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A Review on Floating Pulsatile Tablets Novel Approach for Oral Drug Delivery Systems

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ABSTRACT:

A simple, rapid, economical, precise and accurate RP-HPLC method for simultaneous estimation of Cilostazole and Imipramine has been developed. A reverse phase high performance liquid chromatographic method was developed for the simultaneous estimation of Cilostazole and Imipramine.. The separation was achieved by LC- 20 AT C18 (25 cm × 0.46 cm) Hypersil BDS column and Buffer (pH 4.5)-Methanol (20:80) as mobile phase, at a flow rate of 1 ml/min. Detection was carried out at 222 nm. Retention time of Cilostazole and Imipramine were found to be 5.383 min and 3.153 min, respectively. The method has been validated for linearity, accuracy and precision. Linearity observed for Cilostazole 6-18 µg/ml and for Imipramine 6-18 µg/ml. The percentage recoveries obtained for Cilostazole and Imipramine were found to be in range of 99.61 ± 0.50 and 99.78 ± 0.65 respectively. Developed method was found to be accurate, precise and rapid for simultaneous estimation of Cilostazole and Imipramine.. The proposed method was successfully applied for the simultaneous estimation of both the drugs in commercial Combined dosage form.

Key words: Cilostazole, Imipramine, Simultaneous estimation, RP-HPLC Method, Validation.

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INTRODUCTION:⁽¹⁾

Oral drug delivery has been known for decades as the most widely utilized route of administration.

It can be classified in three categories,

- A. Immediate release- which is designed for immediate release of drug for rapid absorption.
- B. Sustained release- designed on the basis of spansule technology for extended absorption.
- C. Controlled and targeted drug delivery system- which are more of pharmaceutical and clinical superiority over conventional immediate release pharmaceutical products.

Oral drug delivery is one of the most desired drug delivery for achieving systemic and local effects. It is most preferred due to ease of administration, cost effectiveness and flexibility in administration. The development of controlled release formulations continues to be a big success for pharmaceutical industry due to its ease of manufacturing process and reproducibility of desirable pharmaceutical properties. Controlled drug delivery systems are receiving more and more attention as they control the rate of drug release and sustain the duration of therapy.

Pulsatile or floating pulsatile drug delivery system are the novel approaches in the oral drug delivery. These systems tend to release the drug after the desired lag time. Pulsatile drug delivery system are intended to release the drug in different regions of the gastrointestinal tract whereas the floating pulsatile drug delivery is intended to release the drug in the stomach after desired lag time.

Pulsatile Drug Delivery System ⁽²⁾

Presently pulsatile drug delivery systems are gaining interest nowadays. Since many disease are known to show predictable cyclic rhythms, moreover the timing of rhythms can be used to deliver drugs at the desired time. Oral drug delivery of drugs is the largest segment of drug delivery market and the most preferred route of drug administration. Oral control release systems which tends to show a typical pattern of drug release to maintain the drugs in the therapeutic window for the longer duration of time and thereby ensuring sustained action. But there are certain conditions where sustain or controlled release of medication is not required in other way a pulsatile drug delivery is required.

The pulsatile drug delivery is gaining a lot of interest because it release the drug after specific lag time and shows no drug release during the lag time, the total quantity of drug is released after the desired lag time. Pulsatile drug delivery or can also be known as time and site-specific drug delivery provides a spatial and temporal delivery of drug and thus increase patient compliance. Pulsatile drug delivery is defined as therapid and transient release of certain amount of molecules within a short time period immediately after a predetermined no-released period, i.e., lag time, or these systems have a peculiar mechanism of delivering the drug rapidly and completely after a lag time, i.e., a period of no drug release. Such a release pattern is known as pulsatile release.

The principle rationale for the use of pulsatile release is in conditions where a constant drug release, i.e., a zero-order release is not desired. The release of the drug as a pulse after a lag time (an interval of no drug release) has to be designed in such a way that a complete and rapid drug release follows the lag time. The modified release drug preparations provides continuous and constant drug delivery in which the minimum therapeutic levels in the blood are maintained thereby prompting drug efficacy

and reducing adverse effects. Modified release preparation tend to provide less dosing frequency and improved patient compliance in comparison to conventional dosage form⁽²⁾⁽³⁾. Various modified release preparations include slowed-release, delayed-release, prolonged-release, extended-release, sustained-release and controlled-release preparations. But several controlled release preparations tend to show various problems such as drug tolerance, drug resistance, and activation of the physiological system due to longer term constant drug concentration in the blood and tissues. **For example**, many patient are required to change their dosage regimen after one year of treatment with clonidine transdermal patches. Arterial pressure in patient exceeds the pretreatment value during 3-7 days after removal of their previous transdermal patch. Long term use of oral contraceptives are found to show increased risk of cardiovascular disease. Physiological tolerance may develop due to building of resistance to the effects of a drug substance after repeated exposures and these indicates that it is not always desirable to maintain constant plasma levels for longer periods.

Necessity of pulsatile drug delivery systems ⁽⁴⁾

There are many conditions and diseases where sustained release formulations do not show good efficacy so these condition demand the release of drug after a lag time. In other words, it is required that no drug release should be there during the initial phase of dosage form administration. In such cases pulsatile drug delivery system is applicable.

- The lag time is essential for the drugs that undergo degradation in gastric acidic medium. E.g. peptide drugs tend to irritate the gastric mucosa or induced nausea and vomiting.
- Severity of disease like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer and hypertension is time dependent.
- Targeting drug to distal organs of gastro intestinal tract like the colon requires that the drug release is prevented in the upper two third portion of the GIT.
- Many body functions that follow circadian rhythm. E.g. secretion of hormones, acid secretion in stomach, gastric emptying and gastrointestinal blood transfusion.
- Drugs that produce biological tolerance demand for a system that will prevent their continuous presence

of the drug in the bio phase as this tends to reduce their therapeutic effect.

- The drugs that undergo first pass metabolism resulting in reduced bioavailability.

Chronobiology⁽⁵⁾⁽⁶⁾

Biological Rhythm:

Biological rhythm is a self-sustaining oscillation of endogenous origin. The study of biological rhythms and their mechanisms is known as chronobiology and they are regulated by sunlight. There are three types of mechanical rhythms in our body.

1. Ultradian rhythms

2. Infradian rhythms

3. Circadian rhythms

1. Ultradian rhythms:

These rhythms have period shorter than 24 hours.

2. Infradian rhythms:

These rhythms have a frequency ranging from 28 hrs to 6 days.

3. Circadian rhythms:

The term "Circadian", coined by Franz Hal berg, comes from the Latin word circa "around", and diem or dies, "day", meaning literally "approximately one day". Our bodies appear to be genetically programmed to function on roughly a 24-hour cycle. These rhythms allow organisms to anticipate and prepare for precise and regular environmental changes.

The Circadian Rhythm and their implications⁽⁷⁾

The innate biological clock that regulates sleep and waking and controls the daily ups and downs of physiologic processes, including body temperature, blood pressure, and the release of hormones. A metabolic or behavior pattern that repeats in cycles of about every 24 hours is known as circadian rhythm. Normally, circadian rhythms are synchronized according to the body's pacemaker clock, located in the suprachiasmatic nucleus of the hypothalamus. The physiology and biochemistry of human being is not constant over the 24 hours, but variable in a predictable manner as defined by the timing

of peak and trough of each of the body's circadian rhythm and processes. Infact normal biological is influenced just by the time of the day, so it affects the pathophysiology of disease and its treatment.

Disease requiring pulsatile drug delivery⁽⁸⁾⁽⁹⁾⁽¹⁰⁾

Circadian rhythm regulates many body functions in humans, viz., metabolism, behaviour, Physiology, sleep patterns, hormone production, etc

Asthma: The chronotherapy of asthma has been widely studied. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases more at night in asthmatic patients. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. As broncho constriction and exacerbation of symptoms vary in a circadian way, asthma is well suited for chronotherapy. Chronotherapies have been studied for asthma with theophylline, oral corticosteroids and β_2 -agonists.

Arthritis: The circadian behaviour of pain have been extensively reviewed. For instance, there is a circadian rhythm in the plasma concentration of C - reactive protein and interleukin-6 in patients with rheumatoid arthritis. Increasingly, the arthritis have shown statistically quantifiable rhythmic parameters. In addition, a number of drugs used to treat rheumatic diseases have varying therapeutic and toxic effects based on the time of day of administration Patients with osteoarthritis tend to have less pain in the morning and more at night; while those with rheumatoid arthritis, have pain that usually peaks in the morning and decreases throughout the day. Chronotherapy for all forms of arthritis using NSAIDs such as ibuprofen should be time controlled to ensure that the highest blood levels of the drug coincide with peak pain. For osteoarthritis, the optimal time for a non-steroidal anti-inflammatory drug such as ibuprofen would be around noon or mid-afternoon. The same drug would be more effective for people with rheumatoid arthritis when taken after the evening meal.

Duodenal ulcer: Many of the functions of the gastrointestinal tract are subject to circadian rhythms: gastric acid secretion is highest at night, while gastric and small bowel motility and gastric emptying are all slower

at night. In peptic ulcer patients, gastric acid secretion is highest during the night. Suppression of nocturnal acid is an important factor in duodenal ulcer healing. Therefore, for active duodenal ulcer, once daily at bedtime is the recommended dosage regimen for an H₂ antagonist.

Hypercholesterolemia: A circadian rhythm occurs during hepatic cholesterol synthesis. However, this rhythm varies according to individuals and there is a large variation in plasma mevalonate concentrations between individuals. Therefore cholesterol synthesis is generally higher during the night than during daylight, and diurnal synthesis may represent up to 30%–40% of daily cholesterol synthesis. Many individuals display a paradoxical synthesis, with an inverted diurnal cholesterol synthesis. It seems therefore that cholesterol is synthesized during the night as well as during daylight; however the maximal production occurs early in the morning, i.e. 12 h after the last meal. Studies on HMG CoA reductase inhibitors suggest that evening dosing was effective than morning dosing.

Cancer: Human and animal studies suggest that chemotherapy may be more effective and less toxic if cancer drugs are administered at carefully selected times that take advantage of tumor cell cycles while less toxic to normal tissue. The blood flow to tumors was threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase. The chronotherapy concept offers further promise for improving current cancer-treatment options, as well as for optimizing the development of new anticancer or supportive agents.

Cardiovascular diseases: Several functions such as, Blood pressure (BP), heart rate, stroke volume, cardiac output, blood flow of the cardiovascular system is subject to -+circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. It was postulated that modification of these circadian triggers by pharmacologic agents may lead to the prevention of adverse cardiac events. BP is at its lowest during the sleeping period and rises steeply during the early morning period. Most patients with essential hypertension have a similar circadian rhythm of BP as do normotensive persons, hypertensive patients have upward shift in profile.

Diabetes: The circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical importance's in case of insulin substitution in type I diabetes have been previously discussed. The goal of insulin therapy is to mimic the normal physiologic pattern of endogenous insulin secretion in healthy individuals, with continuous basal secretion as well as meal-stimulated secretion.

Colonic delivery: The colon is also seen as the preferred absorption site for oral administration of protein and peptide drugs, because of the relatively low proteolytic enzyme activities in the colon. A colon-specific drug delivery system should prevent drug release in the stomach and small intestine, and affect an abrupt onset of drug release upon entry into the colon. The system can be modified to release the drug in colon by means of time controlled approach or pH sensitive approach. The plug material consists of insoluble but permeable and swellable polymers (e.g. polymethacrylates), erodible compressed polymers (e.g. hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), and enzymatically controlled erodible polymer (e.g., pectin). These formulations were well tolerated in animals and healthy volunteers, and there were no reports of gastrointestinal irritation. However, there was a potential problem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine.

Floating Pulsatile drug delivery system⁽¹¹⁾

The combination of floating and Pulsatile principle are very well suitable for site and time specific oral drug delivery system, which have recently been of greater interest in pharmaceutical field to achieve improved therapeutic efficacy. Gastro-retentive drug delivery system is an approach to specific drug release in the upper gastro-intestinal tract. Pulsatile drug delivery system (PDDS) is characterized by a time period of no release. The combination of Floating Pulsatile delivery provides various advantages such as nearly constant drug level at the site of action, avoidance of undesirable side effects, reduce dose, increased gastric residence of the effects, reduce dose, increased gastric residence of the dosage form.

Advantages of Floating Pulsatile Drug Delivery Systems:⁽¹²⁾

- Retention of drug delivery systems in the stomach prolongs overall residence time.
- Acidic substances like aspirin cause irritation on the stomach wall when comes into contact with it. Hence, floating pulsatile formulation may be useful for the administration of aspirin and other similar drugs.
- It has applications for local drug delivery to the stomach and proximal small intestines, e.g., ranitidine for nocturnal acid breakthrough. No risk of dose dumping. The formulation is to be taken after meal, where immediate releasedose 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 releaseduring 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.
- The dosage form should be administered with a full glass of water (200-250 ml).
- 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.

METHODOLOGIES FOR THE PDDS CAN BE BROADLY CLASSIFIED INTO FOUR CLASSES⁽¹³⁻²²⁾

I. Time controlled pulsatile release

A. Single unit system

- Capsular systems
- PORT systems
- Osmotic pressure based systems
- Based on solubility modification
- Reservoir systems

B. Multi-particulate system

- Rupturable coating systems
- Time controlled explosion systems
- Sigmoidal release systems
- Modified permeation systems
- Floating delivery based systems

II. Stimuli induced

A. Thermo-Responsive Pulsatile release

- Temperature controlled systems

B. Chemical stimuli induced Pulsatile systems

- Glucose sensitive systems
- Inflation induced systems
- Gel based systems
- pH based systems

III. External stimuli pulsatile release

A. Electro responsive pulsatile release

B. Magnetically induced pulsatile release

IV. Pulsatile release systems for vaccine and Hormone products.

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.

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 to improve the floating properties or mucoadhesiveness of the combined system. The novel system could result in a floating dosage form with a prolonged gastric residence time and in 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. 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.

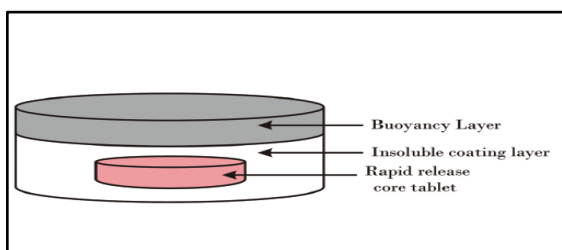


Figure 1: Schematic diagram of floating pulsatile drug delivery system

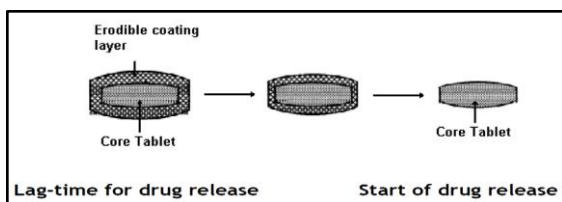


Figure 2: Schematic diagram drug delivery with erodible coating layer

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. The major challenge was to develop a tablet which can float and also provide a burst release once the outer time-lagged coating ruptures. Therefore, we have incorporated 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 released 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.

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. 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 CO₂ 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 3]. 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. 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 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.

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

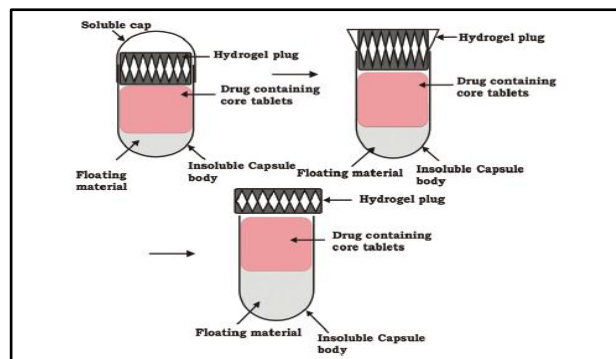


Figure 3: Schematic diagram of drug delivery with release controlling Plug

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 gastric residence of the dosage form having lag phase followed by a burst release.

Evaluation of the Floating-Pulsatile Release Tablets⁽²³⁻²⁸⁾

- **Physical Evaluation such as Thickness and Hardness**
- **Weight Variation**

The weight of the tablets is to be checked on a electronic balance. The test is to be carried out as per Indian Pharmacopoeia (IP) 2010 guidelines.

- **Friability Test**

For each formulation, the friability of the tablets is to be determined using the Roche friabilator. In this test, tablets are to be subjected to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. The tablets are then dusted and reweighed. Percent friability (%F) is calculated as follows:

$$\% F = (\text{loss in weight} / \text{initial weight}) \times 100$$

- **Swelling Index Determination**

Tablets are weighed individually (designated as W1) and placed separately in glass beakers containing 200 ml of 0.1 N HCl and incubated at 37°C±1°C. At regular 1-hour time intervals until 10 hrs, the tablets are removed from the beakers, and the excess surface liquid is to be removed carefully using the paper. The swollen tablets are then reweighed (W2) and the swelling index (SI) is calculated using the following formula:

$$SI = W2 - W1 \times 100$$

- **In Vitro Buoyancy Determination and invitro drug release**

The tablets are subjected to buoyancy studies and invitro drug release studies. These two are one of the important parameters in floating pulsatile drug delivery system. The total floating time and the drug release lag time are to be studied in order to formulate a floating pulsatile drug delivery giving release of drug after required lag time. The invitro drug relate studies are carried out in IP type I paddle dissolution apparatus using 900 ml 0.1 N HCL as the dissolution medium.

Conclusion

In these emerging trending era of novel approaches in delivering the drug at the required area and time, floating pulsatile or pulsatile drug delivery is one of the better approach to achieve the same target. Through the pulsatile drug delivery drugs can be efficiently delivered at right time after the programmed lag time. Moreover the pulsatile or the floating pulsatile drug delivery is also very advantageous in case of the drugs whose action cannot be kept for a longer period of time i.e their sustained dosage forms may lead to harmful side effects

whereas there are very less chance of such effects in case of pulsatile drug delivery.

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