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DESIGN AND INVITRO EVALUATION OF PULSATILE DRUG DELIVERY SYSTEMS OF FLUVASTATIN SODIUM

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ABSRACT

Pulsatile Drug Delivery Systems (PDDS) are advanced drug delivery techniques that have been developed to release the drug after a definite lag time followed by a sudden release of the drug, which is in accordance with the circadian rhythm of the body. In the case of hyperlipidemia, which is a major risk factor for the development of cardiovascular diseases, the circadian rhythm of cholesterol synthesis is observed. In this case, the production of cholesterol is maximum in the early morning. In conventional drug delivery systems, the drug is released without synchronization with the circadian rhythm, which might affect the therapeutic response and side effects of the drug. In the current study, a pulsatile drug delivery system of Fluvastatin sodium, a competitive inhibitor of HMG-CoA Reductase, used in the treatment of hypercholesterolemia and prevention of cardiovascular diseases, is designed and evaluated. Fluvastatin, due to its short half-life, low bioavailability, and extensive metabolism through the liver, is a good candidate for a chronotherapeutic pulsatile drug delivery system. It is to be administered before sleep, and the drug is released at a particular time to coincide with the peak hepatic cholesterol synthesis, which is between 12 a.m. and 4 a.m.

KEYWORDS: Pulsatile Drug Delivery System (PDDS); Chronotherapy; Hyperlipidemia; Fluvastatin Sodium; HMG-CoA Reductase Inhibitor; Circadian Rhythm; Antihyperlipidemics; Controlled Release; Lag Time; Burst Release; Eudragit RS-100; Cholesterol Biosynthesis; Statins; Chronopharmacology; In Vitro Evaluation.

INTRODUCTION

Pulsatile drug delivery systems (PDDS) are a cutting-edge approach to drug administration, coordinating the release of drugs according to the body's chronobiological rhythms for optimal therapeutic efficacy and least toxicity. PDDS are intended to release a drug after a predetermined waiting period, resulting in a sudden, pulsatile release of the drug that matches the body's needs, particularly in situations where a constant level of the drug is not satisfactory. According to a detailed review by Singh et al.[1] PDDS are most appropriate for diseases that show circadian rhythm patterns in symptoms or drug absorption and metabolism.

According to a comprehensive review published on Japs online,[2] PDDS can be classified as time-controlled or stimulus-responsive systems that utilize principles such as soluble/erodible coatings, rupturable membranes, and timed permeation barriers. The main rationale for PDDS is based on chrono pharmacotherapy. Diseases such as asthma, rheumatoid arthritis, hypertension, peptic ulcers, and hyperlipidemia have clear circadian rhythms. For example, nocturnal asthma attacks, morning blood pressure peaks, or the biosynthesis of cholesterol during the night emphasize the need for time-controlled drug delivery.[3,4]

By synchronizing drug delivery with these rhythms, PDDS provide better disease control. PDDS also provide better patient outcomes by ensuring site-specific delivery, bypassing first-pass metabolism, minimizing gastric irritation, and maximizing patient compliance due to less frequent dosing and precise targeting.[5,6] This is especially true for antihyperlipidemic agents such as simvastatin and lovastatin, which have peak efficacy when administered at night, coinciding with the body's natural peak cholesterol synthesis during the night.[7]

Moreover, the application of circadian medicine in pharmacotherapy has recently gained popularity. Studies have shown that about 50% of all physiological functions have a circadian rhythm, which includes the secretion of hormones, gastrointestinal motility, renal function, and activity of hepatic enzymes. Thus, PDDS can greatly improve the efficacy of drugs with narrow therapeutic indices or drugs that require precise timing of absorption and action A study conducted by Lévi et al.[15] showed that cancer patients treated with PDDS also experience improved clinical outcomes because PDDS ensures site-specific delivery, prevents first-pass metabolism, reduces gastric irritation, and improves patient compliance due to less frequent dosing and targeted delivery.[5,6]

This is especially important for antihyperlipidemic medications such as simvastatin and lovastatin, which have been shown to be most effective when taken at night, corresponding to the body's natural peak cholesterol production.[7]

Moreover, the incorporation of circadian rhythms in pharmacotherapy has recently gained popularity. It has been shown that approximately 50% of all physiological events are regulated by circadian rhythms, which include the secretion of hormones, gastrointestinal motility, renal function, and activity of hepatic enzymes. Therefore, PDDS can greatly improve the efficiency of medications with narrow therapeutic indices or those that require precise timing of absorption and onset of action. A study conducted by Lévi et al.[15] showed improved clinical outcomes in cancer patients treated with PDDS, suggesting its potential use in other therapeutic categories, such as cardiovascular and metabolic disorders.• Pulsatile delivery is the release of a fraction of the total drug load in a burst fashion followed by intervals of minimal/no release (lag phase) in a predetermined temporal fashion.

Specifically, oral pulsatile drug delivery is the burst release of drugs according to a predetermined schedule from the time of oral dosing. For instance, Ritalin LA capsule is a pulsatile delivery system that releases IR of 50% of the total drug load orally ingested, followed by a burst release of the rest of the drug load after 4 hours. In the realm of MR, such non-monotonic and multi-drug cargo release profiles have been acknowledged and/or demonstrated to provide clinical advantage in (1) optimizing chronotherapy, (2) simulating natural patterns of endogenous secretion, and (3) delivering optimal therapy for drugs inducing tolerance due to constant drug levels leading to receptor down-regulation. Hence, there has been an increasing interest in the development of drug delivery systems with pulsatile release profiles.

- **Merits of Pulsatile Drug Delivery System**

Targeted Drug Release

PDDS enables the release of drugs at targeted times when the drug's therapeutic action is required, thus improving the efficacy of treatment. Especially beneficial for conditions such as asthma or arthritis, which have a circadian pattern and peak at certain times of the day.

Minimized Side Effects

PDDS enables the release of drugs only when required, thus reducing the drug's exposure and hence minimizing side effects and improving patient safety.

Improved Patient Compliance

The pulsatile system requires a single dose of the drug, thus improving patient compliance**.**

Optimized Therapeutic Effects

The body's natural rhythms can be synchronized to improve the drug's efficacy. For instance, PDDS enables the release of anti-inflammatory drugs prior to the body's inflammatory response.

Ideal for Chronotherapy

Chronotherapy is a technique that tries to synchronize the delivery of the drug with the circadian rhythm of the disease. PDDS is very effective in this therapeutic method.

Enhanced Bioavailability

Narrow absorption windows can be effectively utilized by timed release, which allows the drug to be absorbed at the maximum level when the body is most responsive.

Demerits of Pulsatile Drug Delivery System

Complexity in Design and Manufacturing

The design and manufacturing process of PDDS can be complex and expensive due to the use of specialized materials and technology for time-controlled release.

Inconsistent Release Patterns

Differences in the physiology of individual patients (for example, pH of the digestive system and enzymatic activity) can influence the pattern of drug release, which may cause inconsistent therapeutic effects.

Higher Cost

The technology used in the development and manufacturing of PDDS can make the drugs more expensive, thus making them less available to patients.

Limited Applications

Not all drugs and diseases can be treated by the pulsatile drug delivery system. This system is only useful for drugs that require delayed or time-specific release.

Formulation Challenges

Preparation of stable drug formulations for PDDS can be challenging, particularly for drugs that are sensitive to environmental conditions such as temperature, light, and moisture.

Risk of Dose Dumping

In the event of a failure in the delivery system, there is a possibility of a sudden discharge of the total drug dose, resulting in toxicity or a decrease in the therapeutic effectiveness of the drug.

The Pulsatile Drug Delivery System has numerous benefits, particularly in chronotherapy and targeted drug delivery. However, the complexity, cost, and formulation difficulties associated with the system may hinder its widespread use,[5,6]

MECHANISM OF ACTION OF PULSATILE DRUG DELIVERY SYSTEM

The mechanism of action of a Pulsatile Drug Delivery System (PDDS) is the temporal delivery of the drug in a time-specific manner, according to biological rhythms or therapeutic needs. The aim is to deliver the drug at the right time and right place for maximum therapeutic benefits. The mechanism of action can be divided into several stages, depending on the system.

Key Mechanisms in Pulsatile Drug Delivery Systems

- **Lag Phase (Delay in Drug Release)**

- In pulsatile drug delivery systems, the drug is not released immediately after administration. There is a predetermined "lag time" during which no drug is released.
- The lag phase is very important for synchronizing the release of the drug according to circadian rhythms or disease conditions that peak at certain times e.g., asthma or arthritis.

- **Burst Release Phase**

- After the lag phase, the system releases the drug in a burst release manner to ensure an effective concentration of the drug at the intended (targeted) site.
- The release is stimulated by internal factors (e.g., pH, enzymes activity) or external factors (e.g., temperature, light)

- **Stimuli-Responsive Mechanisms**

PDDS is also designed to respond to certain internal or external stimuli for the release of the drug. The following are some of the mechanisms:

➢ **pH-Triggered Systems**

Certain drugs are designed to be released in certain areas of the gastrointestinal tract. For instance, certain coatings that dissolve at a certain pH value can release the drug only in the intestine, which has a higher pH value, bypassing the stomach, which has an acidic environment.

➢ **Enzyme-Triggered Systems**

Certain enzymes in the body, which are found in specific tissues and organs (such as the colon or liver), break down the coating or matrix of the drug delivery system, causing the release of the drug at the desired site.

➢ **Pressure-Activated Systems**

The increased pressure in the GI tract, especially in the colon, can be a trigger for the release of the drug, as in the case of certain osmotic systems.

➢ **Temperature- or Light-Activated Systems**

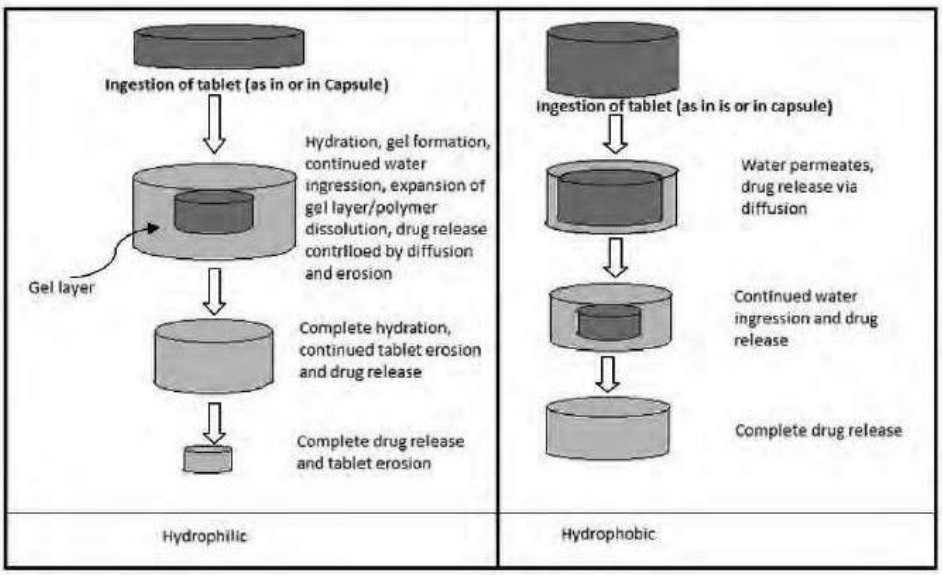
Some systems are temperature- or light-sensitive and release the drug only when they come in contact with these external stimuli, providing greater control over the release of the drug .Reservoir and Coating-Based Systems:

- In some PDDS, the drug is accommodated in a "reservoir" that is surrounded by a coating or polymer layer that controls when and how the drug is released.
- The coating can either dissolve after a certain time(time-controlled systems) or it can be degraded by external factors like pH or enzymes.

EXAMPLES OF PULSATILE DRUGDELIVERY SYSTEMS

- **Chronotropic Systems**: These systems are designed to release drugs in alignment with circadian rhythms. For example, a patient with nocturnal asthma might take a medication that releases bronchodilators late in the evening to prevent nighttime symptoms.

- **Osmotic Release Oral System (OROS):** These systems uses osmotic pressure to control the drug release, providing a consistent pulsatile release over time.



The PDDS mechanism relies on precise control of drug release timing, either through physical or chemical triggers (like pro enzymes, or coatings). The system ensures that the drug is delivered in a "pulsatile" manner after a predetermined time lag, enabling synchronization with the body's rhythms or disease patterns for optimal therapeutic response.[8]

Release of drug from hydrophilic and hydrophobic matrix

CLASSIFICATIONOFPULSATIVEDRUGDELIVERYSYSTEM

Time-controlled pulsatile drug delivery

- Single-Unit Pulsatile Systems
- Capsular-Based System
- Capsular Systems Based on Osmosis
- System with Erodible or Soluble Coating
- System with Rupturable Layers or Membrane

II. Stimuli-induced pulsatile drug delivery system

- Temperature-Induced Systems
- Chemical Stimuli Induced Pulsatile Systems
- Glucose-Responsive Insulin-Releasing System
- PH Sensitive Drug Delivery
- Inflammation-Induced Pulsatile Delivery
- Drug Release from Smart Gel Responding to Antibody Concentration

III. Externally regulated pulsatile drug delivery

- Pulsatile Drug Release by Magnetic Field
- Pulsatile Drug Release by Ultrasound
- Pulsatile Drug Release by Electric Fiel d[9]

ANTI LIPIDEMICS

The lipid lowering drugs are employed for the treatment of hypercholesterolemia and dyslipidemias. These drugs are among the most widely used in the United States. These drugs are usually employed for a long term and often in a combination. The primary effects of the lipid lowering drugs are in the reduction of the serum low density lipoprotein (LDL) cholesterol levels that are thought to predispose to atherosclerosis and its complications, acute myocardial infarction, cerebrovascular ischemic stroke, and peripheral vascular disease. Some of these drugs are also employed for the reduction of the triglyceride levels, and others can increase the high-density lipoprotein (HDL) cholesterol levels that are thought to be protective against atherosclerosis.[11] Patients at high risk of cardiovascular events (cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina) can benefit from lipid-lowering medications.

It is important to note that these medications are best used in conjunction with lifestyle changes. These medications can be employed for the primary or secondary prevention of cardiovascular events. This activity addresses the lipid lowering pharmaceutical therapies that must be reviewed by the interprofessional team members to provide optimal patient care and direct patient care to optimal outcomes.[12]

PATHOPHYSIOLOGY

Cholesterol is a lipophilic compound that is vital for life. It plays various roles that make cells function normally. Cholesterol is a major component of the cell membrane. It is involved in the structural composition of the cell membrane and helps regulate its fluidity. Cholesterol acts as a precursor in the formation of vitamin D, steroid hormones (cortisol, aldosterone, and adrenal androgens), and sex hormones (testosterone, estrogens, and progesterone). Cholesterol is also a component of the bile salt involved in the digestion process of fat-soluble vitamins A, D, E, and K.

Cholesterol is mainly lipophilic. It is transported in the bloodstream, together with triglycerides, in lipoprotein particles (HDL, IDL, LDL, VLDL, and chylomicrons). These lipoproteins can be measured in a clinical setting to approximate the level of cholesterol in the blood. Chylomicrons are absent in non-fasting blood.

Cholesterol can be transported into the bloodstream through the digestion of dietary fat in chylomicrons. However, since cholesterol is a vital substance in cell function, it can also be produced directly by each cell in the body. The process of cholesterol production involves a series of complex reactions that will not be discussed in this article. The location of this process is the liver, which produces most of the de-nove cholesterol in the body.[13] A primary

Since cholesterol is mostly a lipophilic substance, it does not dissolve easily in the bloodstream. For this reason, it is packaged in lipoproteins that have phospholipid and a poly protein. Lipoproteins are outer membrane proteins comprising phospholipid, apolipoprotein, and free cholesterol. This enables the lipid molecules to freely move around the body through the bloodstream and be delivered to cells that require them.

There are different kinds of lipoproteins that exist in the blood, and each one has a different role. There are

1. High-density lipoproteins (HDL)
2. Intermediate-density lipoproteins (IDL). Low-density lipoproteins (LDL).
3. Very-low-density lipoproteins (VLDL).

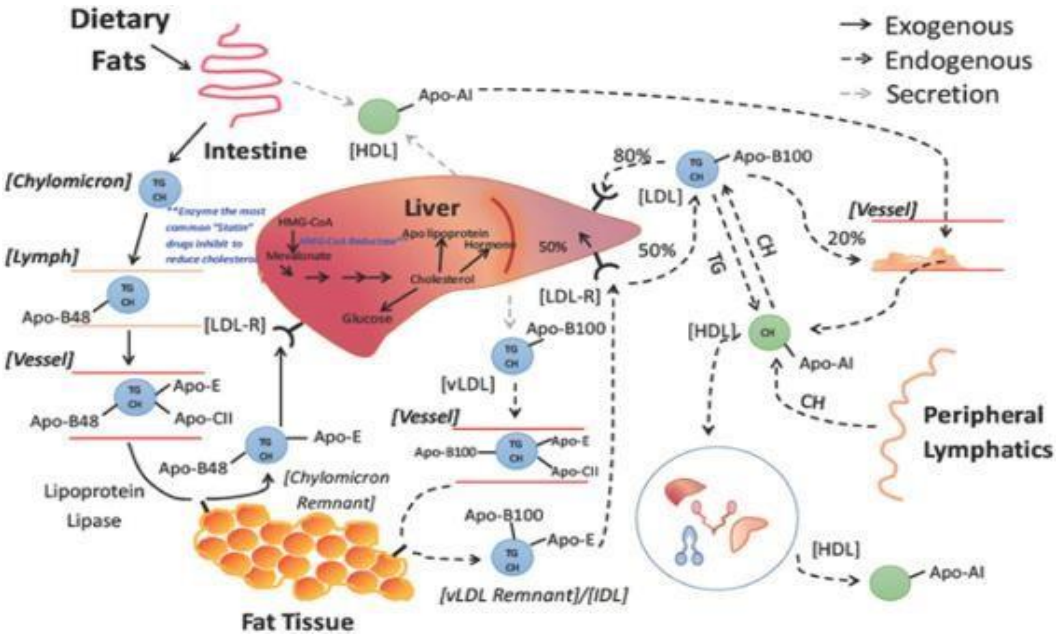
- It is worth noting that the LDL particles are considered to be the major cholesterol transporters; at least two-thirds of the blood cholesterol is transported in the LDL to the peripheral tissues. On the other hand, the HDL molecules are considered to have the reverse role. They remove the excess cholesterol and transport it back to the liver for excretion. Both of these lipoproteins are of clinical importance since high levels of LDL and low levels of HDL are known to increase the patient's risk of atherosclerotic vascular diseases.[14]
- Hypercholesterolemia (high LDL-cholesterol) is one of the major risk factors that contribute to the development of atherosclerotic plaques. Atherosclerotic plaques are associated with an increased risk of several adverse clinical events, including but not limited to, coronary artery disease. PAD, aortic aneurysms, and stroke. One of the major risk factors for the development of atherosclerotic plaques is the high blood level of low-density lipoprotein (LDL).
- In addition, it has been demonstrated that the high blood level of high-density lipoprotein (HDL) is associated with a reduced risk in epidemiological studies, but clinical trials using drugs that increase HDL-cholesterol have failed to show any beneficial effect. Therefore, the major goal of patient management is primarily to reduce LDL.

The mechanism of development of atherosclerotic plaques starts with endothelial injury.

Endothelial damage results in the dysfunction of endothelial cells, which in turn increases the number of LDL particles that can penetrate the vascular wall. Lipoproteins, particularly LDL, can then accumulate in the vessel wall, entrapped by the cellular matrix in the intima. LDL is then modified and ingested via scavenger receptors on macrophages, resulting in foam cell formation. As more lipids accumulate in the vessel wall, smooth muscle cells begin to migrate into the lesion. Finally, these smooth muscle cells encase the newly formed plaque, forming the fibrous plaque, the protector of the lesion, preventing the lipid core from being exposed to the lumen of the vessel. Atherosclerotic plaques can cause vessel occlusion (reducing blood flow distally, causing ischemia) or, more often due to the high lipid and macrophage content (vulnerable plaque), rupture, causing the formation of a thrombus that can completely block the flow of blood (as seen in acute myocardial infarctions, uneatable angina).

The targets for lipid-lowering therapy, as recommended by the National Heart Foundation of Australia, are as follows. These are only guidelines that your doctor may set differently depending on your individual circumstances and risk factors:

- Total cholesterol 4.0mmol/L
- HDL cholesterol 1.0mmol/L
- LDL cholesterol <2.0mmol/L
- Non-HDL cholesterol <2.5mmol/L
- Triglycerides <2.0mmol/L[15]



LIPID METABOLISM

Very-low-density lipoproteins (VLDL) have apoprotein B-100 (apo B), are synthesized in the liver, and transport TGs and cholesterol to peripheral tissues. VLDL is the mechanism by which the liver secretes excess TGs synthesized from plasma free fatty acids and chylomicron remnants. VLDL production is increased when intrahepatic FFAs are increased, as seen in high-fat diets and when excess adipose tissue releases FFAs directly into the circulation (as in obesity and uncontrolled diabetes mellitus). Apo C-II on the surface of VLDL activates endothelial LPL to hydrolyze

TGs into FFAs and glycerol, which are then taken up by cells.
Intermediate-density lipoproteins (IDL) are the result of LPL processing of VLDL.
IDL are cholesterol-rich VLDL remnants that are either cleared by the liver metabolized by hepatic lipase into LDL, which retains apo B-100.

Low-density lipoproteins (LDL), the VLDL and IDI. metabolites, are the most cholesterol-rich of all lipoproteins. Between 40 to 60% of all LDL are removed by the liver in a process mediated by apo B and hepatic LDL. receptors. The remaining particles are removed by either hepatic LDL or non-hepatic non-LDL (scavenger) receptors. Hepatic LDL receptors are down-regulated by the delivery of cholesterol to the liver by chylomicrons and by increased dietary saturated fat; they are up-regulated by decreased dietary fat and cholesterol. Non hepatic scavenger receptors, particularly in macrophages, remove excess LDL that has escaped processing by hepatic receptors. Monocytes migrate into the subendothelial space and become macrophages; these macrophages then take up oxidized LDL and form foam cells in atherosclerotic plaques.

The LDL particle can vary in size from large and buoyant to small and dense. Small, dense LDL is particularly rich in cholesterol esters and is linked to metabolic abnormalities such as hypertriglyceridemia and insulin resistance.

High-density lipoproteins (HDL) are initially cholesterol-free lipoproteins that are produced in both enterocytes and the liver. HDL metabolism is quite complex, but one of the functions of HDL is to acquire cholesterol from peripheral cells and other lipoproteins and deliver it to where it is most needed-other cells, other lipoproteins (via cholesteryl ester transfer protein [CETP]), and the liver (for clearance). Its net effect is anti-atherogenic.

Efflux of free cholesterol from cells is mediated by ATP-binding cassette transporter Al (ABCAI), which covalently associates with apoprotein A-1 (apo A-1) to form nascent HDL. Free cholesterol in nascent HDL is then converted to cholesteryl esters by the enzyme lecithin-cholesterol acyl transferase (LCAT), forming mature HDL. Plasma HDL concentration may not accurately reflect reverse cholesterol transport, and the beneficial role of higher HDL concentration may also be attributed to anti-oxidant and anti-inflammatory actions.

Lipoprotein (a) [L p(a)] is an LDL-like particle that carries apoprotein (a), which has 5 cysteine-rich regions termed kringles. One of these regions is similar to plasminogen, and it competitively inhibits fibrinolysis, thus contributing to thrombus formation. L p(a) can also directly contribute to atherosclerosis. The metabolic clearance and production pathways of L p (a) are not well understood, but it is known that its levels are elevated in patients with, especiall y in patients on dialysis.[16]

- **The following medications for dyslipidemia and hypercholesterolemia are discussed individually in Liver Tox**
- Bile Acid Resins Sequestrants
- Cholestyramine
- Colestipel
- Fibrates
- Clofibrate Fenofibrate
- Gemfibrozil

- Monoclonal Antibodies
- Alirocumab(Anti-PCSK9)
- Evinacumab(Anti-ANGPTL3)
- Evolocumab(Anti-PCSK9)
- Niacin(Nicotinic Acid)
- Omega-3FattyAcids,
- Omega-3fattyEthylEsters
- Omega-3CarboxylicAcids
- Statins
- Omega-3AcidEthylEsters
- Icosapent Ethyl
- Omega-3CarboxylicAcida
- Aorvastatin
- Fluvastatin
- Lovastatin
- Pitavastatin
- Pravastatin
- Rosuvastatin
- Miscellaneous
- BempedoicAcid
- Ezetimibe
- Inclisiran
- Colesevelam
- Bempedoic Acid
- Ezetimibe
- Inclisiran
- Lomitapide

Advantages of PDDS in Anti-Lipidemic Therapy

1. Chronotherapy of Lipid Metabolism

a. Lipid metabolism in the body has a circadian pattern, with a peak in the synthesis of cholesterol at night, particularly between midnight and early morning hours. This indicates that the administration of anti-lipidemic therapy during this peak period may increase its efficacy.

b. PDDS can release the drug just before the peak period of lipid synthesis, thus increasing the efficacy of the drug in lowering cholesterol levels.

2. Minimized Side Effects

Anti-lipidemic drugs, including statins, may cause side effects such as muscle pain or liver failure. Administration of these drugs at specific times when the body requires their maximum effect (at night) may minimize the side effects of the drug.

Enhanced Patient Compliance

Most anti-lipidemic medications need to be taken at night for maximum efficacy. A pulsatile delivery system enables the medication to be delivered once a day, with the drug being released later in the night. This will minimize the need for patients to take their medications at odd hours.

2. Targeted and Controlled Release

PDDS helps in the controlled release of the drug. For example, a statin can be released in the early morning hours when the synthesis of cholesterol is at its peak.

Types of Anti-Lipidemics That Could Benefit From Pdds

1. Statins (HMG-CoA Reductase Inhibitors)

Simvastatin, Atorvastatin, Rosuvastatin, and other statins work by inhibiting the enzyme HMG-CoA reductase, which is involved in cholesterol synthesis.

Statins are usually taken at night because the body produces cholesterol at its peak during sleep. PDDS can be designed to deliver statins in a delayed manner to match the peak cholesterol synthesis rate of the body.

2. Bile Acid Sequestrants

Cholestyramine and Colesevelam are used to bind bile acids in the intestines and remove them from the body, thus lowering cholesterol levels.

Pulsatile delivery systems could be designed to deliver the drug at specific times when bile acid levels are at their peak in the intestines, thus enhancing the binding activity of the drug.

1. Fibrates

Fenofibrate and gemfibrozil are used to reduce triglyceride levels and raise HDL cholesterol. A pulsatile delivery system may help maximize their release during times when triglyceride levels are likely to be highest (usually after meals).

2. Niacin (Nicotinic Acid)

Niacin is useful in raising HDL levels and reducing LDL and triglyceride levels. A pulsatile delivery system may help counteract flushing and other side effects by releasing the drug at the optimal time.

3. PCSK9 Inhibitors

Alirocumab and vedolizumabs are inhibitors of the PCSK9 protein, which decreases the degradation of LDL receptors and increases the clearance of LDL cholesterol from the bloodstream.

EXAMPLE OF A PDDS SYSTEM FOR ANTI-LIPIDEMICS

Chronotherapy with Statins: By employing a time-delayed release mechanism for simvastatin, it is possible to deliver the drug once a day but releases it in the early morning hours when the synthesis of cholesterol is at its peak. This will help improve the efficacy of the drug without increasing the chances of adverse reactions due to higher concentrations of the drug at other times of the day.

Challenges and Considerations

- **Formulation Complexity**: The development of pulsatile formulations for anti-lipidemics requires complex technology.
- **Patient Variability:** Variability in the metabolism rates, diet, and lifestyle of patients may influence the pulsatile delivery of drugs for lipid regulation.

EXAMPLE

HMGCOAREDUCTASE

Fluvastatin sodium is an antilipidemic drug that competitively inhibits HMG-CoA reductase. It is a class of drugs known as statins and is used to lower plasma cholesterol concentrations and prevent cardiovascular diseases. Its short biological half-life (3 hours) and low bioavailability (24%-29%) make it an appropriate candidate for a pulsatile drug delivery system. Therefore, the aim of the current study is to develop a pulsatile drug delivery system of Fluvastatin sodium that can be administered before bedtime (9 pm) and is capable of releasing the drug after a predetermined time delay (5 hours) and can be defined by the ratio of drug concentration in the early morning hours when free cholesterol levels are more common.[19]

PDDS are broadly classified into several design categories

Time-released systems: Use polymeric coatings or hydrogel plugs to time lag before drug release. These systems rely on dissolution, swelling, or erosion processes to trigger drug release after a predetermined time.

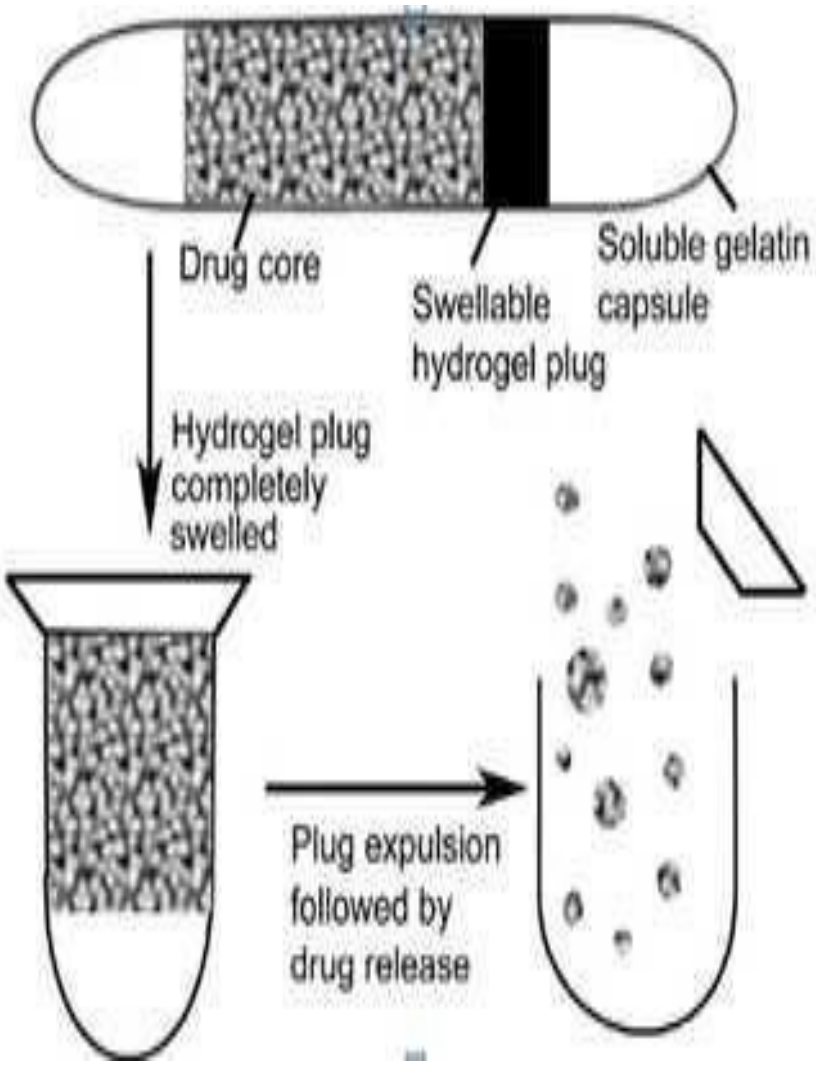
Stimuli-responsive systems: Respond to internal physiological stimuli such as pH (e.g., pH changes in the gastrointestinal tract), enzymatic activity (e.g., colonic enzymes), or body temperature. For example, pH-sensitive polymers such as Eudragit® can be employed to release drugs specifically in the small intestine or colon.

Externally controlled systems: Rely on external stimuli such as magnetic fields, ultrasound, electrical pulses, or light to trigger drug release.[8,9] Although still in the developmental stages, these systems have great potential for creating highly individualized drug delivery profiles. These systems provide programmable control but are not frequently used in oral antihyperlipidemic treatment.[32]

Several marketed platforms validate the feasibility of PDDS

Pulsincap™: Capsule-based formulation with a hydrogel plug for timed release.

Diffucaps® and CODAS®: Multiparticulate formulation with extended lag times. CODAS® (Chronotherapeutic Oral Drug Absorption System) has been specifically used for verapamil to prevent morning surge in blood pressure



Design of Pulsincap® system

OROS: Osmotic pump systems for zero-order release post-lag, which use an orifice and semipermeable membrane to provide a controlled pulse.

PULSYS™: A pulsatile multiparticulate system designed for chronotherapeutics.[10–12]

Commercially available technologies such as CODAS®, OROS®, and Diffucaps® have proven their commercial feasibility and have opened the door to new pulsatile delivery systems in antihyperlipidemic therapy. Moreover, their combination with wearable biosensors and ingestible electronics allows for real-time monitoring and adjustment.

Pharmacogenomics and chronopharmacology are rapidly merging to provide personalized solutions for PDDS. Genome-based drug delivery systems according to individual metabolic and circadian rhythms are soon going to be in vogue. However, issues such as cost of production, scalability, and approval are the major hurdles in the widespread use of these systems.

Along with their efficacy, PDDS help in providing improved pharmacoeconomic profiles by enhancing drug use, lowering rates of hospitalization, and improving compliance. With the increasing prevalence of chronic diseases globally, especially those having a circadian rhythm, PDDS can play a pivotal role in public health initiatives.

These are: enhanced compatibility between the polymer and drug, more efficient management of lag-time variability, more accurate models of in vitro and in vivo correlation (IVIVC), and more ethical concerns regarding programmable drug delivery systems.[13,14] There are also studies on the use of smart polymers and nanotechnology-based PDDS for highly responsive and patient-specific therapies. For antihyperlipidemic medications, which are commonly prone to first-pass effects and need to be taken in the evening, PDDS are a very effective alternative to existing drug delivery systems.

The liver secretes most of its cholesterol production during the night, particularly between 12 a.m. and 4 a.m. Consequently, a PDDS formulation of statins would be able to deliver the active pharmaceutical ingredient exactly during this peak secretion period, enhancing lipid management while minimizing adverse effects such as myopathy or hepatotoxicity.Nanotechnology-based PDDS, such as core-shell microspheres, lipid-polymer hybrid nanoparticles, and smart liposomes, are also emerging in experimental research. These can be designed to react to endogenous stimuli or exogenous cues with picosecond accuracy, paving the way for highly targeted hyperlipidemia therapy that can be synchronized with patient-specific circadian rhythms.

Background & Rationale for Pulsatile Drug Delivery

The use of Pulsatile Drug Delivery Systems (PDDS) for the delivery of antihyperlipidemic drugs is a promising area in the context of circadian biology and cholesterol metabolism. Hyperlipidemia, a major risk factor for cardiovascular diseases, is mainly treated with statins like simvastatin, atorvastatin, and lovastatin. These drugs work by inhibiting the enzyme HMG-CoA reductase, which plays a pivotal role in the body's natural cholesterol production in the liver. Notably, the production of cholesterol follows a circadian rhythm, reaching its peak during the night hours, specifically between 12 a.m. and 4 a.m., when an individual is usually asleep.[16]

Conventional drug delivery systems do not take into account these biological rhythms and may lead to reduced efficacy or increased side effects. In contrast, PDDS enable the administration of a drug in the evening with a delayed release during the peak hours of cholesterol synthesis, matching the drug release with the disease activity.[17] For example, simvastatin and lovastatin have a short half-life and are more effective when the maximum plasma concentration is reached during the peak production of cholesterol in the liver.[18]

Formulations of antihyperlipidemics based on PDDS are designed employing mechanisms such as erodible polymers, time-dependent coating layers, and hydrogel plugs. These facilitate a lag time followed by a burst release of the drug. This not only increases the efficacy of the drug but also decreases the hepatic side effects, increases patient compliance, and may also decrease the dose of the drug.[19]

One of the most important studies was conducted by Pan et al., where the chronotherapy of simvastatin was evaluated. The study showed that evening administration employing a delayed release mechanism was more effective than the conventional method in decreasing the levels of LDL cholesterol.[20] Moreover, Hermida et al. found that lipid profiles and cardiovascular risk were improved when statin therapy was administered according to circadian rhythms.[21] In addition, patient compliance—a very important aspect of managing chronic diseases—can be greatly improved by employing PDDS. This is because PDDS allows once-daily evening administration, which automatically triggers the release of the drug during the biological window of peak need. This eliminates the need for waking-time dosing regimens.[22] Technologies such as multi-layer tablets, osmotic pumps, and lipid

nanoparticles are being investigated for application in antihyperlipidemic PDDS. These technologies have the potential for accurate timing, minimizing systemic exposure, and maximizing targeting of the hepatic pathways involved in lipid metabolism.[23] As the incidence of lifestyle-related metabolic disorders continues to escalate, the development of intelligent PDDS for antihyperlipidemic drugs is one of the most important innovations in the field of personalized medicine. With the current research efforts in smart biomaterials and chronotherapy, the role of PDDS is likely to become even more crucial in the management of cardiovascular risk.[24] Chronotherapeutic Motivation & Disease Applications of Pulsatile Drug Delivery of Antihyperlipidemic.

Chronotherapeutics is a rapidly emerging area that deals with the coordination of drug delivery and biological rhythms to achieve maximum efficacy and minimum toxicity. In the context of antihyperlipidemic therapy, this area of study assumes immense importance because of the circadian rhythm of cholesterol synthesis and lipid metabolism. The liver's cholesterol production reaches its peak during the night hours, making it the best time for the administration of HMG-CoA reductase inhibitors like simvastatin and lovastatin[25] On the other hand, Pulsatile Drug Delivery Systems (PDDS) have a distinct advantage in that they coordinate the pharmacokinetics of drug delivery with the pharmacodynamics of lipid synthesis.[26]

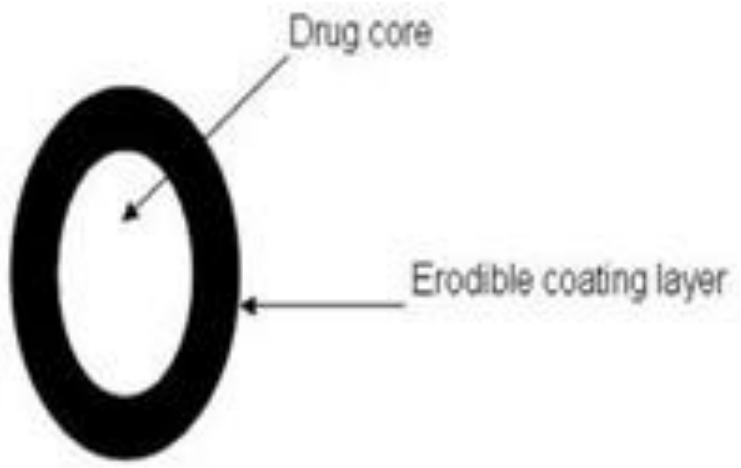
Various clinical and preclinical trials have validated the efficacy of chronotherapy in the treatment of hyperlipidemia. For instance, simvastatin, with a relatively short half-life of 2-3 hours, is found to be highly effective when administered through a PDDS that allows the nocturnal release of the drug rather than an immediate release formulation given in the morning hours.[27]

LDL cholesterol, acutely increases the risk of acute cardiovascular events during these periods. PDDS formulations that deliver antihyperlipidemic drugs in combination with antiplatelet or antihypertensive medications may provide a synergistic strategy for the prevention of cardiovascular risk.[28] An experimental study conducted by Hermida et al. demonstrated that patients on nighttime statin PDDS therapy had significantly improved lipid profile levels compared to those on conventional morning statin therapy.[29]

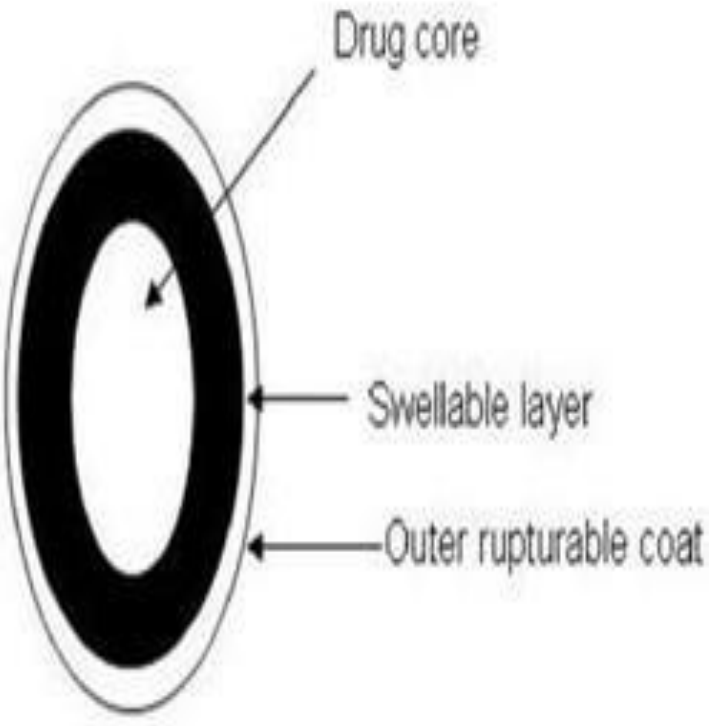
3. Definition & Design Principles of PDDS for Antihyperlipidemics

Pulsatile Drug Delivery Systems (PDDS) are a type of drug delivery formulation designed to release active pharmaceutical ingredients (APIs) after a predetermined lag time, followed by a rapid release of the drug. This distinct release profile is especially useful for drugs such as antihyperlipidemics, where the release of the drug in accordance with the circadian rhythm of cholesterol synthesis is especially advantageous.[34] The development of PDDS for antihyperlipidemics is usually based on two main principles: the selection of a suitable lag time that corresponds to the biological peak of cholesterol synthesis, and the use of smart polymers and coatings to time the release of the drug until this specific moment.[35] A properly designed PDDS not only ensures the release of the drug within the therapeutic window but also helps to preserve the drug stability during its passage through the gastrointestinal tract.

- TherearesevеraldesignprinciplesandformulationstrategiesappliedinPDDS:
- Reservoir-BasedSystems: Inthese, the drug is enclosed within a core surrounded by a polymeric membrane. The membrane may be designed to rupture or erode after a defined period, initiating drug release.[36]



Schematicdiagram of Delivery systems with erodible coating layer.



Schematic diagram of delivery systems with rupturable coating layer.

Capsule-Based Systems (e.g., Pulsincap™): These systems involve hydrogel plugs or erodible barriers at the mouth of the capsule, which allow the capsule to remain intact for a fixed time period before drug release.[37]

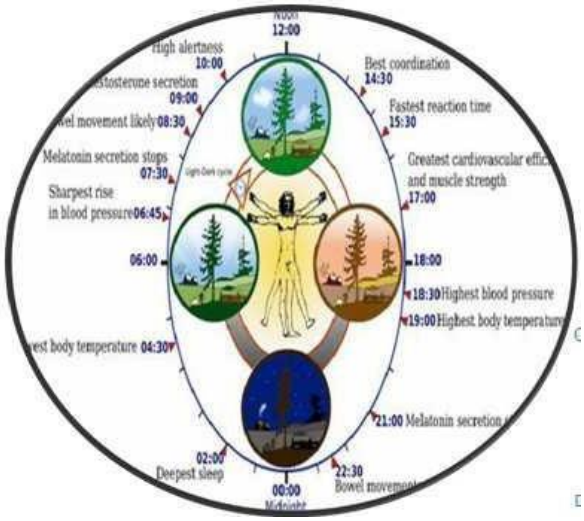
Multilayered Tablet Systems: These systems comprise a core of active drug sandwiched between barrier layers. The layers have different rates of dissolution, thus controlling the lag time before drug release.[38]

Osmotically Controlled Systems: These systems involve an osmotic push mechanism for drug release after a fixed lag time period. These systems are highly accurate and can be used for long-term drug delivery.[39] The choice of polymer, whether hydrophilic, hydrophobic, or biodegradable, is a critical factor in determining the lag time and drug release rate. Ethylcellulose, HPMC, and Eudragit are some of the most commonly used polymers

for this purpose.[40] In the case of antihyperlipidemic PDDS, these polymers are chosen based on their capacity to protect the statin molecule from premature release and degradation in the upper gastrointestinal tract. Advanced PDDS for antihyperlipidemics also include pH-sensitive coatings to deliver drugs to specific sites (e.g., small intestine or colon), thus improving hepatic targeting and minimizing systemic side effects.Ultimately, the goal of PDDS design in hyperlipidemia management is to achieve a pulsatile, site-specific, and time-specific drug release that maximizes therapeutic outcomes while minimizing dosing frequency and adverse effects.

Marketed Technologies & Platforms of Pulsatile Drug Delivery of Antihyperlipidemics

Pulsatile Drug Delivery Systems (PDDS) have received increasing attention in the pharmaceutical sector because of their potential to coordinate the release of drugs according to the circadian rhythm of various diseases. For hyperlipidemia, where the peak production of cholesterol by the liver occurs during the nighttime, PDDS can greatly enhance the efficacy and safety of antihyperlipidemic drugs. Although there are no many PDDS products available in the market for lipid-lowering medications, some platforms designed for other therapeutic categories are being explored for antihyperlipidemic medications as well.[41]

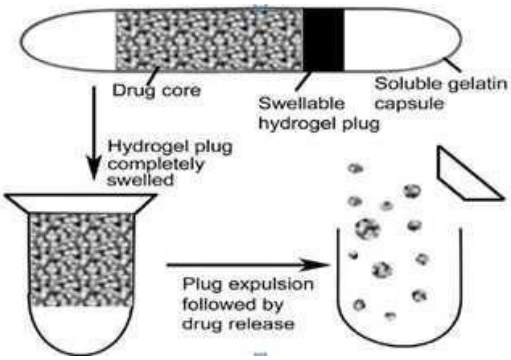


Cycle of Circardian rhythm

CODAS® (Chronotherapeutic Oral Drug Absorption System): The CODAS® system is based on a multiparticulate drug delivery system that is coated with a polymeric membrane to delay the release of the drug for 4-5 hours after ingestion. The CODAS® system enables the pulsatile delivery of statins such as simvastatin or lovastatin, with the drug release synchronized to coincide with early morning hepatic cholesterol synthesis.[42]

Diffucaps®: This is a multiparticulate drug delivery system that consists of drug-loaded cores coated with one or more functional layers. The lag time and drug release profiles can be controlled by the functional layers. Diffucaps® has been found to be promising in pulsatile delivery of cardiovascular drugs and is currently under investigation for statin delivery.[43]

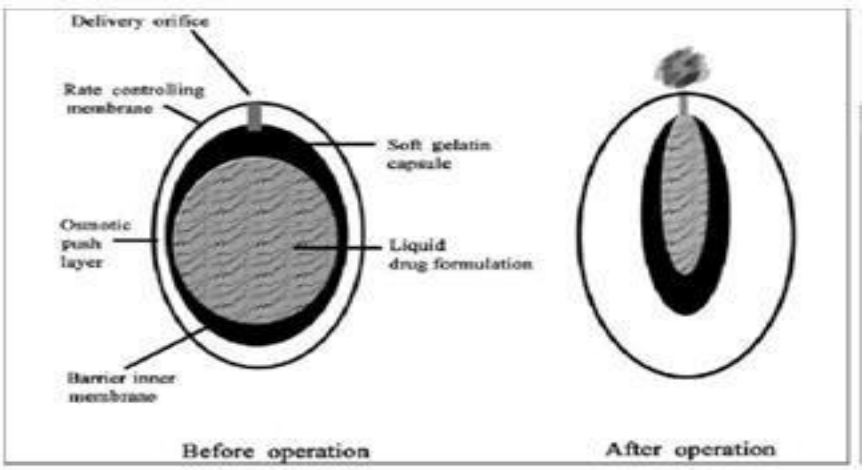
Pulsincap™: This is a well-studied system that consists of a hard gelatin capsule sealed with a hydrogel plug. The drug is released in a burst manner as the plug swells or erodes.



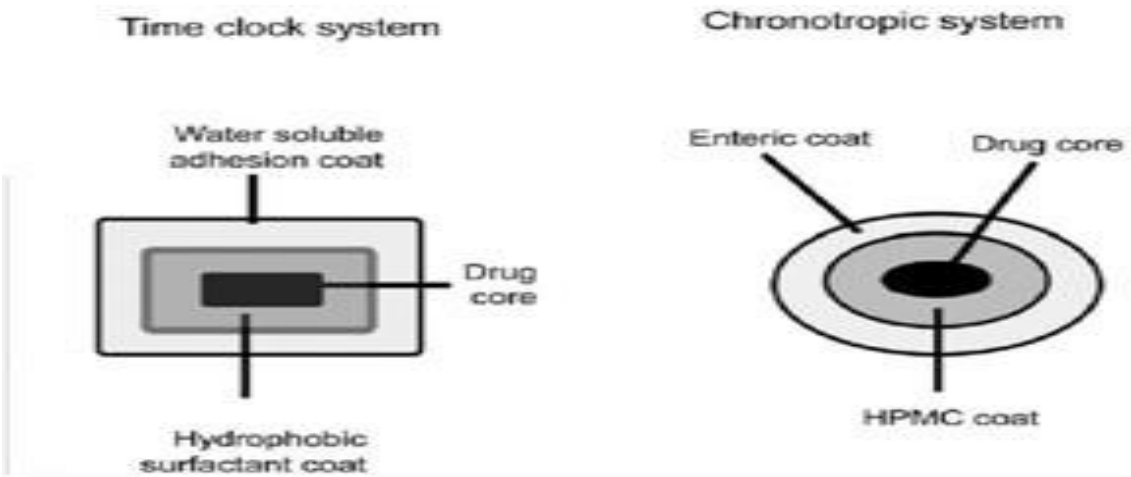
Design of Pulsin cap ® system

Pulsincap™: Pulsincap™ has been studied for simvastatin, and it was proven to be effective in synchronizing drug release with the circadian rhythm of lipid biosynthesis.[44]

OROS® (Osmotic Controlled Release Oral Delivery System): OROS® relies on osmotic pressure to deliver drugs in a time-controlled manner. The modified OROS® system with an initial lag phase can be used for the delivery of antihyperlipidemic drugs, which ensures that the plasma concentration of the drug reaches its peak in the early morning hours.[45]



L- OROS Softcap system



Time-Clock® System: A press-coated tablet system in which the outer layer erodes after a fixed lag time, thus providing pulsatile release. Though mainly evaluated for NSAIDs and antihypertensives, this system also has potential applications in antihyperlipidemic therapy by adjusting lag times and drug doses.[46]

Time clock and Chronotropic systems:

Multiparticulate-Based Chronotherapeutic Systems: These systems use mini-tablets or pellets coated with varied polymeric substances to individualize lag times. These systems are most suited for the simultaneous administration of multiple drugs or a cascading release profile, which is very useful for combination therapy in dyslipidemia.[47]

Floating Pulsatile Drug Delivery Systems: These systems are designed to be buoyant in the stomach and deliver delayed burst release of drugs after a predetermined time period. Clinical studies on floating systems for statins have shown promising pharmacokinetics that match the intended objectives in hyperlipidemia therapy.[48]

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The development of these systems for antihyperlipidemic drugs is dependent on the convergence of circadian pharmacology, patient-friendly dosing regimens, and strong clinical validation. As research continues to unfold, it is expected that personalized PDDS for statins and other lipid-lowering drugs will soon be marketed, revolutionizing the present treatment modalities for hyperlipidemia and cardiovascular risk management.

5. Advantages & Limitations of Pulsatile Drug Delivery of Anti hyperlipidemic s

Pulsatile Drug Delivery Systems (PDDS) have numerous promising advantages in the treatment of hyperlipidemia, mainly because of their ability to synchronize drug release with the circadian rhythm of lipid biosynthesis. However, the use and development of these systems are not without challenges.

ADVANTAGES

Chrono pharmacological Synchronization: Hyperlipidemia, especially cholesterol biosynthesis, has a circadian rhythm with a peak in the early morning hours. PDDS allows the time-controlled release of statins or fibrates to synchronize with this natural rhythm, thus enhancing the therapeutic effect.[49]

Improved Efficacy of Statins: Many statins, including simvastatin and lovastatin, have short plasma half-lives. The efficacy of these drugs can be greatly improved by their time-controlled administration according to the hepatic biosynthetic peak.[50]

Decreased Adverse Effects: Pulsatile delivery provides a lag phase before drug release, thus preventing excessive plasma levels of the drug when it is not required, thus minimizing the possibility of dose-related adverse effects such as myopathy or hepatotoxicity.[51]

Enhanced Patient Compliance: Chronotherapy-based PDDS makes bedtime dosing possible, which could be more patient-friendly. A single dose at bedtime and the consequent delayed release of the drug reduces the need for frequent administration throughout the day.[52]

Targeted Drug Delivery: More sophisticated PDDS technology like site-specific release and floating delivery systems can ensure the drug reaches the target site of absorption or action, thus enhancing bioavailability and reducing first-pass

effects.[53]

Possibility of Combination Therapy: Multi particulate PDDS technology can deliver a combination of multiple drugs with different release patterns. This is especially helpful in patients with co-existing conditions like hypertension or diabetes, along with hyperlipidemia.[54]

Adaptability of Existing Pulsatile Delivery Systems: The existing pulsatile delivery systems (Pulsincap™, CODAS®) can be easily adapted for statins and other antihyperlipidemic drugs with little modification in the formulation.[55]

Limitations

Complexity of Formulation: The development of PDDS involves complex engineering of polymers, coatings, or erodible barriers to achieve a reproducible lag time. This adds complexity to the formulation and production process.[56]

Lack of Commercially Available Formulations: Although PDDS have shown advantages, very few commercial formulations of antihyperlipidemic drugs are available in the market, mainly because of the high cost of development and regulatory issues.[57]

Patient Variability: Individual variations in circadian rhythms exist. Fixed lag-time devices may not synchronize well with the natural rhythms of every individual, which could lower the expected efficacy.[58]

Regulatory Issues: PDDS need extensive studies of chrono pharmacokinetics and pharmacodynamics for their approval, which raises the cost and time of development for drug companies.[59]

Stability Issues: Multi-layer devices and polymer coatings in PDDS may be vulnerable to environmental conditions like temperature, humidity, and gastric environment, which could impact stability and release rates.[60]

Difficulty in Dose Adjustment: For drugs like statins, titration based on patient response is often needed. Pulsatile systems may not allow easy dose adjustments, limiting flexibility in individualized treatment regimens.[61]

Delayed Onset of Action: Since PDDS often incorporate a lag phase, they may not be suitable in scenarios where immediate therapeutic action is required.[62]

6. Recent Advances & Future Directions In Pulsatile Drug Delivery of Anti hyper lipidemics

6.1 Introduction Pulsatile Drug Delivery Systems (PDDS) have been explored as promising strategies to improve the chronotherapeutic potential of anti hyperlipidemic drugs, particularly statins. These systems are designed to deliver drugs in accordance with the body's natural biological rhythms, specifically targeting the peak of cholesterol synthesis in the early morning hours. This strategy has been explored to improve the efficacy of therapy, minimize side effects, and maximize patient compliance. Recent breakthroughs in materials science, pharmaceutical engineering, and chrono pharmacology are propelling the development of next-generation PDDS for the management of hyperlipidemia.[63]

6.2 Smart Polymeric Systems Recent breakthroughs have introduced pH-, temperature-, or enzyme-sensitive polymers that can control the release of drugs in response to external stimuli. Eudragit S100, chitosan, hydroxypropyl methylcellulose (HPMC), and poly(N-isopropylacrylamide) (PNIPAM) polymers have been explored for their potential in designing pH- or temperature-sensitive drug delivery systems for pulsatile delivery of statins such as simvastatin and atorvastatin.[64,65] These systems enable the targeted release of statins in the intestinal tract, where statins exhibit optimal absorption, thus bypassing the gastric degradation and first-pass hepatic metabolism.

6.3 Multi particulate and Multipart Systems Multi particulate pulsatile delivery systems like coated pellets, beads, and mini-tablets are being increasingly used for pulsatile drug delivery. They provide uniform drug distribution, flexible dosing, and minimized intersubject variability in drug absorption. Hydrophilic and hydrophobic polymer coatings facilitate lag time adjustment and targeted drug release during the peak lipid synthesis phase.[66] Feasibility studies using Diffu caps and Time Clock systems have been demonstrated for the modification of release profiles of cardiovascular and lipid-lowering drugs.[67]

6.4 Floating and Mucoadhesive Systems Gastro-retentive floating pulsatile delivery systems for drugs are being developed to prolong gastric residence time and ensure timely drug release. Floating beads made of alginate, chitosan, and HPMC exhibit controlled release and buoyancy for 8-12 hours. These systems synchronize drug release with the early morning lipid biosynthesis phase and reduce plasma concentration fluctuations.[68] Mucoadhesive systems based on polymers like Carbopol and polycarbophil prolong gastric residence time and provide site-specific statin delivery.

6.5 Nanotechnology Integration The use of nanotechnology in PDDS is helping to achieve improved bioavailability and targeted delivery. Nanoparticles, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) encapsulating anti hyperlipidemics have improved solubility, stability, and protection against degradation. Statin-loaded SLNs have been demonstrated to enhance hepatic uptake and minimize systemic side effects.[69,70] Moreover, pH-responsive nanocarriers and enzyme-sensitive nanogels are currently under investigation for pulsatile intestinal delivery.

6.6 Chrono-Responsive Implants and Smart Capsules Chronotherapeutic implants and smart ingestible capsules are the future of PDDS. Ingestible sensors combined with wireless communication technology can detect pH, temperature, or GI transit and release drugs accordingly. These innovations, as seen in platforms such as Proteus Digital Health™, are currently being investigated for use in statin therapy to provide real-time.

7. The main objective of this mini dissertation is to understand and critically evaluate the use of Pulsatile Drug Delivery Systems (PDDS) in the therapeutic management of hyperlipidemia, with special emphasis on antihyperlipidemic drugs such as statins. The dissertation has been carefully planned to not only focus on the scientific principles but also on the recent technological developments, clinical significance, and future directions of PDDS in lipid-lowering pharmacotherapy.

7.1 Scope of the Study

- The scope of this mini dissertation is limited to:
- A comprehensive discussion on the physiological rationale of chronotherapy in hyperlipidemia.
- A detailed discussion on the principles and types of PDDS.
- A critical assessment of the significance of circadian biology in cholesterol homeostasis and statin therapy.
- A critical evaluation of the current state of PDDS technology and its applications in antihyperlipidemic drug therapy.
- A review of preclinical and clinical studies validating the pulsatile delivery of lipid-lowering drugs.
- A critical assessment of the benefits, drawbacks, and challenges in the development of PDDS for hyper lipidemic.
- Future directions in pharmacogenomics, personalized therapy, and smart drug delivery systems.
- This dissertation is intended for pharmacy students and academic researchers with an interest in advanced drug delivery systems, pharmaceutical technology, and chrono therapeutics. It will also serve as a valuable reference for formulation scientists and biomedical engineers exploring new delivery modalities.

LITERATURE REVIEW

1. In their 2014 work, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Loyd V. Allen Jr. and his colleagues provide a comprehensive examination of the fundamental principles underlying advanced drug delivery technologies. The text explores the sophisticated engineering behind time-controlled and modified-release formulations, which are designed to maintain optimal drug concentrations in the bloodstream over extended periods. By moving beyond conventional immediate-release systems, these innovations aim to maximize therapeutic efficacy while significantly reducing side effects. Ultimately, these advancements prioritize the patient experience, fostering better treatment compliance by reducing the frequency of dosing and ensuring a more consistent recovery process.
2. In the 2011 edition of Martin's Physical Pharmacy and Pharmaceutical Sciences, Patrick J. Sinko et al. offer a rigorous exploration of the physicochemical and biopharmaceutical principles that govern the complex mechanisms of drug release. The text delves into the molecular behavior, solubility, and diffusion kinetics that dictate how a therapeutic agent interacts with its biological environment. By establishing this foundational scientific framework, the authors provide the essential groundwork necessary for the development of pulsatile drug delivery systems. These systems are specifically engineered to release medication at precise intervals or in response to specific physiological triggers, aligning treatment with the body's natural circadian rhythms to enhance clinical outcomes.
3. In the 2021 edition of Aulton's Pharmaceutics: The Design and Manufacture of Medicines, Kevin M.G. Taylor et al. provide a detailed roadmap for the modern formulation strategies required to create controlled and pulsatile delivery systems. The text emphasizes the critical role of material science, specifically focusing on polymer-based approaches to achieve programmed drug release. By utilizing specialized polymers—such as those that are pH-sensitive, biodegradable, or swellable—formulators can dictate exactly when and where a drug is liberated in the gastrointestinal tract. This systematic approach allows for a "programmed" delivery schedule, ensuring that the medication is released in a manner that mirrors the therapeutic needs of the patient rather than a simple, immediate burst.
4. In the 2013 edition of the Encyclopedia of Pharmaceutical Science and Technology, James Swarbrick et al. present

an expansive and detailed repository of information regarding novel drug delivery technologies. The text moves beyond traditional dosage forms to explore high-precision engineering solutions such as reservoir systems, where a drug core is surrounded by a rate-controlling membrane, and osmotic devices that utilize internal pressure to pump medication at a constant rate. Furthermore, the authors highlight the importance of chronotherapeutic formulations, which are designed to synchronize drug release with the body's biological clock. By providing this deep technical insight, the encyclopedia serves as a critical resource for understanding how sophisticated delivery architectures can solve complex clinical challenges and improve therapeutic precision.

5. In their 2010 review of pulsatile drug delivery systems (PDDS), Singh et al. provide a compelling clinical rationale for why these specialized formulations are superior to traditional constant-release methods. The authors report that PDDS are uniquely suited for treating diseases that exhibit distinct circadian rhythms, where symptoms do not remain constant but instead peak at specific times of the day or night. For conditions such as hyperlipidemia, asthma, and hypertension, a "one size fits all" dosing approach is often inefficient; instead, PDDS allow for a programmed lag phase followed by a rapid release of the active ingredient. This synchronization ensures that the highest concentration of the drug is available exactly when the patient’s physiological risk is at its highest, thereby significantly improving the overall therapeutic response and minimizing unnecessary systemic exposure during periods of low disease activity.
6. In their 2001 study, Bessemer et al. detailed the mechanical and pharmaceutical design of oral pulsatile systems that utilize rupturable polymer coatings to control the timing of medication delivery. This specific engineering approach is centered on creating a precise lag phase, during which the outer membrane remains intact, preventing any drug release for a predetermined period. As water penetrates the dosage form, internal pressure builds—either through swelling or gas generation—until the polymer shell eventually reaches its mechanical limit and bursts. This rupture triggers a rapid drug release, or "pulse," which the authors demonstrate is an ideal mechanism for chronotherapy-based treatments. By calibrating the thickness and composition of these coatings, researchers can sync the medication's "burst" with the peak of a patient's symptoms, such as the early morning stiffness of rheumatoid arthritis or nocturnal asthma attacks
7. In their 2004 study, Youan et al. conducted a rigorous investigation into the performance of multiparticulate pulsatile systems, comparing them against traditional single-unit dosage forms. The researchers concluded that subdividing a dose into numerous small subunits—such as pellets or granules—offers significantly better reproducibility of lag time, as the overall release profile is the statistical average of many individual units rather than depending on the integrity of a single shell. Furthermore, this approach provides a critical safety advantage by greatly reducing the risk of dose dumping, a phenomenon where a manufacturing defect or premature rupture in a single-unit system could release the entire medication dose at once. By spreading the dose across a multiparticulate population, the formulation ensures a more consistent and reliable "pulse," making it a robust choice for sophisticated chronotherapeutic applications.
8. In their 2007 research, Lévi et al. provided compelling evidence that chronomodulated drug delivery—the practice of timing medication release to coincide with biological rhythms—significantly improves clinical outcomes for patients suffering from metabolic and cardiovascular disorders. By aligning the peak concentration of a drug with the specific time of day when a disease's symptoms or physiological triggers are most active, this approach maximizes the therapeutic benefit while minimizing potential toxicity. The study specifically supports the relevance of pulsatile drug delivery systems (PDDS) for antihyperlipidemic therapy, noting that cholesterol

synthesis in the liver typically peaks during the overnight hours. Consequently, a PDDS designed to release its payload during this nocturnal window ensures that the medication is most potent exactly when the body is producing the most lipids, leading to a more effective reduction in cholesterol levels than standard, non-timed dosing.

9. Roy and Shahiwala (2009): Stimuli-Responsive SystemsIn their 2009 review, Roy and Shahiwala provided an in-depth analysis of stimuli-responsive pulsatile systems, focusing on how environmental triggers can be harnessed for precision medicine. The authors highlighted the significance of pH-triggered and enzyme-activated formulations as sophisticated tools for achieving site-specific drug delivery within the complex landscape of the gastrointestinal tract. By utilizing polymers that dissolve only at specific pH levels—such as the transition from the acidic stomach to the more alkaline small intestine—or coatings that are degraded by unique colonic bacteria, these systems ensure that the drug payload is shielded until it reaches the optimal absorption site. This "smart" delivery approach minimizes premature degradation and reduces systemic side effects, ensuring the therapeutic agent is released exactly where it is most needed.
10. In their 2013 research, Kumar et al. provided a critical analysis of the technical and formulation challenges inherent in developing robust pulsatile drug delivery systems (PDDS). The authors noted that moving from a theoretical model to a stable pharmaceutical product requires overcoming significant hurdles, most notably in the precise selection of polymers. These materials must possess specific mechanical and chemical properties to maintain structural integrity during the lag phase while ensuring a rapid, predictable burst. Furthermore, the researchers highlighted the issue of moisture sensitivity, where environmental humidity or premature water penetration can cause the polymer layer to swell or degrade prematurely, leading to inconsistent performance. These challenges are particularly pronounced when formulating statin-based antihyperlipidemic drugs, which often require a highly accurate lag time to coincide with nocturnal cholesterol synthesis. Achieving this consistency across different batches and within the varying physiological conditions of the human GI tract remains a primary obstacle in ensuring that these life-saving medications are delivered with the reliability required for clinical success.
11. In their 2002 review of modern pulsatile technologies, Nokhodchi and Rubinstein provided a forward-looking perspective on the evolution of pharmaceutical dosage forms. The authors concluded that the strategic integration of chronobiology—the study of biological rhythms—with advanced delivery platforms represents a transformative shift in how chronic conditions are managed. By moving away from static dosing and toward systems that mirror the body’s internal clock, these technologies offer promising future prospects, particularly for the treatment of cardiovascular and metabolic diseases. The researchers emphasized that when a drug's release is timed to match the rhythmic nature of pathological events, such as the early morning rise in blood pressure or nocturnal lipid synthesis, the clinical outcome is vastly superior. This synergy between biological timing and engineering precision not only enhances the efficacy of the medication but also significantly improves the safety profile by reducing systemic exposure during non-critical hours.
12. Gazzaniga et al., 1994 developed time-controlled pulsatile delivery devices based on erodible plugs and reported precise lag time followed by rapid drug release, suitable for chronotherapeutic applications.
13. Wilding et al., 2001 studied press-coated tablets for pulsatile delivery and demonstrated that polymer barrier thickness significantly influences lag time and burst release behavior.
14. Maroni et al., 2005 reviewed oral pulsatile systems and concluded that chronomodulated formulations improve

therapeutic efficacy in diseases showing circadian rhythm, including lipid disorders. Anal and Stevens, 2005 reported that multiparticulate pulsatile systems provide uniform gastric emptying and reduce inter-patient variability compared to single-unit dosage forms.

15. Sharma and Pawar, 2006 formulated pulsatile capsules using hydrogel plugs and observed reproducible delayed release suitable for night-time administration of cardiovascular drugs.
16. Survase and Jangde, 2010 emphasized the importance of chrono pharmaceutical drug delivery for antihyperlipidemic therapy, highlighting that hepatic cholesterol synthesis peaks during night hours. Reddy et al., 2011 developed pH-dependent pulsatile tablets and demonstrated effective intestinal targeting with sharp pulse release after predetermined lag time.
17. Hadi et al., 2012 investigated osmotic-based pulsatile systems and reported controlled lag phase followed by rapid drug release triggered by internal pressure buildup.
18. Patel and Patel, 2013 reviewed polymer-based pulsatile systems and concluded that swellable and rupturable coatings are widely used for achieving programmed drug release.
19. Kamble et al., 2014 prepared chronotherapeutic tablets for lipid-lowering drugs and observed improved bioavailability when drug release was synchronized with circadian rhythm.
20. Bajpai et al., 2016 studied enzyme-responsive delivery systems and suggested their potential for colon-targeted pulsatile release of cardiovascular agents.
21. Verma and Garg, 2018 reviewed recent advances in pulsatile drug delivery and reported that PDDS improves patient compliance by reducing dosing frequency.
22. Patel et al., 2020 concluded that combining chronotherapy with advanced polymer technology offers promising future scope for pulsatile delivery of antihyperlipidemic drugs.

DRUG AND EXCIPIENTS PROFILE

DRUG PROFILE

Fluvastatin sodium

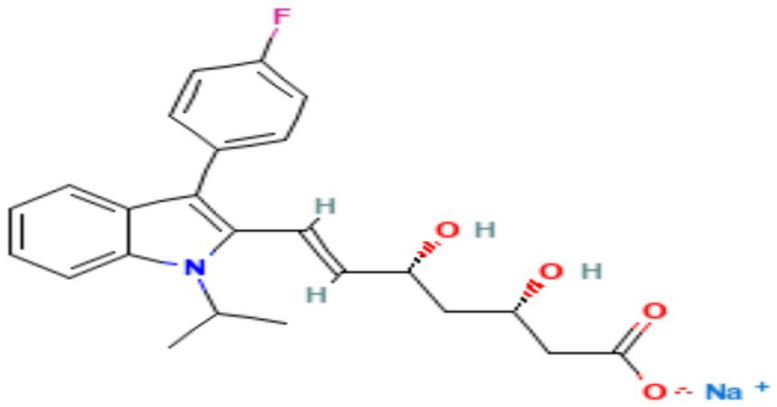
Fluvastatin is a completely synthetic lipid-lowering drug that falls under the class of HMG-CoA reductase inhibitors, also known as statins. The drug is mainly used in the treatment of primary hypercholesterolemia, mixed dyslipidaemia, and the prevention of cardiovascular diseases like coronary artery disease, myocardial infarction, and cardiac stroke. Fluvastatin is chemically a fluvastatin sodium salt with the molecular formula $C_{24}H_{26}FNO_4$ and a molecular weight of 411.47 g/mol, with the CAS number 93957-55-2. The IUPAC name of the drug is (3R,5S,6E)-7-[3-(4-fluorophenyl)-1-(propan-2-yl)-1H-indol-2-yl]-3,5-dihydroxyhept-6-enoic acid, which reveals the presence of unique stereochemistry that is crucial for its pharmacological activity. The structure of the drug consists of an indole ring, a para-fluorophenyl moiety, a conjugated double bond in E-configuration, and a dihydroxy heptanoic acid side chain that resembles the natural substrate HMG-CoA, enabling competitive enzyme inhibition. The drug structure comprises two hydroxyl groups, a carboxylic acid functional group, aromatic ring systems.The fluorine residue improves metabolic stability and efficacy. Fluvastatin is a moderately lipophilic, highly protein-bound drug, which mainly targets the liver, the major site of cholesterol production. It is a substrate for extensive first-pass metabolism, mainly mediated by the CYP2C9 enzyme system and is excreted mainly through biliary secretion. It is available in the market by various trade names such as Lescol and is generally well tolerated when used at therapeutic doses along with dietary and lifestyle modifications.

Pharmacologically, fluvastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme of the mevalonate pathway of cholesterol synthesis. By inhibiting the conversion of HMG-CoA to mevalonate, it decreases the intracellular cholesterol synthesis in the hepatocytes, thereby reducing the hepatic cholesterol stores. In response to the reduced intracellular cholesterol levels, the liver cells increase the expression of low-density lipoprotein (LDL) receptors on their surface, thereby increasing the uptake and degradation of LDL cholesterol from the bloodstream. This leads to a substantial decrease in the serum levels of LDL cholesterol, total cholesterol, apolipoprotein B, and triglycerides, with a slight increase in the levels of HDL cholesterol.

The pharmacodynamic effects include: stabilization of atherosclerotic plaques, improvement of endothelial function, reduction of inflammatory markers such as C-reactive protein, reduction of oxidative stress, improvement of arterial compliance, and reduction of thrombotic risk. The onset of lipid-lowering action is typically evident within 1-2 weeks, with maximal therapeutic effect attained in 4-6 weeks of continuous therapy. It is used in the management of primary and familial hypercholesterolemia, mixed dyslipidemia, cardiovascular risk reduction in diabetic and high-risk patients, secondary prevention following myocardial infarction, and prevention of stroke and recurrent cardiac events. By providing continuous inhibition of the mevalonate pathway and augmentation of LDL receptor uptake, fluvastatin has been shown to effectively lower cardiovascular morbidity and mortality, making it a critical component in the long-term lipid management therapy.

1. Structure

- Fluvastatin sodium contains:
- An indole ring system
- A fluorophenyl group
- A heptenoic acid side chain responsible for HMG-CoA reductase inhibition



Structure Fluvastatin sodium

3. Synonyms

- Fluvastatin sodium
- Lescol (Brand name)
- XU 62-320

4. Iupac Name

(3R,5S,6E)-7-[3-(4-fluorophenyl)-1-(propan-2-yl)-1H-indol-2-yl]-3,5-dihydroxyhept-6-enoic acid

5. CAS Number

93957-55-2

6. Molecular Formula

$C_{24}H_{26}FNO_4$

7. Molecular weight

433.45 g/mol.

PHARMACOLOGY

Fluvastatin is a competitive inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which catalyses the rate-limiting step in the biosynthesis of cholesterol in the liver. By inhibiting this enzyme, fluvastatin reduces the conversion of HMG-CoA to mevalonate, an early precursor of cholesterol. This results in a reduction in intracellular hepatic cholesterol. In response to this reduction, hepatocytes increase the synthesis and expression of LDL receptors on their surface, thereby increasing the uptake and clearance of circulating low-density lipoprotein (LDL) cholesterol from the bloodstream. Consequently, serum LDL cholesterol, total cholesterol, apolipoprotein B, and triglyceride levels are substantially reduced, while high-density lipoprotein (HDL) cholesterol levels are modestly increased.

Pharmacologically, fluvastatin is primarily active in the liver, which is the major site of cholesterol synthesis and lipoprotein metabolism. It has dose-dependent lipid-lowering activity and helps in the stabilization of atherosclerotic plaques. Besides lipid-lowering activity, fluvastatin has pleiotropic effects such as improvement of endothelial function, reduction of oxidative stress, and reduction of inflammatory markers such as C-reactive protein. These properties add to its cardioprotective effects.The lipid-lowering effect usually begins within 1–2 weeks of therapy, with maximum therapeutic response achieved after 4–6 weeks of continuous administration.

Overall, its pharmacological actions significantly reduce the risk of cardiovascular morbidity and mortality in patients with hyperlipidaemia.

INDICATIONS

Fluvastatin Sodium is mainly prescribed for the treatment of hyperlipidaemia and mixed dyslipidaemia. It is prescribed to reduce high levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B, and triglycerides, while modestly increasing high-density lipoprotein cholesterol (HDL-C). It is a cholesterol-lowering medication that acts by inhibiting HMG-CoA reductase, the major enzyme responsible for cholesterol production in the liver. By reducing LDL levels, fluvastatin sodium can help slow the progression of atherosclerosis and improve lipid profiles in patients who do not respond well to diet and lifestyle changes alone.

Fluvastatin Sodium is also prescribed for the prevention of cardiovascular events, such as the prevention of myocardial infarction, coronary revascularization procedures, and other major cardiac events in patients with established coronary heart disease or those who are at high risk. It is usually prescribed as a long-term medication to reduce cardiovascular morbidity and mortality. In some instances, it is also prescribed to pediatric patients (adolescents) with familial hypercholesterolemia to reduce high cholesterol levels.

PHARMACOKINETICS

Absorption: Fluvastatin is rapidly and almost completely absorbed from the gastrointestinal tract after oral administration, with peak plasma concentrations (C_{max})reached in 0.5 to 1.5 hours. However, because of extensive first-pass metabolism in the liver, its absolute bioavailability is only 20-30%. Food slightly delays the rate of absorption but does not affect the extent of absorption (AUC). The drug has dose-proportional pharmacokinetics in the therapeutic dose range.

Distribution: Fluvastatin is highly bound to plasma proteins (98-99%), mainly to albumin. Its volume of distribution is small, indicating its intended site of action in the liver, which is the target for cholesterol synthesis. The drug selectively accumulates in hepatocytes through active transport mechanisms, which is a part of its therapeutic action. Its high protein binding makes it less susceptible to displacement interactions.

Metabolism: Fluvastatin is extensively metabolized in the liver by the cytochrome P450 enzyme system, mainly by CYP2C9 isoenzymes, with a minor contribution from CYP3A4 and CYP2C8 isoenzymes. The drug is metabolized to several inactive metabolites, primarily through hydroxylation and N-dealkylation. Because of extensive metabolism in the liver, patients with liver disease can have significantly elevated plasma concentrations. Drug interactions can occur with inhibitors and inducers of CYP2C9.

Excretion: The drug and its metabolites are excreted largely through the biliary route into the feces (approximately 90%), while a small amount (less than 5%) is excreted unchanged in the urine. The elimination half-life of fluvastatin is short, about 1-3 hours, but its inhibitory action on HMG-CoA reductase lasts longer because of active metabolites and strong binding affinity to the liver. The drug is not affected by renal impairment, but dose adjustment may be necessary in severe hepatic disease**.**

PHARMACODYNAMICS

The pharmacodynamics of Fluvastatin sodium involve its mechanism of action as a competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme in the mevalonate pathway of cholesterol synthesis. By inhibiting this enzyme in hepatocytes, fluvastatin decreases the conversion of HMG-CoA to mevalonate, a precursor of cholesterol. This results in a reduction in intracellular hepatic cholesterol synthesis. As a compensatory mechanism, liver cells increase the expression of LDL receptors on their surface, thereby increasing the clearance of circulating low-density lipoprotein cholesterol (LDL-C) from the bloodstream. The result is a substantial reduction in plasma LDL-C levels.

In addition to its lipid-lowering action, fluvastatin also reduces total cholesterol, triglycerides, and apolipoprotein B levels moderately, with a slight increase in high-density lipoprotein cholesterol (HDL-C) levels. In addition to lipid-lowering action, it also has pleiotropic effects, including improvement in endothelial dysfunction, stabilization of atherosclerotic plaques, reduction in vascular inflammation, and reduction in oxidative stress. These actions make it effective in reducing the risk of cardiovascular events such as myocardial infarction and stroke. The net therapeutic action is a slowing down of the progression of atherosclerosis and a reduction in cardiovascular morbidity and mortality in high-risk patients.

MECHANISM OF ACTION

Mechanism of action of Fluvastatin sodium is mainly due to its selective and competitive inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the hepatic cholesterol synthesis. In

normal circumstances, this enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and crucial step in the synthesis of cholesterol. Fluvastatin, structurally similar to HMG-CoA, binds to the active site of the enzyme and inhibits this conversion. Consequently, the synthesis of mevalonate is decreased, resulting in a reduction in the intracellular cholesterol synthesis in hepatocytes.

The decreased concentration of cholesterol in the liver triggers a compensatory mechanism of increasing the number of LDL (low-density lipoprotein) receptors on the surface of liver cells. This increases the uptake and clearance of LDL cholesterol from the bloodstream. Consequently, the plasma levels of LDL-C are significantly decreased. In addition to the decrease in LDL-C, fluvastatin also decreases the total cholesterol, very-low-density lipoprotein (VLDL), and triglycerides, while modestly increasing the levels of high-density lipoprotein (HDL) cholesterol.

In addition to lipid-lowering activity, fluvastatin has a number of "pleiotropic" or beneficial effects. Through the reduction of mevalonate and isoprenoid production, it affects several cellular signaling pathways. These include inflammation and vascular function. The drug has been shown to improve endothelial function, reduce oxidative stress, inhibit smooth muscle cell proliferation, and stabilize atherosclerotic plaques. All these mechanisms are responsible for the prevention of cardiovascular events and the slowing of atherosclerosis progression**.**

Adverse Effects

The side effects of Fluvastatin sodium are mostly mild and dose-related. The common side effects observed are headache, dyspepsia, abdominal pain, nausea, constipation, diarrhea, and fatigue. Mild elevation of liver transaminases (ALT and AST) may occur because of its hepatic metabolism; hence, liver function tests should be performed before and during the administration of the drug. These elevations are mostly reversible with a reduction in the dose or discontinuation of the drug.

Muscle-related side effects are of clinical significance and include myalgia (muscle pain), muscle weakness, and, rarely, myopathy or rhabdomyolysis. These are more likely to occur when fluvastatin is co-administered with other medications that alter its metabolism or in patients with renal or hepatic impairment. Rare side effects may include hypersensitivity reactions, rash, insomnia, peripheral neuropathy, and, very rarely, interstitial lung disease. Fluvastatin is one of the statins that have a relatively lower risk of severe muscle toxicity compared with other statins.

Shelf Life

The general shelf life of fluvastatin sodium preparations (capsules or extended-release tablets) is usually 2 to 3 years from the date of manufacture. It should be stored at controlled room temperature (usually below 25°C), away from moisture, heat, and direct light. The shelf life may vary depending on the manufacturer, formulation, and packaging, and should always be checked from the product label. Fluvastatin sodium that is exposed to improper storage conditions may affect its stability and efficacy.

POLYMER PROFILE

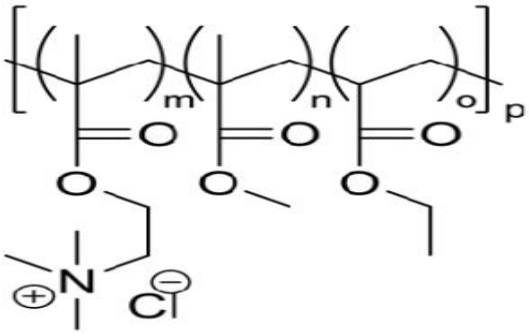
Eudragit RS 100

Eudragit RS-100 is a synthetic, biocompatible acrylic resin and is a member of the class of ammonia methacrylate copolymers. It is a widely used pharmaceutical excipient in controlled release formulations. It is a complex polymer with a copolymer matrix made up of ethyl acrylate, methyl methacrylate, and a small amount of methacrylic acid esters

with quaternary ammonium groups, which are permanently ionized and confer a characteristic permeability to the polymer film. Since it is a polymer, it does not have one specific IUPAC name; however, it is chemically designated as poly(ethyl acrylate-co-methyl methacrylate-co-[2-(trimethylammonium)ethyl methacrylate chloride]). It also has several other names, including Ammonia Methacrylate Copolymer Type B, Eudragit RS, or RS-type acrylic resin. The CAS number most commonly cited is 25212-88-8. Eudragit RS-100 does not have a specific molecular formula or molecular weight since it is a polymeric compound with a repeating chain structure; instead, it is a high molecular weight compound that typically ranges in the hundreds of thousands of Daltons. From a pharmacological standpoint, Eudragit RS-100 is considered an inert pharmaceutical excipient rather than an active therapeutic agent; its role is to control drug delivery by forming water-insoluble but permeable coatings or matrices that regulate drug diffusion.

It is commonly used in sustained release tablets, microcapsules, nanoparticles, coated pellets, and matrix tablets for prolonged and pH-independent release of drugs, especially in oral dosage forms designed for the extended gastrointestinal absorption phase. In terms of pharmacodynamics, the polymer itself does not interact with biological receptors or exhibit pharmacological activity within the body; rather, its functional role is based on its physicochemical properties, namely its low permeability and slight ionic character because of the presence of quaternary ammonium groups, which enable the slow penetration of gastrointestinal fluids. The mechanism of action is mainly diffusion-controlled. That is, upon the introduction of the dosage form into the gastrointestinal tract, the penetration of fluids into the polymer matrix is slow, resulting in little swelling with retention of structural integrity; thereafter, the diffusion of dissolved drug molecules through microscopic pores or channels within the polymer matrix occurs, resulting in a controlled, sustained release profile rather than rapid disintegration. The distinct properties of structural integrity, controlled permeability, and biocompatibility with various drugs make Eudragit RS-100 an essential polymer in contemporary modified-release drug formulations.

Structure



Structure of eudragit RS 100

Synonyms

Ammonia methacrylate copolymer type B, Eudragit® RS, Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride), RS-type acrylic resin.

IUPAC Name

Since Eudragit RS-100 is a polymeric mixture rather than a single defined molecule, it does not have one strict IUPAC name. It is generally described as a copolymer of ethyl acrylate, methyl methacrylate, and [2-(trimethylammonio)ethyl] methacrylate chloride.

CAS Number

Typical reference CAS number: 25212-88-8 (ammonia methacrylate copolymer).

Molecular Weight

It has no single molecular weight because it is a high-molecular-weight polymer; the average molecular weight usually ranges from several hundred thousand Daltons depending on grade and manufacturing conditions.

Molecular Formula

No fixed molecular formula exists due to its copolymeric nature; it is composed of repeating units derived from ethyl acrylate, methyl methacrylate, and quaternary ammonium methacrylate.

PHARMACOLOGY

The pharmacology of Eudragit RS-100 is primarily associated with its use as an inert excipient in pharmaceuticals, which helps in the controlled release of drugs. Eudragit RS-100 is an ammonia methacrylate copolymer and is pharmacologically inert as it does not bind to receptors, affect biochemical pathways, or demonstrate any systemic pharmacological effects upon administration. The primary significance of this polymer is its physicochemical properties, which include its water-insoluble but permeable nature, thereby facilitating the controlled release of drugs. The polymer has a low concentration of quaternary ammonium groups that are always ionically charged, thereby enabling a limited interaction with the aqueous gastrointestinal fluids. This property helps in the formation of a semi-permeable membrane that controls the penetration of fluids and diffusion of drugs in a predictable manner.

From a biopharmaceutical point of view, Eudragit RS-100 is a polymer that enhances the pharmacokinetic profile of many drugs by extending the release of drugs, reducing the frequency of drug administration, and reducing concentration fluctuations of drugs in the plasma. By controlling the dissolution of drugs, the polymer helps to maintain a stable concentration of drugs in the body for a longer period, which can improve patient compliance and reduce side effects of drugs that result from high peak concentrations. The polymer also helps to enhance the stability of moisture-sensitive and gastric irritant drugs by forming a protective coating that protects the drugs from immediate exposure to gastric fluids. In oral drug delivery, the polymer acts independently of the pH of gastrointestinal fluids, meaning that its release properties are not affected by the pH of the gastrointestinal tract. From a pharmacological point of view, it is considered safe and non-toxic because it is not readily absorbed from the gastrointestinal tract; rather, it passes through the gastrointestinal tract unchanged after it has completed its drug release function.

Moreover, Eudragit RS-100 is commonly employed in matrix tablets, microcapsules, nanoparticles, transdermal patches, and film coating to regulate diffusion-controlled release. The lower permeability of Eudragit RS-100 than other Eudragit types enables the formulation of controlled release products by adjusting the concentration of the polymer, thickness of the film, or blending it with more permeable materials such as RL-series polymers. Hence, although Eudragit RS-100 lacks pharmacodynamic properties, the pharmacological importance of Eudragit RS-100 is based on its capacity to regulate drug delivery kinetics and improve the efficiency of therapeutic agents.

Indication

Used widely in modified-release tablets, coated pellets, microencapsulation, and matrix systems. It is especially indicated where slow, pH-independent drug release is required, such as in gastrointestinal sustained-release formulations.

Pharmacodynamics

The pharmacodynamics of Eudragit RS-100 is different from that of conventional drugs since Eudragit RS-100 does not have any direct biological or receptor-mediated action in the body. The pharmacodynamic function of Eudragit RS-100 is therefore dependent on its physicochemical interaction with the surrounding environment of the dosage form, especially the gastrointestinal fluids. Eudragit RS-100 is an ammonia methacrylate copolymer that has a low percentage of quaternary ammonium groups that are ionized at all times. This gives the polymer a controlled permeability to water and dissolved substances. When a dosage form containing this polymer is in contact with the physiological fluids, water slowly diffuses into the polymeric matrix through ionic channels without causing rapid dissolution or disintegration. This process of hydration results in the formation of microscopic pathways that allow dissolved drug molecules to diffuse outwards at a controlled rate.

Unlike active pharmaceutical agents, the polymer does not interact with enzymes, receptors, or targets, nor does it affect biochemical signaling pathways. The pharmacodynamic property of the polymer is based on its ability to control the rate and amount of drug release, thereby indirectly affecting the therapeutic action of the drug. The sustained diffusion process of Eudragit RS-100 ensures that the plasma concentration of the drug remains stable, reducing the peaks and troughs that are normally associated with immediate release formulations. This property can be used to improve the therapeutic action of the drug, reduce side effects caused by high concentrations of the drug, and improve patient compliance due to the reduced frequency of dosing.

Moreover, due to its relative insensitivity to the pH of the gastrointestinal tract, the pharmacodynamic activity is fairly consistent across various parts of the gastrointestinal tract. The polymer is not broken down to any significant extent as it passes through the body, and it works as a semi-permeable membrane that controls the release rate of the drug rather than having any pharmacological activity of its own. In the end, the pharmacodynamics of Eudragit RS-100 can be said to be a formulation-related phenomenon, where the properties of the polymer control the release rate of the drug and, hence, its pharmacologicalactivity.

MECHANISM OF ACTION

Eudragit RS-100 is mainly known to work through a diffusion-controlled process, where the polymer serves as a semi-permeable membrane around the drug particles or as a matrix in the dosage form. Once the dosage form is administered orally, upon exposure to gastrointestinal fluids, the aqueous environment slowly diffuses through the polymeric membrane. This is because the polymer has a limited number of fixed, permanently charged quaternary ammonium groups that attract a small amount of water while still retaining the insoluble nature of the coating. The polymer, therefore, swells slightly and forms small aqueous channels or pores in the membrane due to concentration gradients between the inside of the dosage form and the external gastrointestinal environment.These concentration gradients cause the drug molecules to diffuse out through the microscopic pores at a controlled rate. The low permeability of Eudragit RS-100 ensures that the diffusion process is slow, thus preventing the immediate release of the drug. The pH independence of this diffusion process ensures that the drug release is consistent along the gastrointestinal tract. The

mechanism of action is not pharmacological but relies on physical and chemical principles of fluid penetration, matrix swelling, and diffusion, thus ensuring a controlled drug release system rather than an immediate dissolution release system.

Adverse Effects

Eudragit RS 100 is a copolymer of ethyl acrylate and methyl methacrylate with a low degree of quaternary ammonium groups, which is widely used as a pharmaceutical excipient for sustained release and controlled release formulations. As it is pharmacologically inactive and non-systemically absorbed, it is not expected to cause typical drug-related side effects.

In rare instances, hypersensitivity reactions can occur in patients with sensitivity to methacrylate polymers. It can, when used in large doses or in improper formulation, contribute to slight gastrointestinal irritation due to its sustained release properties rather than its toxicity. In its industrial application, slight irritation to the respiratory tract due to inhalation of polymer dust can occur, and slight irritation to the eyes and skin can also occur.

Shelf Life

The usual shelf life of Eudragit RS 100 is normally 3 to 5 years when stored under recommended conditions. It should be stored in a tightly closed container, away from moisture, heat, and direct sunlight. The recommended storage temperature is normally below 25-30°C in a dry environment. As a stable polymer, it has good physicochemical stability, but exposure to high temperatures may affect its film-forming properties and release-controlling properties. The shelf life should always be confirmed from the manufacturer's specifications and certificate of analysis.

EXCIPIENT OF KARAYA GUM

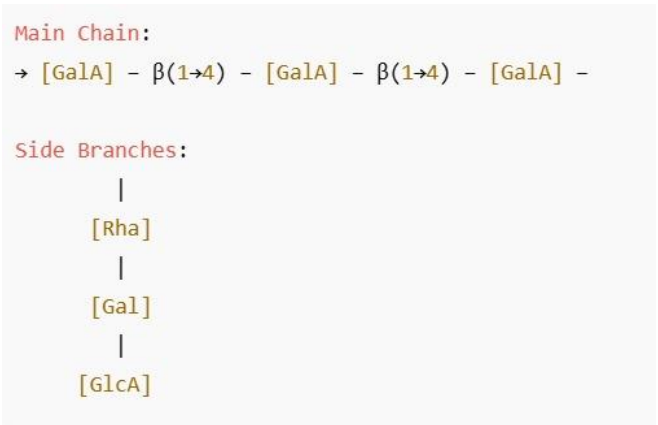
Karaya Gum

Synonyms

- Sterculia gum
- Indian Tragacanth
- Sterculia urens gum

Karaya gum is a complex polysaccharide, primarily composed of galactose, mannose, rhamnose, and galacturonic acid units. It forms a highly branched, water-soluble structure, similar to tragacanth gum.

Chemical Structure



Chemical Composition

- Main Components: Galactose, mannose, rhamnose, uronic acid.
- Molecular Weight: Approximately 10,000–50,000 Da (depending on the source and processing).

Functional Category

- Thickening agent
- Emulsifier
- Stabilizer
- Applications:
- Pharmaceuticals: Used as a binder in tablet formulations, especially in sustained-release dosage forms.
- Food Industry: Used as a thickening agent in various food products (e.g., dairy, sauces, and soups).
- Cosmetics: In creams, lotions, and emulsions for its stabilizing properties.

Description

Karaya gum is a natural gum obtained from the exudate of the Sterculia urens tree, native to India. The gum has thickening, binding, and emulsifying properties and is widely used in pharmaceuticals, cosmetics, and food products.

Solubility:

- Water-soluble: Forms a viscous solution when hydrated in water.
- Not soluble in alcohol or most organic solvents.

Storage Conditions:

- Store in a cool, dry place away from moisture.
- Keep in airtight containers to avoid exposure to humidity.

Incompatibilities:

- May interact negatively with high concentrations of salts (electrolytes) which can reduce its viscosity and gelling ability.

Safety:

- Generally regarded as safe for consumption and topical use when used within recommended limits.

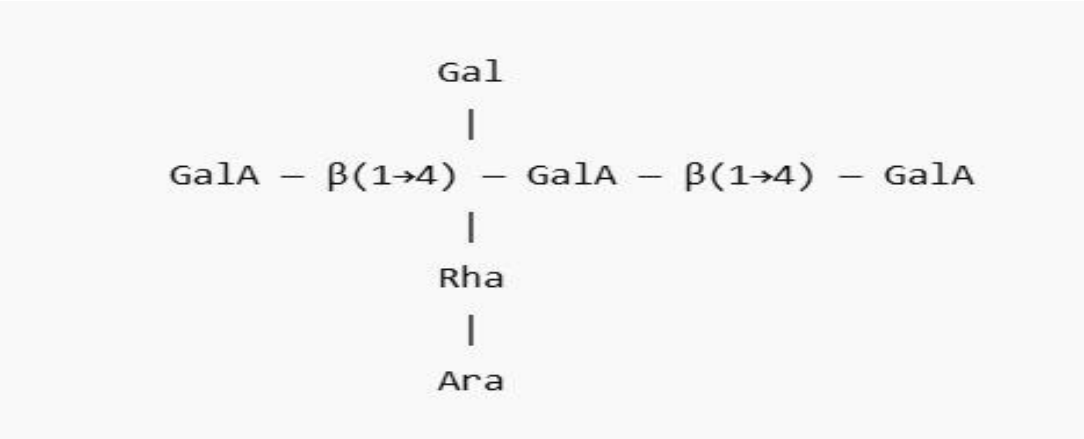
2. Kondagogu Gum

Synonyms

- Cochlospermum religiosum,
- Cochlospermum gossypium,
- Bombax gossypium,
- Wittelsbachia gossypium,
- Maximilianea gossypium.

Kondagogu gum is a polysaccharide composed of galactose, mannose, and glucuronic acid units, similar to other plant-derived gums.

Chemical Structure



Chemical Composition

- Main Components: Galactose, mannose, glucuronic acid, and rhamnose.
- Molecular Weight: Similar to that of gum tragacanth, varies but typically in the range of 10,000–100,000 Da.

Functional Category

- Thickening agent
- Emulsifier
- Suspending agent
- Binder

Applications

- Pharmaceuticals: Used in oral suspensions and emulsions. Also used in tablet formulations as a binder.
- Food Industry: Used for thickening and stabilizing dairy products and sauces.
- Cosmetics: Used for stabilizing emulsions in creams and lotions.

Description

Kondagogu gum is obtained from the Cochlospermumgossypium tree, which is native to India. It is a water-soluble, viscous substance used primarily for emulsifying and thickening purposes in various applications.

Solubility:

- Water-soluble, forms a gel-like consistency when hydrated.

Storage Conditions

- Store in a cool, dry place in airtight containers to prevent moisture absorption.
- Protect from direct sunlight and excessive heat.

Incompatibilities

- May lose its viscosity in the presence of high concentrations of salts or other electrolytes.

Safety

- Considered to be non-toxic and generally safe when used as directed in food and pharmaceuticals.
- No significant safety concerns but excessive consumption can lead to mild gastrointestinal distress.

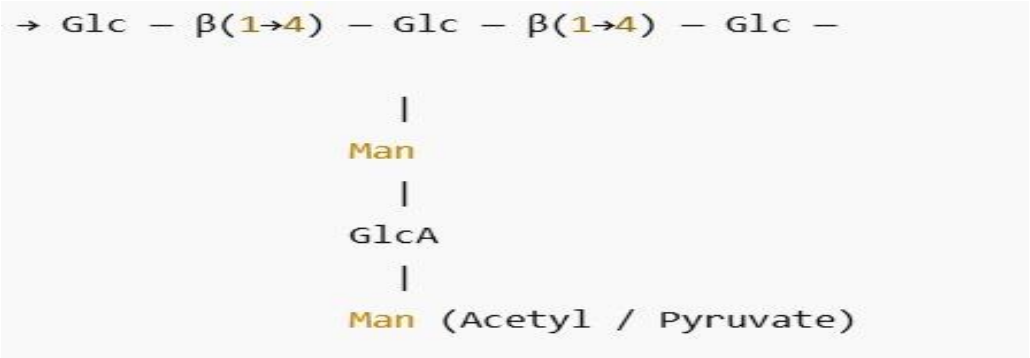
3. Xanthan Gum

Synonyms

- Xanthan polysaccharide
- Xanthan

Xanthan gum is a complex polysaccharide consisting of a backbone of β-D-glucose with alternating side chains of mannose and glucuronic acid. It is produced by fermentation using the bacterium *Xanthomonas campestris*.

Chemical Structure



Chemical Composition

- Main Components: D-glucose, D-mannose, D-glucuronic acid.
- Molecular Weight: 1,000,000–2,000,000 Da, which contributes to its high viscosity in aqueous solutions.

Functional Category

- Thickening agent
- Suspending agent
- Stabilizer
- Emulsifier

Applications

- Pharmaceuticals: Used in liquid formulations as a suspending agent. It is also used in controlled-release formulations and topical gels.
- Food Industry: Widely used as a thickener, especially in salad dressings, sauces, and beverages.
- Cosmetics: Used in lotions, shampoos, creams, and gels for improving texture and stability.

Description

Xanthan gum is a natural biopolymer produced by the bacterium *Xanthomonas campestris* during the fermentation of glucose or sucrose. It has excellent thickening, stabilizing, and emulsifying properties, which is why it is extensively used in various industries.

Solubility

- Water-soluble: Forms a viscous solution even at low concentrations.
- Can also disperse in both hot and cold water, forming a gel-like substance.

Storage Conditions

- Store in a cool, dry place, away from excessive humidity and direct sunlight.
- Keep in airtight containers to maintain quality.

Incompatibilities

- May experience a reduction in viscosity when exposed to high concentrations of salts (such as NaCl) or acids.

Safety

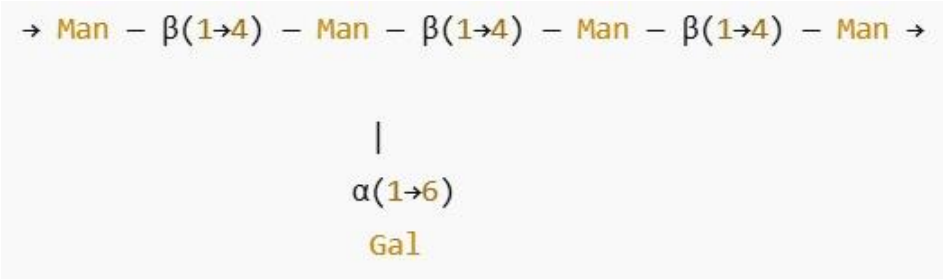
- Generally recognized as safe (GRAS) for food and pharmaceutical uses.
- No significant toxicity, although excessive intake may cause gastrointestinal discomfort (e.g., bloating).

4. Guar Gum

Synonyms

- Guar, Guaran, Guar gum is a polysaccharide consisting of galactose and mannose units in a 1:2 ratio, with the mannose backbone and galactose side chains. The molecular structure provides excellent water-binding capacity.

Chemical Structure



Chemical Composition

- Main Components: Galactose, mannose.
- Molecular Weight: 200,000–2,000,000 Da (varies depending on the processing).

Functional Category

- Thickening agent
- Suspending agent
- Binding agent
- Stabilizer

Applications

- Pharmaceuticals: Used in tablet and capsule formulations, especially for its binding and sustained release properties.
- Food Industry: Widely used as a thickening agent in sauces, gravies, dairy products, and baked goods.
- Cosmetics: Used to improve the texture and consistency of creams, lotions, and gels.

Description

Guar gum is derived from the seeds of the Cyamopsis tetragonoloba plant. It is a natural gum that provides high viscosity and is widely used for thickening, stabilizing, and binding in various industries.

Solubility

- Water-soluble: Forms a viscous solution when hydrated in water.
- Not soluble in most organic solvents.

Storage Conditions

- Store in a cool, dry place, and avoid exposure to moisture or humidity.
- Store in airtight containers to prevent absorption of water.

Incompatibilities

- May lose its thickening properties in the presence of high salt concentrations or acids.

Safety

- Generally regarded as safe (GRAS) for use in food and pharmaceuticals.
- Large quantities may cause gastrointestinal issues like bloating or gas.

MERITS OF PULSATILE DRUG DELIVERY SYSTEM

- **Targeted Drug Release**

PDDS enables the controlled release of drugs at a desired time when the drug's therapeutic action is required. This increases the efficacy of treatment. Especially beneficial for conditions such as asthma and arthritis, which have a circadian rhythm and peak at a particular time of the day.

- **Minimized Side Effects**

PDDS enables the controlled release of drugs only when required, thereby reducing the drug's exposure and minimizing side effects.

- **Enhanced Patient Compliance**

The pulsatile system enables a single dose to be administered, which is beneficial for patient compliance.

- **Optimized Therapeutic Effects**

The synchronization of the drug with the body's natural cycles can enhance the drug's efficacy. For instance, PDDS can release anti-inflammatory drugs before the body's inflammatory response reaches its peak.

- **Chronotherapy**

Chronotherapy is the attempt to time the drug release according to the circadian rhythm of the disease. PDDS is very effective in this therapeutic modality.

- **Enhanced Bioavailability**

The timed release of drugs with a narrow absorption window can enhance the drug's absorption.

DEMERITS OF PULSATILE DRUG DELIVERY SYSTEM

- **Complexity in Design and Manufacturing**

The design and manufacturing of PDDS can be complex and expensive because of the need for specialized materials and technology for time-controlled release.

- **Inconsistent Release Patterns**

Individual differences in patient physiology (for example, pH and enzymatic levels in the digestive system) may influence the release patterns of drugs, which could result in inconsistent therapeutic responses.

- **Higher Cost**

The technology used in the design and manufacturing of PDDS may contribute to the higher cost of the drugs, which could limit their availability to patients.

- **Limited Applications**

Not all drugs or diseases qualify for pulsatile delivery. This type of delivery is only applicable to drugs that require delayed or time-specific release.

- **Formulation Challenges**

Formulations of drugs in PDDS can be difficult, particularly for drugs that are sensitive to environmental conditions such as temperature, light, and moisture.

- **Risk of Dose Dumping**

In case the delivery system is not functioning properly, there may be a sudden discharge of the whole dose of the drug, resulting in toxicity or decreased efficacy of the drug.

The Pulsatile Drug Delivery System has numerous advantages, particularly in chronotherapy and drug targeting. However, its complexity, cost, and difficulties in formulation may restrict its extensive use.(75,76) .

The aim of chronopharmaceutics is to administer drugs at a time that preferably corresponds to the biological demand for the treatment or prevention of a particular disease.[71] Cholesterol biosynthesis exhibits a circadian rhythm. Cholesterol synthesis is generally elevated during the night rather than during the daylight hours, and diurnal synthesis may account for as much as 30-40% of daily cholesterol synthesis. This is because the activity of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase is increased at midnight.[72] Chronotherapy with inhibitors of this enzyme has suggested that evening administration may be more effective than morning administration.[73]

MATERIALS AND METHODS

Material

Fluvastatin sodium,
Eudragit RS 100,
Karagaya gum,
Kondagogu gum,
Guar gum,
Xanthan gum,
Cellulose acetate phthalate,
n-dibutyle phthalate,
All reagents used were of analytical-reagent grade.

METHODOLOGY

Confirmation of Fluvastatin sodium through UV-spectral Ananlysis

The λmax of Fluvastatin sodium was determined by scanning the standard drug solution. A accurately weighed amount of Fluvastatin sodium (25mg) was dissolved in distilled water to prepare a clear solution and it was made up to volume in 25ml volumetric flask with distilled water.1 ml of this solution was transferred in to 100 ml of volumetric flask and it was made up to volume with pH 1.2 buffer, PH 6.8 phosphate buffer and PH 7.4 phosphate buffer. The resulting solution (10 µg/ml of phosphate buffer) was scanned over the range 200-400 nm against pH 1.2 buffer and pH 6.8 phosphate buffer and PH 7.4 phosphate buffer as blank using UV spectrophotometer. The wavelength at which maximum absorbance was detected was recorded as the λmax. The absorption spectrum was noted at 304nm.

Preparation of Required concentrations: 1ml of stock solution was taken and diluted to volume with respective buffers in 10ml volumetric flask to get 100µg/ml concentration. 0.2ml, 0.4ml, 0.6ml, 0.8ml, and 1ml of solution was taken from 100µg/ml concentration and diluted to volume with respective buffers in 10ml volumetric flak to get 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml, and 10µg/ml concentrations respectively. These samples were then analyzed Spectroph.

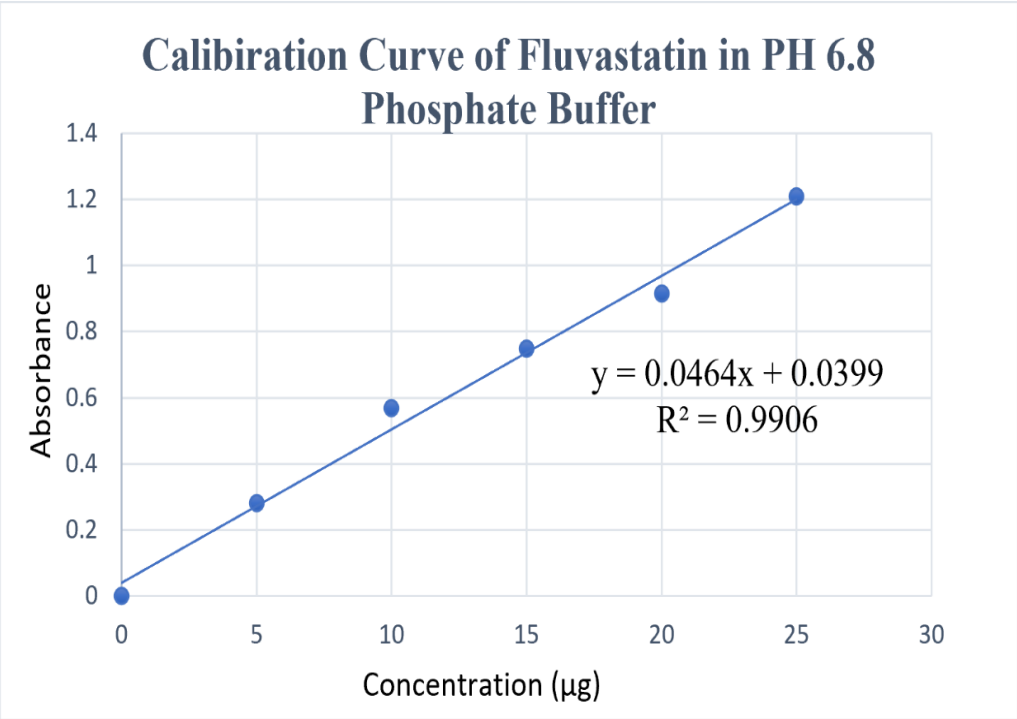
Preparation of Required concentrations: 1ml of stock solution was taken and diluted to volume with pH 6.8 phosphate buffer in 10ml volumetric flask to get 100µg/ml concentration. 0.5ml, 1.0ml, 1.5ml, 2.0ml, and 2.5ml of solution were taken from the 100µg/ml concentration and diluted to volume with pH 6.8 phosphate buffer in 10ml volumetric flask to get 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml, and 25µg/ml concentrations respectively.

Determination of calibration curve of Fluvastatin sodium:

The standard calibration curve of fluvastatin sodium was obtained by using phosphate buffer pH 6.8 as solvent. calibration curve was obtained by plotting Absorbance Vs. Concentration. Table shows the absorbance values of fluvastatin sodium. The standard curve is shown in figure, the standard calibration curve shows the correlation coefficient of 0.9998. The curve was found to be linear in the concentration range of 5-25 ug/ml at 304.0 nm. Thus, the standard curve followed the Beer-Lamberts Law.

Absorbance values of Fluvastatin sodium in Phosphate buffer pH 6.8

S.No	Concentration (mcg/ml)	Absorbance
1	0	0
2	5	0.281
3	10	0.568
4	15	0.748
5	20	0.914
6	25	1.208



Standard Calibration Curve of Fluvastatin in PH 6.8 Phosphate Buffer

IR spectral studies

The IR Spectra of the formulation, pure drugs, and excipients were recorded on JASCO FT-Infra Red Spectrophotometer using KBr pellet method at the resolution rate of 4 cm-1. The spectrum was integrated in transmittance mode at wave number range of 380 to 4368 cm-1.

Drug and excipient compatability studies

The FTIR spectrum of Fluvastatin sodium pure drug (Figure) showed characteristic peaks at wave numbers were 1013.16cm-1,3688.12 cm-1,1214.96cm-1and 1481.32cm-1denoting stretching vibration of C-F stretching, O-H stretching, C-O stretching and CH3 deformations respectively.The FTIR spectrum (Figure 4) of optimized formulation showed characteristic peaks at wave numbers were 1009.53cm-1,3644.11cm-1,1214.67cm-1 and 1480.31 cm-1 denoting stretching vibration of C-F stretching, O-H stretching, C-O stretching and CH3 deformations respectively.

From the figures it was observed that similar peaks were also reported in optimized formulation.The absence of change or shift in the characteristic peaks of the drug loaded microspheres indicated that there was no significant interaction between the drug and polymer, which signifies the stability of the drug in the optimized formulation. The thermal curve of Fluvastatin sodium is represented by a sharp endothermic peak at 211.29° C (Figure) corresponding to the melting point of the drugs, and an identical peak (211.11° C) was also observed in the optimized formulation (Figure) . The thermo graphic result indicates that the drugs have retained their identity in the optimized formulation.

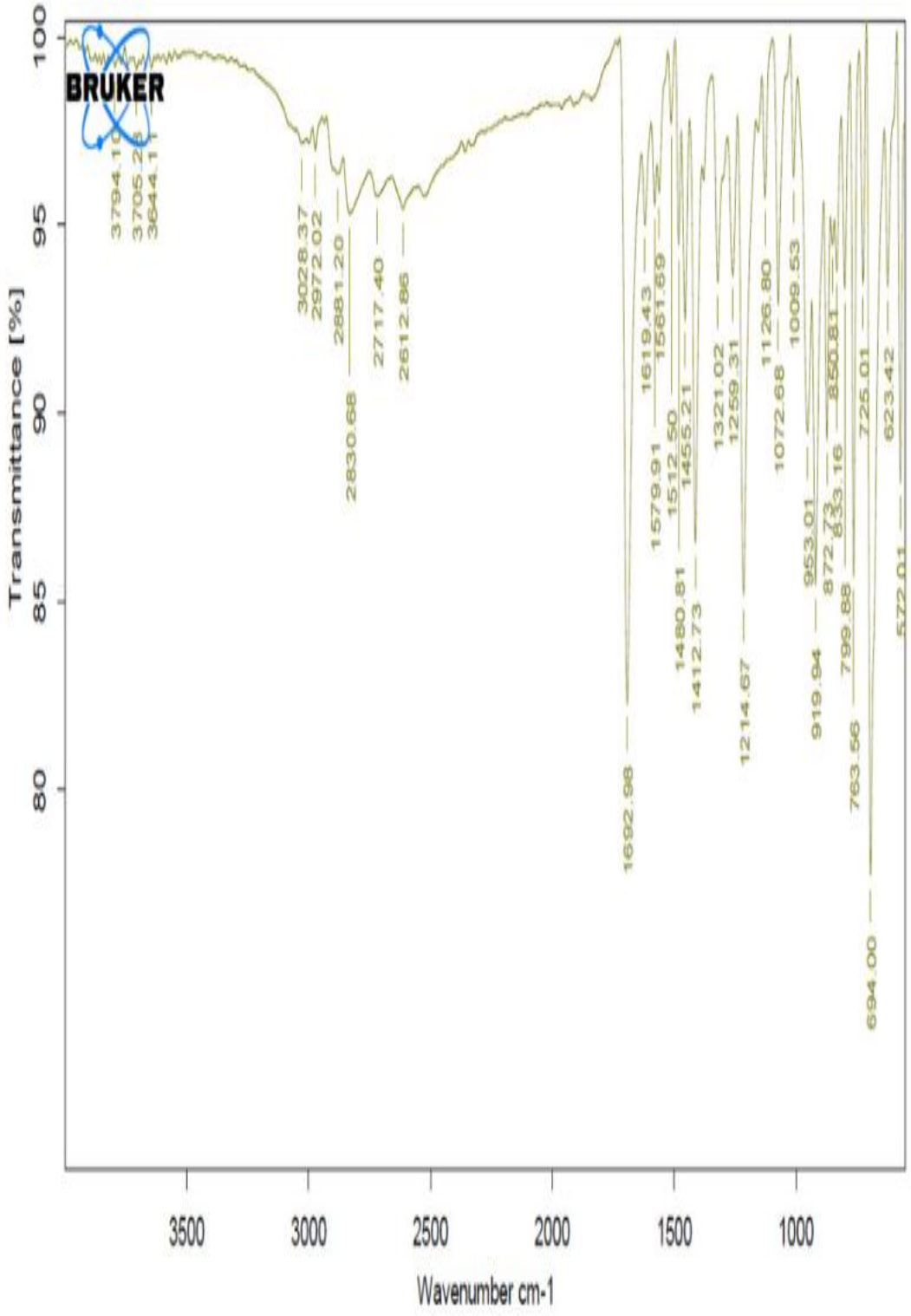


Figure: FTIR spectrum of Fluvastatin sodium

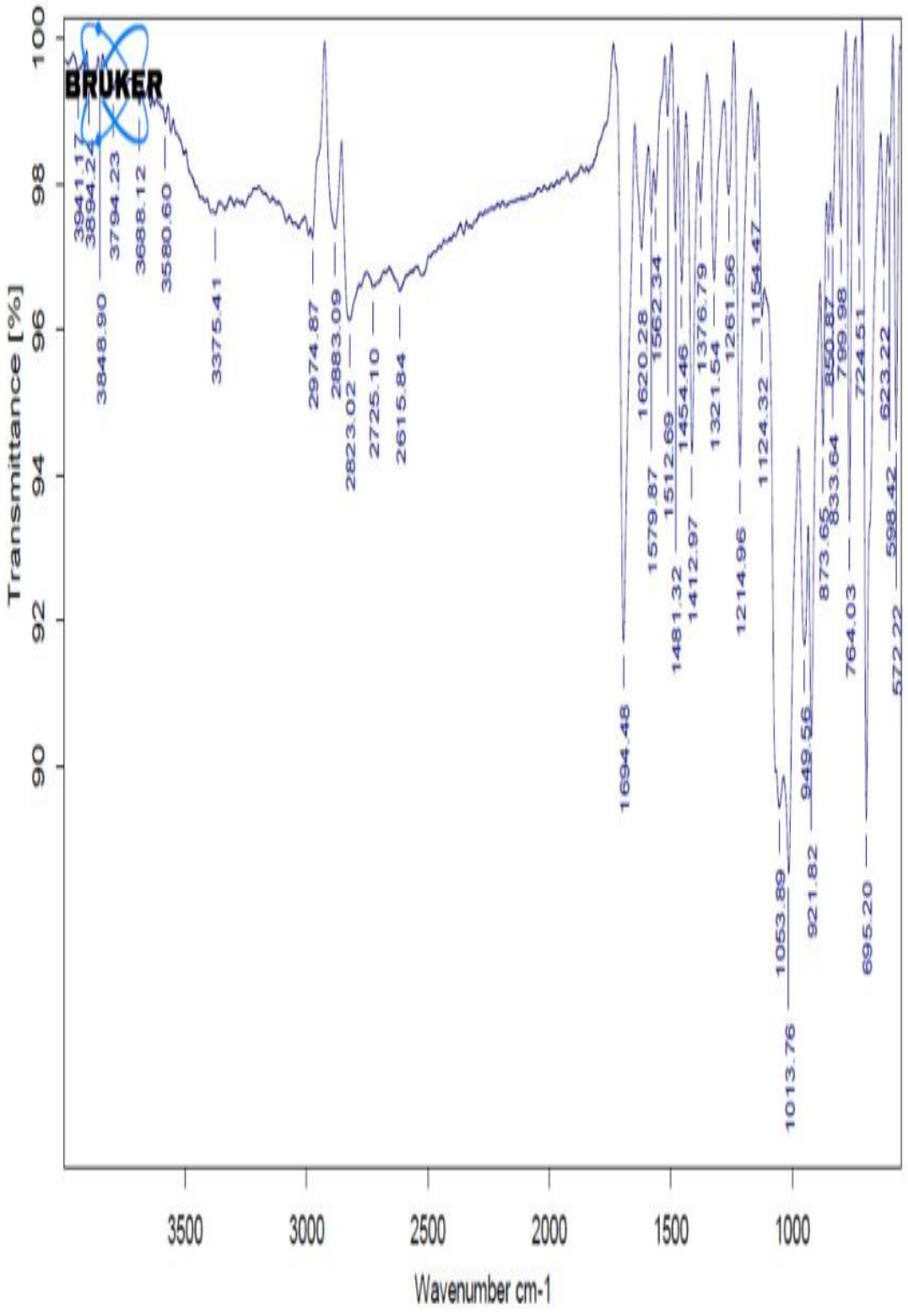


Figure: FTIR spectrum of optimized formulation of Fluvastatin sodium.

Differential scanning calorimetry (DSC) studies

The pure drug and optimized formulation were analyzed using the differential scanning calorimeter equipped with an intra cooler (NETZSCH, Japan). The indium/zinc standards were used to calibrate the temperature and enthalpy scale

of the DSC. The samples were placed in aluminum pans and heated at a constant rate of 20°C/min from 20-250°C. An inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min.

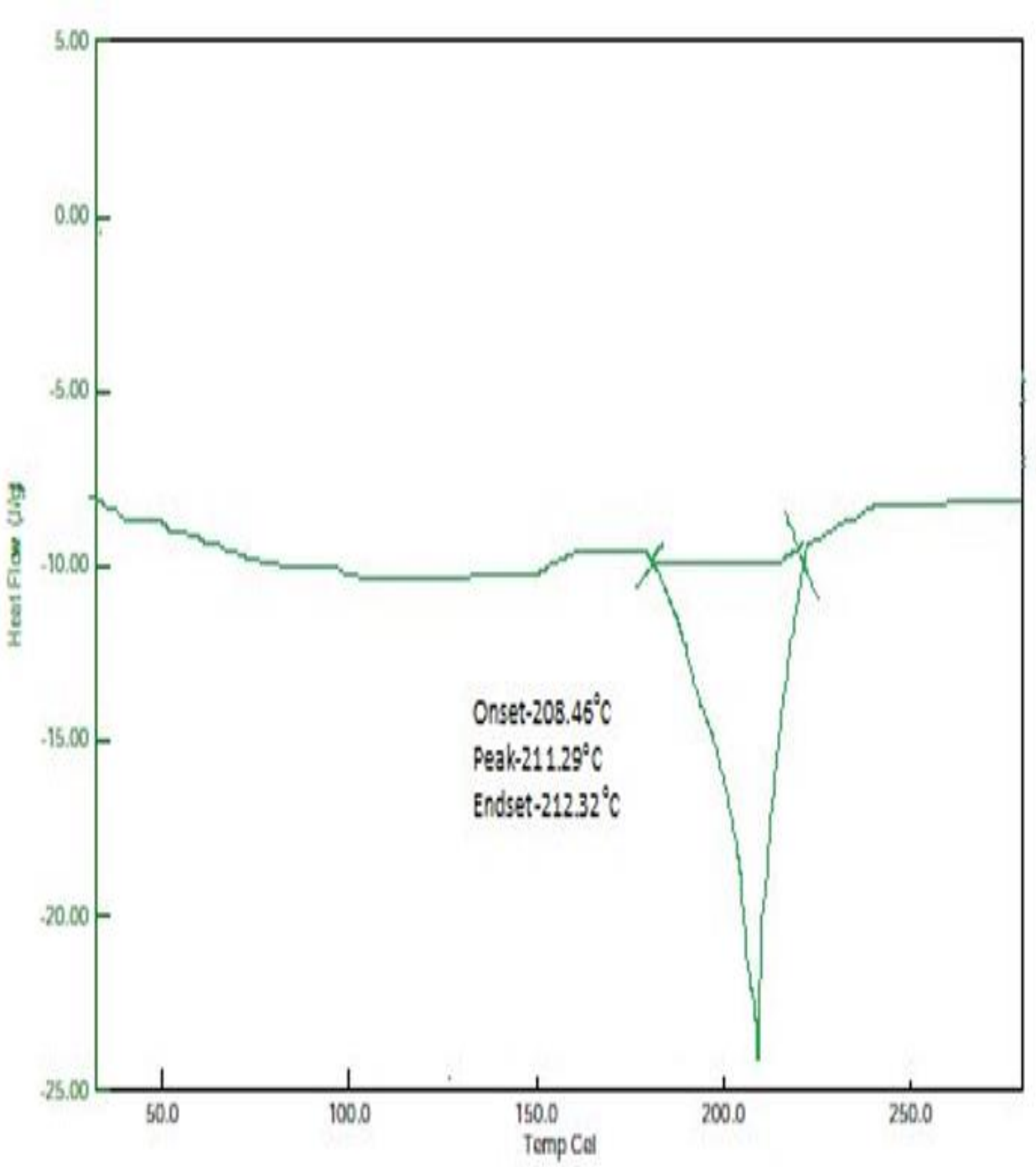


Figure: DSC thermo gram of Fluvastatin sodi.

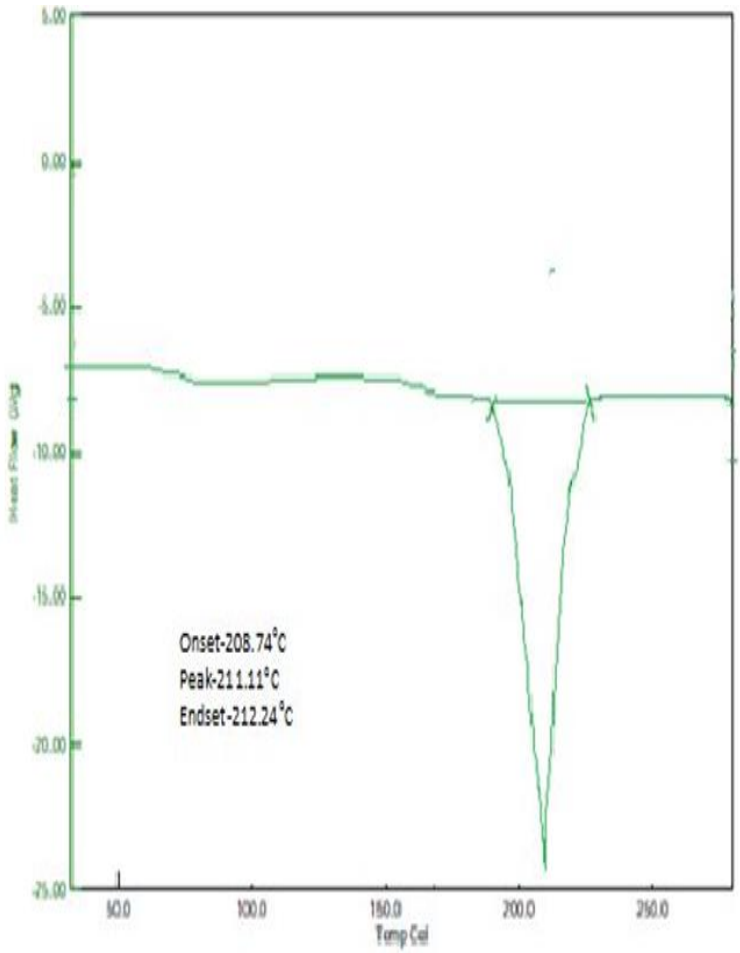


Figure: DSC thermo gram of optimized formulation of Fluvastatin sodium

PREFORMULATION STUDIES

Bulk Density

The powder blend of all formulations was evaluated separately in order to determine their bulk densities. Powder blend was weighed (M) and later the weighed powder blend was transferred in to the measuring cylinder and volume occupied was noted (V_b).

$$D_b = \frac{\text{Mass of the powder blend (M)}}{\text{Vol. occupied by powder blend}(V_b)}$$

V_b is known as the Bulk volume and Bulk density is expressed in terms of g/ml.

Tapped Density

Powder blend was transferred into the measuring cylinder and subjected for 100 tappings. The obtained volume was noted as the tapped volume. Tapped density is expressed as g/ml and tapped density is given by the formula;

$$D_t = \frac{\text{Mass of the powder blend (M)}}{\text{Tapped volume } (V_t).}$$

Angle of Repose

Angle of repose is the maximum angle possible between the surface of the pile of granules and the horizontal plane. This is one of the measures for flow properties. Powder blend was allowed to flow through the funnel attached to a

stand and later height and radius of the heap of the powder blend formed was noted. Based on the height and radius obtained Angle of repose was calculated using the formula.

$$\tan(\theta) = \frac{\text{Height of the heap (h)}}{\text{Radius of the heap(r)}}$$

Specifications of Angle of Repose

Angle of repose	Flow property
<25	Excellent
25-30	Good
30-40	Passable
>40	Poor

Carr's Index (or) % Compressibility

Carr's Index is one more measure to know the flow properties. It is indicated by the letter (I) and expressed in terms of percentage.

$$I = \frac{\text{Tapped density - bulk density} \times 100}{\text{Tapped density}}$$

Specifications of %Compressibility

Compressibility index (%)	Flow properties
<10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very very poor

Hausner's Ratio

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material.

Hausner's ratio was calculated by using the formula;

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Specifications of Hausners ratio

Hausners Ratio	Type of flow
Less than 1.25	Good Flow
1.25 – 1.5	Moderate
Greater than.5	Poor flow

DRUG RELEASE KINETICS

To study the mechanism of drug release from the SR layer of the matrix tablets, the dissolution data were fitted into the following equations:

Zero order equation

$$Q_t = Q_0 + k_{0t} \quad \text{---------- (1)}$$

Where, Q_t is the amount of drug released at time t, Q_0 is the initial amount of drug in the solution (more times, $Q_0 = 0$) and k_0 is the zero-order release rate (Kenneth A. Connors, 1991).

First order equation

$$\ln Q_t = \ln Q_0 = k_1 t \quad \text{---------- (2)}$$

Where, Q_t is the amount of drug released at time t, Q_0 is the initial amount of drug in the solution and k_1 is the first-order release rate constant (Kenneth A. Connors, 1991).

Higuchi's equation

$$Q = k_H t^{1/2} \quad \text{---------- (3)}$$

Where, Q is the amount of drug released at time t, $k_H$is the Higuchi diffusion rate constant (Higuchi W I, 1962).

Koresmeyer's equation

$$M_t / M_\infty = Kt^n \quad \text{---------- (4)}$$

Where M_t is the amount of drug released at time t, M_∞ is the amount of drug released after infinite time, k is a kinetic constant incorporating structural and geometric characteristics of the tablet, and n is the diffusional exponent of the drug release mechanism (Koresmeyer et al., 1977).

Similarity factor

The similarity factor (f2) is employed to compare the dissolution profile of each formulation with that of the marketed formulation. In this method, recommended by the FDA guidance for the industry, a value between 50 and 100, both profiles are almost equivalent (Shah V.P et al 1998).

Preparation of cross-linked gelatin capsules

The "0" sized hard gelatin capsules (approx. 100 numbers) were used. The bodies of the capsules were then put on wire mesh, which was maintained in a desiccator. An aliquot of 25 ml of 15% v/v formaldehyde was taken into the bottom of desiccators, and a pinch of potassium permanganate was added to it to produce formalin vapors. The reaction was allowed to happen for 12 hrs. After which, the bodies were removed and dried at 50°C for 30 minutes to ensure completion of the reaction between gelatin and formaldehyde vapor. The bodies were dried at room temperature to enable the removal of the residual formaldehyde.[76] The capsule bodies were closed with untreated caps and stored in an air tight container.

Preparation of hydrogel plug (HP)

The plug used for sealing the capsule body was prepared by compressing an equal amount of Karaya gum/Kondagogu gum/Xanthum gum/Guar gum and lactose using 7 mm punches and dies on rotary tablet press (7)

Preparation of microspheres

All the microspheres formulations were prepared by emulsion solvent evaporation technique[78] and the composition was shown in Table. The effect of various formulation and processing factors on microspheres characteristics were investigated by changing polymer: drug ratio. Weighed amount of Fluvastatin sodium and polymer Ethyl cellulose in 1:1 ratio were dissolved in 10ml of acetone. The homogeneous drug and polymer organic solution was then slowly added in a thin stream to 100ml of liquid paraffin containing 1% surfactant (tween 80/span 80) with constant stirring for 1h. The resulting microspheres were separated by filtration and washed with petroleum ether. The microspheres

finally air dried over a period of 12 hrs and stored in a desiccator. In case of 1:1.5, 1:2 and 1:3 core: coat ratios, the corresponding polymer get varied respectively.

Designing of Pulsincap

The Pulsincap was developed by filling the microspheres equivalent to 40mg of Fluvastatin sodium into the formaldehyde treated bodies by hand filling. The capsules containing microspheres were then plugged with optimized hydrogel plug. The joint of the capsule body and cap was sealed with a small amount of the 5% ethyl cellulose ethanolic solution.[9] The sealed capsules were completely coated by dip coating method with 5% cellulose acetate phthalate in 5:5 (v/v) mixture of acetone: ethanol plasticized with n-dibutyl phthalate (0.75%), to prevent variable gastric emptying. Coating was repeated until an 8–12% increase in weight is obtained. Percentage weight gain of the capsules before and after coating was determined.

Physicochemical Characterization of Hydrogel Plug

Hydrogel Plugs were evaluated for hardness, friability, weight variation and lag time.[80]

Drug content uniformity

Then encapsulated microspheres equivalent to 40mg of Fluvastatin sodium were taken into mortar and ground using the help of pestle. The ground powder mixture was dissolved in 6.8 pH buffer, filtered, and estimated spectrophotometrically at 304 nm[81]

In vitro release profile of pulsatile capsule

Dissolution studies were carried out by using USP XXIII dissolution test apparatus (paddle method). Capsule was tied to paddle with a cotton thread so that the capsule should be immersed completely in dissolution media but not float. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used referred to as sequential pH change method.. 900ml of the dissolution medium was used at each time. 5ml of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 304 nm, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times.[82]

RESULTS AND DISCUSSION

Strategy of the Pulsincap dosage form

The Pulsincap dosage form was a capsule that consisted of a water-insoluble body and a water-soluble cap. The microspheres were packed inside the capsule body using a hydrogel plug. When the pulsing cap was ingested, the water-soluble cap dissolved in the gastric juice, and the hydrogel plug started to swell. At a predetermined time after ingestion, the swollen plug was pushed out, and the encapsulated drug formulation was released into the colon, where it was dissolved and then absorbed into the bloodstream. In the current study, the capsule bodies that were hardened using formaldehyde treatment for 12 hours were used for the preparation of pulsing caps. It was sealed with an unhardened cap of the capsule. The microspheres were prepared using the emulsion solvent evaporation technique. The technique used provided discrete, spherical, non-sticky, and free-flowing microspheres. The creation of a stable emulsion in the initial stages is crucial if discrete microspheres are to be separated. An optimal concentration of emulsifier is needed to provide the finest stable dispersion. Below the optimal concentration, the dispersed globules/droplets tend to merge and form larger globules due to the lack of reduction in interfacial tension, whereas above the optimal concentration, no

notable reduction in size is noticed, as a large amount of emulsifying agent causes an increase in the viscosity of the dispersion medium. The optimal concentration of the surfactant was determined to be 1.0%. Microscopic studies of the formulations showed that the microspheres were spherical in shape and were found as aggregates or separate particles.

Evaluation of the microspheres

All the formulations showed good flow characteristics. The size of the microspheres varied from 135.13 to 179.33µm. The application of the surfactant allows the significant reduction in the size of the microspheres due to the reduction in the interfacial tension. All the formulations showed a narrow size distribution. The mean size of the microspheres depends on the type of surfactant used and the proportion of the polymer in the formulation. The mean size of the microspheres increases with the increase in the proportion of the polymer in the formulation. It seems that the increase in the proportion of the polymer increases the viscosity of the internal phase significantly, resulting in the increase in the size of the emulsion droplets and finally the microspheres size. Microspheres were prepared with 1:1, 1:1.5, 1:2, 1:3 ratios of core to coat material to study the effect of concentration of coating material on the release rate of Fluvastatin sodium. These microspheres were evaluated for Drug content and % Encapsulation Efficiency. The results are shown in Table . The method also showed good entrapment efficiency. Both the types of surfactants used have an effect on the size distribution of the microspheres. The hydrophilic surfactant Tween 80 (Polyoxyethylene 20) is found to produce smaller particle size microspheres compared to hydrophobic surfactant Span 80 (Sorbitan mono oleate, HLB 4.3).

Evaluation of the Hydrogel Plug

The Hydrogel Plugs were evaluated for hardness, friability, weight variation, and lag time, and the results are shown in Table 3. The formulations with the different hydrogel plugs HP1, HP2, HP3, HP4 shown 0.01% , 5.23% , 13.23 % and 17.45 % of drug release respectively at the end of 5th hour. It was found that 100 mg hydrogel plug (Karaya gum and Lactose in 1:1 ratio) with 4.8kg/cm2 hardness was satisfactory to retard the drug release in small intestinal fluid and to eject out the plug in colonic fluid and releasing the microspheres into colonic fluid. This indicated that the lag time can also be varied and dependent on the composition of the plug.

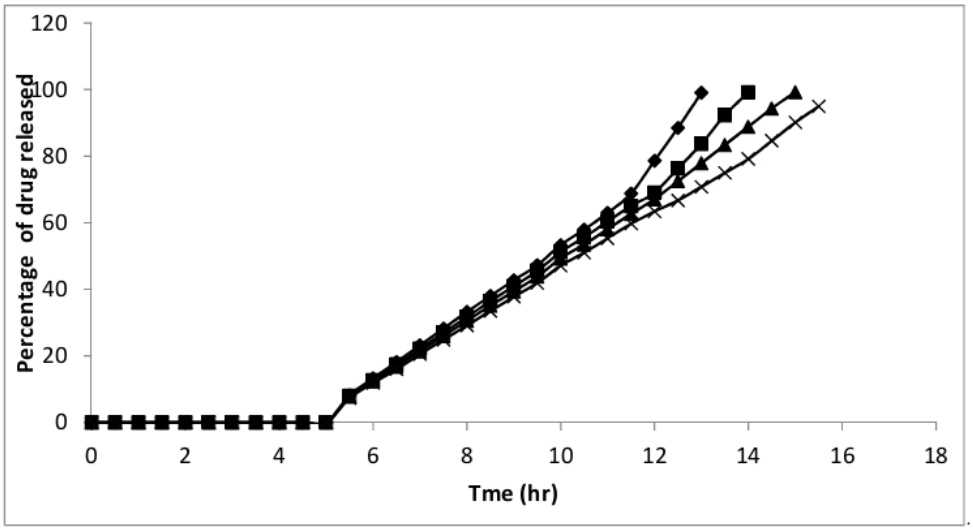


Figure: Comparative In-vitro drug release profiles plot of fluvastatin sodium from microspheres prepared with Ethyl cellulose in different ratios by employing span 80 as surfactant.

F1(-■-)Fluvastatin sodium microspheres prepared with Ethyl cellulose in 1:1 ratio

F2(-♦-)Fluvastatin sodium microspheres prepared with Ethyl cellulose in 1:1.5 ratio

F3(-▲-)Fluvastatin sodium microspheres prepared with Ethyl cellulose in 1:2ratio

F4(×-) Fluvastatin sodium microspheres prepared with Ethyl cellulose in 1:3 ratio

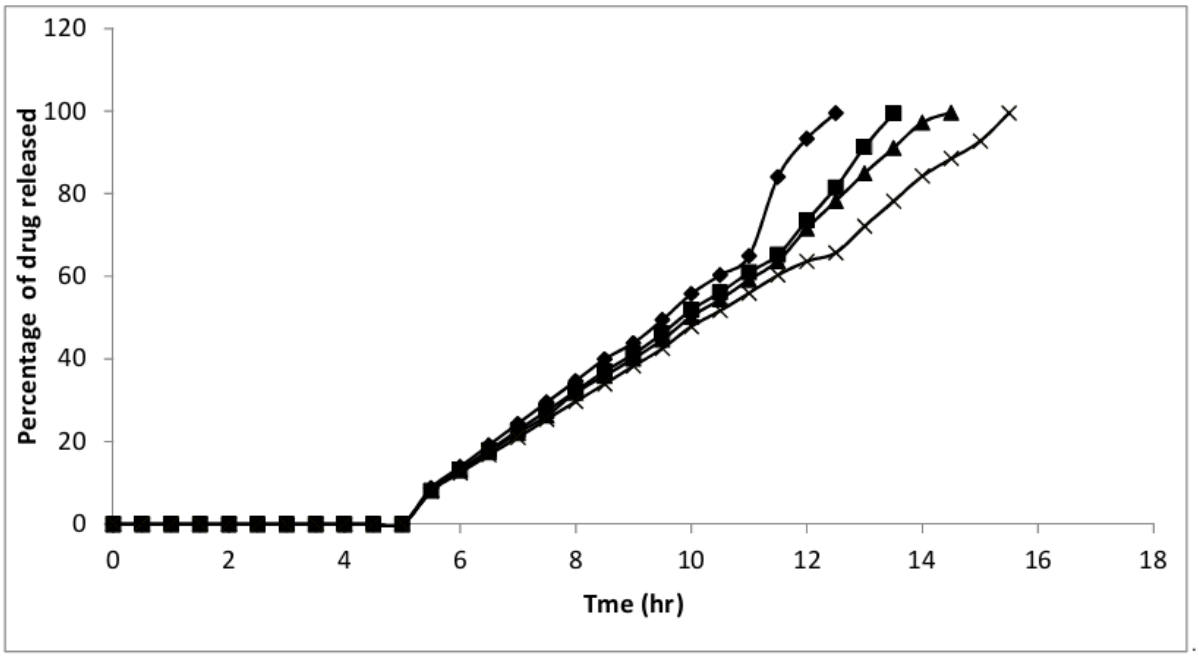


Figure: Comparative In-vitro drug release profiles plot of fluvastatin sodium from microspheres prepared with Ethyl cellulose in different ratios by employing Tween 80 as surfactant.

Dissolution studies of Pulsin caps

During the dissolution studies, it was noticed that, the enteric coat of the cellulose acetate phthalate was intact for 2 hours in pH 1.2, but dissolved in intestinal pH, leaving the soluble cap of capsule, which also dissolved in pH 7.4, then the exposed polymer plug absorbed the surrounding fluid, swelled and released the drug through the swollen microspheres. After complete wetting of the plug, it formed a soft mass, which was then easily ejected out of the capsule body; releasing the microspheres into simulated colonic fluid (pH 6.8 phosphate buffer). From the In-vitro release studies of device, it was observed that, with all formulation, there was absolutely no drug release in simulated gastric fluid (acidic pH 1.2) for 2 hours and in simulated intestinal fluid (pH 7.4 phosphate buffer). Burst effect was found in colonic medium (pH 6.8 phosphate buffer).

Pulsincaps loaded with microspheres prepared with Fluvastatin sodium and Ethyl cellulose in 1:1,1:1.5, 1:2 and 1:3 ratios by employing span 80 as surfactant revealed controlled drug release for a period of 8 hours (5th hour to 13th hour), 9 hours (5th hour to 14thhour) and 10 hours (5th hour to 15th hour), 11hours (5th hour to 16th hour) respectively and are shown in figure .

Pulsin caps loaded with microspheres prepared with Fluvastatin sodium and ethyl cellulose in 1:1,1:1.5,1:2 and 1:3 by employing Tween 80 as surfactant ratios shown controlled drug release for a period of 7.5 hours (5th hour to 13th hour), 8.5 hours (5th hour to 14thhour) and 9.5 hours (5th hour to 15th hour), 10.5 hours (5th hour to 16th hour) respectively and are shown in figure.

The ratio of surfactant used also influences the in-vitro release of the microspheres. In vitro release study reveals that the rate of drug release was faster in case of hydrophilic tween 80. This is because of the hydrophilic nature of the surfactant. Drug release was found to be slower in case of microspheres prepared with span 80.

Surfactants used	Ethyl cellulose	
	Formulation code	Core : Coat
SPAN 80	F1	1:1
	F2	1:1.5
	F3	1:2
	F4	1:3
TWEEN 80	F5	1:1
	F6	1:1.5
	F7	1:2
	F8	1:3

Formulation of Fluvastatin sodium microspheres

Formulation	Angle of Repose	Bulk Density (g/cm3)	Carr's Index	Hausner's Ratio	Average Particle Size (µm)	Drug Content	% Encapsulation Efficiency
F1	27.64±0.05	0.514±0.07	15.87±0.09	1.188±0.09	139.44±0.07	46.56±0.03	93.12±0.06
F2	26.93±0.04	0.519±0.06	15.49±0.08	1.183±0.10	156.47±0.03	37.16±0.07	92.90±0.05
F3	26.10±0.06	0.521±0.08	15.42±0.10	1.182±0.10	168.39±0.09	31.25±0.08	94.39±0.04
F4	26.75±0.10	0.531±0.09	15.31±0.08	1.181±0.08	179.33±0.10	23.47±0.10	93.88±0.10
F5	26.52±0.03	0.514±0.06	15.87±0.07	1.188±0.07	135.13±0.03	44.13±0.07	88.26±0.05
F6	26.14±0.04	0.522±0.05	15.67±0.06	1.185±0.10	157.24±0.05	37.34±0.09	93.35±0.07
F7	25.71±0.08	0.534±0.04	15.48±0.10	1.183±0.10	168.49±0.10	32.23±0.10	97.66±0.09
F8	26.71±0.07	0.527±0.03	15.27±0.09	1.180±0.04	179.18±0.02	23.41±0.07	93.64±0.04

Evaluation data of Fluvastatin sodium microspheres prepared with Ethyl cellulose in different ratios by employing different surfactants(Mean±S.D)

Hydrogel Plug code	Composition (1:1)	Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Lag time
HP1	Karagayam:lactose	100±1.4	3.45±0.12	4.8±0.04	5 ± 0.02
HP2	Kondagogugum:lactose	100±1.3	3.42±0.14	4.6±0,03	4.5 ± 0.03
HP3	Xanthangum:lactose	100±1.5	3.41±0.08	4.3±0.05	4 ± 0.03
HP4	Guargum:lactose	100±1.2	3.42±0.10	4.1±0.02	3.5 ± 0.02

Evaluation characteristics of hydrogel plugs prepared with various natural polymers (Mean±S.D)

Formulation	Correlation coefficient				Release kinetics			Diffusion exponent value(n)
	Zero order	First order	Higuchi	Peppas	$K_{0\ (mg/hr)}$	$T_{50(\ hr)}$	$T_{90(hr)}$	
F1	0.9937	0.7408	0.9097	0.9952	4.55	4.6	8	0.8892
F2	0.9979	0.7706	0.9178	0.9971	4.27	4.9	8.7	0.8815
F3	0.9999	0.7995	0.9289	0.9982	3.94	5.3	9.3	0.8761
F4	0.9990	0.8096	0.9363	0.9994	3.74	5.6	10	0.8662
F5	0.9873	0.7256	0.8963	0.9913	4.98	4.2	7.5	0.8967
F6	0.9951	0.7337	0.9128	0.9959	4.45	4.7	8.4	0.8859
F7	0.9986	0.7694	0.9189	0.9957	4.27	4.9	8.8	0.8789
F8	0.9989	0.7718	0.9326	0.9979	3.81	5.5	9.8	0.8515

In-vitro dissolution kinetics parameters of Fluvastatin sodium microspheres prepared with ethylcellulose in different ratios by employing different surfactants

Drug and excipient compatability studies

The FTIR spectrum of Fluvastatin sodium pure drug (Figure) showed characteristic peaks at wave numbers were

1013.16cm-1,3688.12 cm-1,1214.96cm-1 and 1481.32cm-1 denoting stretching vibration of C-F stretching, O-H stretching, C-O stretching and CH3 deformations respectively. The FTIR spectrum (Figure) of optimized formulation showed characteristic peaks at wave numbers were 1009.53cm-1,3644.11cm-1,1214.67cm-1 and 1480.31 cm-1 denoting stretching vibration of C-F stretching, O-H stretching, C-O stretching and CH3 deformations respectively. From the figures it was observed that similar peaks were also reported in optimized formulation. There was no change or shifting of characteristic peaks in drug loaded microspheres suggested that there was no significant drug polymer interaction which indicates the stable nature of the drug in optimized formulation. The Fluvastatin sodium thermal curve is characterized by a sharp endothermic peak at 211.29° C (Figure) corresponding to the melting point of the drugs and an identical peak (211.11° C) was also observed in the optimized formulation(Figure) . The thermo graphic result shows that the drugs retain its identity in the optimized formulation.

CONCLUSION

Among all the formulations, Fluvastatin sodium microspheres prepared with Ethyl cellulose in 1:3 ratio exhibited prolonged release for a period of 11 hours. The results obtained demonstrated the ability of the system in retarding the release of the drug for a programmable period of time and the potential of utilizing the retardation effect for colon targeting. Based on the chrono modulated therapy of hepatic cholesterol synthesis, the lag time criterion of 5 hours and controlled release for a period of 11 hours was met. The dosage form can be administered at bedtime and will release the drug in the early morning hours when cholesterol synthesis is more prominent.

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