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Review Article

Formulation And Evaluation Of Gastroretentive Floating Tablet Of Atorvastatin Calcium As A Model Drug: A Review

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ABSTRACT

Oral solid dosage forms are the preferred administration route for many drugs, especially for modified release products. However, for optimal therapeutic effect, the drug must be well absorbed throughout the gastrointestinal tract (GIT). Challenges arise when drugs have a narrow absorption window in the GIT or when they are unstable in GI fluids. Developing oral controlled release dosage forms becomes crucial not only to prolong drug delivery but also to enhance retention within the stomach or small intestine until complete drug release occurs. Gastro Retentive Drug Delivery Systems (GRDDS) offer a promising approach to address these challenges, particularly for drugs like Atorvastatin calcium, which undergo rapid clearance in the intestine. Successful formulation of a Gastro Retentive Drug Delivery System for Atorvastatin calcium was achieved using direct compression technique, employing different viscosity grades of Hydroxypropyl methylcellulose (HPMC) as binder, Avicel PH102 as diluent, sodium bicarbonate as a gas generating agent, talc as a glidant, and magnesium stearate as a lubricant. The optimized tablet formulation demonstrated 99.74% drug release over 24 hours, with sustained release characteristics and buoyancy throughout the study duration. Among the various HPMC grades tested, HPMC K100M exhibited the most significant retardation in drug release. The in vitro dissolution profile followed zero-order kinetics, indicating a controlled release mechanism.

INTRODUCTION

Drug administration through oral route has been reported to be the most Popular route of drug administration due to safety considerations, patient Compliance, and flexibility of oral dosage forms design than most other dosage forms[1]. Tablets and capsules are The most common marketed oral dosage forms; still, tablets are more widely

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marketed because of patient swallowing convenience, ease of handling, and lower manufacturing cost. Oral controlled release formulations that are able to deliver the drug locally or systemically at predetermined rates for a specified period of time have become an integral part of research centers and pharmaceutical industry due to their many benefits over conventional dosage forms. Such systems can reduce the frequency of dosing which suites patients with chronic illnesses and improve their compliance. Also, they can reduce side effects due to better control of therapeutic drug concentrations[4]. Oral drug administration is prevalent due to several benefits, including convenience, patient preference, cost-effectiveness, and the ease of large-scale manufacturing of oral dosage forms. Roughly 60% of commercially available small-molecule drug products are administered orally. It's estimated that oral formulations account for approximately 90% of the global market share for pharmaceutical formulations intended for human use. Moreover, about 84% of the top-selling pharmaceutical products are taken orally, collectively valued at $35 billion, with an annual growth rate of 10%[3]. The compliance of patients to oral formulations is generally higher than that to other parenteral routes such as intravenous, subcutaneous, and intramuscular injections, as well as to inhalation for asthma medications. Furthermore, orally administered drugs can be targeted to particular regions within the gastrointestinal (GI) tract for localized treatment of pathological conditions such as stomach and colorectal cancers, infections, inflammations, bowel diseases, gastro-duodenal ulcers, and gastro esophageal reflux disorders etc. Oral drug delivery system generally including solid dosage forms like powders, tablets, granules, capsules, pills, lozenges etc[12].

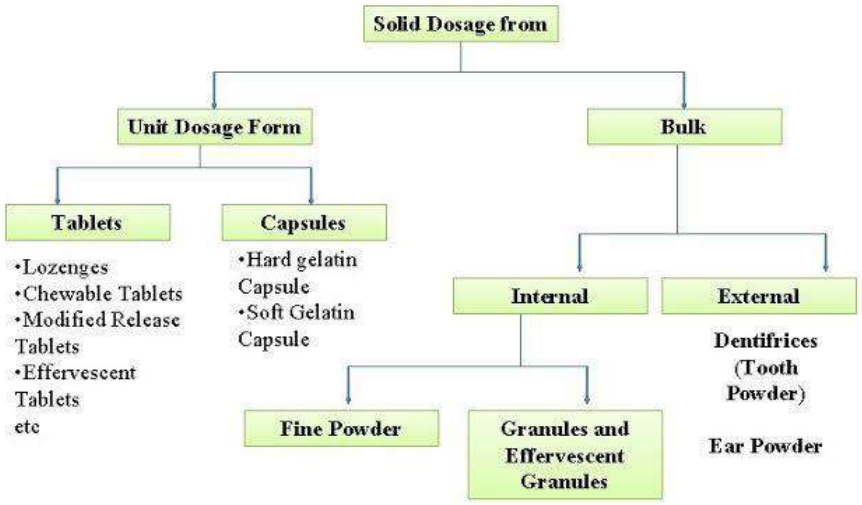

Figure.no. 1 Solid Dosage Form

Tablets:

Tablets may be defined as the solid unit dosage form of medication with suitable excipients. It comprises a mixture of active substances and excipients, usually in powder form, that are pressed or compacted into a solid dose[10].

Ideal Characteristics Of Tablets

- Tablet Should be an elegant product having its own identity.
- It Should have the chemical and physical stability to maintain its physical attributes over time.

- Must be able to release the medicinal agent(s) in the body in a predictable and reproducible manner.
- The appearance of the tablet should be elegant and its weight, size and appearance should be consistent.
- The drug should be released from the tablet in a controlled and reproducible way.
- The tablet should be of sufficient mechanical strength to withstand fracture and erosion during handling.
- The tablets should be free from any contamination and should not produce any harmful effect to the patient.

Advantage Of The Tablet Dosage Form

- They are unit dosage form and great dose precision and the lease content variability.
- Cost is lowest of all oral dosage form.
- Lighter and compact.
- Easiest and cheapest to package and strip.
- Easy to swallow. Objectionable odour and bitter taste cab be masked by coating technique.
- Suitable for large scale
- They are unit dosage form and great dose precision and the lease content variability.
- Cost is lowest of all oral dosage form.

Disadvantages Of Tablet Dosage Form

- Difficult to swallow in case of children and unconscious patients.
- Some drugs resist compression into dense compacts, owing to amorphous nature, lower density character.
- Drug with poor wetting, slow dissolution properties, optimum absorption in GIT may be difficult to formulate.

GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS[2]

Gastroprotective systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients also increase gastric retention of drug. GRDDS offer several advantages, including enhancing patient compliance by reducing dosing frequency, improving the efficacy of drugs with short half-lives, delivering medications to specific sites, providing sustained and controlled release in the stomach, prolonging drug residence at absorption sites, enhancing bioavailability in the gastrointestinal tract, and preventing dose dumping of medications. GRDDS are suitable for those drugs, which are absorbed from the stomach (e.g. albuterol), soluble at alkaline pH (e.g. ranitidine and metformin), poorly soluble at alkaline pH (e.g. furosemide and diazepam), and having a narrow window of absorption (e.g. riboflavin and levodopa).

Advantages Of Gastro Retentive Drug Delivery Systems [9]

- Enhanced bioavailability.
- Enhanced first-pass biotransformation.
- Sustained drug delivery/reduced frequency of dosing.
- Targeted therapy for local ailments in the upper GIT.
- Reduced fluctuations of drug concentration.
- Improved selectivity in receptor activation.
- Reduced counter-activity of the body.
- Extended time over critical (effective) concentration.
- Minimized adverse activity at the colon.
- Site specific drug delivery.

Disadvantages Of Gastro Retentive Drug Delivery Systems [9]

- The drugs that may irritate the stomach lining.
- The drugs are unstable in its acidic environment should not be formulated in gastro retentive systems.

Limitations Of Gastro Retentive Drug Delivery Systems [2]

- Requirement of high levels of fluids in stomach for the delivery system to float and work efficiently.
- Requires the presence of food to delay gastric emptying.
- Drugs having solubility or stability problems in the highly acidic gastric Environment or which are irritants to gastric mucosa cannot be formulated as GRDDS.
- In case of bioadhesive systems, the acidic environment, thick mucus as well as high turnover rate of mucous prevents bond formation at the mucous-polymer interface.
- For swellable systems, the dosage form maintaining a size is larger than the aperture of the resting pylorus for required time period.

Approaches of Gastro Retentive drug Delivery System:

A. High Density System (HDS)
B. Low Density System (Floating System)
C. Swellable System
D. Mucoadhesive system

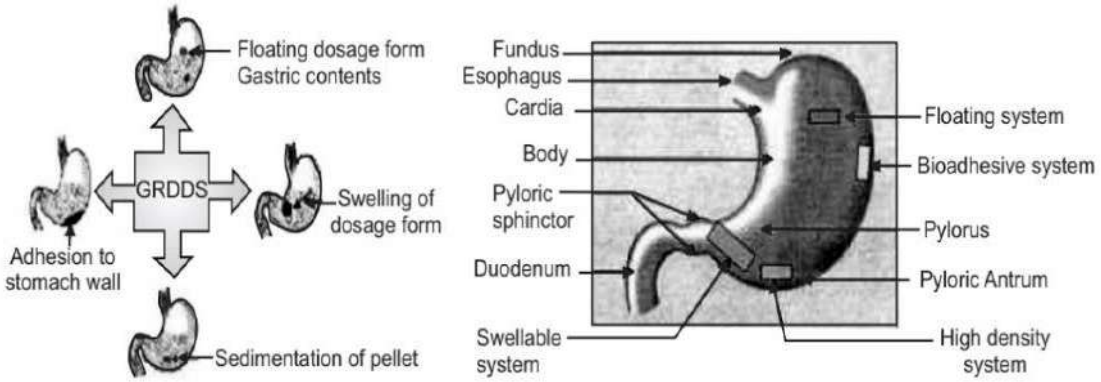

Figure no. 2 Approaches of Gastro Retentive drug Delivery System

LOW DENSITY SYSTEM (FLOATING SYSTEM)

Definition:

Floating Oral Drug Delivery System (FDDS) are retained in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. Floating drug delivery system (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, theresidual system is emptied from the stomach. This results in an increased GRT and a better control fluctuation in plasma drug concentration.

Advantages of FDDS:

- Enhanced bioavailability
- Sustained drug delivery/reduced frequency of dosing.
- Targeted therapy for local ailments in the upper GIT.
- Reduced fluctuations of drug concentration.
- Improved selectivity in receptor activeation.
- Reduced counter-activity of the body.
- Extended effective concentration.
- Minimized adverse activity at the colon.

Disadvantages of FDDS:

- The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the system

- The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the system.
- Not suitable for drugs that have solubility or stability problem in GIT.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.

DRUG PROFILE

ATORVASTATIN

Synonyms	Cardyl, Lipitor, Torvast, Xavatot, etc.
IUPSE	(3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid
Molecular Formula	C33H35FN2O5
Molar Mass	558.650 g·mol−1
Melting Point	176 °c
Boiling Point	722 °c
Appearance	White to off-white crystalline powder.
Solubility	Freely soluble in methanol; slightly soluble in ethanol; very slightly soluble in acetonitrile, distilled water

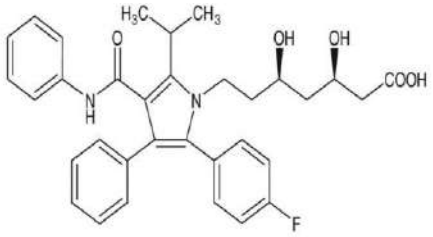

Fig.no. 3 Structure : Atorvastatin

Atorvastatin is used along with a proper diet to help lower “bad” cholesterol and fats (such as LDL, triglycerides) and raise good cholesterol (HDL) in the blood. It belongs to a group of drugs known as statins. Also used to prevent cardiovascular disease in those at high risk and to treat abnormal lipid levels. For the prevention of cardiovascular disease, statins are a first-line treatment. It works by reducing the amount of cholesterol made by the liver. Lowering bad cholesterol and triglycerides and raising good cholesterol decreases the risk of heart disease and helps prevent strokes and heart attacks.

MOA

Atorvastatin competitively inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. By preventing the conversion of HMG-CoA to mevalonate, statin medications Decrease cholesterol production in the liver.

MATERIALS AND METHODS

Material

Atorvastatin calcium was obtained from Morepen Laboratories Ltd., Sodium bicarbonate, HPMC, Talc, Lactose power and other ingredients.

Pre-formulation of sustained released tablet of Atorvastatin Calcium

All ingredients were collected and weighed accurately. Atorvastatin calcium, HPMC, Lactose power and sodium bicarbonate was shifted and passed through #40 mesh. And talc, Magnesium stearate was passed through #60 mesh. Then the major raw materials were mixed with the lubricant. Lubricated blend was Compressed using 9.5 mm flat oval shaped punches plain on both sides in 10 station compression machines.

RESULTS AND DISCUSSION

The aim of this study was to develop floating tablets containing Atorvastatin calcium. Controlled release formulations are designed to release the drug gradually over an extended duration. Atorvastatin calcium, being rapidly absorbed in acidic pH with high intestinal clearance, necessitates its formulation as a floating tablet to maintain optimal blood concentration levels. Tablets prepared using direct compression technique offer advantages over those made through wet granulation, including reduced time and energy consumption, thus lowering overall formulation costs. Additionally, the flexibility of hydrophilic polymer matrix systems makes them widely utilized in oral controlled drug delivery.

RESULT

Gastro Retentive Drug Delivery System of Atorvastatin calcium could be successfully formulated by direct compression technique, The study concluded that the Gastro Retentive Drug Delivery System containing Atorvastatin calcium, formulated with the higher viscosity grade HPMC K100M, effectively sustained drug release in the gastrointestinal tract (GIT). This approach holds promise as it enables the release of the necessary drug quantity into the body, thereby minimizing major side effects like rhabdomyolysis by regulating drug concentration in the blood. Moreover, the entire dose was released in an acidic medium, optimizing Atorvastatin absorption and potentially improving patient therapy outcomes.

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