidic medium with no drug release followed by burst release in basic medium.	[61]

Table 7. Case studies for *in vitro* evaluation parameters for single Unit FPPDS

Name of the drugs & excipients	Parameters	Outcome	Reference number
Drug: Sumatriptan Excipents: Xanthan gum, Polyox WSR 205	FTIR	Drugs and excipients are compatible as there was no change in characteristic peaks of drug in IR spectra in physical mixture of drug and excipients compared to IR spectra of pure drug.	[62]
	DSC	It revealed M.P of pure drug as 159-162ºC, polyox as 75-80ºC and xanthan gum as 95-100ºC. But in optimized formulation DSC spectra showed MP at 75-80ºC that might be due to interlinking of both the polymers. Whereas drug has shown MP at 159ºC	
	Weight variation	323.87±0.1 mg	
	Hardness	6±0.1 kg/cm^2	
	Thickness and diameter	4.1±0.2 mm and 9.1±0.1 mm	
	Friability	0.7±1	
	Content uniformity/ drug content	99.85±0.2%	
	Floating lag time	55±2 s	
	Swelling Index at 4 hr	226	
	Pulsatile lag time	7±0.1 h	
	% drug release	98.69±2%	
Drug:Nizatidine Excipients: Chitosan , HPMCK15	FTIR	Drugs and excipients are compatible as there was no change in characteristic peaks of drug in IR spectra in physical mixture of drug and excipients compared to IR spectra of pure drug.	[63]
	Weight variation	550±5%	
	Hardness	5.34±0.12 kg/cm^2	
	Thickness and diameter	4.05±0.6 mm and 12±0 mm	
	Friability	0.554±0.05%	
	Content uniformity/ drug content	101.14±0.7%	
	Floating lag time	150 s	
	Total floating time	>8h	
	Pulsatile lag time	4 h	
	% drug release	99.88±0.39%	
Drug: Metoprolol tartrate Excipients:HPMCK15M, cross caramellose sodium ,crosspovidone	FTIR	Drugs and excipients are compatible as there was no change in characteristic peaks of drug in IR spectra in physical mixture of drug and excipients compared to IR spectra of pure drug.	[64]
	Hardness	5.68±0.17 kg/cm^2	
	Thickness and diameter	4.2±0 mm and 10±0 mm	
	Floating lag time	4.6 min	
	Total floating time	>12 h	
	Pulsatile lag time	6 h	
	% drug release	105.6±0.1%	

Table 8. Case studies for *in vitro* evaluation parameters for Multi Unit FPPDS

Name of the drugs & excipients	Parameters	Outcome	Reference number
Drug: Piroxicam Excipients: Eudragit S100	DSC	Melting peak of drug disappeared in microballons. Upon increasing the drug: polymer ratio from 1:1 to 1:2. Even though the melting peak was observed in drug: polymer physical mixture with the same ratio which reveals that drug has been dispersed in the polymer matrix as amorphous form.	[65]
	XRPD	XRPD characteristic peaks of piroxicam were observed in case of pure drug and 1:1 drug: polymer ratio at diffraction angle of 2Ɵ. But no such peaks were observed in case of 1:2 drug: polymer ratio.	
	Particle size(µ)	250-380	
	% yield	65.5-73.8%	
	% entrapment efficiency	90-98%	
	Surface topography	No major surface irregularities	
	Total floating time	8h	
	Pulsatile lag time	6h	
	Dissolution study	99% of drug was released within 3 h	
Drug: Diclofenac sodium Excipient: Pectin	FTIR	Drug and polymer were compatible. Same peaks retained in drug loaded calcium pectinate beads compared to pure drug and blank calcium pectinate beads.	[66]
	Particle size(µ)	1430-1970	
	% yield	88.5-93.55%	
	% entrapment efficiency	63%	
	Surface topography	Rough and porous	
	Total floating time	12h	
	Pulsatile lag time	6h	
	Dissolution study	Complete drug was released within 30-45 min.	

Table 9. Case studies on *in vivo* evaluation parameters

Name of the drugs & excipients	Parameters	Outcome	Reference number
Drug: Diclofenac sodium Excipient: pectin	Gamma Scintigraphy	Gamma Scinitigraphic studies were carried out for calcium pectinate beads of diclofenac sodium using 3 New Zealand white rabbits as animal model. This study revealed that beads remained floating for 6 h *in vivo*.	[66]
Drug: Metoprolol tartrate Excipients:HPMCK15M, cross caramellose sodium, crosspovidone	X Ray study	This was carried on 3 human volunteers by using Barium sulphate loaded formulation to study the floating behaviour of tablets in fast and fed state. Radiographs were taken at 0, 0.5, 2, 4, 6, 8h. In both fed and fast state tablets showed buoyancy in radiographs taken at 0.5h. Radiographs revealed that tablet remained floating in stomach for 6.5±0.5 h.	[64]
Losartan potassium sulphated cordial myxa	*In vivo* pharmacokinetics	Dissolution studies revealed that sulphated cordial myxa showed 99.34% of drug release at the end of 24 h. The *in vivo* study showed 4.4 times higher $AUC_{0-\infty}$ values of tablets formulated with sulphated cordial myxa than tablets formulated with carbopol934. These results indicated that sulphated cordial myxa polymer can be successfully used as polymer for formulating gastro retentive muco adhesive tablets of Losartan potassium for treating hypertension.	[67]

The novel system which is a combination of floating and pulsatile principles will prolong gastric residence time to obtain lag phase during floating followed by rapid release of drug in accordance with time specific condition by erosion of coating layer.

5.3 Reservoir System with Rupturable Coating

In this systems core expansion results in both floating and pulsatile properties. Expansion of core makes the system less denser than gastric fluids hence floats and as core expands pressure is created on coating layer and finally ruptures resulting in pulsatile release [46].

This mechanism is involved in the development of floating pulsatile drug delivery of ranitidine HCl [47]

5.4 Capsule Shape System Containing Floating Material and Release Retarding Hydrogel Plug

This system consists of a insoluble capsule body and soluble cap where buoyant material is placed at the bottom of insoluble body followed by drug tablet above that erodible drug-free hydrogel plug was placed which closes the body followed by soluble cap. When this system is exposed to aqueous fluids cap solubilises and after that hydrogel plug swells and erodes gradually responsible for obtaining lag phase.when this plug degrades completely drug release starts and buoyant material at the bottom of capsule body is responsible for obtaining floating property.

Eg: Krogel I and Bodmeir R developed void, impermeable cylinder system made up of polypropylene for rapid release of ibuprofen. Air filled spaces are responsible for floating property. Length and composition of HPMC hydro-gel plug controlls lag phase [48].

5.5 Multi Particulate Dosage Forms

This includes floating pulsatile microspheres and floating pulsatile pellets. Floating pulsatile microspheres are prepared by non aqueous (o/o) solvent evaporation method for water soluble drugs like Ivabradine HCl [43] and o/w solvent evaporation method for water insoluble drugs (Aceclofenac) [49]. Floating pulsatile pellets are prepared in three steps, Step 1: preparation of drug containing core pellets by extrusion spheronization technique. Step 2: core pellets are coated with p^H sensitive polymer for obtaining lag phase. Step 3: Coated core pellets are further coated with buoyant materials for obtaining floating property [50]

6. *In vitro* EVALUATION PARAMETERS FOR SINGLE UNIT FPPDS: (TABLET)

1. Drug excipient compatibility 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

7. *In vitro* EVALUATION PARAMETERS FOR MULTI PARTICULATE FPDDS

1. Drug excipient compatibility study
   (i) FTIR
   (ii) DSC
   (iii) XRPD
2. Particle size analysis
3. Percent yield
4. Entrapment efficiency
5. Surface topography
6. Buoyancy study
7. Floating lag time
8. Pulsatile lag time
9. Dissolution study

8. *In vivo* EVALUATION PARAMETERS

1. Gamma Scinitigraphy
2. X –Ray Study

9. RECENT APPROACHES BASED ON QBD

QBD: A systematic approach to development that begins with predetermined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Table 10. Case studies based on QBD approach

Name of the drugs & excipients	Outcome	Reference number
Drug: Rifampicin Excipient: HPMC, NaHCO3 and glyceryl behenate	The optimized formulation exhibited Q1 of 20.9%, Q4 of 59.1%, and Q8 of 94.8% and floating lag time of 4 min. It followed Korsmeyer – Peppas power law	[68]
Drug: Cefuroxime Axetil PEO303, Excipient: HPMCK 100LV CR	The best formulation exhibited excellent floating behaviour and drug release was extended for prolonged period of time which was further confirmed by *in vivo* studies.	[69]
Drug: Itopride hydrochloride Excipient: Eudragit S100	The optimized formulation besides adequate drug release exhibited good floating character which was confirmed by *in vivo x*-ray imaging studies in rabbits for 8 h in upper GIT.	[70]

10. CONCLUSION

This review emphasizes on different drug delivery systems it advantages and draw backs, circadian rhythms and treatment of diseases that rely on circadian rhythms. i.e chronotherapeutic drug delivery based on novel concept which is a blend of floating pulsatile principles. Conventional pulsatile release dosage forms exhibits highly variable nature of gastric emptying process that results in *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 disorders associated with lungs, heart, liver, stomach etc. that rely on circadian rhythms which is genetically present in human beings.

The article also describes the modification of FPDDS and evaluation parameters of single unit and multi particulate floating pulsatile drug delivery system different approaches based on QBD. Thus this article envisages that FPDDS will flourish well in future for increasing safety and life span of patients.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Misal Ravikumar, Waghmare Atish, Aqueel Shaikh, et al. Matrix tablet: A promising technique for controlled drug delivery. Indo American Journal of Pharmaceutical Research. 2013;3(4):3791-3805.
2. Deore K Rakesh, Kuncha Kavita, Theetha G Tamizhmani. Preparation and evaluation of sustained release matrix tablets of tramadol hydrochloride using Glyceryl Palmitostearate. Tropical Journal of Pharmaceutical Research. 2010;9(3):275-2818.
3. Jant zen GM, Robinson JR. Sustained and controlled release drug delivery system, In Banker GS, Rhodes CT (Eds) Modern Pharmaceutics, Third Ed, Revised and expanded, Drugs and the pharmaceutical sciences, vol 72. Marcel Dekker, Inc, Newyork 1995;575-609.
4. Chugh I, Seth N, Rana Ac, Gupta S. Oral sustained drug delivery system: An overview. IRJP. 2012;3(5):57-62.
5. Thakor RS, Majumdar FD, Patel JL, Raj pit JC. Review: Osmotic drug delivery system Current Scenario. Journal of Pharmacy Research. 2010;3(4):771-775.
6. Patel H, Panchal DR, Patel U, Brahmabhatt T, Suthar M. Matrix type drug delivery system. A Review. Journal of Pharmaceutical sciences and Bio Scientific Research. 2011;1(3):143-151.
7. Kammalakkannan V, et al. Design and development of SR matrix tablets of Tramadol HCL using Gum kondagogu as a natural polymer. SAJP. 2015;4(3):199-207.

8. Paresh Patel, et al. Formulation and characterization of sustained release dosage form of moisture sensitive drug. Int. J Pharm Investing. 2015;5(2):92-100.
9. Arunabh Mishra, et al. Preparation and evaluation of SR tablets of cefixime Trihydrate using natural excipients. International Journal of Pharma Research and Review. 2015;4(6):1-6.
10. Vairappan K, Ayarivan P, Viswanadhan P, Krishna Moorthi M. Enhancement of drugs bio -availability by FDDS- A Review. International Journal of Drug Delivery. 2011;3:558-570.
11. Brahma N Singh, Khun H Kim. Floating drug delivery system: an approach to oral controlled drug delivery via gastricretention. Journal of Controlled Release. 2000; 63(3):235-259.
12. Nayak A, Maji R, Das B. Gastro retentive drug delivery system; A review. Asian Journal of Pharmaceutical Research. 2011;7(1):6-20.
13. Dixit N. Floating drug delivery system. Journal of Current Pharmaceutical Research. 2011;7(1):6-20.
14. Reddy S, Chakravarthy V, Bijika S, Rao S. Approaches to GRDDS: An overview. Int. Journal of Review in Life Sciences. 2011;1(2):62-75.
15. Borase CB. Floating systems for oral controlled release drug delivery. Int. Journal of Applied Pharmaceutics. 2012;4(2):1-3.
16. Katakam V, Somagoni, Reddy S, Eagac. floating drug delivery systems, a review. Current Trends in Biotech. And Pharmacy. 2010;4(2):610-647.
17. Nayak AK, Maji R, Das B, Gastro retentive drug delivery systems: A review. Asian J Pharma. Clinical Res. 2010;1(5):1-10.
18. Andrian C, Hogben M, Lewis S, Schanter Dominick J Tocco, Bernard B Brodier. The Journal of Pharmacology and Experimental Therapeutics. 1957;120(4):540-545.
19. Shim BH, Kim DK, Lee J, et al. Gastro floating matrices designed for simultaneous improvement of floating and drug release capabilities an in vitro case study of matrices loaded with ciprofloxacin HCl. J. Drug DEL. Sci. TECH. 2011;21(3): 279-281.
20. Choure Soniya, et al. Formulation and evaluation of floating tablets of Nizatidine. Int. J. Res. Ayurveda Pharm. 2015;6(2): 290-298.
21. Eshan Taghizadeh Davondi, et al. Preparation and characterization of a gastric floating dosage form of capecitabine. Biomed Research International; 2013.
22. Sajan J, Cinu TA, Chacko AJ, Litty J, Jaseeda T. Chronotherapeutics and chronotherapeutic drug delivery systems. Tropical J Pharm Res. 2009;8(5):467-75.
23. Trivedi RV, Wadher KJ, Taksande JB, Mahore JG, Umekar MJ. Chronotherapy: A concept, pauperism and approches. Int J Pharma Dev Tech. 2011;1(1):1-10.
24. Sudhamani T, Radhakrishanan M, Deepthlakshmi M, GanseanV, Chronotherapeutic floating pulsatile drug delivery: An approach for time specific and site specification absorption of drugs. Research Journal of Pharmaceutical Technology. 2011;4(5):685-690.
25. Manpreet Kaur, Rajni Bala. Chronotherapy: A review. IJPSR. 2013; 4(1):90-102.
26. Evans RM, Marain C. Taking your medication: A question of timing. American Medical Association. 1996;3-8. Marain C, editors, eds.
27. Li JJ. Circardian variation in myocardial ischemia: The possible mechanisms involving in this phenomenon. Med Hypotheses. 2003;61(2):240-243.
28. Halbeg F, Stephens A. susceptibility to auabain and physiological circadian periodicity. Proc Minn Acsd Sci. 1959;27: 139-43.
29. Gunny R, Junginger HE, Peppas N, Pulsatile drug delivery system: Current applications and future trends, stuftgart, Germany, Wissenchtflich, Velagsggels; 1993.
30. Devdhawala Mehul G, Seth Avinash K. Current status of chronotherapeutic drug delivery system: An overview. J. Chem. Pharm. Res. 2011;2(3):312-328,
31. Vinupama S, Shwetha S, Kamath K, Keerthi S, Senthil Kumar. Pulsatile drug delivery system: A review. International Bulletin of Drug Research. 1(1): 19-31.
32. Leemer B. Chronopharmacokinetic: Implication for drug treatment. Journal of Pharmacy & Pharmacology. 1999;51:887-890.
33. Srinivas P. Chronotherapy-Clock of curing. International Journal of Pharma and Biosciences. 2011;2(1):19-23.

34. Smolensky GE. Medical chronobiology: Concepts and applications. Am Rev Respir Dis. 1993;147(6Pt):S2-19.
35. Survase S, Kumar N. Pulsatile drug delivery: Current scenario. CRIPS. 2007;8: 27-33.
36. Nidhi Nainwal. Chronotherapeutics — A chronopharmaceutical approach to drug delivery in the treatment of asthma. Journal of Controlled Release. 2012; 163(3):353-360.
37. Tangri P, Khurana S. Pulsatile drug delivery systems: Methods and advances. International Journal of Drug Formulation and Research. 2011;2(3):100-114.
38. Bhandawalkar K, Tamizarasi S, Nande H, Sivakumar T. Recent trends in pulsatile drug delivery systems: A review. International Journal of Institutional Pharmacy and Life Sciences. 2002;2(3): 167-185.
39. Rajesh Asija et al. Formulation and evaluation of pulsatile tablet of Ramipril. Journal of Chemical and Pharmaceutical Research. 2015;7(2):789-797.
40. Mehul Nayak, et al. Formulation and evaluation of pulsatile tablet of Nebivolol for chronotherapy of hypertension. IJPRBS. 2015;4(2):388-401.
41. Chawla G, Gupta P, Koradia V, Bansal AK. Gastroretention: A means to address regional variability in intestinal drug absorption. Pharm Tech. 2003;27:50-58.
42. Shivkumar HG, Gwda DV, Kumar Pramod TM. Floating controlled drug delivery systems for prolong gastric residence. Indian J Pharm Educ. 2004;38:172-179.
43. Vani Prasanna et al. Design and *In-vitro* evaluation of floating pulsatile microspheres of ivabradine hydrochloride. Inventi Journal. 2015;3.
44. Shivkumar HG, Gwda DV, Kumar Pramod TM. Floating controlled drug delivery systems for prolong gastric residence. Indian J Pharm Educ. 2004;38:172-9.
45. Li S, Lin S, Daggy BP, Mirchandani HL, Chien YW. Effect of HPMC and Carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. Int J Pharm 2003;253:13-22.
46. Hao Zou, Xuetao Jiang, Lingshan Kong, Shen Gao. Design and evaluation of a dry coated drug delivery system with floating-Pulsatile release. J Pharm Sci. 2008; 97:263-3.
47. Galgatte, et al. Floating pulsatile drug delivery of ranitidine hcl for nocturnal acid break through. Design, Optimization. Invitro & Invivo Evaluation. Int J Pharm Pharmsci. 2013;5:722-727.
48. Krögel I, Bodmeier R. Development of multifunctional matrix drug delivery system surrounded by an impermeable cylinder. J Controlled Release. 1999;61:43-50.
49. Shaji Jessy, Shinde Amol. Formulation & optimization of floating pulsatile aceclofenac microspheres using response surface methodology. IRJP. 2012;3;166-169.
50. Shaji J, Patole V. Novel floating pulsatile approach for chronotherapeutic release of indomethacin. Dhaka Uni J Pharm Sci. 2007;6:37-1.
51. Sunil Patel, et al. Design & development of floating pulsatile drug delivery system using meloxicam. International Journal of Pharmaceutical Research & Bioscience. 2012;2;215-235.
52. Sher P, Ingavle G, Ponrathnam S, Benson JR, Li NH, Pawar AP. Novel/Conceptual floating pulsatile system using high internal phase emulsion based porous material intended for chronotherapy. AAPS Pharm Sci Tech. 2009;10:1368-80.
53. Shivhare UD, et al. Development and evaluation of floating pulsatile microspheres of metoprolol tartrate using emulsion solvent evaporation technique. SAJP. 2013;2:365-372.
54. Sharma S, Pawar A. Low density multiparticulate system for pulsatile release of meloxicam. Int J Pharm. 2006;313:150-8.
55. Sher P, Ingavle G, Ponrathnam S, Pawar AP. Low density porous carrier based conceptual drug delivery system. Microporous and Mesoporous Mater. 2007;102:290-298.
56. Badve SS, Sher P, Korde A, Pawar AP. Development of hollow/porous calcium pectinate beads for floating-pulsatile drug delivery. Eur J Pharm Biopharm. 2007; 65:85-93.
57. Anuradhak, Salvnkhe, et al. Formulation and evaluation of floating pulsatile drug delivery system of metoprolol tartrate. Der Pharmacia Lettre. 2011;3:147-160.
58 Shaji J, Patole V. Development of a novel floating pulsatile system for chronotherapeutic release of diclofenac sodium. Journal of Pharmacy & Bioresources. 2007;4:32-38.

59 Khirsagar, et al. Statistical optimization of floating pulsatile drug delivery system for chronotherapy of hypertension. International Journal of Pharmaceutical Investigation. 2011;1.

60 Somani VG, Shahi SR, Udavant YK, Atram SC, Satpute R, Shinde NM. A floating pulsatile drug delivery system based on hollow calcium pectinate beads. Asian J Pharm. 2009;3:120-4.

61 Jain, et al. Formulation and evaluation of floating pulsatile drug delivery systemfor chronotherapy of Rheumatoid arthritis. Novel Science International Journal of Pharmaceutical Science. 2012;1:212-215.

62 Swati C, Jagdale, Chandhrakala R Pawar. Application of design of experiment for polyox xanthan gum coated floating pulsatile delivery of sumatriptan duccinate in migraine treatment. Biomed Research International. 2014;1-10.

63 Durga Rao Duppada, et al. Formulation & invitro evaluation of novel floating pulsatile approach for the chronotherapeutic release of nizatidine-a time & site specific drug delivery system. International Journal of Biological & Pharmaceutical Research. 2014;5(5):436-442.

64 Anuradha K Salunkhe. Formulation and evaluation of floating pulsatile drug delivery systemsof metoprolol tartrate. Der Pharmacia Letter. 2011;3(3):147-160.

65 Maryam Maghsoodi, Elham Hemati, Bahram Qadermazi, Zahra Yari. Hollow microspheres for gastroretentive floating-pulsatile drug delivery: Preparation and in vitro evaluation. Advanced Pharmaceutical Bulletin. 2011;1(2):55-61.

66 Badve SS, et al. Development of hollow porous calcium pectinate beads for floating pulsatile drug delivery. European Journal of Pharmaceutics and Biopharmaceutics. 2007;65:85–93.

67 Abhay Asthana, et al. Development and evaluation of novel *Cordia myxa* fruit gum based mucoadhesive tablets for gastro retentive delivery of losartan potassium. Journal of Pharmaceutical Sciences and Research. 2015;7(9):652-661.

68 Chintan Vora, et al. Risk based approach for design and optimization of stomach specific delivery of rifampacin. International Journal of Pharmaceutics. 2013;455:169-181.

69 Abhay Asthana, et al. QbD-Oriented development and characterization of effervescent floating-bioadhesive tablets of cefuroxime axetil. AAPS Pharm Sci Tech; 2015.
DOI: 1208/S 12249-015-0431-9

70 Sanjay Bansal, et al. Qbd enabled systematic development of gastroretentive multi-unit microballons of itopride hydrochloride. Drug Delivery. 2016;23(2): 437-451.

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