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Formulation And Evaluation Of Floating Gastroretentive Microsphere Of Antiviral Agent (Acyclovir).

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ABSTRACT

This study focuses on the formulation and evaluation of floating gastroretentive microspheres containing the antiviral agent acyclovir. The aim is to enhance the bioavailability and therapeutic efficacy of acyclovir by prolonging its gastric residence time. Microspheres were prepared using the solvent evaporation method, employing different polymers such as ethyl cellulose, and carbopol 934P to achieve sustained release and buoyancy.Various formulations were developed by altering the polymer concentration and drug-to-polymer ratios. The prepared microspheres were evaluated for particle size, surface morphology, drug loading, entrapment efficiency, in vitro buoyancy, and in vitro drug release. Particle size analysis indicated that the microspheres were in the range of 150-300 micrometers. Scanning electron microscopy (SEM) revealed that the microspheres were spherical with a smooth surface.The drug entrapment efficiency of the microspheres ranged from 60% to 85%, and the buoyancy tests demonstrated that more than 75% of the microspheres remained floating for over 12 hours. In vitro drug release studies were conducted in simulated gastric fluid (pH 1.2) using a USP type II dissolution apparatus. The results showed a sustained release of acyclovir from the microspheres, with drug release extending up to 12 hours, depending on the formulation. The optimized formulation, which contained HPMC as the primary polymer, exhibited a desirable balance between buoyancy and sustained release, with an entrapment efficiency of 82% and 88% of the microspheres remaining buoyant for 12 hours. The release kinetics followed a non-Fickian diffusion model, indicating that drug release was controlled by both diffusion and polymer erosion.

In conclusion, the floating gastroretentive microspheres of acyclovir formulated in this study showed promising potential for enhancing the bioavailability and sustained delivery of the drug, thereby potentially improving its therapeutic effectiveness in the treatment of viral infections. Further in vivo studies are warranted to confirm these findings.

KEYWORDS : Acyclovir, Drug delivery system, HPMC, Gastroretentive dosage forms.

INTRODUCTION

Virus: Viruses are very small infectious agents, made up of a piece of genetic material, such as DNA or RNA, that's enclosed in a coat of protein. Viruses invade cells in your body and use components of those cells to help them multiply. This process often damages or destroys infected cells. Not all viral diseases are contagious. This means they aren't always spread from person to person. But many of them are. Common examples of contagious viral diseases include the flu, the common cold, HIV, and herpes. Other types of viral diseases spread through other means, such as the bite of an infected insect.

A viral disease is any illness or health condition caused by a virus. Viruses are probably the most common cause of infectious disease acquired within indoor environments and have considerable impact on human health, ranging from severe life–threatening illnesses to relatively mild and self limiting or asymptomatic diseases. In particular, viruses causing gastrointestinal and respiratory diseases spread rapidly in the community and cause considerable morbidity. Viruses are spread easily through closed environments such as the home, schools, workplaces, transport systems, etc. Although many of the respiratory and gastrointestinal infections caused by viruses can be asymptomatic or relatively mild and self– limiting (coughs and colds, etc.), they still represent a significant economic burden.

Viral diseases are one of the most acute health problems that the world is facing today. There were approximately 35.3 (32.2–38.8) million people living with AIDS (Acute Immuno Deficiency Syndrome) in 2012 and has claimed more than 36 million lives so far. In India alone, there were about 2.2 million people living with HIV (Human Immunodeficiency virus) and about 1.5 lacs deaths in 2011 **(Mourya et. al., 2019).**

Viruses are the ultimate expression of parasitism. They not only take nutrition from the host cell but also direct its metabolic machinery to synthesize new virus particles. Viral chemotherapy, therefore was considered impossible, as it would require interference with cellular metabolism in the host. However, in the past 50 years virus directed enzymes have been identified in the infected cell and some viruses have few enzymes of their own which may have higher affinities for some antimetabolites or inhibitors than the regular cellular enzymes. In addition, drugs have been developed which target virus steps like penetration, uncoating, reverse transcription, virus assembly or maturation, etc. Another stumbling block is that in majority of acute infections viral replication is already at its peak when symptoms appear. To be effective, therefore, therapy has to be started in the incubation period, i.e. has to be prophylactic or preemptive.

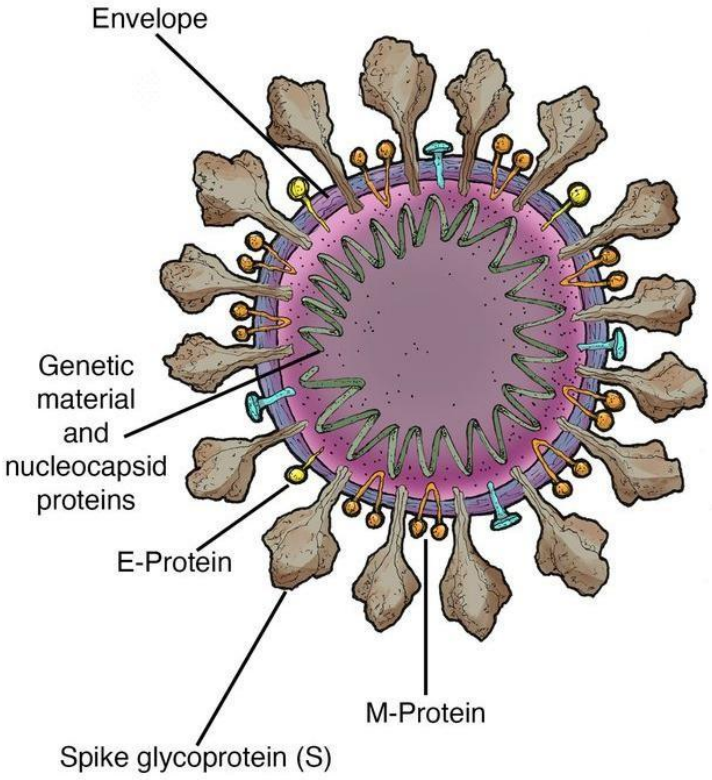


Figure 1.1: Structure of Virus

Classification

1. Anti-Herpes virus: Idoxuridine, Trifluridine, Acyclovir, Valacyclovir, Famciclovir, Ganciclovir, Valganciclovir, Cidofovir, Foscarnet, Fomivirsen

2. Anti-Influenza virus: Amantadine, Rimantadine, Oseltamivir, Zanamivir

3. Anti-Hepatitis virus/Nonselective antiviral drugs:

Primarily for hepatitis B: Lamivudine, Adefovir dipivoxil, TenofovirPrimarily for hepatitis C: Ribavirin, Interferon α

4. Anti-Retrovirus

(a) Nucleoside reverse transcriptase inhibitors (NRTIs): Zidovudine (AZT), Didanosine, Stavudine, Lamivudine, Abacavir, Emtricitabine, Tenofovir (Nt RTI)

(b) Nonnucleoside reverse transcriptase inhibitors (NNRTIs): Nevirapine, Efavirenz, Delavirdine

(c) Protease inhibitors: Ritonavir, Atazanavir, Indinavir, Nelfinavir, Saquinavir, Amprenavir, Lopinavir

(d) Entry (Fusion) inhibitor: Enfuvirtide

(e) CCR5 receptor inhibitor: Maraviroc

(f) Integrase inhibitor: Raltegravir

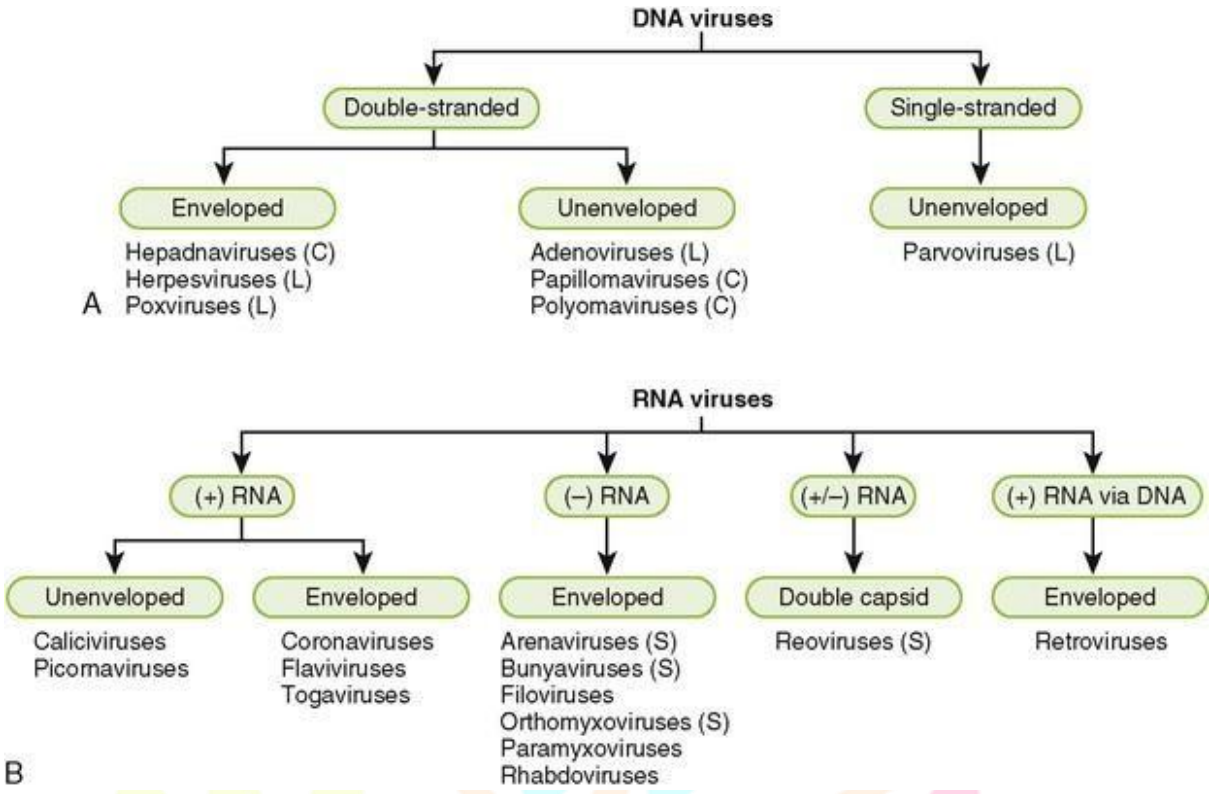


Figure 1.2. Classification of Virus

Drug delivery system: The drug delivery device need to deliver drug at a charge dictated with the aid of the wishes of the frame over a specified time period. Oral intake has been the maximum sought-after path of drug delivery through each patients and drug producers for the remedy of maximum pathological states. Despite terrific strides made in novel non oral drug shipping structures to date, the majority of the medicine to be had commercially is oral formulations. Nevertheless, with oral delivery, over one-half of the drug compounds are dwindled within the gastrointestinal (GI) tract because of their high lipophilicity and consequently poor aqueous solubility. Oral bioavailability of such drugs, being on the whole a feature of their solubility and dissolution, tends to show off inadequate significance with high intra- and inter subject variability. Further, oral bioavailability additionally depends upon a multitude of other drug factors which include stability in GI fluids, intestinal permeability, and resistance to metabolism by using cytochrome P450 circle of relatives of enzymes present in intestine enterocytes and liver hepatocytes, and interactions with efflux transporter structures including P-glycoprotein (P-gp). Several techniques had been employed to improve the oral bioavailability of diverse pills at some stage in formula.The intention of any drug delivery device is to provide a healing amount of drug to a proper site within the frame, so that the desired drug awareness may be done directly after which maintained. The idealized objective points to the 2 components maximum vital to drug shipping, namely, spatial placement and temporal transport **(Tripathi, 1985; Selin and Pasrija, 2006)**.

Oral Drug Delivery: Oral drug transport has been recognized for decades as the most widely used path of administration amongst all the routes. The reasons that the oral path done such reputation can be in component attributed to its ease of administration as well as the traditional belief. Pharmaceutical merchandise designed for oral transport which can be currently available in the market primarily is instant-launch or conventional release, which keeps the drug attention in the therapeutically effective variety most effective even when administered several times

a day. These consequences in a enormous fluctuation in the drug stage.

Recently, numerous technical advancements have led to the development of numerous novel drug transport structures (NDDS) that would revolutionize technique of medicine and provide

a number of therapeutic advantages. The most critical goal of these New Drug Delivery Systems is it might be unmarried dose, the length of treatment, which releases the energetic factor over an prolonged time frame. Second, it must supply the active entity at once to the site of motion, accordingly minimizing or casting off aspect outcomes. Sustain-launch formulation without a doubt prolongs the discharge and for this reason plasma drug stage maintained for an prolonged period of time, no longer necessarily at a predetermined charge. These makes oral controlled release an awful lot vital, which presents a entire and managed launch of drug in the course of the GI tract **(Robinson and Vincent, 1968)**.

Oral Controlled Drug Delivery System: The time period oral managed release implies a machine that gives non-stop delivery of drug for a predetermined duration in a predictable and reproducible manner which will increase the bioavailability. It includes the machine and presents manipulate over motion of dosage shape via the GI tract for both a local and a systemic motion. Increased bioavailability of CDDS excluded via several physiological difficulties and noticeably variable nature of gastric emptying manner turns to unpredictable and reduced bioavailability. Most limiting organic element in improvement of once each day oral controlled release is the transit time of dosage shape via the GI tract **(Robinson and Vincent, 1968; Chien, 1997)**.

A. Advantages of changed drug therapy: **(Shivakumar et. al., 2004)**

1. Avoid patient compliance problems
2. Employ less overall drug
3. Improve performance in treatment
4. Economic financial savings

Anatomy and Physiology of Stomach: Stomach is an organ with capacity for storage and mixing. It is located just below the diaphragm in the epigastric and left hydrochondriac region of the abdomen.

The stomach is anatomically divided into three parts:

1. Fundus.
2. Body.

3. Pylorus (or antrum).

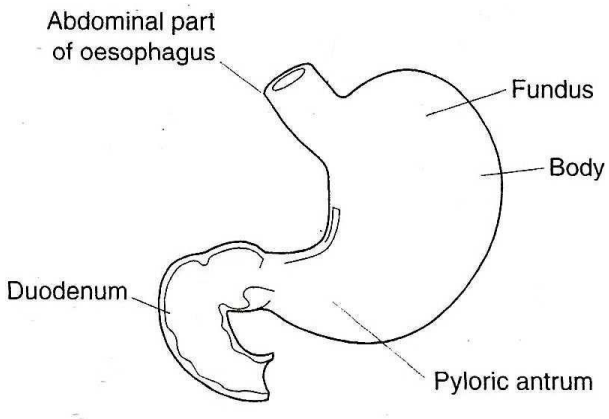


Figure 1.3: Anatomy of Stomach

Stomach made from Fundus and frame regions. They are able to displaying a massive expansion to deal with meals without a whole lot increase in intragastric strain. Stomach lining is without villi and it includes widespread variety of gastric pits that make a contribution to garage capability of the stomach. Antrum area is accountable for the integration and grinding of gastric content material. There are primary secretion mucus and acid, produced with the aid of specialized cell in belly lining. Mucus is secreted by using goblet cells and gastric acid through parietal cells (oxyntric) The Mucus spread and cowl the relaxation of GI tract. Under fasting situation the belly is a collapsed bag with a residual quantity of fifty ml and includes a small quantity of gastric fluid (pH 1-3) and air **(Vyas and Khar, 2002; Guyton and Hall, 1996; Tortora and Grabowski, 2002)**.

Physiological condition: At the physiological conditions, the gastric absorption of the maximum tablets is insignificant, due to its confined surface area, (0.1-zero.2) m2 thick layer of mucous coating, the lack of villi on the mucosal surface, and the short residence time. It contain Kecking fold, which own finger like projections referred to as as villi which increase the surface location 30 instances and its pH range is 5 to7.5.

Different capabilities of belly:

- Gastric pH: Fasted healthful problem 1.1±zero.15 Fed healthful challenge 3.6±0.Four
- Volume: Resting extent is set 25-50 ml.

Gastric emptying: The procedure of gastric emptying happens during fasting in addition to fed states. However, the pattern of motility is distinct within the 2 states Figure 3. In the fasting country, it's miles characterized via an inter digestive collection of electrical occasions that cycle both thru belly and small intestine each 2 to a few hours. This pastime is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into four consecutive phases as defined with the aid of wilson and Washington.

Factor Affecting Gastric Retention (Garg and Sharma, 2003)

- **Density:** GRT is a characteristic of dosage form buoyancy that is dependent on the density of dosage shape which influences the gastric emptying fee **(Khosla and Davis, 1990)**

• **Size:** Dosage form unit having a diameter of greater than 7.5 mm are reported to have an elevated gastric house time in comparison with the ones having a diameter of nine.9 mm (Abrahamsson et. Al., 1993)

• **Shape of dosage shape:** The six shapes tested (ring, tetrahedron, cloverleaf, disk, string and pellet) displayed one-of-a-kind gastric retention instances, because of their size and geometry of the systems. The tetrahedron resided in the belly for longer intervals than different devices of a comparable length.

• **Single or multiple unit components:** a couple of unit formulations display a more predictable release profile and insignificant impairing of performance due to failure of gadgets, allow co-management of devices with extraordinary release profiles or containing incompatible materials and allow a bigger margin of protection against dosage form failure in comparison with single unit dosage bureaucracy.

• **Effect of buoyancy:** On assessment of floating and nonfloating dosage gadgets, it become concluded that irrespective of their sizes the floating dosage devices remained buoyant at the gastric contents during their residence inside the gastrointestinal tract, whilst the nonfloating dosage devices sank and remained in the decrease a part of the belly. Floating gadgets faraway from the gastro-duodenal junction were included from the peristaltic wavesat some stage in digestive phase whilst the nonfloating forms stayed close to the pylorus and

had been subjected to propelling and retropelling waves of the digestive phase **(Coupe et al., 1991).**

Absorption window: The G.I tract gives a numerous surroundings capable of affecting the absorption of poorly administered capsules. Anatomical features, physiological phenomenon, and nature of gastrointestinal milieu make contributions these modifications. This can result in the versions in the intestinal permeability of drug molecules, ensuing inside the phenomenon of "Absorption window", in which within the drug is preferentially absorbed simplest from a selected area of the G.I. Tract.

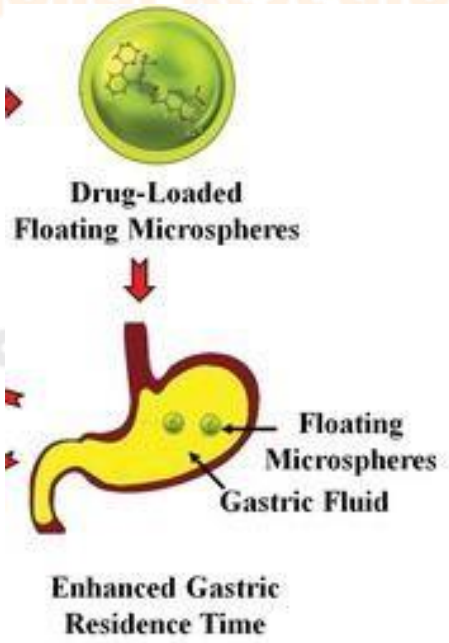


Figure 1.4: Floating Microsphere

Absorption window could result from the following factors (Bolton and Desai 1989)

A. Physico-chemical factors:

A) pH-dependent solubility and stability: A drug experiences a pH variety of one-8 throughout the G.I tract and desires to be insolubilised form to efficaciously move the organic membrane. Most of the medication is passively absorbed, of their un-ionized shape and the extant of ionization at specific pH based solubility, balance and ionization through converting the bodily houses of the drug in special portions of the G.I tract, can lead to nearby variabilityin absorption of drugs.

B. Physiological elements:

A) Mechanism of absorption: Perorally administered pills are absorbed both through passive diffusion in addition to through non-passive method of absorption. Drugs absorbed through energetic and facilitated shipping mechanism display better regional mainly due to the superiority of these mechanisms display higher nearby specificity because of the superiority of those mechanisms most effective in a selected location of G.I tract.

B) Metabolic enzymes: Presence of certain enzymes in a particular area of G.I tract also can cause nearby variability in absorption of medication which are substrates to the ones enzymes. The non-uniform distribution of cytochrome P450 reasons nearby variability inside the absorption of medicine which might be substrate to those enzymes.

Approaches for Gastroretantive Drug Delivery System: The bioavailability of drugs with an absorption window within the top small gut is typically restricted with traditional pharmaceutical dosage paperwork. These attempts encompass introducing floating dosage forms (gas-generating systems and swelling or increasing systems), mucoadhesive structures, excessive-density structures, modified shape systems, gastric-emptying delaying gadgets and co-administration of gastric-emptying delaying tablets **(Talukder and Fassihi 2004, Jain 2004, Streubel et. al., 2006)**

Hydrodynamically balanced structuresBioadhesive or Mucoadhesive
Raft structures incorporating alginate gelsModified form systems
High density structuresSwelling device Magnetic structures Floating drug shipping
Colloidal gel barrier gadget

Microporous compartment gadgetAlginate beads

Hollow microspheres / MicroballonsEffervescent structures

Drug release from bubbling (gas generating) systems: This machine can also be inaddition described as:

(i) Volatile liquid containing systems

(ii) Gas-generating Systems

Among these the subsequent were studied appreciably.

- Floating drug transport structures
- Non bubbling systems
- Gas producing structures
- High density structures
- Bioadhesive gadget

Floating device: Drug shipping system that glide immediately upon contact with gastric fluids gift promising technique for growing the bioavailability of medication with absorption window in the upper small intestine. However, on the spot floating can simplestbe finished if the density of the device is low at the very beginning. Devices with an to start with excessive density (which decreases with time) first calm down within the stomach and hence go through the chance of premature emptying. Inherent low density can, for example, be supplied by using the entrapment of air (e.G. Hollow chambers) or by way of the (additional) incorporation of low density substances e.G. Fatty materials or oils or foam powder **(Timmermans, 1994).**

Non effervescent systems: This type of system, after swallowing, swells unrestrained via imbibition of gastric fluid to an volume that it prevents their exit from the stomach .These structures may be called the 'plug-type systems' due to the fact they will be predisposed to remain lodged close to the pyloric sphincter. One of the method techniques of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and continues a relative integrity of shape and a bulk density of less than one inside the outer gelatinous barrier. The air trapped via the swollen polymer confers buoyancy to those dosage paperwork.

Gas producing structures: These buoyant systems utilise matrices prepared with swellable polymers like methocel, polysaccharides like chitosan and effervescent additives like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature **(Timmermans 1994).**

High density systems: Sedimentation has been hired as a retention mechanism for pellets that are small sufficient to be retained within the rugae or folds of the belly frame near the pyloric area, which is the part of the organ with the bottom function in an upright posture. Dense pellets (about 3g/cm3) trapped in rugae also have a tendency to withstand the peristaltic moves of the belly wall.

Bioadhesive drug delivery structures: Bioadhesive drug shipping structures (BDDS) are used to localize a transport tool inside the lumen to enhance the drug absorption in a website-particular way. This approach includes using bioadhesive polymers which could adhere to the epithelial surface inside the belly. A microbalance-primarily based machine is pronounced for measuring the forces of interaction between the GI mucosa and the individual polymers. The Cahn Dynamic Contact A ıe the

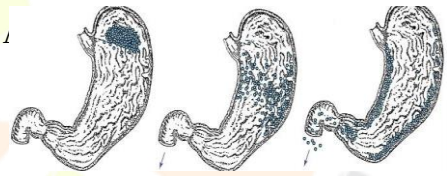


Figure 1.4: (a) microspheres floats on stomach contents. (b & c) microspheres adhere tostomach wall

Advantages of GRDDs (Floating dosage forms)

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.

Disadvantages of GRDDs (Floating dosage forms)

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 significant first pass metabolism, may not be suitable candidates for FDDS.

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 dosage form floats therein and work efficiently.

4. These systems also require the presence of food to delay their gastric emptying.

Potential drug candidates for gastro retentive drug delivery Systems

1. Drugs those are locally active in the stomach e.g misoprostol, antacids etc.

2. Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. L-DOPA, para-aminobenzoic acid, furosemide, riboflavin etc.

3. Drugs those are unstable in the intestinal or colonic environment e.g. captopril,ranitidine HCl,

4. Drugs that disturb normal colonic microbes e.g.antibiotics against Helicobacter pylori.

5. Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide,verapamil HCl.

Drugs those are unsuitable for gastroretentive drug delivery systems

1. Drugs that have very limited acid solubility e.g. phenytoin etc.

2. Drugs that suffer instability in the gastric environment e.g. erythromycin etc.

3. Drugs intended for selective release in the colon. eg. 5- amino salicylic acid andcorticosteroids etc.**(Singh and Kim 2000)**

Applications of microspheres: Some of the applications of microspheres aredescribed in detail as following: -

- Controlled and sustained release dosage forms.
- Microsphere may be used to put together enteric-coated dosage paperwork, in orderthat the medicament can be selectively absorbed inside the gut as opposed to the stomach.
- It has been used to protect tablets from environmental hazards which includes humidity, mild, oxygen or warmness. Microsphere does now not but provide a great barrier for substances, which degrade in the presence of oxygen, moisture or warmth, but a brilliant diploma of protection in opposition to those elements may be supplied. For instance, vitaminA and K were proven to be covered from moisture and oxygen through microsphere.
- The separations of incompatible substances, for example, pharmaceutical eutectics were achieved by

encapsulation. This is a case in which direct touch of materials brings about liquid formation. The stability enhancement of incompatible aspirin chlorpheniramine maleate mixture is done by means of microencapsulating both of them before mixing.

- Microsphere may be used to decrease the volatility. An encapsulated volatile substance can be stored for longer instances without big evaporation.

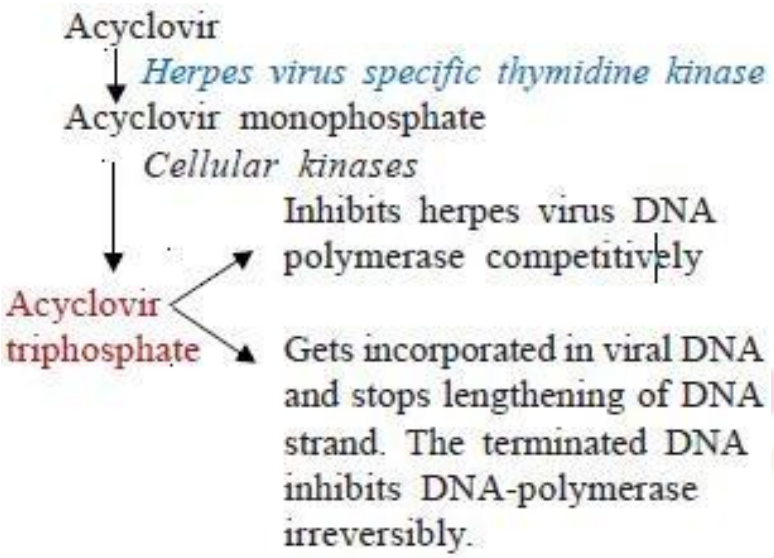
- Microsphere has additionally been used to decrease capability risk of managing of poisonous or noxious materials. The toxicity came about due to coping with of fumigants, herbicides, pesticides and pesticides were advantageously reduced after microencapsulation..

- Many capsules were microencapsulated to lessen gastric irritation.
- Microsphere technique has also been proposed to prepare intrauterine contraceptive tool.
- Therapeutic magnetic microspheres are used to supply chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be centered through this device. Mucoadhesive microspheres exhibit a extended house time on the site of utility and reasons intimate touch with the absorption site and produces better therapeutic motion
- Radioactive microspheres are used for imaging of liver, spleen, bone marrow, lung etc or even imaging of thrombus in deep vein thrombosis can be finished **(Moy et. al., 2011)**

DRUG PROFILE

Acyclovir

Acyclovir is deoxiguanosine analogue antiviral drug requires a virus specific enzyme for conversion to the active metabolite that inhibits DNA synthesis and viral replication.



Acyclovir is preferentially taken up by the virus infected cells. Because of selective generation of the active inhibitor in the virus infected cell and its greater inhibitory effect on viral DNA synthesis, acyclovir has low toxicity for host cells: a several hundred-fold chemotherapeutic index has been noted. Acyclovir is active only against herpes group of viruses; HSV-1 is most sensitive followed by HSV-2 > VZV=EBV, while CMV is practically not affected. HSV and VZV have been found to develop resistance to acyclovir during therapy; the former primarily due to mutants deficient in thymidine kinase activity and the latter primarily by change in specificity of virus directed enzyme so that its affinity foracyclovir is decreased. Pharmacokinetics Only approximately 20% of an oral dose of acyclovir is absorbed. It is little plasma protein bound and is broadly dispensed accomplishing CSF attention that is 50% of plasma concentration. After topical software, it penetrates cornea properly. Acyclovir is in the main excreted unchanged in urine, each through glomerular filtration and tubular secretion; plasma t½ is two–3 hours. Renal impairment necessitates dose discount.

ZOVIRAX 2 hundred mg tab, 250 mg/vial for i.V. Inj; CYCLOVIR 200 mg tab, five% skin cream; HERPEX 200 mg tab, three% eye ointment, 5% skin cream; OCUVIR 2 hundred, 400, 800 mg tab, 3% eye oint, ACIVIRDT two hundred, four hundred, 800 mg tab. ACIVIR EYE three% oint.

Use: Acyclovir is powerful in sufferers with everyday as well as deficient immune repute. 1. Genital Herpes simplex Generally resulting from kind-2 virus; can be dealt with with the aid of topical, oral or parenteral acyclovir depending on stage and severity of ailment. Primary disease: Topical treatment has low efficacy; 5% ointment is implemented locally 6 instancesa day for 10 days. This is useful best if started early and in mild instances. Late and extra severe instances must acquire oral remedy (1 g/day in 5 divided doses or four hundred mg TDS for 10 days) in addition to local remedy. Both nearby and oral treatment plans manageto pay for symptomatic relief and speedy recovery of lesions, however do now not prevent recurrences. Recurrent disorder: Topical remedy is absolutely

useless. Response to oral remedy is gradual and incomplete; excessive cases can be treated parenterally—five mg/kg

i.v. Infused over 1 hr, repeated 8 hourly for 10 days. Suppressive oral therapy with 400 mgBD has been proven to save you recurrences as long as given. It is recommended to prevent remedy after 1 yr and confirm whether or not the affected person remains having recurrences; if so restart treatment. After prolonged remedy frequency of recurrences is decreased. Continuous acyclovir prophylaxis is commonly endorsed in patients with > 8 recurrences in line with yr. However, suppressive therapy reduces, but does now not toally prevent, disease transmission to sexual partner.

Mucocutaneous H. Simplex It is a kind-1 virus disease, remains localized to lips and gums; does now not generally require unique remedy, but acyclovir skin cream may additionally provide a few relief. Spreading lesions may be treated with 10 day oral acyclovir. Prophylactic oral remedy may additionally save you sun exposure associated recurrences. The ailment frequently gets disseminated in immunocompromised people and may be treated with oral or i.V. Acyclovir (15 mg/kg/day) for 7 days, but recurrences are not avoided.

H. Simplex encephalitis (kind-1 virus): Acyclovir 10 to twenty mg/kg/8 hr i.V. For >10 days is the drug of preference. Treatment is powerful simplest if started early: postpone precludes salutary impact on mortality and neurological complications.

H. Simplex (kind I) keratitis: Acyclovir is similarly effective as idoxuridine in superficial dendritic corneal ulcer, and can be higher for deep stromal infections due to suitable corneal penetration. Though acyclovir eye ointment acts slower than idoxuridine eye drops, blindness may be averted. The eye ointment should be carried out five times every day till 3 days after recuperation.

Herpes zoster: The varicella-zoster virus is much less at risk of acyclovir. As such, better doses are needed and it ought to be used only in immunodeficient people or in severe instances: 10 mg/kg/8 hr i.V. For 7 days. Oral therapy with 800 mg five instances day by dayis beneficial only if commenced early. It presents symptomatic relief and quicker recuperation of lesions. Postherpetic neuralgia is not avoided, even though its duration may be shortened. Acyclovir pores and skin cream can be applied on herpetic ulcers.

Chickenpox: in sufferers with immunodeficiency and in neonates most effective requires specific therapy. Acyclovir (15 mg/kg/day i.V. × 7 days) is the drug of desire: reduces fever, eruptions, hastens recuperation and prevents visceral headaches. Oral acyclovir 400 mg 4 instances an afternoon for 7 days given all through the incubation period may additionally abort chickenpox in inclined contacts.

Adverse outcomes: Topical: Stinging and burning sensation after every software.

Oral: The drug is properly tolerated; headache, nausea, malaise and a few CNS effects are said.

Intravenous: Rashes, sweating, emesis and fall in BP arise handiest in few patients.

Dose: based lower in g.F.R. Is the maximum critical toxicity; occurs especially in people with kidney disease; normalises on discontinuation of the drug.

MATERIAL AND METHODS

Analytical Methods

Determination of absorption maxima (λ_{max})

The absorption maxima of drug (ayclovir) were determined by scanning drug solution in double beam ultraviolet spectrophotometer between 200 to 400 nm wavelengths.

One hundred mg of drug was dissolved in one hundred ml of various dissolution medium (0.1N HCl answer) in 50 ml volumetric flask with the help of sonication in bath sonicator for20 min to achieve a 100 µg/ml concentration. The resulting answer turned into categorized as Stock-I. 1 ml of this solution became diluted up to a hundred ml with same solvent one byone with the useful resource of sonication for 20 min to reap 10 µg / ml concentration. The spectrum of those solutions was run in 2 hundred – four hundred nm varieties in double beam UV spectrophotometer (Shimadzu, UV-1800, A11454500755/UV-1800, Shimadzu Corporation, Kyoto, Japan). The spectrums are proven in **Figure 6.1**.

Validation of Analytical approach:

A. Preparation of calibration curve of ayclovir in dissolution media

Procedure: one hundred mg of drug turned into dissolved in one hundred ml of diverse dissolution medium (0.1N HCl solution) in 100 ml volumetric flask with the assist of sonication in bathtub sonicator for 20 min to attain a thousand µg/ml answer. The resulting solution was classified as Stock Solution-I. From the above stock solution 10 ml became once more diluted with a hundred ml of dissolution medium (0.1 N HCl answer) to gain 100 µg /ml answer. The ensuing solution changed into categorized as Standard Stock Solution-II.

From above trendy inventory answer-II 0.Five ml, 1 ml, 1.Five ml and a pair of.Zero ml aliquots had been withdrawn and diluted up to ten ml with respective solvent (0.1 N HCl answer, phosphate buffer pH 7.Four and phosphate buffer pH 6.Eight) in 10 ml volumetric flasks to get attention of five µg / ml, 10 µg / ml, 15 µg / ml, 20 µg / ml respectively. The absorbance of every solution became measured one after the other at 253 nm for 0.1 N HCl answer for ayclovir. The absorbance was measured and popular curve turned into plotted

among absorbance vs. Attention. The end result of linearity is as shown in **Table 6.1 and Figure 6.2**.

i. Specificity: Specificity is described because the ability to locate the analyte of hobby inside the presence of interfering substances. Specificity may be proven via spiking known stages of impurities or degrading dealers in to a pattern with a acknowledged quantity of the analyte of hobby. Result is given in Table 6.2.

ii. Precision: The ICH hints categorised precision in to two elements; repeatability and intermediate precision.

Intermediate precision:

Intra-day precision changed into determined by using measuring the absorbance of 10 µg / ml drug answer of drug in zero.1 N HCl at predetermined interval within an afternoon.

Inter-day precision test turned into determined with the aid of measuring the absorbance of 10 µg / ml drug answer in 0.1 N HCl on 3 one of a kind days.

The absorbance of every answer turned into measured one after the other. The percent RSD of the absorbance need to be much less than 1 %. The end result of intra-day and inter-day precision are shown in **Table 6.3**.

iii. Accuracy: Accuracy is the distinction between the measured fee and the taken value. The result of accuracy test is shown in **Table 6.4**.

PREFORMULATION STUDIES

Organoleptic character: The organoleptic properties of drug (ayclovir) inclusive of shade, scent and taste had been stated visually

Microscopic examination: The microscopic examination of the drug (ayclovir) sample turned into executed to perceive the nature of the powder. The required quantity of powder became unfold on a glass slide and tested underneath optical microscope. The shapeof drug changed into crystalline in nature.

Physical Characteristics:

Density: The drug (ayclovir) powder become weighed accurately and stored via a tumbler funnel into graduated cylinder. During this experiment the volume was stated and bulk density turned into decided. The tapped density become determined the usage of tapped density apparatus.

Particle size: The average particle size (davg) of drug (ayclovir) was decided with the aid of optical microscope (66172/Olympus, 100 X, Olympus (India) Pvt. Ltd., New Delhi) fitted with ocular micrometer and degree micrometer. The particle size of unmilled powder turned into 101 µm.

Flow behavior: The flow residences of drug powder had been characterized for identity of waft individual of powder in phrases of carr's index, hausner's ratio and perspective of repose. The Carr's index ((IC)) and Hausner's ratio (HR) of drug powders were calculating in step with following equation:

Carr's Index (IC) = ρTapped - ρBulk / ρTappedHausner's ratio (HR) = ρTapped / ρBulk

The perspective of repose (θ) was measured by using fixed peak method. This changed into calculated via following equation:

Angle of repose (θ) = tan-1 2 H / D

Where H is the floor vicinity of the free standing height of the powder pile and D is diameterof pile that shaped after powder go with the flow from the glass funnel. The result is given in **Table 6.5**.

Solubility study: Saturation solubility of ayclovir turned into determined in distilled water and 0.1N HCI. All media were organized and excess amount of ayclovir became added to10 ml of respective medium then kept for shaking at 37oC for 72 hours in orbital shaking incubator. Aliquots had been withdrawn, filtered through whatman filter paper, No.41. Filtrates have been diluted with respective medium (i.e. Distilled water and 0.1N HCI). The end result is proven in **Table 6.6**.

Partition coefficient: The partition coefficient of drug was decided in n-octanol: 0.1N HCl solutions. An precisely weighed (50 mg) quantity of drug was delivered into 25 ml each of an n-octanol and 0.1 N HCl containing in a seperating funnel. The aggregate changed into shaken, separated and collected separately, filtered. The amount of drug solubilized determined via measuring the absorbance at 253 nm for by means of UV spectrophotometer. The partition coefficient of drug changed into calculated from the ratio between the concentrations of drug in natural and aqueous section the use of following equation.

Log P (n-oct / 0.1 N HCl) = Log (C n-Oct / C 0.1 N HCl) equilibrium

Drug-excipient compatibility research: The Infrared spectra were obtained using an FTIR spectrometer. The samples were ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:1:100 (pattern/KBr). The KBr discs were prepared with the aid of compressing the powders at a pressure of 5 heaps for 5 min in a hydraulic press. Scans have been acquired from 3500 to 500 cm-1. The compatibility i.e. Drug-excipients interaction studies are beneficial for dosage form design. For compatibility research drug / excipients ratio are decided on and investigated based at the reasonable drug / excipient ratio inside the very last product.

Procedure of pattern preparation for compatibility studies: Drug and other Excipients were weighed as per ratio shown in **Table 5.1 and 5.2** and handed thru sieve # forty, combined nicely. The combo turned into stuffed in amber color glass vials and stopped with gray rubber stoppers followed via aluminium seal. The FTIR spectrum is proven in **Figure 6.3 to 6.4**.

Table 5.1: Protocol for drug-excipients compatibility study was as below:

Drug: excipients ratio	. Drug
	Drug: Polymer
Pack details	mber colored glass vials with rubber stoppers and aluminium als
Storage conditions	t room temperature or 25º C
Tests to be performed	TIR studies

Table 5.2: Drug-excipient combinations for compatibility study

Batch no.	Drug-excipient combinations	Ratio	Qty. (gm)	Batch size (gm)
S1	Pure drug Ayclovir	-	-	0.5
S2	Drug + All Excipients	1:1	0.50 + 0.50	1

FORMULATION OF BUOYANT MICROSPHERES: The buoyant microspheres could be prepared by using the usage of diverse composition of prescribe polymers.

Calcium alginate: These microspheres containing calcium alginate polymer were made via losing or spraying sodium alginate. Sodium right into a calcium chloride solution, the divalent calcium ions go link the alginate forming gelled droplets. These gel droplets canbe permanently passing related by addition to a polylysine answer. Smaller droplets can be formed by using the usage of a pump to pressure until alginate via the pipette.

Ethyl cellulose: Solvent evaporation is one of the earliest techniques of microsphere manufacture. The polymer and drug must be soluble in an organic solvent, frequently used organic solvent is methylene chloride. The solution containing the polymer and the drug may be dispersed in an aqueous section to form droplets. Continuous mixing and extended temperature have been hired to evaporate the more unstable natural solvent as to leave the strong polymer drug particles suspended within the aqueous medium. It was filtered, washed and dried.

Egg albumin: Egg albumin microspheres have been prepared in a polymer drug ratio 20:1 by stirring on the magnetic stirrer, after which dispersed slowly on the solution containing liquid paraffin a hundred ml [on water bath]. Microsphere have been prepared after rotation velocity of 400 to 500 rpm for 4-5 h, decanted the unused liquid and microspheres washed with the usage of petroleum ether 50 ml in 3 instances every amount and dried at room temperature. Finally yellowish colored microspheres had been collected.

Table 5.3: Various parameters of characterization of formulations

No.	**rug as core**	**olymers**	**ode**	**ore : Coat ratio**
	yclovir	alcium alginate	1**	:02
	yclovir	alcium alginate	2*	:02
	yclovir	alcium alginate	3*	:01
	yclovir	hyl cellulose	4**	:02
	yclovir	hyl cellulose	5*	:02
	yclovir	hyl cellulose	6*	:01
	yclovir	gg albumin	7**	:02
	yclovir	gg albumin	8*	:02
	yclovir	gg albumin	9*	:01

Stirring rate = * 300 rpm, ** 500 rpm

Characterization of buoyant microspheres: These prepared structures could be evaluated with various parameters along with the bodily houses i.e., Flow residences willpower, particle size dimension, shape and surface morphology, percentage yield, drug entrapment performance, in-vitro buoyancy percentage, in-vitro drug release studies and stability studies etc.

Size and form of microspheres: The size of microspheres turned into determined using a microscope (Olympus NWF 10x, Educational Scientific Stores, India) outfitted with an ocular micrometer and degree micrometer. Scanning electron microscopy (SEM) (Philips- XL-20, The Netherlands) changed into done to represent the surface of shaped microspheres. Microspheres have been installed immediately into the sample stub and lined with gold film (˜200 nm) underneath decreased strain (0.133 Pa).

Particle length evaluation: Buoyant microspheres were studied microscopically for his or her length and size distribution the use of calibrated ocular micrometer. The result changed into proven in **Table 6.7**.

Flow properties: It was determined in terms of Carr's index (I_C) and Hauser' ratio (H_R) using following equation:

$H_R = \rho_t / \rho_b$

$I_c = \rho_t - \rho_b / \rho_t$

The angle of repose (θ) of the microspheres, which measures the resistance to particle flow,was determined by fixed funnel method by using following equation:

$\text{Tan } \theta = 2H / D$

Where, 2H / D is the surface area of the free standing height of the microspheres that formed after making the microspheres flow from the glass funnel. The result was shown in **Table 6.7**.

Estimation Of The Amount Of Drug Incorporated:

Calcium alginate microsphere: Drug loaded calcium alginate microspheres have been powdered with the usage of glass mortar and dissolved in 0.1 N HcL and tested specrophotometrically at 276 nm after suitable dilution.

Ethyl cellulose microsphere: Drug loaded ethyl cellulose microspheres one hundred mg were freely powdered in a pitcher mortar then dichloromethane 10 ml had been broughtto dissolve ethyl cellulose coat and 0.1 N HcL become brought at 32-34°C temperature to evaporate dichloromethane. Solution become filtered, and examined specrophotometrically at 253 nm after appropriate dilution.

Egg albumin microsphere: 100 mg portion of drug loaded albumin microspheres had been incubated with 15 ml of 5% HCl in absolute ethanol at 4°C for twenty-four h of incubation. The microspheres have been separated by way of excessive speed centrifugation at 4000 rpm and the drug content material turned into analysed in supernatant by UV spectrophotometrically. The result turned into proven in **Table 6.7**.

The encapsulation efficiency and percent yield have been calculated using the following formula:

% Entrapment efficiency = Mass of integrated drug / Mass of drug used for microsphere training × a hundred

In-vitro buoyancy percent: The buoyant microspheres (0.3 g) were unfold over the surface of USP XXIV dissolution equipment (type II) filled with 900 ml zero.1 N hydrochloric acid containing 0.02 % Tween eighty. The medium turned into agitated with paddle rotating at one hundred rpm for 12 h. The floating and the setteled part of microspheres have been recovered one after the other. The buoyant microspheres had been dried and weighed. The buoyancy percent was calculated as the ratio of the mass of the microspheres, that remained floating and the overall mass of microspheres. The end result was proven in Table 6.8.

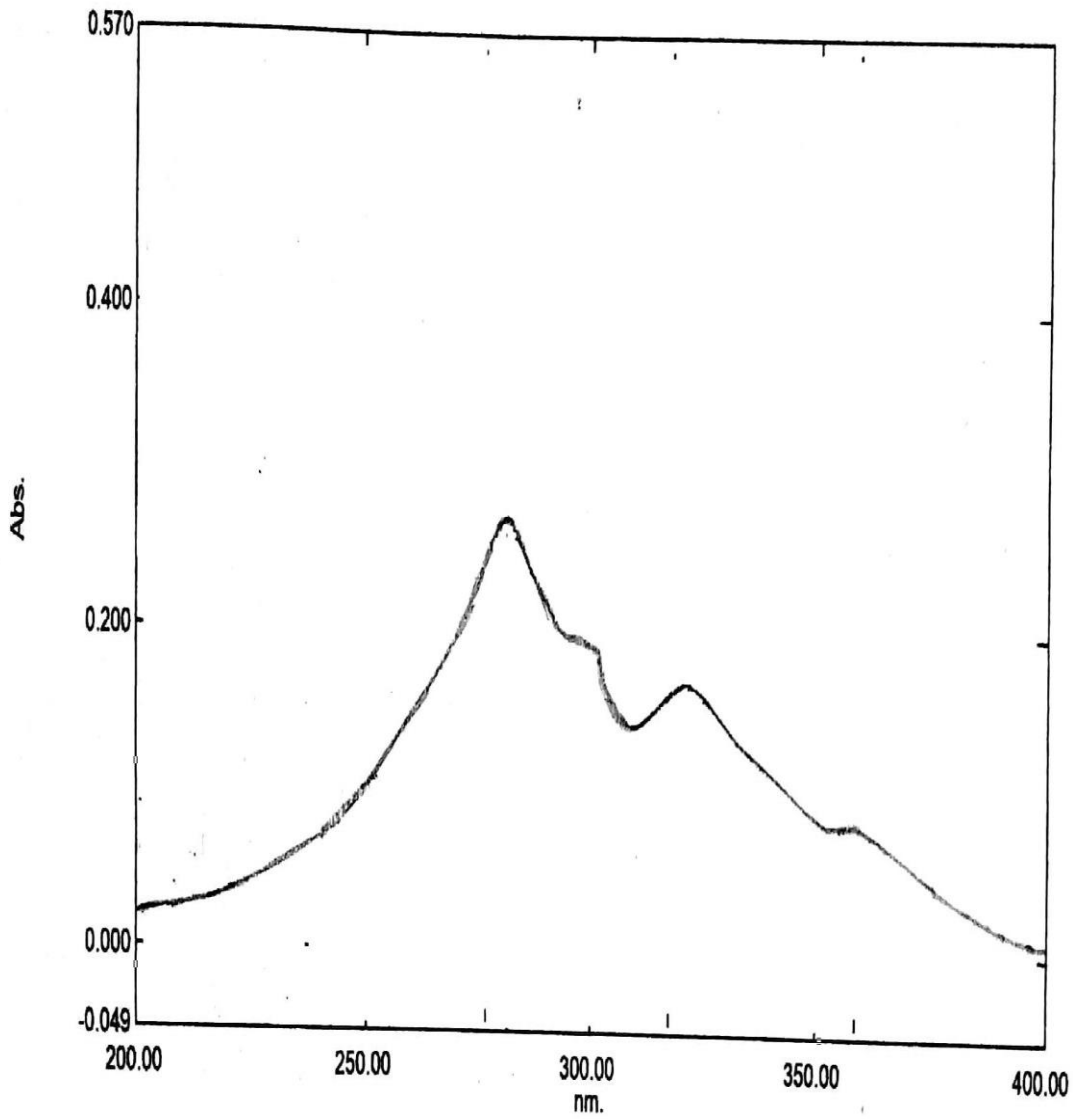
In vitro drug launch research in simulated gastrointestinal fluids: The dissolution check of ayclovir buoyant microspheres become performed by means of the paddle kind-II dissolution apparatus specified in USP XXIII. 500 mg of ayclovir loaded microspheres turned into weighed accurately and lightly unfold over the floor of 900 mL of dissolution medium. The content become circled at one hundred rpm and thermostatically controlled at 37±0.5°C.

Perfect sink condition became prevailed all through the drug dissolution. The launch turned into examined in dissolution medium of SGF (pH 1.2). An aliquot of the release medium turned into withdrawn at predetermined time intervals and an equal quantity of clean medium became introduced to the discharge medium. The accumulated samples had been filtered via

0.45 µm-syringe filter (Millipore millex HN) and analyzed spectrophotometricaly. The observations are recorded in **Table 6.9 – 6.19** and graphically shown in **Figure 6.7 – 6.10**..

RESULT AND DISCUSSION

Analytical Methods



Determination of absorption maxima (λ_{max})

Figure 6.1: Absorption maxima (λ-max) of ayclovir in 0.1 N HCl solutions

Calibration curve: The absorbance of each solution was measured separately at 253 nm for 0.1 N HCl solutions for ayclovir. The absorbance was measured and standard curvewas plotted between absorbance vs. concentration. The result of linearity is as shown in **Table 6.1 and Figure 6.2.**

Table 6.1: Standard curve of ayclovir in 0.1 N HCl solution

No.	**oncentration (µg/ml)**	**bsorbance**
	000	154
	.000	285
	.000	452
	.000	598

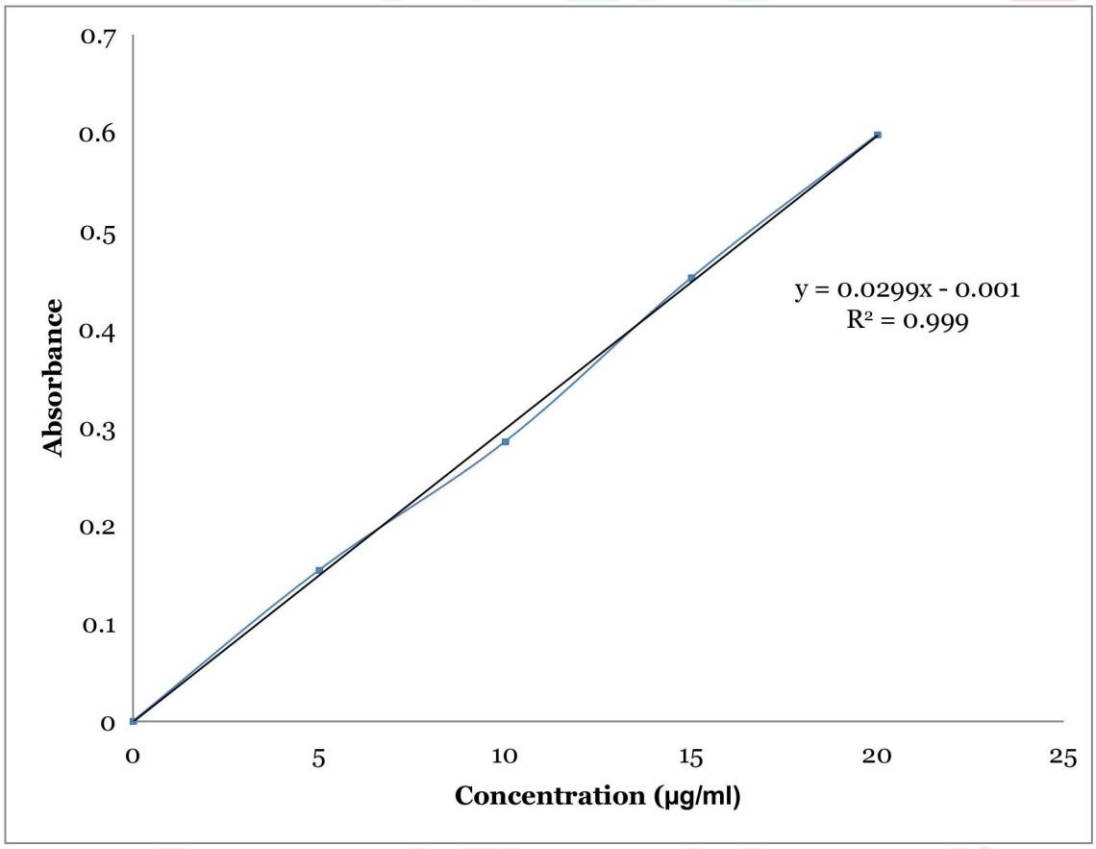


Figure 6.2: Standard curve of ayclovir in 0.1 N HCl solution

i. Specificity: The result is given in **Table 6.2**.

Table 6.2: Results of specificity test

est solution	**yclovir (Drug content)**
	1 N HCl
	53 nm
tandard drug solution	9.26
lacebo solution	
rug solution containing Excipients	01.08

ii. Precision: The ICH guidelines classified precision in to two parts; repeatability andintermediate precision.

The result of intra-day and inter-day precision are shown in **Table 6.3.**

Table 6.3: Results of intra-day precision of 10 µg / ml drug solution

ime	**yclovir (Drug content)**
	1 N HCl
	53 nm
hr	154
hr	153
hr	153
hr	156
hr	151
hr	154
hr	156
lean	153

iii. Accuracy: Accuracy is the difference between the measured value and the taken value.The result of accuracy test is shown in **Table 6.4.**

Table 6.4: Results of accuracy test for Ayclovir

ecovery vel	mount of drug covered	mount of drug lded (mg)	recovery	lean
5%	4.25	5	9.81	9.89
	4.01	5	3.96	
	4.11	5	00.02	
0%	9.85	0	9.27	9.49
	9.05	0	9.98	
	3.85	0	9.79	
00%	00.1	00	9.19	9.98
	9.01	00	00.06	
	9.07	00	9.92	

Ayclovir drug was estimated in-vitro by reported UV spectrophotometric methods. The reported UV spectrophotometric methods were slightly modified and optimized according to the existing laboratory conditions. The drugs were estimated in the dissolutionmedium (0.1 N HCl). The calibration curves in the dissolution medium i.e. 0.1 N HCl solution prepared with drug solutions of known concentrations. The absorbance of each solution was measured separately at 253 nm for ayclovir. The absorbance was measured and standard curve was plotted between absorbance vs. concentration. The result of linearity is as shown in **Table 6.1** and **Figure 6.1 to 6.2**. The calibration curves show excellent linearity of data as evidenced by the values of correlation coefficients that were found to be greater than

0.99. The curves were found to be recti-linear in the concentration range 5 µg / ml to 20 µg /ml for the drug.

The result of Specificity is given in **Table 6.2**, all result showed specific in nature. Inter-day and Intra-day precision of the UV spectrophotometric methods was evaluated for drug in same concentration i.e. 10 µg / ml with variability in time period of estimation. The

results of inter-day and intra-day precision are shown in **Table 6.3**. The percent relative standard deviation was found

to be less than 1 % i.e. the method was precise. The recovery of Ayclovir is reported in **Table 6.4**. Quantitative recoveries were recorded for the drugs, ranging from 99.49 to 99.98 %. The estimation procedures for drugs were found to be sensitive, precise and reproducible.

Ayclovir drug changed into anticipated in-vitro by means of suggested UV spectrophotometric methods. The said UV spectrophotometric strategies have been slightly modified and optimized consistent with the existing laboratory conditions. The drugs had been expected within the dissolution medium (0.1 N HCl). The calibration curves within the dissolution medium i.e. 0.1 N HCl solution organized with drug answers of acknowledged concentrations. The absorbance of every solution become measured one by one at 253 nm for ayclovir. The absorbance changed into measured and well known curve was plotted among absorbance vs. Awareness. The end result of linearity is as proven in Table 6.1 and Figure 6.1 to 6.2. The calibration curves display tremendous linearity of statistics as evidenced by using the values of correlation coefficients that had been located to be greater than 0.99. The curves have been discovered to be recti-linear inside the range 5 µg / ml to 20 µg / ml for the drug.

The end result of Specificity is given in Table 6.2, all end result confirmed uniquein nature. Inter-day and Intra-day precision of the UV spectrophotometric techniques was evaluated for drug in same concentration i.e. 10 µg / ml with variability in term of estimation. The outcomes of inter-day and intra-day precision are shown in **Table 6.3**. The percent relative fashionable deviation changed into determined to be less than 1 % i.e. the method changed into specific. The healing of Ayclovir is reported in Table 6.4. Quantitative recoveries had been recorded for the medication, starting from 99.Forty nine to 99.98 %. The estimation strategies for drugs had been observed to be sensitive, unique and reproducible.

PREFORMULATION STUDIES:

Preformulation studies are the first step for the rational development of dosage formsof model drug substances. It is an investigation of physical and chemical properties of drug substances alone and in combination with excipients in research. The overall objective of preformulation studies is to produce information constructive to the formulator in

development of stable and bioavailable dosage forms. Ayclovir was found to be light yellow, practically odorless, Vertigo metallic taste in nature. The microscopic examination of the drug (Ayclovir) sample was crystalline powder **(Figure 6.3)**. The drug (Ayclovir) powder bulk and tapped densities to be 0.231 gm / cm^3 and 0.238 gm / cm^3, respectively. The particle size of unmilled powder was 101 µm. The flow of unmilled drug powder was good to excellent flow characteristics. The result is given in **Table 6.5**. The solubility of drug ayclovir was very less

soluble in all dissolution media and the result is shown in **Table 6.6**. The partition coefficient of Ayclovir was found to be 0.367 and the value of partition coefficient of drug showed that the drug was lipophilic in nature. The Infrared spectra were obtained using an FTIR spectrometer. Drug and other Excipients were weighed as per ratio shown in **Table 5.3 and 5.4** and passed through sieve # 40, mixed well. The blend was filled in amber color glass vials and stopped with grey rubber stoppers followed by aluminium seal. The FTIR spectrum is shown in **Figure 6.3 to 6.4**.

Table 6.5: Flow properties of drug (n = 3)

Drug	Type of powder	Carr's index (%)	Hausner's ratio	Angle of repose θ
Ayclovir	Unmilled	14.18±0.011	1.11±0.023	25.1±0.011

Table 6.6: The solubility of Ayclovir at different pH medium (n=3)

Media	Solubility (mg / ml)
Water	12.98
0.1 N HCl	18.18

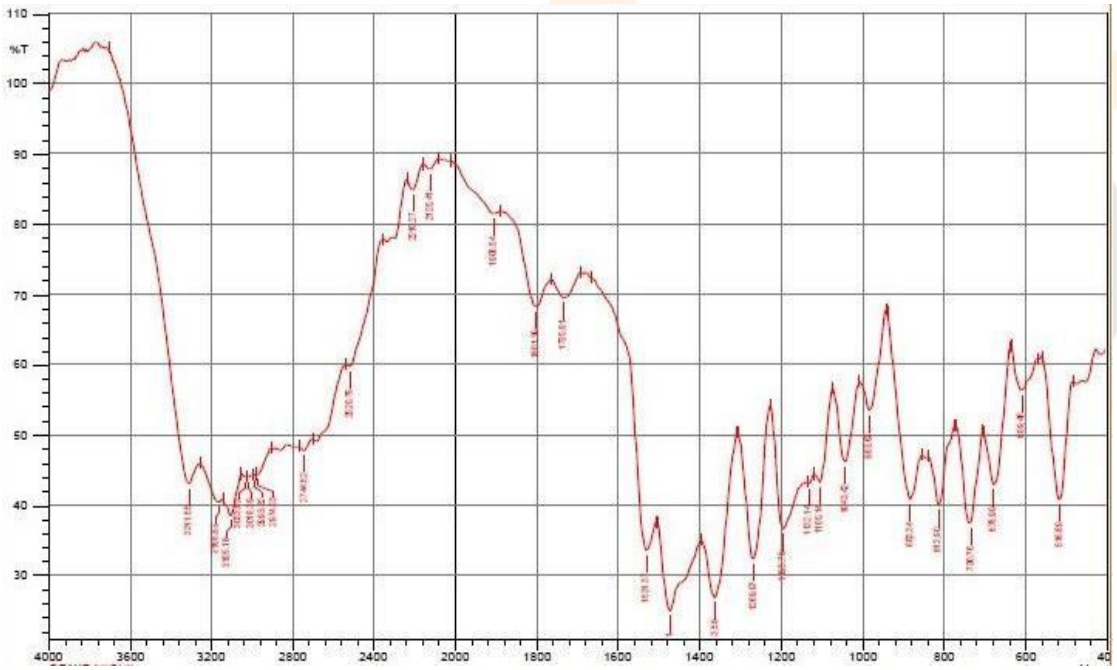


Figure 6.3: The I. R. Spectrum of Ayclovir sample (S1)

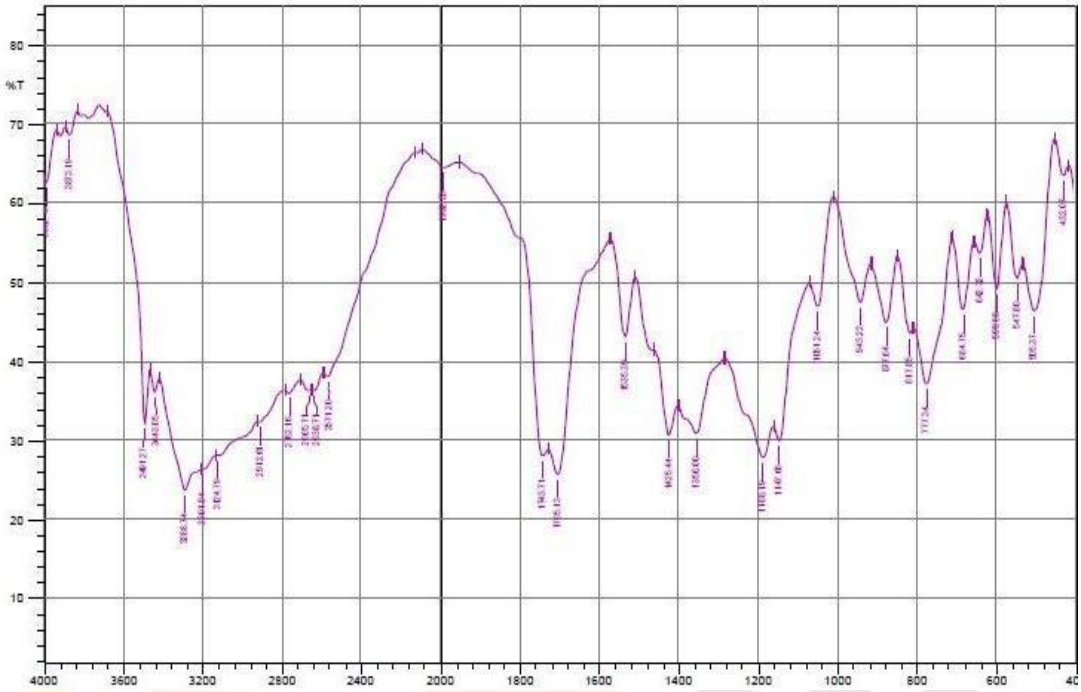


Figure 6.4: The I. R. Spectrum of drug and all excipient (S2)

Characterization of buoyant microspheres

Solvent evaporation method was found suitable for preparation of microspheres. The yield obtained in all batches was good. The prepared microspheres showed variability in size, which is increasing with increasing polymeric concentration of same polymer. The average particle size d_{avg} was also having variability with variations of coating polymeric material as calcium alginate, ethyl cellulose and egg albumin. The microspheres prepared of egg albumin as coating material and stirring rate 500 rpm showed good flow property because finer droplets were prepared with increasing stirring rate **(Table 5.3)**. All the micromeritics properties of prepared microspheres showed good to excellent flow property of highly viscous polymeric solutions but having large size particles (co-relation between **Table 6.7**). As the stirring rate during the preparation of microspheres was changed, the particle size, surface property and drug content efficiency also changed. The size of microsphere ranged between 36.45 µm to 39.86 µm of all polymer containing microspheres. The particle size distribution of prepared microspheres was uniform and

narrow **(Table 6.7)**. Scanning electron microscopic photograph of calcium alginate containing as polymeric material with 1:1 ratio showed smoother surface than other prepared microspheres with different polymers **(Figure 6.5)**. Surface of microspheres with containing highly viscous coating material was changed to rough surface. It was found that percent entrapment of drug was between 92.24- 100.24% depending on the different polymers with polymer: drug ratio. Entrapment efficiency of drug in prepared microspheres showed microspheres containing highly viscous coating material decrease but increase their particle size **(Table 6.7)**. The in-vitro buoyancy profile also shown that prepared microspheres buoyant more than 25% upto 12 h **(Table 6.8)**. The in-vitro release profile obtained indicated a biphasic pattern, i.e. initial fast release of drug called 'burst effect' and later on a sustained release effect. Initial burst effect may bedue to some drug particles on microspheres surface and later slow release due to drug diffusion from polymer matrix, which gets swollen in dissolution media. Drug loaded microspheres containing calcium alginate shows 99.24-99.99% till to 24h but polymer ethyl cellulose containing microspheres release 63.64-69.75% and egg albumin containing only 57.58-61.35% drug release **(Table 6.9 – 6.18 and Figure 6.6 – 6.9)**. It seems drug only release after 12 h about 58.67% from capsular shell. The data obtained for in-vitro release were fitted into equations for the zero-order, first-order and Higuchi release models. The in- vitro drug release showed the highest regression coefficient values for Higuchi's model,

indicating diffusion to be the predominant mechanism of drug release **(Table 6.19)**. All the results indicated that calcium alginate coated prepared microspheres were excellent formulation for treatment of bacterial infection.

Drug release pattern was evaluated in 0.1 N HCl. Release rate of F1-F9 formulations were found to be slow dissolution profile. It was found that drug release rate increased due to particle size of microspheres mainly low stirring rate respectively. Kinetics and mechanismof drug release from all formulation was evaluated on the basis of zero order, Higuchi equation and Peppas model. Correlation coefficient (r2) and slope value for each equation in the range of (r2=0.752-0.937 and n=0.568-0.785 was calculated. Zero order plots for all formulations were found to be linear in acidic solution.Which indicates that it may follow zero order kinetics. Higuchi plot was found to be linear, which indicates diffusion may be the mechanism of drug release for each formulation. Peppas plot was found good linear, n > 0.5 for all formulations, indicated that drug release may follow anomalous diffusion (range=0.993-0.998). Zero order plots for F1** and F2* formulation was found to be linear in dissolution medium, it considered as a best fit for drug release. That indicates it may follow zero order mechanism. Regression analysis was performed and the r^2 values suggested that the curves were fairly linear and slope values were computed from the graph..

Floating buoyant microspheres F2* was the best formulations was best formulation due on the basis of drug

polymer combination in the ratio of 1:2 and stirring rate is 300rpm. This as formulate the needful particle size for better retardant drug release upto 12 hr with better release profile.

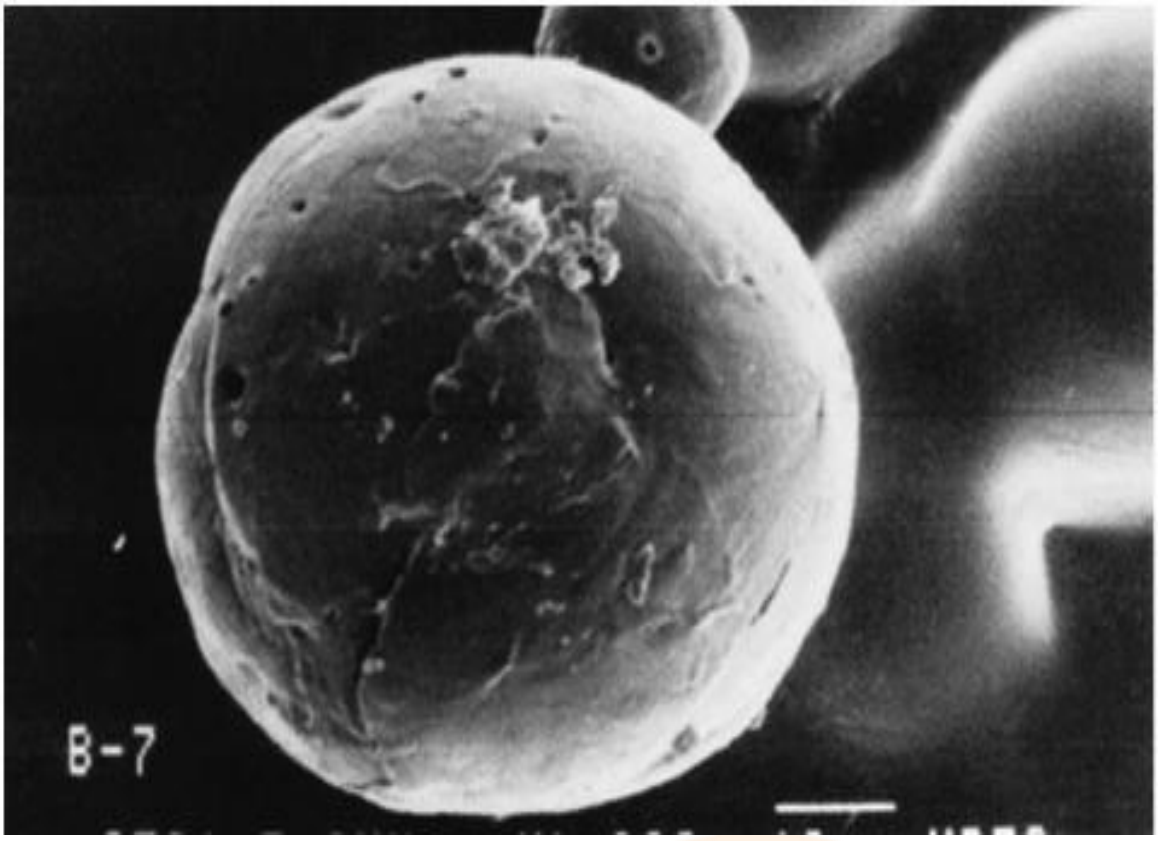


Figure 6.5: Scanning electrone microscopic of ayclovir microspheres with calciumalginate 1:2 drug polymer ratio (F1)**

Table 6.7: Various evaluation parameters of buoyant microspheres

Code	Angle of Repose[a] (θ)	Carr's Index[a] (%)	Hausner's Ratio[a]	Particle size in d_{avg} (µm) [a]	Percent entrapment efficiency [b]
F1**	21.390+0.671	13.253+0.624	1.245+0.013	36.45±0.540	99.24±1.2%
F2*	23.410+0.035	14.285+0.345	1.160+0.023	37.86±0.436	98.46±1.8%

F3*	22.820+0.553	13.496+0.413	1.142+0.072	37.15±0.495	100.24±1.6%
F4**	25.390+0.308	13.812+0.823	1.265+0.062	37.10±0.512	95.43±1.3%
F5*	29.810+0.071	12.972+0.316	1.132+0.012	38.12±0.436	96.65±1.7%
F6*	22.520+0.351	12.359+0.749	1.134+0.039	37.95±0.378	97.56±1.5%
F7**	23.460+0.421	10.054+0.613	1.267+0.013	38.17±0.435	95.64±1.8%
F8*	24.310+0.312	11.053+0.931	1.148+0.027	39.86±0.532	96.83±1.6%
F9*	25.310+0.412	12.053+0.721	1.145+0.028	38.24±0435	97.43±1.4%

[a] Mean ± SD, n = 10, [b] Mean ± SD, n = 3, Stirring rate = * 300 rpm, ** 500 rpm

Table 6.8: Percentage Buoyancy for different formulation

F. Code	1 hour	4 hours	8 hours	12 hours
F1**	98.41	97.08	56.04	25.09
F2*	98.11	95.58	61.04	28.09
F3*	98.54	95.64	41.8	11.17
F4**	99.54	92.49	49.5	16.21
F5*	98.72	91.95	39.4	15.41
F6*	98.45	86.62	42.7	16.65
F7**	88.34	75.41	39.2	17.78
F8*	81.51	67.23	31.2	14.05
F9*	85.51	61.23	30.2	13.78

Table 6.9: in-vitro drug release study of buoyant microspheres

Time	F1**	F2*	F3*	F4**	F5*	F6*	F7**	F8*	F9*
0	0	0	0	0	0	0	0	0	0
1	3.01	1.54	4.71	0.322	0.571	1.23	0.781	3.23	4.68

2	8.23	5.43	13.21	2.45	1.76	3.39	3.45	9.23	10.12
3	10.34	9.23	18.68	4.67	5.67	3.39	7.46	15.67	18.34
4	19.87	19.87	35.67	16.46	12.34	14.5	13.23	26.78	27.45
5	31.23	31.25	45.27	26.56	25.67	21.34	26.56	33.24	38.54
6	41.34	44.78	53.25	38.78	36.45	37.56	38.34	44.28	47.65
7	53.37	52.34	66.34	49.87	46.78	58.45	48.34	53.68	59.67
8	65.78	64.21	76.54	59.03	59.04	74.23	58.34	69.76	75.6
9	77.45	74.34	88.74	71.23	69.34	86.46	69.87	79.32	84.34
10	87.32	82.1	95.37	81.23	79.67	93.6	81.26	89.65	91.23
11	97.51	92.1	98.12	91.13	90.23	98.01	91.36	94.78	96.99
12	99.24	99.68	99.99	98.13	99.01	99.34	99.21	99.78	99.98

Stirring rate = * 300 rpm, ** 500 rpm

Table 6.10: in-vitro drug release study of buoyant microspheres (F1)

Time	**√Time**	**Logtime**	**Cummulative drug released**	**Cummulative % drug released**	**Log cummulative % drug released**	**Cummulative % drug retained**	**Log cummulative % drug retained**
0	0.000	#NUM!	0.000	0	#NUM!	100.000	2.000
1	1.000	0.000	4.515	3.01	0.479	96.990	1.987
2	1.414	0.301	12.345	8.23	0.915	91.770	1.963
3	1.732	0.477	15.510	10.34	1.015	89.660	1.953

4	2.000	0.602	29.805	19.87	1.298	80.130	1.904
5	2.236	0.699	46.845	31.23	1.495	68.770	1.837
6	2.449	0.778	62.010	41.34	1.616	58.660	1.768
7	2.646	0.845	80.055	53.37	1.727	46.630	1.669
8	2.828	0.903	98.670	65.78	1.818	34.220	1.534
9	3.000	0.954	116.175	77.45	1.889	22.550	1.353
10	3.162	1.000	130.980	87.32	1.941	12.680	1.103
11	3.317	1.041	146.265	97.51	1.989	2.490	0.396
12	3.464	1.079	148.860	99.24	1.997	0.760	-0.119

Table 6.11: in-vitro drug release study of buoyant microspheres (F2)

Time	**√Time**	**Log time**	**Cummulative drug released**	**Cummulative % drug released**	**Log cummulative % drug released**	**Cummulative % drug retained**	**Log cummulative % drug retained**
0	0.000	#NUM!	0.000	0	#NUM!	100.000	2.000
1	1.000	0.000	2.310	1.54	0.188	98.460	1.993
2	1.414	0.301	8.145	5.43	0.735	94.570	1.976
3	1.732	0.477	13.845	9.23	0.965	90.770	1.958
4	2.000	0.602	29.805	19.87	1.298	80.130	1.904
5	2.236	0.699	46.875	31.25	1.495	68.750	1.837
6	2.449	0.778	67.170	44.78	1.651	55.220	1.742

7	2.646	0.845	78.510	52.34	1.719	47.660	1.678
8	2.828	0.903	96.315	64.21	1.808	35.790	1.554
9	3.000	0.954	111.510	74.34	1.871	25.660	1.409
10	3.162	1.000	123.150	82.1	1.914	17.900	1.253
11	3.317	1.041	138.150	92.1	1.964	7.900	0.898
12	3.464	1.079	149.520	99.68	1.999	0.320	-0.495

Table 6.12: in-vitro drug release study of buoyant microspheres (F3)

Time	**√Time**	**Log time**	**Cummulative drug released**	**Cummulative % drug released**	**Log cummulative % drug released**	**Cummulative % drug retained**	**Log cummulative % drug retained**
0	0.000	#NUM!	0.000	0	#NUM!	100.000	2.000
1	1.000	0.000	7.065	4.71	0.673	95.290	1.979
2	1.414	0.301	19.815	13.21	1.121	86.790	1.938
3	1.732	0.477	28.020	18.68	1.271	81.320	1.910
4	2.000	0.602	53.505	35.67	1.552	64.330	1.808
5	2.236	0.699	67.905	45.27	1.656	54.730	1.738

6	2.449	0.778	79.875	53.25	1.726	46.750	1.670
7	2.646	0.845	99.510	66.34	1.822	33.660	1.527
8	2.828	0.903	114.810	76.54	1.884	23.460	1.370
9	3.000	0.954	133.110	88.74	1.948	11.260	1.052
10	3.162	1.000	143.055	95.37	1.979	4.630	0.666
11	3.317	1.041	147.180	98.12	1.992	1.880	0.274
12	3.464	1.079	149.985	99.99	2.000	0.010	-2.000

Table 6.13: in-vitro drug release study of buoyant microspheres (F4)

Time	**√Time**	**Log time**	**Cummulative drug released**	**Cummulative % drug released**	**Log cummulative % drug**	**Cummulative % drug retained**	**Log cummulative % drug**

					released		**retained**
0	0.000	#NUM!	0.000	0	#NUM!	100.000	2.000
1	1.000	0.000	0.483	0.322	-0.492	99.678	1.999
2	1.414	0.301	3.675	2.45	0.389	97.550	1.989
3	1.732	0.477	7.005	4.67	0.669	95.330	1.979
4	2.000	0.602	24.690	16.46	1.216	83.540	1.922
5	2.236	0.699	39.840	26.56	1.424	73.440	1.866
6	2.449	0.778	58.170	38.78	1.589	61.220	1.787
7	2.646	0.845	74.805	49.87	1.698	50.130	1.700
8	2.828	0.903	88.545	59.03	1.771	40.970	1.612
9	3.000	0.954	106.845	71.23	1.853	28.770	1.459
10	3.162	1.000	121.845	81.23	1.910	18.770	1.273
11	3.317	1.041	136.695	91.13	1.960	8.870	0.948
12	3.464	1.079	147.195	98.13	1.992	1.870	0.272

Table 6.14: in-vitro drug release study of buoyant microspheres (F5)

Time	√Time	Log time	Cummulative drug released	Cummulative % drug released	Log cummulative % drug released	Cummulative % drug retained	Log cummulative % drug retained
0	0.000	#NUM!	0.000	0	#NUM!	100.000	2.000
1	1.000	0.000	0.857	0.571	-0.243	99.429	1.998
2	1.414	0.301	2.640	1.76	0.246	98.240	1.992
3	1.732	0.477	8.505	5.67	0.754	94.330	1.975
4	2.000	0.602	18.510	12.34	1.091	87.660	1.943
5	2.236	0.699	38.505	25.67	1.409	74.330	1.871
6	2.449	0.778	54.675	36.45	1.562	63.550	1.803
7	2.646	0.845	70.170	46.78	1.670	53.220	1.726
8	2.828	0.903	88.560	59.04	1.771	40.960	1.612
9	3.000	0.954	104.010	69.34	1.841	30.660	1.487
10	3.162	1.000	119.505	79.67	1.901	20.330	1.308
11	3.317	1.041	135.345	90.23	1.955	9.770	0.990
12	3.464	1.079	148.515	99.01	1.996	0.990	-0.004

Table 6.15: in-vitro drug release study of buoyant microspheres (F6)

Time	√Time	Log time	Cummulative rug released	Cummulative % drug released	og cummulative % drug released	Cummulative % drug retained	og cummulative % drug retained
0	0.000	#NUM!	0.000	0	#NUM!	100.000	2.000
1	1.000	0.000	1.845	1.23	0.090	98.770	1.995
2	1.414	0.301	5.085	3.39	0.530	96.610	1.985
3	1.732	0.477	5.085	3.39	0.530	96.610	1.985
4	2.000	0.602	21.750	14.5	1.161	85.500	1.932
5	2.236	0.699	32.010	21.34	1.329	78.660	1.896
6	2.449	0.778	56.340	37.56	1.575	62.440	1.795
7	2.646	0.845	87.675	58.45	1.767	41.550	1.619
8	2.828	0.903	111.345	74.23	1.871	25.770	1.411
9	3.000	0.954	129.690	86.46	1.937	13.540	1.132
10	3.162	1.000	140.400	93.6	1.971	6.400	0.806
11	3.317	1.041	147.015	98.01	1.991	1.990	0.299
12	3.464	1.079	149.010	99.34	1.997	0.660	-0.180

Table 6.16: in-vitro drug release study of buoyant microspheres (F7)

Time	√Time	Log time	Cummulative drug released	Cummulative % drug released	Log cummulative % drug released	Cummulative % drug retained	Log cummulative % drug retained
0	0.000	#NUM!	0.000	0	#NUM!	100.000	2.000
1	1.000	0.000	1.172	0.781	-0.107	99.219	1.997
2	1.414	0.301	5.175	3.45	0.538	96.550	1.985
3	1.732	0.477	11.190	7.46	0.873	92.540	1.966
4	2.000	0.602	19.845	13.23	1.122	86.770	1.938
5	2.236	0.699	39.840	26.56	1.424	73.440	1.866
6	2.449	0.778	57.510	38.34	1.584	61.660	1.790
7	2.646	0.845	72.510	48.34	1.684	51.660	1.713
8	2.828	0.903	87.510	58.34	1.766	41.660	1.620

9	3.000	0.954	104.805	69.87	1.844	30.130	1.479
10	3.162	1.000	121.890	81.26	1.910	18.740	1.273
11	3.317	1.041	137.040	91.36	1.961	8.640	0.937
12	3.464	1.079	148.815	99.21	1.997	0.790	-0.102

Table 6.17: in-vitro drug release study of buoyant microspheres (F8)

Time	**√Time**	**Log time**	**Cummulative drug released**	**ummulative % drug released**	**og cummulative % drug**	**ummulative % drug retained**	**og cummulative % drug**
					eleased		**tained**
	000	NUM!	000		NUM!	00.000	000
	000	000	845	23	509	6.770	986
	414	301	8.845	23	965	0.770	958
	732	477	8.505	6.67	195	4.330	926
	000	602	0.170	6.78	428	3.220	865
	236	699	9.860	3.24	522	6.760	825
	449	778	6.420	4.28	646	6.720	746
	646	845	0.520	3.68	730	6.320	666
	828	903	04.640	9.76	844	0.240	481
	000	954	18.980	9.32	899	0.680	316
)	162	000	34.475	9.65	953	0.350	015
	317	041	42.170	4.78	977	220	718

2	464	079	49.670	9.78	999	220	.658

Table 6.18: in-vitro drug release study of buoyant microspheres (F9)

ime	Time	og time	ummula tive rug released	ummulati ve drug eleased	og cummulat e % rug	ummul ive % drug	og cummulat e % rug
					eleased	etained	etained
	000	NUM!	000		NUM!	00.000	000
	000	000	020	68	670	5.320	979
	414	301	5.180	0.12	005	9.880	954
	732	477	7.510	3.34	263	1.660	912
	000	602	1.175	7.45	439	2.550	861
	236	699	7.810	3.54	586	1.460	789
	449	778	1.475	7.65	678	2.350	719
	646	845	0.505	0.67	776	0.330	606
	828	903	13.400	5.6	879	4.400	387
	000	954	26.510	4.34	926	5.660	195
0	162	000	36.845	1.23	960	770	943
1	317	041	45.485	5.99	987	010	479
2	464	079	49.970	0.98	000	020	.699

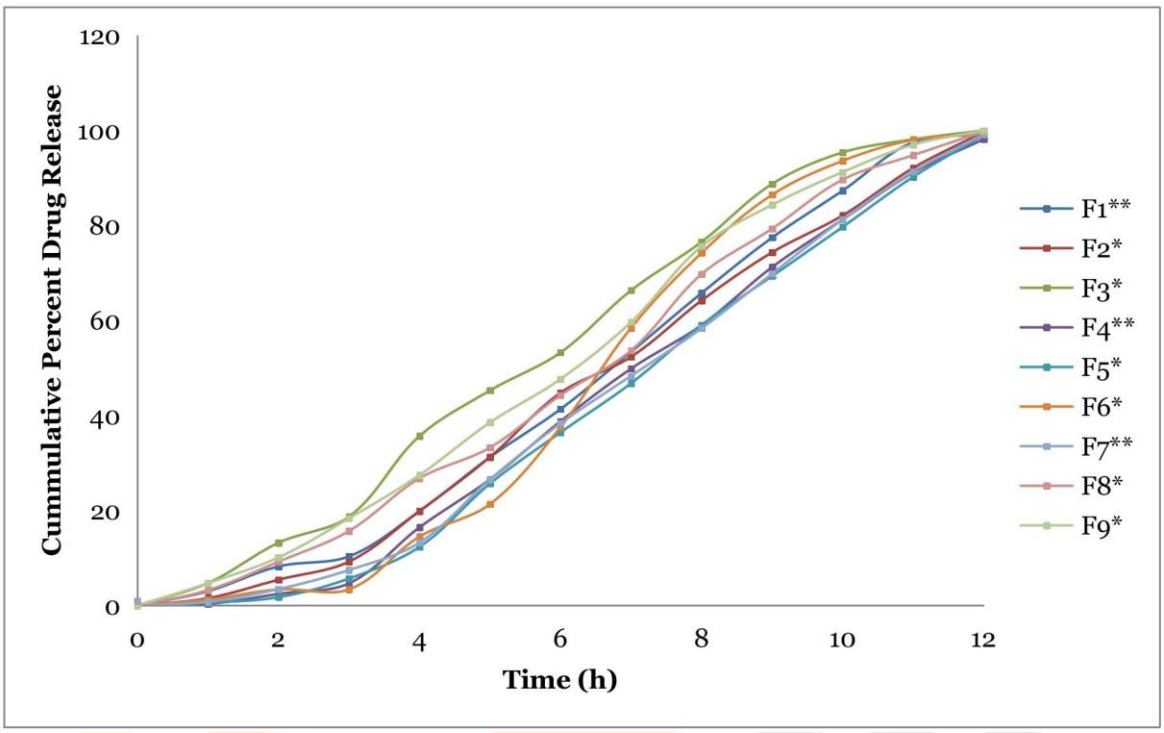


Figure 6.6: Zero-order plots for buoyant microspheres of ayclovir (F1 – F9)

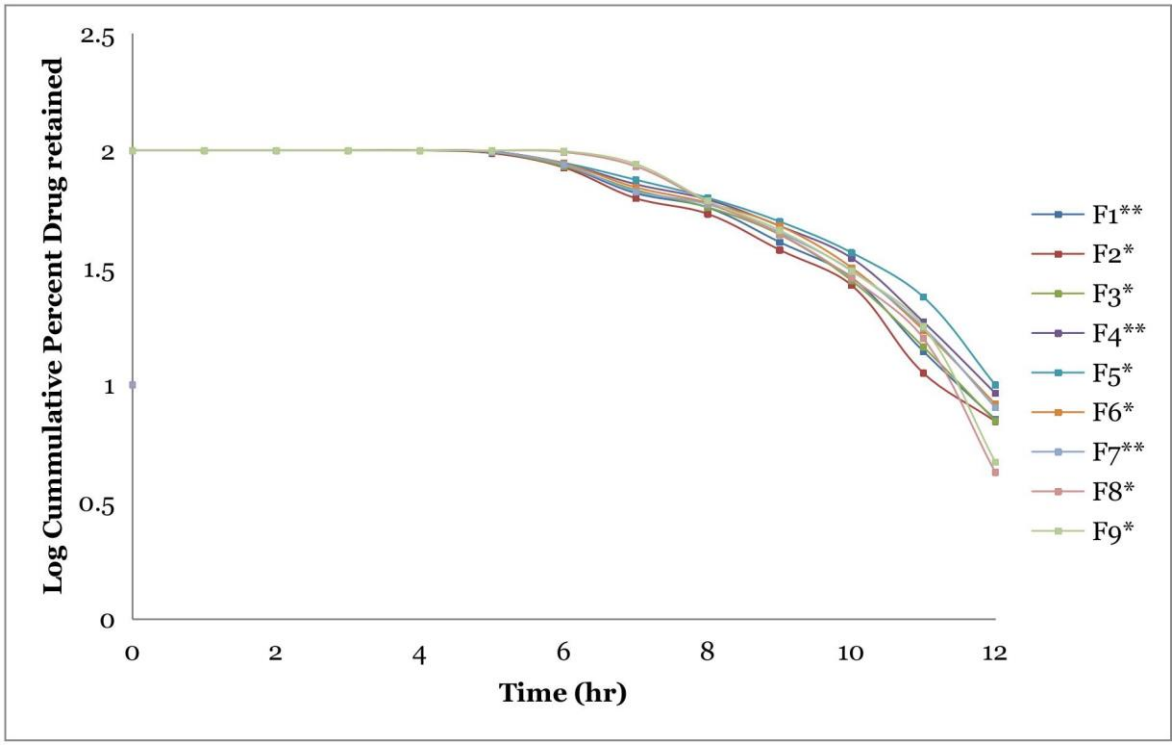


Figure 6.7: First-order plots for buoyant microspheres of ayclovir (F1 – F9)

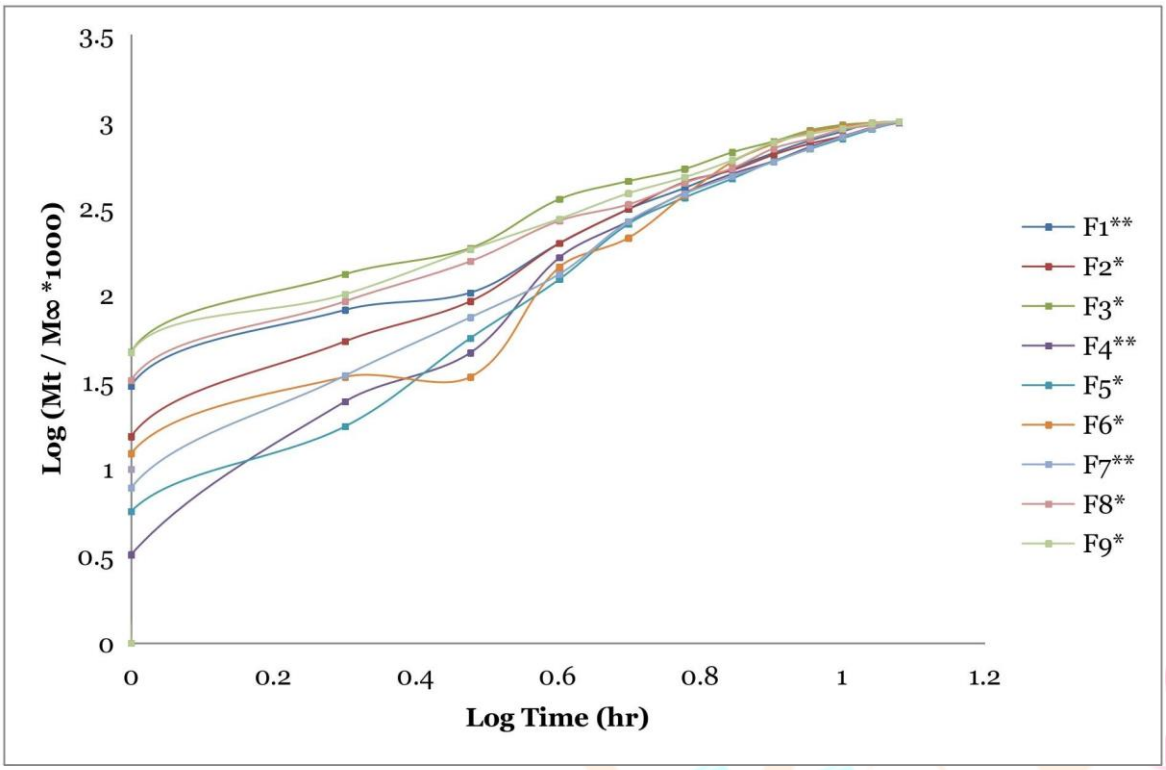


Figure 6.8: Korsmeyer's peppas plots for buoyant microspheres of ayclovir (F1 – F9)

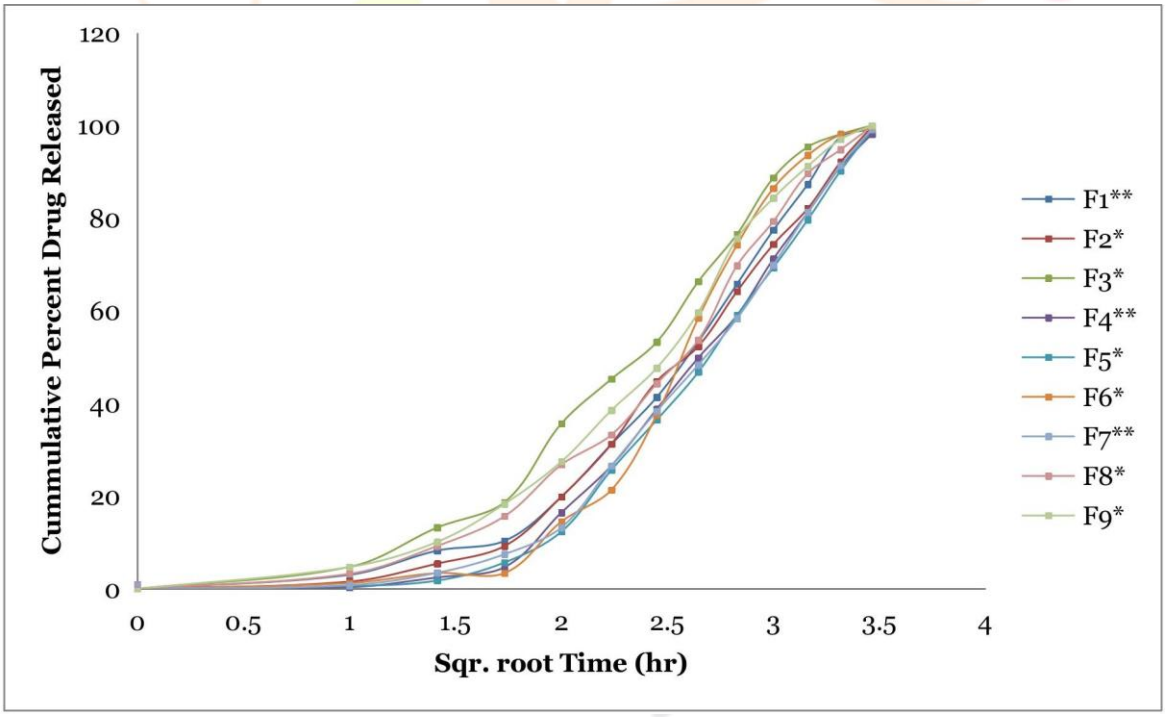


Figure 6.9: Higuchi plots for buoyant microspheres of ayclovir (F1 – F9)

Table 6.19: Release Kinetics of Floating Microsphere in 0.1 N HCl

ormulationCode	Zero Order		Higuchi Equation		Peppas Equation	
	r^2	K_0	r^2	K_H	r^2	n
F1**	0.951	1.81	0.989	6.946	0.937	1.156
F2*	0.954	2.08	0.998	8.141	0.817	1.185
F3*	0.963	2.86	0.994	11.04	0.872	1.169
F4**	0.948	3.49	0.996	13.66	0.835	1.134
F5*	0.932	4.03	0.993	16.09	0.752	1.164
F6*	0.964	4.68	0.996	18.08	0.822	1.112
F7**	0.956	5.81	0.998	22.42	0.833	1.181
F8*	0.954	5.85	0.997	22.86	0.759	1.168
F9*	0.922	4.61	0.946	19.07	0.922	1.112

Stirring rate = * 300 rpm, ** 500 rpm

CONCLUSION

The proposed studies work compiled various formula of ayclovir active moeighty for remedyof viral infection. The formulation primarily based on pulsatile launch of drug via diffusion mechanism through microspheres. The pulsatile buoyant microsize particulate system keeps drug at the web site of stomach. It is a treasured buoyant system, have the exceptional rewardof more than one unit structures as well as superior floating homes, because the system have vital hollow space inside the frame. This conduct the method much appropriate sustained- launch dosage sorts of ayclovir inside the belly to promote a fast and effective eradication of
H. Pylori to remedy peptic ulcer with better affected person's compliance. Ayclovir drug turned into envisioned in-vitro by using stated UV spectrophotometric methods. The said UV spectrophotometric strategies at 253 nm for ayclovir. The values of correlation coefficients that had been located to be greater than 0.99. The curves were observed to be recti-linear in the attention range 5 µg / ml to 20 µg / ml for the drug. The estimation approaches for drugs were determined to be touchy, particular and reproducible.

Ayclovir changed into determined to be mild yellow, nearly odorless, Vertigo metallic taste in nature. The microscopic examination of the drug (Ayclovir) sample turned into crystalline powder The particle length of unmilled powder became 101 µm. The flow of unmilled drug powder changed into right to outstanding float. The solubility of drug ayclovir become very much less soluble in all dissolution media and the partition coefficient of Ayclovir became located drug changed into lipophilic in nature. The Infrared spectra had been obtained the useof an FTIR spectrometer. Drug and other Excipients were no longer incompatible with each other.

Solvent evaporation technique became located suitable for practise of microspheres. The yield received in all batches became exact. The prepared microspheres confirmed variability in size, that is increasing with increasing polymeric attention of equal polymer. The common particle length davg became additionally having variability with variations of coating polymeric fabric as calcium alginate, ethyl cellulose and egg albumin. The microspheres prepared of egg albumin as coating cloth and stirring charge 500 rpm showed true float property because finer droplets had been prepared with growing stirring price. All the micromeritics houses of prepared microspheres showed good to terrific flow belongings of

notably viscous polymeric answers however having large length particles (co-relation between The in-vitro buoyancy profile also shown that prepared microspheres buoyant greater than 25 % upto 12 h. Drug release pattern changed into evaluated in 0.1 N HCl. Zero order plots for F1** and F2* method changed into found to be linear in dissolution medium, it considered as a high-quality healthy for drug launch. That indicates it couldcomply with 0 order mechanism. Floating buoyant microspheres F2* changed into the satisfactory formulations become nice method due on the basis of drug polymer aggregate in the ratio of 1:2 and stirring fee s 300rpm. This as formulate the considered necessary particle length for higher retardant drug launch upto 12 hr with better release profile.

REFERENCE

1. Abrahamsson B, Alpsten M, Hugosson M, Jonsson UE, "Sundgren M, Svenheden A, Tölli J. Absorption, gastrointestinal transit, and tablet erosion of felodipine extended- release (ER) tablets." Pharm. Res. 1993, 10, 5, 709-714.

2. Arora S, Floating Drug Delivery Systems. A Review, AAPS Pharm Sci Tech. 2005; 6 (3): Article 47, E.372-390.

3. Bharat W, Tekade VM, Thakare U, Jadhao T, Kazi F, "Optimization and In vitro evaluation of verapamil hydrochloride floating bilayer tablet." The Pharma Innov. J. 2014, 3, 6, 48-56.

4. Chien, Y.W.; Noval drug delivery system, II Edn., Marcel Dekker, New York, 1997; 50: 161-163.

5. Coupe AJ, Davis SS, Evans DF, Wilding IR, "Correlation of the gastric emptying of nondisintegrating tablets with gastrointestinal motility." Pharm. Res., 1991, 8, 10, 1281- 1285.

6. Dawang SR, Saboo SS, Khadabadi S, "Formulation and evaluation of floating tablets of Verapamil hydrochloride by using gastroretentive technology." Int. J. Pharm. Sci. Rev.Res. 2015, 34, 1, 263-269.

7. Dawang SR, Saboo SS, Khadabadi S, Formulation and evaluation of floating tablets of Verapamil hydrochloride by using gastroretentive technology, International Journal of Pharmaceutical Sciences Review and Research, 2015, 34(1):263-269.

8. El Nabarawi MA, Teaima MH, Abd El-Monem RA, El Nabarawy NA, Gaber DA. Formulation, release characteristics, and bioavailability study of gastroretentive floating matrix tablet and floating raft system of Mebeverine HCl. Drug Des Devel Ther. 2017; 11:1081–1093.

9. El Nabarawi MA, Teaima MH, El-Monem RA, "Formulation, release characteristics, and bioavailability study of gastroretentive floating matrix tablet and floating raft system of Mebeverine HCl." Drug Des. Dev. Ther. 2017, 11, 1081–1093.

10. Fujimori J, Machida Y, Nagai T. Preparation of a magnetically – responsive tablet and configuration of its gastric residence in beagle dogs. STP Pharma Sci. 1994; 4: 425-430.

11. Gangadharappa HV, M. Rahamath-Ulla2, T. M. Pramod-Kumar1, and F. Shakeel, Floating drug delivery system of verapamil hydrochloride using karaya gum and HPMC, Clinical Research and Regulatory Affairs, 2010; 27(1): 13–20.

12. Gangadharappa HV, Pramod Kumar TM, and Shiva Kumar HG. Gastric floating drug delivery systems. Indian J Pharm Educ Res. Oct-Dec 2007; 41 (4): 295-306.

13. Gangadharappa HV, Rahamath-Ulla M, Kumar TMP, Shakeel F, "Floating drug delivery system of verapamil hydrochloride using karaya gum and HPMC." Clin. Res. Reg. Aff. 2010, 27, 1, 13–20.

14. Garg S, Sharma S, "Gastroretentive drug delivery systems", Pharmtech. 2003,160-166.

15. Guyton, A.C., Hall, J.E.; Text book of medical physiology, IX Edn., Sqender company, Piladelpcia, 1996: 803-805.

16. Hou J, Yuntai S, Zihao L, Jiaqi W, Yongjun G, Weifeng Z, Han Z, Dayong N, "Numerical simulation and experimental study on flexible buoyancy material of hollow glass microsphere and silicone rubber for small deep-sea soft robots." App. Mat. Today. 2020, 21, 100875.

17. Jafar M, Mohsin AA, Khalid MS, Alshahrani AM, Alkhateeb FS, Alqarni AS, "Ranitidine hydrochloride stomach specific bouyant microsponge: Preparation, in-vitro characterization, and in-vivo anti-ulcer activity." J. Drug Del. Sci. Tech., 2020, 55, 101453.

18. Jain M N, "Development and characterization of gastroretentive mucoadhesive tablets of riboflavin." Ind. J. Drug. 2018, 6, 2, 105-111.

19. Jain NK. In progress in controlled and novel drug delivery systems, 1st Edn; CBS Publishers and Distributors, New Delhi, Bangalore. 2004, pp. 84-85.

20. Jimenez-Castellanos NR, Zia H, Rhodes CT. Mucoadhesive Drug Delivery Systems. Drug Development and Industrial pharmacy. 1993; 19:143.

21. Khosla R, Davis SS, "The Effect of Tablet Size on the Gastric-Emptying of Nondisintegrating Tablets." Int. J. Pharm. 1990, 62, R9–R11.

22. Kumari SU, B.Ramu2*, G.Srikanth2, Dr.Bigala Rajkamal, Formulation and Evaluation of Sustained Release Verapamil Hydrochloride Using Natural Polymers, International Journal of Applied Pharmaceutical Sciences and Research 2016; 1(2):76-87.

23. Kumari SU, Ramu B, Srikanth G, Rajkamal B, "Formulation and Evaluation of Sustained Release Verapamil Hydrochloride Using Natural Polymers." Int. J. App. Pharm. Sci. Res. 2016, 1, 2, 76-87.

24. Mathur V, Kalpana Nagpal, Shailendra Kumar Singh, Dina Nath Mishra, Comparative release profile of sustained release matrix tablets of verapamil HCl, International Journal of Pharmaceutical Investigation, 2013, 3 (1), 60-65.

25. Mathur V, Nagpal K, Singh SK, Mishra DN, "Comparative release profile of sustained release matrix tablets of verapamil HCl." Int. J. Pharm. Investig. 2013, 3, 1, 60-65.

26. Molke M, Iqbal MM, Rao KS, "Formulation and Evaluation of Verapamil HCL Gastroretentive Floating Tablet from matrices prepared using Compritol ATO 888." Res.J. Pharm. Bio. Chem. Sci. 2010, 1, 3, 422-430.

27. Molke M, MD.Majid Iqbal, Dr. K.S Rao, Formulation and Evaluation of Verapamil HCL Gastroretentive Floating Tablet from matrices prepared using Compritol ATO 888, Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2010, 1 (3), 422- 430).

28. More S, Gavali K, Doke O, Kasgawade P, "Gastroretentive drug delivery system." J. Drug Del. Therap. 2018, 8, 4, 24-35.

29. More S, Kaustubh Gavali , Onkar Doke, Prasad Kasgawade, Gastroretentive drug delivery system, Journal of Drug Delivery & Therapeutics. 2018; 8(4):24-35.

30. Mourya, D. T., Yadav, P. D., Ullas, P. T., Bhardwaj, S. D., Sahay, R. R., Chadha, M. S., Shete, A. M., Jadhav, S., Gupta, N., Gangakhedkar, R. R., Khasnobis, P., & Singh, S. K. (2019). Emerging/re-emerging viral diseases & new viruses on the Indian horizon. The Indian journal of medical research, 149(4), 447–467.

31. Moy AC, Mathew ST, Mathapan R, Prasanth VV. Microsphere-An Overview. International Journal of Pharmaceutical and Biomedical Sciences 2011; 2(2): 332-338.

32. Nikam VK, Sachin B Somwanshi1, Ramdas T Dolas1, Vivekanand A Kashid, Kiran B Dhamak, Vinayak M Gaware, Atul N Khadse and Kiran B Kotade, A novel gastro retentive controlled release drug delivery system of Verapamil Hydrochloride: Formulation and evaluation, J. Chem. Pharm. Res., 2011, 3(2):932-939.

33. Nikam VK, Somwanshi SB, Dolas RT, Kashid VA, Dhamak KB, Gaware VM, Khadse AN, Kotade KB, "A novel gastro retentive controlled release drug delivery system of

34. erapamil Hydrochloride: Formulation and evaluation." J. Chem. Pharm. Res. 2011, 3, 2, 932-939.

35. Patel A, Modasiya M, Shah D, Patel V, "Development and In Vivo Floating Behavior of Verapamil HCl Intragastric Floating Tablets." AAPS Pharm. Sci. Tech., 2009, 1, 1, 310- 315.

36. Patel A, Moin Modasiya,1 Dushyant Shah,1 and Vishnu Patel, Development and In Vivo Floating Behavior of Verapamil HCl Intragastric Floating Tablets, AAPS PharmSciTech, 2009, 1 (1), 310-315)

37. Rahamathulla M, Srinivasan S, Gangadharappa HV, "Development of Valsartan Floating Matrix Tablets Using Low Density Polypropylene Foam Powder: In vitro and In vivo Evaluation," AAPS Pharm. Sci. Tech. 2019, 20, 1, 20-35.

38. Rahamathulla M, Srinivasan S, Gangadharappa HV, Development of Valsartan Floating Matrix Tablets Using Low Density Polypropylene Foam Powder: In vitro and In vivo Evaluation, 2019, AAPS PharmSciTech 20(1), 20-35.

39. Ray B, Gupta MM, "Formulation and Evaluation of Once Daily Sustained Release Matrix Tablet of Verapamil Hydrochloride." J. Drug Del. Ther., 2013, 3, 1, 55-58.

40. Reddy KR, Rathnam G, Kiran I, Raju S, Mulpuri KS, "Formulation development and evaluation of sustained release matrix tablets of verapamil hydrochloride." Int. J. Pharm. Sci. Res. 2014, 5, 5, 2066-2073.

41. Robinson, J., Vincent, H.L.L.; Controlled Drug Delivery Fundamentals and Applications, II Edn., Marcel Dekker, Inc, New york, 1968: 346-374.

42. Selin JH, Pasrija PJ. Pharmacotherapy of Inflammatory Bowel Disease. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 11th edition. New York: McGraw Hill companies, Inc., USA; 2006. P. 1010.

43. Shivakumar HG, Vishakante D, Kumar TMP. Floating Controlled Drug Delivery Systems for Prolong Gastric Residence. Indian J Pharm Educ. 2004; 38(4):172-179.

44. Shivhare K, Garg C, Priyam A, Gupta A, Sharma AK, Kumar P, "Enzyme sensitive smart inulin-dehydropeptide conjugate self-assembles into nanostructures useful for targeted delivery of ornidazole." Int. J. Biol. Macromol. 2018, 106, 775-783.

45. ingh BN and Kim KH, "Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention." J. Control Rel. 2000, 63, 235–259.

46. Srivastava A, Verma A, Saraf S, Jain A, Tiwari A, Panda PK, Jain SK. Mucoadhesive gastroretentive microparticulate system for programmed delivery of famotidine and clarithromycin. J Microencapsul. 2021 May;38(3):151-163.

47. Streubel A, Siepmann J, Bodmeier R, "Gastroretentive drug delivery system." Expert Opin. Drug Deliv. 2006, 3, 2, 217- 33.

48. Syeda AM, Masum MAA, Sharmin F, Sultana S, Reza MS, Bhuiyan MA, "Development and in vitro evaluation of floating drug delivery system of verapamil HCl." IJPSR. 2013, 4, 2, 724-730.

49. Talukder R and Fassihi R, "Gastroretentive delivery systems." Drug Dev. Ind. Pharm. 2004, 30, 10, 1019-1028.

50. Timmermans J, Moës AJ, "Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: new data for reconsidering the controversy", J. Pharm Sci. 1994, 83, 1, 18-24.

51. Tolia G and S. Kevin Li, Silicone Adhesive Matrix of Verapamil Hydrochloride to Provide pH-Independent Sustained Release, AAPS PharmSciTech, 2014, 15 (1), 1-10.)

52. Tort H, Oktay EA, Tort S, Bayar GR, Topcu FT, Kilic E, Acarturk F, "Evaluation of ornidazole-loaded nanofibers as an alternative material for direct pulp capping." J. Drug Del. Sci. Tech. 2017, 41, 317-324.

53. Tortora, G.J., Grabowski., S.R.; Principles of Anatomy and Physiology, X Edn, John Willey & Sons, Inc., USA, 2002: 868-870.

54. Tripathi KD (2013) Essentials of Medical Pharmacology, seventh edition, published by Jaypee Brothers Medical Publishers (P) Ltd, 4838/24, Ansari Road, Daryaganj, New Delhi, 110 002, India, first edition 1985, pp 663.

55. Vidyadhara S, Nagaraju R, "Design and Development of Polyethylene Oxide Based Matrix Tablets for Verapamil Hydrochloride." Ind. J. Pharm. Sci. 2013, 1, 185-190.

56. Vidyadhara S, Sasidhar and Nagaraju, Design and Development of Polyethylene Oxide Based Matrix Tablets for Verapamil Hydrochloride, Indian Journal of Pharmaceutical Sciences, 2013, 1, 185-190.

57. idyadhara S, Sasidhar RLC, Rao VUM, Babu, CHS, Harika DL, "Formulation and evaluation of verapamil hydrochloride osmotic controlled release matrix tablets." Asi. J. Pharmac. 2014, 1, 4, 102-109.

58. Vidyadhara, R. L. C. Sasidhar, V. Uma Maheswara Rao, C. H. Showri Babu, D. Lakshmi Harika, Formulation and evaluation of verapamil hydrochloride osmotic controlled release matrix tablets, Asian Journal of Pharmaceutics, 2014, 1 (4), 102-109.

59. Vrettos NN, Roberts CJ, Zhu Z. Gastroretentive Technologies in Tandem with Controlled-Release Strategies: A Potent Answer to Oral Drug Bioavailability and Patient Compliance Implications. Pharmaceutics. 2021 Sep 30;13(10):1591.

60. Vyas SP, Khar RK. Gastroretentive systems. In: Controlled drug Delivery. Vallabh Prakashan, Delhi, India. 2006; 197-217.

61. Vyas, S.P., Khar, R.K.; Controlled drug delivery concepts and Advances, I Edn., Vallabh prakashan, Delhi, 2002: 196-205.

62. Wagh PK, Ahirrao SP, Kshirsagar SJ, "Gastroretentive drug delivery systems: a review on expandable system." Ind. J.Drugs. 2018, 6, 3, 142-151.

63. Yie W, Chein. Novel Drug Delivery System 2nd ed. Marcel dekker Inc. New York. 1992; 1-3.