Review Article

Time and/or Site Specific Drug Delivery of Floating Pulsatile Release Delivery System

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ARTICLE INFO

Article history:
Received 14 October 2010
Accepted 16 February 2011
Available online 02 August 2011

Keywords:
Chronotherapeutic
Controlling plug
Eroding or soluble barrier
Multiparticulate
Rupturable coating

ABSTRACT

Pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimizing side effects. Recent trends indicate that drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain desirable release patterns with less inter- and intra-subject variability. 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. Floating pulsatile drug delivery system (FPDDS) concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. Diseases wherein FPDDS are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, and attention deficit syndrome in children. To overcome limitations of various approaches for imparting, buoyancy and lag controlling were prepared by floating pulsatile delivery systems, for which time-controlling system like swelling and rupturable membranes, soluble or erodible coating, capsule-shaped system, and multiparticulate system are primarily involved in the control of release. FPDDS showed excellent lag phase followed by burst release in distal part of small intestine which gives site- and time-specific release of drugs acting as per chronotherapy of the diseases. The current article focuses on the diseases requiring FPDDS, methodologies involved for the existing systems, recent update.

Introduction

Site- and time-specific oral drug deliveries have recently been of great interest in pharmaceutical field to achieve improved therapeutic efficacy. Drug delivery system is an approach to prolong gastric residence time, thereby targeting site-specific or time-specific drug release in upper gastrointestinal (GI) tract.[1,2]

Over the last three decades, various approaches have been pursued to increase the retention of an oral dosage form in the stomach, including floating systems[3,4] which decrease in density upon contact with gastric fluids based on swelling of polymer or carbon dioxide (CO_2) generation, mucoadhesive systems which adhere to mucosal surfaces,[5,6] modified-shape systems,[7-9] expandable (size-increasing),[10,11] high-density systems,[12] and other delayed gastric emptying devices.[13] The dosage forms possessing gastric retention capabilities have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Floating approach has been used for gastric retention of pulsatile dosage form. Floating-pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release.

Chronopharmacotherapy, the drug regime based on circadian rhythm, regulates many body functions in human beings, viz., metabolism, physiology, behavior, sleep patterns, hormone production, etc. Human beings greatly vary in their biochemical and physiologic status over a 24-hour period due to the existence of a number of circadian rhythms. The rhythmic alterations in our clinical or functional status may cause daytime or night-time differences in susceptibility to and/or patterns of disease state expression. Various diseases like asthma has been reported to have

Access this article online	
Website: www.sysrevpharm.org	Quick Response Code:
DOI: 10.4103/0975-8453.83441	

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increased airway responsiveness and worsening of lung function measured over a 24-hour cycle will show a characteristic circadian rhythm with the peak during the afternoon and the trough in the early hours of the morning.[14-16] Heart rate and blood pressure both exhibit a strong circadian pattern with values for blood pressure, double product typically peaking in the early morning period compare with till late afternoon, and then drops off during night (hypertension),[17-19] gastric acidity was observed toward an increase in intragastric acidity during the time period from the middle of the night to the early dawn, and toward a decrease in intragastric acidity during the early morning,[20-22] rheumatoid arthritis feel more pain in the morning hours show circadian variation that demand time-dependant drug release for effective drug action, for example, more pain with morning body stiffness, asthma, and heart attack in early hours of the day.[23] Circadian rhythm disturbances are observed in children with attention-deficit/hyperactivity disorder and sleep-onset insomnia.[24]

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.[25] To overcome this, novel/conceptual approach termed as "floating pulsatile drug delivery system" was developed.

The floating pulsatile concept was thus applied to increase the gastric residence of the dosage form having lag phase followed by a burst release in either stomach or distal part of small intestine. 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.[26] A pulsatile drug delivery that can be administered at bed time but releases drug in early morning would be a promising chronotherapeutic system. The potential benefits as shown in Table 1.

Table 1: Advantages and disadvantages of floating pulsatile drug delivery systems

Advantages:
Retention of drug delivery systems in the stomach prolongs overall.
Acidic substances like aspirin cause irritation on the stomach wall when come into contact with it. Hence, floating pulsatile formulation may be useful for the administration of aspirin and other similar drugs.
It has applications also for local drug delivery to the stomach and proximal small intestines, e.g., ranitidine for nocturnal acid breakthrough. No risk of dose dumping.[19]
The formulation is to be taken after meal, where immediate release dose will provide relief from acid secretion in response to the meal, while timed-controlled floating pulsatile tablet with delayed "burst" release will attenuate midnight acidity. This will provide an ideal therapeutic regimen with enhanced patient compliance.
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 followed by pulsed drug release in basic medium.
When there is vigorous intestinal movement and a shorted transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances, it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
Floating pulsatile drug delivery is increased bioavailability; predictable, reproducible, and improve generally short gastric residence time; no risk of dose dumping; local drug action; and the flexibility to blend dosage forms with different compositions or release patterns.
Disadvantages:
Drugs which are irritant to gastric mucosa is also not desirable or suitable.[25]
The dosage form should be administered with a full glass of water (200-250 ml).[26]
Manufacturing this type of dosage form require multiple formulation steps, higher cost of production, need of advanced technology, and trained/skilled personal needed for manufacturing

Design of floating pulsatile drug delivery system

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 multiparticulate 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 multiparticulate pulsed release dosage forms possessing gastric retention capabilities has also been addressed with increasing focus on the upcoming multiparticulate-pulsatile technologies being exploited on an industrial scale.

Time-controlling floating pulsatile drug delivery

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. List of polymers used for floating-pulsatile drug delivery and dissolution method are shown in Table 2.

Reservoir systems with eroding polymer or soluble barrier coatings

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 1. One layer is for buoyancy and the other for drug pulsatile release.

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[27,28] 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

Table 2: List of polymers used for floating and pulsatile drug delivery

Drug and dosage form	Polymer use for buoyancy layer	Polymer use for pulsatile release	Dissolution Medium and Method
Verapamil Hydrochloride Tablets	Carbopol® 934P, Methocel® K4M	Methocel® E15	900 ml dissolution medium of 0.1MHCl, pH 7.4 phosphate buffered saline, PBS and purified water at 100 rpm using USP dissolution apparatus. 5 ml of the solution was withdrawn, filtered, and assayed
Verapamil Hydrochloride Capsule	Hydrogenated Castor Oil	Ethocel® 45P	USP 26 type I dissolution apparatus, 900 ml (V) dissolution medium at 50 or 100 rpm. Dissolution media use 0.1M HCl and pH 7.4 phosphate buffered saline; PBS
Diclofenac sodium Multiparticulate system	Low methoxy pectin	Low methoxy pectin	USP XXIII type I dissolution test apparatus 900 ml 0.1N HCl for initial 2 or 6 hours depending upon floating characteristics of beads, followed by dissolution in phosphate buffer, pH 7.4 at 100 rpm.
Indomethacin Multiparticulate system	HPMC K100M and Sodium bicarbonate, PVP K-30	Eudragit S100	USP XXIII type I dissolution test apparatus dissolution medium 900 ml at 100 rpm. Carried out in 0.1N HCl (pH 1.2), later 2 hours in phosphate buffer pH 6.4 and finally at phosphate buffer pH 7.4 till complete release of drug.
Chlorpheniramine maleate Multiparticulate system	cellulose acetate or HPMC, polyethylene glycol 4000, anhydrous citric acid, sodium bicarbonate	Eudragit® RS 100 and RL 100, cellulose Acetate, ethyl cellulose, Eudragit NE 30 D	USP XXIII paddle dissolution Apparatus. Samples were withdrawn after predetermined time intervals, not replaced with medium
Ranitidine HCl Tablets	Glyceryl behenate (Compritol 888), hydroxypropyl methyl cellulose (Methocel E5)	Ethyl cellulose (Aqualon EC N10), Hydroxypropyl methyl cellulose (Methocel E15)	900ml 0.1N hydrochloric acid (pH 1.2) as medium and using USP XXIII dissolution apparatus I at 100 rpm, 5 ml sample was withdrawn every 1 hour. samples were filtered through 0.22_m Millipore® (Polyvinylidene difluoride, PVDF) filter and analyzed immediately

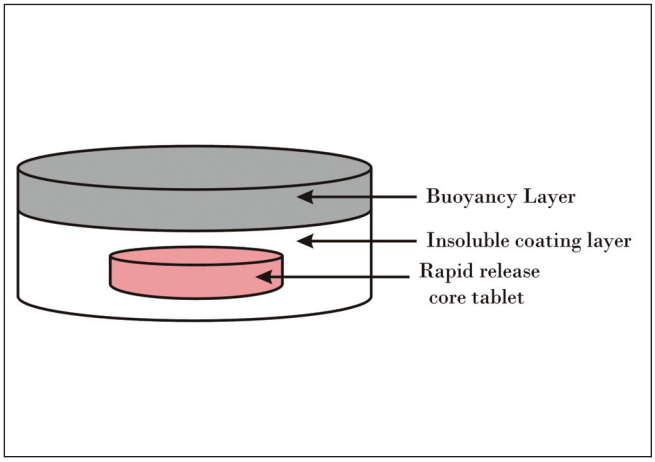

Figure 1: Schematic diagram of the floating–pulsatile release delivery system with rutpurable coating layer

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.[29] We generated the system which consisted of three different parts, a core tablet, containing the active ingredient; an erodible outer shell; and a top cover buoyant layer. The dry coated tablet consists in a drug-containing core, coated by a hydrophilic erodible polymer which is responsible for a lag phase in the onset of pulsatile release. The buoyant layer, prepared with HPMC K4M, Carbopol® 934P, and sodium bicarbonate, provides buoyancy to increase the retention of the oral dosage form in the stomach. The effect of the hydrophilic erodible polymer characteristics on the lag time and drug release was investigated.

Reservoir systems with rupturable polymeric coatings

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.[30]

The major challenge was to develop a tablet which can float and also provide a burst release once the outer time-lagged coating ruptures.[22] Therefore, we have incorporating low-density material like wax and other excipients like superdisintegrants 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 (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.

Krögel 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.[31] 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.[32] The mechanical properties of acrylic polymers (Eudragit® RL 30D, RS 30D, NE 30D) and EC were characterized. Eudragit® RL 30D was chosen as a 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 gastroretentive drug delivery system.

Capsule-shaped system provided with release controlling plug

The 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 [Figure 2]. 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.

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.[33] System was to develop and evaluate a floating and

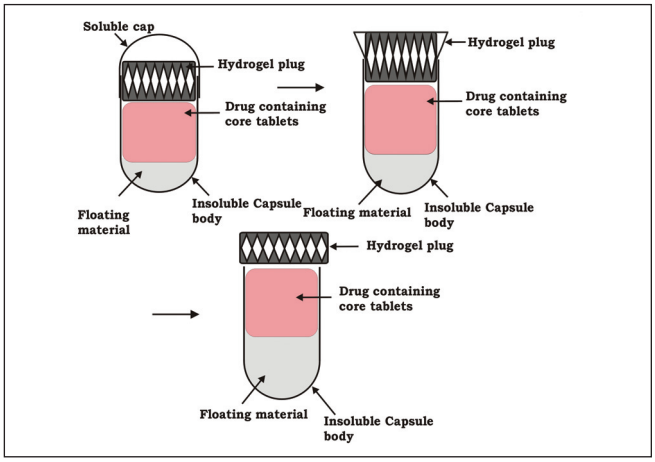

Figure 2: Schematic diagram of the floating–pulsatile release delivery system with release controlling plug

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 we prepared could achieve a rapid release after lag time *in vivo*, which was longer than that *in vitro*. 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[34] 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).

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 3].

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 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

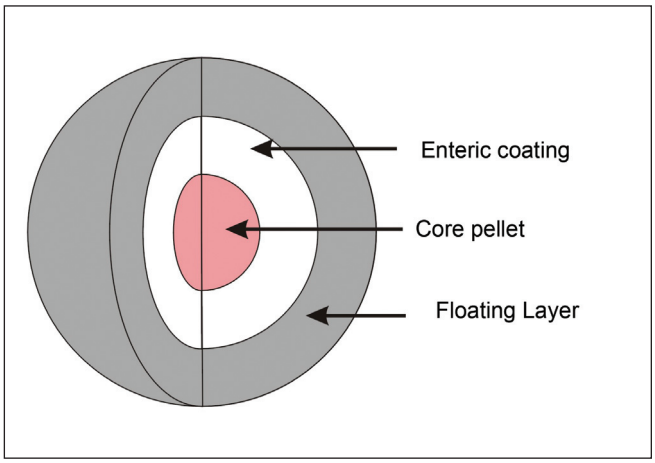

Figure 3: Schematic diagram of the floating multiparticulate pulsatile drug delivery system with multiple coating

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.[35] 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.[36] To overcome limitations of various approaches for imparting buoyancy, hollow/porous beads[37] 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 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.[38] 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[39] 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,[40] 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 behavior 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 release also.

A novel multiparticulate gastroretentive drug delivery system has been developed.[41] 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 behavior, *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.

Current and future development

The development of floating pulsatile-release products is most challenging as to get the right drug to the right place at the right time. The novel FPDDS pays more attention on site- and time-specific drug delivery. In these systems, there is release of the drug after eroding or rupturing the polymer coating of dosage form. During the last two decades, technologies to ensure time-controlled floating pulsatile release of bioactive compounds or drug have been developed. Significant progress has been made toward achieving floating and pulsatile drug delivery systems combination that can

effectively treat diseases with non-constant dosing therapies, such as hypertension.

Conclusion

The present review demonstrates that system could be successfully delivered to provide night-time or early morning relief of symptom by designing a floating pulsatile chronopharmaceutical formulation. Circadian rhythms have been extensively described for various diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, diabetes, attention deficit syndrome, hypercholesterolemia, and hypertension. Thus, more and more attempts are being made to adjust drug delivery systems accurately to patient requirements, both in terms of therapeutic efficacy and compliance. The developed system offers a simple and novel technique for pulse release of drugs in stomach or upper part of small intestine. System can be extended for time-scheduled drug release of drugs having low solubility, poor absorption, or degradation in lower GI tract. Different methodologies are employed for developing pulsatile drug delivery like 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.

It was shown that system can be successfully used in the development of time-lagged coating formulations based on rupturable, erodible polymers, and capsule-shaped to achieve the desired pulsed release profile after a programmed lag time.

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Cite this article as: Patel JK, Dalvadi HP, Shah DP. Time and/or site specific drug delivery of floating pulsatile release delivery system. Syst Rev Pharm 2011;2:59-65.

Source of Support: Nil, **Conflict of Interest:** None declared.

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3.	Printer's Name	:	Medknow Publications & Media Pvt. Ltd.
	Nationality	:	Indian
	Address	:	B5-12, Kanara Business Center, Off Link Rd, Ghatkopar (E),\ Mumbai - 400075, India Phone: 91-22-6649 1818
4.	Publisher's Name	:	Hemant Manjrekar For M/s Medknow Publications & Media Pvt. Ltd.
	Nationality	:	Indian
	Address	:	B5-12, Kanara Business Center, Off Link Rd, Ghatkopar (E), Mumbai - 400075, India. Phone: 91-22-6649 1818
5.	Editor's Name	:	Dr. Mueen Ahmed KK
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	Address	:	Systematic Reviews in Pharmacy, 1713, 41 A Cross 18 Main Jayanagar, Bangalore 41, India. Website: www.sysrevpharm.org
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Date: 15th May, 2011 **Dr. Mueen Ahmed KK**