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Design & Evaluation of Pulsatile drug delivery of Diltiazem HCL

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ABSTRACT:

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates.The oral controlled release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action .The tablets were evaluated for weight variation, friability, hardness, drug content, in-vitro disintegration time, wetting time, in-vitro dissolution studies. All the formulations show within house specifications for physicochemical properties. Formulations containing Poly(ethylacrylate,methyl methacrylate) , Poly(methacrylic acid,methylmethacrylate),Poly(ethylacrylate,methylmethacrylate,trimethylammonioethylmethacrylate chloride). But there are certain conditions which demand release of drug after a lag time. i.e., Chronopharmacotherapy of diseases which shows Circadian rhythms in their pathophysiology. Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions.

1.INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. The oral controlled release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action . But there are certain conditions which demand release of drug after a lag time. i.e., Chronopharmacotherapy of diseases which shows Circadian rhythms in their pathophysiology. Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions.

There are many conditions that demand pulsatile release like

a. Many body functions that follow circadian rhythm. e.g: Secretion of hormones, acid secretion in stomach, gastric emptying, and gastrointestinal blood transfusion.
b. Chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension.

c. Drugs that produce biological tolerance demand for a system that will prevent their continuous presence at the biophase as this tends to reduce their therapeutic effect.
d. The lag time is essential for the drugs that undergo degradation in gastric acidic medium (e.g: peptide drugs) and irritate the gastric mucosa or induce nausea and vomiting.
e. Targeting a drug to distal organs of gastro-intestinal tract (GIT) like the colon requires that the drug release is prevented in the upper two-third portion of the GIT.
f. The drugs that undergo first-pass metabolism resulting in reduced bioavailability, altered steady state levels of drug and metabolite, and potential fooddrug interactions require delayed release of the drug to the extent possible.

All of these conditions demand for a time controlled therapeutic scheme releasing the right amount of drug at the right time. This requirement is fulfilled by Pulsatile Drug Delivery Systems.

Diseases Requiring Pulsatile Delivery

Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions.

Methods For Pulsatile Drug Delivery

Single unit systems

Capsular system

Single unit systems are mostly developed in capsule form. The lag time is continued by a plug, which gets pushed away by swelling or erosion, and the drug is released as a pulse from the insoluble capsule body. e.g.: Pulsincap® system

In this system a water insoluble body containing the drug formulation, system is closed with a swellable hydrogel. Plugged (insoluble but permeable & swellable) at open end. Upon contact with, gastrointestinal fluid or dissolution medium the plug swells pushing itself out of the capsule after lag-time. Position & dimensions of plug, control lag-time. For rapid release of water insoluble drug effervescent or disintegrating agents are added. Plug material is generally made up of following:

- Swellable materials coated with but¬ permeable polymer (polymethacrylates).
- Erodible compressed polymer (HPMC,¬ polyvinyl alcohol).
- Congealed melted polymer (glyceryl¬ mono oleate).
- Enzymatically controlled erodible¬ polymer (pectin).

1.1 INTRODUCTION FLOATING PULSATILE DRUG DELIVERY SYSTEM

The oral route is the most preferred route of administration of drugs because of low cost of therapy, ease of administration, patient compliance and flexibility in formulation, etc. During the past few decades, numerous oral drug delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a specific period of time at a predetermined and controlled rate

1. It is evident from the recent scientific and patent literatures that an increased interest in novel oral controlled release dosage forms that designed to be retained in the gastrointestinal tract (GIT) for a prolonged and predictable period of time exists today
2. Several approaches are currently utilized in the prolongation of the gastric residence times (GRT), including floating drug delivery systems (FDDS)

3. Low- density systems
4. Raft systems incorporating alginate gels
5. Bioadhesive or mucoadhesive systems
6. High-density systems
7. Superporous hydrogels
8. Magnetic systems

The current review addresses briefly about the FDDS that is one of the most leading methodologies in gastroretentive drug formulations**.**

1.2. Floating Drug Delivery System

Floating drug delivery systems (FDDS) or hydro dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal . Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres. Table 1 enlists examples of various drugs formulated as different forms of FDDS.

1.3.Drug Candidates Suitable for FDDS

- Drugs that have narrow absorption window in GIT (e.g. L-DOPA, paminobenzoic acid, furosemide, riboflavin)
- Drugs those are locally active in the stomach (e.g. misroprostol, antacids)
- Drugs those are unstable in the intestinal or colonic environment
  (e.g. captopril, ranitidine HCl, metronidazole)
- Drugs that disturb normal colonic microbes (e.g. antibiotics used for the eradication of Helicobacter pylori, such as tetracycline,clarithromycin, amoxicillin)
- Drugs that exhibit low solubility at high pH values (e.g. diazepam, chlordiazepoxide, verapamil.

1.4. Advantages of FDDS ,

1. The Floating systems are advantageous for drugs meant for local action in the stomach. E.g. antacids.
2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence FDDS may be useful for the administration of aspirin and other similar drugs.
3. The Floating systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.
4. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents.

5. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.

1.5. Disadvantages of FDDS

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently coat, water.
3. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.

1.6. Types of Floating Drug Delivery Systems

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in the development of FDDS.

i) Non-Effervescent FDDS

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in noneffervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as Chitosan and carbopol. The various types of this system are as:

- **Single Layer Floating Tablets:**

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity. They are formulated by intimate mixing of drug with low-density enteric materials such as HPMC.

- **Bi-layer Floating Tablets:**

A bi-layer tablet contain two layer one immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach

- **Alginate Beads:**

Multi-unit floating dosage forms were developed from freeze dried alcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours

- **Hollow Microspheres:**

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol:dichloromethane solution of the drug and an enteric acrylic polymer is pouredinto an agitated aqueous solution of PVA that is thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by evaporation ofdichloromethane forms an internal cavity in microsphere of polymer with drug.

ii) Effervescent FDDS

a. Volatile liquid containing system:

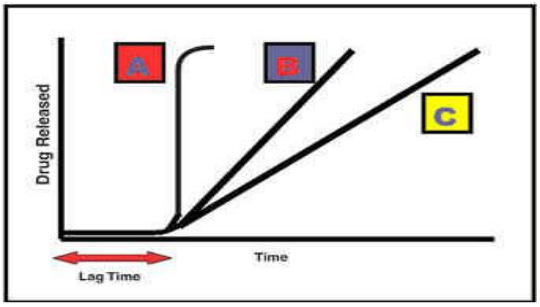
The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of abioerodible plug made up of Poly vinyl alcohol, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.

b. Gas-generating Systems:

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chime

2. Pulsatile Drug Delivery System

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance. However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release. A pulsatile drug delivery system is characterized by a lag time that is an interval of no drug release followed by rapid drug release.



In this context, the aim of the research was to achieve a so-called sigmoidal release pattern (pattern A in Figure).The characteristic feature of the formulation was a defined lag time followed by a drug pulse with the enclosed active quantity being released at once. Thus, the major challenge in the development of pulsatile drug delivery system is to achieve a rapid drug release after the lag time. Often, the drug is released over an extended period of time (patterns B & C in Figure).

1.7 NECESSITIES OF PULSATILE DRUG DELIVERY SYSTEMS:

1. First pass metabolism:

Some drugs, such as beta blockers, and salicylamide, undergo extensive first pass metabolism and require fast drug input to saturate metabolizing enzymes in order to minimize pre-systemic metabolism. Thus, a constant/sustained oral method of delivery would result in reduced oral bioavailability.

2. Biological tolerance:

Drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g.,biological tolerance of transdermal nitroglycerin, salbutamol sulphate.

3. Special chronopharmacological needs:

Circadian rhythms in certain physiological functions are well established. It has been recognized that many symptoms and onset of disease occur during specific time periods of the 24 hour day, e.g., asthma and angina pectoris attacks are most frequently in the morning hours.

4. Local therapeutic need:

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

5. Gastric irritation or drug instability in gastric fluid:

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

1.8 Merits:

- Predictable, reproducible and short gastric residence time
- Less inter- and intra-subject variability
- Improve bioavailability
- Limited risk of local irritation
- No risk of dose dumping
- Flexibility in design
- Improve stability

1.9. Demerits:

- Lack of manufacturing reproducibility and efficacy
- Large number of process variables
- Batch manufacturing process

1.10. Floating Pulsatile Drug Delivery System

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 tract.Over the last three decades, various approaches have been pursued to increasethe retention of an oral dosage form in the stomach, including floatingsystems 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, modified-shape systems expandable (size-increasing), high-density systems, and otherdelayed gastric emptying devices. 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 bya 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 Various diseases like asthma has been reported to have 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. 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), 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, rheumatoid arthritis feelmore 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.Circadian rhythm disturbances are observed in children with attentiondeficit/hyperactivity disorder and sleep onset insomnia.

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.to overcome this novel approach term as floating pulsatile drug delivery system was developed.

A combination of floating and pulsatile principles of drug delivery system would have the advantage that a drug can be released in upper GI tract after a defined time period of no drug release. 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 of floating pulsatile drug delivery system:

1.11. Advantages of Floating pulsating drug delivery systems.

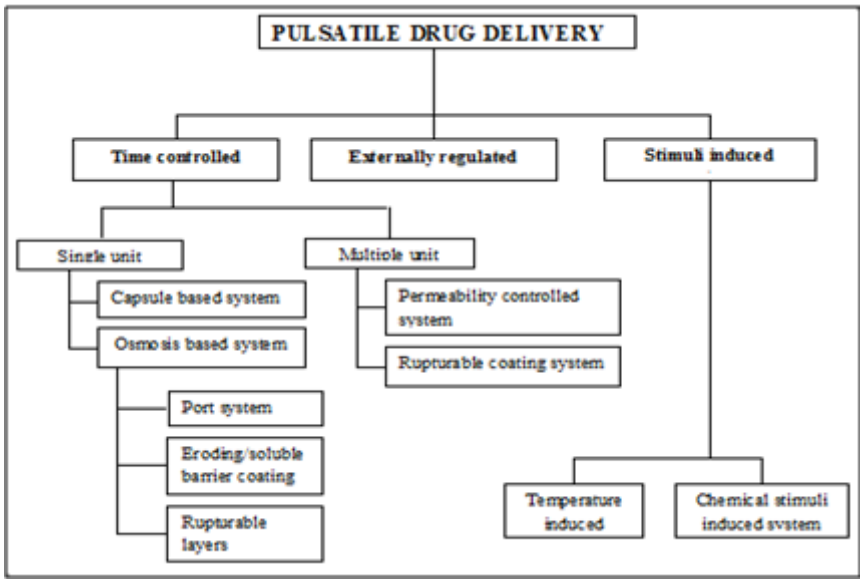
- Retention of drug delivery system in stomach prolongs overall.
- Acidic substance like aspirin cause irritation on the stomach wall when come into contact with it hence floating pulsatile formulation may be useful for administration of aspirin and other similar drugs.
- It has application also local drug delivery to the stomach and proximal small intestine e.g., ranitidine for nocturnal acid breakthrough.
- No risk of dose dumping.

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

Floating pulsatile drug delivery system for obtaining no drug release during floating and rapid drug release in distal small intestine to achieve chronotherapeutic release e.g. indomethacin. Floating with no drug release in acidic medium by pulse drug release in basic medium When there is vigorous intestine movement and short 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 relative better response.

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



1.12. Disadvantages of floating pulsatile drug delivery systems

Drug which are irritant to gastric mucosa is also not desirable or suitable. The dosage form should be administered with full glass of water(200-250ml) Manufacturing this type of dosage form requires multiple formulation steps, higher cost of production, need of advance technology,and trained or skilled personnel needed form manufacturing

1.13. Design of Floating Pulsatile Drug Delivery System

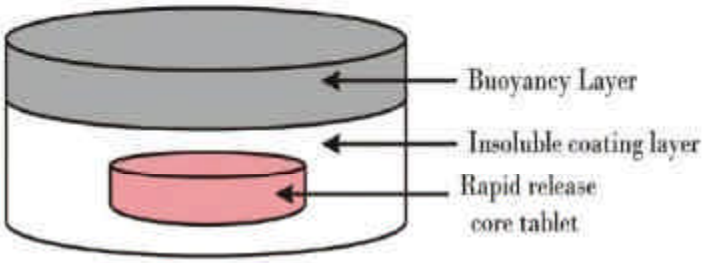
The purpose of designing by which the drug is released from dosage form depends on the type of coating; insoluble coating under all physiological conditions, pH-dependent coating whose solubility changes dramatically at some point in GI tract, and slowly erodible coating. The method of application and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

1.14. 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.

1.15 Reservoir System with Eroding Polymer or Soluble Barrier Coating

A pulsatile-floating drug delivery system consists of three different parts, a core tablet, containing the active ingredient; an erodible outer shell; and a top cover buoyant layer, as



Design of floating pulsatile release tablet.

One layer is for buoyancy and the other for drug pulsatile release. The pulsatile release system with various lag times was prepared bycompression 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 (1) a floating dosage form with a prolonged gastric residence time and in (2) a pulsatile dosage form, in which the drug is releasedrapidly 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 generatedthe 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.

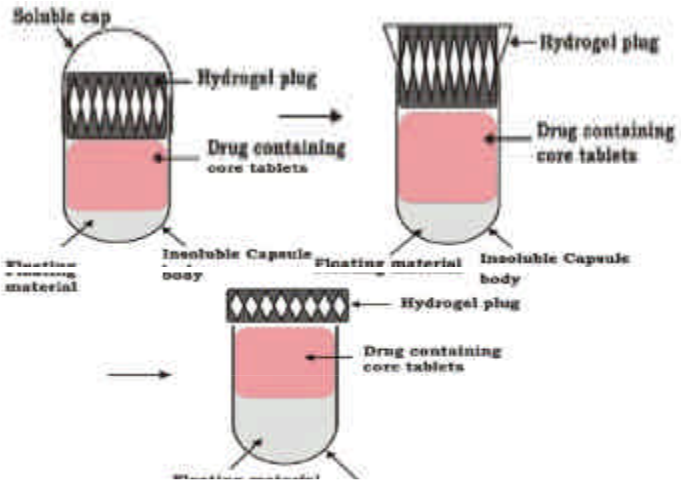
1.16. Reservoir systems with ruputurable coating

Reservoir-type delivery systems based on the expansion of the core have been evaluated for both floating delivery systems having a lower density than GI fluids, and for pulsatile systems in which the core expansion causes rupturing of the coating to allow rapid drug release.The major challenge was to develop a tablet which can float and also provide a burst release once theouter time-lagged coating ruptures.

Krogel and Bodmeier developed floating and pulsatile drug delivery systems based on a reservoir system consisting of a drug-containing effervescent core and a polymeric coating Studies identified important core and coating properties for the two systems. 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, respectively54. 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.

1.17 Capsule shape 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 theformulation



Schematic diagram of the floating– pulsatile release delivery

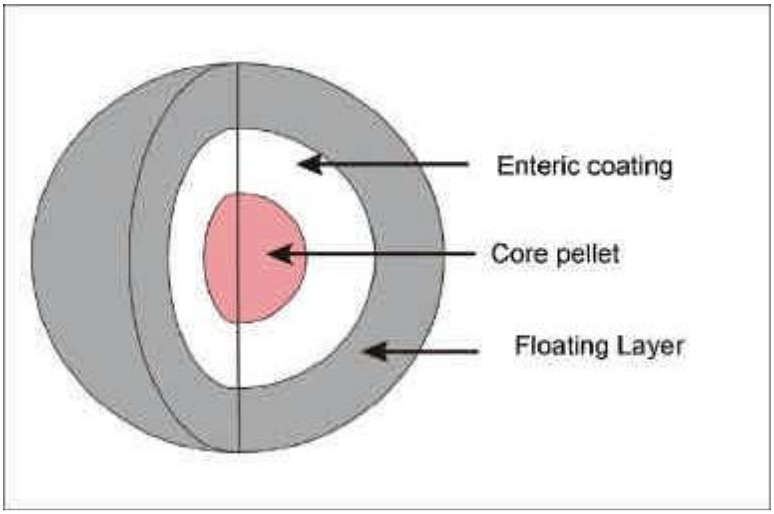
Release controlling plug

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 andevaluate 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.

A multifunctional drug delivery system based on HPMC-matrices (tablets) placed within an impermeable polymeric cylinder 56 was developed. 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.

1.18 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.



Schematic diagram of the floating multiparticulate pulsatile

drug delivery system with multiple coating 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.

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 anddue 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.

2. Literature review

Rajesh Asija et.al.,2015

The goal of the study was to formulate pulsatile release tablets of ramipril by using a combination of core material croscarmellose sodium and coating hydrophilic polymer HPMC K100M and hydrophobic polymer ethylcellulose. Ramipril is used in the treatment of hypertension. It has a short half life (2-4 hrs). Ramipril 2.5mg pulsatile release tablets were prepared by direct compression method and evaluated for thickness, hardness, weight variation, friability, drug content and in-vitro release of drug. In-vitro drug release was carried out using USP type II apparatus at 50 rpm in 900ml of dissolution media for 7 hrs. Mean dissolution time is used to evaluate drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer. Various kinetics models were applied to the dissolution profile to determine the drug release kinetics. All the physical characteristics evaluated for the tablets were obtained to be within the acceptable limits. The release profile of optimized formulation of ramipril was close to korsmeyer peppas model. Irrespective of the polymer type and its concentration, the prepared optimized pulsatile tablets showed non fickian (anomalous) release.

Archana S Patil et.al.,2015

Background: Hypertension shows circadian rhythm that there is a rise in pressure from the time of waking or before (about 4 to 8 a.m.), in most people. Conventional drug delivery system of captopril is inappropriate for the delivery of drug, as they cannot be administered just before the symptoms are

worsened, because during this time the patients are asleep, bedtime dosing of captopril will not provide a therapeutic plasma drug concentration at the early hours of morning because of poor pharmacokinetic profile and shorter half-life of 1.9 hours. Thus, this study attempts to design and evaluate a chronomodulated pulsatile drug delivery system of captopril which was aimed to release the drug after a lag time of 6 hours. Materials and Methods: Present delivery system was prepared by rupturable coating method. The core containing captopril as a bioactive compound were prepared by direct compression method and then coated sequentially with an inner swelling layer containing hydrocolloid HPMC E5 and an outer rupturable layer consisted of Eudragit RL/RS (1 : 1). Total 12 formulations with different levels of inner swelling layer and outer polymeric layer were prepared and subjected to various processing and formulative parameters like the effect of core composition, level of swelling layer, and rupturable coating on lag time was investigated.

R. Asija et.al.,2014

Pulsatile Drug Delivery Systems are gaining a lot of interest as they deliver the drug at the right place at the right time and in the right amt. hence providing temporal delivery and increasing patient compliance. Pulsatile drug delivery systems are designed according to the circadian rhythm of the body. Thus the principle rationale for the use of pulsatile release of the drugs is where a constant drug release is not required. A pulse has to be designed in such a way that a complete and rapid drug release is achieved after the definite lag time. Pulsatile systems are beneficial for the drugs having chronopharmacological behavior where night time dosing is desired, such as antiasthmatic, antihypertensive and antiarhythmic. Current review article discussed the development of pulsatile drug delivery system, types of disease in which pulsatile release is required, advantages, disadvantages, classification, limitation, evaluation and work done on pulsatile drug delivery system.

Subashini Rajaram et.al.,2014

The present study aimed to formulate and evaluate pulsatile tablet of Ramipril and Telmisartan in capsule device using Eudragit RL100 and Eudragit RS100 polymers for the treatment of hypertension. The core tablet of telmisartan for sustained release was prepared by direct compression method. The blend of ramipril produced immediate release to the environment (acidic). The blend and core tablet were incorporated with hard gelatin capsule with “1” in its size and the filled capsules were evaluated for its physico-chemical characteristics. The pre, post compression evaluation result complies with the standard limits with minimum standard deviations. The in-vitro drug release profile of immediate release layer shows that formulation FM3 results 60% drug release at 20 min and it was achieved to 98% at 50 min. The in-vitro release study of core tablet such as telmisartan start its release at 3 rd hour and 98% of drug release was achieved by FS3 at 12 th hour and it was linear compare to other formulations prepared. In conclusion, pulsatile drug delivery could be beneficial to deliver the drug at right time and right environment for hypertensive therapy and also it improves the patient’s compliance

RAMYASREE DOMALA et.al.,2014

Objective: The objective of present work was to formulate and evaluate an oral pulsatile drug delivery system to achieve time release of felodipine, based on chronopharmaceutical approach for management of hypertension. Methods: The strategy adopted was to improve solubility of felodipine by using novel solubilizers like Sepitrap 4000 and Sepitrap 80 in different ratios. Core tablets (CR) of felodipine were

prepared by direct compression method using optimum ratio of felodipine and solubilizers. CR tablet was then press coated using different grades of HPMC like E5, E15 and E50 in varying ratios. Pulsatile tablets were evaluated for pre-compressional and post-compressional parameters. Swelling studies and water uptake studies were also carried out to select optimum concentration of polymer that could provide desired lag time. Results: CR tablet formulated with Sepitrap 4000 and Sepitrap 80 (1:1 ratio) showed 100.16±2.06% release in 15 and 30 min respectively. On the basis of in vitro release profile it was found that the optimized formulation F6showed the lag time of about 7.5h which showed compliance with chronotherapeutic objective of hypertension. A direct correlation between swelling and lag time was observed from swelling index and water uptake studies. Solid state characterization (FTIR, XRD studies) indicated that there was decrease in crystallinity of the drug with no interaction between drug and excipients. Conclusion: Pulsatile drug delivery system is capable of delivering the drug when and where it is required. Drug is released as a burst after a lag time (during peak morning hours) giving relief from morning surge hypertension effect.

SATANI R. R et.al.,2014

The past several decades have seen the development of many controlled-release preparations featuring constant release rates to maintain drug concentrations in the human body, regardless of the patient's physiological condition.Oral pulsatile/Time-controlled drug delivery systems are designed to elicit programmable lag phases preceding a prompt and quantitative, repeated or prolonged release of drugs. Accordingly, they draw increasing interest because of the inherent suitability for accomplishing chronotherapeutic goals, which have recently been highlighted in connection with a number of widespread chronic diseases with typical night or early morning recurrence of symptoms (e.g. bronchial asthma, cardiovascular disease, rheumatoid arthritis, early-morning awakening).However, long-term constant drug concentrations in the blood and tissue can cause problems such as resistance, tolerability, and drug side effects. People vary considerably in their physiological and biochemical conditions during any 24 h period, due to the circadian rhythm, and thus, the constant delivery of a drug into the body seems both unnecessary and undesirable. The press coating technique is a simple and unique technology used to provide tablets with a programmable lag phase, followed by a fast, or rate-controlled, drug release after administration. The technique offers many advantages, and no special coating solvent or coating equipment is required for manufacturing this type of tablet. The present review article introduces chronopharmaceutical press-coated products from a patient physiological needs perspective. The contents of this article include biological rhythms and pulsatile hormone secretion in humans, the reasons for using pulsatile drug delivery for disease treatment, recent chronopharmaceutical preparations appearing on the market, updated compilation of all research articles and press-coated delivery techniques, factors affecting the performance and drug release characteristics of press-coated delivery systems, and recent challenges for the press coating technique.We also provide a brief overview of press-coating approaches intended for chronotherapy.

SIRAJ SHAIKH et.al.,2014

Solid dosage form represents the preferred class of product among the drugs that are given orally. Presently, oral delivery of drug is still by far the most preferable route due to the ease of administration, patient compliance and flexibility in its formulations. It is probable that at least 90% of all the drugs given by oral route. Gastroretentive techniques are increase the gastric retention time of the dosage form

and to control drug release. Various approaches of gastroretentive delivery systems. floating, swelling, mucoadhesive, and high-density systems have been developed to increase gastric retention time of the dosage forms. Recent Combinational Approaches for Gastroretention includes Floating Pulsatile,floating Bioadhesive,floating swellable,bioadhesing swelling,Bioadhesion and high density etc.Bodys circadian rhythm affect normal physiological function. Pulsatile drug delivery system is designed according to circadian rhythm of body. Gastroretntive Floating pulsatile drug delivery system concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. A combination of floating and pulsatile principles offers an advantage that the system can achieve long residence time in the stomach, sufficient for delivering an adequate amount of drug at the right time, particularly in diseases requiring medication during sleeping and awakening. This review focus on various perspectives of Gastroretntive Floating pulsatile drug.

Ali K. Abbas Al-Obaidy et.al.,2013

The role of chronotherapeutics in hypertension management is based on the recognition that blood pressure does not remain constant throughout the day Instead, it tends to be higher in the earlymorning hours and lower in the evening hours. An oral press-coated tablet was developed by means of direct compression to achieve time-controlled tablet with a distinct predetermined lag time. This press-coated tablet containing; Atenolol in the inner core tablet which is formulated with varioustypes and concentrations of superdisintegrants, and an outer shell tablet which is formulated withdifferent weight ratios of hydrophobic (Ethylcellulose) and hydrophilic polymers (Hydroxy propylmethylcellulose). The effects of the formulation of core tablet and outer shell of press coatedtablets; on drug release and the lag time were investigated. The Formulation was optimized on basisof acceptable tablet properties and in vitro drug release. The results indicate that press-coated tabletcomposed of C8 (as core tablet formula) and T4 (as coat formula) achieve a burst release within 4minutes after 6 hours lag time which is promising applicable pulsatile drug delivery for Atenolol tocontrol morning blood pressure surge through providing appropriate concentration at time of itsmaximum need.

UPENDRA C. GALGATTE et.al.,2013

Objective: In chronopharmacotherapy, drug administration is synchronized with circadian rhythms. The present study was based on objective whether drug delivery would provide a maximum drug release approximately in 6 h after taken orally at bedtime. Methods: The strategy adopted for tablet formulation include preparation of core tablet by direct compression containing drug, ranitidine hydrochloride (RH), which was coated with ethyl cellulose (EC N10) and hydroxypropyl methylcellulose (HPMC E15) followed by coating of HPMC E15 and sodium bicarbonate for generation of effervescence which was further coated by eudragit RL 100 for effervescence entrapment to produce density

Krishnaveni.G et.al.,2013

The aim of the study was to develop press coated time release tablets of montelukast, to achieve the time controlled disintegrating or rupturing function with a distinct predetermined lag time and produce sustained drug delivery released to suite the chronotherapeutics of the disease i.e., bronchial asthma.The tablets, each consisting of a core and a coat, were prepared using compression coating technique. The core tablet was then coated with a natural polymers such xanthan gum, guar gum and mixture of it respectively. Fourier transform infra-red (FTIR) spectrometry, differential scanning calorimetry (DSC),

were applied to investigate the drug-excipients compatibility of the formulation and the studies revealed no chemical interactions between drug and polymers used.Stability studies also were performed for 3 months at 40ºC and 55ºC at 75% RH as per ICH guidelines for optimized formulation and it was found to be stable. The effect of formulation composition on the barrier layer comprising both polymers, excipients on the lag time of drug release was investigated. It was observed that when compared with all other formulations developed, formulation P5F3 shows great ideal in pulsatile drug delivery. The release data from the formulation was found to fit in peppas model with R2 of 0.983.

Vaibhav J. Gadade et.al.,2013

The current research in the field of drug delivery by which pulsatile release can be achieved has been intensified. The present study was an attempt to develop and evaluate an oral pulsatile drug delivery system using Luffa aegyptica mill powder as a novel superdisintegrant. The basic design of the device consisted of a rapid release tabletted core and a controlled release coat. The rapid release tableted core contained a model drug (Diclofenac sodium) and novel superdisintegrant (Luffa aegyptica mill) and controlled release effect was achieved with a combination of coating material (Polyvinylpyrrolidone K30 and Hydroxypropyl methyl cellulose K4M. A 32 full factorial design was employed for the optimization of developed formulation considering concentration of superdisintegrant and coating ratio as independent variables with lag time and drug release as dependent variables. The developed formulations showed uniform appearance, average weight, drug content and adequate hardness. The increase in lag time was observed with an increase in HPMC concentration and decreased concentration of novel Superdisintegrant. Design expert software ® was used to give the solution for optimized formulation based on the evaluation of the developed formulations. Further comparison of Luffa aegyptica mill powder in concentration suggested in the optimized formulation with pharmaceutically acceptable superdisintegrant in same concentration showed almost similar drug release behavior. It can be concluded from the outcome of the present research that Luffa aegyptica mill powder, a natural superdisintegrant, can prove to be best alternative to the existing semisynthetic or synthetic superdisintegrants.

BK Garg et.al.,2012

objective of this study was to develop and evaluate a pulsatile drug delivery system consisting of cores coated with two layers of swelling and rupturable coatings was prepared and evaluated as pulsatile drug delivery system. Cores containing Diltiazem as model drug were prepared by direct compression of different ratios of spray-dried lactose and microcrystalline cellulose and were then coated sequentially with an inner swelling layer containing a superdisintegrant (croscarmellose sodium) and an outer rupturable layer of ethylcellulose. The effect of level of swelling layer was investigated. Rupture and dissolution tests were performed using the USP XXIV paddle method at 50 rpm in 0.1 N HCl. The lag time of the pulsatile release tablets decreased with increasing levels of swelling layer. Increasing levels of the ethylcellulose coating retarded the water uptake and thus prolonged the lag time.

Sumit Patil et.al.,2011

Background: The objective of this study was to develop and evaluate a press-coated pulsatile drug delivery system intended for treatment of early morning stiffness and symptomatic relief from pain in patients with rheumatoid arthritis. Methods: The formulation involved press coating of a rupturable coat

around a rapidly disintegrating core tablet of aceclofenac. A three-factor, two-level, full factorial design was used to investigate the influence of amount of glyceryl behenate, amount of sodium chloride in the coating composition, and the coating level on the responses, ie, lag time to release and amount of aceclofenac released in 450 minutes. Results: Glyceryl behenate and the coating level had a significant influence on lag time, while sodium chloride helped in the rupture of the coat by acting as a channeling agent. After the coat was ruptured, the core tablet showed a rapid release of aceclofenac due to the presence of Ac-Di-Sol®. Graphical analysis of effects by Lenth's method and Bayesian analysis of coefficients enabled identification of variables active on the selected responses. The optimized formulation comprised 20% w/w glyceryl behenate and 2.2% w/w sodium chloride with a 650 mg coating level, and showed a desired lag time of 358.23 minutes, which mimics the fluctuating symptoms of rheumatoid arthritis, followed by rapid release of aceclofenac

C.NITHYA SHANTHI et.al.,2010

Captopril provides effective treatment for hypertension and congestive heart failure. However clinical userequires the daily dose of 37.5-75mg to be taken at three times. Development of a prolonged action dosage form for captopril will bring many benefits. The development of oral controlled or sustained captopril formulationshas been a challenge for a long period of time. The reason being the drug is highly water soluble, unstable inalkaline intestinal pH and decrease in bioavailability in presence of food. Various attempts have been made toregulate the release and increase the bioavailability of the drug. This review focuses the recent progress and attempts made on the oral sustained or controlled release formulation for captopril

3. AIM AND OBJECTIVE

The present work is aimed at formulating floating pulsatile delivery of Diltiazem using various grades of HPMC polymers.

- ✓ To study the effect of Drug polymer ratio or concentration of polymer on drug release.
- ✓ To study the effect of Sodium bicarbonate on floating lag time and on drug release.
- ✓ To study the effect of polymer, polymer grades on the parameters like duration of buoyancy and drug release.
- ✓ To study the effect of hardness on floating lag time.
- ✓ To determine the kinetics and mechanism of drug release.

4. PLAN OF WORK

- ✓ To achieve the above objectives the experimental work was framed as below
- ✓ Formulation of floating core tablets of Diltiazem
- ✓ Formulation of Diltiazem effervescent floating tablets with HPMC K4M, HPMC K15M, HPMC K100M.
- ✓ Formulation of Diltiazem effervescent floating tablets using of combination of polymers i.e., HPMC K4 M and K15M.
- ✓ Determination of effect of sodium bicarbonate concentration on floating lag time and drug release.
- ✓ Evaluation of effervescent floating core tablets of Diltiazem
- ✓ Construction of calibration curve of Diltiazem in 0.1 N HCl.
- ✓ To evaluate prepared formulations for floating lag time and total floating time.

- ✓ To evaluate prepared core tablets for various physical parameters like Weight variation, Thickness, Hardness & Friability.
- ✓ To determine content uniformity of effervescent floating tablets.
- ✓ To carry out swelling studies of the formulations.
- ✓ Determination of in vitro drug release from the formulations in 0.1 HCl for 10 hours.
- ✓ In vitro release data was fitted into various kinetic models for suggesting the suitable mechanism of drug release.

1. Selection of the best batch of tablets based on the in-vitro release data.(optimized formulations-Coating of the optimized formulations of core floating tablets of Diltiazem with polymer solution.
2. Selection of the best batch of tablets based on the in-vitro release data.

5. MATERIALS AND METHODS

Materials used in this study were obtained from different sources. Diltiazem is an antilipemic agent that competitively inhibits hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase. Poly(ethyl acrylate, methyl methacrylate) 2 : 1, sodium bicarbonate , Microcry,stalline cellulose**,** Magnesium stearate, Talc**.**

5.1 METHODOLOGY;

Analytical method development:

a) Determination of absorption maxima:

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1NHCl UVspectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400nm.

b) Preparation calibration curve:

100mg of Diltiazem pure drug was dissolved in 100ml of water(stock solution)10ml of solution was taken and make up with100ml of water (100µg/ml).from this 10ml was taken and make up with 100 ml of water (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 2,4,6,8,10,20,30,40,50,60,70,80,90 and 100µg/ml of Diltiazem per ml of solution. The absorbance of the above dilutions was measured at 271 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axiswhich gives a straight line Linearity of standard curvewasassessed from the square of correlation coefficient (R^2)which determined by least-square linear regression analysis.

5.2. Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

5.3. Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per

Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force.The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface.The blend was carefully pored through the funnel until the apex of the conicalpile just touches the tip of the funnel. The radius (r) of the base of the conical pile wasmeasured. The angle of repose was calculated using the following formula:

$\tan\theta = h / r$ $\tan\theta$= Angle of repose

h = Height of the cone ,r = Radius of the cone base

Angle of Repose	**Nature of Flow**
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Table 5.1: Angle of Repose values (as per USP)

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment.10gm powder blend was sieved and introduced into a dry 20ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

$\text{Bulk Density} = M / V_o$

Where,M = weight of sample

V_o = apparent volume of powder

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is lessthan 2% and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm perL, using the formula:

$\text{Tap} = M / V$

Where,Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of inter particulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will becloser in value.

For poorer flowing materials, there are frequently greaterinter particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk Density

Tap= Tapped Density

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Table 5.2: Carr's index value (as per USP)

5.4. Formulation development of Tablets:

All the formulations were prepared by direct compression. The compression of different formulations are given in Table 6.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Diltiazem . Total weight of the tablet was considered as 200mg.

Procedure:

1) Diltiazem and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

5.6. Evaluation of post compression parameters for prepared Tablets

The designed formulation compression coated tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated

using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Average weight of tablet (mg) (I.P)	**Average weight of tablet (mg) (U.S.P)**	**Maximum percentage difference allowed**
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

Table 5.7 Pharmacopoeial specifications for tablet weight variation

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2) / W] × 100

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Determination of drug content:

Both compression-coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Meloxicam were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

In vitro Buoyancy studies:

The in vitro buoyancy was determined by floating lag time, and total floating time. (As per the method described by Rosa et al) The tablets were placed in a 100ml beaker containing 0.1N HCl. The

time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).

In vitro drug release studies

Dissolution parameters:

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	0.1 N HCl
RPM	--	75
Sampling intervals (hrs)	--	0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature	--	37°c + 0.5°c

As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

Procedure:

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c + 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 12 hours and then the medium 0.1 N HCl was taken and process was continued from 0 to 12 hrs at 75 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometricallyat271 nm using UV-spectrophotometer.

Application of Release Rate Kinetics To Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics:

To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

$F = K_o t$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$Log (100-F) = kt$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$F = k\ t1/2$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$M_t/ M_\infty = K\ t^n$

Where,M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' isthe diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0;while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport),n=1; and for supercase II transport, n > 1.In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

Hixson-Crowell release model:

$(100-Q_t)^{1/3}= 100^{1/3}– K_{HC}.t$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

6. RESULTS AND DISCUSSION

The present study was aimed to developing gastro retentive floating tablets of Diltiazem using various Eudragit polymers. All the formulations were evaluated for physicochemical propertiesand invitro drug release studies.

6.1. Analytical Method

Graphs of Diltiazem was taken in Simulated Gastric fluid (pH 1.2) at 271 nm.

Table 6.1 Observations for graph of Diltiazem in 0.1N HCl (271 nm)

Conc [µg/l]	Abs
0	0
2	0.172
4	0.310
6	0.438
8	0.563
10	0.719

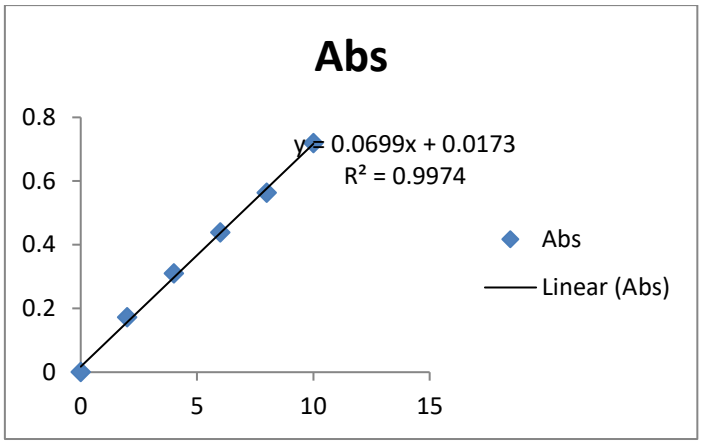


Figure 6.1: Standard graph of Diltiazemin 0.1N HCl

6.2. Preformulation parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	26.01	0.49±0.07	0.57±0.01	16.21±0.06	0.86±0.06
F2	24.8	0.56±0.06	0.62±0.05	16.87±0.05	0.98±0.05
F3	22.74	0.52±0.03	0.68±0.07	17.11±0.01	0.64±0.03
F4	25.33	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04
F5	26.24	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
F6	26.12	0.56±0.05	0.66±0.06	17.65±0.09	1.06±0.09
F7	27.08	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03
F8	25.12	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09
F9	25.45	0.54±0.08	0.62±0.03	17.54±0.09	1.17±0.02

Table6.2: Pre-formulation parameters of blend

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.07 to 0.58±0.06(gm/cm3) showing that the powder has good flow properties.The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties.The compressibility index of all the formulations was found to be ranging between 16 to 18 which shows that the powder has good flow properties.All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

6.3. Optimization of sodium bicarbonate concentration:

Three formulations were prepared with varying concentrations of sodium bicarbonate. The formulation containing sodium bicarbonate in 30mg concentration showed less floating lag time of 4 min and the tablet was in floating condition for more than 12 hours.

6.4.Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and

drugreleasestudiesindifferentmediawereperformedon the tablets.

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Flaoting lag time (min)
F1	202.5	3.5	0.52	4.8	99.76	4.0
F2	205.4	3.2	0.54	4.9	99.45	4.2
F3	198.6	3.4	0.51	4.9	99.34	4.5
F4	210.6	3.5	0.55	4.9	99.87	4.1
F5	209.4	3.4	0.56	4.7	99.14	4.0
F6	210.7	3.2	0.45	4.5	98.56	4.4
F7	202.3	3.1	0.51	4.4	98.42	4.5
F8	201.2	3.3	0.49	4.7	99.65	4.6
F9	198.3	3.5	0.55	4.6	99.12	4.7

6.4. Invitro quality control parameters for tablets

All the parameters such as weight variation, friability,hardness,thickness and drug content were found to be within limits.

6.4. Invitro quality control parameters for tablets

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

6.5. In-Vitro Drug Release Studies

Table 6.5 Dissolution Data of Diltiazem Tablets

TIME(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	18.81	19.89	14.21	19.62	18.42	19.62	21.73	18.52	19.53
1	29.02	28.04	18.87	27.86	27.73	27.86	30.23	37.47	28.97
2	35.70	35.43	27.19	36.35	35.63	36.35	44.9	59.93	35.89
3	43.32	41.65	35.66	41.45	42.04	41.45	50.87	65.85	45.7
4	49.25	47.18	43.32	47.80	57.25	47.80	54.73	77.54	54.38
5	55.28	53.81	51.06	55.25	64.33	55.25	66.37	89.55	61.2
6	60.92	58.89	57.13	60.24	75.41	60.24	70.84	96.67	67.06
7	66.08	64.53	63.63	66.73	83.84	66.73	73.17	104.28	72.52
8	70.44	69.43	69.71	71.34	102.80	76.34	79.01		77.88
9	80.90	79.98	79.27	80.17		88.52	84.23		86.6
10	87.27	83.98	89.02	93.28		98.97	90.18		89.09

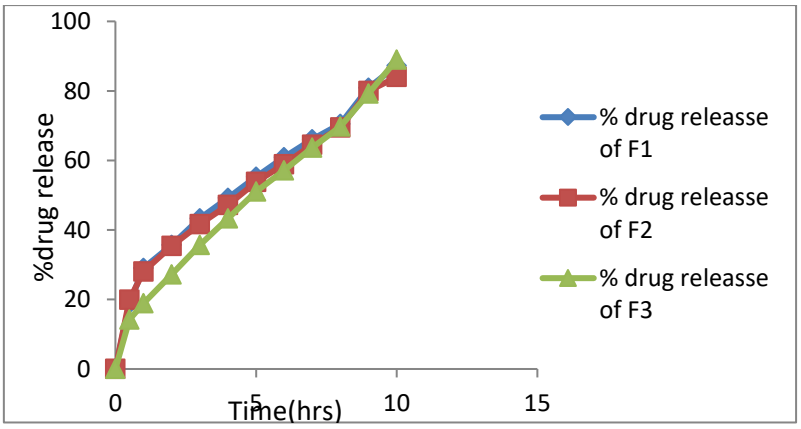


Fig 6.2: Dissolution profile of DILTIAZEM floating tablets (F1, F2, F3 formulations).

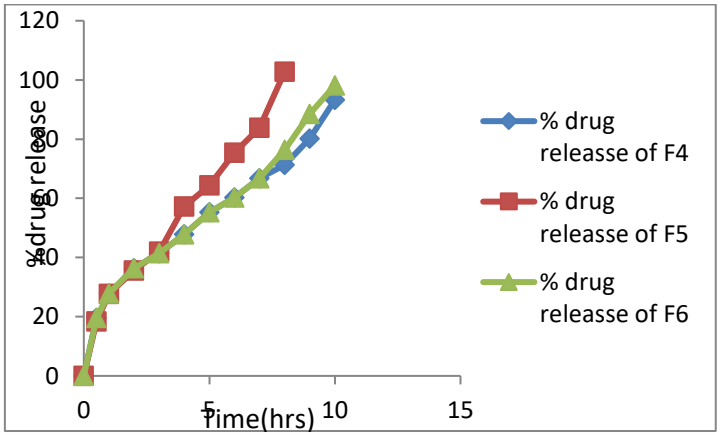


Fig6.3: Dissolution profile of Diltiazem HCl floating tablets (F4, F5, F6 formulations).

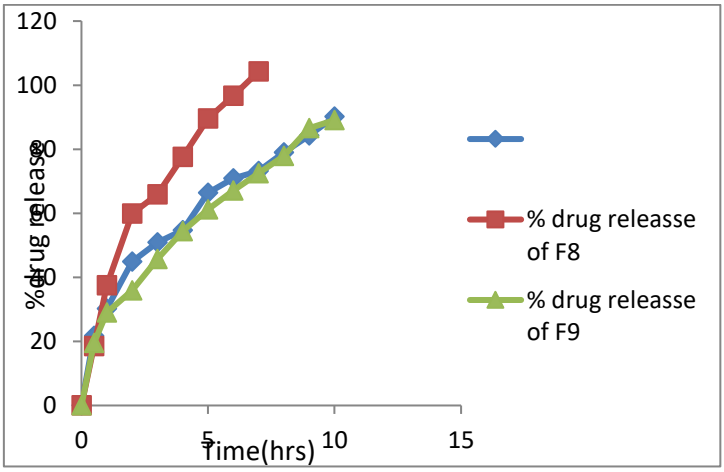


Fig 6.4: Dissolution profile of Diltiazem floating tablets (F7, F8, F9 formulations)

From the dissolution data it was evident that the formulations prepared with Guar gum as polymer were unable to retard the drug release up to desired time period i.e., 10 hours.

Whereas the formulations prepared with Eudragit L 100 retarded the drug release in the concentration of 60 mg (F6)showed required release pattern i.e., retarded the drug release up to 10 hours and showed maximum of 98.97 % in 10 hours with good floating lag time and floating buoyancy time.

The formulations prepared with Eudragit L 100 showed more retardation even after 10 hours they were not shown total drug release. Hence they were not considered.

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