FORMULATION DESIGN, DEVELOPMENT AND *INVITRO* EVALUATION OF ABACAVIR SULPHATE GASTRORETENTIVE MICROSPHERES

A Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY,

CHENNAI- 600 032

In partial fulfilment of the award of the degree of

MASTER OF PHARMACY

IN

Branch-I -- PHARMACEUTICS

Submitted by

Name: SHYAMALA. J. K

REG.No.261510262

Under the Guidance of

Mr. K. JAGANATHAN, M.Pharm.,

DEPARTMENT OF PHARMACEUTICS

J.K.K. NATTARAJA COLLEGE OF PHARMACY

KUMARAPALAYAM – 638183

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CERTIFICATES

EVALUATION CERTIFICATE

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Internal Examiner **External Examiner**

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DECLARATON

I do hereby declared that the dissertation **"FORMULATION DESIGN, DEVELOPMENT AND *INVITRO* EVALUATION OF ABACAVIR SULPHATE GASTRORETENTIVE MICROSPHERES"** submitted to "**The Tamil Nadu Dr. M.G.R Medical University - Chennai",** for the partial fulfilment of the degree of **Master of Pharmacy** in **Pharmaceutics,** is a bonafide research work has been carried out by me during the academic year 2016-2017, under the guidance and supervision of **Mr. K. JAGANATHAN, M.Pharm.,** Assistant Professor, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

I further declare that this work is original and this dissertation has not been submitted previously for the award of any other degree, diploma, associate ship and fellowship or any other similar title. The information furnished in this dissertation is genuine to the best of my knowledge.

Place: Kumarapalayam **Mrs. SHYAMALA. J. K**

Date: **Reg.no. 261510262**

Dedicated to Parents, Teachers & My Family

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ACKNOWLEDGEMENT

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SYMBOL INDEX

Symbols		Explanation
Rpm	:	Revolutions per minute
°C	:	Degree celsius
Fig	:	Figure
E.g.	:	Example
Mg	:	Milligram
Min	:	Minutes
Ml	:	Milliliter
µg (mcg)	:	Microgram
µg/ml	:	Microgram per milliliter
%	:	Percentage
SDN	:	Standard deviation
R^2	:	Regression

FORMULATION DESIGN, DEVELOPMENT AND *INVITRO* EVALUATION OF ABACAVIR SULPHATE GASTRORETENTIVE MICROSPHERES

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ABSTRACT

The aim of present work is to prepare floating microspheres of Abacavir sulphate using HPMC K100M and HPMC K4M as polymer. Floating drug delivery system have a bulk density less than gastric fluids and so remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. Abacavir sulphate an anti HIV drug . The short half life of Abacavir sulphate and multiple administration dose make Abacavir sulphate a very good candidate for formulation of floating drug delivery system. Floating microspheres of Abacavir sulphate were prepared by solvent evaporation method using HPMC K100M and HPMC K4M as polymer. The floating microspheres was evaluated such as micromeritic properties, percentage yield, *invitro* buoyancy, incorporation efficiency, drug polymer compatibility (IR study), scanning electron microscopy and drug release of microspheres. The micromeritic properties was found to be good and scanning electron microscopy confirmed their hollow structure with smooth surface. Formulation F7 prepared with combination of HPMC K100M and HPMC K4M with drug which exhibited excellent micromeritic properties, percentage yield, *invitro* buoyancy, incorporation efficiency and percentage drug release 90.12 % for a period of 12 hrs. The data obtained in this study thus suggest that a floating microspheres of Abacavir sulphate are promising for sustained drug delivery which can reduce dosing frequency.

1. INTRODUCTION

During the last three decade many studies have been performed concerning the sustained release dosage form of drugs, which have aimed at the prolongation of gastric emptying time (GET). The GET has been reported to be from 2 to 6 hours in humans in the fed state. Accordingly orally, sufficient bioavailability and prolongation of the effective plasma level occasionally cannot be obtained.

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the 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 gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal 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 absorbed[(1)].

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

1.1. GASTRO RETENTIVE DOSAGE FORMS (GRDF)[(2)]

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage

form (GRDF or GRDS). GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form. Dosage form with prolonged GRT, i.e. gastro retentive dosage form (GRDF), will bring about new and important therapeutic options such as –

1) This application is especially effective in sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To override this problem, erodible, gastro retentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.
2) GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (For e.g. Eradicating Helicobacter pylori from the sub mucosal tissue of stomach) making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis, reduce the risk of gastric carcinoma and administer non-systemic controlled release antacid formulations (calcium carbonate).
3) GRDFs can be used as carriers for drugs with so-called absorption windows. These substances for e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillin, cephalosporin, amino glycosides, tetracycline etc.), are taken up only from very specific sites of the GI mucosa.

1.1.1. BASIC GASTROINTESTINAL TRACT ANATOMY & PHYSIOLOGY[1,2,5,7,10]

Anatomy

The stomach is an organ for storage and mixing. Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, capable of displaying a large expansion to accomadate food without much increase in intragastric pressure. Whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. The opening nearer to esophagus is called as cardiac end characterized

by pyrolic sphincter. Under fasting conditions the stomach is collapsed bag with residual volume of 50 ml and contains a small amount of gastric fluid and air.

Mucosa

When stomach is empty the mucous membrane lining is thrown in longitudinal folds or rugae, and when full the rugae are ignored out and the surface is a smooth velvety appearance. There are numerous gastric glands situated below the surface in the mucous membrane consisting of the specialized cells that secrete gastric juice into the stomach.

Nerve supply

The sympathetic supply to the stomach is mainly from coeliac plexus and parasympathetic supply is from vagus nerves. Sympathetic stimulation reduces motility of the stomach and the secretion of the gastric juice, vagus stimulation has the opposite effect.

Under the physiological conditions, the gastric absorption of the drugs are insignificant as a result of the limited surface area covered by a thick layer of mucosal coating, the lack of villi on the mucosal surface, and the short residence time of the drugs in the stomach.

Blood supply

Aterial blood is supplied to the stomach by branches of coeliae artery and venous drainage into the portal vein.

Gastric juice composition

About 2 to 3 litres of gastric juice secreted daily by specialized cells in the mucosa. About 60 ml with approximately 4 m mol of hydrogen ions per hour.

It consists of,

- Water
- Gastric enzymes(pepsin, gastric lipase, gastrin, renin and other enzymes)
- Mucus- glycoprotein
- Intrinsic factor
- Hydrochloric acid, sodium, calcium, potassium, chloride, bicarbonate, phosphate and sulfate.

Salient Features of Upper Gastrointestinal Tract[7]

Table 1. Features of upper GIT.

Section	Length (m)	Transit time (h)	pH	Microbial count	Absorbing surface area (m2)	Absorption pathway
Stomach	0.2	Variable	1-4	<103	0.1	P, C, A
Small Intestine	6-10	3 ± 1	5-7.5	103 – 1010	120-200	P, C, A, F, I, E, CM

Where,

P – Passive diffusion.

C – Aqueous channel transport.

A – Active transport.

F – Facilitated transport.

I – Ion-pair transport.

E – Entero-or pinocytosis.

CM – Carrier mediated transport.

Gastric pH

- Fasted healthy subject 1.1 ± 0.15.
- Fed healthy subject 3.6 ± 0.4.

Volume - Resting volume is about 25-50 ml.

Gastric emptying and motility[6]

Gastric emptying occurs during fasting as well as fed states. The passage of drug from stomach to the small intestine is called gastric emptying. It is the rate limiting step for drug absorption because the major site for absorption in intestine. Generally rapid gastric emptying increase bioavailability of the drug. Faster onset requires for drugs that degrade in gastric environment. Delayed gastric emptying promotes dissolution of the drugs, which are poorly soluble drugs and for the drugs that is majorly absorbed from stomach or proximal part of the intestine.

The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases are,

- Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
- Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
- 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 the housekeeper wave.
- Phase IV Period of transition from phase III and phase I lasts for 0 to 5 minutes.

After the ingestion of a mixed meal, the pattern of contractions 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 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of myloelectric cycle (MMC) is delayed resulting in slowdown of gastric emptying rate.

Many Scientigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.

Gastric Transit time

The transit time of gastrointestinal drug delivery system along GI tract is the most limiting physiological factor in the development of controlled- release gastrointestinal drug delivery systems. The pattern of GI transit depends on the fasted or fed state.

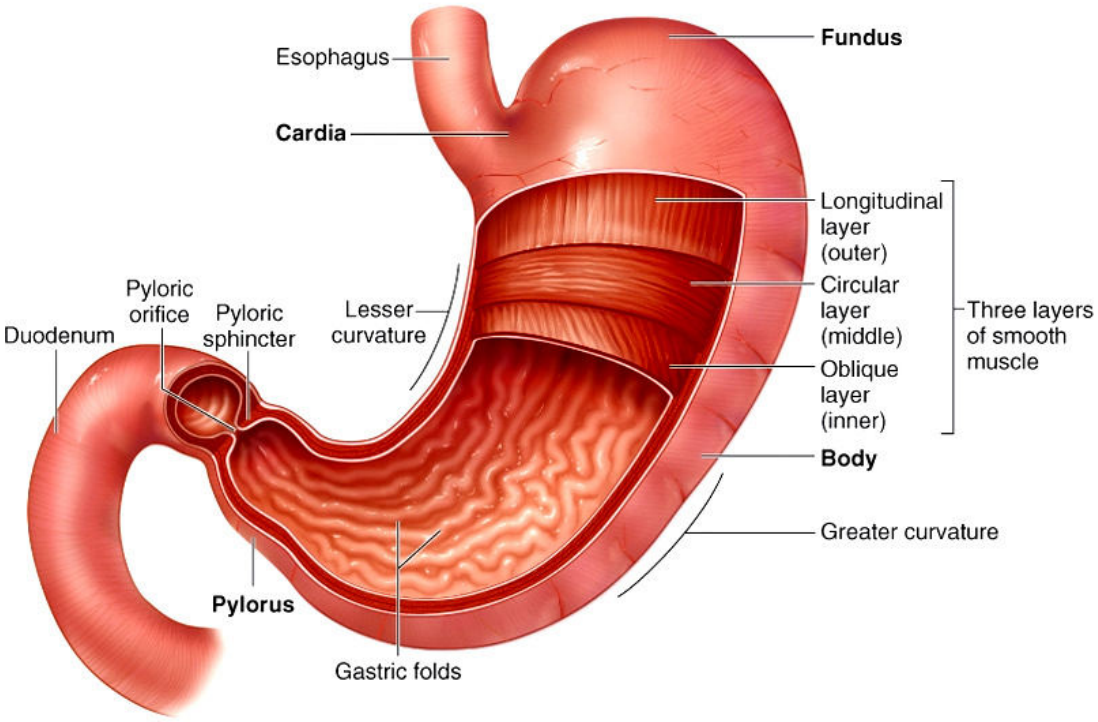


Fig. 1. Internal structure of stomach

1.1.2. APPROACHES TO GASTRIC RETENTION[2,5]

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts. These include –

a) Floating Systems

Floating Drug Delivery Systems(FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT

and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories, noneffervescent and effervescent systems.

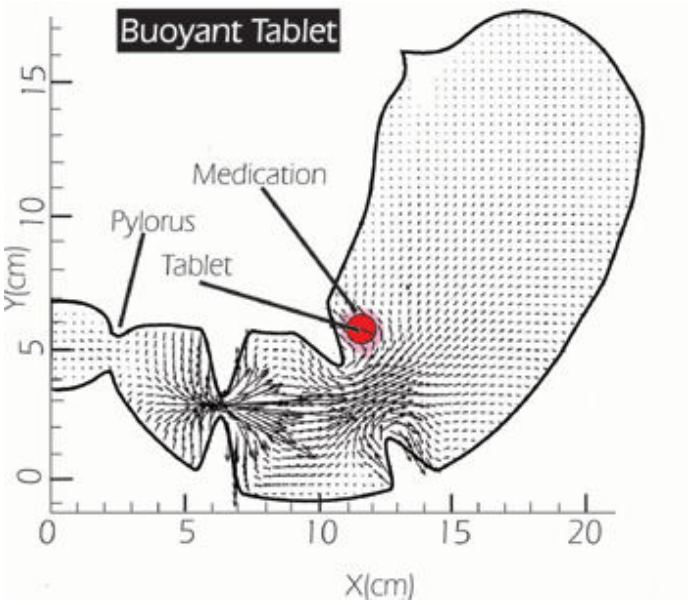


Fig. 2. Graphic of Buoyant tablet which is less dense than the stomach fluid and therefore remains in the fundus.

b) Bio/Muco-adhesive Systems

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery system (DDS) in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bio/muco-adhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI wall provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect.

Binding of polymers to the mucin/epithelial surface can be divided into three broad categories :–

- Hydration-mediated adhesion.
- Bonding-mediated adhesion.
- Receptor-mediated adhesion.

c) Swelling and Expanding Systems

These are the dosage forms, which after swallowing, swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as "*plug type system*", since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state. A balance between the extent and duration of swelling is maintained by the degree of crosslinking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period.

d) High Density Systems

These systems with a density of about 3 g/cm3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm3 acts as a threshold value after which such systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc. They are retained in the antrum of stomach as shown in Fig. 3.

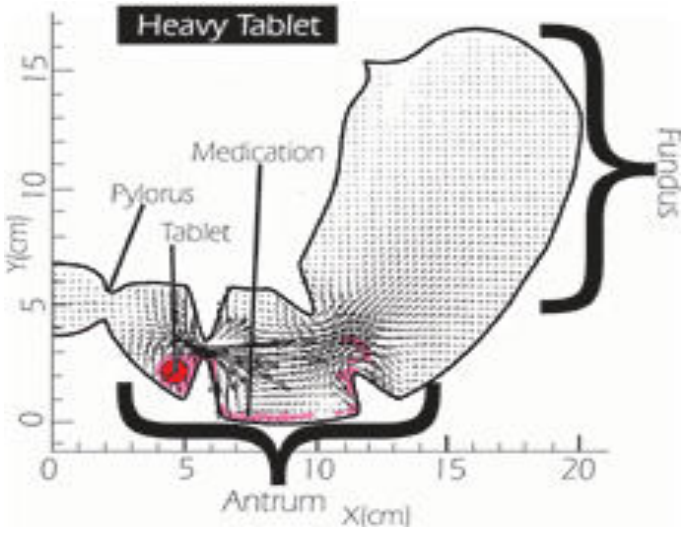


Fig. 3. Graphic of heavy tablet which is denser than the stomach fluid and therefore sinks to the antrum

e) Incorporation of Passage Delaying Food Agents

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of thestomach to a fed state, thereby decreasing gastric emptying rate and permitting considerableprolongation of release. The delay in the gastric emptying after meals rich in fats is largelycaused by saturated fatty acids with chain length of C10-C14.

f) Ion Exchange Resins

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in the membrane there by carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

g) Osmotic Regulated Systems

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric 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 controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment**.**

1.1.3. APPROACHES (gastro retentive) [3,7,10]

Several approaches have been attempted in the preparation of gastro-retentive drug delivery systems. This include,

- Floating systems,
- Bioadhesive systems,
- Swellable systems,
- High density systems,
- Modified-shape systems.
- Co-administration of gastric- emptying delaying drugs.

a) Floating systems

Floating systems have low bulk density so that they can float on the gastric juice in the stomach without affecting gastric emptying.

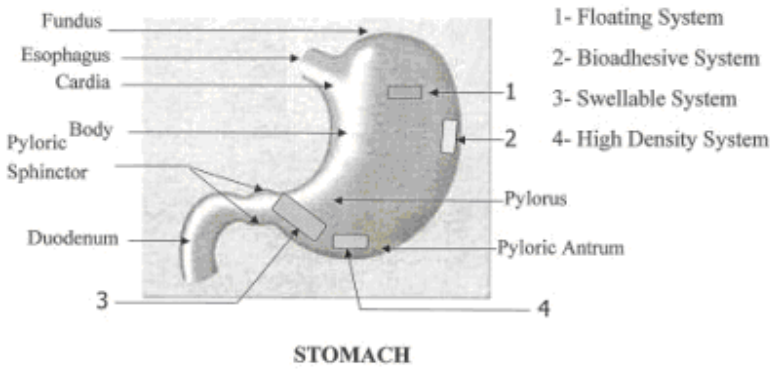


Fig. 4. Gastro retentive dosage forms

1.2. FLOATING DRUG DELIVERY SYSTEMS [1,2,7,9,10]

Floating drug delivery system have a bulk density less than gastric fluids(less than 1.004 g/ml) and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration.

The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically 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 on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents.

Fig.5. Floating Tablets.

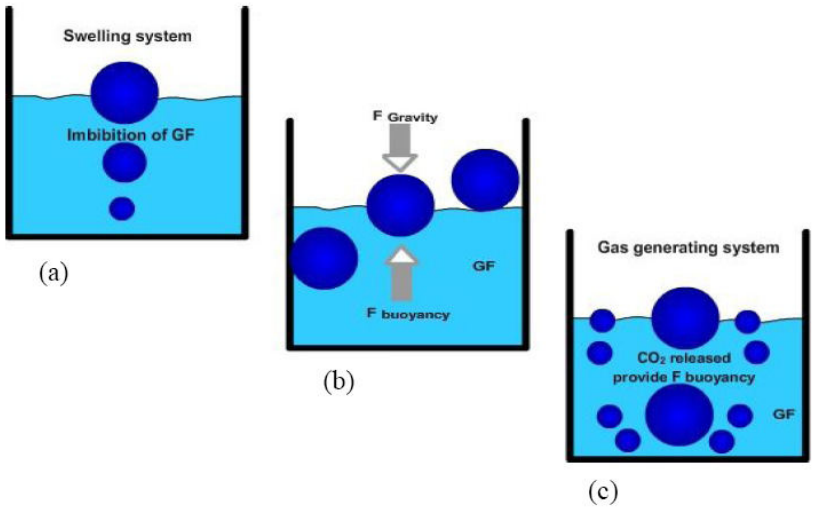


Fig.6. Mechanism of floating systems

GF= Gastric fluid

1.2.1. MECHANISM OF FLOATING SYSTEMS[7,9,10]

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations,

F = F buoyancy - F gravity

= (Df - Ds) gv--- (1)

Where,

F = total vertical force,

D_f = fluid density,

Ds = object density,

v = volume and

g = acceleration due to gravity.

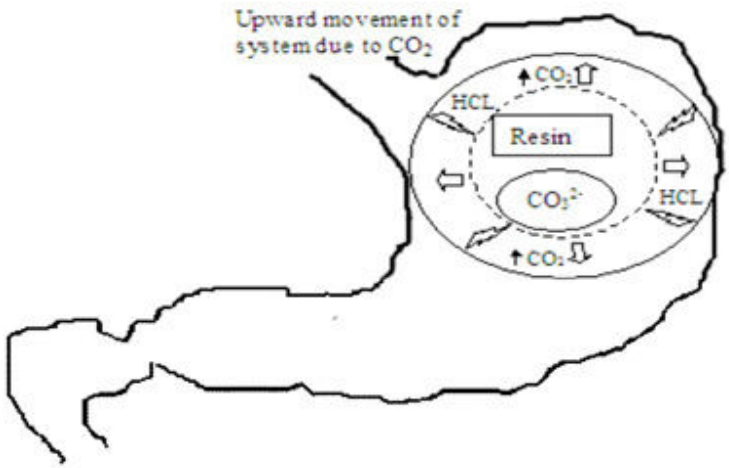


Fig.7. Mechanism of Effervescent floating systems

1.2.2. ADVANTAGES OF FDDS[6]

1. Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.
2. FDDS are advantageous for drugs meant for local action in the stomach eg Antacids
3. FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhea to keep the drug in floating condition in stomach to get a relatively better response.
4. Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs.
5. The FDDS are advantageous for drugs absorbed through the stomach eg: Ferrous salts, antacids.

1.2.3. DISADVANTAGES OF FDDS[6]

1. Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.
2. Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo sig-nificant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric empty-ing may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.
3. One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach, so that the drug dosages form float therein and work efficiently.
4. These systems also require the presence of food to delay their gastric emptying.
5. Single unit floating DDS show all or none gastric emptying phenomena

1.2.4. COMPONENTS ARE USED IN PREPARATION OF FLOATING DRUGS[2,10]

Materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. E.g. Bees wax, fatty acids, long chain fatty alcohols etc.

Polymers: The following polymers are used in the preparations of floating drugs delivery systems like Hydroxymethyl cellulose, Carbapol, Xanthum gum, Guar gum etc

Inert fatty materials: Edible oils

Effervescent agents: Sodium bicarbonate, citric acid, tartaric acid.

Low density material: Polypropylene foam powder (Accurel MP 1000®), Calcium silicate etc

1.2.5. METHODS FOR PREPARING FLOATING DOSAGE FORM[6]

Following approaches can be used for preparing floating dosage forms:

1. Using gel forming hydrocolloids such as hydrophilic gums, gelatin, alginates, cellulose derivatives, etc.

2. Using low density enteric materials such as methacrylic polymer, cellulose Acetate phthalate.
3. By reducing particle size and filling it in a capsule.
4. By forming carbon dioxide gas and subsequent entrapment of it in the gel network.
5. By preparing hollow micro-balloons of drug using acrylic polymer and filled in capsules.
6. By incorporation of inflatable chamber which contained in a liquid e.g. solvent that gasifies at body temperature to cause the chambers to inflate in the stomach.

The factors which govern the effectiveness of active medicaments in HBS are:

1) Amounts of active medicament to produce therapeutic effect.
2) Bulk density
3) Hydrophilic and hydrophobic properties
4) Stability in gastric fluids.

1.2.6. FACTORS AFFECTING THE FLOATING DRUG DELIVERY SYSTEM[11]

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include use of floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastro retentive system:

- **Density** – gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density.

- **Size** – dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.

- **Caloric content** – GRT can be increased by four to 10 hours with a meal that is high in protein and fats.

- **Shape** of dosage form – tetrahedron and ring shaped devices with a flexural 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.
- **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 coadministration 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.
- **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.
- **Nature 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.
- **Frequency of feed** – 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.
- **Gender** – mean ambulatory GRT in males (3.4±0.6 hours) is less compared with
- their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface).
- **Age** – elderly people, especially those over 70, have a significantly longer GRT.
- **Posture** – GRT can vary between supine and upright ambulatory states of the patient
- **Concomitant drug administration** – anticholinergics like atropine and propantheline, opiateslike codeine and prokinetic agents like metoclopramide and cisapride, can affect floating time.
- **Biological factors** – diabetes and Crohn's disease, etc.

1.2.7. TYPES OF FLOATING DRUG DELIVERY SYSTEM[6]

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

1. Effervescent System, and

2. Non- Effervescent System

1. EFFERVESCENT FDDS

Volatile liquid containing system:

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

Gas-generating Systems

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

2. NON-EFFERVESCENT FDDS

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

- **Single Layer Floating Tablets:**

  They are formulated by intimate mixing of drug with a gelforming hydrocolloid, which swells in contact with gastric fluid and maintains bulk

density of less than unity. They are formulated by intimate mixing of drug with low-density enteric materials such as HPMC.

- **Bi-layer Floating Tablets:**

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

- **Alginate Beads**

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

- **Hollow Microspheres**

  Hollow microspheres (micro balloons), loaded with drug in their outer polymer shells are prepared by a novel emulsion solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 40 °C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The micro balloons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours.

1.2.8. EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS[9,12]

Various parameters that need to be evaluated in gastro retentive formulations which includesfloating duration, dissolution profiles, specific gravity, content uniformity, hardness and friabilityin case of solid dosage forms. In case of multiparticulate drug delivery systems particle sizeanalysis, flow properties, surface morphology are also performed.

1. SIZE AND SHAPE EVALUATION

The particle size and shape plays a major role in determining solubility rate of the drugs and thus potentially its bioavailability. The particle size of the formulation was determined using Sieve analysis, Air elutriation (BahcoTM) analysis, Photoanalysis, Optical counting method, microscope, Electroresistance counting methods (Coulter counter), Sedimentation techniques, Laser diffraction methods, ultrasound attenuation spectroscopy , Air Pollution Emissions Measurements etc.

2. BUOYANCY LAG TIME

- **Buoyancy lag time (BLT):** The time taken for dosage form to emerge on surface of medium called floating lag time (FLT) or buoyancy lag time (BLT).
- **Buoyancy time:** The time during which the dosage form remains buoyant were measured.

3. FLOATING TIME

Test for buoyancy is usually performed in (SGF) Simulated Gastric Fluid maintained at 370˚C.The time for which the dosage form continuously floats on the dissolution media is termed as floating time.

4. SPECIFIC GRAVITY / DENSITY

Density can be determined by the displacement method by using benzeneas displacement medium. The density of the system should be less than unity to confer the buoyancy of the system.

5. WATER UPTAKE

It is an indirect measurement of swelling property of swellable matrix. In this the weighed dosage form is placed in the dissolution medium and removed out after a regular time interval and weight. The changes are determined with respect to time and swelling index is calculated by using the formula.

Swelling index = Changes in weight / Initial weight.

6. *IN-VITRO* RELEASE STUDIES

In vitro dissolution test is generally done by using USP paddle type apparatus. The dosage form is placed on the dissolution medium. But sometimes as the vessel is large and paddles are at bottom, there is much lesser paddle force acts on floating dosage form which generally floats on surface. As floating dosage form not rotates may not give proper result and also not reproducible results. Similar problem occur with swellable dosage form, as they are hydro gel may stick to surface of vessel or paddle and gives irreproducible results. In order to prevent such problems, various types of modification in dissolution assembly made are as follows.

- To prevent sticking at vessel or paddle and to improve movement of dosage form, method suggested is to keep paddle at surface and not too deep inside dissolution medium.
- Floating unit can be made fully submerged, by attaching some small, loose, non-reacting material, such as few turns of wire helix, around dosage form. However this method can inhibit three dimensional swelling of some dosage form and also affects drug release.

1.2.9. LIMITATIONS[10]

1) 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.
2) Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids.

3) The dosage form should be administered with a minimum of glass full of water (200-250 ml).
4) The drugs, which are absorbed throughout gastro-intestinal tract, which under go first-pass metabolism (nifedipine, propranolol etc.), are not desirable candidate.
5) Some drugs present in the floating system causes irritation to gastric mucosa.

1.2.10. APPLICATION OF FLOATING DRUG DELIVERY SYSTEM[12,13]

1. Sustained Drug Delivery

HBS system can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral controlled release formulation, hence, can be overcome with these systems. These systems have bulk density of <1, as a result of which they can float on the gastric contents. Recently sustained release floating capsules of nicardipine were developed and evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD cap (8 hours).

2. Site specific drug delivery

These systems are particularly advantages for drugs that are specifically absorbed from stomach or the proximal part of the small intestine eg riboflavin, furosemide and misoprostal. A bilayer floating capsule was developed for local delivery of misoprostol, which is a synthetic analog of prostaglandin E, used as protectant of gastric ulcer caused by administration of NSAIDs. By targeting slow delivery of misoprostol to the stomach, desired therapeutic level could be achieved and drug waste could be reduced.

3. Absorption Enhancement

Drugs that have poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. A significant increase in the bioavalibiling

of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablet (33.4%) and enteric coated LASIX-long product (29.5%).

4. Maintenance of Constant Blood Level

These systems provide an easy way of maintaining constant blood level with an ease of administration and better patient compliance.

1.2.11. DRUGS USED IN THE FORMULATIONS OF FLOATING DOSAGE FORMS [7]

Table 2. Drugs used in FDDS

S.No.	Dosage forms	Drugs
1.	Floating microspheres	Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Ketoprofen, Piroxicam, Verapamil, Nifedipine, Cholestyramine, Theophylline, Nicardipine, Flavoxate,Dipyridamol, Terfinadine and Tranilast
2.	Floating granules	Diclofenac sodium, Indomethacin and Prednisolone
3.	Films	Cinnarizine and Albendazole.
4.	Floating Capsules	Chlordiazepoxide hydrogen chloride, Diazepam, Furosemide, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid, Pepstatin and Propranolol.
5.	Floating tablets and Pills	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxycillin trihydrate, Atenolol, Diltiazem, Fluorouracil, Isosorbide mononitrate, Para-aminobenzoic acid, Piretamide, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol, pentoxyfilline, Theophylline and Verapamil hydrochloride.

1.3. FLOATING MICROSPHERES

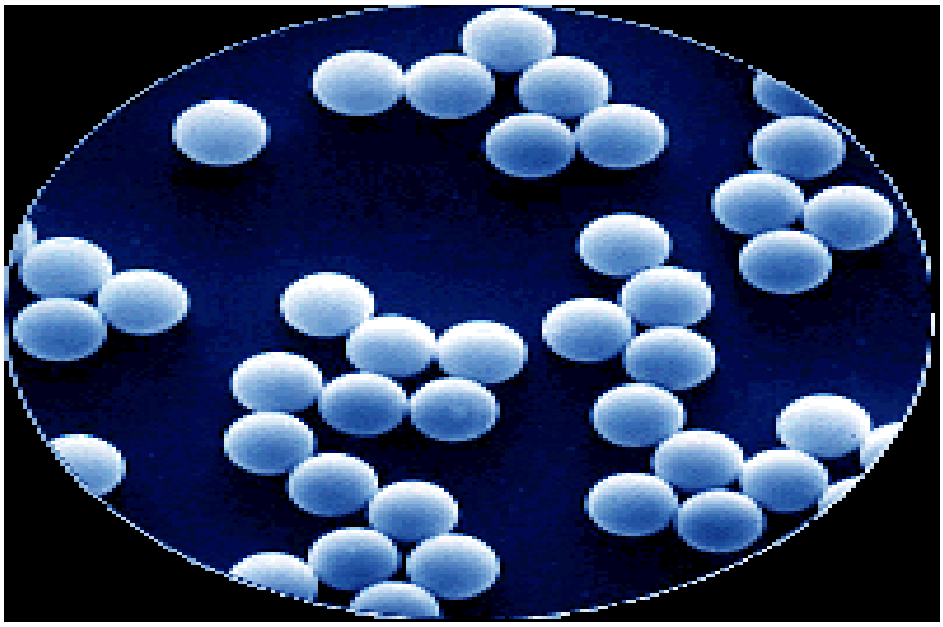


Fig.8. Microspheres

1.3.1. DEFINITION AND GENERAL DESCRIPTION [11]

Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000µm.They are made of polymeric, waxy or other protective materials, that is biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes. The natural polymers include albumin and gelatin, the synthetic polymer include poly lactic acid and polyglycolic acid. The solvents used to dissolve the polymeric materials chosen according to the polymer and drug solubilities and stabilities, process safety and economic considerations. Microspheres are small and have large surface-to-volume ratio. At the lower end of their size range they have colloidal properties. The interfacial properties of microspheres are extremely important, often indicating their activity.

Polyethylene and polystyrene microspheres are two most common types of polymermicrospheres. Polystyrene microspheres are typically used in biomedical applications due to their ability to facilitate procedures such as cell sorting and immune precipitation. Proteins and ligands adsorbed onto polystyrene readily and permanently,

which makes polystyrene microspheres suitable for medical research and biological laboratory experiments.

Polyethylene microspheres are commonly used as permanent or temporaryfiller. Lower melting temperature enables polyethylene microspheres to create porous structures in ceramics and other materials. High sphericity of polyethylene microspheres, as well as availability of colored and fluorescent microspheres, makes them highly desirable for flow visualization and fluid flow analysis, microscopy techniques, health sciences, process trouble shooting and numerous research applications.

Glass microspheres are primarily used as a filler and volumizer for weight reduction, retro-reflector for highway safety, additive for cosmetics and adhesives, with limited applications in medical technology .Ceramic microspheres are used primarily as grinding media. Microspheres varywidely in quality, sphericity, uniformity, and particle size and particle size distribution. The appropriate microsphere needs to be chosen for each unique application.

1.3.2. SALIENT FEATURES OF MICROSPHERES[11,12]

- Taste and odour masking
- Conversion of oil and other liquids, facilitating ease of handling
- Protaction of the drug from the environment
- Delay of volatillisation
- Freedom from incompatibilities between drug and excipients, the buffers
- Improvement of flow properties
- Safe handling of taste masking
- Dispersion of water insoluble substance in aqueous media
- Production of sustained release, controlled release and targeted medication.

1.3.3 ADVANTAGES[11,12]

- They facilitate accurate delivery of small quantities of potent drug and reduced concentration of drug at site other than the target organ or tissue.
- They provide protection for unstable drug before and after administration, prior to their availability at the site of action.
- They provide the ability to manipulate the in vivo action of the drug, pharmacokinetic profile, tissue distribution and cellular interaction of the drug.

- They enable controlled release of drug.
- Ex: narcotic, antagonist, steroid hormones
- Microspheres in Vaccine delivery
- Targeting of Drug
- Magnetic Microspheres
- Immunomicrospheres
- Micro sponges: Topical Porous Microspheres
- Imaging
- Surface modified Microspheres

1.3.4. DISADVANTAGES[11,12]

- At the same time they encounter with the disadvantages of common modified release formulations. The release rate of controlled-release products can be altered by various factors including food and the rate of transit through the gut.
- There may be some differences in the release rate from one dose to another, but these have been minimized by modern formulations.
- Extended-release or controlled release products generally contain a higher drug load and any loss of integrity of the release characteristics of the dosage form may lead to potential toxic problems. Some extended-release products can be divided to provide half-doses, others should only be taken whole.
- Dosage forms of this category should not be crushed or chewed as the slow-release characteristics may be lost and toxicity may result.
- Further larger size of extended-release products may cause difficulties in ingestion or transit through the gut.
- Even though they have number of pharmacological advantages, the distal intestinal toxicological manifestations of sustained release and enteric-coated NSAID formulations should not be forgotten.
- One consequence has been to shift the site of GI inflammation from the stomach to the small intestine, where damage can remain asymptomatic until more serious problems arise.

1.3.5. APPLICATIONS [13]

The brief outline of various applications of microsphere is explained as follows:

a. Microspheres in chemotherapy

The most promising application of microspheres are possible to used as carriers for anti- tumor agents. Enhanced endocytic activity and leaky vasculature administrated microspheres. Stealth microspheres are prepared by coating with soluble polyoxy ethylene. The accumulation of non-stealth microspheres in Reticulo Endothelial System (RES) may also be exploited for cancer chemo-therapy.

b. Microspheres for DNA Delivery

Microspheres have been recently used as a delivery vehicle for the transfer of plasmid DNA which leads to improve the transfer of plasmid DNA and their stability in the bio- environment38. Truong-Le & Co workers developed a novel system for gene delivery based on the use of DNA-gelatin microspheres/ nanoparticles formed by salt induced complex coacervation of gelatin & plasmid DNA.

c. Fluorescent microspheres

These are made up of polystyrene or poly vinyl toluene, mono disperse system ranging in size from 20nm to 4µm. Preparation of fluorescent microspheres comprising, swelling the polymeric microsphere so that fluorescent dyes may enter the microsphere pores. Unswelling the polymeric microspheres so that the fluorescent dyes become physically entrapped in the pores39.

d. Adjuvant effect for vaccines

An adjuvant effect of the microspheres/nanoparticles with either matrix en-trapped or surface adsorbed vaccines have been demonstrated in several studies on substances or oral administration. “Kreuter & Co-workers” observed that Poly methyl methacrylate microspheres containing the influenza antigen induced significant antibody response. Oral delivery of antigens with microspheres may be an elegant means of producing an increase Immunoglobin A (Ig A) antibody response.

e. Microspheres for Ocular delivery

The most applications of drug loaded ophthalmic delivery systems are for glaucoma therapy, especially cholinergic agonists like pilocarpine. The short elimination half life of aqueous eye drops can be extended from a very short time (1-3 min) to

prolonged time (15-20 min) using microspheres which have biodegradable properties e.g. Poly alkyl cyano acrylate.

f. Microspheres for Lymph targeting

The major purpose of lymph targeting is to provide an effective anticancer chemotherapy to prevent the metastasis of tumor cells by accumulating the drug in the regional lymph node. Example: Poly alkyl cyanoacrylate microspheres bearing anticancer drugs for tumor of peritoneal cavity. Poly (lactide-co-glycolide) microspheres for the lymphatic of diagnostic agents.

1.3.6. TYPES OF MICROSPHERES [(12)]

a. Bioadhesive microspheres

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bioadhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.

b. Magnetic microspheres

This kind of delivery system is very much important which localizes the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. The different types are therapeutic magnetic microspheres and diagnostic microspheres.

i. Therapeutic magnetic microspheres

It is used to deliver chemotherapeutic agent to liver tumor. Drugs like proteins and peptides can also be targeted through this system.

ii. Diagnostic microspheres

It can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles super magnetic iron oxides.

c. Floating microspheres

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies.

d. Radioactive microspheres

Radio immobilization therapy microspheres sized 10-30 nm is of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumor of interest. So all these conditions radioactive microspheres deliver high radiation dose to the targeted areas with- out damaging the normal surrounding tissues. It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are emitters.

e. Polymeric microspheres

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and synthetic polymeric microspheres.

i. Biodegradable polymeric microspheres

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bioadhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to it's high degree of swelling property with aqueous medium, results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release.

ii. Synthetic polymeric microspheres

The interest of synthetic polymeric microspheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc and proved to be safe and biocompatible. But the main disadvantage

of these kinds of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage.

1.3.7. METHOD OF PREPARATION[12,13]

Production of sustained release, controlled release and targeted medications reduce the dose dumping potential compared to large implantable devices. Different methods of microspheres are as follow

- Wax coating and hot melt
- Spray coating and pan coating
- Coacervation
- Spray drying
- Solvent Evaporation
- Precipitation
- Freeze drying
- Chemical and thermal cross– linking

a. Wax coating and hot melt

Wax may be used to coat the core particles, encapsulating the drug by dissolution or dispersion in molten wax. The waxy solution or suspension is dispersed by high speed mixing into cold solution, such as cold liquid paraffin. The mixture is agitated for at least one hour. The external phase (liquid paraffin) is then decanted and the microspheres are suspended in a non- miscible solvent and allowed to air dry. Carnauba wax and beeswax can be used as the coating materials and these can be mixed in order to achieve desired characteristics.

b. Spray coating and pan coating spray

Coating and pan coating employ heat- jacketed coating pans in which the solid drug core particles are rotated and the coating material is sprayed. The core particles are in size range of micrometers up to few millimeters. The coating material is usually sprayed at angle from the side into the pan. The process is continued until an even coating is completed. In addition, several batches of microspheres cab be prepared with different coating thickness and mixed to achieve specific controlled release pattern.

c. Coacervation

This process is a simple separation of macromolecular solution into two immiscible liquid phases, a dense coacervate phase, which is relatively concentrated in macromolecules and a dilute equilibrium phase. In presence of only one macro-molecule, this process is referred to as simple coacervation. When two or more macromolecules of opposite charge are present, it is referred to as complex coacervation. Former one is induced by various parameters like change in temperature, addition of non-solvent or micro ions, which results in dehydration of macromolecules because they promote polymer-polymer interactions over polymer solvent interaction. These can be manipulated to produce microspheres with specific properties.

d. Spray drying

It is single step, closed- system process applicable to wide variety of materials, including heat-sensitive materials. The drug and polymer coating materials are dissolved in suitable solvent (aqueous or non-aqueous) or the drug may be present as a suspension in the polymer solution. Alternatively, it may be dissolved or suspended within an emulsion or coacervate system. For example, biodegradable polylactide microspheres can be prepared by dissolving the drug and the polymer in methylene chloride. The microsphere size is controlled by the rate of spraying, the feed rate of the polymer drug solution, the nozzle size, the temperature in drying and collecting chambers, and the size of the two chambers. The quality of the spray dried products are improved by the addition of plasticizers that promote the polymer coalescence and film formation and enhance the formation of smooth surfaced and spherical microspheres.

e. Solvent evaporation

In this method, the drug and the polymer must be soluble in organic solvent, frequently ethylene chloride. The solution containing polymer and drug may be dispersed in an aqueous phase to form droplets. Continuous mixing and elevated temperatures may be employed to evaporate the more volatile organic solvents and leave the solid polymer-drug particles suspended in an aqueous medium. The particles are finally filtered from the suspension.

f. Precipitation

It is a variation on the evaporation method. The emulsion consists of polar

droplets dispersed in a non-polar medium. Solvent may be removed from the droplets by the use of a co solvent. The resulting increase in the polymer concentration causes precipitation forming a suspension of microspheres.

g. Freeze Drying

This technique involves the freezing of the emulsion and the relative freezing points of the continuous and dispersed phases are important. The continuous phase solvent is usually organic and is removed by sublimation at low temperature and pressure. Finally the dispersed phase solvent of the droplets is removed by sublimation, leaving polymer- drug particles.

h. Chemical and thermal cross - linking

Microspheres made from natural polymers are prepared by a cross-linking process, polymer includes gelatin, albumin, starch and dextrin. A water-oil emulsion is prepared, where the water phase is a solution of polymer that contains drug to be incorporated. The oil phase is a suitable vegetable oil or oil-organic solvent mixture containing an oil soluble emulsifier. Once the desired water-oil emulsion is formed, the water soluble polymer is solidified by thermal treatment or addition of a chemical cross-linking agent such as glutaraldehyde to form a stable chemical cross link.

Table 3.List of floating microspheres

Dosage form	Drug
Floating microspheres	Ketoprofen
	Stavudine
	Verapamil Hydrochloride
	Boswellic Acid
	Captopril
	Metformin Hydrochloride
	Famotidine
	Ranitidine Hydrochloride
	Ofloxacin Hydrochloride
	Glipizide
	Acyclovir
	Silymarin
	Gabapentin

2. LITERATURE REVIEW

- **M. NAJMUDDIN *et al.,*** studied on the Floating drug delivery system have a bulk density less than gastric fluids and so remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. Ketoprofen is nonsteroidal antiinflammatory drug with short elimination half life 1-3 hours. The short half life of ketoprofen and multiple administration dose make ketoprofen a very good candidate for formulation of floating drug delivery system. Floating microspheres of ketoprofen were prepared by emulsion solvent diffusion method using Eudragit S 100 and Eudragit L 100 as polymer. The floating microspheres was evaluated such as micromeritic properties, particle size, percentage yield, in vitro buoyancy, incorporation efficiency, drug polymer compatibility(IR study), scanning electron microscopy and drug release of microsphere The micromeritic properties was found to be good and scanning electron microscopy confirmed their hollow structure with smooth surface. Formulation EU2 prepared with Eudragit S 100 drug: polymer ratio (1:2) which exhibited excellent micromeritic properties, percentage yield, in vitro buoyancy, incorporation efficiency and percentage drug release 92.26 % for a period of 12 hrs. Results show that as increase in drug: polymer ratio affects the particle size, percentage yield, in vitro buoyancy and drug release of microspheres.

- **YUVERJ SINGH TANWAR *et al.,*** prepared and evaluated floating microspheres of verapamil hydrochloride for improving the drug bioavailability by prolongation of gastric residence time. Cellulose acetate, acrycoat S100 and eudragit S100 microspheres loaded with verapamil hydrochloride were prepared by solvent diffusion evaporation method. The microspheres had smooth surfaces, with free-flowing and good-packing properties. The yield of the microspheres was up to 70.51% and cellulose acetate microspheres entrapped the maximum amount of the drug. Scanning electron microscopy confirmed their hollow structures with sizes in the range 251.80 to 350.75 μm. The prepared microspheres exhibited prolonged drug release and remained buoyant for more than 12 h.

- **SURESH FARTVAL *et al.,*** carried a research on floating microspheres using boswellic (BA) as model drug for prolongation of the gastric retention time. BA is a lipophilic drug

hence it is absorbed rapidly from the stomach and having the half-life of 6 Hrs. So it is suitable candidate to formulate GRDDS. The microspheres were prepared by the solvent evaporation method using polymers hydroxypropyl methylcellulose (HPMC) in fixed ratio and Ethyl cellulose in variant ratios. The shape and surface morphology of prepared microspheres were characterized by optical and scanning electron microscopy, respectively. Drug polymer compatibility study was done by TLC and IR spectroscopy. The Percentage yield, Particle size distribution, Buoyancy percentage, Entrapment Efficiency and *In vitro* drug release studies were performed and drug release kinetics was evaluated using the linear regression method. The prepared microspheres exhibited prolonged drug release (18h) and remained buoyant for > 12 h. The mean particle size increased and the drug release rate decreased at higher polymer concentration. *In vitro* studies demonstrated diffusion- controlled drug release from the microspheres.

- **J JOSEPHINE *et al.,*** developed the research work was to prepare and evaluate the floating microspheres of stavudine as a model drug for prolongation of gastric retention time for oral delivery. Stavudine is a synthetic analog of reverse transcriptase inhibitor with short half life (0.8 to 1.5hr). The floating microspheres of Stavudine were prepared by emulsion solvent diffusion method using Eudragit RS 100 as a rate controlling polymer. The floating microspheres were evaluated for micromeritic properties, particle size, % yield, *in vitro* buoyancy, incorporation efficiency and drug release. The size or average diameter of prepared microspheres were recognized and characterized by scanning electron microscopic methods. The prepared microspheres were found to be spherical and free flowing and remain buoyant for more than 12 hrs. The drug-loaded microspheres (A1) showed encapsulation efficiencies up to 88% and also showed good micromeritic properties for their suitability as oral dosage forms. The microspheres having lower densities exhibited good buoyancy effect and hence, these could be retained in the gastric environment for more than12 h. Thus, the present formulations would be capable of reducing the frequency of administration and the dose-dependent side effects associated with the repeated administration of conventional stavudine tablets.

- **AZHAR DANISH KHAN *et al.,*** developed a multi-unit gastroretentive sustained release dosage form of a water-soluble drug, Verapamil hydrochloride, from a completely

aqueous environment. avoiding the use of any organic solvent, thus releasing the drug for a prolonged duration of time. Emulsion gelation technique was used to prepare emulsion gel beads using sodium alginate as the polymer. The gel beads containing oil was prepared by gently mixing and homogenizing oil and water phase containing sodium alginate which was then extruded in to calcium chloride solution. The effects of factors like concentration of oil, drug: polymer ratio and alginate: pectin ratio on drug entrapment efficiency, floating lag time and morphology and drug release was studied. The use of sodium alginate and combinations of sodium alginate and pectin were used to study the effect on the sustaining property of the formed beads**.** It was found that sodium alginate was not sufficient to sustain the drug release at gastric pH. Instead of it, appropriate combination of alginate and pectin could provide the sustain release of drug**.** The results show that these beads can entrap even a water soluble drug as Verapamil hydrochloride in sufficient amount and also can successfully deliver the drug in stomach for a prolong duration of time without using any organic solvent and any time consuming step in the preparation.

- **DEVESH KAPOOR *et al.,*** studied on floating microspheres of tween80 as the surfactant. Differential Scanning Calorimeter (DSC) study shows that drug and other excipients are compatible with each other. The effects of polymers concentration on drug release profile were investigated. A 32 full factorial design was applied to systemically optimize the drug release profile. Polymer to drug ratio (X1) and stirring speed (X2) were selected as independent variables. The floating microspheres were characterized by and results obtained are % yield, particle size analysis, drug entrapment efficiency, buoyancy percentage, *in-vitro* drug release was studied for 12 hour and scanning electron microscopy. Accelerated stability study was also performed for three months indicated that optimized formulation was stable. The floating microspheres showed better result and it may be use full for prolong the drug release in stomach and improve the bioavailability.

- **GHODAKE J.D *et al.,*** prepared and evaluated floating microspheres with Metformin Hydrochloride as model drug for prolongation of gastric residence time. The

microspheres were prepared by the emulsification solvent diffusion technique using polymers Hydroxypropyl methyl cellulose K4M and Eudragit RS100. The shape and surface morphology of prepared microspheres were characterized by scanning electron microscopy, respectively. *In vitro* drug release studies were performed and drug release kinetics was evaluated using the linear regression method. Effects of the stirring rate during preparation, polymer concentration, solvent composition and dissolution medium on the size of microspheres and drug release were also observed. The prepared microspheres exhibited prolonged drug release (8 h). The mean particle size increased and the drug release rate decreased at higher polymer concentration. No significant effect of the stirring rate during preparation on drug release was observed. In most cases good *in vitro* floating behavior was observed and a broad variety of drug release pattern could be achieved by variation of the polymer and solvent ratio, which was optimized to match target release profile. The developed floating microspheres of metformin hydrochloride may be used in clinic for prolonged drug release in stomach for at least 8 hrs, thereby improving the bioavailability and patient compliance.

- **PANDEY MANISHA *et al.,*** carried out a research of famotidine floating microspheres, evaluation of Floating Drug Delivery System (FDDS) in vitro, prediction of the release, and optimization of stirring speed and polymers ratio to match target release profile was investigated. Floating microspheres were prepared by solvent evaporation (Oil-in-water emulsion) technique using hydroxylpropyl methylcellulose (HPMC) and Ethylcellulose (EC) as the rate controlling polymers. Particle size analysis, drug entrapment efficiency, surface topography, buoyancy percentage and release studies were performed. Results showed that the polymer ratio and stirring speed affected the size, incorporation efficiency and drug release of microspheres (> 12 h), floating time (> 12 hr) and the best results were obtained at the ratio of HPMC:EC (1:6). The mean particle size of prepared floating microspheres increased but the drug release rate from the microspheres decreased as the polymer concentration increased. The developed floating microspheres of famotidine may be used in clinic for prolonged drug release in stomach for at least 12 hrs, thereby improving the bioavailability and patient compliance.

- **PUNITHA.K *et al.,*** studied the preparation of floating microspheres of Ranitidine Hydrochloride with HPMC 15 cps and Eudragit E-100 in various ratios of 1: 1, 1: 2, and 1: 3. Floating microspheres were aimed to achieve an extended retention in the upper gastrointestinal tract, which may result in enhanced absorption and thereby improved bioavailability. The formulations were evaluated for FTIR, drug loading, % entrapment, particle size, SEM, buoyancy, dissolution study and the drug release kinetics. The enhanced floatability of the formulation and its retention in GIT may attribute for the increased bioavailability and decrease in frequency of administration. Comparison of both the polymers revealed HPMC to be a suitable candidate for sustained release.

- **AJAY BAGHERWAL *et al.,*** carried out research on sustained release dosage form for this drug. HPMC and carbomer are the polymers, used as suspending agent, viscosity increasing agent and tablet binder coating agents. In the present study, it was aimed to formulate floating tablet of ciprofloxacin HCl with HPMC and carbomer in different proportion (4%, 8% and 12%) by direct compression techniques using polymers lactose, Magnesium Sterate, talc with sodium bicarbonate. All the prepared formulation were found to complies with the official tests like precompression parameter like angle of repose and post compression parameters like Shape, tablet dimensions, hardness, friability test, weight variation test, floating test, content uniformity and *in-vitro* dissolution study. *In-vitro* release studies were carried out using USP XXII dissolution test apparatus. The mean percentage of ciprofloxacin released at various time intervals was calculated and plotted against time. The mechanism of drug release with all the formulations was dominantly diffusion and followed zero order kinetics. It was observed that the integrity of the drug is not affected by formulation procedure. The results revealed the drug polymer ratio showed greater drug release than other formulations.

- **BATHINI SREE TEJASWI., *et al.,*** studied on Floating Microspheres of Clarithromycin (FMC) were prepared by Solvent Evaporation Technique using ethyl cellulose as a polymer. The prepared microspheres were subjected to evaluation for particle size, incorporation efficiency, *in vitro* buoyancy, *in vitro* drug release characteristics and stability studies. These microspheres showed good buoyancy. The

formulation variables like polymer concentration and drug concentration influenced the *in vitro* drug release significantly in simulated gastric fluid (pH. 2.0). It was also noted that the required amount of Clarithromycin for eradication of H. pylori was significantly less in FMC than from corresponding Clarithromycin suspension. About 82% of the prepared microspheres floated in hydrochloric acid buffer solution for 12h. 71% of the Clarithromycin contained in the microspheres were released within 12 h in a sustained manner. These results suggest that FMC will be a promising drug delivery system for the treatment of H. pylori infection.

- **SHASHIKANT D.BARHATEL *et al.,*** carried out a research on gastro retentive drug delivery system can be prepared to improve the absorption and bioavailability of ketorolac trometamol by retaining the system in to the stomach for prolonged period of time. The floating drug delivery system of ketorolac trometamol was prepared by emulsion solvent diffusion method by using ethyl cellulose, HPMC K4M, Eudragit R 100, Eudragit S 100 polymers in varying concentration. Formulations were evaluated for percent yield, particle size, entrapment efficiency, *in vitro* buoyancy and *in vitro* release studies. The optimized formulations show good buoyancy and *in vitro* controlled release of ketorolac trometamol.

- **ANAND GADADANAND GADAD *et al.,*** studied on floating microspheres was formulated using biocompatible polymers like Eudragit S100 and Ethyl cellulose in different proportions by solvent evaporation technique. The prepared microspheres were evaluated for percentage yield, micromeritic properties, particle size, morphology, drug entrapment, buoyancy studies, *In vitro* drug release studies. Practical yield of the microspheres was up to 76.40%. The formulated microspheres were free flowing with good packing properties. Scanning electron microscopy confirmed spherical structure and the particles were of the size range of 57.66 to 93.21µm. The microspheres with Ethyl cellulose showed higher buoyancy when compared with Eudragit S-100. All formulation showed good *in vitro* percent buoyancy. *In vitro* release studies showed cumulative % drug release between 75.95-88.27%. *In vitro* release studies demonstrated non-Fickian diffusion of drug from the microsphere.

- **S. M. SARODE *et al.,*** developed glipizide floating system, as these will release the drug slowly in to the GIT and maintain a constant drug concentration in the serum for a longer period of time. Glipizide is commercially available as conventional tablet form. Single unit dosage form of Glipizide causes gastric irritation. To convert it in to the multiple unit dosage form will release the drug uniformly throughout the stomach which suppresses the irritation. The present study aim towards formulation and evaluation of floating multiparticulate drug delivery system, which can provide control release of the model drug. The work also aims to study various parameters affecting the behavior of floating multi particulate in oral dosage form.

- **PARMAR KUNAL VINODBHAI *et al.,*** studied on Acyclovir loaded floating microspheres were prepared by double emulsion solvent evaporation method. The 32 full factorial design was applied to optimize the formulation. The resultant microspheres were evaluated for average particle size, percentage encapsulation efficiency, *in vitro* drug release and model fitting kinetics. Scanning electron microscopy, Fourier transform infrared (FTIR) spectroscopy and differential scanning calorimeter were used to investigate the physical state of the drug in the microspheres. Microspheres remained buoyant for more than about 12 h. The results of FT-IR spectroscopy and differential scanning calorimeter indicated the stable character of acyclovir in microspheres and also revealed absence of drug polymer interaction. The *in vitro* drug release study showed that acyclovir release from the microspheres was slow and sustained for more than about 10 h. Drug release followed Korsemeyer-peppas model. The results of factorial batches revealed that the concentration of ethyl cellulose and stirring speed significantly affected drug encapsulation efficiency and particle size of the microspheres. Thus we can conclude that floating microspheres can successfully be developed to sustain the drug release.

- **GD GUPTA *et al.,*** carried out a research on floating microspheres were evaluated for flow properties based on parameters such as angle of repose and compressibility index, as well as for various other physicochemical properties including particle size, incorporation efficiency, *in vitro* floatability, and *in vitro* drug release. The shape and surface

morphology of the microspheres were characterised by optical and scanning electron microscopy. The drug retained in the floating microparticles decreased with increase in ERL content. Scanning electron microscopy and particle size analysis revealed differences between the formulations as to their appearance and size distribution. X-ray and DSC examination showed the amorphous nature of the drug. Release rates were generally low in 0.1 N HCl especially in presence of high content of ES while in phosphate buffer pH 6.8, high amounts of ES tended to give a higher release rate. Floating ability in 0.1 N HCl, 0.1 N HCl containing 0.02% Tween 20 and simulated gastric fluid without pepsin was also tested.

- **C.SHARON KUMAR *et al.,*** prepared floating gabapentin microspheres were evaluated for different evaluation parameters such as percentage yield, particle size determination, drug content determination, Encapsulation efficiency, *In-Vitro* buoyancy, *in-vitro* drug release. The *in vitro* drug release revealed that batch C was having 75% cumulative release at the end of 12 th hour when compared with batch A & B ,due to increase in polymer concentration as seen in formulation C (1:3). The release kinetics of Gabapentin followed Supercase II transport diffusion.

- **FRAZ JAMIL*et al.,*** reviewed a major constraint in oral controlled drug delivery system is that not all drug candidates are absorbed uniformly throughout the GIT. Some drugs are absorbed in a particular segment of GIT only or are absorbed to a different extent in various segments of GIT and diminished their bioavailability.

- **SUNIL KUMAR *et al.,*** studied on Floating drug delivery systems have a bulk density less than gastric fluids and so, remain buoyant in the stomach for a prolonged period of time, releasing the drug slowly at the desired rate from the system and increase the bioavailability of narrow absorption window drugs.

- **SAURABH SHARMA *et al.,*** studied on Floating Drug delivery system are designed to prolong the gastric residence time after oraladministration, at particular site and controlling the release of drug especially useful forachieving controlled plasma level as well as improving bioavailability.

- **LALIT SINGH *et al.,*** reviewed about scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence times and unpredictable gastric emptying times.

- **DEBJIT BHOWMIK *et al.,*** studied on Floating 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. Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery.

- **K.P.SAMPATH KUMAR *et al.,*** studied on Treatment of gastrointestinal disorders such as gastro-esophageal reflux. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site. Ease of administration and better patient compliance. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.

- **HWANG SJ *et al.,*** developed of a long-term oral controlled-release dosage form has been difficult mainly because of the transit of the dosage form through the gastrointestinal (GI) tract. Several approaches to extend gastric residence time have been tried. The most commonly used systems are (1) intragastric floating systems, (2) high-density systems, (3) mucoadhesive systems, (4) magnetic systems, (5) unfoldable, extendible, or swellable systems, and (6) superporous hydrogel systems.

- **PARK H *et al.,*** reviewed a concept of each approach is examined, and improvements that are needed for further development are discussed. Background materials in the GI physiology that are necessary for understanding the concept and usefulness of each approach are also provided.

3. AIM AND OBJECTIVES

The aim of the present work was to formulate and evaluate sustained release floating microspheres of Abacavir Sulphate.

Abacavir Sulphate is used to in combination with other antiretroviral agents, are indicated for the treatment of human immunodeficiency virus (HIV-1) infection. Existing marketed products of the formulation has a dose of 300mg with dosing frequency of two to three times a day and very shorter biological half-life of about 1.54±0.63hour.

Further a floating sustained release microsphere has been endeavored by employing polymer combination system to achieve effective plasma concentration with reduced side effects.

Floating drug delivery system have a bulk density less than gastric fluids and so remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time.

Floating microspheres of Abacavir Sulphate for improving the drug bioavailability by prolongation of gastric residence time.

Solubility of the selected drug decrease with increase in pH making stomach better site of absorption. Hence an attempt has been made to formulate a GI floating microsphere of the selected drug. Floating microspheres helps in retaining the microspheres in stomach fluids for longer duration and better absorption with site specificity.

Formulation techniques involved solvent evaporation method and optimization of stirring speed technique and hydroxylpropyl methylcellulose (HPMC) as the rate controlling polymers.

4. PLAN OF WORK

I. Pre formulation studies

a) Organoleptic properties

b) Flow properties

c) Bulk density

d) Tapped density

e) Measurement of powder compressibility

f) Melting point

g) pH of the solution

h) Solubility

i) Drug excipient compatibility studies

j) Calibration curve of Abacavir Sulphate

II. Formulation of Abacavir Sulphate floating microspheres

III. Evaluation of Abacavir Sulphate floating microspheres

a) Micromeritic properties

i) Angle of repose

ii) Determination of bulk density and tapped density

iii) Measurement of compressibility index and Hausner ratio

b) Percentage yield of microspheres

c) Drug entrapment

d) Buoyancy studies

e) *Invitro* dissolution studies

f) Kinetics of drug release

g) IR spectroscopy(Drug excipient compatibility)

h) Scanning electron microscopy

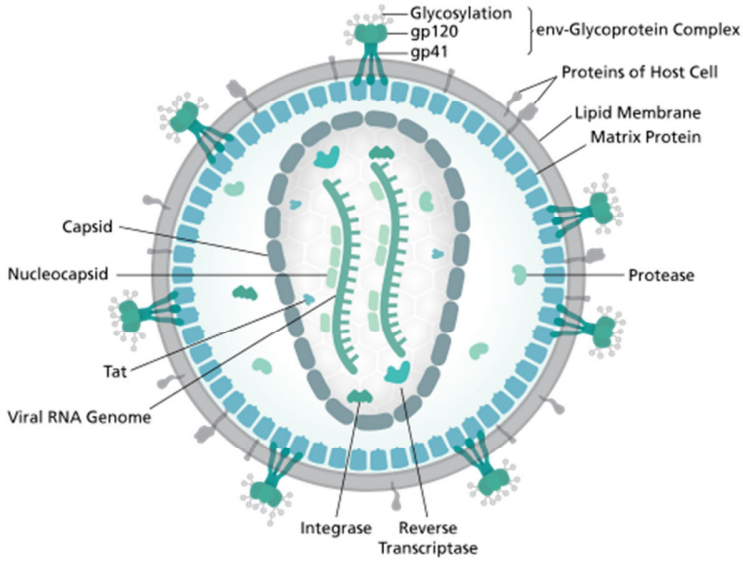
5. DISEASE PROFILE [14,15]

Abacavir is a nucleoside analog reverse transcriptase inhibitor (NRTI). It works by slowing down the growth of HIV, the virus that causes AIDS. Abacavir is used in combination with other drugs to treat human immunodeficiency virus (HIV) infection. It's approved for adults and children who are at least 3 months old. Abacavir doesn't cure HIV, but it may help to control it. Abacavir works by blocking an enzyme called reverse transcriptase.

HIV:

HIV is a virus that attacks the immune system, which is our body's natural defence against illness. The virus destroys a type of white blood cell in the immune system called a T-helper cell, and makes copies of itself inside these cells. T-helper cells are also referred to as CD4 cells. As HIV destroys more CD4 cells and makes more copies of itself, it gradually breaks down a person's immune system. This means someone living with HIV, who is not receiving treatment, will find it harder and harder to fight off infections and diseases.

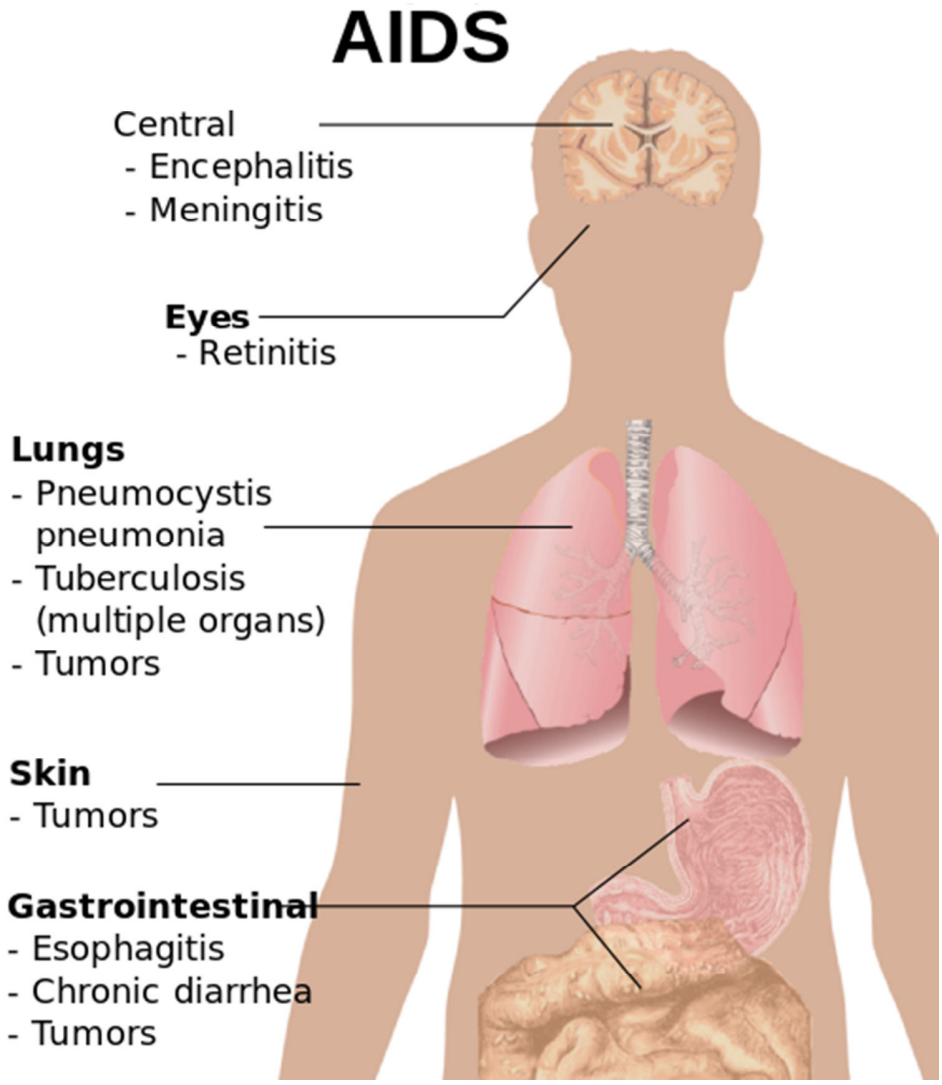
Fig.No.9: Structure of HIV Virus



If HIV is left untreated, it may take up to 10 or 15 years for the immune system to be so severely damaged it can no longer defend itself at all. However, the speed HIV progresses will vary depending on age, health and background. Human

immunodeficiency virus (HIV) needs this enzyme to make copies of itself. In 2015 about 37.3 million people were living with HIV and it resulted in 1.2 million deaths.

Fig.No.10: Symptoms of AIDS



Signs and Symptoms:

Symptoms of early HIV infection:

Many people with HIV have no symptoms for several months to even years after becoming infected. Others may develop symptoms similar to flu, usually 2-6 weeks after catching the virus.

The symptoms of early HIV infection may includes, fever, chills, joint pain, muscle aches, sore throat, sweats (particularly at night), enlarged glands, a red rash, tiredness, weakness, unintentional weight loss.

Asymptomatic HIV

In many cases, after the initial symptoms disappear, there will not be any further symptoms for many years. During this time, the virus carries on developing and damaging the immune system and organs. Without being on medications to stop HIV's replication, this process can take up to 10 years on average. The infected person often experiences no symptoms, feels well, and appears healthy.

Late-stage HIV infection

If left untreated, HIV weakens the ability to fight infection. The person becomes vulnerable to serious illnesses. This stage of infection is known as AIDS.

Symptoms of late-stage HIV infection may include:

blurred vision, diarrhea, which is usually persistent or chronic, dry cough, fever of above 100 °F (37 °C) lasting for weeks, night sweats, permanent tiredness, shortness of breath (dyspnea), swollen glands lasting for weeks, unintentional weight loss,white spots on the tongue or mouth,.

During late-stage HIV infection, the risk of developing a life-threatening illness is much greater. Life-threatening illnesses may be controlled, avoided and/or treated with proper medications, often including HIV treatment.

Causes:

HIV is a retrovirus that infects the vital organs and cells of the human immune system.

Treatment:

- There is currently no cure for HIV or AIDS. Treatments can slow the course of the condition - and allow most infected people the opportunity to live a long and relatively healthy life.
- Earlier HIV antiretroviral treatment is crucial - it improves quality of life, extends life expectancy, and reduces the risk of transmission, according to the World Health Organization's guidelines issued in June 2013.
- Currently, there is no vaccine or cure for HIV, but treatments have evolved which are much more effective and better tolerated - they can improve patients' general health and quality of life considerably, in as little as one pill per day.

Table. No. 4: Classification of Antiretroviral Drugs:

Class	Drug
NRTIs	Zidovudine
	Stavudine didanosine
	Abacavir
	Tenofovir
NNRTIs	Efavirenz
	Nevirapine
	Etravirine
	Rilpivirine
"QUAD"	elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate
Protease Inhibitors	All PIs
	Atazanavir
	Indinavir
	Darunavir
	Fosamprenavir
	Nelfinavir
	Lopinavir/ ritonavir
	Tipranavir
Entry inhibitors	Enfuvirtide
Chemokine coreceptor antagonists	Maraviroc
Integrase inhibitors	Raltegravir
	Elvitegravir/cobicistat

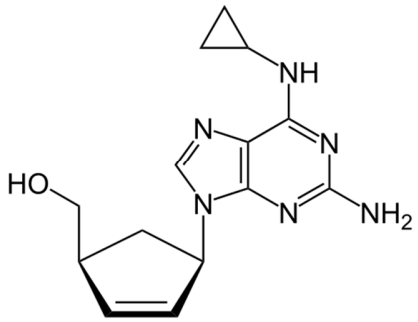
6. DRUG PROFILE [15,16,17,18.19]

Drug: Abacavir sulfate

Description[15,16]

Abacavir sulfate is a nucleoside analog reverse transcriptase inhibitor (NRTI). It works by slowing down the growth of HIV, the virus that causes AIDS. Abacavir is used in combination with other drugs to treat human immunodeficiency virus (HIV) infection. It's approved for adults and children who are at least 3 months old. Abacavir doesn't cure HIV, but it may help to control it. Abacavir works by blocking an enzyme called reverse transcriptase.

Structural formula



Systemic (IUPAC) name

[(1S,4R)-4-[2-amino-6-(cyclopropylamino)purin-9-yl]cyclopent-2-en-1-yl] methanol.

Chemical data [17]

Formula : C14H18N6O

Molecular weight : 286.339 g/mol.

CAS Registry number : 136470-78-5

Melting point : 165 °C

Water Solubility : 1.21 mg/mL or 77 mg/mL (sulfate salt)

Physical state

White to off-white Powder, solid Form.

Solubility

Abacavir sulfate occurs as white powder. Soluble in Water, DMSO (< 1 mg/ml at 25° C), ethanol (< 1 mg/ml at 25° C), and methanol.

Mechanism of action[15]

Abacavir is a carbocyclic synthetic nucleoside analogue and an antiviral agent. Intracellularly, abacavir is converted by cellular enzymes to the active metabolite carbovir triphosphate, an analogue of deoxyguanosine-5'-triphosphate (dGTP). Carbovir triphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. Viral DNA growth is terminated because the incorporated nucleotide lacks a 3'-OH group, which is needed to form the 5′ to 3′ phosphodiester linkage essential for DNA chain elongation.

Pharmacokinetics [18]

ABSORPTION:

Rapid and extensive after oral administration (83% bioavailability, tablet). Moderate (approximately 50%).

BINDING:

Binding of abacavir to plasma protein was independent of concentration.

METABOLISM:

Hepatic, by alcohol dehydrogenase and glucuronosyltransferase to a 5′-carboxylic acid metabolite and 5′-glucuronide metabolite, respectively. These metabolites have no antiviral activity. Abacavir is not significantly metabolized by cytochrome P450 enzymes.

EXCRETION:

1.2% was excreted in the urine as abacavir, 30% as the 5′-carboxylic acid metabolite, 36% as the 5′-glucuronide metabolite, and 15% as unidentified minor metabolites in the urine. Fecal elimination accounted for 16% of the dose. Renal excretion of unchanged abacavir is a minor route of elimination in humans.

Indications and usage

For the treatment of HIV-1 infection, in combination with other antiretroviral agents.

Drug category: Antiretroviral agents

Dosage and administration

Adults : 300 mg orally twice a day or 600 mg orally once a day.

Infants & Child Dose:

3 months or older:

Oral solution: 8 mg/kg orally twice a day or 16 mg/kg orally once a day

Maximum dose: 600 mg/day

Tablets:

14 to less than 20 kg: 150 mg orally twice a day or 300 mg orally once a day

20 to less than 25 kg: 150 mg orally in the morning and 300 mg in the evening, or 450 mg orally once a day

25 kg or more: 300 mg orally twice a day or 600 mg orally once a day

Dosage forms: Tablets

Special precautions[19]

Patient information:

Serious and sometimes fatal hypersensitivity reactions (with multiple organ involvement) reported with this drug. Patients with the human leukocyte antigen subtype B*5701 (HLA-B*5701) allele.

Pediatric Use

The safety and effectiveness of abacavir have been established in pediatric patients aged 3 months and older.

Adverse reactions

Commonly reported side effects of abacavir include: arthralgia, cough, fatigue, lethargy, myalgia, pruritus, vomiting, chills, and malaise.

Other side effects include: hypersensitivity, pharyngitis, and tachypnea. See below for a comprehensive list of adverse effects.

Over dosage

There is no known specific treatment for overdose with abacavir. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required. It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

7. EXCIPIENTS PROFILE

7.1. SODIUM ALGINATE[24,25]

Nonproprietary Names

Sodium alginate (BP)

Natrii alginas (PhEur)

Sodium alginate (USPNF)

Synonyms

Algin, alginic acid, sodium salt, E401, Kelcosol, Keltone, Protanal, sodium polymannuronate.

Chemical Name and CAS Registry Number

Sodium alginate [9005-38-3]

Empirical Formula and Molecular Weight

Sodium alginate consists chiefly of the sodium salt of alginic acid, which is a mixture of polyuronic acids composed of residues of D-mannuronic acid and L-guluronic acid.

The block structure and molecular weight of sodium alginate samples has been investigated.

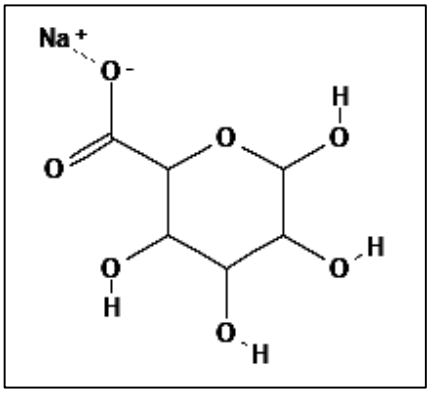
Description

Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored powder.

Solubility

Practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%. Also, practically insoluble in other organic solvents and aqueous acidic solutions in which the pH is less than 3. Slowly soluble in water, forming a viscous colloidal solution.

Structural Formula [25]



Viscosity: 20–400 mPa s .

Loss on drying ≤15.0%

Stability and Storage Conditions

Sodium alginate is a hygroscopic material, although it is stable if stored at low relative humidities and a cool temperature. Aqueous solutions of sodium alginate are most stable at ph 4–10. The bulk material should be stored in an airtight container in a cool, dry place.

Incompatibilities

Sodium alginate is incompatible with acridine derivatives, crystal violet, phenylmercuric acetate and nitrate, calcium salts, heavy metals, and ethanol in concentrations greater than 5%. Low concentrations of electrolytes cause an increase in viscosity but high electrolyte concentrations cause salting-out of sodium alginate; salting-out occurs if more than 4% of sodium chloride is present.

Safety

It is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may be harmful.

7.2. HYDROXYPROPYL METHYLCELLULOSE[24,27]

Synonyms

Cellulose, hydroxypropyl methyl ether, HPMC, methocel, metolose, and pharmacoat

Empirical Formula

HPMC is a partially o-methylated and o-(2-hydroxypropylated) cellulose. It is available in several grades, which vary in viscosity and extent of substitution.

Molecular Weight

10,000 – 15,00,000

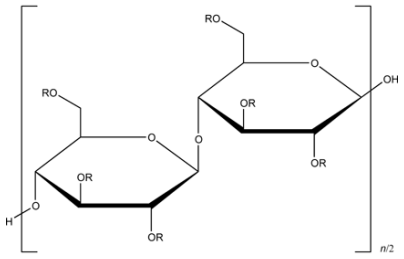
Description

HPMC is an odorless and taste less, white or creamy white colored fibrous or granular powder.

Functional Category

Coating agent, film-former, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent

Structural Formula [27]



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

Applications in Pharmaceutical Formulation

HPMC is widely used in oral and topical pharmaceutical formulations. In oral product it is primarily used as a tablet binder, in film coating and as an extended release tablet matrix. Concentration of between 2-5% w/w may be used as a binder either in wet or in dry granulation process. High viscosity grades may be used to retard the release of water-soluble drug from a matrix. Lower viscosity grades are used in aqueous film coating while higher viscosity grades are used with organic solvents.

Solubility

Soluble in cold water, forming a viscous colloidal solution, practically insoluble in chloroform, ethanol, and ether, but soluble in mixture of ethanol and dichloromethane, and mixture of methanol and dichloromethane.

Stability and Storage Conditions

HPMC is a stable material although it is hygroscopic after drying. Solutions are stable between pH 3-11. Increasing temperature reduces the viscosity of solutions. It undergoes a reversible sol to gel transformation upon heating and cooling respectively.

HPMC powder should be stored in a well-closed container, in a cool, dry place.

Incompatibilities

It is incompatible with some oxidizing agent. Since it is nonionic, it will not complex with metallic salts and ionic organics to form insoluble precipitates.

Safety

It is generally regarded as a nontoxic and non-irritant material although excessive oral consumption may have a laxative effect.

7.3. SODIUM CARBOXY METHYL CELLULOSE[24,28]

Nonproprietary Names

Carmellose sodium (BP)

Carmellose sodium (JP)

Carmellosum natricum (PhEur)

Carboxymethylcellulose sodium (USP)

Synonyms

Akucell**,** Aquasorb, Blanose, cellulose gum, E466, Finnfix, Nymcel, SCMC, sodium cellulose glycolate , Tylose CB.

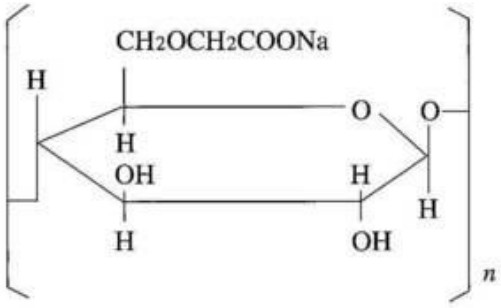
Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, sodium salt [9004-32-4]

Empirical Formula and Molecular Weight

Carboxymethyl cellulose sodium as the sodium salt of polycarboxy methyl ether of cellulose. Molecular weight is 90 000–700 000.

Structural Formula [28]



n: degree of polymerization

Description

Sodium Carboxy methyl cellulose occurs as a white to almost white, odorless, granular powder.

Solubility

Practically insoluble in acetone, ethanol (95%), ether, and toluene. Easily dispersed in water at all temperatures, forming clear, colloidal solutions.

Moisture content

It contains less than 10% water. Sodium carboxy methyl cellulose is hygroscopic and absorbs significant amounts of water at temperatures up to 378°C at relative humidity's of about 80%.

Viscosities: 5–13 000 mPas

Density: Density (bulk): 0.52 g/cm3
Density (tapped): 0.78 g/cm3

Melting point: browns at approximately 2278°C, and chars at approximately 2528°C.

Loss on drying: ≤10.0%

Functional Category

Coating agent, stabilizing agent, suspending agent, tablet and capsule disintegrate, tablet binder, viscosity-increasing agent, water-absorbing agent.

Applications in Pharmaceutical Formulation or Technology

Sodium Carboxy methyl cellulose is widely used in oral and topical pharmaceutical formulations, primarily for its viscosity increasing properties.

Sodium Carboxy methyl cellulose is additionally one of the main ingredients of self-adhesive ostomy, wound care, and dermatological patches, where it is used as a muco-adhesive and to absorb wound exudates or transepidermal water and sweat. Encapsulation with sodium carboxy methyl cellulose can affect drug protection and delivery. Its use as a cytoprotective agent.

Sodium Carboxymethylcellulose is also used in cosmetics, toiletries, surgical prosthetics, and incontinence, personal hygiene, and food products.

Incompatibilities

Sodium Carboxymethylcellulose is incompatible with strongly acidic solutions and with the soluble salts of iron and some other metals, such as aluminum, mercury, and zinc. Precipitation may occur at pH <2, and also when it is mixed with ethanol (95%).

Stability and Storage Conditions

Sodium Carboxymethylcellulose is a stable, although it is slightly hygroscopic. The bulk material should be stored in a well-closed container in a cool, dry place

Safety

Sodium Carboxymethylcellulose is used in oral, topical, and some parenteral formulations. It is generally regarded as a nontoxic and nonirritant material although excessive consumption may have laxative effect.

8. MATERIALS AND INSTRUMENTS

8.1. Materials used

Table.No.5 : Materials used

S. No	MATERIALS	SUPPLIERS/MANUFACTURERS
1	Abacavir sulfate	Molecules India Pvt Ltd, Chennai
2	Sodium alginate	s.d.fine chem. Ltd. Mumbai
3	Sodium carboxy methyl cellulose	s.d.fine chem. Ltd Mumbai
4	Hydroxy propyl methyl cellulose K4M	Otto chem. Laboratories Pvt.Ltd
5	Hydroxy propyl methyl cellulose K100M	Otto chem. Laboratories Pvt.Ltd
6	Sodium phosphate dibasic dehydrate	RANKEM,RFCL Ltd, New Delhi
7	Potassium dihydrogen ortho phosphate	RANKEM,RFCL Ltd, New Delhi
8	Sodium chloride	RANKEM,RFCL Ltd, New Delhi
9	Paraffin liquid colorless light	Molychem, Mumbai
10	Polysorbate 80 (tween 80)	Sisco Research laboratories Pvt.Ltd.
11	Dichloromethane	RANKEM,RFCL Ltd, New Delhi
12	Methanol	Merck Specialities Pvt.Ltd, Mumbai
13	n-hexane	s.d.fine chem. Ltd, Mumbai

8.2 Instruments used

Table.No.6 : Instruments used

S. No	INSTRUMENTS	SUPPLIERS/MANUFACTURERS
1	Digital Balance	Wensar PGB - 300
2	UV-Visible Spectrophotometer	LAB INDIA UV 3000+
3	Dissolution Test Apparatus	Labindia Analytical Instruments Pvt Ltd. Mumbai , Model-DISSO 2000
4	Temperature controller(hot air oven)	GABAKS
5	pH Meter	Chemline digital pH meter, CL-110
6	Stirrer	Remi Laboratory stirrer
7	FTIR	BRUKER HTS-XT

9. PREFORMULATION

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

Preformulation studies relate to pharmaceutical and analytical investigation carried out in supporting formulation development efforts of the dosage forms.

The following preformulation studies were performed for obtained sample of drug.

9.1. ORGANOLEPTIC PROPERTIES

9.1.1. Color and nature

Transferred small quantity of the sample on a white piece of paper spreaded the powder and examined visually.

9.1.2. Taste and odour

Very less quantity of Abacavir sulfate was used to get taste with the help of tongue as well as smelled to get the odor.

9.2. PHYSICAL CHARACTERISTICS

9.2.1. Flow properties

The flow properties of powder are critical for an efficient microsphere preparing. If the drug is identified at pre formulation stage to be “poorly flowable” the problem can be solved by selecting appropriate excipients. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

Procedure

A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom is closed and 10gm of sample powder is filled in funnel. Then funnel was open to release the powder on the paper to form a smooth conical heap, is found by measuring in a different directions. The height of the heap was measured by using scale. The values of angle of repose are calculated by using the following formula.

$$\theta = \tan^{-1} (h/r)$$

Where,

θ = Angle of the repose

h = Height of the heap

r = Radius of the heap

Table 7. ANGLE OF REPOSE LIMITS

ANGLE OF REPOSE	FLOWABILITY
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

9.2.2. Bulk density

Bulk density is the ratio of mass of powder to the bulk volume. Bulk density largely depends on particular shape as the particle become more spherical in shape, bulk density is increases.

Bulk density is determined by measuring the volume of a known mass of a powder sample that has been passed through a screen into a graduated cylinder.

Procedure

A known quantity of powder was poured into measuring cylinder carefully level the powder without compacting , if necessary and read the unsettled apparent value. Calculate the bulk density, in gm per ml, by the formula.

$$\rho_b = m / V_b$$

Where,

ρ_b = Bulk density

m = mass of powder

V_b = initial/bulk volume

The results are shown in results and discussion.

9.2.3. Tapped density

Tapped density is the ratio of mass of powder to the tapped volume**.**

Procedure

A quantity 5gm of the powder (W) from each formula was introduced in to a 25ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. Calculate the tapped density, in gm per ml, by the formula**.**

$$\rho_t = m / V_t$$

Where,

ρ_t = Tapped density

m = Mass of the powder

V_t = Final/tapped volume

9.3.1. Measurement of powder compressibility

The compressibility index is measures of the propensity of a powder to be compressed. As such, they are measures relative importance of inter particulate interactions. In a free flowing powder, such interactions generally less and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particulate interactions, and a greater difference between bulk and tapped densities will be observed. These differences are reflected in the compressibility index calculated by the formula.

$$\%\text{compressibility (Carr's index)} = \frac{\text{Tapped density - Initial bulk density}}{\text{Tapped density}} \times 100$$

Table 8. Compressibility index limits.

% Compressibility	Flow ability
5-12	Excellent
12-16	Good
18-21	fair
23-25	poor
33-38	Very poor
More than 40	Very, very poor

9.3.2. Hausner ratio

It is the ratio of volume of tapped volume is tapped density to bulk density

Hausner ratio = V_b/V_t **or** ρ_t/ρ_b

Table 9. Hausner Ratio index limits

Hausner Ratio	Flowability
1.2-1.3	Excellent
1.3-1.4	Good
1.4-1.5	Fair
1.3-1.4	Poor

9.3.3. Melting point

It is one of the parameters to judge the purity of crude drug. In case of pure chemicals, melting points are very sharp and constant**.**

Procedure

A small quantity of powder was placed into a fusion tube. That tube is placed in the melting point apparatus containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted. The results are shown in results and discussion.

9.4. SOLUTION PROPERTIES

9.4.1. pH of the solution

Weighed and transferred accurately about 1.0 g of sample in a 200ml clean and dried beaker, dissolved in carbondioxide free water and made up the volume to 100ml with same solvent, mixed. Read the pH of freshly prepared solution by using precalibrated pH meter. The results are shown in results and discussion.

9.4.2. Solubility

A semi quantitative determination of the solubility was made by adding solvent in small incremental amount to a test tube containing fixed quantity of solute of vice versa. After each addition, the system is vigorously shaken and examined visually for any undissolved solute particles. The solubility is expressed in terms of ratio of solute and solvent. The results are shown in results and discussion.

9.5. IDENTIFICATION OF DRUG AND COMPATABILITY STUDY

9.5.1. Drug –excipient compatibility studies

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect stability of the drug. Knowledge of drug-excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information is already be in existence for known drugs. For new drugs or new excipients, the pre formulations scientist must generate the needed information.

By physical observation

It was determined as per procedure given in method section the following table illustrated the result.

Table 10. Physical compatibility studies

Test	Observation	Inference
Physical compatibility	No change of color	These materials are compatible for formulation

Procedure by FT-IR Studies

The IR spectrums of Abacavir sulfate with excipients were taken by preparing dispersion in dry potassium bromide under dry condition. Superimposed these spectra. The transmission minima (absorption maxima) in the spectra obtained with the sample in corresponded in position and relative size to those in the spectrum obtained with the standards.

9.6 UV SPECTROSCOPIC METHOD FOR ANALYSIS OF ABACAVIR SULFATE

Preparation of stock solution

Weighed accurately 100mg of drug and transferred it to 100ml volumetric flask, then add water and the volume was made up to 100ml with water**.**

Preparation of standard solution

Then pipette out 1ml from above solution in a 10ml volumetric flask and made the volume with water to 10ml. From standard stock solution 0.2ml, 0.4ml, 0.6ml, 0.8ml and 1ml solution was pipette out in five 10ml volumetric flasks and make up the volume with water to get 2µg, 4µg, 6µg, 8µg and 10 µg/ml concentration**.**

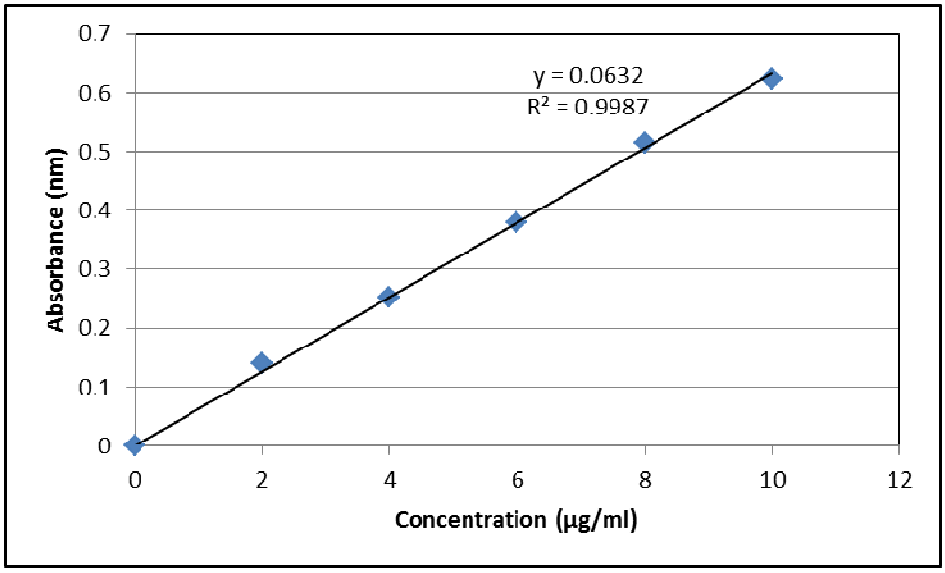
CALIBRATION CURVE OF ABACAVIR SULFATE

Measured the absorbance of the above prepared standard solution at 296 nm . plotted a graph of concentration (in µg/ml) on X axis and absorbance (in nm) on Y axis

Table 11. Calibration curve for Abacavir sulfate

S.No.	Concentration(µg/ml)	Absorbance (nm)
1	0	0
2	2	0.152
3	4	0.279
4	6	0.392
5	8	0.514
6	10	0.623
Slope	0.0632	
R^2	0.9987	

Fig.11. Calibration curve for Abacavir sulfate



10. FORMULATIONS OF ABACAVIR SULFATE FLOATING MICROSPHERES

Table 12. FORMULATIONS

INGREDIENTS in mg	FORMULATION BATCHES									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Abacavir sulfate	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
HPMC K4M	1000	-	-	-	500	500	500	-	-	-
Sodium alginate	-	1000	-	-	500	-	-	500	500	-
Sodium CMC	-	-	1000	-	-	500	-	500	-	500
HPMC K100M	-	-	-	1000	-	-	500	-	500	500
Methanol	5	5	5	5	5	5	5	5	5	5
Dichloromethane	5	5	5	5	5	5	5	5	5	5

Floating microspheres were prepared by the solvent evaporation method using 1000 mg of Abacavir sulfate and with different polymer as shown in Table, were dissolved in methanol (5 ml), dichloromethane (5 ml) with vigorous agitation to form uniform drug polymer dispersion. This was slowly poured into the dispersion medium consisting of light liquid paraffin (100ml) containing 1.1% tween 80. The system is stirred using propeller at 1000 rpm at room temperature for 1hr 30 min – 2 hr. The liquid paraffin was decanted and the microparticles were separated by filtration through a whatmann filter paper, was head thrice with 180 ml of n-Hexane and air dried for 6-8 hrs.

12.a 12.b

Fig. 12.a : Preparation of Microspheres; 12.b : after drying microspheres

11. EVALUATION OF FLAVOXATE HCL FLOATING MICROSPHERES

a) Micromeritic properties

i) Angle of repose

5 gms of the sample was taken in a funnel fixed in a holder (6 cm) above the surface at an appropriate height and graph of sheet was placed below the funnel. The sample was passed through the funnel slowly. The height of the powder heap formed was measured. The circumference of the heap formed was drawn with a pencil on the graph paper. The radius was measured and angle of repose was determined using the above formula. This was repeated five times for a sample.

$$\theta = \tan^{-1}(h/r)$$

Where,

h = height

r = radius

θ = angle of repose

The results are given in results and discussion.

ii) Determination of bulk density and tapped density

A quantity 5gm of the powder (W) from each formula was introduced in to a 25ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The bulk density and tapped density were calculated using the following the formula

$$\text{Bulk density } (\rho_b) = m/V_b$$

$$\text{Tapped density}(\rho_t) =) = m/V_t$$

Where,

m = mass of the powder

V_b = initial or bulk volume

V_t = final or tapped volume

The results are given in results and discussion.

iii) Measurement of compressibility index and Hausner ratio

Compressibility index and Hausner ratio are measured by using the following formula

$$\%\ \text{compressibility (carr's index)} = \frac{\text{Tapped density - Intial bulk density}}{\text{Tapped density}} \times 100$$

The result is given in in results and discussion.

$$\text{Hausner ratio} = V_b / V_t$$

Where,

V_b = initial or bulk volume

V_t = final or tapped volume

The results are given in results and discussion.

b) Percentage yield of microspheres

The prepared microspheres of all batches were accurately weighed. The weight quantity of prepared microspheres was divided by the total amount of all the excipients and drug used in the preparation of the microspheres, which give the total percentage yield of floating microspheres. It was calculated by using following equation,

$$\text{Percentage yield} = \frac{\text{Actual yield of product}}{\text{Total weight of excipients and drug}} \times 100$$

The results are given in results and discussion.

c) Drug entrapment

According to dose 100mg actual drug present in total microspheres (drug 1gm+ excipients) is calculated. That amount mixed in 0.1 M HCL by sonication. From that pipette 1ml into 10ml volumetric flask and made upto 10ml using buffer. The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically at 296 nm against appropriate blank. The amount of drug entrapped in the microspheres was calculated by the following formulae.

$$\text{Percentage drug entrapment} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

The results are given in results and discussion.

d) Buoyancy studies

Microspheres (300mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 ml of 0.1 M HCL. The medium was agitated with a paddle rotating at 75 rpm for 12 h. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres.

$$\% \text{ Buoyancy} = \frac{W_f}{(W_f + W_s)} \times 100$$

Where,

W_f = weight of the floating

W_s= settled microspheres respectively.

The results are given in results and discussion.

e) ***Invitro*** **dissolution studies**

Preparation of buffer solution

Measure 4 ml of concentrated Hydrochloric acid, in a 1000ml volumetric flask and make up the volume upto 1000ml using distilled water and stir until it mix.

In-vitro **release profile:**

Medium : 0.1 M HCL

Apparatus : USP II (Paddle)

Speed : 75 rpm

Time : 1hr, for every 2hrs up to 12hr

Temperature : 37.5 °C

λ max : 296 nm

Perform the test on microspheres place in each dissolution vessel containing 900ml of 0.1 M HCL maintained at 37 °C ± 0.5 °C. At specified time withdrawn required

amount the sample and replace the same amount with (maintain sink conditions) phosphate buffer, then absorbance was taken and calculate percentage release.

$$\% \text{ Purity} = \frac{\text{Absorbance} \times 900 \times \text{dilution}}{\text{Slope} \times 1000 \times \text{label claim.}} \times 100$$

f) Kinetics of drug release

The *invitro* dissolution profile of all batches were fitted to Zero order, First order,Higuchi model, Korsemeyer-peppas model to ascertain the kinetic modeling of drug release. Correlation coefficient (R^2) values were calculated for linear curves obtained by the regression analysis of the above plot.

Zero-order kinetic model –Cumulative % drug released vs. time

First order kinetic model -log cumulative % drug remaining vs. time

Higuchi model -Cumulative % drug released vs. square root of time

Korsemeyer-peppas model -log cumulative % drug released vs. log time

Zero order- kinetic model

Zero order release would be predicted by the following equation.

$$A_t = A_o - K_o t$$

Where,

A_t - Drug release at time‘t’

A_o- Initial drug concentration

K_o - Zero order rate constant (hr^{-1})

When the data plotted as cumulative % drug release Vstime and the plot is linear , then the data obeys Zero-order equal to K_o.

First order kinetics

First order release would be predicted by the following equation

$$LogC = \log C_o - K_t/2.303$$

Where,

Log C - Amount of drug remained at time ‘t’

$\log C_o$ - initial drug concentration

K - first order rate constant (hr^{-1})

When the data plotted as log cumulative % remaining Vs time yields a straight line, then the release obeys first order kinetics. The constant 'K' obtained by multiplying 2.303 with the slope values.

Korsemeyer-peppas model.

To study the mechanism of drug release from microspheres, the *invitro* data were fitted to the well known exponential equation (korsemeyer peppas model) which is often used to describe the drug release behavior from polymeric systems.

$$Mt/M\alpha = Kt^n$$

Where,

Mt/Mα - The fraction of drug released at 't'

K - Constant incorporating structural and geometrical characteristics of the drug / polymer system

n - Diffusion exponent related to mechanism the drug release

When the data plotted as log % drug released Vs log time yields a straight line with a slope equal to 'n' and the K can be obtained by y- intercept.

Mechanism of drug release as per korsemeyer-peppas equation / peppas model

Table 13.Mechanism of drug release

S . No	n values	Drug release
1	0-0.5	Fickian release
2	0.5-1.0	Non-Fickian release
3	>1.0	Class II transport

g) IR spectroscopy (Drug excipient compatibility

FT-IR spectrocopy was found to be the most reliable technique for predicting the possible interaction between the drug and polymers. The IR spectra of physical mixtures were studied using KBr disc method.

h) Scanning Electron Microscopy

The morphological study was carried out by Scanning Electron Microscope (SEM). Microspheres were scanned and examined under Electron Microscope BRUKER HTS-XT. The sample was loaded on copper sample holder.

12. RESULTS AND DISCUSSIONS

PRE FORMULATION STUDIES

Organoleptic properties

These tests were performed as procedure given, Preformulation part. The results are illustrated in following table.

Table 14. Organoleptic properties

Test	Specifications/limits	Observations
Color	White to off white	Off White powder
Odour	odorless	odorless

The results complies as per specifications

Angle of repose

It was determined as per procedure preformulation in material and method part. The results are illustrated in following table**.**

Table 15. Flow properties

Material	Angle of repose
Abacavir sulphate	29°.28”

The result shows that drug having poor flow

Bulk density and tapped density.

It was determined as per procedure given preformulation in material and method part. The results are illustrated in table**.**

Table 16. Density

Materials	Bulk Density(gm/ml)	Tapped density(gm/ml)
Abacavir sulphate	0.19	0.26

Powder compressibility

It was determined as per procedure given in preformulation in material and method part. The results are illustrated in table**.**

Table 17. Powder compressibility

Material	Compressibility index	Hausner ratio
Abacavir sulphate	28.04%	1.34

The results shows that drug having poor flow property

Melting point

It was determined as per procedure given in preformulation in material and method part. The results are illustrated in following table**.**

Table 18. Melting point

Material	Material point range	result
Abacavir sulphate	165 ℃	Complies

The result complies as per specification.

SOLUTION PROPERTIES

pH of the solution

It was determined as per procedure given in preformulation in material and method part. The results are illustrated in following table**.**

Table 19. pH

Material	Test	Specification	Observation
Abacavir sulphate	pH	7.5	7.5

The result complies as per specification

Solubility

It was determined as per procedure given in preformulation in material and method part. The results are illustrated in following table.

Table 20. Solubility

Test	Specification	Result
solubility	Freely soluble in water, Sparingly soluble in DMSO, ethanol, methanol	Complies

The result complies as per specification.

DRUG-EXCIPIENT COMPATABILITY STUDIES

Discussion:

Drug excipient interactions play a vital role with respect to release of drug from formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipient used.

Table 21. Drug – Excipients Compatibility Study Results

Drug + Excipients	Initial	After 1 month at		Compatible
		40^0C/75% RH	60^0C	
Drug	White powder	No change	No change	Yes
Drug + Methanol	White powder	No change	No change	Yes
Drug + Tween 80	White powder	No change	No change	Yes
Drug + HPMC K100M	White powder	No change	No change	Yes
Drug + HPMC K4M	White powder	No change	No change	Yes
Drug + Dichloro methane	White powder	No change	No change	Yes

IR GRAPHS

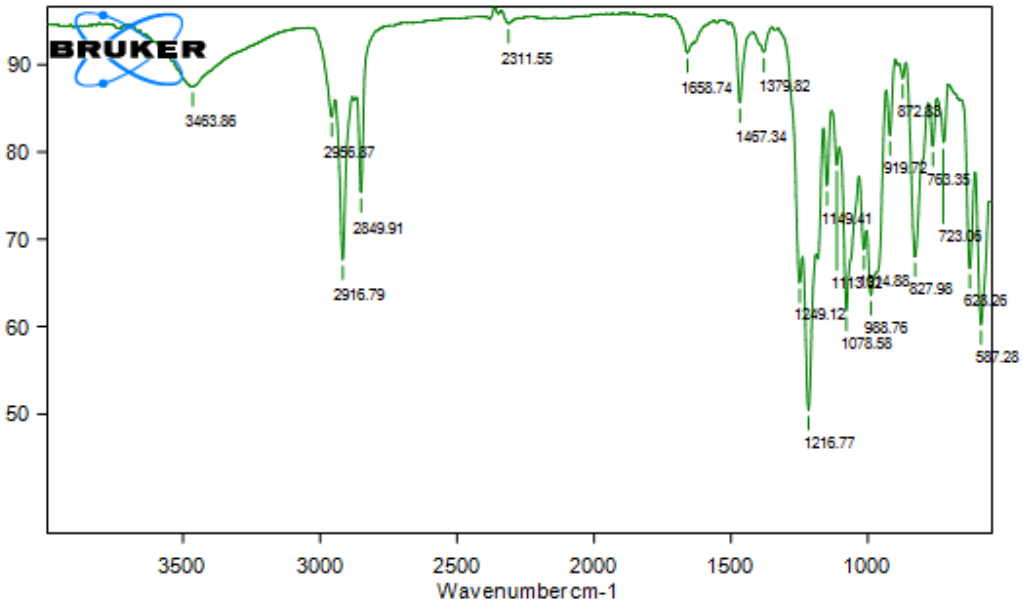


Fig. 13(a) FT-IR of Abacavir Sulphate

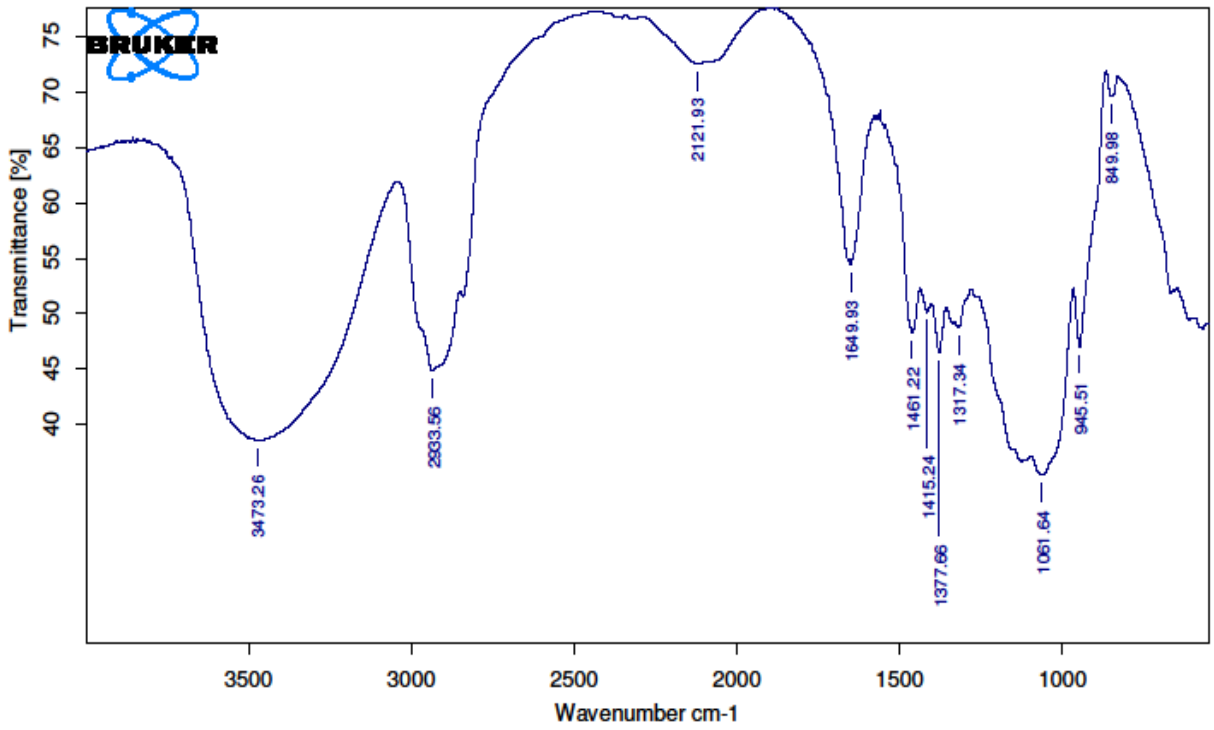


Fig. 13(b) FT-IR Graph of HPMC K4M

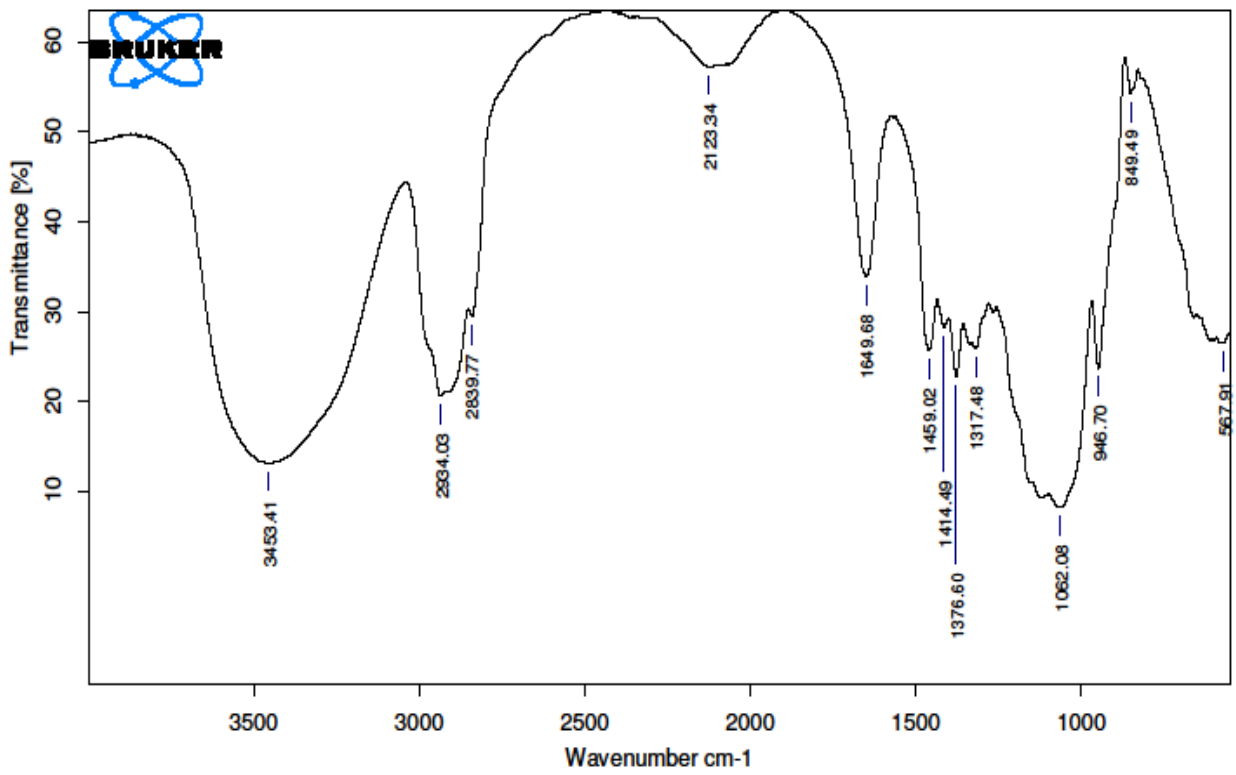


Fig. 13(c) FT-IR Graph of HPMC K100M

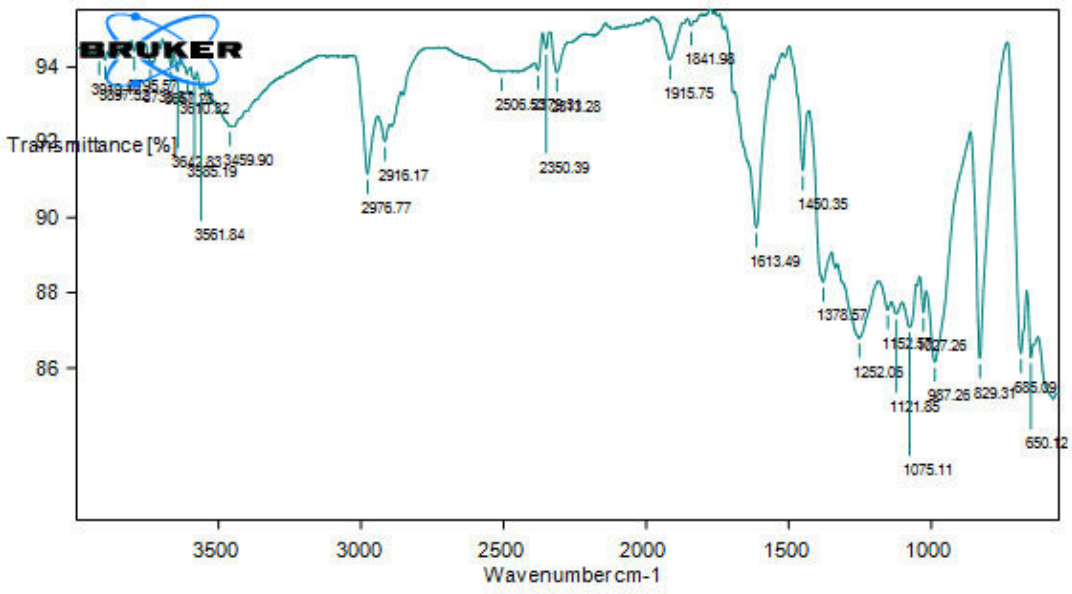


Fig. 13(d) FT-IR Graph of Mixture of

Abacavir Sulphate + HPMC K4M +HPMC K100M

Table.No.22: Band Assignments for the Infrared Absorption Spectrum of Abacavir Sulphate

Band Energy (cm-1)	Assignment
3463.2	tertiary amine hydrochloride (N-H) stretch
2958.6	O-H stretch
2849.7	C-H Stretch
1660.0	Cyclopentene Ring C=C stretch
1451.6	C-H Bending (CH_2 Scissoring)

In the present study, it has been observed that there is no chemical interaction between Abacavir sulphate and the polymers used. From the figures 11(a),11(b),11(c) and 11(d) it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymer.

Table.No. 23. EVALUATION OF MICROSPHERES

Batch NO.	Angle of Repose(°)	Bulk Density (g/ml)	Tapped Density(g/ml)	Carr's Index (%)	Huasner Ratio
F1	25°08′	0.2826	0.3177	10.38	1.11
F2	23°52′	0.2671	0.3242	14.07	1.19
F3	24°24′	0.2841	0.3318	16.47	1.15
F4	27°62′	0.2853	0.3420	16.13	1.19
F5	24°09′	0.2965	0.3446	14.47	1.16
F6	27°37′	0.2924	0.3321	11.94	1.13
F7	26°64′	0.2768	0.3394	13.68	1.22
F8	24°71′	0.2891	0.3503	16.04	1.21
F9	26°14′	0.2965	0.3446	13.54	1.16
F10	25°50′	0.2721	0.3242	15.07	1.19

Discussion

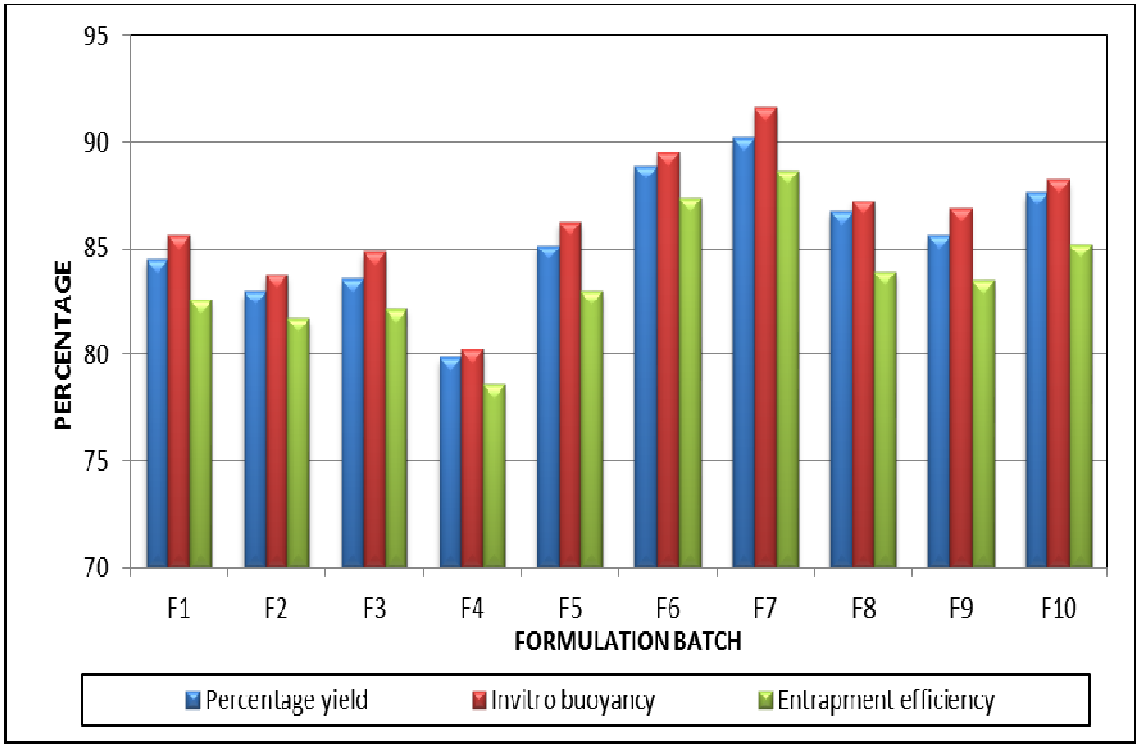
The angle of repose for the formulations F1-F10 was found to be in the range 23°52′ to 27°62′ shows good flow property

Compressibility index for the formulations F1-F10 found between 10.38% to 16.13% indicating the good flow property.

Table 24.PERCENTAGE YIELD, *INVITRO* BUOYANCY, DRUG ENTRAPMENT EFFICIENCY OF FLOATING MICROSPHERES OF ABACAVIR SULPHATE

Batch No.	Percentage yield	*Invitro* buoyancy	Entrapment efficiency
F1	84.52	85.65	82.60
F2	82.98	83.75	81.73
F3	83.54	84.82	82.17
F4	79.89	80.23	78.61
F5	85.15	86.24	83.04
F6	88.91	89.54	87.39
F7	90.21	91.66	88.69
F8	86.78	87.26	83.92
F9	85.59	86.92	83.47
F10	87.66	88.22	85.21

Fig.No. 14: Buoyancy, Entrapment efficiency Study of Floating Microspheres



Percentage yield

The maximum percentage yield was found in F7 formulation and was noted to be 90.21 % among all formulations.

The floating microspheres were prepared with different and combination of two polymer of HPMC K4M, HPMC K100M, Sodium Alginate and Sodium CMC to investigate the influence of encapsulation efficiency and were used to determine its influence on floating behavior.

***Invitro* Buoyancy**

Discussion

The different polymers with same ratios of formulation were selected for optimization of their buoyancy property. The formulations in which combination of HPMC K4M, HPMC K100Mare giving the better results.

The formulations, are selected as the best formulations depending upon their buoyancy, encapsulation efficiency. From the results of all the ten formulations, it is confirmed that the change in polymers of Sodium Alginate, Sodium CMC, HPMC K4M, K100M influences the properties of the formulations. The formulation F7 with drug and combination of two polymer 1:1 ratio, is giving the best result of buoyancy property.

The microspheres, having lower densities (having a hollow core) exhibited buoyancy and are expected to be retained in gastric environment for more than 12 hrs. This may be attributed to a decrease in density of microspheres with an increase in polymer concentration.

Fig.No. 15: Buoyancy Study of Floating Microspheres

Entrapment efficiency

Discussion

The percentage entrapment efficiency of various formulation parameters of the prepared microspheres were shown in table. The entrapment efficiency varied from 78.61 to 88.69.

The formulation F7 is having high encapsulation efficiency of 88.69% and F4 is having low encapsulation efficiency of 78.61%.

The low encapsulation is because of using single polymer of HPMC K100M than the drug concentration where the quantity of HPMC K100M is insufficient to entrap the drug. The high encapsulation efficiency is because of using combination of polymers of HPMC K100M, HPMC K4 where the increase in the HPMC concentration forms larger microspheres encapsulating more amount of drug.

Table 25. *INVITRO* RELEASE PROFILE

Time (hours)	BATCH NO.									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	20.03	12.05	14.18	10.01	12.91	10.56	8.25	15.23	12.11	9.54
2	35.56	32.56	31.56	28.19	22.12	15.99	13.11	25.76	22.77	13.84
4	54.14	53.29	45.25	62.43	35.12	28.21	24.72	37.45	30.99	24.15
6	69.65	77.38	63.14	76.37	52.64	44.14	40.99	53.28	48.12	43.09
8	89.14	96.38	92.02	98.24	78.11	58.98	56.25	79.54	69.82	54.69
10					94.42	78.68	72.84	90.47	93.51	72.74
12						87.04	90.12			85.25

Fig.16. *Invitro* Dissolution Release Profile for F1 – F10 Formulations

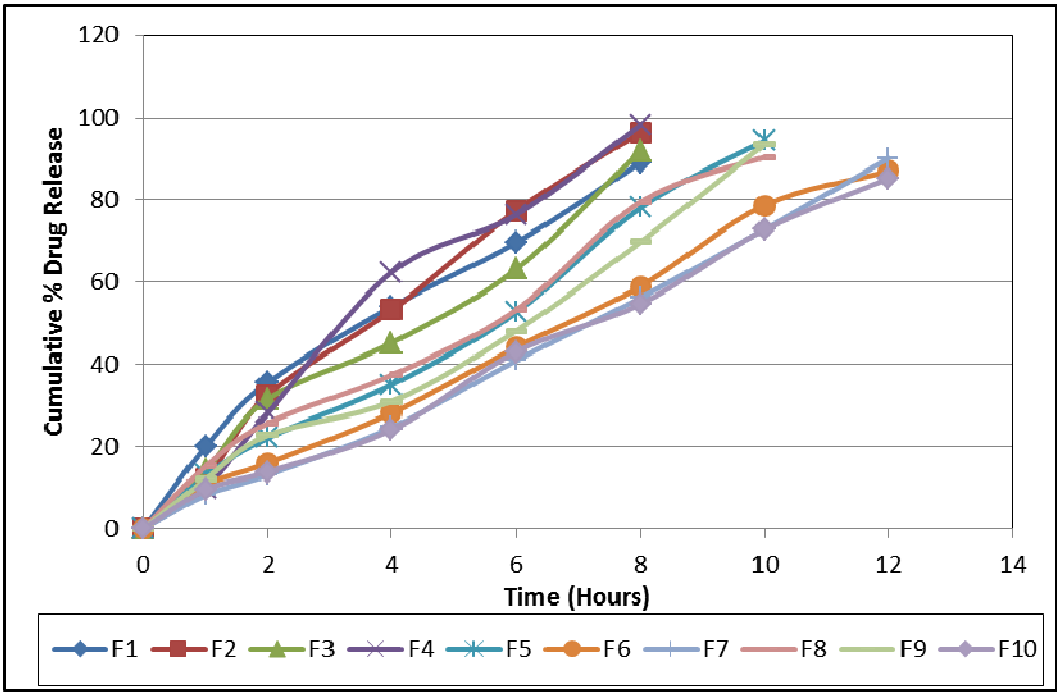


Fig.17. *Invitro* Dissolution Release Profile for F1 – F5 Formulations

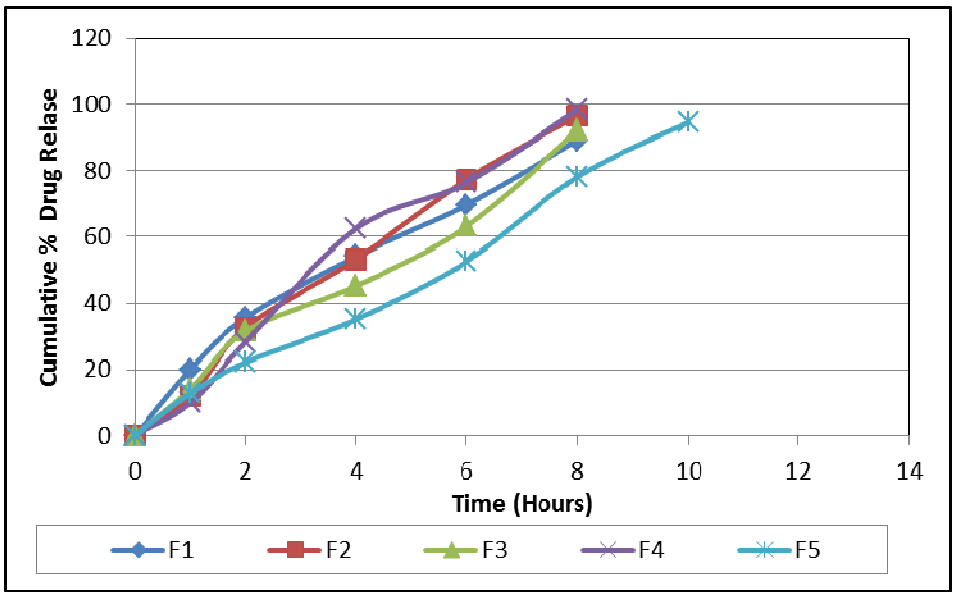


Fig.18. *Invitro* Dissolution Release Profile for F6 – F10 Formulations

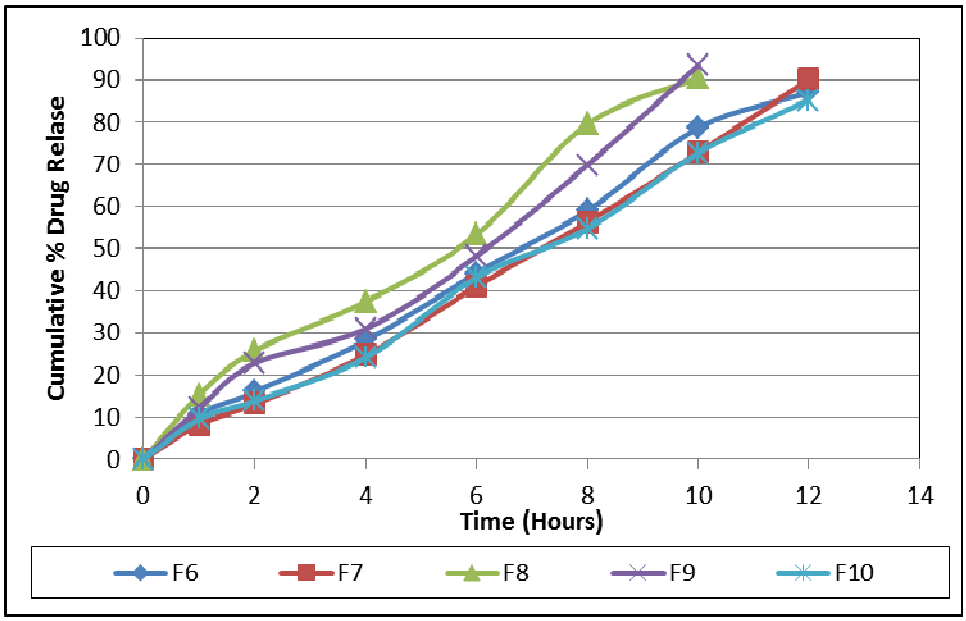
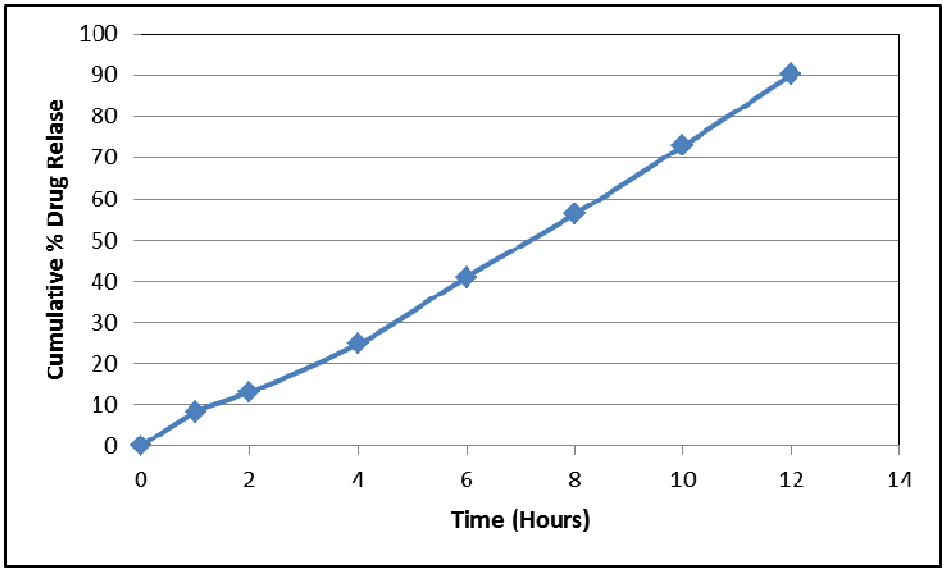


Fig.19. *Invitro* Dissolution Release Profile for Best Formulation F7



Discussion:

From the *Invitro* dissolution study of all formulations (F1-F10), formulation F7 release around 90.12% of drug at the end of 12 hours for a sustained release. Therefore the F7 formulation chosen as the best formulation from all ten batches.

Kinetics of drug release :

Table 26. Drug release kinetics of formulation F7

Time (Hr)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remainining	log time	log Cumu % drug released
0	0	100	0.000	2.000	0.000	0.000
1	8.25	91.75	1.000	1.963	0.000	0.916
2	13.11	86.89	1.414	1.939	0.301	1.118
4	24.72	75.28	2.000	1.877	0.602	1.393
6	40.99	59.01	2.449	1.771	0.778	1.613
8	56.25	43.75	2.828	1.641	0.903	1.750
10	72.84	27.16	3.162	1.434	1.000	1.862
12	90.12	9.88	3.464	0.995	1.079	1.955

Fig. 20. ZERO ORDER KINETIC MODEL

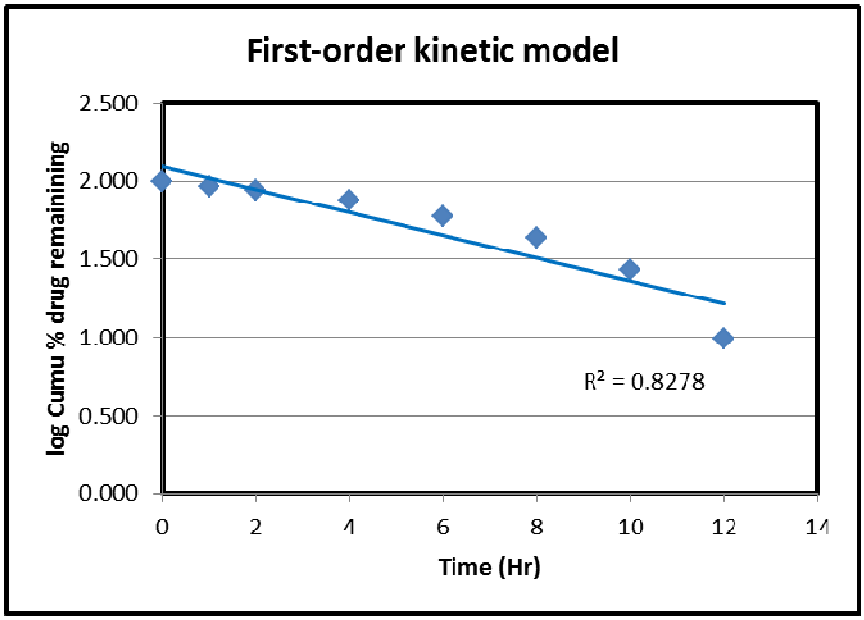


Fig. 21. ZERO ORDER KINETIC MODEL

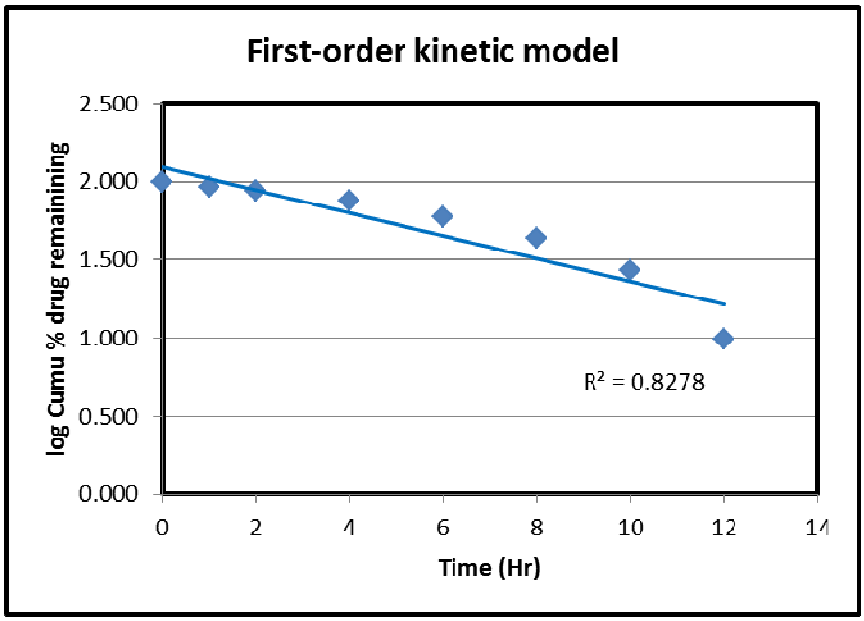


Fig. 22. ZERO ORDER KINETIC MODEL

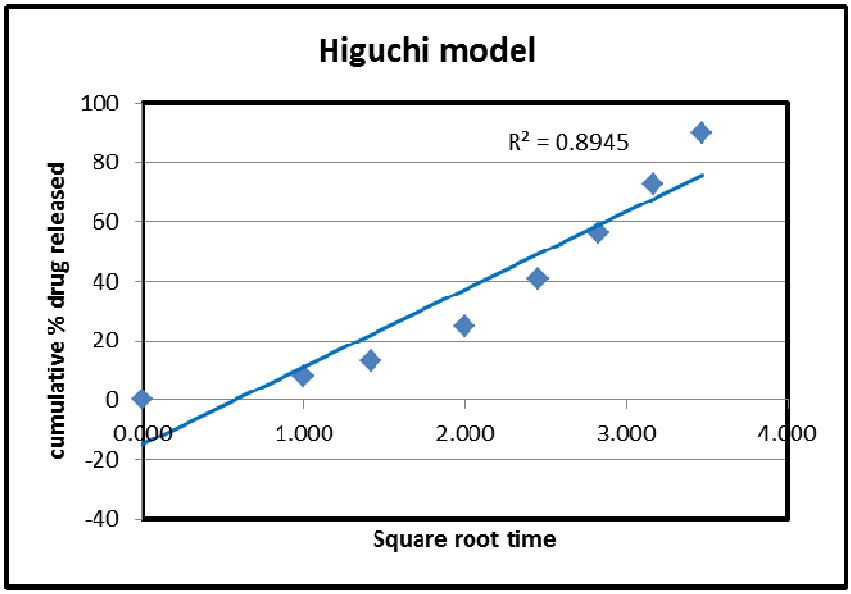


Fig.23. KORSEMEYER PEPPAS MODEL

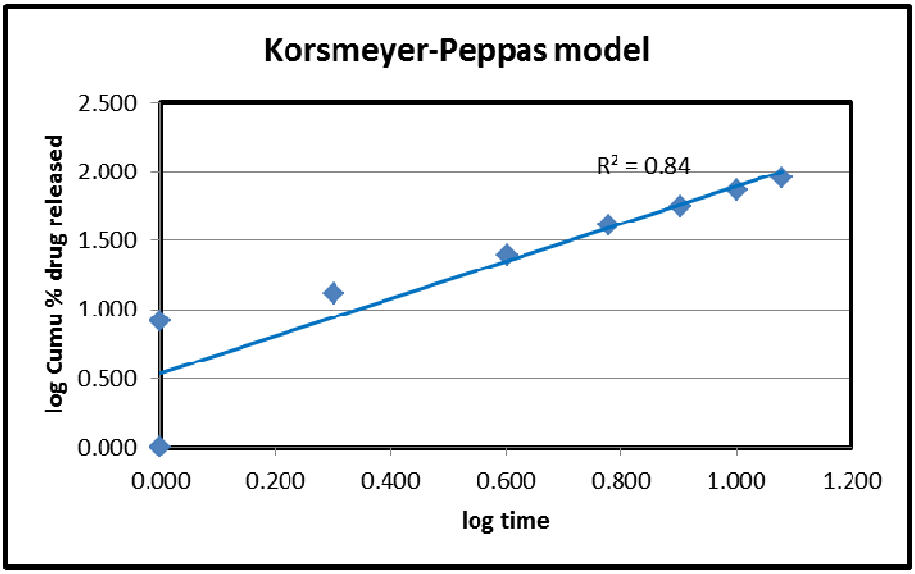


Table 27. Regression Coefficient of F7

Formulation	Regression coefficient (R^2) values			
	Zero order	**First Order**	**Higuchi Model**	**Korsemeyer - peppas**
Abacavir sulphate Floating Microspheres	0.9955	0.8278	0.8945	0.8400

n = 0.9735

The regression coefficient values and n values show that the drug releases follow Non - Fickian release (Diffusion and swelling).

Scanning Electron Microscopy (SEM)

Fig **24 (a)**

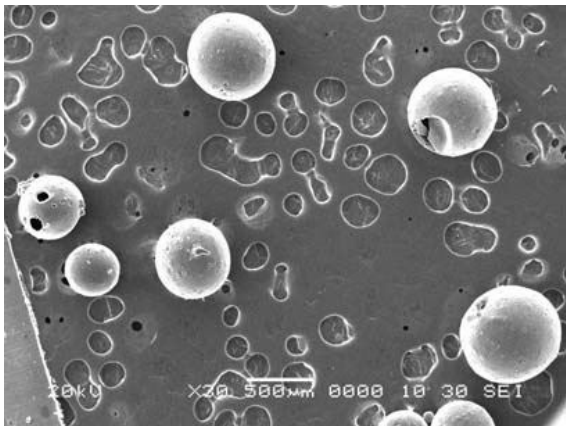
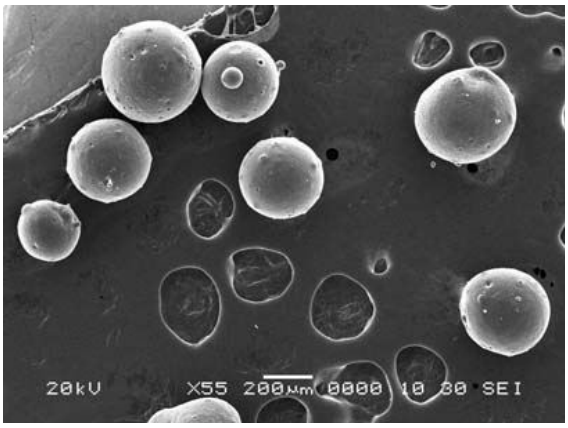


Fig 24 (b)



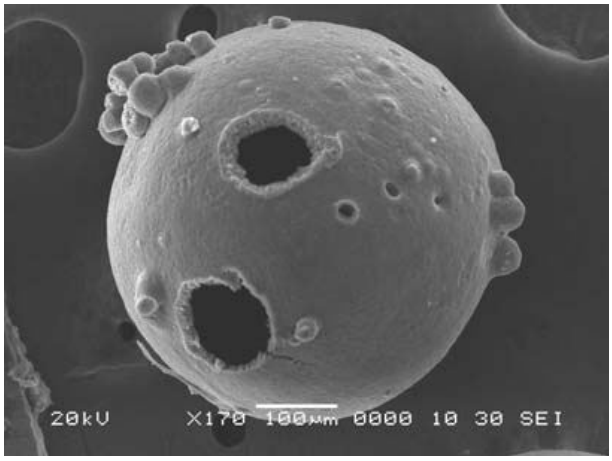


Fig **24(c)**

Fig. 24 Scanning electron microphotographs of floating microsphere of Abacavir sulphate:24(a) &24(b) smoothness of the surface of spherical shaped microsphere 24(c) Internal view of the shell having porous structure**.**

DISCUSSION

Morphology of floating microspheres was examined by scanning electron microscopy. The view of the microspheres showed hollow structure with a smooth surface morphology exhibited range of sizes within each batch. The outer surface of microspheres was smooth and dense, while the internal surface was porous. The shell of microspheres also showed some porous structure it may be caused by evaporation of solvent entrapped within the shell of microsphere after forming smooth and dense layer.

13. SUMMARY

The present study involves formulation and evaluation of sustained release floating microspheres of Abacavir sulphate. Endeavour's with respect to floating mechanism are inculcated in the formulation to achieve longer stay of microsphere in stomach which happen to better site of absorption for the selected drug.

Preformulation studies involving organoleptic bulk density, tapped density, angle of repose, compressibility of index, hausner ratio, melting point range, pH, solubility were carried out as per IP specification.

Drug excipient compatibilities were carried out and evaluation and FT-IR, SEM. This showed no significant change in any way to the Mixture.

Different polymers like sodium alginate, sodium carboxy methyl cellulose, HPMC K4M, HPMC K100M were utilized in the trials. All the physical evaluations are carried in preformulation studies were carried out on all the three different polymers utililized. All the formulations exhibited values within the acceptable range.

Microspheres were evaluated for buoyancy studies, drug entrapment efficient.

Release studies were carried out in 0.1N HCL for 12 hours. Evaluated samples for all the four polymer system. Results indicated that formulation F7, gave 90.12 % release up to 12 hrs which is formulated with HPMC K100M and HPMCK4M combination. Assay was carried out for formulation F7 and was found to be 88.69 %. The mechanism of drug release from microspheres follows Non-Ficknian release.

Remaining formulations gave fluctuating release profiles. The formulation F7 was considered to be better among the trails accomplished.

14. CONCLUSION

The ultimate goal for sustained drug release is to maximize therapeutic activity while minimizing the negative side effects of the drug. In this regard, floating microspheres have emerged as a novel drug delivery system to treat HIV with Abacavir sulphate.

The type of polymer affects the drug release rate and the mechanism. Polymer swelling is crucial in determining the drug release rate and is also important for flotation. A lesser FLT and a prolonged floating duration could be achieved by using different polymer combinations. In this study sustained release Floating Microsphere approach for Abacavir sulphate purposes that with hydrophilic polymers the GI retention can be enhanced and reduce frequency of dosing, thereby minimizing the occurrence of side effects, site specificity, increase the effectiveness of the drug and better patient compliance This gives a signal to extending this approach to similar combinations of drugs used in clinical practice so as to improve bioavailability of poorly absorbed drugs in GIT.

When these floating microspheres compared to other floating dosage forms like floating tablets have bulk density less than gastric fluid and so remain buoyant in the stomach for prolonged period of time and these are used as multiunit dosage form and drug release optimization and show efficiency level. So, Sustained release floating microspheres of Abacavir sulphate may provide a convenient dosage form for achieving best performance and release and show good bioavailability.

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