FORMULATION AND DEVOLOPMENT OF FLOATING MATRIX TABLETS OF LAMIVUDINE

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

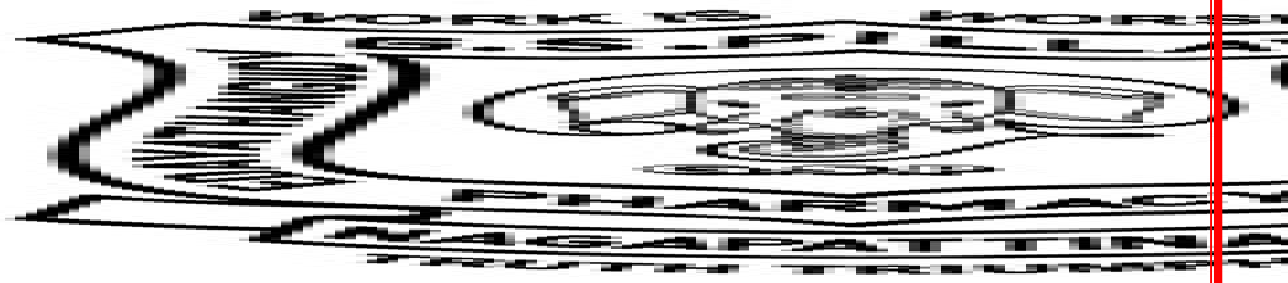
MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted
By

Reg No:261211156



DEPARTMENT OF PHARMACEUTICS

EDAYATHANGUDY.G.S PILLAY COLLEGE OF PHARMACY

NAGAPATTINAM-611002

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Under the guidance of

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CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION AND DEVOLOPMENT OF FLOATING MATRIX TABLETS OF LAMIVUDINE"** submitted by **PAVAN KUMAR BODIGALLA** (Reg No:261211156) 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.

Place: Nagapattinam **Mr.M.Pitchaipillai, M.Pharm.,**

Date:

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Place: Nagapattinam **Prof.Dr.D.BabuAnanth,M.Pharm., Ph.D.,**

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INDEX

INTRODUCTION

Oral route is the most desired, convenient and preferred method of administering the drug for its systemic effect due to its ease of administration, low cost of therapy and patient compliance. Oral route of administration has received more attention in the pharmaceutical field because of more flexibility in the designing of dosage form than the other routes of drug delivery[1]. The release of drug from the delivery system may be by diffusion, dissolution or by combination of both mechanisms in a desired and controlled manner. One main prerequisite for the oral performance of the drug delivery system is that drug should have good absorption throughout the gastrointestinal tract (GIT).

Floating drug delivery systems (FDDS) are aimed to retain the drug in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. The principle is very simple i.e., to make the dosage form less dense than the gastric fluids so that it can float on them. Floating systems or Hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. After release of drug, the residual system is emptied from the stomach. This result an increased gastric residence time and a better control of the fluctuations in plasma drug concentration. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release 1. Under certain circumstances prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug substance. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract and drugs that are less soluble in or are degraded by the alkaline pH may benefit from prolonged gastric retention. In addition, for local and sustained drug delivery to the stomach and proximal small intestine to treat certain conditions, prolonged gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability and therapeutic efficacy, and possible reduction of dose size.[2]

Gastro retentive drug delivery systems are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs[3].

Gastric emptying of dosage form is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms .Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability .One of such difficulties is the inability to confine the dosage form in the desired area of the GIT .Drug absorption from the GIT is a complex procedure and is subject to many variables, it is widely acknowledged that the extent of gastro intestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus small intestinal transit time is an important parameter for drugs that are incompletely aabsorbed[4].

The oral controlled drug delivery systems should be primarily used to achieving more predictable and increased bioavailability of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, useful for drugs acting locally in the GIT, drugs which are poorly soluble and unstable in the intestinal fluids. Among the various gastro retentive systems, gastric floating drug delivery systems (GFDDS) offer numerous advantages over the gastric retentive systems. These systems have a density lower than the gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time .While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the stomach. Floating drug delivery and mucoadhesive systems gained significant attention in the past decade because of its effectiveness in gaining bioavailability, cost-effective compared to other NDDS and better scale up technical opportunities.

Issues related to gastric emptying:

It is well recognized that the stomach may be used as a ‘depot ‘for sustained release dosage forms, both in human and veterinary applications. Anatomically the stomach is divided into 3 regions: fundus, body and anthrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, where as the anthrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions[5].

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fating state an inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours[6].

This is called as the inter digestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington[6].

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (pre burst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes .It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine .it is also known as house keeper wave. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles. After the ingestion of a mixed meal, the pattern of concentrations changes from fasted to that of fed state.

This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1mm), which are propelled towards the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in showdown of gastric emptying rate.

Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric emptying residence time and unpredictable gastric emptying rate. Yet another major adversity encountered through the oral route is the first-pass effect, which leads to reduced systemic bioavailability of a large number of drugs. Overall, the relatively brief GI transit time of most drug products, which is approximately 8-12 hours, impedes the formulation of a once daily dosage form for most drugs such as age, race, sex and disease states, as they may seriously affect the release of a drug from the DDS. It is, therefore desirable to have a CR product that exhibits an extended GI residence and a drug release profile independent of patient related variables[7].

Table 1: Regional specific characteristics of GIT influencing gastro retention

Region	*Surface area(m^2)*	*Liquid secretion (ml/min)*	*Reaction PH*	*Transit time (hr)*
Oral cavity	About 0.05	0.5-2	5.2-6.8	Short
Stomach	0.1-0.2	2-4	1.2-3.5	0.5-3
Duodenum	About 0.04	1-2	4.6-6	1-2
Small intestine	4500*	0.2	4.7-6.5	1-10
Large intestine	0.5-1	0.2	7.5-8.0	4-20

**Taking microvilli area in to account*

Need for gastro retentive drug delivery system

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effect and provide their therapeutic effects without the need for repeated dosages or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, which is where absorption occurs and contact time is limited. Under normal or average conditions, for example material passes through the small intestine in as 1-3 hours. In general, appropriate candidates for CRGRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT[7]:

I. Drugs acting locally in the stomach

   E.g. Antacids and drugs for H.Pylori viz., Misoprostol

II. Drugs that are primarily absorbed in the stomach

   E.g. Amoxicillin

III. Drugs that is poorly soluble at alkaline PH

   E.g. Frusemide, Diazepam, Verapamil, etc.

IV. Drugs with a narrow window of absorption

   E.g. Cyclosporine, Methotrexate, Levodopa, etc

V. Drugs which are absorbed rapidly from the GIT.

   E.g. Metronidazole, tetracycline.

VI. Drugs that degrade in the colon.

   E.g. Ranitidine, Metformin HCL.

VII. Drugs that disturb normal colonic microbes

E.g. Antibiotics against H.Pylori.

Drugs that would benefit from GRDDS

CNS drugs (for Parkinson disease, epilepsy, Alzheimer and migraine), Anti-viral products (for HIV, herpes and hepatitis) and certain antibiotics, Anti-hypertension drugs, Anti-diabetic agents for Type-2 diabetes, Drugs for local treatment of GI infections and gastric enzyme replacement[8].

Formulation considerations for GRDDS

It must be effective retention in the stomach to suit for the clinical demand

I) it must have sufficient drug loading capacity

II) It must be control the drug release profile

III) It must have full degradation and evacuation of the system once the drug release is over

IV) It should not have effect on gastric motility including emptying pattern

V) It should not have other local adverse effects[9].

Approaches to gastric retention

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms, swelling and expanding systems, Mucoadhesive systems, High density systems, Modified shape systems. Gastric emptying delaying devices and co-administration of gastric delaying drugs. Among these, the floating dosage forms have been used most commonly.

A. Floating drug delivery system:

Floating drug delivery systems (or) hydro-dynamically balanced systems have a bulk density lower than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is slowly released at a desired rate from the stomach. After the release of drug,

the residual system is emptied from the stomach. This results an increase in the gastric retention time and better control of fluctuations in the plasma drug concentration.

The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as hydro dynamically balanced systems(HBS) since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices.

These forms are expected to remain buoyant (3-4 hours) on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of gastric contents.

Among the different hydrocolloids recommended for floating form formulations, cellulose and ether polymer are most popular, especially hydroxy propyl methyl cellulose. Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase bouncy[10, 11].

Parallel to formulation studies, investigations have been undertaken in animals and humans to evaluate the intra gastric retention performances of floating forms. These assessments were realized either indirectly through pharmacokinetic studies with a drug tracer, or directly by means of x-ray and gamma scintigraphic monitoring of the form transit in the gastrointestinal tract. when a floating capsule is administered to the subjects with a fat and protein meal, it can be observed that it remains buoyant at the surface of the gastric content in the upper part of the stomach and moves down progressively while the meals empties. The reported gastric retention times range from 4 to 10 hours.

Pharmacokinetic and bioavailability evaluation studies confirm the favorable incidence of this prolonged gastric residence time[12].

The floating drug delivery system (FDDS) can be divided into effervescent systems and non effervescent systems.

I. Effervescent systems:

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas[13].

These are matrix type systems prepared with the help of swellable polymers such as HPMC, methylcellulose, chitosan and various effervescent compounds, e.g. sodium bicarbonate, calcium carbonate, tartaric acid and citric acid. They are formulated in such away that when in contact

with the gastric contents, **Co_2** is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms[14].

i) Volatile liquid / vacuum Containing Systems:-

These have an inflatable chamber which contains a liquid e.g. ether, cyclopentane, that gasifies body temperature to cause the inflation chamber in the stomach. These systems are osmotically controlled floating systems containing a hollow deformable unit. There are two chambers in system first contains the drug and the second chamber contains the volatile liquid .These systems are classified into 3 categories

1. Intra gastric floating drug delivery system

2. Inflatable gastrointestinal delivery systems

3. Intra-gastric osmotically controlled drug delivery system

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 microporous compartment.

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, then 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.

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 intragastirc 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 vapor and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi-permeable housing.

In the stomach, the water in the GI fluid is continuously absorbed through the semi-permeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.

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

ii) Gas generating systems:

These buoyant delivery systems utilizes effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate Co2, which gets entrapped in the jellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it float over chime. A multiple unit type of floating pills, which generate co_2, have also been developed.

The system consists of a sustained release pill as seed, surrounded by double layers. The inner layer is an effervescent layer containing sodium bicarbonate and tartaric acid. The outer layer is of a swellable membrane layer containing PVA, shellac etc. Another effervescent system consisting of a collapsible spring, which controls the release of drug from the polymer matrix, has also been developed.

The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating which is insoluble but permeable, allows permeation

of water. Thus carbon dioxide is released, causing the beads to float in the stomach[15]. Earlier we have reported fabrication of gas liberating Lanzoprazole microsphere[16].

iii) Matrix tablets

Single layer matrix tablet is prepared by incorporating bicarbonates in matrix forming hydrocolloid gelling agent like HPMC, chitosan, alginate or other polymers and drug.

Bilayer tabet can also be prepared by gas generating matrix in one layer and second layer with drug for its sustained release effect.

Floating capsule also prepared by incorporating such mixtures. Triple layer tablet also prepared having first swellable floating layer, second sustained release layer of two drugs (metronidazole and tetracycline) and third rapid dissolving layer of bismuth salt. This tablet is prepared as single dosage form for triple therapy of H.Pylori[14].

II. Non effervescent system:

Non effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, poly methacrylate, and polystyrene. The formulation methods include a simple approach of thoroughly mixing the drug and the gel forming hydrocolloid. After oral administration the dosage form swells in contact with gastric fluids and attains a bulk density of less than one. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. These formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass [17, 18]. Corresponding author have utilized compressed carbon dioxide in the system slurry to produce microspheres with air pockets by which it becomes buoyant[19].

i) Hydro dynamically balanced systems:

Hydro dynamically balanced (HBS), which contains drugs with gel forming hydrocolloids meant to remain buoyant on the stomach content. These are single unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxy propyl methyl cellulose(HPMC), hydroxyl ethyl cellulose (HEC), hydroxyl propyl cellulose (HPC), sodium carboxymethylcellulose

(NaCMC), polycarbophil, polystyrene, polyacrylate, agar carrageenans or alginic acid are commonly used excipients to develop these systems. The polymer is mixed with drugs and usually administered in hydro dynamically balanced system capsule.

The capsule shell dissolves in contact with gastric fluids; the hydrocolloids in the system hydrate and form a colloidal gel barrier around its surface. This gel barrier controls the rate of fluid penetration into the device and consequent release of the drug [4, 17, 18].

ii) Micro porous compartment systems:

This technology is based on the encapsulation of a drug reservoir inside a micro porous compartment with apertures along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug. Gastric fluid enters through the aperture, dissolves the drug for continuous transport across the intestine for drug absorption.[19]

iii) Multi particulate system: Floating beads

Multi particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm. Thus multi particulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet[19].

iv) Micro balloons / hollow microspheres:

There are various approaches in delivering substances to the target site in a controlled release fashion. One such approach is using polymeric micro balloons as carrier for drugs. Hollow microspheres are known as the micro balloons.

Hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion evaporation methods to prolong the gastric retention

time of the dosage form[20].Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer and polymer ratio and the solvent used for formulation. The micro balloons floated continuously over the surface of acidic dissolution media contain surfactant for more than 12 hours[21]. At present hollow microspheres are considered to be one of the promising buoyant systems because they combine the advantages of multiple-unit system and good floating.

B. Mucoadhesive systems:

Mucoadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the gastro retention of drug delivery system (DDS) in the stomach by increasing the intimacy and duration of contact of drug with the biological membrane.

A bio/muco-adhesive substance is a natural or synthetic polymer capable of producing an adhesive interaction based on hydration –mediated, bonding mediated or receptor mediated adhesion with a biological membrane or mucus lining of GI mucosal surface [22, 23].

C. Swellable systems:

Swellable systems are also retained because of their mechanical properties. The swelling usually results from osmotic absorption of water. On coming in contact with gastric fluid, the polymer imbibes water and swells. These are the dosage forms, which after swallowing, swells to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a longer period of time. These systems may be named as plug type systems. Sustained and controlled drug release may be achieved by selection of polymer of proper molecular weight and swelling of the polymer retards the drug release.

D. Expandable system:

After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus[24]. As a result, the dosage form is retained in the stomach for a longer period of time. These systems are sometimes referred to as plug type systems because they tend to remain

lodged at the pyloric sphincter. As dosage form coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of this polymer is a result of the presence of physical-chemical crosslink's in the hydrophilic polymer network. These crosslink's prevented the dissolution of the polymer and thus maintain the physical integrity of the dosage form. A balance between the extent and duration of swelling is maintained by the degree of cross linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system and maintains its physical integrity for a prolonged period .On the other hand, a low degree of cross-linking results in extensive swelling followed by the rapid dissolution of the polymer[25]. An optimum amount of cross linking is required to maintain a balance between swelling and dissolution .The swollen system eventually will lose its integrity because of a loss of mechanical strength caused by abrasion or erosion or will burst into small fragments when the membrane ruptures because of continuous expansion[26]. These systems also may erode in the presence of gastric juices so that after a predetermined time the device no longer can attain or retain the expanded configuration

The expandable GRDFs are usually based on three configurations [27]:

I) A small collapsed configuration which enables sufficient oral intake

II) Expanded form that is achieved in the stomach and thus prevents passage through the pyloric sphincter.

III) A smaller form that is achieved in the stomach when the retention is no longer required i.e. after the GRDF has released its active ingredient, thereby enabling evacuation.

The expansion can be achieved by

I) swelling system

II) Unfolding system

E. Self-unfolding systems/Modified shaped system:

These are non-disintegrating geometric shapes molded from silastic elastomer or extruded from polyethylene blends which extend the GRT depending on size, shape and flexural modulus of the drug delivery system[28].

The self unfoldable systems are capable of mechanically increasing in size relative to the initial dimensions. This increase prevents the system from passing via the pylorus and provides for its prolonged stay in the stomach .A drug can be either contained in a polymeric composition of the gastro retentive system or includes as a separate compartment. Several methods were suggested to provide for the self –unfolding effect[29].

1) The use of hydro gels swelling in contact with the gastric juice.

2) Osmotic systems, comprising an osmotic medium in a semi permeable membrane.

3) System based on low boiling liquids converting into a gas at the body temperature.

F. Magnetic systems:

This system is based on a simple idea that the dosage form contains a small internal magnet and magnet placed on the abdomen over the position of the stomach. Despite numerous reports bout 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 [30, 31].

G. High density systems:

These systems with a density of about 3g/cm3 are retained in the anthrum part of the stomach and are capable of withstanding its peristaltic movements. The only major draw backs with such system is that it is technically difficult to manufacture such formulations with high amount of drug (>50%) and to achieve a density of about 2.8g/cm3. It is necessary to use diluents like barium sulfate, zinc oxide, titanium dioxide, iron powder etc to manufacture such high density formulations [32, 33].

H. Raft forming systems:

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, where in each portion of the liquid swells forming a continuous layer called a raft. These systems contains a gel forming agent and alkaline bi carbonate or carbonates responsible for the formation of CO2 to make the system less dense and float on the gastric fluids6. Formulations also typically contain antacids such as aluminum hydroxide or calcium carbonate to reduce gastric acidity. Because raft forming systems produce a layer on the top of gastric fluids, they are often used for gastro esophageal reflux treatment as with liquid gaviscon [25, 26, 27].

I. Super porous hydro gels:

Although these are swellable systems, they differ sufficiently from the conventional types to warrant separate classification with pore size ranging between 10nm and 10micro meter .Absorption of water by conventional hydro gel is very slow process and several hours may be needed to reach an equilibrium state during which premature evacuation of dosage form may occur. Super porous hydro gel ,average pore size >100 micro meter, swell to equilibrium size within a minute, due to water uptake by capillary wetting through numerous inter connected open pores. Moreover they swell to a large size (swelling ratio 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contractions. This is achieved by a co-formulation of a hydrophilic particulate material, Ac-Di-Sol (croscarmellose sodium).

3. Factors affecting the gastro retentive systems:

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. Most of approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastro retentive system[34].

3.1. Dosage related physical factors

The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach .Both positions may isolate the dosage system from the pylorus. A density of <1.0gm/cm3 is required to exhibit floating property.

Size and shape have found to have effect on gastro retention. Dosage form units with a diameter of more than 7.5mm are reported to have an increased GRT compared with those with a diameter of 9.9mm. Tetrahedron and ring shaped devices with a flexible modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.

3.2. Single or multiple unit formulation:

Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to 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. For single unit dosage form, either the whole dosage form retains within the stomach, but if fails no drug will be released in the gastric region, thus shows ‘all or non hypothesis’.

Table 2: Various reported gastroretentive systems and the APIs and polymers used

Type of Gastro Retentive Systems	Active Ingredients	Polymers
Gastro retentive Tablets	Ofloxacin	HPMCK4M, HPMC 5cps
	Itopride hydrochloride[45,47]	HPMCK15M, HPMC K100M
Floating Tablets	Theophylline	HPMCK15MCR, HPMC K100M
	Cephalexin[45]	HPMCK4M, Xanthan Gum, Guar Gum
	Salbutamol Sulfate[50,52]	HPMC K4M
	Ranitidine Hydrochloride	HPMCK15M, HPMC K100M
	Clarithromycin	HPMC K4M
	Cefuroxime axetil	HPMC K4M, HPMC100LV
	Acetohydroxamic acid & Chlorpheniramine maleate	Eudragit RSPO, Eudragit EPO
	Imatinib mesylate[46,48]	HPMCK4M, HPMC K15M, HPMC K100M,
Bilayered Floating Tablets	Tizanidine hydrochloride	HPMC K 15M, HPMC 100M, Xanthun gum
	Captopril[45]	HPMC K4M, HPMC K15M, HPMC K100M
Bioadhesive Bilayered floating tablet	Rosiglitazone maleate[48]	HPMC
	Imatinib mesylate[49,51]	Carbopol947P, Sodium CMC
Floating microspheres	Acyclovir	Ethyl cellulose
	Cefpodoxime proxetil	Ethyl cellulose, HPMC K15M
	Famotidine[52]	Polymethyl methacrylate
	Ranitidine hydrochloride[47]	Sodium alginate. Pectin pure
	Keterolac trametamol	Eudragit100, Ethyl cellulose, Eudragit S 100, HPMC K4M
	Diltiazem hydrochloride[50,53]	Eudragit RS 100, Ethyl cellulose
	DIltiazem	Alginate, Chitosan, Eudragit
	Verapamil hydrochloride	Eudragit S 100, Cellulose acetate, Acrycoat S 100
	Acetohydroxamic acid	Gellan (Gelrite)
	Metformin hydro chloride	Ethyl celllulose
	Cimetidine [45]	HPMC, Ethyl cellulose
Floating microparticles	Aceclofenac	Eudragit RS 100
	Verapamil hydro chloride[53]	EudragitRS ,Ethylcellulose, Poly methyl Methacrylate
	Ketoprofen	Eudragit S100, Eudragit RL
Micro capsules	Melatonin[49]	Chitosan
Floating micro pellets	Lansoprazole	HPMC, Methyl cellulose, Chitoisan
Floating minimatrices	Aceclofenac[50]	HPMC 15 LV
Hollow microspheres/Microballons	Aceclofenac	Pectin
	Diclofenac sodium	Eudragit S100
	Theophylline	Xanthan gum, Gelatin
	Riboflavin[51]	Eudragit S100

3.3. Fed or unfed state:

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer [25].

3.4. Nature and frequency of meal:

Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release[35]. GRT can be increased by 4 to 10 hours with a high calorie meal (in proteins and fats) [36, 37]. The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

3.5. Gender, age, exercise and body posture of subject:

Mean ambulatory GRT in males (3.4 +-0.6 hours) I less compared with their age and race matched female counterparts (4.6+_1.2 hours), regardless of the weight, height and body surface36. Elderly people, especially those over 70 years of age, have a significant longer GRT25. Vigorous physical activity retards gastric emptying. Gastric emptying is favored while standing and by lying on the right side since the normal curvature of the stomach provides a downhill path where as lying on the left side or in supine position retards it since the contents have to go against gravity [37].

3.6. Emotional state of subject:

The influence of emotional factors on gastric motility and secretion may be either augmentative or inhibitory depending upon whether the emotional experience is of an aggressive or a depressive type[34].

3.7. Gastro intestinal PH:

Gastric emptying is retarded at low stomach PH and promoted at higher or alkaline PH. Chemicals that effect gastrointestinal PH also alters gastric emptying. The inhibitory effect of various acids on gastric emptying decreases with increase in molecular weight and is in the following order HCL>Acetic>lactic>tartaric>citric acids. With alkaline solutions, a low base concentration (1% NaHCO3) increases the gastric emptying rate more than the 1 of higher concentration (5%).

3.8. Concomitant drug administration and disease state:

Anti cholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride can affect floating time. Gastric ulcer, diabetes, hypothyroidism increase GRT. Hyperthyroidism, duodenal ulcers decrease GRT [7, 24].

Evaluation of Floating Drug Delivery System[38, 39]:

I. Pre-compression parameters like angle of Repose (θ), Compressibility Index. bulk density, tapped density, Carr's index.

II. Post-compression parameters: Shape of Tablets[40]: Compressed tablets were examined under the magnifying lens for the shape of the tablet.

Tablet Dimensions: Thickness and diameter were measured using a calibrated varniear caliper. Three tablets of each formulation were picked randomly and thickness was measured individually.

Determination of hardness of tablet: Randomly sampled twenty tablets in each batch of formulations should be used for the determination of hardness with the help of Monsanto type hardness tester.

Determination of weight variation: Twenty tablets selected at the random are weighed accurately and the average weight of the tablet is calculated. Then the deviation of individual weight from the average weight is calculated.

Determination of thickness of the tablet: The individual crown – to – crown thickness of ten tablets is determined using slide calipers for each batch.

Measurement of Floating Capacity:

Three individual tablets are put in individual flask containing 400ml of 0.1(N) HCL solutions. Then the time in minutes for each tablets to go from the bottom to the top of the flask (floating lag time) and the time for which tablets constantly float on the water surface (duration of floating) are measured. The sample mean and standard deviation are then calculated.

Measurement of the Density of the formulation[40]: The apparent densities of the tablets are calculated from their volumes and masses in triplicate. The volume V of the cylindrical tablets are calculated from their height h and radius (both determined with a micrometer gauge) using the mathematical equation for a cylinder

$$(V = A \times r2 \times h).$$

Determination of drug content in tablets: Three tablets from each batch are selected randomly and transferred to a 100ml volumetric flask filled up with 0.1(N) HCL. Kept it for 48hours then took 1ml from each of volumetric flask and transferred to the test tubes. Samples are then filtered, suitably diluted and analyzed spectrophotometrically at a suitable wavelength.

In-vitro dissolution study: The tablet was placed inside the dissolution vessel. 5ml of sample were withdrawn at time intervals of 1h, 2h, 3h, 4h, 5h, 6h, 8h, 10 h and 12h. The volume of dissolution fluid adjusted to 900 ml by replacing fresh 5ml of dissolution medium after each sampling. The release studies were conducted with 3 tablets, and the mean values were plotted versus time. Each sample was analyzed at maximum wavelength using double beam UV visible spectrophotometer against reagent blank and the corresponding concentration was determined from the respective calibration curve.

Buoyancy / Floating Test: The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag

Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT)[41].

Swelling Study: The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of percent weight gain, as given by the equation.

$$W_U = (W_1 - W_0)/ W_0 \times 100$$

Where, W_t = Weight of dosage form at time t.

W_0 = Initial weight of dosage form.

Advantages of Floating Drug Delivery System[42]: Floating dosage systems are important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages Include:

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.

2. Controlled delivery of drugs.

3. Delivery of drugs for local action in the stomach.

4. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.

5. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.

6. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.

7. When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

8. Treatment of gastrointestinal disorders such as gastro esophageal reflux.

9. Simple and conventional equipment for manufacture.

10. Ease of administration and better patient compliance.

11. Site-specific drug delivery.

Disadvantages of Floating Drug Delivery System [42]

The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach .

I. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.

II. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.

III. Some drugs present in the floating system causes irritation to gastric mucosa.

IV. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size. Therefore patients should not be dosed with floating forms just before going to bed.

Criteria Selection of Drug Candidate for FDDS[42]

1. Absorption from upper GIT e.g. Ciprofloxacin.

2. Drugs having low pKa, which remains unionized in stomach for better absorption.

3. Drugs having reduced solubility at higher pH, e.g. Rosiglitazone maleate, captopril and chordiazepoxide.
4. Local action as it seen in the treatment of *Helicobacter pylori* by Amoxicillin.
5. The bioavailability of drugs that get degraded in alkaline pH can be increased by formulating gastro-retentive dosage forms, e.g. Doxifluridine, which degrades in small intestine.
6. To minimize gastric irritation this may be sudden increase of drug concentration in the stomach, e.g. NSAID.

Limitations of FDDS[42]

1. The residence time in the stomach depends upon the digestive state. Hence, FDDS should be administered after the meal.
2. The ability to float relies in the hydration state of the dosage form. In order to keep these tablets floating *In vivo*, intermittent administration of water (a tumbler full, every 2 hrs) is beneficial.
3. The ability of drug to remain in the stomach depends upon the subject being positioned upright.
4. FDDS are not suitable for the drugs that have solubility or stability problems in the gastric fluid.
5. Drug like Nifedipine is well absorbed along the entire GIT and undergoes significant first pass metabolism, but it is not a desirable candidate for FDDS since the slow gastric emptying may lead to the reduced systemic bio-availability.

Application of FDDS[42]

1. Recent study indicated that the administration of diltiazem floating tablets twice a day might be more effective compared to normal tablets in controlling the blood pressure of hypertensive patients.

2. Modapar® HBS containing L-DOPA and Benserazide, here the drug was absorbed over a period of 6-8 hrs and maintained substantial plasma concentration for Parkinsonian patients. Cytotech® containing Misoprostol, a synthetic prostaglandin–EL analogue, for prevention of gastric ulcer caused by non-steroidal anti-inflammatory drugs (NSAIDS).4

3. Site specific drug delivery: These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., Riboflavin and Furosemide.

4. FDDS also serves as an excellent drug delivery system for the eradication of *Helicobacter pylori*, which causes chronic gastritis and peptic ulcers.

5. Developing HBS dosage form for Tacrin provide better delivery systems and reduced its GI side effects.

6. Treatment of gastric and duodenal ulcer.

Literature review

Literature review for understanding the study was done by referring to various national and international journals, published articles in various official standard books and referring to various websites.

K.Karunakar et. al [71]., prepare and evaluate floating drug delivery system of Lamivudine. Floating matrix tablets of Lamivudine were developed to prolong gastric residence time and increase its bioavailability. Rapid gastrointestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of the administered dose. The tablets were prepared by direct compression technique, using polymers such as hydroxyl propyl methyl cellulose (HPMC E15), Ethyl cellulose and Xanthan gum combination and other standard excipients. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of different concentrations of HPMC, EC and Xanthan gum on drug release profile and floating properties were investigated. Comparable release profiles between the commercial product and the designed system were obtained. The model fitting showed that the optimized formulation F2 formulations followed Korsmeyer and Peppas model, which had a higher value of correlation coefficient (r). While tablet hardness had little or no effect on the release kinetics and was found to be a determining factor with regards to the buoyancy of the tablets.

Varun Dasari et. al[72]., Formulation of potent drug molecules as dosage form still draws continuous interest and challenges against its optimization towards pharmacokinetics parameters like absorption, bioavailability, onset of action, duration of action Besides it has been proved that by increasing gastric retention time will increase the drug absorption effectively..Lamivudine is an potential anti-HIV agent, used for the long term treatment of HIV-1 infection.It is approved by the U.S Food and Drug Administration (FDA). The dissolution characteristics of optimized multi unit formulation MF8 is compared with that of the pure drug and Marketed formulation (EPIVIR). Compatibility among the drug and optimized polymer i.e., Geleol Pastilles was assessed by performing IR spectroscopy studies Characteristics with the aid of Geleol Pastilles as polymer. , very promising *in vitro* results were observed with multi unit floating formulations of

Lamivudine, further there is a scope to conduct the bioavailability studies in human volunteers to know the exact pharmacokinetics of the developed multi unit GFDDS of Lamivudine.

Ichikawa et al [43] developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sublayers to avoid direct contact between the 2 agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37ºC, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO2 was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/mL. It was found that the system had good floating ability independent of pH and viscosity and the drug (Para-amino benzoic acid) released in a sustained manner (Figure 1, A and B).

Stock well et al[44] prepared floating capsules by filling with a mixture of sodium alginate and sodium bicarbonate. The systems 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. The carbonates also provide the initial alkaline microenvironment for polymers to gel. Moreover, the release of CO 2 helps to accelerate the hydration of the floating tablets, which is essential for the formation of a bioadhesive hydrogel. This provides an additional mechanism (‘bioadhesion’) for retaining the dosage form in the stomach, apart from floatation. Floating dosage forms with an in situ gas generating mechanism are expected to have grater buoyancy and improved drug release characteristics. However, the optimization of the drug release may alter the buoyancy and, therefore, it is sometimes necessary to separate the control of buoyancy from that of drug release kinetics during formulation optimization.

Yang et al [45] 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 hydroxy propyl methyl cellulose (HPMC) and poly (ethylene oxide) (PEO) as the rate-controllingpolymeric membrane excipients. The design of the delivery system was based on the swellable asymmetric triple-layer

tablet approach. Hydroxypropylmethylcellulose and poly (ethylene 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 layers for instant release. 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.

Fahan Jalees ahmed[46] et al., Development and Evaluation of Floating Matrix Tablets of Acyclovir October – December 2011 RJPBCS Volume 2 Issue 4 Page No. 547 Acyclovir [9-(2-hydroxyethoxymethyl) guanine] is an acyclic nucleoside analogue of guanosine that is a potent and selective antiviral agent. It has a relatively short plasma half-life (3 hr). When orally administered, it is slowly and scarcely absorbed from the gastrointestinal tract. The plasma concentration reaches its therapeutic level in 1.5 to 2 hr. The short biological half life of drug favors the development of a sustained release formulation which retain in the stomach for a prolonged period of time.The present work emphasis on the study of dissolution studies and in vitro buoyancy of acyclovir floating system.

A. M Mahale et al, formulation and *in-vitro* evaluation of gastroretentive drug delivery system for acyclovir. International journal of comprehensive Pharmacy, DOI : 2011 [47]

Floating matrix tablets of acyclovir were developed to prolong gastric residence time and increase its bioavailability. The tablets were prepared by direct compression technique, using polymers such as Hydroxypropylmethylcellulose (HPMC, Methocel K100M), Carbopol and Sodium alginate alone or in combination. Sodium bicarbonate and Citric acid was incorporated as a gas-generating agent. All the tablets passed the compendial tests and other tests like weight variation, drug content, hardness, friability. The floating time was found to be more than 12 hrs. All the tablets showed the floating lag time of less than 10 minute.

T. Akelesh et al. Formulation development of gastro retentive floating tablet of acyclovir using natural gums, Scholars Research Library,2011,3(1): 254-261[48].

Floating tablets of Acyclovir was developed by using gas forming agents like sodium bicarbonate and natural gums like Locust bean gum, Sodium alginate and Xanthan gum by effervescent technique. Various combinations of floating polymers were used in this formulation. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, in vitro buoyance, and buoyancy lag time and dissolution studies. The formulation optimized for different concentration of natural gums like Locust bean gum, Sodium alginate and Xanthan gum.

J. Padmavathy et al, Formulation and evaluation of ofloxacin floating tablets using HPMC, International Journal of Pharmacy and Pharmaceutical Sciences, Vol 3, Issue 1, 2011[49]

The present study outlines a systematic approach for designing and development of Ofloxacin floating tablets to enhance the bioavailability and therapeutic efficacy of the drug. Different formulations were formulated by wet granulation technique using HPMC K4M, HPMC K15M and HPMC K100M (floating agent) as polymers along with sodium bicarbonate as gas generating agent. The formulations were evaluated for their physicochemical properties, buoyancy lag time, total floating time, swelling index and *invitro*drug release. It was found that the hardness of the tablets affects the Buoyancy characteristic of the dosage form. All six formulations possessed good floating properties with total floating time between 8 – 12 hrs.

Jaimini Manish et. al.[50], delayed release tablets of Losartan Potassium were formulated using two different grades of methocel K100 and K15 by effervescent technique. Sodium bi carbonate was employed as gas generating agent. Tablets prepared by wet granulation method were further evaluated for hardness, friability, weight variation, drug content, in-vitro buoyancy and dissolution studies. All the prepared tablets showed good in-vitro buoyancy. The effect of citric acid and two different grades of methocel on drug release profile and floating property were investigated.

Kumar.et. al.[51]developed floating tablets of metformin hydrochloride and evaluated for increase bioavailability by increasing gastric residence time and sustained release of drug on the upper part of gastrointestinal tract thereby diminishing side effects and enhanced patient compliance. Metformin hydrochloride, an oral anti-diabetic having narrow absorption window in the upper part of gastrointestinal tract, was formulated as floating matrix tablet using gas generating agent (potassium bicarbonate) and hydrophilic gelling polymer hydroxyl propyl methyl cellulose (hypromellose) by wet granulation technique. The prepared formulations were evaluated for floating time and *in-vitro* drug release studies by modified dissolution method.

Chodavarapuet al [52]**.,** investigated that the effectiveness of the edible gum of Abelmoschusesculentus as a polymer in the development of a gastric floating dosage form of metformin HCl. Abelmoschusesculentus, popularly known as okra, was shown to aid in the formulation of floating tablets. In the present study, it was used as a pharmaceutical excipient along with HPMC E15 in the formulation of floating tablets. The prepared tablets were tested for physicochemical properties, drug content uniformity, *in-vitro* drug release patterns and FT-IR spectral analysis. From the study, it was evident that the formulations which included abelmoschusesculentus gum (F1, F3, and F4) have lesser floating capacity but show a sustained release of drug whereas the formulation (F2) which contained only HPMC has higher floating capacity but poor sustained release of drug. The formulation of okra gum manifested a prolonged release of the activeingredients**.**

Kshirsagaret al[53]**.,**have developed a hydro dynamically balanced system of metformin as a single unit floating tablet. Various grades of low-density polymers were used for the formulation of this system. They prepared by physical blending of metformin and the polymers in varying ratios. The formulation was optimized on the basis of *in-vitro* buoyancy and *in-vitro* release in simulated gastric fluid pH 1.2. Tablets prepared with HPMC K15M and carbopol showed best *in-vitro* percentage release and selected as a optimize formulation. All the formulations were robust tablets with optimum hardness, consistent weight uniformity with low tablet friability. *In-*

vitro drug release tests of the tablets indicated the sustained release of metformin HCl was reported.

***Narayanet al*[54].,**have formulated the salbutamol sulphate as a floating matrix tablets and control the drug release up to 24 h for administration as once daily dose. Salbutamol sulphate is a short acting bronchodilators which have short biological half life about 2-4 h. Floating matrix tablets were formulated by using swelling polymer like methylcellulose, hydroxy propyl methyl cellulose (K100M, K4M) with different concentrations in the preparation of floating matrix tablets. Their formulation variables like hardness, polymer concentrations, and shape of the tablets were optimized to achieve the floating nature of the tablet in stomach for 24 h. In addition stearic acid is included in this formulation to evaluated release characteristics.

***Liandong et al*[55].,**have developed the dextromethorphan hydrobromide sustained-release (DMB-SR) tablets using floating technique to prolong the gastric residence time and compared pharmacokinetic behaviour with conventional sustained release tablets. DMB-SR floating tablets wereprepared employing hydroxypropyl methylcellulose as hydrophilic gel material, sodium bicarbonateas gas-generating agent and hexadecanol as floating assistant agent. An orthogonal experimentdesign method was used to select the optimized formulation. The floating tablets were evaluated foruniformity of weight, hardness, friability, drug content, floating characteristics, *in-vitro* release and *in-vivo* bioavailability.

***Varmaet al.*[56],**have developed sustained release gastroretentive dosage forms which were enabled to prolong the drug input to the upper parts of gastrointestinal tract and improve the bioavailability of medication that is characterized by narrow absorption window. Metformin hydrochloride was selected as a model drug because of poor absorption from low GI tract and less bioavailability above 50%. Hydroxy propyl methyl cellulose (HPMC K4M) and carbopol 934P were used as polymers and sodium bicarbonate as gas generating agent to reduce floating lag time. Tablets were prepared by wet granulation method. Floating tablets were evaluated for hardness, friability, weight variation, drug content, floating properties and *in-vitro* release pattern. The *in-vitro* drug release followed first order kinetics and drug release was found to be diffusion controlled.

Deshpande *et al*. [57](Deshpande et al., 1997a; Deshpande et al., 1997b) developed a controlled-release gastric retention system composed of a swellable core, which consisted of the drug, chlorphenamine maleate or riboflavin 5′ phosphate, and the expanding agents polyvinyl pyrrolidone (PVP), Carbopol 934P and calcium carbonate. The tablet core was coated with a permeable coating, consisting of blends of Eudragit RL® 30 D and NE 30 D in different ratios. The tablets swelled to 2- 4 times their original volume, while releasing the drug in a controlled manner. The optimal ratio of Eudragit® RL 30 D: NE 30 D was found to be 70: 30, which was optimum for sufficient elasticity to withstand the pressure of expansion during the initial swelling phase, and allowing the breakdown of the tablet following release of the drug.

Shalaby et al.[58]described enzyme-digestible hydrogels consisting of poly(vinyl pyrrolidone) crosslinked with albumin (Shalaby et al., 1992; Shalaby and Park, 1990). These gastroretentivehydrogels, swelled to a significant extent depending on the albumin content and degree of albumin alkylation and were degraded in the presence of pepsin. Even under fasted conditions, the gastric residence time in dogs exceeded 24 h. These hydrogels were used to deliver flavin mononucleotide, which is known to be absorbed only from the upper part of the small intestine, where the drug could be detected up to 50 h after administration in the blood, suggesting its efficient retention in the stomach.

Omidianet al.[59]developed superporous hydrogel hybrids, which are prepared by crosslinking a water-soluble or water-dispersible polymer to the formed superporous hydrogel (Omidian et al., 2005; Omidian et al., 2006). Examples for hybrid agents are polysaccharides, such as sodium alginate, pectin, chitosan or synthetic water-soluble hydrophilic polymers, e.g. poly(vinyl alcohol). Unlike superporous hydrogels and superporous hydrogel composites, superporous hydrogel hybrids are not easily breakable when stretched due to their highly elastic properties in the swollen state, which may be very useful for developing gastrointestinal DDS.

Yuasa *et al.*[60](Yuasa et al., 1996) developed intragastric floating and sustained release granules of diclofenac sodium using a polymer solution of HPC-L grade and EC, and calcium silicate as a floating carrier, which has a characteristically porous structure. The coated granules acquired floating ability from the air trapped in the pores of calcium silicate when they were coated with a polymer.

Whitehead *et al.*[61](Whitehead et al., 1996) developed multiple unit floating freeze dried calcium alginate beads. These beads maintained a positive floating force for over 12 h, and the density measurement, using a helium pycnometer, was less than 1 g/cm. The *in vivo* behavior of this system compared to non-floating multiple-unit dosage forms manufactured from identical material have also been performed using γ-scintigraphy in the fed state (Whitehead et al., 1998). Prolonged gastric residence times of over 5.5 h were achieved for the floating formulations, while the non-floating beads displayed short gastric residence times, with a mean onset emptying time of 1 h.This approach provides floating drug delivery systems based on the formation of CO2 gas. It utilizes effervescent components such as sodium bicarbonate (NaHCO3) or sodium carbonate, and additionally citric or tartaric acid (Rubinstein and Friend, 1994). Alternatively matrices containing chambers of liquids that gasify at body temperature could be used (Michaels, 1975; Micheals, 1974; Ritschel, 1991). Upon contact with the acidic environment, a gas is liberated, which produces an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float on the chyme.

Gröning et al[62](Gröning et al., 2007; Groning et al., 2006) developed gastroretentive dosage forms prepared from compressed collagen sponges. The sponges were manufactured by freeze-drying a riboflavin-containing collagen solution. The precompressed collagen was transported into a tablet machine for tablet compression. A second type of tablet was manufactured by combining compressed collagen sponges with hydrophilic matrix layers of hydroxypropyl methylcellulose (HPMC) containing captopril or acyclovir into a bilayer tablet. Following contact with aqueous fluids, the collagen sponge expanded to a large size. Both systems released the drug in a controlled manner. *In vivo* studies on riboflavin tablets have shown that the drug was absorbed for a long time period.

AIM

1. The basic goal of therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal.

2. Floating tablets are drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose in stomach region.

3. The main aim is to Formulate and Evaluate Floating tablets of Lamuvudine using various hydrophilic polymers.

Objective of the study:

The present study is planned with the following objectives:

- To prepare Lamuvudine floating tablets.
- To improve the floating time of the tablet.
- To prepare tablets by direct compression method.
- To investigate the pre compression & post compression parameters of the developed formulations.
- *In-vitro* characterization of the developed floating tablets.
- To determine the *In-vitro* drug release studies.

PLAN OF WORK

I. Literature survey

II. Pre-formulation studies

a) Pre-formulation study of Lamuvudine
b) Organoleptic Properties
c) Melting point of drug
d) Determination of solubility
e) Drug-Excipient compatibility studies

III. Evaluation of blends

a) Bulk density
b) Tapped density
c) Angle of repose
d) Carr's Index (Compressibility Index)
e) Hausner's Ratio

IV. Preparation of Floating tablets by using various concentrations of Polymers

- Direct compression Technique.

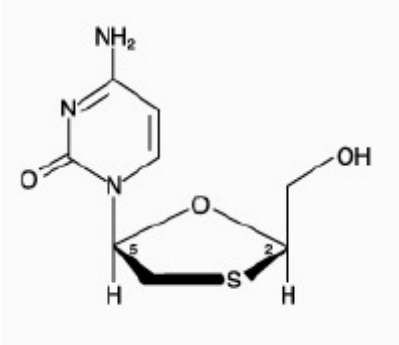
V. Evaluation of Matrix tablets

- Thickness
- Hardness
- Weight variation
- Friability
- Buoyancy test (Floating time)
- In-vitro drug release study
- Assay

DRUG PROFILE[63, 64]

Lamivudine: A reverse transcriptase inhibitor and zalcitabine analog in which a sulfur atom replaces the 3' carbon of the pentose ring. It is used to treat Human Immunodeficiency Virus Type 1 (HIV-1) and hepatitis B (HBV).

Structure



Structure of Lamivudine

Chemical name:

4-amino-1-[(2R, 5S)-2-(hydroxymethyl)-1, 3-oxathiolan-5-yl]-1,2 dihydropyrimidin-2-one

Molecular formula: $C_8H_{11}N_3O_3S$

Molecular weight: 229.25

Category: Antiretroviral (Nucleoside Reverse Transcriptase Inhibitor).

Biological profile

Mechanism of action

Lamivudine is a synthetic nucleoside analogue and is phosphorylated intracellularly to its active 5'-triphosphate metabolite, lamivudine triphosphate (L-TP). This nucleoside analogue is incorporated into viral DNA by HIV reverse transcriptase and HBV polymerase, resulting in DNA chain termination.

Pharmacokinetics:

Absorption: Rapidly absorbed, food effects on absorption T max – 0.9 ± 0.3 hrs in fasted state, 3.2 ± 1.3 hrs in fed state, there is no significant difference in systemic exposure (AUC) in the fed and fasted states. Absolute bioavailability: about 86% (range 86 ± 16%).

Distribution: Volume of distribution (Vd) oral: 1.3 ± 0.4 L/kg (range 12-14 L/kg). protein binding: < 36%. The single- and multiple dose Pharmacokinetics of Lamivudine are linear and dose proportional in a dose range of 10 to 60 mg/day. Steady-state achieved in 1-2 weeks. Average plasma concentration is about 83 ng/mL (n=114) with a range from 30 to 200 ng/mL.

Metabolism: Approximately 70% of an intravenous dose of Lamivudine is recovered as unchanged drug in the urine. In humans, the only known metabolite is the trans-sulfoxide metabolite Approximately 70% of the administered dose is excreted slowly in the urine, reaching a peak 7 to 10 hours after administration. Metabolites are detectable in the urine 120 hours after administration. Faecal elimination accounts for approximately 11 % of the administered dose. Lamivudine is usually completely eliminated within 144 hours post dose.

Excretion: Elimination half-life: 5 to 7 hours. The systemic clearance is 0.33±0.06 L/hr/kg. Elimination via the kidneys; approximately 5.2% ± 1.4% (range 5.1272 – 5.2728) of the daily dose is excreted in urine as unchanged Lamivudine.

Indication : For the treatment of HIV infection and chronic hepatitis B (HBV).

Dosage : For adults with HIV (or children over 12), the dose is 300mg once daily, or 150mg twice a day. Lamivudine is never used on its own in the treatment of HIV.

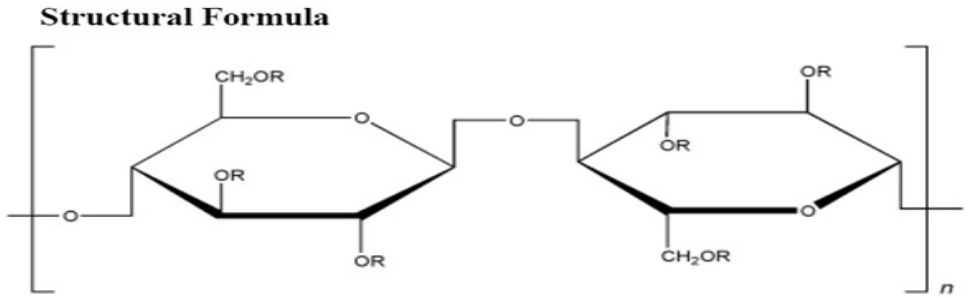
For the treatment of adults with hepatitis B, the dose is 100mg once daily. If co-infected with HIV, then the dose is as for HIV.

For a child 3 months to 12 years old, about 1.4-2 mg per lb. of body weight twice a day, no more than 150 mg per dose.

1. Hypromellose [65, 66, 67]:

Hypromellose is a semi synthetic, inert, viscoelastic polymer used as anophthalmic lubricant, as well as an excipient and controlled-delivery component in oral medicaments. Hypromellose is a partly O-methylated and O-(2-hydroxypropylated) cellulose.

Structural formula:



where R is H, CH_3, or $CH_3CH(OH)CH_2$

Synonyms: BenecelHydroxypropylmethylcellulose (HPMC), Methocel, Metolose.

Description: Odorless and tasteless, white or creamy-white fibrous or granular powder.

Acidity/alkalinity: pH = 5.5–8.0 for a 1% w/w aqueous solution.

Density (true): 1.326g/cm3.

Stability: Stable material, although it is hygroscopic after drying.

Viscosity: Ranges from 3-1, 00,000 cps.

Egs: Metolose 60SH, Metolose 65SH, Metolose 90 SH etc.

Functional Category

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

Solubility:

Soluble in cold water, forming a viscous colloidal solution; practically insoluble inchloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol anddichloromethane, mixtures of methanol and dichloromethane, and mixtures of water andalcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures ofdichloromethane and propan-2-ol, and other organic solvents.

Table II: Typical viscosity values for 2% (w/v) aqueous solutions of *Methocel* (Dow Chemical Co.). Viscosities measured at 20°C.

***Methocel* product**	**USP 28 designation**	**Nominal viscosity (mPa s)**
Methocel K100 Premium LVEP	2208	100
Methocel K4M Premium	2208	4000
Methocel K15M Premium	2208	15 000
Methocel K100M Premium	2208	100 000
Methocel E4M Premium	2910	4000
Methocel F50 Premium	2906	50
Methocel E10M Premium CR	2906	10 000
Methocel E3 Premium LV	2906	3
Methocel E5 Premium LV	2906	5
Methocel E6 Premium LV	2906	6
Methocel E15 Premium LV	2906	15
Methocel E50 Premium LV	2906	50
Metolose 60SH	2910	50, 4000, 10 000
Metolose 65SH	2906	50, 400, 1500, 4000
Metolose 90SH	2208	100, 400, 4000, 15 000

Safety: Non-toxic and non-irritant material, although excessive oralConsumptionmayhave a laxative effect.

Applications:

- As a tablet binder and as a matrix for use in extended-release tabletformulations.
- As a film forming agent at the concentrations of 2–20% w/w to coat thetablets.
- As an emulsifier, suspending agent, and stabilizing agent in topical gelsandointments.
- As a protective colloid, it can prevent droplets and particles from coalescing oragglomeratingthus inhibiting the formation of sediments.
- As a thickening agent (0.45–1.0% w/w), vehicles for eye drops and artificialtear solutions.
- In addition, it is used in the manufacture of capsules, as an adhesive in plasticbandages and asa wetting agent for hard contact lenses. It is also widely usedin cosmetics and food products.

SODIUM BICARBONATE:

Baking soda usually appears as a fine powder, but can also appear as a white solid that is crystalline. Ancients Egyptians used natural deposits of Natron, a mixture of sodium carbonate and sodium bicarbonate, as a cleansing agent like soap for a variety of purposes. In 1791 a French Chemist produced sodium bicarbonate as we know it today. In 1846, two New York bakers developed the process of making sodium bicarbonate and carbon dioxide into baking soda to help dough to rise quicker and more efficiently. Each of them started a company on their own, but later merged and became the makers of Arm & Hammer baking soda.

Summary: We are finding new uses for baking soda all the time, and here are just a few.

- A paste can be made that is very effective in cleaning and scrubbing.
- It has long been used as a natural tooth whitening agent. It has been used as a dry chemical for fire extinguishers.
- Antiquarian booksellers use it to absorb and remove the musty odor of older books.

- Everyone at one time or another has had a box of it in their refrigerator to help absorb odor.
- It adds a smooth texture to creams and lotions.
- It acts as a pH stabilizer

Precautions

People on sodium reduced diets should check with a doctor before consuming baking soda.

Citric Acid Monohydrate

1. Nonproprietary Names

• BP: Citric acid monohydrate

• JP: Citric acid

• PhEur: Acidumcitricummonohydricum

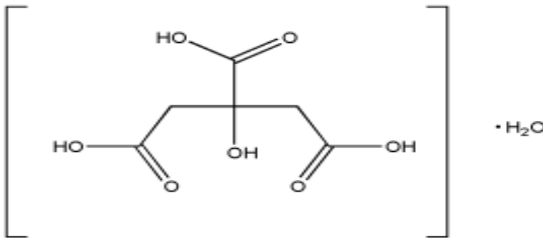
• USP: Citric acid

2. Synonyms E330; 2-hydroxypropane-1,2,3-tricarboxylic acid monohydrate.

3. Chemical Name and CAS Registry Number 2-Hydroxy-1,2,3-propanetricarboxylic acid monohydrate [5949-29-1]

4. Empirical Formula and Molecular Weight C6H8O7·H2O 210.14

5. Structural Formula



6. Functional Category

Acidifying agent; antioxidant; buffering agent; chelating agent; flavor enhancer.

7. Applications in Pharmaceutical Formulation or Technology

Citric acid (as either the monohydrate or anhydrous material) is widely used inpharmaceutical formulations and food products, primarily to adjust the pH of solutions. It hasalso been used experimentally to adjust the pH of tablet matrices in enteric-coatedformulations for colon-specific drug delivery.1 Citric acid monohydrate is used in thepreparation of effervescent granules, while anhydrous citric acid is widely used in thepreparation of effervescent tablets. Citric acid has also been shown to improve the stabilityof spray-dried insulin powder in inhalation formulations.In food products, citric acid is used as a flavor enhancer for its tart, acidic taste. Citric acidmonohydrate is used as a sequestering agent and antioxidant synergist. It is also a component of anticoagulant citrate solutions. Therapeutically, preparations containing citricacid have been used to dissolve renal calculi.

8. Description

Citric acid monohydrate occurs as colorless or translucent crystals, or as a white crystalline, efflorescent powder. It is odorless and has a strong acidic taste. The crystal structure is orthorhombic.

MICROCRYSTALLINE CELLULOSE [68, 69]

Synonyms: Avicel PH, Celex, Cellulose gel, Celphere, Ceolus KG, Emcocel, Ethisphere, Fibro-cel, Pharmacel, Tabulose.

Description:

It is a white, odourless, tasteless, extra free flowing powder which is relatively free from organic and non-organic contaminants. It is metabolically inert, and has excellent water absorptive, swelling & dispersion properties, is insoluble in water, dilute acid, common organic solvents and oils. It is partially soluble in dilute alkali.

Solubility:

Slightly soluble in 5%w/v sodium hydroxide solution. PracticallyInsoluble in water, dilute acids and most organic solvents.

Applications in Pharmaceutical Technology:

- MCC is widely used in pharmaceuticals primarily as a binder / Diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes (20-90%).
- In addition to its use as binder/diluents, microcrystalline cellulose also has some lubricant and disintegrating properties that make it useful in tableting.
- It is used in cosmetics and food products.

MAGNESIUM STEARATE

Synonyms: Magnesium octadecananoate, Octadecanoic acid, Magnesium salt, stearic acid magnesium salt.

Description: Magnesium stearate is a fine, white, precipitated or milled, Impalpable powder of low bulk density, having a faint odor or and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Solubility: Practically insoluble in ethanol, ethanol (95%), ether and Water, slightly soluble in warm benzene and warm ethanol (95%).

Applications in Pharmaceutical Technology:

- Magnesium stearate 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%w/w. It is also used in barrier creams.

INSTRUMENTS DETAILS

S.NO	EQUIPMENT NAME	SOURCE

1	DIGITAL WEIGHING MACHINE	SHIMADZU ATY 244
2	TABLET COMPRESSION MACHINE	KARNAVATHI MINI PRESS-II
3	PFIZER HARDNESS TESTER	CINTEX IND. CORPORATION, MUMBAI
4	FRIABILITY TESTER	ELECTROLAB PVT LTD. INDIA
5	USP DISSOLUTION APPARATUS	LAB INDIA DS 8000
6	TRAY DRYER	SISCO
7	UV-VIS DOUBLE BEAM SPECTROPHOTOMETER	ELICO SL 164 DOUBLE BEAM SPECTROPHOTOMETER

INGREDIENT DETAILS

S.NO	DRUG/EXCIPIENTS	NAME OF SUPPLIER

1	LAMUVUDINE	ALKEM PVT MUMBAI
2	HPMC E15	COLORCON
3	HPMC K15M	COLORCON
4	SODIUM BI CARBONATE	SD FINE –CHEM PVT, MUMBAI
5	CITRIC ACID	SD FINE –CHEM PVT, MUMBAI
6	MICROCRYSTALLINE CELLULOSE	SD FINE –CHEM PVT, MUMBAI
7	MAGNESIUM STEARATE	SD FINE –CHEM PVT, MUMBAI
8	TALC	SD FINE –CHEM PVT, MUMBAI

METHODOLOGY

Colour, odor, taste and appearance:

The color, odor and taste of the drug were recorded using descriptive terminology.

Melting point determination:

Melting point of the drug sample was determined by capillary method by using melting point apparatus. The reported and observed melting point is shown in Table.

Determination of solubility:

The solubility of the Lamuvudine was determined by adding excess amount of drug in the solvent and equilibrium solubility was determined by taking supernatant and analyzing it on Lab India, double beam spectrophotometer. The reported and observed melting point is shown in Table.

% solubility = sample absorbance /standard absorbance × dilution factor ×100

Fourier Transformation Infra-red (FTIR) analysis:

Infra-red spectroscopy analysis was performed by Fourier Transformation Infrared Spectrophotometer Alpha Brooker FTIR (Tokyo, Japan).The instrument was calibrated by using polystyrene film.

Ultraviolet Visible (UV-visible) spectroscopy:

Construction of Calibration curve of model drugs by UV-Visible spectroscopy:

Preparation of Standard stock solutions:

Lamuvudine equivalent to 100 mg was weighed and transferred to 100 ml volumetric flask, dissolved in methanol and the final volume was made upto 100ml with 0.1N HCL. The resulted solution had the concentration of 1mg/ml (1000µg/ml) which was labeled as “stock solution A”.

From the stock solution A, 1 ml was pipette out in 10ml volumetric flask and the final volume was made upto 10ml with 0.1N HCL. The resulted solution had the concentration of 0.1mg/ml (100µg/ml) which was labeled as “stock solution B”. This stock solution B is used as working stock solution for further study. Further dilutions were prepared from the same solution.

Preparation of Standard solutions:

From the stock solution B, further dilution was made with 0.1N HCL in 10 ml volumetric flasks to get the solutions in the range of 2-10 µg/ml concentration and absorbance was recorded at 280 nm against suitable blank using UV-Spectrophotometer (UV-1601, Shimadzu, Japan).A calibration curve of absorbance against concentration was plotted and the drug follows the Beer's & Lambert's law in the concentration range of 2-10µg/ml. The Regression equation and correlation coefficient was determined.

Evaluation of Blend:

Angle of Repose:

The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

$$\text{Angle of repose} = \tan^{-1}(h/r)$$

Where, h = height r = radius

Procedure:

- 20gms of the sample was taken
- The sample was passed through the funnel slowly to form a heap.
- The height of the powder heap formed was measured.
- The circumference formed was drawn with a pencil on the graph paper.

The radius was measured and the angle of repose was determined. This was repeated three times for a sample.

Bulk density:

Bulk density is ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduated cylinder or through volume measuring apparatus in to cup.

Bulk density = M / V_0

Where M= mass of the powder; V_0=bulk volume of the powder.

Tapped density:

A known quantity of powder was transferred to a graduated cylinder and volume V0 was noted. The cylinder fixed to a density determination apparatus, tapped for 200 times then reading was observed. The density is achieved by mechanically tapped by a measuring cylinder containing the powder sample. After observing the initial volume the cylinder is mechanically tapped and volume reading were taken until little further volume changes is observed.

$$\text{Tap density} = M / V_r$$

Where M = mass of the powder, V_r = final tapping volume of the powder.

Compressibility index and Hausner ratio:

Basic methods for the determination of compressibility index and Hausner ratio:

While there are some variations in the method of determining the compressibility index and Hausner ratio, the basic procedure is to measure the unsettled apparent volume,(V_O), and the final tapped volume, (V_f), of the powder after tapping the material until no further volume changes occur. The compressibility index and the Hausner ratio are calculated as follows:

Compressibility index = $100 \times Vo\text{-}V_f/Vo$

Hausner ratio = Vo/V_f

Where, V_o = apparent volume, V_f= final tapped volume. Alternatively, the compressibility index and hausner ratio may be calculated using measuredvalues of bulk density and tapped density as follows:

Compressibility index = 100 ×{ tapped density - bulk density / bulk density}

Hausner ratio = tapped density / bulk density

In a variation of these methods, the rate of consolidation is sometimes measured rather than, or in addition to, the change in volume that occurs on tapping. For the compressibility index and the hausner ratio, the generally accepted scale of flow ability is described in the following table.

Flow properties and corresponding Angle of repose, Compressibility index and Hausner ratio:

Table 5: Flow properties determination

S. No	Flow properties	Angleof repose(θ)	Compressibility Index (%)	Hausner ratio
1	Excellent	25-30	<10	1.00-1.11
2	Good	31-35	11-15	1.12-1.18
3	Fair	36-40	16-20	1.19-1.25
4	Passable	41-45	21-25	1.26-1.34
5	Poor	46-55	26-31	1.35-1.45
6	Very poor	56-65	32-37	1.46-1.59
7	Very very poor	> 66	>38	>1.6

EVALUATION OF TABLETS:

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, Friability, Buoyancy test and invitro-dissolution characters.

1. Physical Appearance:

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc.

2. Size& Shape:

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

3. Weight variation test:

This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests.. These tests are primarily based on the comparison of the weight of the individual tablets (xi) of a sample of tablets with an upper and lower percentage limit of the observed sample average (x-mean). The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form.

Method:

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Table 6: Limits for Tablet Weight variation test:

Average weight of tablet (mg)	**% Difference allowed**
130 or less	10 %
From 130 to 324	7.5 %
> 324	5 %

4. Content Uniformity:

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated tablets and all capsules intended for oral administration where the range of size of the dosage form available include 50mg or smaller sizes.

Method:

Randomly select 30 tablets. 10 of these assayed individually. The Tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labeled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labeled content. If these conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

Friability:

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

Method:

A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

$$\% \text{ friability} = (W_1 - W_2) / W_1 \times 100$$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

Floating lag time:

The time between the introduction of the tablet into the medium and its rise to upper one third of the dissolution vesselis termed as floating lag time and the time for which the dosage form flo ats is termed as the floating or flotation time. These tests are usually performed in simulated gast ric fluid or 0.1NHCl maintained at 37 ^{0}C, by using USP dissolution apparatus containing 900 ml of 0.1N HCl as the dissolution medium.

Drug release

The drug release from the Lamuvudine tablets was investigated in a USP-II (paddle) apparatus, 900 ml of 0.1N HCl (50 rpm, 37°C). At predetermined time intervals, 5-ml samples were withdrawn and take 1ml sample and diluted to 10 ml and then analyzed with UV spectrophotometry at λmax=280 nm.

Drug release kinetics[70]:

Dissolution data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

Zero-Order Kinetics:

Zero order as cumulative amount of ***Percentage drug released v_s time***

$$\mathbf{C = K_0 t}$$

Where *K0* is the zero-order rate constant expressed in units of concentration/time and *t* is the time in hours. A graph of concentration vs time would yield a straight line witha slope equal to *K0* and intercept the origin of the axes.

First order kinetics:

First order as log cumulative percentage of ***log (%) cumulative drug remaining $v_s$time*****,**

$$\mathbf{Log\ C = Log\ C_o - k\ t / 2.303}$$

Where $C_0$is the initial concentration of drug, *k* is the first order constant, and *t* is the time.

Higuchi Model:

Higuchi's model as ***cumulative percentage of drug released v_s square root of time***

$$\mathbf{Q = K\ t_{1/2}}$$

Where *K* is the constant reflecting the design variables of the system and *t* is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Korsmayer Peppas equations:

Korsmeyerpeppas equation used to determine the mechanism of drug release form the polymer matrix of the tablet***. Log cumulative percentage of drug released VS Logtime***, and the exponent *n* was calculated through the slope of the straight line.

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

Where *Mt/M_* is the fractional solute release, *t* is the release time, *K* is a kinetic constant characteristic of the drug/polymer system, and *n* is an exponent that characterizes the mechanism of release of tracers. For cylindrical matrix tablets, if the exponent $n = 0.45$, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release.

Hixsoncrowell erosion equation:

Hixson-Crowell cube root law, as the ***cube root of percentage drug remaining vs. time*** correlated the release from systems with polymer erosion/dissolution resulting in a change in surface area and diameter of particles or tablets.

$$Q_0^{1/3} - Q_t^{1/3} = kHC_t \ldots\ldots..(4)$$

Where, Qt is the amount of drug released in time t, Q0 is the initial amount of the drug in the tablets, and kHC is the rate constant for the Hixson-Crowell rate equation.

Stability studies:

Selected Formulation was subjected to stability studies as per ICH guidelines.

Following conditions were used for Stability Testing.

1. 25^0C/60% RH analyzed every month for period of three months.
2. 30^0C/75% RH analyzed every month for period of three months.
3. 40^0C/75% RH analyzed every month for period of three months.

FORMULATION DEVELOPMENT

Procedures:

The Purpose of key ingredients included in the formulation.

Table: COMPOSITION OF LAMUVUDINE FLOATING TABLETS

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	**F10**	F11
Lamuvudine	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	**100 mg**	100 mg
HPMC E 15	50 mg	100 mg	150 mg	200 mg	---	---	---	---	50 mg	**100 mg**	150 mg
HPMC K 15M	---	---	---	---	50 mg	100 mg	150 mg	200 mg	150 mg	**100 mg**	50 mg
Sodium bi carbonate	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	**30 mg**	30 mg
Citric acid	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	**5 mg**	5 mg
Micro Crystalline Cellulose	255 mg	205 mg	155 mg	105 mg	255 mg	205 mg	155 mg	105 mg	105 mg	**105 mg**	105 mg
Megnesium stearate	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	**5mg**	5mg
Talc	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	**5mg**	5mg
Total Weight	450 mg	450 mg	450 mg	450 mg	450 mg	450 mg	450 mg	450 mg	450 mg	**450 mg**	450 mg

Preparation of Formulation:

1. Drug and polymers pass through 40 # mesh separately and then transfer the polymer (i.e. HPMC E15 or HPMC K15M or in combination) into china dish and melt it and then add the drug and cool to room temperature.
2. Add diluents and other excipients to the above mixture. Finally add the Glidant (Magnesium Stearate) to the above blend mix it for 2min.
3. Compressed the above lubricated blend by using 8 mm round punches.

RESULTS AND DISCUSSION

PREFORMULATION:

S.NO	API CHARACTERISATION	RESULTS
1	Physical Appearance	Lamivudine is a white to off-white crystalline solid
2	Melting point	160-162 °C
3	Solubility	Soluble in water; sparingly soluble in methanol, practically insoluble in acetone.
4	Bulk density	1.16 gm/ml
5	Tapped Density	1.35 gm/ml
6	Carr's index/Compressibility index	14.07
7	Hausner's Ratio	0.99

Conclusion:

The value of compressibility index above 25%, 15-25%, less than 15% indicates poor flowability, optimum flowability and high flowability respectively.

List of Micromeritic properties of directly compressible powder:

parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Angleof repose	$27^0$55'	29^o39'	$26^0$74'	$28^0$81'	$28^0$65'	$26^0$74'	28^o39'	$21^0$81'	$23^0$81'	26^o39'	$20^0$81'
Bulk density	0.48	0.50	0.66	0.77	0.60	0.55	0.46	0.48	0.66	0.46	0.77
Tapped density	0.53	0.51	0.76	0.82	0.64	0.58	0.51	0.53	0.76	0.51	0.82
%Compressibility	9.09	3.33	13.15	5.88	5.88	5.00	9.80	9.09	13.15	9.80	5.88
Hausner's ratio	1.10	1.03	1.15	1.06	1.06	1.05	1.10	1.10	1.15	1.10	1.06

Lamivudine equivalent to 100 mg was weighed and transferred to 100 ml volumetric flask, dissolved in methanol and the final volume was made upto 100 ml with 0.1N HCL. The resulted solution had the concentration of 1mg/ml (1000µg/ml) which was labeled as "stock solution A".

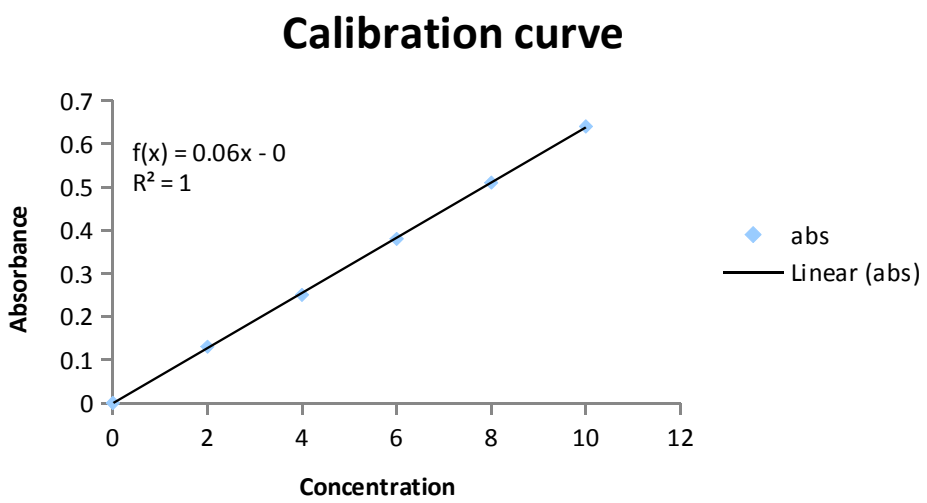
From the stock solution A, 1 ml was pipette out in 10ml volumetric flask and the final volume was made up to 10ml with 0.1N HCL. The resulted solution had the concentration of 0.1mg/ml (100µg/ml) which was labeled as "stock solution B". This stock solution B is used as working stock solution for further study. Further dilutions were prepared from the same solution.

Preparation of Standard solutions:

From the stock solution B, further dilution was made with 0.1N HCL in 10 ml volumetric flasks to get the solutions in the range of 2-10 µg/ml concentration and absorbance was recorded at 280 nm against suitable blank using UV-Spectrophotometer (UV-1601, Shimadzu, Japan).A calibration curve of absorbance against concentration was plotted and the drug follows the Beer's & Lambert's law in the concentration range of 2-10µg/ml. The Regression equation and correlation coefficient was determined.

Table 14: Standard graph of Lamivudine in 0.1 N HCl at λ_{max}= 280nm

S. NO.	CONCENTRATION(µg/ml)	ABSORBANCE
1	0	0
2	2	0.130
3	4	0.250
4	6	0.380
5	8	0.510
6	10	0.640



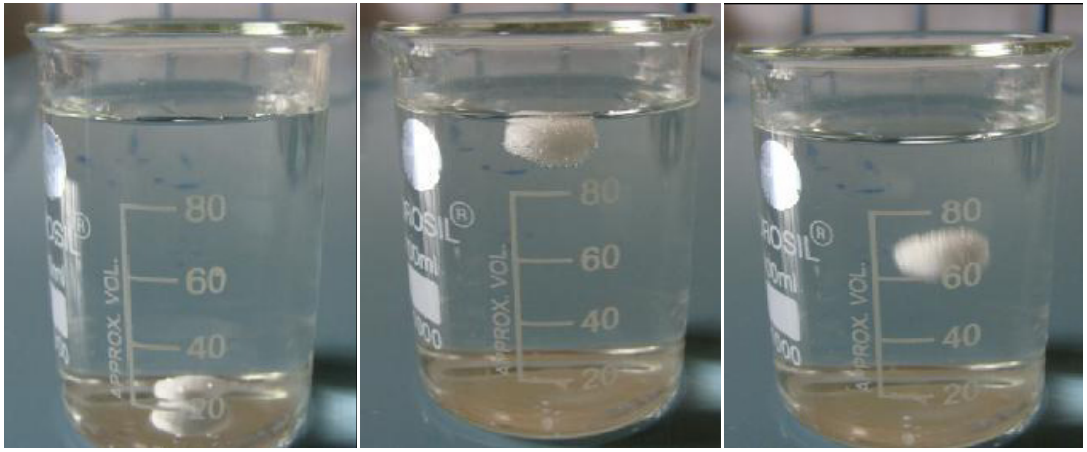
Evaluation of the Prepared Tablets for Physical Parameters:

All formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeial limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

Table 15: Results for Evaluation parameters of all formulations

parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Weight variation	450±0.4	449±0.5	449±0.4	450±0.5	449±0.1	450±0.3	450±0.2	450±0.4	450±0.7	450±0.3	450±0.1
Thickness (mm)	2.9±0.4	2.8±0.9	2.9±0.2	2.9±0.3	2.8±0.8	2.9±0.2	2.8±0.9	2.5±0.1	2.5±0.2	2.8±0.9	2.5±0.2
Hardness (kg/cm^2)	8.9±1.4	7.4±1.2	8.2±1.2	6.9±0.9	8.4±1.9	8.1±1.7	8.2±1.5	8.3±1.6	8.2±1.4	8.2±1.5	8.3±1.5
Friability	0.22% ±0.2	0.26% ±0.1	0.25% ±0.19	0.25% ±0.3	0.25% ±0.1	0.22% ±0.1	0.21% ±0.4	0.21% ±0.5	0.21% ±0.7	0.21% ±0.4	0.21% ±0.5

The floating tablets of Lamivudine were prepared by using HPMC E15 and HPMC K15M. Nine different formulations were prepared using different ratios of polymers. The prepared formulations were evaluated for floating lag time and buoyancy time. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N HCl). It was observed that the gas generated is trapped and protected within the matrix, formed by polymers, thus density of the tablet decreased and it becomes buoyant. The floating lag time of the optimized formulation F-10 was 30 sec.



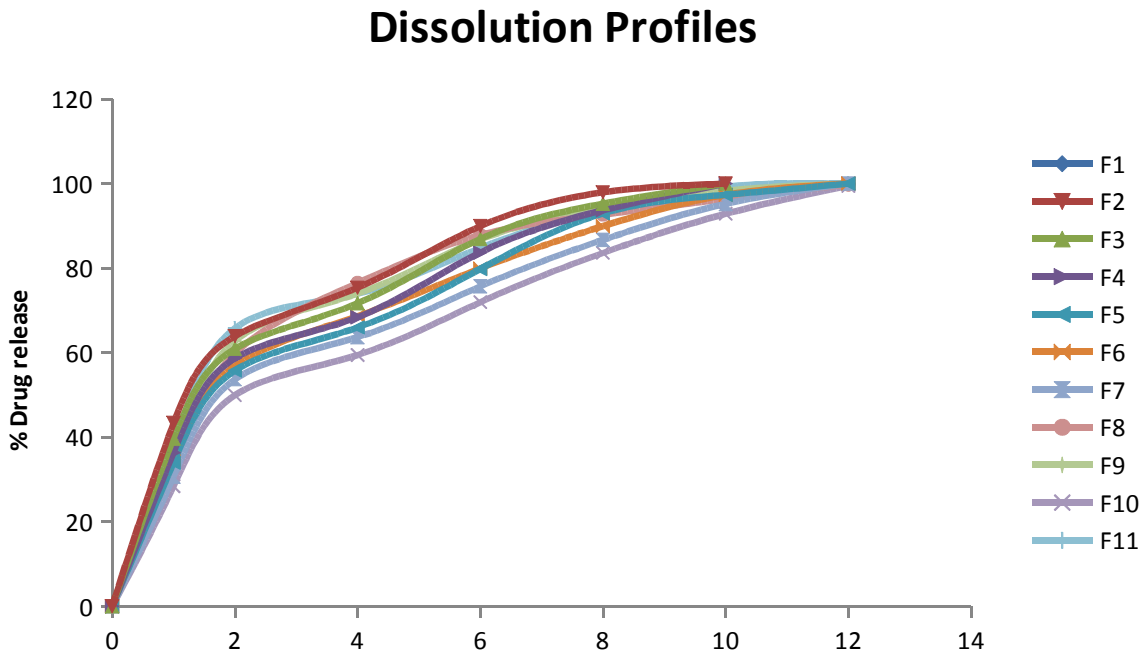
In vitro Dissolution studies:

The dissolution conditions used for studying the drug release from tablet of Lamivudine are:

Apparatus	: USP apparatus II (Paddle)
Agitation speed (rpm)	: 50rpm
Medium	: 0.1N HCl
Volume	: 900 ml
Temperature	: 37.0 ± 0.5 C

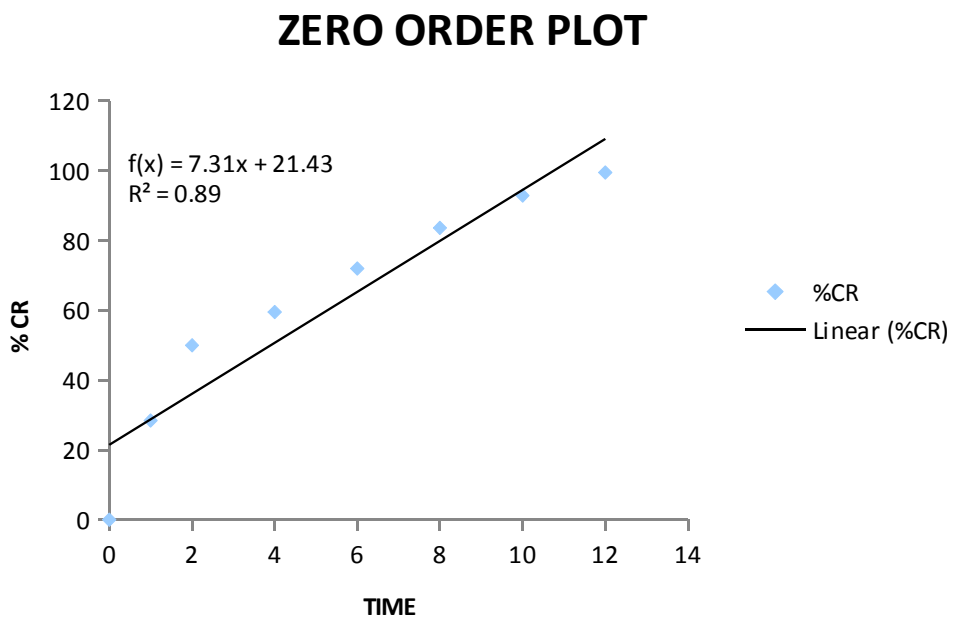
Table 16: Results of Dissolution profile for F1-F11:

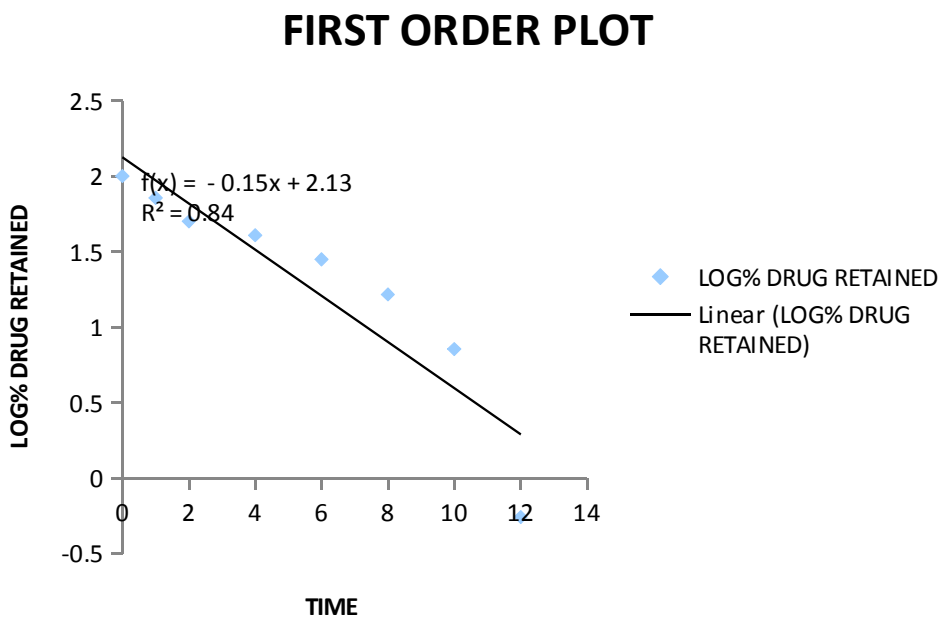
Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
0	0	0	0	0	0	0	0	0	0	0	0
1	48.67	43.36	39.67	36.37	33.95	34.67	30.67	33.33	34.95	28.41	37.95
2	66.91	63.92	60.91	58.68	55.78	56.91	53.68	59.76	62.78	49.94	65.78
4	79.67	75.36	71.67	68.37	65.95	68.67	63.67	76.49	73.95	59.45	73.95
6	91.91	89.92	86.91	83.68	79.78	79.91	75.68	87.81	86.78	71.94	84.78
8	99.24	97.92	95.24	93.68	92.94	89.92	86.68	92.67	93.94	83.59	93.94
10	100	100	100	100	97.35	97.32	95.19	96.35	98.28	92.86	99.28
12					100	100	100	99.78	100	99.45	100



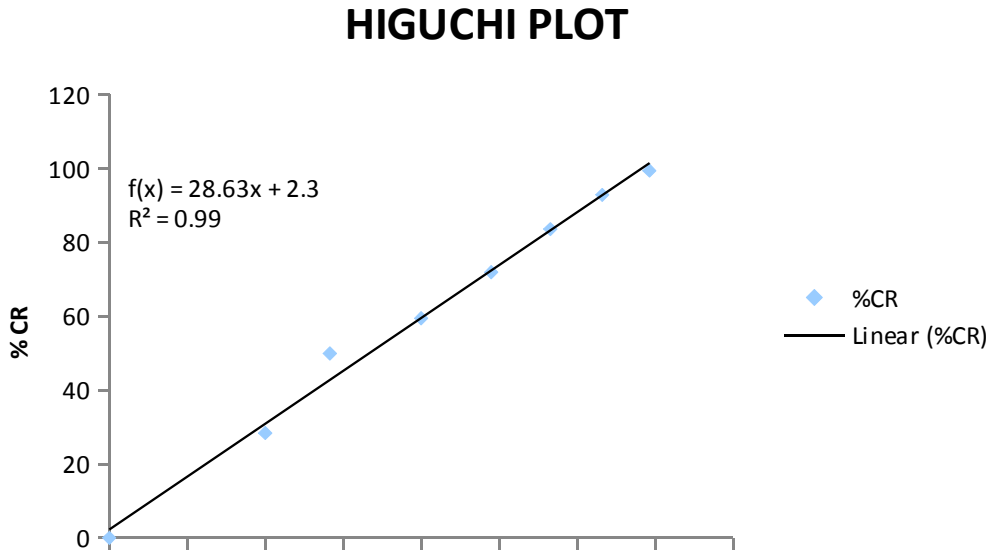
Dissolution data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

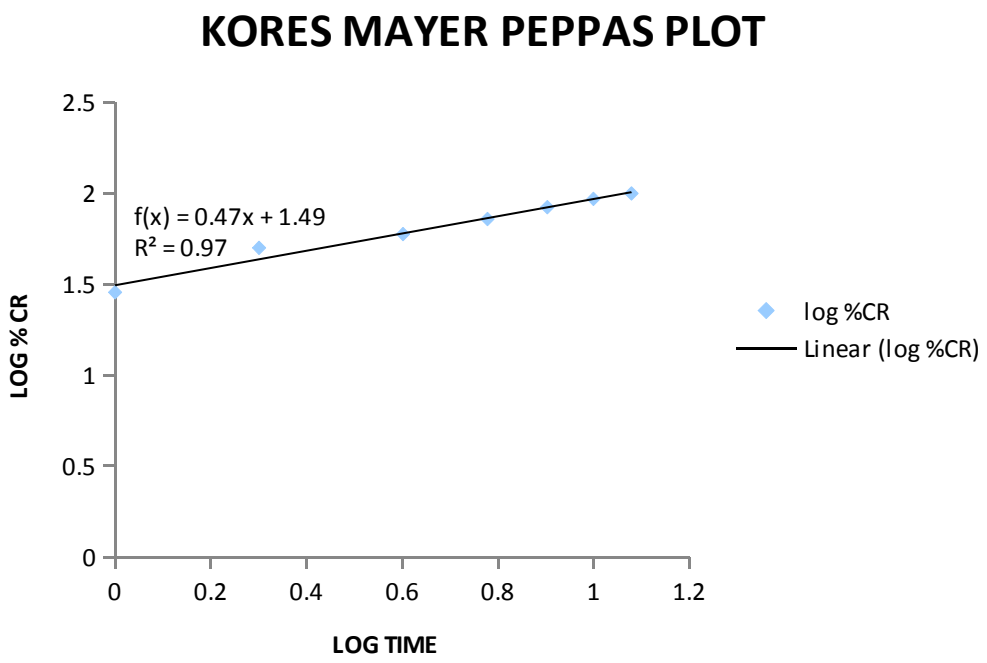
S.NO	time	log T	Square root of Time	%CR	%Drug remaining	log %CR	LOG% DRUG RETAINED	cube root of %drug remaining
0	0	0	0	0	100	0	2	4.641589
1	1	0	1	28.41	71.59	1.453471	1.854852	4.152256
2	2	0.30103	1.414214	49.94	50.06	1.698449	1.699491	3.685505
3	4	0.60206	2	59.45	40.55	1.774152	1.607991	3.435555
4	6	0.778151	2.44949	71.94	28.06	1.85697	1.448088	3.038756
5	8	0.90309	2.828427	83.59	16.41	1.922154	1.215109	2.541184
6	10	1	3.162278	92.86	7.14	1.967829	0.853698	1.9256
7	12	1.079181	3.464102	99.45	0.55	1.997605	-0.25964	0.819321



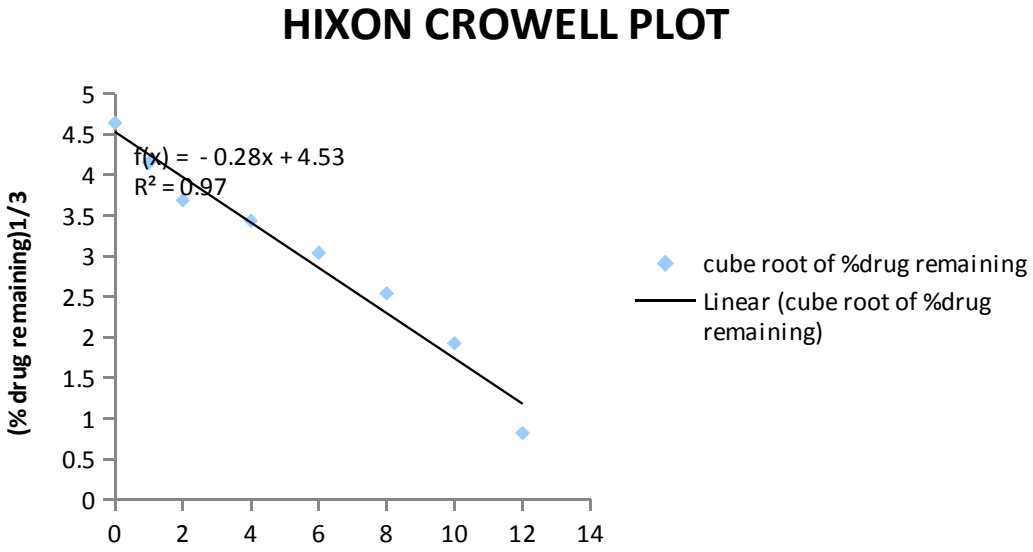


First order plot for optimized formulation





Korsmayer plot for optimized formulation



Stability Study

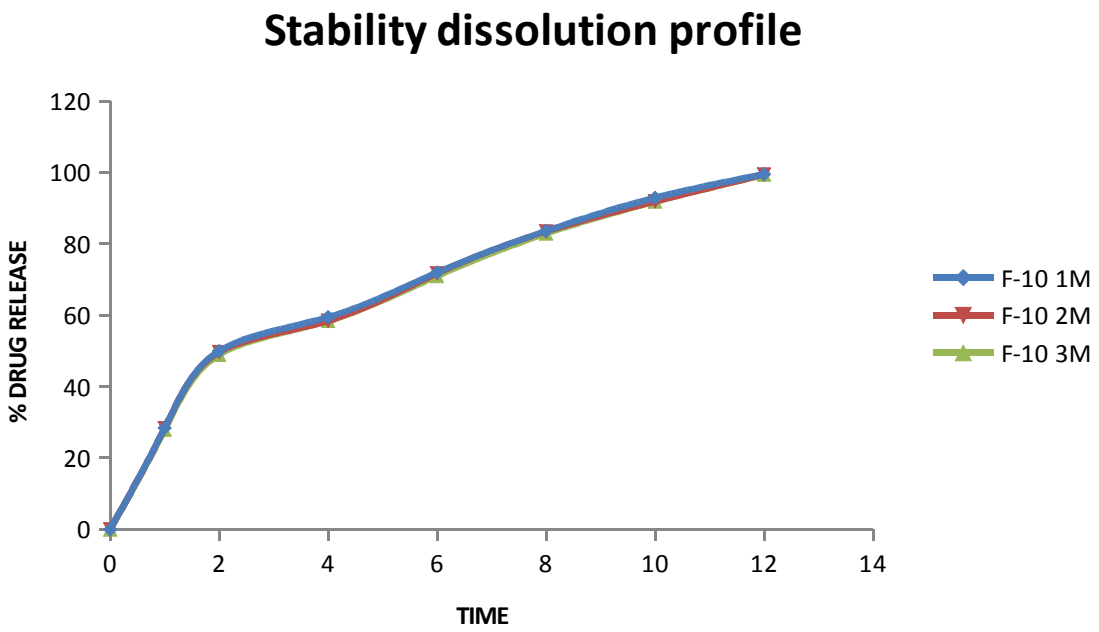
There was no significant change in physical and chemical properties of the tablets of formulation F-10 after 3 Months. Parameters quantified at various time intervals were shown;

Results of stability studies of optimized formulation F-10

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F10	25^{0}C/60%RH % Release	99.45	99.44	99.38	99.32	Not less than 85 %
F10	30^{0}C/75% RH % Release	99.45	99.34	99.33	99.31	Not less than 85 %
F10	40^{0}C/75% RH % Release	99.45	99.43	99.38	99.32	Not less than 85 %
F10	25^{0}C/60% RH Assay Value	99.78	99.67	99.64	99.63	Not less than 90 % Not more than 110 %
F10	30^{0}C/75% RH Assay Value	99.77	99.66	99.64	99.64	Not less than 90 % Not more than 110 %
F10	40^{0}C/75% RH Assay Value	99.77	99.65	99.65	99.64	Not less than 90 % Not more than 110 %

Stability dissolution profile of F-10 for 1st, 2nd & 3rd months

S.NO.	TIME(Hrs)	F-10 1M	F-10 2M	F-10 3M
1	0	0	0	0
2	1	28.41	28.35	27.88
3	2	49.94	49.62	48.91
4	4	59.45	58.40	58.38
5	6	71.94	71.69	70.96
6	8	83.59	83.42	82.83



Stability dissolution profile of F-10 for 1st, 2nd & 3rd months

CONCLUSION

The objective of the present study is to develop a Floating matrix tablets of Lamivudine. In this present study an attempt was made to increase the therapeutic effect of Lamivudine by continuously releasing the drug up to an extended period of time by formulating the Floating matrix tablets.

Systematic studies were conducted using different concentration of rate releasing polymers like HPMC E15 and HPMC K15M for extending the drug release up to 12 hrs. All the prepared systems were evaluated for the different properties. Before the preparation of tablets, preformulation studies to find out the micromeritic properties to assess flowability, compressibility properties and solubility studies. And all the formulations gave good results for above preformulation studies.

Formulated tablets gave satisfactory results for various physical tablet evaluation parameters like tablet dimensions, hardness, friability, weight variation, content uniformity, all the formulations were found within the permissible range.

Finally it was concluded that:

Amongall the formulations (F1-F11), it was observed that Formulation-10 has shown better dissolution profile. So Formulation-10 was found to be the best formulation when compared with other prepared formulations. The polymers were used at the different concentrations in the formula, much difference were observed in the release characteristics of the floating tablets prepared. The release data were analyzed as per zero order, first order, Higuchi and Korsmeyer & Peppas models. The correlation coefficient (r2) values in the analysis of release data as per various models are mentioned. Analysis of the release data as per zero order and first order kinetic models indicated that the drug release from floating tablets formulated followed First

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