GASTRORETENTIVE FLOATING MATRIX TABLETS OF ATAZANAVIR SULPHATE USING LOW DENSITY POLYMERS

A dissertation submitted to

THE TAMILNADU Dr.M.G.R MEDICAL UNIVERSITY

CHENNAI- 600 032.

In partial fulfillment of the requirements for the award of Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted
By

Reg No: 261211158

DEPARTMENT OF PHARMACEUTICS

EDAYATHANGUDY.G.S PILLAY COLLEGE OF PHARMACY

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Under the guidance of

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CERTIFICATE

This is to certify that the dissertation entitled **"Gastroretentive floating matrix tablets of atazanavir sulphate using low density polymers"** submitted by **S. Pugazhendan** (Reg No:261211158) in partial fulfillment for the award of degree of Master of Pharmacy to the Tamilnadu Dr. M.G.R Medical University, Chennai is an independent bonafide work of the candidate carried out under my guidance in the Department of Pharmaceutics, Edayathangudy.G.S Pillay College of Pharmacy during the academic year 2013-2014.

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GASTRORETENTIVE FLOATING MATRIX TABLETS OF ATAZANAVIR SULPHATE USING LOW DENSITY POLYMERS

ABSTRACT

The study was aimed at formulation and evaluation of Fast Disintegrating Tablets (FDTs). Using a taste masking polymer Eudragit E100, to mask the taste of a delivered drug i.e., Quetiapine Fumarate (QTF). Taste masking was done by solvent evaporation technique in absolute Ethanol as solvent system. Fast Disintegrating Tablets of QTF were prepared by using different echniques like Superdisintegrants addition method (Croscarmellose sodium (CCS), Sodium starch glycolate (SSG) and crospovidone (CP)), sublimation method (Camphor) and Effervescent formulation approach (sodiumbicarbonate+citrcacid). All the formulations were evaluated for flow properties, hardness, friability, content uniformity, wetting time, in vivo disintegration time (DT), release profiles. All the formulations showed satisfactory mechanical strength and other formulation parameters within the range. Dissolution parameters such as, Initial Dissolution Rate (IDR), Dissolution Efficiency (DE), Mean Dissolution Time (MDT) and Relative Dissolution Rate (RDR) were calculated. The optimized formula D5 prepared by using 10 % CP as a superdisintegrant and 12 % Camphor as subliming agent, which showed shortest DT (17 Sec) (Q10= 88%, WT= 37Sec). The drug polymer complex was subjected to FTIR studies to understand the degree of interaction between drug and polymer. The dissolution parameters such as IDR, DE, RDR for the optimized formulation exhibited 1.8 fold increase when compared to marketed product. It can be concluded that the orally fast disintegrating tablets of QTF with better biopharmaceutical properties than conventional marketed tablet obtained using formula D5.

ABBREVIATIONS

BP	=	British Pharmacopoeia
Conc.	=	Concentration
ºC	=	Degree Centigrade
F	=	Formulation
HCl	=	Hydrochloric acid
GRDDS	=	Gastroretentive Drug Delivery System
GIT	=	Gastro Intestinal Tract
GRT	=	Gastric Retention Time
HPMC	=	Hydroxy propyl methyl cellulose
h	=	Hour
min	=	Minute
mL	=	Milliliter
N	=	Normality
n	=	Diffusion coefficient
nm	=	Nanometer
rpm	=	Revolution per minute
SBC	=	Sodium bicarbonate
MCC	=	Micro Crystalline Cellulose
BLT	=	Buoyancy Lag Time

INTRODUCTION

The oral route is the predominant and most preferable route for drug delivery, but drug absorption is unsatisfactory and highly variable in the individuals despite excellent in vitro release patterns. The major problem is in physiological variability such as gastrointestinal transit as well as GRT; the later plays a dominating role in overall transit of the dosage forms. GRT of the oral controlled release system is always less the 12 h. (pawar et al., 2011,)

There are numerous drugs that demonstrate poor efficacy and bioavailability when administered via the oral route. Such drugs include those that a) act locally within the stomach (e.g. amoxicillin), b) are absorbed within the stomach or specific regions of the upper intestine (e.g. furosemide), c) are unstable in intestinal fluids (e.g. captopril) and d) are poorly soluble within the alkaline environment of the intestine (e.g. diazepam). A significant factors leading to the poor bioavailability of numerous drugs is due to their narrow absorption window (NAW), most commonly located in the upper region of the small intestine i.e. the duodenum and jejunum. These segments of the small intestine posses extensive drug absorptive properties and absorption of NAW drugs is limited due to the rapid transport of drug past these regions. Therefore this has led to researchers exploring the possibilities of extending the gastric residence time (GRT) of the drug and therefore indirectly prolonging the time drug is in contact with its absorption window for maximal site-specific absorption (Murphy et al.,2009).

One of the most feasible approaches for this in the gastrointestinal tract (GIT) is to control GRT using GRDF that will provide us with new and important therapeutic options. GRDF are designed on the basis of one of the several approaches like formulating low density dosage form that remain buoyant above the gastric fluid (FDDS) or high density dosage form that is retained at the bottom of the stomach, imparting bio-adhesion to the stomach mucosa, reducing motility of the GIT by

concomitant administration of drugs or pharmaceuticalexicipients, expanding the dosage form by swelling or unfolding to a large size which limits the emptying of the dosage form through the polymeric sphincter, utilizing ion–exchange resin which adheres to mucosa, or using a modified shape system (Pawar et al. 2011).

GASTROINTESTINAL TRACT PHYSIOLOGY

The intrinsic properties of the drug molecule and the target environment for delivery are the major determining factors in bioavailability of the drug. Factors such as pH, enzymes, nature and volume of secretions, residence time, and effective absorbing surface area of the site delivery play an important role in drug liberation and absorption.

The stomach is situated in the left upper part of the abdominal cavity immediately under the diaphragm. Its size varies according to the amount of distension: up to 1500 ml following a meal; after food has emptied, a collapsed state is obtained with resting volume of 25–50 ml.

The stomach is anatomically divided into three parts: fundus, body, and antrum (or pylorus). The proximal stomach, made up of fundus and body regions, serves as a reservoir for the ingested materials, while the distal region (antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying(Pawar et al. 2011). In stomach there are several types of cells that secrete up to 2–3 liters of gastric juice daily. For example, goblet cells secrete mucus, parietal cells secrete hydrochlororic acid, and chief cells secrete pepsinogen. The contraction forces of the stomach churn the chyme and mix it thoroughly with the gastric juice. The average length of the stomach is about 0.2 meter, and the apparent absorbing surface area is about 0.1 m2 (Talukder and Fassihi et al., 2004).

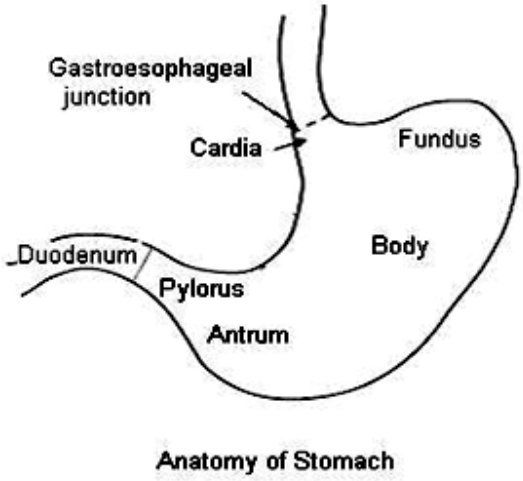


Figure 1. Anatomy of stomach

Gastric pH

The gastric pH is not constant rather it is influenced by various factors like diet, disease, presence of gases, fatty acids, and other fermentation products (Rubinstein).In addition, the gastric pH exhibits intra-as well as inter-subject variation. This variation in pH may significantly influence the performance of orally administered drugs. Radiotelemetry, a noninvasive device, has successfully been used to measure the gastrointestinal pH in human. It has been reported that the mean value of gastric pH in fasted healthy subjects is 1.1±0.15.(lui et al). On the contrary, the mean gastric pH in fed state in healthy males has been reported to be 3.6±0.4, [14] and the pH returns to basal level in about 2 to 4 hours. However, in fasted state, basal gastric secretion in women is slightly lower than that of in Men (charman et al.,1997).

Gastric pH may be influenced by age, pathological conditions and drugs. About 20% of the elderly people exhibit either diminished (hypochlorohydria) or no gastric acid secretion (achlorohydia) leading to basal pH value over 5.0.(varis et al.,1979) Pathological conditions such as pernicious anemia and AIDS may significantly reduce

gastric acid secretion leading to elevated gastric pH. In addition, drugs like H2 receptor antagonists and proton pump inhibitors significantly reduce gastric acid secretion.

The pH in the proximal duodenum may rise as high as 4 pH units from the stomach.(benn et al., 1971) This increase in pH is caused by the bicarbonate secreted by the pancreas and the duodenal mucosa that neutralize the acidic chyme peristalsed from the stomach. The mean pH value in fasted duodenum has been reported to be 5.8±0.3 in healthy subjects (Mojaverian et al., 1989) while the fasted small intestine has been observed to have a mean pH of 6.0±0.14. Passing from jejunum through the mid small intestine and ileum, pH rises from about 6.6 to_7.5.

Table 1. Salient features of upper gastrointestinal tract.

Section	Length (m)	Transit time (h)	pH	Microbil count[(a)]	absorbing surface area (m^2)	Absorption pathways[(b)]
Stomach	0.2	Variable	1–4	$<10^3$	0.1	P,C,A
small intestine	6–10	3±1	5–7.5	10^3–10^{10}	120–200	P,C,A,F.I,E,CM

Where,

a - Number of microorganisms per gram of gastrointestinal contents.

P, Passive diffusion;

C, Convective or aqueous channel transport;

A, Active transport;

F, Facilitated transport;

I, ion-pair transport;

E, entero-or pinocytocis;

CM, Caveolin mediated transport.

Gastrointestinal motility:

Two distinct patterns of gastrointestinal motility and secretion exist corresponding to the fasted and fed states. As a result the bioavailability of orally administered drugs will vary depending on the state of feeding. In the fasted state, it is characterized by an inter-digestive series of electrical event and cycle, both through the stomach and small intestine every 2–3 h. This activity is called the interdigestive myoelectric cycle or Migrating motor complex (MMC). MMC is often divided into four consecutive phases: basal (Phase I), pre-burst (Phase II), burst (Phase III), and Phase IV intervals.

• Phase I (basal phase) lasts from 40–60 min with rare contractions.

• Phase II (pre-burst phase) lasts for 40–60 min with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

• Phase III (burst phase) lasts for 4–6 min. It includes intense and regular contractions for short periods. Due to this contraction all the undigested material is swept out of the stomach down to the small intestine. This is also known as the housekeeper wave.

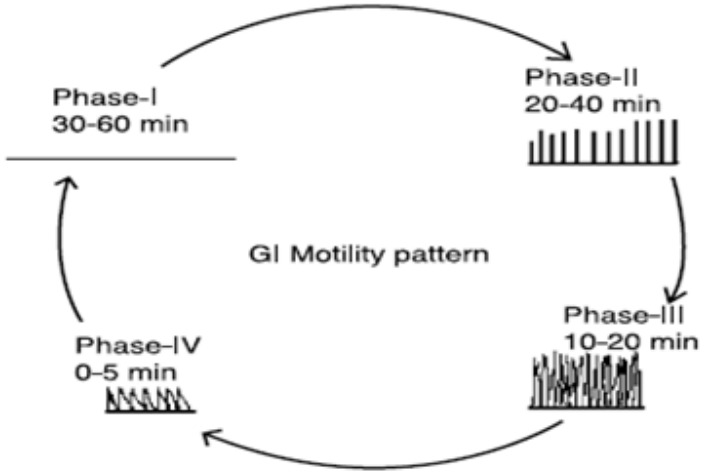


Figure 2. Schematic representation of interdigestive motility pattern.

• Phase IV lasts for 0–5 min and occurs between phases III and I for two consecutive cycles.

The motor activity in the fed state is induced 5–10 min after the ingestion of a meal and persists as long as food remains in the stomach. The larger the amount of food ingested, the longer the period of fed activity, with usual time spans of 2–6 h, and more typically 3–4 h, with phasic contractions similar to Phase II of MMC.

Emptying of dosage form from the stomach:

To achieve gastric retention, the dosage form must resist premature gastric emptying. For this, the dosage form must be able to withstand in the stomach against the force caused by peristaltic waves. Furthermore, once its purpose has been served the dosage form should be removed from the body with ease. Table 2 explains the GIT transit time of various dosage forms (Pawar et al., 2011).

Table 2. Transit times of various dosage forms across the GIT.

Transit time in (h)

Dosage form	stomach	intestine	total
Tablets	2.7±1.5	3.1±0.4	5.8
Pellets	1.2±1.3	3.4±14.	6
Capsules	0.8±1.2	3.2±0.8	4
Solution	0.3±0.07	4.1±0.5	4.4

Factors Affecting Gastric Retention:

a) Density: GRT is a function of dosage form buoyancy that is dependent on the density.

b) Size: Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared to those with a diameter of 9.9 mm.

c) Shape of dosage form: Tetrahedron and ring shaped unfolding expandable GRDF with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI), respectively, are reported to have better GRT ≈ 90–100% retention at 24 h compared with other shapes like continuous stick, planar disc, planar multilobe, and string.

Table 3.polymers used in FDDS.

d) Single or multiple unit formulation: Multiple unit formulations show a more predictable release profile and insignificant impairing of the performance due to the failure of units, allow co-administration of units with different release profiles or

containing incompatible substances, and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

e) Fed state: Under fasting conditions, the gastrointestinal motility is characterized by the periods of strong motor activity or the MMC that occur every 2–3 h. The MMC sweeps undigested material from the stomach and, if the timing of administration of formulation coincides with that of the MMC, then GRT of the unit may be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

f) Nature of meal: Feeding of indigestible polymers or fatty acid salts like cellulose, starch, polydextrose, and reffinose can change the motility pattern of the stomach by delaying the MMC, thus decreasing the gastric emptying rate and prolonging drug release.

g) Caloric content: GRT can be increased by 4–10 h with a meal that is high in proteins and fats.

h) Frequency of feed: The GRT can increase by over 400 min when successive meals are given compared with a single meal due to the low frequency of MMC.

i) Gender: It was observed that mean GRT in males (3.4 ± 0.6 h) is less than the female subjects (4.6 ± 1.2 h) of same age and race. Females emptied their stomach slowly in comparison to male candidates, regardless of their weight, height, and body surface area.

j) Age: Elderly people, especially those over 70, have a significantly longer GRT.

k) Posture: GRT can vary between supine and upright ambulatory states of the patient. For the floating systems it was reported that when subjects were kept in the upright ambulatory position the dosage form stayed continuously on gastric content in comparison to the supine state of the patients. Thus, in the upright position of the patients floating dosage forms protected against post-prandial emptying.

l) Concomitant drug administration: Clonidine, lithium, nicotine, progesterone, anti-cholinergics like atropine and propantheline, and opiates like codeine prolong GRT. On

the other hand, erythromycin and octreotide enhance the gastric emptying. (pawar et al.,2011)

MECHANISTIC ATTEMPTS AT GASTRORETENTION

Various polymeric drug delivery systems have been developed that attempt to exploit the anatomy and physiology of the GIT environment. These include buoyant systems, bioadhesive systems, high density systems, modified shape systems, gastric-emptying delaying devices and coadministration of gastric-emptying delaying drugs (Figure 3). Among these, buoyant drug delivery systems have been used most often.

HIGH DENSITY SYSTEMS

The density of gastric fluid is approximately 1.004g/cm3. Pellets with a density of between 2.4-2.8g/cm3 have shown to sink to the bottom of the stomach when a patient is in an upright position. The pellets become entrapped within the folds of the mucosa thereby withstanding the effects caused by peristalsis (Rouge et al., 1998). conducted a comparative study with an immediate release system, a high density system and a low density system. The results showed gastric residence times of 0.5, 1 and 2 hours respectively, indicating that the high density system did not demonstrate any significant extension of the gastric residence time.

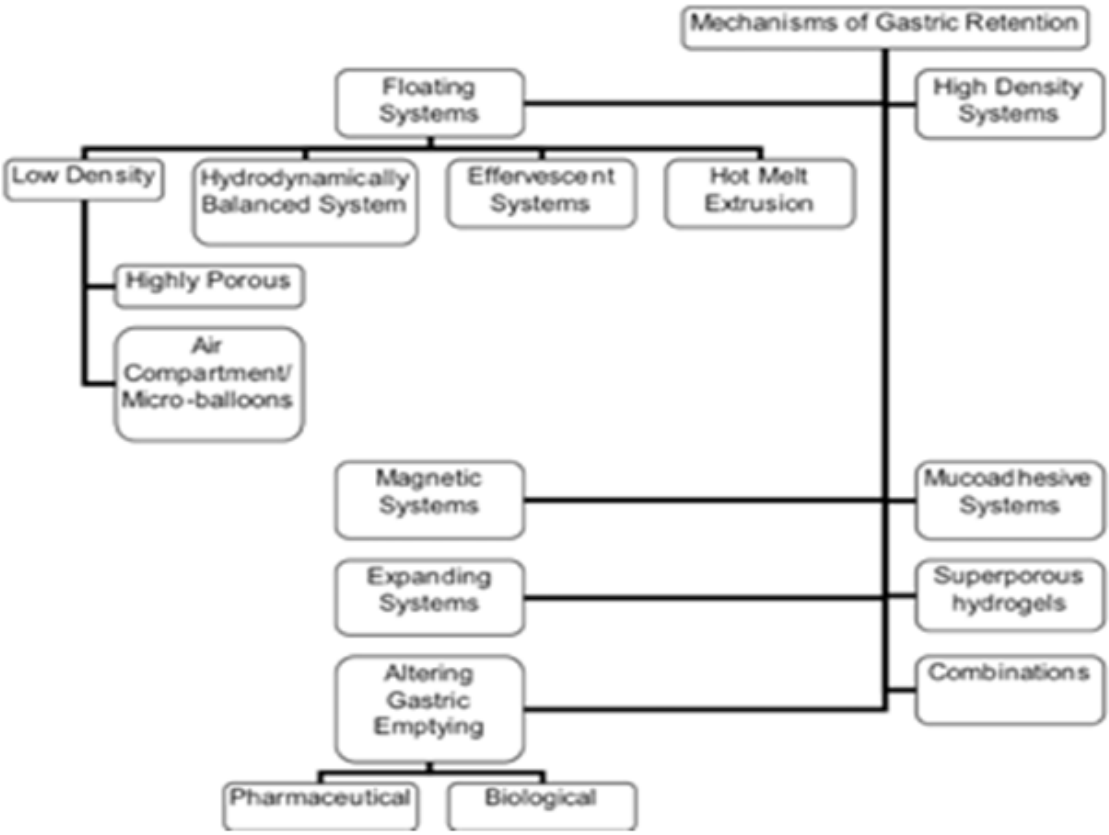


Figure 3. Schematic depicting the classification of gastric retentive systems.

Excipients which are commonly used in order to increase the density of drug delivery systems include: barium sulphate, zinc oxide, iron powder and titanium dioxide. Although high density drug delivery systems have not shown remarkable significance for the delivery of drugs in a human model, success has been illustrated with the administration of pellets with a density of 2.0g/cm3 in the bovine model.

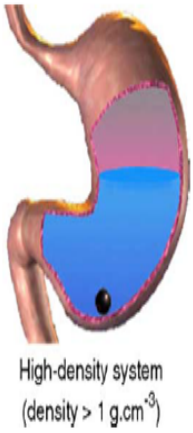


Figure 4: Schematic localization of high density system in the stomach.

FLOATING SYSTEMS

The concept of FDDS was described in literature as early as 1968 (D.W. Davis et al), when Davis disclosed a method for overcoming the difficulty experienced by some persons of gagging or choking while swallowing medicinal pills. The author suggested that such difficulty could be overcome by providing pills having a density of less than 1.0 g/ml so that pill will float on water surface. Since then development of FDDS. Several approaches have been used to develop an in ideal floating delivery system.

Based on the mechanism of buoyancy, two distinctly different technologies, i.e., noneffervescent andeffervescent systems have been utilized in the development of FDDS. The various approaches used in and their mechanisms of buoyancy are discussed in the following subsections.

1. **Noneffervescent FDDS**

The most commonly used excipients in noneffer-vescent FDDS are gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene. One of the approaches to the formulation of such floating dosage forms involves intimate

mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier (Hilton et al., 1992). The air trapped by the swollen polymer confers buoyancy to these dosage forms. In addition, the gel structure acts as a reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier.

Sheth and Tossounian (Sheth and Tossounian et al., 1978) postulated that when such dosage forms come in contact with an aqueous medium, the hydrocolloid starts to hydrate by first forming a gel at the surface of the dosage form. The resultant gel structure then controls the rate of diffusion of solvent-in and drug-out of the dosage form. As the exterior surface of the dosage form goes into solution, the gel layer is maintained by the immediate adjacent hydrocolloid layer becoming hydrated. As a result, the drug dissolves in and diffuses out with the diffusing solvent, creating a 'receding boundary.

The various types of this system are as:

A. Single Layer Floating Tablets:

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

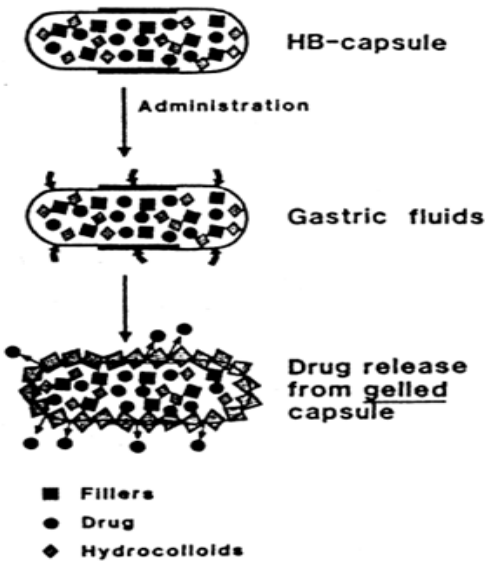


Figure 5. Working principle of the hydrodynamically balanced system (HBS).

B. Bi-layer Floating Tablets:

A bi-layer tablet contain two layer one immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach (Oth et al., 1992).

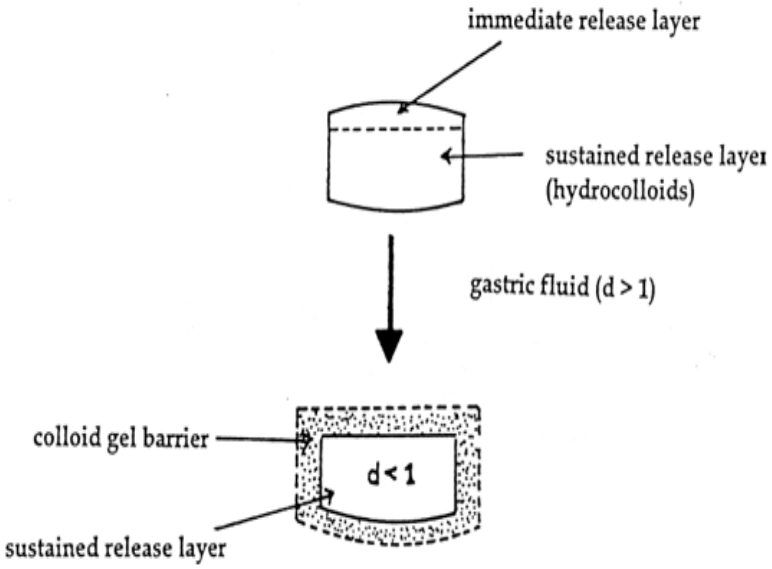


Figure 6. Intragastric floating bilayer tablet

C. Alginate Beads:

Multi-unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours (katayama et al., 1999).

D. Hollow Microspheres:

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 400C. The gas phase

generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours in vitro (Kawashima, 1992).

2) Effervescent FDDS

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature.

These effervescent systems further classified into two types.

1. Gas generating systems
2. Volatile Liquid/Vacuum Containing Systems.

1. Gas Generating Systems:

A. Tablets:

Floating bilayer tablets with controlled release for furosemide were developed by Ozdemir et al., 2000. The low solubility of the dru could be enhanced by using the kneading method, preparing a solid dispersion with β cyclodextrin mixed in a 1:1 ratio (Singh and Brahma, 2000). One layer contained the polymers HPMC K4M, HPMC K100M and CMC (for the control of the drug delivery) and the drug. The second layer contained theeffervescent mixture of sodium bicarbonate and citric acid. The in vitro floating studies revealed that the lesser the compression force the shorter is the time of onset of floating, i.e., when the tablets were compressed at 15 MPa, these could begin to float at 20 minutes whereas at a force of 32 MPa the time was prolonged to 45 minutes. Radiographic studies on 6 healthy male volunteers revealed that floating tablets were retained in stomach for 6 hours and further

blood analysis studies showed that bioavailability of these tablets was 1.8 times that of the conventional tablets. On measuring the volume of urine the peak diuretic effect seen in the conventional tablets was decreased and prolonged in the case of floating dosage form.Yang et al., 1999. Developed a swellable asymmetric triple-layer tablet with floating ability to prolong the gastric residence time of triple drug regimen (tetracycline, metronidazole, and clarithromycin) in Helicobacter pylori – associated peptic ulcers using hydroxypropylmethyl cellulose (HPMC) and polyethylene oxide (PEO) as the rate-controlling polymeric membrane excipients. The design of the delivery system was based on the swellable asymmetric triple-layer tablet approach. Hydroxypropylmethylcellulose and polyethylene oxide were the major rate- controlling polymeric excipients. Tetracycline and metronidazole were incorporated into the core layer of the triple-layer matrix for controlled delivery, while bismuth salt was included in one of the outer layer for instant release

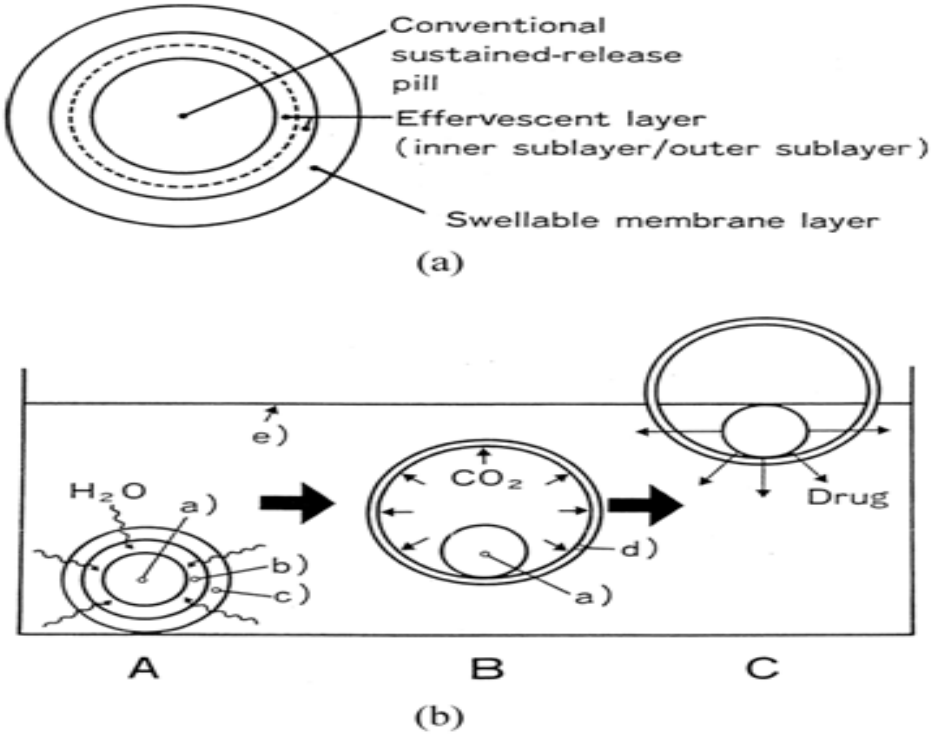


Figure 7.

(a) A multiple-unit oral floating dosage system.(b) stages of floating mechanism: (A) penetration of water; (B) generation of CO and floating; (C) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (370C).

The floatation was accomplished by incorporating a gas-generating layer consisting

of sodium bicarbonate: calcium carbonate (1:2 ratios) along with the polymers. The in vitro results revealed that the sustained delivery of tetracycline and metronidazole over 6 to 8 hours could be achieved while the tablet remained afloat. The floating feature aided in prolonging the gastric residence time of this system to maintain high localized concentration of tetracycline and metronidazole.

B. Floating capsules:

Floating capsules are prepared by filling with a mixture of sodium alginate and sodium bicarbonate. The systems were shown to float during in vitro tests as a result of the generation of CO2 that was trapped in the hydrating gel network on exposure to an acidic environment.

C. Multiple unit type floating pills:

The system consists of sustained release pills as ‘seeds’ surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO2 within the system.

D. Floating system with Ion-Exchange resins:

A floating system using ion exchange resin that was loaded with bicarbonate by mixing the beads with 1M sodium bicarbonate solution (Shweta Arora et al., 2005). The

loaded beads were then surrounded by a semipermeable membrane to avoid sudden loss of CO2. Upon coming in contact with gastric contents an exchange of chloride and bicarbonate ions took place that resulted in CO2 generation thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads. The in vivo behavior of the coated and uncoated beads was monitored using a single channel analyzing study in 12 healthy human volunteers by gamma radio scintigraphy. Studies showed that the gastric residence time was prolonged considerably (24 hours) compared with uncoated beads (1 to 3 hours).

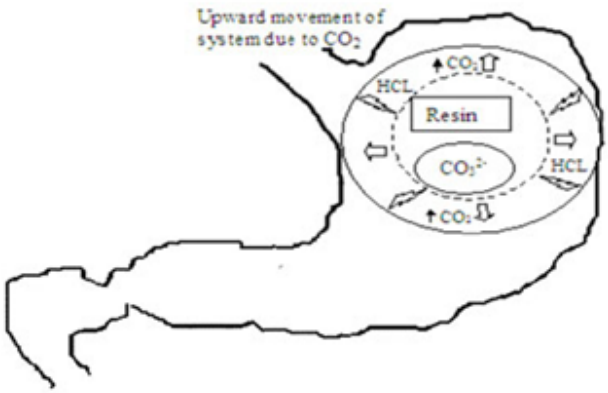


Figure 8. Pictorial presentation of working of effervescent floating drug delivery system based on ion exchange resin.

Highly Porous Systems:

The inclusion of low density polymeric carriers in a formulation may result in a matrix with a density of less than 1g/cm3, thereby becoming buoyant. There are numerous low density polymeric carriers available, including porous silicon dioxide, polypropylene foam, magnesium aluminometa silicate, porous calcium silicate [Jain, S.K et al] and polypropylene foam powder [Sher a et al]. These porous carriers possess certain characteristics which add to their attractiveness for use in drug delivery systems design, including a high surface area, tunable pore sizes with narrow distributions,

stable uniform porous structures and well-defined surface properties thus allowing for the absorption of drugs and drug release in a reproducible and predictable manner [Sher et al., 2007].

Hot-Melt Extrusion:

Hot melt extrusion is a method of continuous mixing and design of moldable materials. It is possible to produce tablets, microspheres, granules, transdermal and transmucosal delivery systems through this approach [Mididoddi et al., 2007]. Polymethacrylate polymers are the most commonly used polymers for this approach due to their thermoplastic properties. When selecting a polymer, it is important to consider the glass transition temperature, melt viscosity and stability under high temperature. Hot-melt extrusion is associated with numerous advantages. These advantages include fewer processing steps are involved, the absence of solvents, no need for compressionand the thorough mixing of formulation components [Mididoddi et al., 2007].

2. Volatile Liquid / Vacuum Containing Systems

A. Intra-gastric floating gastrointestinal drug delivery system:

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a micro-porous compartment.

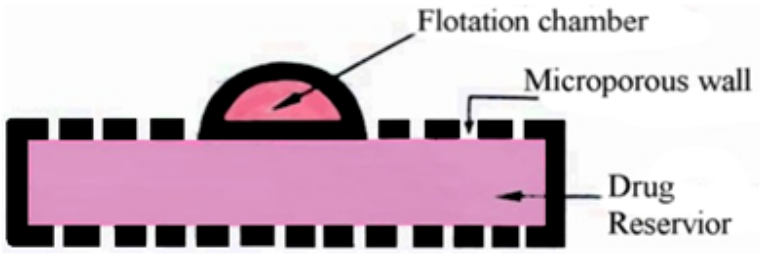


Figure 9. Intra gastric floating gastrointestinal drug delivery device.

B. Inflatable gastrointestinal delivery systems:

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach.

These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid.

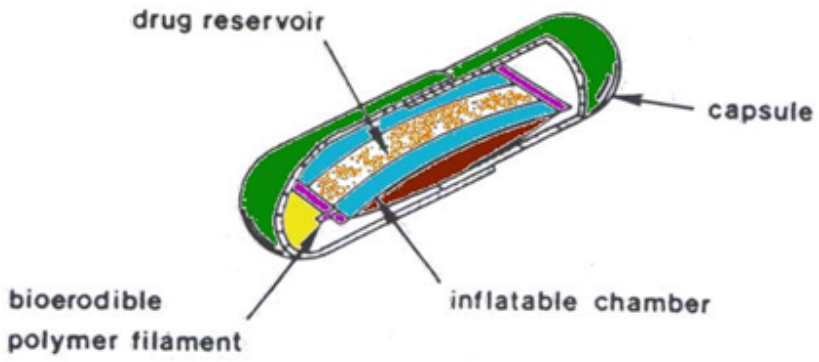


Figure 10. Inflatable gastrointestinal delivery system.

C. Intragastric osmotically controlled drug delivery system:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intra-gastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the

stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. The osmotic pressure thus created acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate drug release through the delivery orifice.

The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.

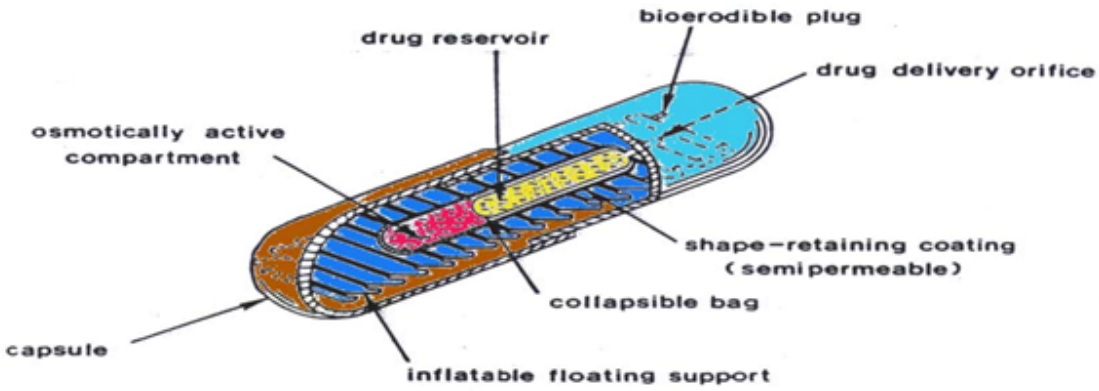


Figure 11. Intragastric osmotically controlled drug delivery system.

Bioadhesive drug delivery systems:

Bioadhesive polymers are usually macromolecular, hydrophilic gelling substances with numerous hydrogen-bond forming groups, such as carboxyl, hydroxyl, amide and sulfate groups (e.g., crosslinked polyacrylic acids, sodium carboxymethyl cellulose, sodium alginate and carrageenan). In addition to hydrogen bondings, covalent and electrostatic interactions are known to be of importance.

Although the exact mechanisms of bioadhesion are not yet completely understood, certain elements of the process are known to be of significance, such as

spreading the bioadhesive over the substrate to increase the surface area of contact; diffusion/penetration of polymer chains of the bioadhesive into the substrate; and domination of the attractive forces over the repulsive ones.

Several types of dosage forms have been proposed to allow prolonged residence within the stomach based on bioadhesive polymers. For example, (Akiyama and Nagahara et al., 1999) developed mucoadhesive microspheres consisting of a drug and Carbopol ® 934P being dispersed within a waxy matrix of polyglycerol esters of fatty acids.

These systems were reported to adhere to the stomach mucosa in rats and Mongolian gerbils, and to prolong the gastrointestinal residence of the drug after oral administration. The adherence can probably be explained by the hydration and swelling of the Carbopol in the microspheres on contact with water. Importantly, parts of the polymer remained within the microspheres, whereas the rest was 'anchored' within the mucus layer.

Jackson et al., 2000 observed extended gastric residence times of the positively charged ion-exchange resin colestyramine. In addition, this substance had the ability to coat the gastric mucosa uniformly. The adherent behaviour was considered to be responsible for the prolonged gastric residence. As the oppositely charged ion-exchange resin Amberlite IRP-69 did not possess the same characteristics, and as the coating of the colestyramine with ethylcellulose (EC) reduced the effects, the surface charge of the resin obviously plays a significant role in mucoadhesion and subsequent retention.

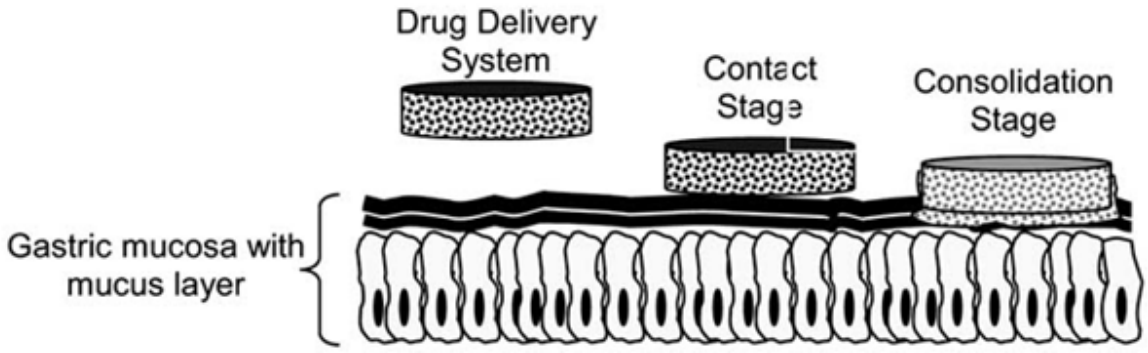


Figure 12. The two stages involved in muco-adhesion

Expanding Systems

Expanding drug delivery systems are retained within the stomach due to their size that is larger than the diameter of the pyloric sphincter, thereby inhibiting its transport into the intestine. When developing an expanding drug delivery system, there are a few criteria which should be met. These criteria include:

a) The delivery system should be small enough and convenient to swallow,

b) It should expand rapidly to an effective size so as to prevent premature evacuation from the stomach and

c) The delivery system should degrade in order to prevent a luminal blockage. Expansion of delivery systems is achieved by two mechanisms namely swelling and unfolding. Both these mechanisms result in an increase in size which inhibits the passage of thedelivery system through the pyloric sphincter into the intestine. Swelling occurs due to the absorption of water, usually by osmosis, whereas unfolding occurs due to the mechanical shape memory of thepharmaceutical carrier.

Several geometric shapes, such as tetrahedron, ring, cloverleaf, disk, string and pellet/sphere, which can be packed tightly into a gelatin capsule and unfold after dissolution of the capsule shell, have been patented by Caldwell et al..

These systems consist of at least one erodible polymer (e.g., hydroxypropyl cellulose, Eudragit®), one nonerodible polymer (e.g., polyolefins, polyamides, polyurethanes), and a drug that is dispersed within the polymer matrix. The importance of the physicalcharacteristics of this type of systems, such as size, shape and flexibility on the resulting gastric emptying was studied in beagle dogs (cargill et al., 1988).

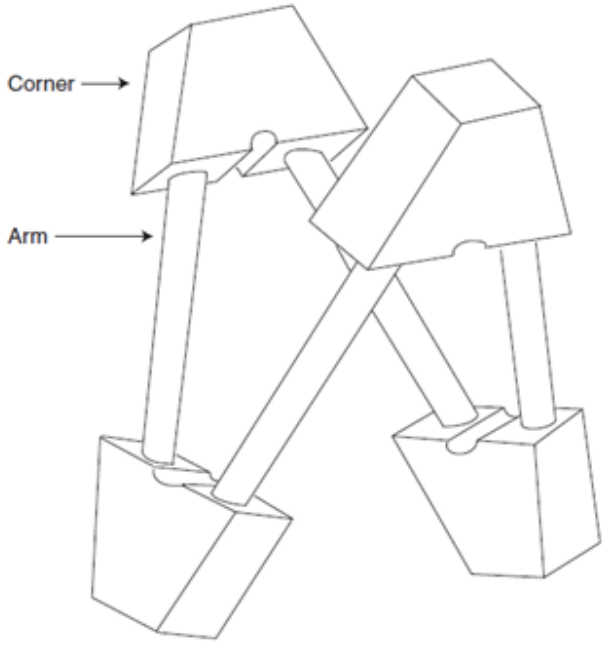


Figure 13. Tetrahedron-shaped drug delivery system formed by assembling two components: silastic corners and erodible arms.

Super porous Hydrogels:

The superporous hydrogel is an expanding system which is currently being researched by (Chen et al., 1999). It is due to the unique characteristics associated with these superporous hydrogels that they are classified as a new mechanism of gastric retention.

The superporous hydrogel, when dried, contains open pores which form capillary channels. It is due to these open pore channels within the dehydrated hydrogel, water is rapidly absorbed, allowing swelling to take place within a few minutes, up to a few hundred times its original volume.

The most unique aspect of the superporous hydrogel is that the average pore size is usually in the range of a few hundred micrometers. On hydration, water is taken up by capillary wetting as opposed to diffusion.

In order to increase the mechanical strength of the hydrogels and to withstand peristaltic pressure the superporous hydrogel composites were synthesized by adding croscarmellose sodium (Ac-Di- Sol®; FMC Biopolymer).

Superporous hydrogel can be divided into two groups that are differentiated by their swelling ratio and their mechanical stability. is a soft polymer which swells very quickly, but has poor mechanical stability, whereas a superporous hydrogel composite has a slower swelling rate, but is mechanically stable.

The composite is therefore utilized as a retentive drug delivery system. Through the incorporation of biodegradable crosslinkers, the superporous hydrogel degrades in the body thus preventing obstructions within the GIT.

In vivo animal studies demonstrate that the superporous hydrogel remained within the stomach for more than 24 hours after feeding. After approximately 30 hours there was evidence of fragmentation and the delivery system was cleared from the stomach (chen et al., 1999).

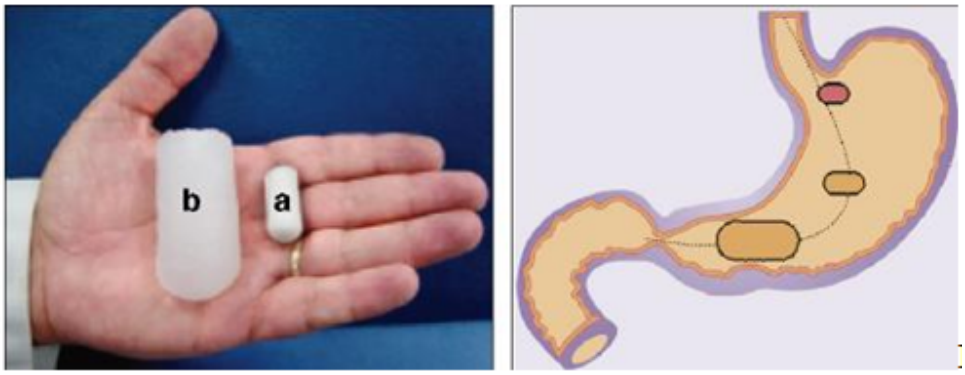


Figure 14.

On the left, superporous hydrogel in its dry (a) and water-swollen (b) state.On the right, schematic illustration of the transit of superporous hydrogel.

Magnetic system:

These systems appear as small gastroretentive capsules containing a magnetic material, whose elimination from the stomach is prevented by the interaction with a sufficiently strong magnet applied to the body surface in the region of the stomach. Despite numerous reports about successful tests, the real applicability of such systems is doubtful because the desired results can be achieved only provided that the magnet position is selected with very high precision. Probably, the development of new conveniently applied magnetic field sources will improve this concept.

Pharmaceutically or biologically altered gastric emptying:

Pharmaceutical:

A rather simple method to improve gastric retention involves the inclusion of either an excipient or pharmaceutical substance which possesses gastric motility retardation characteristics. (Stops et al., 2006) investigated the use of citric acid to prolong the gastric residence time of floating calcium alginate beads. It has been proposed that the intake of citric acid decreases duodenal pH to below 6, thereby halting gastric motility. A negative feedback system is thus activated to restore the pH, allowing re-commence. In vivo studies demonstrated that citric acid effectively delayed gastric emptying in the fasted state.

Biological:

Certain dietary components, such as fats, peptides and some amino acids posses the characteristic to prolong gastric emptying and intestinal transit. This phenomenon is known as the ileal brake, which is believed to be a feedback process in order to improve digestion of dietary components. Components from other biological species have been investigated for their ability to delay gastric and intestinal transit. It is known that

tapeworms decrease intestinal transit in hosts. For this reason (Kroening et al 2005). Investigated the effect of compounds excreted by tapeworms and concluded that cGMP is most likely responsible for this delay. It was therefore suggested that the addition of cGMP into pharmaceutical formulations may improve drug absorption.

Combinatory Mechanisms Employed For Gastro retention:

Researchers have recently been investigating the possible advantages of combining more than one mechanisms of gastroretention in order to achieve an additional enhancement and prolongation of gastric residence time. Visualization is a vital step in the development of novel gastroretentive drug delivery systems. Numerous approaches have been used in order to explicitly view the positioning and characteristics of gastroretentive systems in the GIT. The techniques described hereunder have been reported to produce superior results

AIM AND OBJECTIVE

OBJECTIVE

- Atazanavir sulphate is a highly selective inhibitor of HIV protease and the seventh protease inhibitor approved for HIV treatment. Atazanavir is available as 200-, 150- and 100-mg twice daily capsules. Oral bioavailability of the drug is 69% at fasting state. Its t1\2 range from 5-7. As the pH increases the solubility of atazanavir sulphate decreases, leading to poor absorption in the intestine. To improve the absorption of atzanavir sulphate in stomach and to reduce dosing frequency, atazanavir can be formulated into the floating drug delivery system.

- The present work is aimed at preparing gastric retentive floating matrix tablet formulations of Atazanavir sulphate using various low-density polymers. The composition of these formulations will be selected by using trial and error methods.

- To study the effect of various factors like drug polymer ratio, drug sodium bicarbonate ratio and polymer grade on the parameters like duration of buoyancy and release rate.

PLAN OF WORK

- To prepare gastric retentive floating tablets of Atazanavir sulphate using different low-density polymers.
- To select the formulation composition by using trial and error methods.
- To test all the physical evaluation parameters.
- To determine floating lag time and total buoyancy time of all the formulations
- To determine percentage swelling of the formulations.
- To construct the calibration curve for Atazanavir sulphate
- To study the release pattern of drug from these formulations using suitable in vitro model.

- Suggest a suitable mechanism of drug release.
- To select the best formulation based on the above studies.
- Determination of in vivo gastric retention time of Atazanavir sulphate floating tablets by using X-ray radiography.
- Determination of drug-excipients interaction of optimized formulation.

LITERATURE SURVEY

Liandong Hu et al., (2011) developed the dextromethorphan hydrobromide sustained-release tablets using floating technique to prolong the gastric residence time and compared their pharmacokinetic behavior with conventional sustained release tablets. DMB-SR floating tablets were prepared employing hydroxypropyl methylcellulose (HPMC) as hydrophilic gel material, sodium bicarbonate as gas-generating agent and hexadecanol as floating assistant agent The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, floating characteristics, in vitro release and in vivo bioavailability. The optimized tablets were prepared with HPMC K4M 25 mg, sodium bicarbonate 20mg and hexadecanol 18 mg. The prepared tablets could float within 3 min and maintain for more than 24 h. The data of physical parameters were all lie within the limits. Drug release at 12 h was more than 85%. The comparative pharmacokinetic study was performed by administration of the DMB-SR floating tablets and conventional DMB-SR tablets.

Gangadharappa et al., (2010)develop a controlled release floating drug delivery system (tablet) of verapamil hydrochloride. The floating matrix tablets were prepared by direct compression technique using a combination of hydroxyl propyl methyl cellulose (HPMC) and karaya gum as polymers and sodium bicarbonate as generating agent. The prepared floating tablets were evaluated for weight variation test, hardness, thickness, swelling index, in vitro floating capabilities, floating lag time, compatibility studies, and in vitro drug release. This swellable hydrophilic natural karaya gum was used to control the release of drug. The results showed that the optimized formulation F8 containing 23.3% of karaya gum (70 mg) and 13.3% of HPMC (40 mg) had good floating capability, shorter floating lag time, and sustained drug release for the period of 8 h.

Jiménez-Martínez et al., (2010) The sustained release of captopril from floating matrices has been studied varying the antioxidant load, the sodium bicarbonate proportion and the compaction pressure. Although in many cases the effect of compaction pressure remains hidden, actual results show that matrices compacted at 55 MPa have smaller density and float in the dissolution medium while those compacted at 165 MPa float only adding sodium bicarbonate. The increase of compaction pressure reduces the hydration volume and increases the time necessary to attain its maximum. These changes are attributed to lower matrix porosity and to the consequent diminution of water and drug transport. Increasing ascorbic acid proportions increase the matrix hydration volume and the drug released. The use of sodium ascorbate and the substitution of 15% polymer with sodium bicarbonate reduce the matrix hydration volume, shorten the matrix hydration process and increase the drug released. This is attributed to carbon dioxide bubbles that decrease the matrix coherence and expand the matrix volume, facilitating drug dissolution and only a limited further matrix expansion.

Bandari et al., (2010) investigated floating sustained-release matrices of metoprolol succinate using Gelucire 43/01 and Gelucire 44/14 by a melt-solidification technique. The in vitro and in vivo characteristics of the prepared matrices were evaluated. The in vitro drug release studies performed in 0.1 N HCl revealed a proportional increase in drug release pattern with increased concentration of Gelucire 44/14. The results indicate that Gelucire 43/01 is an appropriate carrier for the development of sustained-release floating drug delivery systems and Gelucire 44/14, a highly hydrophilic and lipophilic balance (HLB) excipient, acts as release enhancer in the formulations studied.

Bandari S & Yamsani R et al.,(2010)developed a biphasic gastroretentive drug delivery system of acyclovir consisted of loading dose tablet and floating multiple matrix tablets was prepared by direct compression process. The delivery system was designed by hydroxy propyl methyl cellulose as retardant polymer with an effervescent

component to get the desired buoyant and sustained release characteristics. All formulations compile within the limits. The FTIR studies did not show any evidence of an interaction between acyclovir and polymers. Dissolution studies revealed biphasic drug release pattern, with loading dose released within 30 min and floating multiple matrix tablets provided zero order sustained release profile for 12 h.

Kalpana Swain et al., (2009) investigated controlled release gastroretentive floating drug delivery system of theophylline was developed employing response surface methodology. A 32 randomized full factorial design was developed to study the effect of formulation variables like various viscosity grades and contents of hydroxypropyl methylcellulose (HPMC) and their interactions on response variables. The floating lag time for all nine experimental trial batches were less than 2 min and floatation time of more than 12 h. Theophylline release from the polymeric matrix system followed non-Fickian anomalous transport.

Boldhane & Kuchekar et al., (2009)aimed to develop novel gastroretentive (GR) drug delivery system, which releases the drug in the absorption window. As well to provide controlled release drug profile that can result patient compliance and therapeutic success. Floating tablets of MF was prepared using sodium alginate, and sodium carboxymethylcellulose as a gelling agent, and release modifier, respectively. Eudragit NE 30 D was used as sustained release polymer to control the initial burst release. Drug and excipients compatibility studies were monitored by thermal analysis using differential scanning calorimeter. 32 full factorial design was applied to optimize the formulation.

Gutiérrez & Sánchez et al., (2008) Theeffect of sodium bicarbonate (SB) on the swelling behavior a3nd the sustained release of floating systems was studied with varied proportions of this excipient and metronidazole. Two polymers with different hydration characteristics, Methocel K4M and Carbopol 971P NF, were used to formulate the matrices. Under in vitro dissolution conditions, the addition of SB to metronidazole sustained-release tablets modifies the matrix hydration volume, increasing at the

beginning, reaching a maximum, and then declining. Pure Carbopol matrices show a rapid hydration with a limited further effect of the SB and metronidazole loads. Methocel show a significant increase of the apparent hydration volume due to SB addition with no further notable change due to metronidazole load. Methocel matrices release the drug 10% to 15% faster than Carbopol matrices. SB increases the cumulative amount of drug released from Methocel but not that releasing from Carbopol.

Sandra Strübing et al., (2008)Floating Kollidon® SR matrix tablets containing Propranolol HCl were developed and characterized with respect to drug release characteristics and floating strength. Kollidon® SR was able to delay Propranolol HCl release efficiently. Drug release kinetics was evaluated using the Korsmeyer– Peppas model and found to be governed by Fickian diffusion. Tablet floating started immediately and continued for 24 h. Floating strength was related to Kollidon® SR level with improved floating characteristics for samples with a high polymer/drug ratio. The influence of the polymer content on swelling characteristics was found to be only marginal. Furthermore, the new method of benchtop MRI was introduced to study the water diffusion and swelling behaviour non-invasively and continuously.

Mastiholimath et al., (2008)delivered an anti-ulcer drug, ranitidine hydrochloride through a gastroretentive ethyl cellulosebased microparticulate system capable of floating on simulated gastric fluid for 12 h. Preparation of microparticles is done by solvent evaporation technique with modification by using an ethanol co-solvent system. The formulated microspheres were free flowing with good packability and encapsulation efficiencies were up to 96%.The data obtained thus suggests that a microparticulate floating delivery system can be successfully designed to give controlled drug delivery, improved oral bioavailability and many other desirable characteristics.

Lingam Meka et al., (2008)developed a gastro retentive floating drug delivery system with multiple-unit minitablets based on gas formation technique for furosemide. The system consists of core units (solid dispersion of furosemide:povidone and other excipients), prepared by direct compression process, which are coated with two

successive layers, one of which is an effervescent (sodium bicarbonate) layer and other one an outer polymeric layer of polymethacrylatesOnly the system using Eudragit RL30D and combination of them as polymeric layer could float within acceptable time. The time to float decreased as amount of the effervescent agent increased and, when the coating level of polymeric layer decreased. The drug release was controlled and linear with the square root of time. By increasing coating level of polymeric layer decreased the drug release. The in vivo gastric residence time was examined by radiograms and it was observed that the units remained in the stomach for about 6 h.

Gupta & Pathak et al., (2008)optimizeed floating microballoons of famotidine by the emulsion solvent diffusion technique using central composite design. Formulations F1–F15 were prepared using three independent variables (pH of medium, drug: Eudragit® S100 ratio and ethanol : dichloromethane ratio) and evaluated for dependent variables (shape, percentage buoyancy, and encapsulation). The optimized formulation F9 was fractionated and a polymer combination of (Eudragit® S100 : Eudragit® L100-55, 9.5:0.5) resulted in microballoons that exhibited zero order release (94.73%) with 84.20% buoyancy at the end of the eighth hour when studied in the mesh-designed modified USP type II apparatus.

Singh et al., (2007) developed of floating matrix tablets of metoclopramide hydrochloride (MHCl) for improving its bioavailability by prolonging gastric residence time. Floating matrix tablets (FMT) of MHCl were prepared using the polymers guar gum (GG), karaya gum (KG), HPMC E15 (HE) alone and in combination with HPMC K15M (HK) and gas generating agents such as calcium carbonate and citric acid. The fabricated tablets were evaluated for their physical characteristics such as hardness, drug content, buoyancy, swelling properties and in vitro release studies in 0.1N HCl.

Jaimini et al., (2007)prepared a gastroretentive drug delivery system of famotidine. Floating tablets of famotidine were prepared employing two different grades of methocel K100 and methocel K15M by effervescent technique. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, in vitro buoyancy and dissolution studies. The effect of citric acid on drug release profile

and floating properties was investigated. The prepared tablets exhibited satisfactory physico-chemical characteristics. All the prepared batches showed good in vitro buoyancy. The tablet swelled radially and axially during in vitro buoyancy studies. It was observed that the tablet remained buoyant for 6-10 hours. Decrease in the citric acid level increased the floating lag time but tablets floated for longer duration. A combination of sodium bicarbonate (130mg) and citric acid (10mg) was found to achieve optimum in vitro buoyancy. The tablets with methocel K100 were found to float for longer duration as compared with formulations containing methocel K15M. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.

Patel et al.,(2007)developed a gastroretentive drug delivery system of carbamazepine using HPMC, sodium bicarbonate, and EC as matrixing agent, gas-generating agent, and floating enhancer, respectively. A simplex lattice design was applied to investigate the combined effect of 3 formulation variables (ie, amount of HPMC (X 1), EC (X 2), and sodium bicarbonate (X 3). Results of multiple regression analysis indicated that low levels ofX 1 andX 2 and a high level ofX3 should be used to manufacture the tablet formulation with desired in vitro floating time and dissolution.

Cedillo & Ramírez et al.,(2006) In vitro dissolution of metronidazole from sustained release floating tablets was studied with varied proportions of sodium bicarbonate (SB) and Pharmatose DCL 11. Two polymers with different hydration characteristics, Methocel K4M and Carbopol 971P NF, were used to formulate the matrices. The variables studied include the matrices' release profile, hydration volume, and floating behavior. All Methocel matrices floated more than 8 h with SB proportions up to 24%, while Carbopol matrices floated more than 8 h with SB proportions only up to 12%.Methocel matrices showed greater hydration volumes and greater drug dissolution compared to Carbopol matrices. After adding increasing quantities of Pharmatose to matrices containing 12% SB, hydration volume decreased while dissolution increased.

Srivastava et al., (2005)developed floating matrix tablets of atenolol to prolong gastric residence time and increase drug bioavailability. Atenolol was chosen as a model drug because it is poorly absorbed from the lower gastrointestinal tract. The tablets were prepared by direct compression technique, using polymers such as hydroxypropyl methylcellulose (HPMC K15M, K4M), guargum (GG), and sodium carboxymethylcellulose (SCMC), alone or in combination, and other standard excipients. Tablets were evaluated for physical characteristics viz. hardness, swelling index, floating capacity, thickness, and weight variation. Further, tablets were evaluated for in vitro release characteristics for 8 hr. The effect of effervescent on buoyancy and drug release pattern was also studied.

Bhaskar Chauhan et al., (2005)prepared Single and multi-unit floating matrices of risedronate sodium using Gelucire1 43/01 by melt solidification and melt granulation technique, respectively. The controlled release floating matrices were evaluated for in vitro and in vivo floating ability and in vitro drug release. Effect of aging on Gelucire1 43/01 was evaluated by hot stage microscopy (HSM), scanning electron microscopy (SEM), differential scanning calorimetry (DSC), in vitro floating ability, and in vitro drug release. Multi-unit system obtained has shown initial burst release, which was suppressed in single unitsystem. Both single- as well as multi-unit systems showed increase in rate of drug release on aging due to changes in the properties of the Gelucire1 43/01.

Anant Paradkar et al., (2004) explored the application of Gelucire 43/01 for the design of multi-unit floating systems of a highly water-soluble drug diltiazem HCl. Diltiazem HCl-Gelucire 43/01 granules were prepared by melt granulation technique. The granules were evaluated for in vitro and in vivo floating ability, surface topography, and in vitro drug release. Aging effect on storage was evaluated using scanning electron microscopy, hot stage polarizing microscopy (HSPM), differential scanning calorimetry (DSC), and in vitro drug release. Granules were retained in stomach at least for 6 hours. Approximately 65% to 80% drug was released over 6 hours with initial fast release from the surface.

Moursy et al., (2003) *d*eveloped sustained release floating capsules of nicardipine HCl. For floating, hydrocolloids of high viscosity grades were used and to aid in buoyancy sodium bicarbonate was added to allow evolution of CO2. In vitro analysis of a commercially available 20-mg capsule of nicardipine HCl (MICARD) was performed for comparison. Results showed an increase in floating with increase in proportion of hydrocolloid. Inclusion of sodium bicarbonate increased buoyancy. The optimized sustained release floating capsule formulation was evaluated in vivo and compared with MICARD capsules using rabbits at a dose equivalent to a human dose of 40 mg. Drug duration after the administration of sustained release capsules significantly exceeded that of the MICARD capsules. In the latter case the drug was traced for 8 hours compared with 16 hours in former case.

Yie W. Chien et al., (2002) evaluated the contribution of formulation variables on the floating properties of a gastric floating drug delivery system (GFDDS) using a continuous floating monitoring system and statistical experimental design. Several formulation variables, such as different types of hydroxypropyl methylcellulose (HPMC), varying HPMC/Carbopol ratio, and addition of magnesium stearate, were evaluated using Taguchi design, and the effects of these variables were subjected to statistical analysis. It was found that the HPMC of higher viscosity grade generally exhibited a greater floating capacity, but the effect was not statistically significant. For polymers with the same viscosity, i.e., K4M and E4M, the degree of substitution of the function group did not show any significant contribution. A better floating behavior was achieved at higher HPMC/Carbopol ratio. Carbopol appeared to have a negative effect on the floating behavior of GFDDS.

Talwar et al., (2001) developed a once-daily formulation for oral administration of ciprofloxacin. The formulation was composed of 69.9% ciprofloxacin base, 0.34% sodium alginate, 1.03% xanthum gum, 13.7% sodium bicarbonate, and 12.1% cross-linked poly vinyl pyrrolidine. The viscolysing agent initially and the gel-forming polymer later formed a hydrated gel matrix that entrapped the gas, causing the tablet to

float and be retained in the stomach or upper part of the small intestine (spatial control). The hydrated gel matrix created a tortuous diffusion path for the drug, resulting in sustained release of the.

Sasa Baumgartner et al., (2000)development of the floating matrix tablets, which after oral administration are designed to prolong the gastric residence time, increase the drug bioavailability and diminish the side effects of irritating drugs. Tablets containing hydroxypropyl methylcellulose (HPMC), drug and different additives were compressed. The investigation shows that tablet composition and mechanical strength have the greatest influence on the floating properties and drug release. With the incorporation of a gas-generating agent together with microcrystalline cellulose, besides optimum floating (floating lag time, 30 s; duration of floating, >8 h), the drug content was also increased. The drug release from those tablets was sufficiently sustained (more than 8 h) and non-Fickian transport of the drug from tablets was confirmed.

Krogel and Bodmeier., (1999)developed and evaluated floating drug delivery system based on effervescent core and a polymeric coating. The mechanical properties (puncture strength and elongation) of acrylic (Eudragit RS, RL and NE) and cellulose (cellulose acetate, ethyl cellulose) polymer, which primarily determined the type of delivery system, a polymer coating with a high elongation value and high water low carbon dioxide permeability was selected (Eudragit RL/ acetyl tributyl citrate 20%w/w) in order to initiate the effervescent reaction and the floating process rapidly. HPMC was also added in the core to retard drug release. The composition and hardness of the tablet core and the composition and hardness of the coating could control the time of flotation.

Chen and Hao., (1998)studied the in vitro performance of floating sustained release capsule of verapamil. Capsules filled with mixture of verapamil, HPC and effervescent materials are proposed to provide floating and sustained release for over 10 hrs. The effects of weight filled in the capsule, amount of HPC and the addition of effervescent material on the dissolution kinetics were studied. They concluded that the

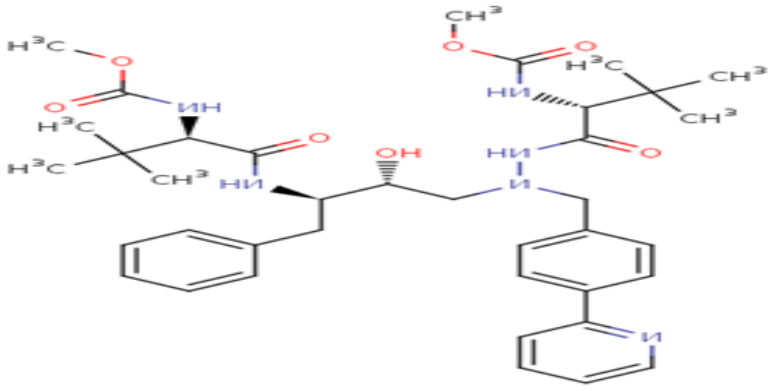
release of Verapamil from the capsule followed Higuchi release model. However, when effervescent material was added, the system showed a zero-order release.

Doelkar et al., (1996) have showed the effect of film forming polymers on floating behavior of coated floating formulations. Films plasticized with water-soluble plasticizers are more permeable for aqueous medium but should rupture earlier than films prepared with water insoluble plasticizers. Cellulose acetate, mechanically strong polymer, is too rigid and do not expand to large extent when comes in contact with dissolution medium. Ethyl polymers mechanically weak polymer, it is not flexible and easily ruptures upon CO2 formation; acrylic polymers are more suitable for the FDDS. The floatation time decreases with increasing Eudragit RL content in Eudragit RS/RL coating and was longer with coatings containing acetyl tributyl citrate (ATBC) as plasticizer than with coating containing triethyl citrate (TEC).

Jimenez et al., (1994)designed and tested the in vitro floating and bioadhesive property of Sotalol for oral application. Tablets were prepared by mixing the active ingredient with Sodiumcarboxymethylcellulose, hydroxy propylcellulose and a carbonate to generate gas. In vitro tests for release of drug, floatation and bioadhesion of the tablets were carried out. They concluded that this system showed good characteristics for controlled drug delivery system.

DRUG PROFILE

Non Proprietary Name:		Atazanavir Sulphate
Proprietary name	:	Latazanavir, Reyataz, Zrivada
Chemical name	:	methyl N-[(1S)-1-{N'-[(2S,3S)-2-hydroxy-3-[(2S)-2-(methoxycarbonyl)amino]-3,3-dimethylbutanamido]-4-phenylbutyl]-N'-{[4-(pyridin-2-yl) phenyl] methyl} hydrazinecarbonyl} -2,2dimethylpropyl] carbamate.
Empirical formula	:	$C_{38}H_{52}N_6O_7$
Molecular weight	:	704.856 g/mol
Structure	:	



Physicochemical Properties:

Description:

Atazanavir Sulphate White to pale yellow crystalline powder .

Solubility:

Freely soluble in water and methanol.

Pharmaceutical Profile:

Dosage Forms and dose: 100mg, 150mg, 200mg, 300mg capsules.

Pharmacopoeial status:

United States Pharmacopoeia

Analytical Profile:

Spectrophotometry: Spectrophotometric determination of Atazanavir Sulphate in methanol with the λmax at 301nm has been reported.

PHARMACOKINETIC PROFILE

Oral absorption: 60-68%.

Plasma half life: 5-7 hours.

Protein binding: 86 %

PHARMACOLOGICAL PROFILE

Therapeutical category: Anti HIV.

Mechanism of action: Atazanavir selectively inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells by binding to the active site of HIV-1 protease, thus preventing the formation of mature virions. Atazanavir is not active against HIV-2.

Therapeutic/clinical uses: Used in combination with other antiretroviral agents for the treatment of HIV-1 infection, as well as post exposure prophylaxis of HIV infection in individuals who have had occupational or nonoccupational exposure to potentially

infectious body fluids of a person known to be infected with HIV when that exposure represents a substantial risk for HIV transmission.

Adverse effects:

Bilirubin levels in the blood are normally asymptomatically raised with atazanavir. A single case of torsades de pointes attributable to atazanavir therapy has been described.

Contraindication:

Atazanavir should not be used with proton pump inhibitors, such as omeprazole (Prilosec), esomeprazole (Nexium), or rabeprazole (Aciphex). According to the FDA, "A 76% reduction in atazanavir area under the concentration-time curve (AUC) and a 78% reduction in atazanavir trough plasma concentration (Cmin) were observed when REYATAZ/ritonavir [a protease inhibitor, the same class as Atazanavir] 300/100 mg was co administered with omeprazole 40 mg." In other words, proton pump inhibitors reduce the effects of atazanavir.

HYDROXYPROPYLMETHYLCELLULOSE (HPMC) (SS)

Nomenclature

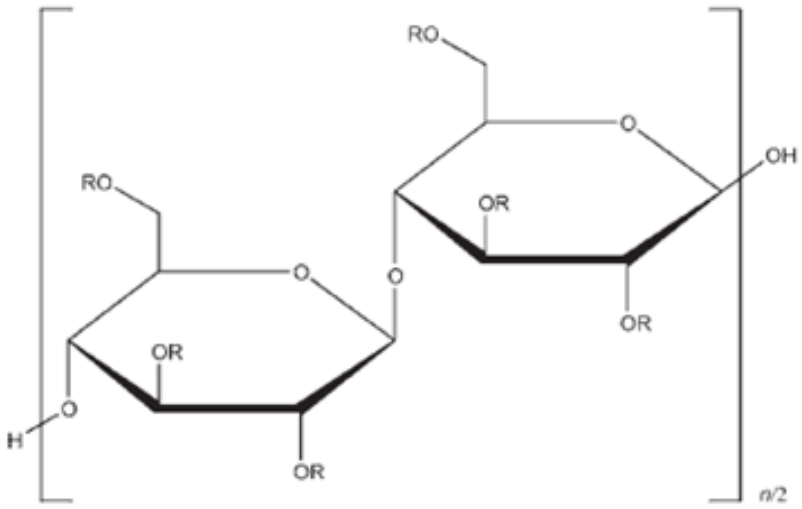
Non-proprietary names

- JP : Hydroxypropylmethylcellulose
- BP : Hypromellose
- Ph Eur : Methylhydroxypropylcellulosum
- USP : Hypromellose

Chemical Name: Cellulose hydroxypropyl methyl ether

Synonyms: Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; hypromellosum; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; MHPC; Pharmacoat; Tylopur; Tylose MO.

Structural Formula:



Where R is H, CH3, or CH3CH(OH)CH2

Physical and chemical properties:

* Molecular weight: 10,000 - 15, 00,000

* Color: White to creamy-white

* Nature: Fibrous or granular powder

* Odour: Odourless

* Taste: Tasteless

* Density: 0.3-1.3 g/ml

* Specific gravity:

1.26* Solubility: Soluble in cold water, practically insoluble in Chloroform, ethanol (95%) and ether but Soluble in mixture of ethanol and Dichloromethane.

* Viscosity: HPMC K100LV: 80-120 mPas

HPMC-K4M: 2663–4970

HPMC K15M: 14 000-16 000

HPMC K100M: 72,750–135,800

* Melting point:

Browns at 190-200 ºC, chars at 225-230 ºC, Glass transition temperature is 170-180ºC.

Functional Category

Coating agent, film-forming, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

Application

• In oral product HPMC is primarily used as tablet binder, in film coating and as an extended release tablet matrix. Concentration between 2-5% w/w may be used as a binder in either wet or dry granulation process. High viscosity grade may be used to retard the release of water-soluble drug from a matrix.

• HPMC is widely used in oral and topical pharmaceutical formulation.

• Concentration of 0.45-1% w/w may be added as a thickening agent to vehicle for eye drop and artificial tear solution.

• HPMC is used as an adhesive in plastic bandage and as a wetting agent for hard contact lenses. It is widely used in cosmetics and food products.

• In addition, HPMC is used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particle from coalescing or agglomerating thus, inhibiting the formation of sediments.

Stability and storage

It is stable although it is slightly hygroscopic. The bulk material should be stored in an airtight container in a cool and dry place. Increased in temperature reduces the viscosity of the solution.

Safety

It is generally regarded as a non-toxic and non-irritant material so it is widely used in many oral and topical pharmaceutical formulations. Excessive consumption of HPMC may have laxative effect.

SODIUM BICARBONATE

Nomenclature

Non-proprietary names

- JP: Sodium bicarbonate
- BP: Sodium bicarbonate
- Ph Eur : Natrii hydrogencarbonas
- USP: Sodium bicarbonate

Chemical Name: Carbonic acid monosodium salt

Molecular weight: 84.01

Structural Formula: NaHCO

Physical and chemical properties

Colour: White

Nature: Crystalline powder

Odour: Odourless

Taste: Saline/slight alkaline

Density: 0.869-2.173 g/cm3

Moisture content: less than 1%w/w

Solubility: Soluble in water, practically insoluble in ethanol (95%) and ether.

Osmolarity: 1.39% w/v aqueous solution is isoosmotic with serum.

Melting point: 270 ºC (with decomposition)

Functional category

Alkalizing agent, therapeutic agent.

Applications

- Used in pharmaceutical formulation as a source of carbon dioxide in effervescent tablets and granules.
- Used to produce or maintain an alkaline pH in a preparation, like solution of Erythromycin, Lidocaine, and Niacin etc.
- Used to produce a sodium salt of the active ingredient that has enhanced solubility.

- Used as a freeze-drying stabilizer and in toothpaste.
- Used as a gas forming agent in alginate raft system and in floating drug delivery system.

Stability and Storage

Sodium bicarbonate is stable in dry air but slowly decomposed in moist air and should therefore be store in well-closed container in a cool dry place.

Safety

Orally ingested sodium bicarbonate neutralizes gastric acid with the evolution of carbon dioxide and may cause stomach cramps and flatulence (Rowe et al., 2003).

LACTOSE ANHYDROUS:

Nonproprietary Names:

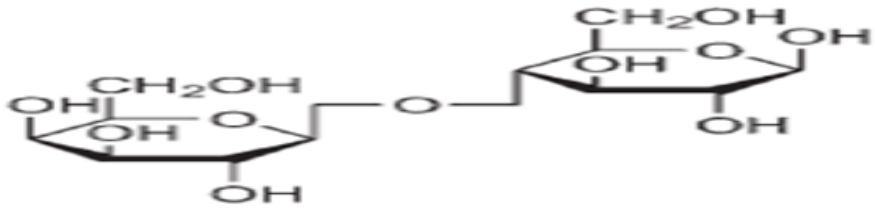
- BP: Anhydrous Lactose
- JP: Anhydrous Lactose
- PhEur: Lactose, Anhydrous
- USP-NF: Anhydrous Lactose

Synonyms: Anhydrous 60M; Anhydrous Direct Tableting (DT); Anhydrous DT High Velocity; Anhydrous Impalpable; Lactopress Anhydrous; Lactopress Anhydrous 250; lactosum anhydricum; lattosio; milk sugar; SuperTab 21AN; SuperTab 22AN; saccharum lactis.

Chemical Name: O-b-D-Galactopyranosyl-(1!4)-b-D-glucopyranose

Structural Formula:

Anhydrous α-lactose



Anhydrous β-lactose

Description:

Anhydrous lactose occurs as white to off-white crystalline particles or powder. Several different brands of anhydrous lactose are commercially available which contain anhydrous b-lactose and anhydrous a-lactose. Anhydrous lactose typically contains 70–80% anhydrous b-lactose and 20–30% anhydrous a-lactose.

Functional Category:

Directly compressible tablet excipient; dry powder inhaler carrier; lyophilization aid; tablet and capsule diluents; tablet and capsule filler.

Applications in Pharmaceutical Formulation or Technology:

Anhydrous lactose is widely used in direct compression tableting applications, and as a tablet and capsule filler and binder. Anhydrous lactose can be used with moisture-sensitive drugs due to its low moisture content. It may also be used in intravenous injections.

Stability and Storage Conditions:

Mold growth may occur under humid conditions (80% RH and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions. Lactose anhydrous should be stored in a well-closed container in a cool, dry place.

Safety:

Adverse reactions to lactose are largely due to lactose intolerance, which occurs in individuals with a deficiency of the intestinal enzyme lactase, and is associated with oral ingestion of amounts well over those found in solid dosage forms.

MAGNESIUM STEARATE:

Magnesium Stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin. It is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams. It is practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%). Magnesium Stearate is officially available in IP, BP, and USP.

TALC:

It is very fine, white to grayish -white, odorless, impalpable and unctuous crystalline powder. Powder is soft to touch and readily adhere to the skin and free from grittiness. It is used as anti caking agent, tablet and capsule diluents and tablet and capsule lubricant. It is insoluble in dilute acids, alkalis, organic solvents and water. It is stable and should be stored in a well-closed container, in a cool and dry place. Talc is officially available in IP, BP, and USP.

METHODOLOGY

Standard graph of Atazanavir sulphate:

Principle:

The calibration curve is based on the spectrophotometry. The maximum absorption was observed at 301nm. It obeyed Beer's law in the concentration range of 5-40µg/ml.

Method:

Standard stock solution:

The stock solutions was freshly prepared by dissolving 100mg of atazanavir sulphate in a 100ml volumetric flask and then make up the solution upto the mark using 0.1N HCl for obtaining the solution of strength 1000 µg/mL (stock I). 10ml of this solution is diluted to 100ml with 0.1N HCl to obtain a solution of strength 100 µg/mL (stock II). From this secondary stock required concentrations 5,10,15,20,25,30,35 and 40µg/mL was prepared. The absorbance was measured at 301 nm using a UV spectrophotometer (Systronic, Ahmedabad, India). Standard calibration curve values were shown in Table (7).

Preparation of Atazanavir sulphate floating matrix tablets:

Tablets containing Atazanavir sulphate were prepared by direct compression method. The respective powders drug, polymers(HPMC K4M, HPMC K 15M, HPMC K100M), sodium bicarbonate(20%), lactose were blended thoroughly with mortar and pestle. The powder blend was then lubricated with magnesium stearate and talc mixed for about 3 minutes. The required amount of the blend was weighed and finally this mixture was compressed on a 16-station rotary tablet machine (Cadmach, Ahmedabad, India) using a 10-mm standard flat-face punches.

Table 5. Formula for Preparing Floating Matrix Tablets of Atazanavir sulphate:

S.No	Formulation	Atazanavir sulphate	HPMC K4M	HPMC K15M	HPMC K100 M	SBC	Lactose	Talc	Mg Stearate
1	F1	150	52.5			70	70.5	3.5	3.5
2	F2	150	42			70	81	3.5	3.5
3	F3	150	28			70	95	3.5	3.5
4	F4	150	28			80	85	3.5	3.5
5	F5	150	28			90	75	3.5	3.5
6	F6	150	21			70	102	3.5	3.5
7	F7	150	21			80	92	3.5	3.5
8	F8	150	21			90	82	3.5	3.5
9	F9	150	14			70	109	3.5	3.5
10	F10	150		52.5		70	70.5	3.5	3.5
11	F11	150		42		70	81	3.5	3.5
12	F12	150		28		70	95	3.5	3.5
13	F13	150		21		70	102	3.5	3.5
14	F14	150		14		70	109	3.5	3.5
15	F15	150			42	70	81	3.5	3.5
16	F16	150			28	70	95	3.5	3.5
17	F17	150			21	70	102	3.5	3.5
18	F18	150			14	70	109	3.5	3.5

Where,

Drug= Atazanavir sulphate;

HPMC= Hydroxypropylmethylcellulose;

SBC=sodium bicarbonate;

MCC= Microcrystalline cellulose.

Lactose and MCC was used as filler in formulations F1 to F19.

All the numerical values were expressed in mg.

EVALUATION OF TABLETS:

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations. Following parameters were evaluated.

Tablet thickness:

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using vernier calipers. The average thickness and standard deviation were reported.

Weight variation:

Twenty (20) tablets from each batch were individually weighed in grams (gm) on an analytical balance. The average weight and standard deviation were calculated and the results were expressed as compliance or non-compliance of set limits.

Average weight (mg)	% Deviation allowed
130 or less	10
130-323	7.5
More than 324	5

Table 6.Weight variation tolerance

Hardness of the tablets:

Ten tablets were measured in the hardness examination. Tablet hardness was measured using a Monsanto hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kg/cm2 and the average hardness and standard deviation was reported.

Friability of the tablets:

Twenty tablets of the formulation were weighed and measured in a Roche type friabilator. The tablets were rotated at 25rpm for 4min, and the samples were then reweighed. The percentage friability was calculated using the equation.

$$F\ \% = (W1-W2)/W1 \times 100$$

F% represents the percentage weight loss, and W1 and W2 are the initial and final tablets weights, respectively.

Content uniformity:

Ten tablets were weighed and triturated to get fine powder. Weight equivalent to 10 mg of Atazanavir sulphate was dissolved in 10 ml of 0.1 N HCl and agitated for 15 min, the volume was adjusted to 100 ml using 0.1 N HCl with continuous agitation for 5min. The solution was filtered and suitable dilutions were prepared with 0.1 N HCl. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 301nm by using UV-Visible spectrophotometer.

The floating lag time and the total floating time:

This test was characterized by floating lag time and total floating time. The test was performed using USP XXIII type II paddle apparatus using 900 ml of 0.1 N HCl at paddle rotation of 50 rpm at 37 ± 0.5o C. The time required for tablet to rise to surface of dissolution medium and duration of time the tablet constantly float on dissolution medium was noted as floating lag time and total floating time

Water uptake studies:

The swelling behavior of dosage unit can be measured either by studying its dimensional changes, weight gain or water uptake. The water uptake study of the dosage form was conducted by using USP dissolutionapparatus-II in a 900ml of distilled water which was maintained at 37o + 0.5oc, rotated at 50 rpm. At selectedregular intervals the tablet was withdrawn and weighed. Percentage swelling of the tablet was expressed aspercentage water uptake (%WU) (Chavanpatil et al.,2006).

$$\%\text{Water Uptake} = (Wt - Wo) * 100 / Wo$$

Where,

Wt - is the weight of the swollen tablet and

Wo - is the initial weight of the tablet.

Drug–excipients interaction studies:

In order to evaluate the integrity and compatibility of the drug in the formulation, drug–excipient interaction studies were performed. The infrared spectra of pure drug, physical mixture of drug and excipients, polymer and formulation were recorded between 4000 to 400 cm-1on FTIR. The IR spectra for the test samples were obtained using KBr disk method using an FTIR spectrometer.

Dissolution Study of tablets:

Apparatus: Dissolution test apparatus (USP XXIII)

Method: USP type 2 apparatus (paddle method)

Dissolution medium: 0.1N HCl

Volume: 900 ml

Temperature: 37 + 0.5 ºC

Speed: 50 rpm

The tablet was placed inside the dissolution vessel. 5ml of sample were withdrawn at time intervals of 0.5, 1, 2, 3, 4, 6, 8, 10 and 12h. The volume of dissolution fluid adjusted to 900 ml by replacing 5ml of dissolution medium after each

sampling. The release studies were conducted with 3 tablets, & the mean values were plotted versus time. Each sample was analyzed at 301 nm using double beam UV and Visible Spectrophotometer against reagent blank.

Thedrug concentration was calculated using standard calibration curve.

Mechanism of drug release:

The different mathematical models may be applied for describing the kinetics of the drug release process from tablets; the most suited being the one which best fits to the experimental results.

The kinetics of Atazanavir sulphate release from tablets formulations were determined by finding the best fit of the release data to zero order, first order, matrix, Hixson-Crowell, Higuchi, and Korsmeyer-Peppas plots. Zero order release rate kinetics. To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$F = Ko.t$$

Where 'F' is the drug release,

'K' is the release rate constant and

't' is the release time.

The plot of % drug release versus time is linear. First order release rate kinetics. The release rate data are fitted to the following equation

$$Log (100-F) = kt$$

A plot of log % drug release versus time is linear.

Higuchi release model:

According to this model, drug release was described as a square root of time-dependent diffusion process based on Fick's law.

$$Qt = KH\ t1/2$$

where KH is Higuchi's rate constant, and Qt is the amount of drug released at time t. If a plot of square root of time vs cumulative amount of drug released yields a straight

line, then the particular dosage form is considered to follow Higuchi kinetics of drug release

Korsmeyer and Peppas release model:

Under some experimental situations the release mechanism deviates from the Fick's equation, following an anomalous behavior (Non-Fickian release). In these cases a more generic equation can be used. Korsmeyer et al. (23) developed a simple, semi-empirical, relating exponentially the drug release to the lapsed time.

$$Qt / Q\infty = K.tn$$

Where, $Qt / Q\infty$ is the fraction of drug released,

'K' is the release constant,

't' is the release time,

'n' is diffusion exponent if n is equal to 0.89, the release is zero order. If n is equal to 0.45 the release is best explained by Fickian diffusion, and if $0.45 < n < 0.89$ then the release is through anomalous diffusion or nonfickian diffusion (Swellable & Cylindrical Matrix).In this model, a plot of log $(Qt/Q\infty)$ versus log (time) is linear.

In vivo confirmation of buoyancy by using radiographic studies:

For this study the tablets were prepared by replacing half of the amount of drug with barium sulfate. After overnight fasting of three healthy volunteers they were fed with low calorie food and allowed to take water after these tablets were administered orally. Radiographs were obtained at 0.5, 1, 2, 3, 4 and 6 h. Over these periods volunteers were allowed to take water.

RESULTS AND DISCUSSION

STANDARD GRAPH

Table 7. Standard Curve values of Atazanavir sulphate at 301nm

Concentration	Absorbance
0	0
5	0.096
10	0.178
15	0.247
20	0.314
25	0.384
30	0.443
35	0.514
40	0.58

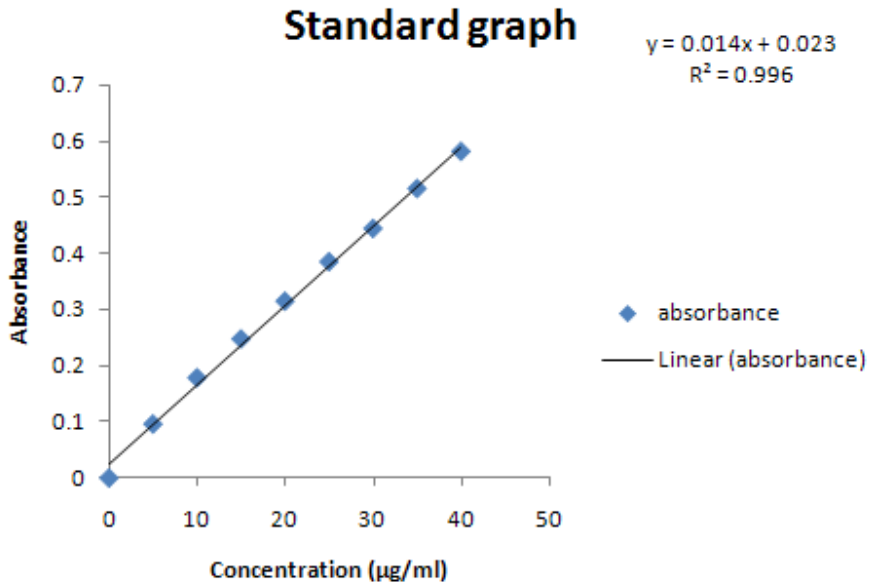


Figure 15. Standard Curve values of Atazanavir sulphate at 301nm

The study started with the construction of standard calibration curve of Atazanavir sulphate.The l_{max} of Atazanavir sulphate in 0.1N HCl was scanned and found to have the maximum absorbance at 301 nm. Standard graph of Atazanavir sulphate in 0.1N HCl was plotted by taking concentration ranging from 5 to 40 µg/mL and a good correlation was obtained with R^2 value of 0.996.

The fabricated matrix tablets of Atazanavir sulphate were evaluated for their physical characteristics such as weight variation, hardness, thickness, friability, drug content, buoyancy. The possibility of drug excipients interaction was determined with the help of and FTIR.

Table 8. Physical evaluation parameters

Formulacode	Weight variation(mg)	Hardness kg/cm2	Thickness (mm)	Friability (%)	Lag time (sec)	Total floating time (h)	Drug Content (%)
F1	347±2.3	4±0.5	3.21±0.08	0.26	118	>12	97.32±2.3
F2	351±3.8	4±0.5	3.23±0.06	0.23	148	>12	98.56±2.0
F3	356±4.5	4±0.3	3.21±0.06	0.48	290	>12	98.21±1.8
F4	351±8.3	4±0.5	3.22±0.09	0.51	85	>12	95.91±1.5
F5	345±5.3	4±0.2	3.26±0.08	0.22	54	6	97.75±2.3
F6	349±2.3	4±0.5	3.21±0.05	0.41	>300	6	96.25±1.8
F7	353±5.5	4±0.5	3.24±0.05	0.35	139	6	97.48±2.8
F8	344±5.6	4±0.2	3.28±0.02	0.38	103	4	97.69±2.4
F9	348±3.3	4±0.5	3.23±0.02	0.41	-	-	97.35±1.7
F10	346±6.2	4±0.3	3.21±0.16	0.29	98	>12	96.55±2.4

F11	351±4.3	4±0.5	3.28±0.05	0.38	103	>12	94.48±1.8
F12	349±2.3	4±0.4	3.19±0.09	0.41	112	>12	95.42±.09
F13	345±2.9	4±0.5	3.29±0.05	0.52	169	>12	95.99±1.3
F14	348±8.3	4±0.5	3.26±0.02	0.34	-	-	98.91±2.8
F15	353±3.8	4±0.4	3.23±0.02	0.45	52	>12	98.46±3.2
F16	346±4.9	4±0.3	3.27±0.02	0.25	67	>12	97.41±2.1
F17	349±8.3	4±0.1	3.23±0.02	0.28	79	>12	97.97±2.6
F18	347±6.33	4±0.7	3.28±0.02	0.38	>200	6	98.91±2.8

Weight variation data of the prepared tablets indicated no significant difference in the weight of individualtablet from the average value. The weight variations of the tablets were within the permissible limits of 5%, as specified for tablet weighing more than 324mg (Table 8). Weight of the tablet was fixed at 350 mg and the weight variation for every batch was tested and found within the acceptance limits

Hardness of the tablet was fixed 4 kg/cm^2 and was maintained for all the batches in order to minimize the effect of hardness on the drug release because, the effect of polymer concentration is the only area of interest.

Tablet thickness was also used to assess the quality of tablets. Under uniform conditions of manufacture, the total weight of tablet and thickness were linearly related. The thickness of floating tablets ranged from 3.19 to 3.29 mm and linearly correlated with the weight of the tablets (Table 8). Friability test of all the formulations was found satisfactory showing enough resistance to the mechanical shock and abrasion. Drug content uniformity in all formulations was calculated and the percent of active ingredient ranged from 95-98% (Table 8).

Floating capacity of fabricated tablets was determined in 0.1N HCl, and the results are presented in Table 8. Sodium bicarbonate was added as a gas-generating agent. TheCO_2 generated by effervescent gets entrapped in the gel layer and helps the tablets become buoyant in less time. However, incorporation of larger amounts of effervescent may cause quicker depletion of tablet matrices (Deshpande et al., 1996; Hwang et al., 1998) with an expected decrease in floating duration.

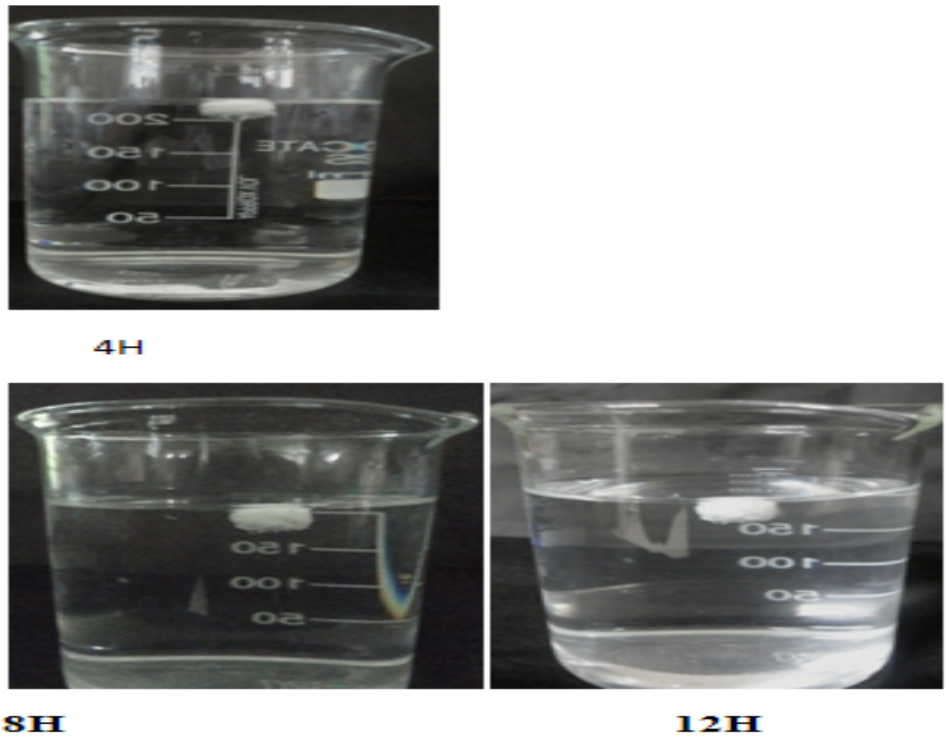


Figure 16.*In vitro*buoyancy study of Atazanavir sulphate floating tablets

All the batches showed good *in vitro* buoyancy. The results of the *invitro* buoyancy study of atazanavir sulphate tablets are shown in Figure 19. The figure clearly indicates the floating lag time (2 min) of the atazanavir sulphate tablet and swelling tendency of the formulation.Hydroxypropylmethylcellulose (HPMC) K4M, HPMC K15M, K100M was evaluated varying the sodium bicarbonate portion 70,80,90mg per tablet.When the concentration of sodium bicarbonate was 70 mg/tablet, the tablets could not float immediately. When amount of sodium bicarbonate was increased above 90 mg, the tablets could not retain its physical integrity for more than 6h.Finally, lag time was observed less than 2 min for all the formulations and then optimizing the sodium bicarbonate portion at 80mg per tablet(22.8%w/w) to the total tablet weight.

The results of percentage swelling obtained from the water uptake studies of the formulations containing HPMC K4M were shown in table 9 and 10. The formulations with HPMC K4M , HPMC K15M and HPMC K100M showed the swelling and tablet

integrity (Figure 16-18). Maximum swelling was observed for formulations with HPMC K4M, HPMC K 15M and HPMC K100M at the end of 6h, then after wards no increase in the water uptake was observed. The formulation F1 containing K4M (15 %w/w that of tablet weight) shows the higher swelling compared to that of the formulations containing K15M (12.5% w/w that of total tablet weight).

As HPMC K15M and HPMC K100M are high viscosity polymers there is an increase in water uptake with less percent of polymer in comparison with same ratio. The swelling index of the tablets increases with an increase in the polymer viscosity grades as shown in figure 17to 19.

Table 9. Percent swelling of formulations with HPMC K4M

Time(H)	F1	F2	F3	F4	F5
1	16.97±0.30	14.05±0.69	14.87±0.94	13.87±0.28	13.62±0.86
2	22.47±0.02	21.25±0.38	22.73±0.92	25.01±0.10	23.54±0.31
3	48.34±0.31	47.60±0.66	35.68±0.53	38.21±0.33	35.27±0.15
4	69.19±0.66	60.67±0.82	55.39±0.35	50.08±0.66	53.13±0.35
6	80.83±0.33	74.51±0.33	67.33±0.71	69.86±0.66	60.32±1.18
8	75.59±0.66	71.97±0.98	64.69±0.53	66.87±0.98	21.91±0.15
10	71.20±0.66	71.17±1.02	63.93±0.88	65.28±0.50	
12	70.99±0.82	66.78±0.33	57.29±0.53	59.94±0.83	

Data represents mean ± SD (n=3)

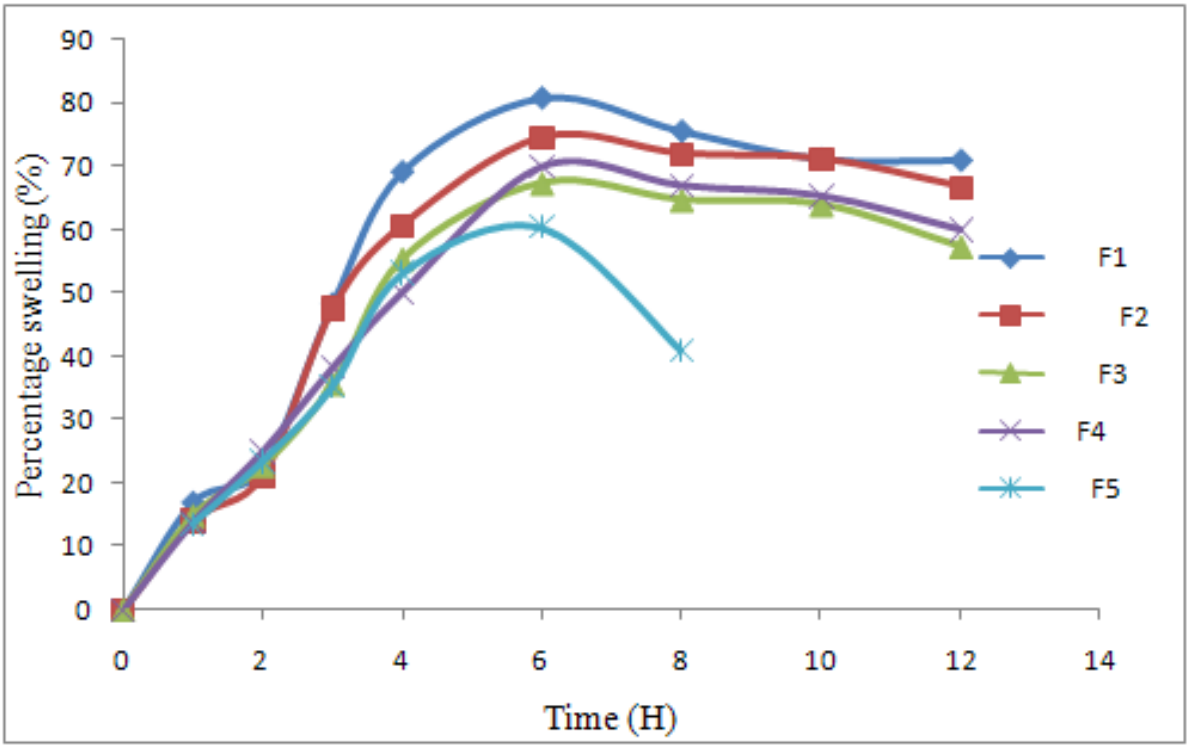


Figure 17- Percentage swelling of HPMC K4M Vs Time

Table 10. Percent swelling of formulations with HPMC K15M

Time(H)	F10	F11	F12	F13	F14
1	16.97±0.30	14.05±0.69	14.87±0.94	13.87±0.28	10.62±0.86
2	22.47±0.02	21.25±0.38	19.73±0.92	18.01±0.10	15.54±0.31
3	48.34±0.31	47.60±0.66	44.68±0.53	38.21±0.33	20.27±0.15
4	69.19±0.66	60.67±0.82	58.39±0.35	56.08±0.66	31.13±0.35
6	81.83±0.33	74.51±0.33	70.33±0.71	65.86±0.66	45.32±1.18
8	79.59±0.66	72.97±0.98	68.69±0.53	62.87±0.98	
10	76.20±0.66	68.17±1.02	66.93±0.88	61.28±0.50	
12	70.99±0.82	64.78±0.33	60.29±0.53	57.94±0.83	

Data represents mean ± SD (n=3)

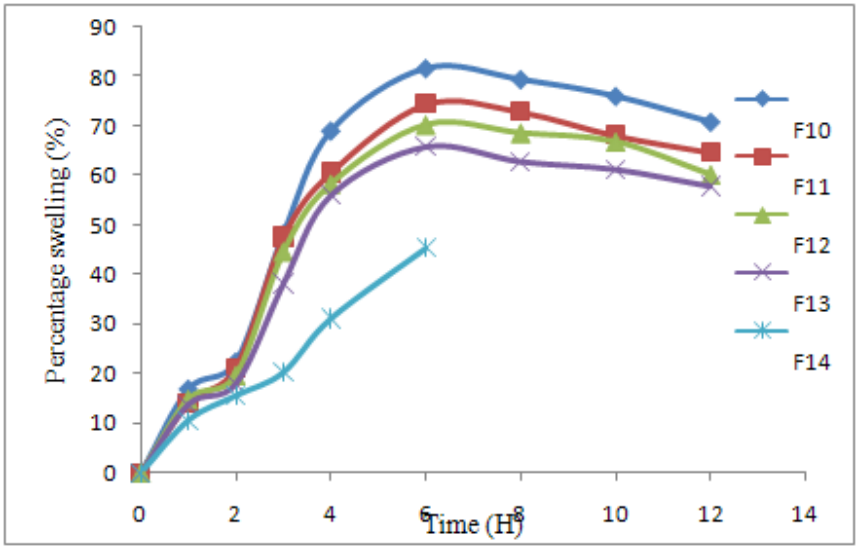


Figure 18- Percentage swelling of HPMC K15M Vs Time

Table 11. Percent swelling of formulations with HPMC K100M

Time(h)	F15	F16	F17	F18
1	25±0.65	21.50±0.34	18.33±0.90	10.62±0.86
2	36.24±0.34	31.17±0.87	22.17±0.67	15.54±0.31
3	69.50±0.98	64.67±0.71	59.67±1.45	20.27±0.15
4	87.00±0.78	78.17±0.61	66.50±1.56	39.13±0.35
6	96.50±0.65	84.67±0.85	72.83±0.34	48.32±1.18
8	80.17±2.34	76.67±1.45	68.00±0.67	51.91±0.15
10	76.83±0.92	74.50±0.64	68.33±0.81	
12	70.50±1.32	64.50±0.78	62.33±0.64	

Data represents mean ± SD (n=3)

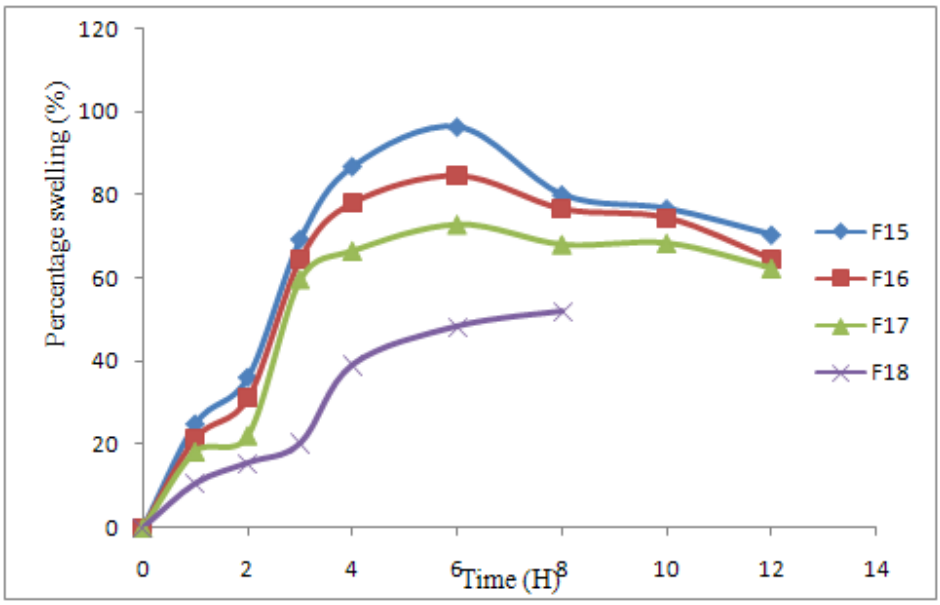


Figure 19- Percentage swelling of HPMC K100M Vs Time.

The in vitro dissolution testing was performed and the results of the formulations were expressed in tables 12, 13, 14 and 15.

The release of Atazanavir sulphate was studied using USP dissolution apparatus II. The dissolution media were 900 ml 0.1 N HCl maintained at 37 ± 0.50C with rotation speed of 50 rpm. Aliquots of 5 ml was collected at predetermined time intervals and replenished with equivalent volume of fresh medium. The samples were diluted to a suitable concentration with 0.1N HCl and were analyzed by using UV/VIS double beam spectrophotometer at 301nm.The results are expressed as mean±S.D (n=3).

In vitro dissolution study of formulations F1, F2, F3 , F4 and F5 were done in 0.1 N HCl and the Percent of drug release from formulations F1, F2, F3, F4 and F5 was 61.79, 69.85, 82.43, 89.43 and 94.07 in 12 hours respectively. F1, F2, F3, F4 formulations floated for 12 h. All this formulations contain a lower viscosity grade polymer compared with that of other two polymers.The release rate was faster with lower viscosity grades of HPMC, probably owing to less polymer entanglement and less gel strength and also to the larger effective molecular diffusion area at lower viscosity as compared with higher viscosity grades of HPMC. Moreover, the tablets formed by the higher viscosity grade HPMC would have more gel strength than the one formed by the lower viscosity grade because of which, the erosion would be less.

As the concentration of the polymer decreased from F1 to F3 the drug release was increased. It is increased from 61.79 to 82.43 from F1 to F3 respectively. The differences in the release may be due to the amount of gel layer formed on the surface of the tablets. HPMC K4M at higher concentrations results in a greater amount of gel being formed. This gel increases diffusion length so that drug release was decreased.

The formulations F3,F4 and F5 are formulated by varying the concentrations of sodium bicarbonate. When the concentration of sodium bicarbonate was 70 mg/tablet, the tablets could not float immediately. This might be due to the gas generated was not sufficient to keep the formulation float immediately. When amount of sodium bicarbonate was increased above 90 mg, the tablets could not retain its physical integrity for 6 h. when the sodium bicarbonate concentration was 80 mg(F4) the tablet float immediately and release was good.

Table 12: Percent drug release of formulations with HPMC K4M

Time(h)	F1	F2	F3	F4	F5
1	5.4±0.30	6.51±0.69	11.28±0.94	9.3±0.28	9.08±0.86
2	10.92±0.02	10.56±0.38	20.96±0.92	13.97±0.10	14.48±0.31
4	17.82±0.66	13.45±0.82	44.82±0.35	21.77±0.66	22.75±0.35
6	22.41±0.33	21.08±0.33	58.81±0.71	40.5±0.66	43.28±1.18
8	39.21±0.66	42.42±0.98	68.87±0.53	61.71±0.98	69.42±0.15
10	50.35±0.66	51±1.02	76.96±0.88	78.43±0.50	85.92±0.35
12	61.71±0.82	69.85±0.33	82.43±0.53	89.43±0.83	94.07±1.18

Data represents mean ± SD (n=3)

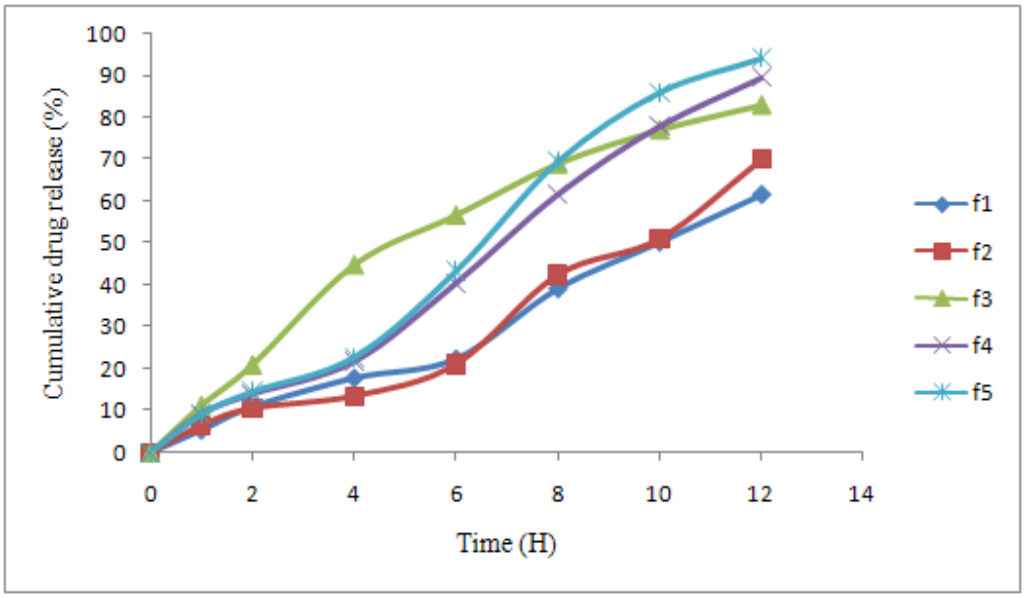


Figure 20- Percent drug release of HPMC K4M Vs Time.

Further test is carried out by decreasing the polymer concentration further in order to increase the drug release. Formulations F6, F7, and F9 are prepared but the floating tablets could not retain its physical integrity for desired period of time. If its physical integrity could not be maintained, tablet would be broken down into smaller fragments and escape from the upper part of the gastrointestinal tract. At higher sodium bicarbonate concentrations F8 showed good release.

The in vitro dissolution studies for the formulations F10, F11, F12, F13 and F14 prepared with HPMC K15M were done in 0.1N HCl and the percent of drug release from formulation F10, F11, F12, F13 was 51.29, 55.97, 74.05, 78.96 in 12 hours respectively (Figure 8). As the concentration of the polymer is decreased the amount of drug release increases. Among these the formulation F13 has shown maximum drug release in 12 hours with floating lag time of 169 seconds.

The in vitro dissolution studies for the formulations F15, F16, F17 and F18 prepared with HPMC K100M were done in 0.1N HCl and the percent of drug release from formulation F15, F16, F17 was 43.3, 51.25, 69.46 in 12 hours respectively

(Figure 9). Formulations floated for 12 h. As the concentration of the polymer is decreasedthe amount of drug release increases.

Table 13: Percent drug release of formulations with HPMC K4M

Time(H)	F6	F7	F8	F9
1	38.14±0.20	7.2±0.96	11.01±0.49	44.34±0.81
2	56.35±0.80	26.57±0.36	16.28±0.92	57.85±0.10
4	70.78±0.61	49.9±0.84	25.15±0.33	83.5±0.67
6	82±0.39	68.14±0.34	52.28±0.77	85.5±0.63
8	89.35±0.67	76.9±0.99	71.78±0.53	94.7±0.97
10	90±0.69	89.35±1.02	94.71±0.88	96.87±0.50
11	94.07±0.86	94.5±0.33	92.71±0.53	94.07±0.89

Data represents mean ± SD (n=3)

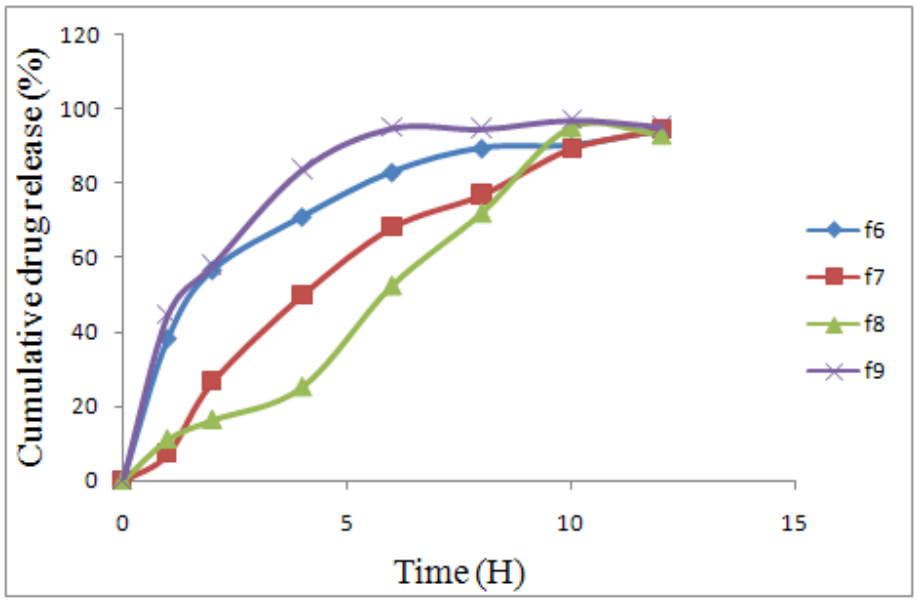


Figure 21-Percent drug release of HPMC K4M Vs Time.

Table 14: Percent drug release of formulations with HPMC K15M

Time (h)	F10	F11	F12	F13	F14
1	4.05±0.01	6.64±0.17	9.05±0.45	9.77±0.78	32.77±0.25
2	5.59±0.15	10.77±0.41	12.40±0.46	16.28±0.33	38.48±0.69
4	11.62±2.56	13.73±0.03	22.65±0.30	33.85±0.39	71.68±5.34
6	15.76±0.79	19.61±0.61	37.78±0.65	46.92±0.62	85.64±0.62
8	19.37±3.54	28.09±0.77	53.53±0.70	55.92±0.70	90.29±0.70
10	36.32±0.91	38.26±2.15	64.72±2.5	68.67±2.5	94.10±2.5
12	51.29±1.23	55.97±0.61	74.05±0.78	78.96±0.78	93.67±0.78

Data represents mean ± SD (n=3)

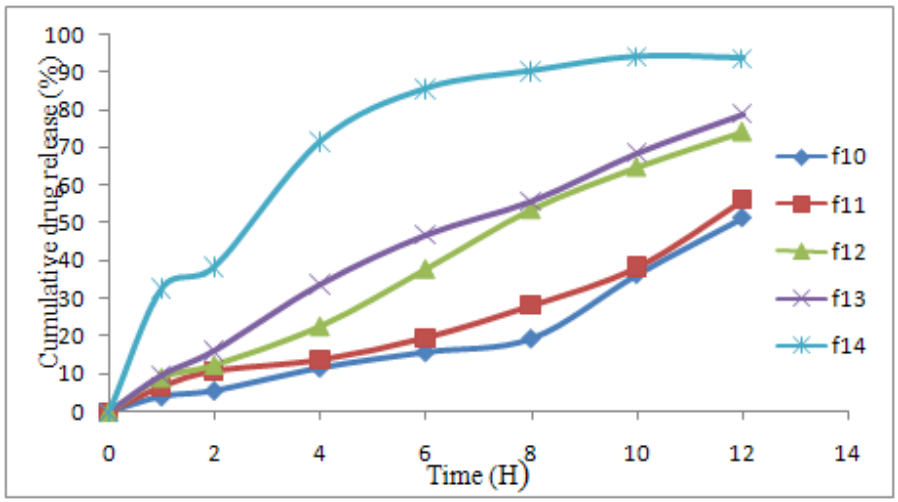


Figure 22-Percent drug release of HPMC K15M Vs Time**.**

Table 15 .Percent drug release of formulations with HPMC K100M

Time (h)	F15	F16	F17	F18
1	4.3±1.19	6.29±0.66	6.51±0.84	31.70±0.25
2	5.73±0.03	9.16±0.71	11.0±0.61	44.95±0.69
4	9.23±7.57	10.64±1.30	17.64±0.31	72.53±5.34
6	11.39±2.30	13.94±1.40	33.00±0.78	84.04±0.62
8	14.84±0.53	17.41±1.40	45.51±1.09	86.67±0.70
10	24.37±1.69	29.53±2.02	59.53±1.09	92.08±2.5
12	43.3±0.30	51.25±0.27	69.46±0.78	94.69±0.78

Data represents mean ± SD (n=3)

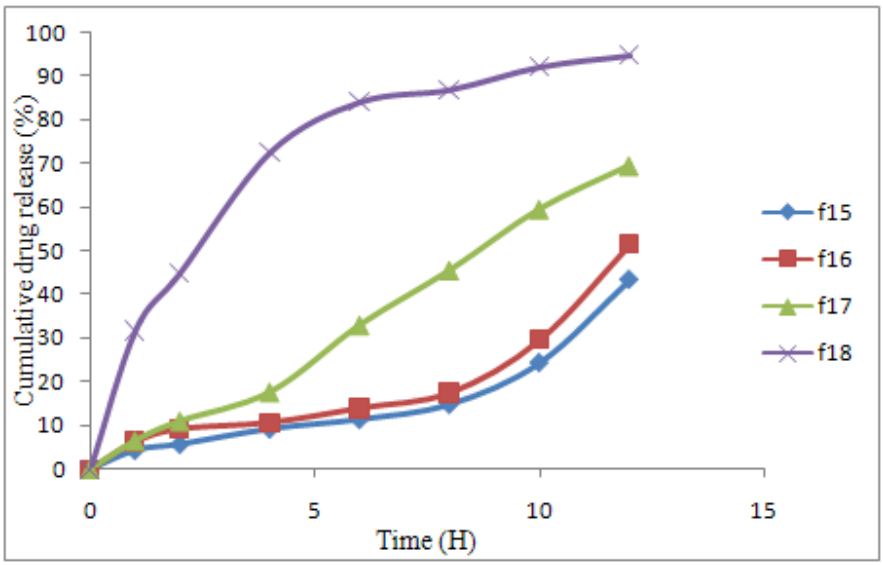


Figure 23-Percent drug release of HPMC K100M Vs Time.

The regression coefficient (R^2) values of release data of all formulations obtained by curve fitting method for zeroorder, first-order, and Higuchi and Krosmeyer-Peppas model are reported in Table 16. Most of the formulations follow the zero order and Higuchi model. For the optimized formulation F4, the R^2 value of zero order 0.985 (nearer to 1) is dominant than the other models.

The mechanism of drug release is predicted by using according to Krosmeyer–Peppas. The n value of optimized formulation F4 is 0.832. This indicates that the drug release mechanism is of non-fickian diffusion. The R^2 value of F4 formulation for Zero-order is near to 1 which indicated the drug release mechanism is of zero-order resulting from constant surface area and controlled swelling/ erosion provided by the changing geometry of the system.

Table 16: Release kinetics of optimized formulations

Formulation	Zero order	First order	Higuchi	Korsmeyer & Peppas	Peppas(n)
F4	0.985	0.957	0.940	0.842	0.832
F1	0.991	0.943	0.963	0.941	0.807

To get evidence of possible chemical interaction of drug with the excipients, FTIR analysis was used . Figure xxx shows the IR spectra of Atazanavir sulphate , HPMC K4M , and the F3 formulation. Pure drug shows a characteristic peak at 1699.29, 1674.21, 1651.07 cm^{-1} that is due to C=O stretching of ketonic group and 3261.63, 3215.34 cm^{-1} are due to N-H stretching. HPMC K4M show important bands at 1456.26 and 1417.68 cm-1, respectively. The FTIR spectrum of the optimized formulation displays the characteristic peaks of both drug and HPMC K4M. Overall, there was no alteration in the characteristic peaks of drug and HPMC K4M suggesting that there was no interaction between the drug and HPMC K4M.

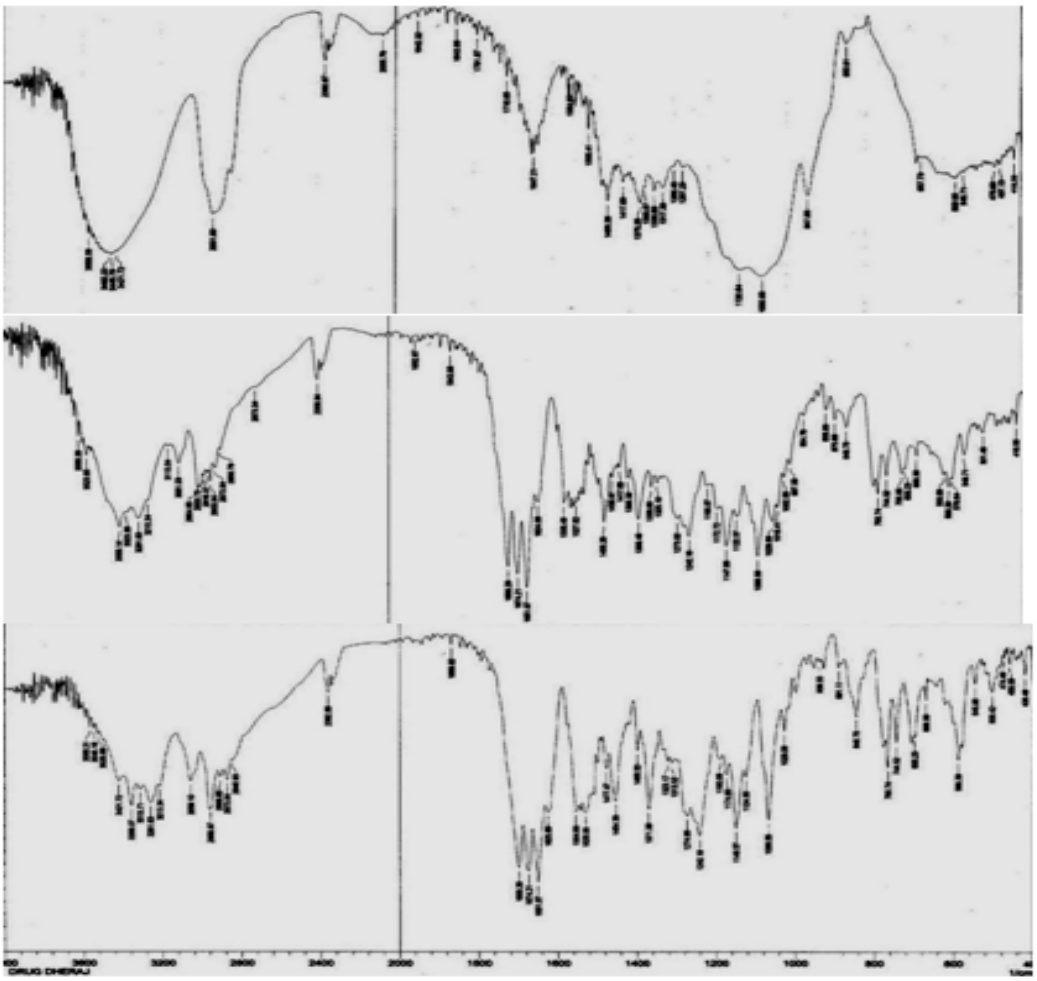


Figure 24. Ftir Results of Atazanavir, polymer And Tablet Composition.

SUMMARY

- Gastroretentive floating matrix tablets of Atazanavir sulphate were successfully prepared with hydrophilic polymers like HPMC K4M, HPMC K15M.,HPMC 100M.
- The formulated batches were evaluated for physicochemical parameters, floating properties and dissolution profiles. From the evaluation results it was observed that the tablets contain the higher viscosity HPMC showed long floating lag time when compared to tablets prepared with lower viscosity HPMC. The physical properties like hardness, weight variation and friability of majority of the batches complied with the pharmacopoeial specifications. The drug content of all tablets was in the range of 95 – 100%.
- In vitro dissolution study of all the formulations were done in 0.1 N HCl The release rate was faster with lower viscosity grades of HPMC, probably owing to less polymer entanglement and less gel strength and also to the larger effective molecular diffusion area at lower viscosity as compared with higher viscosity grades of HPMC.

- The regression coefficient (R2) values of release data of all formulations obtained by curve fitting method for zero-order, first-order, and Higuchi and Krosmeyer-Peppas model.
- For the optimized formulation F4, the R2 value of Zero order is 0.985 (nearer to 1) is dominant than the other models which indicates that the drug release follows zero order. The n value of optimized formulation F4 is 0.832. This indicates that the drug release mechanism is of non-fickian diffusion.
- FTIR studies showed there was no interaction between drug and polymer.
- The in- vivo X-ray studies, conducted in the healthy human volunteers, it was found that the gastric retention time was 6 hours.

CONCLUSION

The Atazanavir sulphate floating tablets were successfully prepared. The addition of gel-forming polymer HPMC (K4M) and gas-generating agent sodium bicarbonate were provided the buoyancy and drug release. The prepared tablets could float within 3min and maintain for more than 12 h. The drug release at 12 h was more than 85%. The uniformity of weight, hardness, friability, drug content were all lying within the limits. The FTIR results showed there was no exipient interactions. Finally In-vivo studies showed that the tablet was retained in stomach for 6 hours.

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