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Mechanistic Development of Buoyancy-Based Microspheres Gastroretentive System for Ranitidine HCl and Glipizide.

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ABSTRACT

In recent years oral dosage form for gastric retention (floating drug delivery systems) has drawn increasingly more consideration for their theoretical convenience in permitting control over time and site of drug release.

The present study intended to develop floating microspheres of Ranitidine HCL and Glipizide, which belong to the class of Histsamine2 blockers. Floating microspheres Ranitidine HCL and Glipizide floating microspheres was prepared by the emulsion solvent evaporation method using PLGA and ethylcellulose as polymer. Four different formulations were developed. The floating microsphere was assessed for the angle of repose, particle size, percentage yield, in vitro lightness, manifestation efficiency, drug-polymer compatibility (IR-study), scanning electron microscopy, drug release of the microsphere.

The outcome of the experiment shows that as the concentration of polymer influences its result the particle size, percentage yield, in vitro buoyancy and drug release of the microsphere. Formulations produced with HPMC K15M exhibited superb Micromeritic properties, percentage yield, in vitro buoyancy, manifestation efficiency, and percentage drug release when contrasted with ethylcellulose polymer. Consequences of our present study propose that the floating microsphere of Ranitidine HCL and Glipizide can be effectively intended to develop controlled drug delivery which can lessen dosing recurrence thus this formulation can be considered as an alternative to conventional dosage forms.

Keywords: Floating drug delivery systems, ranitidine HCL, incorporation efficiency, dosing frequency

INTRODUCTION

1.1 Basic physiology of gastrointestinal tract

Anatomically stomach is bound into three territories: fundus, body, and antrum (pylorus). The proximal part made of fundus and body goes about as supply for undigested material; however, antrum is executive site for blending updates and go about as pump for gastric discharging by pushing actions.

Gastric discharging happens amidst fasting other than observed over states. The representation of motility is however particular in two states. Amidst fasting express interdigestive outline of electrical occasions happen, which push both through stomach and digestive tract each 2 to 3 hours.29 This is known as interdigestive myoelectric cycle or moving myoelectric cycle (MMC), which is further detached into taking after 4 stages as depicted by Wilson and Washington.30 (Figure 1.1).

1. Phase I (basal stage) keeps setting off from 40 to hour with striking changing impacts.

2. Phase II (pre-burst stage) proceeds for hour with whimsical progression potential and settling impacts. As stage drives force and rehash moreover growths sensibly.

3. Phase III (burst stage) proceeds for 4 to 6 minutes. It joins terrific and general covering impacts for brief time. It is possible result of this wave that all undigested 27 material is escaped beginning from stomach to immaterial digestive structure. It is taking all things into account called house expert wave.

4. Phase IV proceeds for 0 to 5 minutes and happens between stages III and I of 2 constant cycles.

After intake of blended eating up data, example of compressions alters from without food to that of looked after state. These withdrawals see lessening level of sustenance particles (to under 1 mm), which are pushed toward pylorus in suspension structure. Amidst empowered state onset of MMC is surrendered seeing yield in gastric debilitating rate.

Scintigraphy studies picking gastric refining rates uncovered that orally enabled controlled discharge estimations structures are subjected to in wide sense two intricacies that of short gastric home time and unconventional gastric exhausting rate.

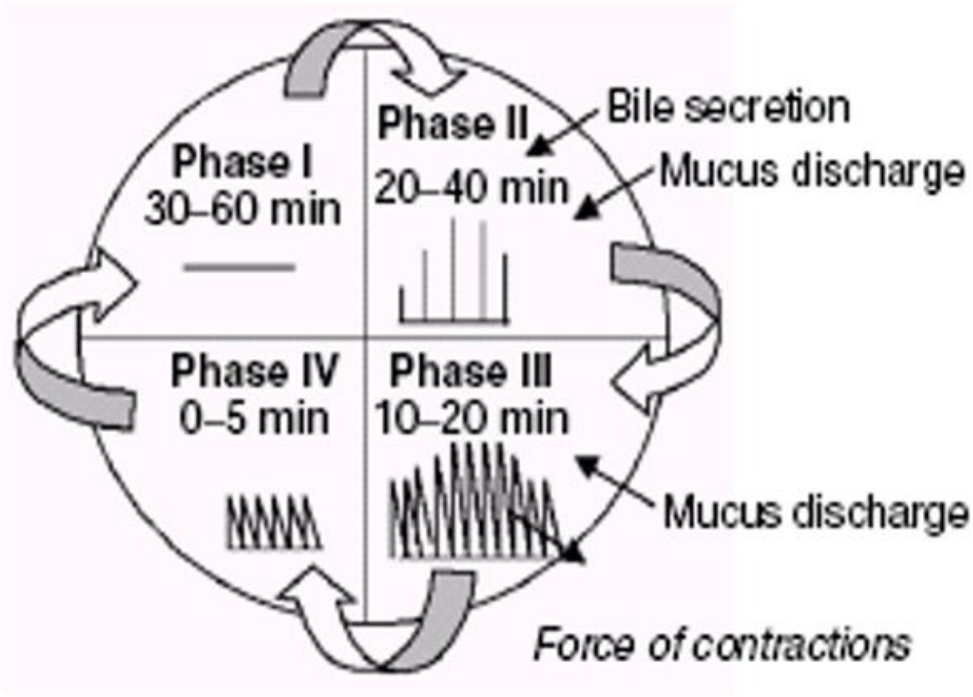

Figure 1: Gastric phases.

1.2 Gastric emptying and problems

It is all that much seen that stomach may be utilized as station for Sustained discharge estimation shapes, both in human and veterinary applications, stomach is anatomically bound into three regions: Fundus, body and pylorus.

The proximal stomach made up of fundus and body region serves as supply for ingested materials, while distal domain (antrum) is isolating site for blending change, set about as pump to finish gastric purging. The arrangement of gastric discharging happens both amidst fasting and associated with stages.

1.3 APPROACHES TO ACHIEVE GASTRIC RETENTION

The following strategies are employed to extend the duration drugs spend in the gastrointestinal tract:

A. Pharmacological Strategy

This method involves using drugs or integrating them into the dosage form to slow down gastrointestinal example, antimuscarinic emptying. agents for like propantheline are used to achieve this effect.

B. Physiological Strategy

This approach utilizes natural substances or fat derivatives, such as triethanolamine myristate, to activate receptors in the duodenum or jejunum, thereby slowing gastric emptying

C. Pharmaceutical Strategy

Given the toxicity concerns associated with the first two methods, various pharmaceutical techniques are employed, including:

1. **Low Density or Floating Drug Delivery System**

   This system has a bulk density lower than that of gastric fluids, allowing it to stay buoyant in the stomach. These systems, also known as Hydrodynamically Balanced Systems (HBS), can be further classified into:

   i. **Effervescent Systems:** These include gas generating and volatile liquid-containing systems.

   ii. Non-Effervescent Systems: These consist of expandable or swellable systems and inherently low-density systems.

2. **High Density or Sinking Drug Delivery System**

   This system ensures that the drug remains at the bottom of the stomach.

3. **Modified Shape or Unfolding System** • This design allows the drug to expand to a larger size, preventing it from passing through the pyloric sphincter too quickly.

4. **Bio adhesive or Mucoadhesive Drug Delivery System**: • This type of system enables the drug to stick to the gastric mucosa

5. **Super Porous Hydrogel System** •

6. **Magnetic System**

7.

1.4 LOW DENSITY OR FLOATING DRUG DELIVERY SYSTEM

To enhance drug bioavailability, a floating drug delivery system is employed to ensure optimal gastric retention. This approach is suitable for drugs that are absorbed in the stomach or the upper part of the small intestine. Unlike other methods, it does not affect the rate at which the stomach empties over time. Due to its lower density compared to gastric fluids, the system remains afloat in the stomach, allowing for a gradual release of the drug. The release of the drug follows the emptying of the residual system from the stomach, which prolongs gastric retention and stabilizes plasma drug levels.

Floating pharmaceutical transport structure structures are managed ward upon use of two asking for variables: sputtering and non-frothing frameworks.

1.5 Foaming Floating Dosage Forms

The floating drug delivery system releases the drug at a controlled rate while navigating through the gastric contents. Once the drug is released, the system is subsequently removed from the stomach. To ensure effective buoyancy and maintain the dosage form's floatation over the meal surface, there must be a minimum level of gastric contents and an appropriate floating force (F).

The floating force's kinetics can be assessed using a device that measures the force equivalent to F over time while the object remains submerged. A higher positive force indicates better object flow

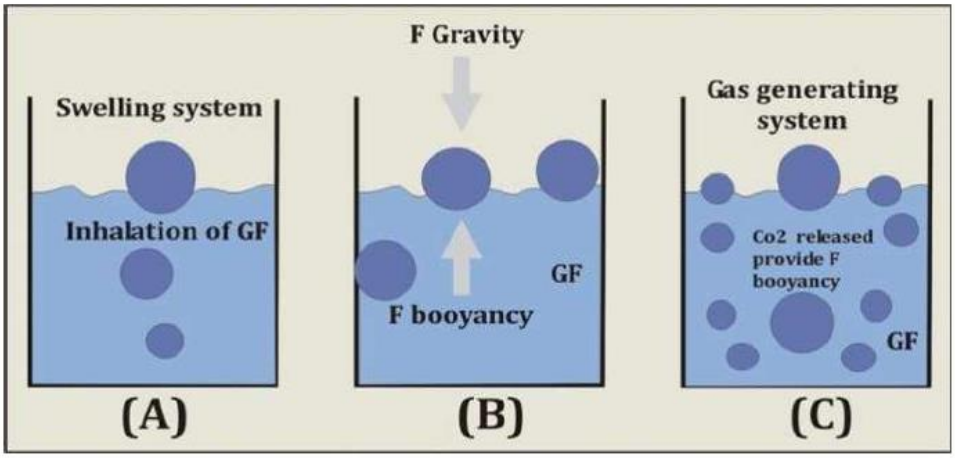

Figure 2: Foaming Floating Dosage Forms

This device helps in optimizing floating drug delivery systems (FDDS) and mitigating issues related to unexpected variations in intragastric buoyancy, stability, and durability.

The floating force (F) can be calculated using the equation:

$F\ buoyancy - F$ gravity = $(f - D\ s) \cdot v \cdot g$ $F = (D\ f - D\ s) \cdot v \cdot g$

Where: F = Total vertical force, f = Fluid density, s = Object density, = Volume, = Acceleration due to gravity.

1.6 CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM

Floating drug delivery system is classified as shown in figure 2, based on the buoyancy mechanism

EFFERVESCENT SYSTEMS

Effervescent systems utilize gas-producing agents, such as carbonates (e.g., sodium bicarbonate) and organic acids (e.g., citric acid, tartaric acid), to generate carbon dioxide (CO2) gas.

This process reduces the system's density, enabling it to float on gastric fluids. Alternatively, some systems incorporate a liquid-containing matrix that releases a gas upon reaching body temperature.

Effervescent systems can be divided into two main categories:

1) **Effervescent/Gas-Generating Systems** These systems create gas bubbles to achieve buoyancy. They often use matrices composed of swellable polymers, like polysaccharides (e.g., chitosan), alongside effervescent agents (e.g., sodium bicarbonate, citric acid, tartaric acid). An ideal ratio of citric acid to sodium bicarbonate for optimal gas production is 0.76:1.
   In these systems, CO2 is released, causing the formulation to float in the stomach. Various materials and methods are also employed, including mixtures of sodium alginate and sodium bicarbonate, multiple-unit floating dosage forms that generate CO2 upon ingestion, and floating mini capsules containing sodium bicarbonate, lactose, and PVP, coated with HPMC.

Additionally, floating systems based on ion exchange resins and bilayer or multilayer systems—where drugs and excipients are independently formulated and gas-generating agents are included in one of the layers—are used. Some systems are further modified with a polymer coating that is water-permeable but carbon dioxide-impermeable.

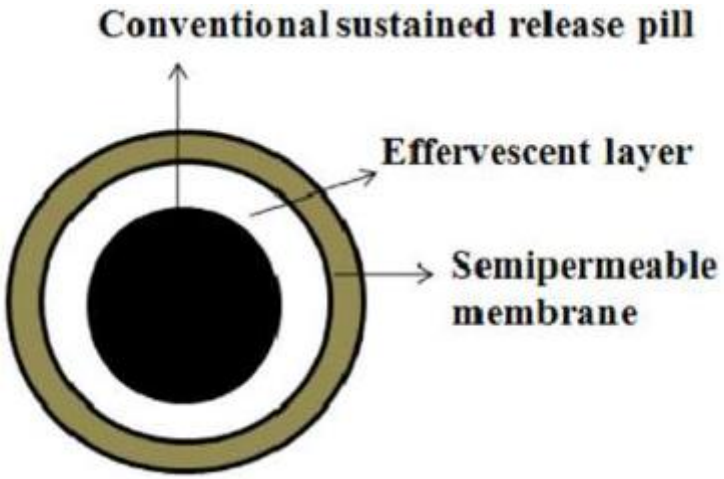

Figure 3: Effervescent/Gas-Generating Systems

These systems are often categorized as follows:

i) **Single Layer Floating Tablet or Hydrodynamically Balanced System (HBS)**

This system, illustrated in Figure 5, involves incorporating CO2-generating agents into the matrix tablet alongside the drug. Due to the lower bulk density of this system compared to gastric fluids, the tablet remains buoyant in the stomach for extended periods, independent of the gastric emptying rate. The drug is gradually released from the floating tablet at a controlled rate. Once the drug is fully released, the remaining tablet is expelled from the stomach. This mechanism enhances the gastric residence time (GRT) and stabilizes plasma drug concentration levels

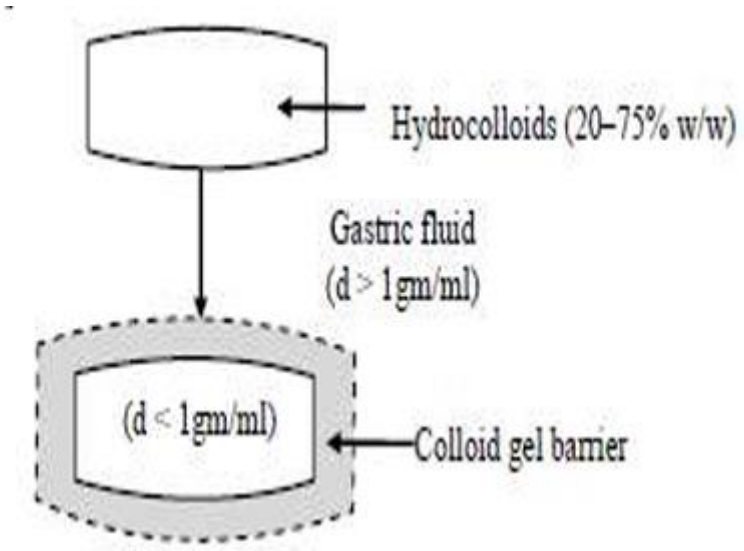

Figure 4: Single Layer Floating Tablet

Bilayer Floating Tablet

This formulation consists of a tablet with two distinct layers: one for immediate release and the other for sustained release.

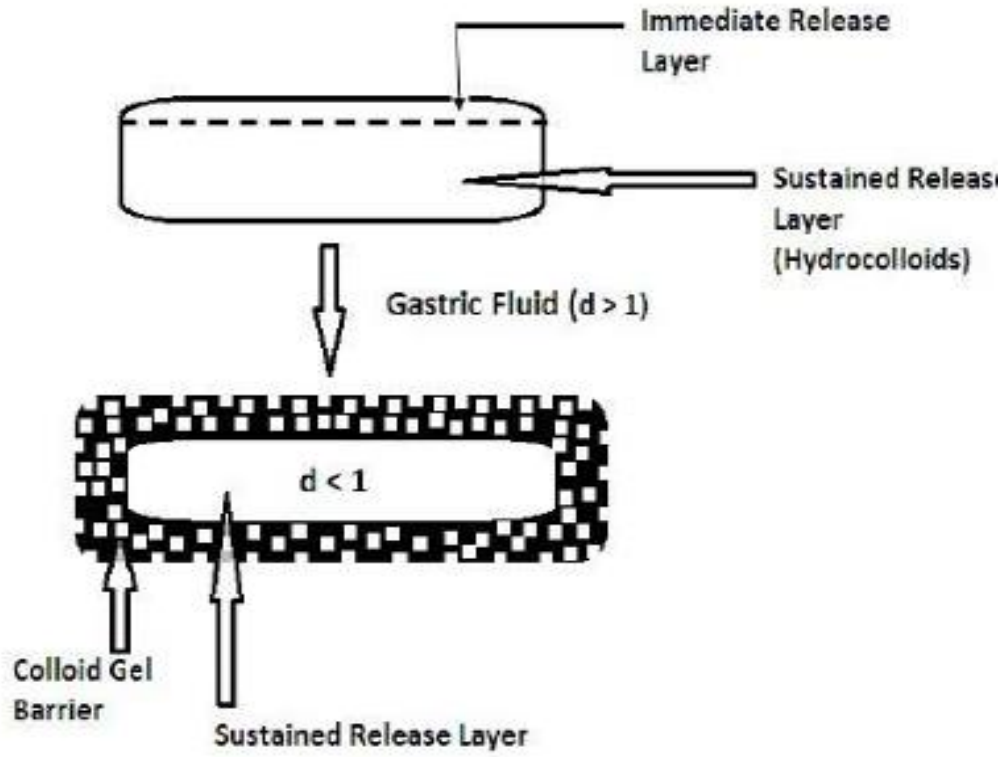

Figure 5: Bilayer Layer Floating Tablet

ii) Multiple Unit Floating Pill

This type of system features sustained-release pills encased in two layers. The inner layer has effervescent agents, while the outer layer is made of a swellable membrane. Upon contact with the dissolution medium at body temperature, the system sinks and forms swollen pills

that float due to their reduced density. This low-density results from CO2 generation and entrapment within the system.

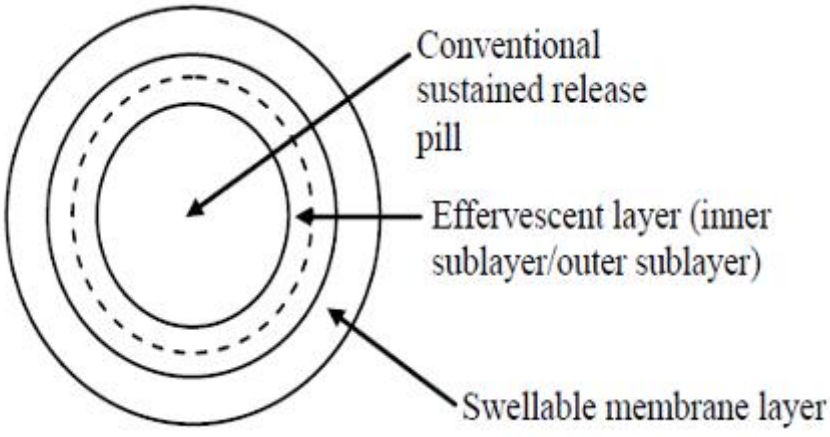

Figure 6: Multiple Unit Floating Pill

iv) Ion Exchange Resin System

This multiple-unit oral dosage system extends the gastric residence time of the medication. It includes drug-resin complex beads that are charged with bicarbonate ions and covered with a hydrophobic polymer. When the beads enter the stomach, chloride ions are swapped with bicarbonate and drug ions, producing CO2 gas that is captured by the polymer coating, causing the beads to float.

v)Volatile Liquid-Containing System

To enhance the gastric retention time, this system contains an inflatable chamber filled with a liquid (e.g., ether, cyclopentane) that vaporizes at body temperature, causing the chamber to expand in the stomach. It may also feature a bioerodible plug made of materials like polyvinyl alcohol or polyethylene, which dissolves over time to release gas from the chamber. This results in the chamber collapsing after a set period, allowing the system to exit the stomach.

vi)Intragastric Floating Gastrointestinal Drug Delivery System

This system (see Figure 8) includes a flotation chamber designed to keep the system buoyant in the stomach. The chamber is either vacuum-sealed or filled with air or a safe gas, and the drug is contained within microporous compartment.

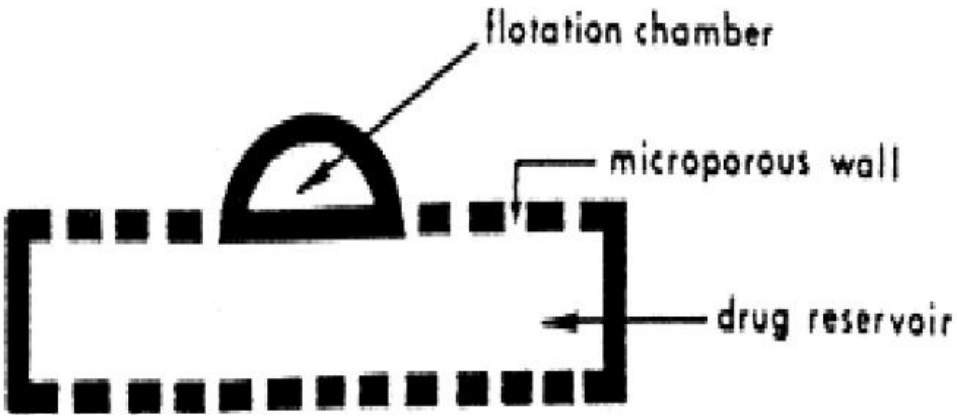

Figure 7: Intragastric Floating Gastrointestinal Drug Delivery System

vii) Inflatable Gastrointestinal Delivery System

This system incorporates an inflatable chamber filled with liquid ether that vaporizes at body temperature, leading to chamber inflation in the stomach (see Figure 9). It is constructed by combining an inflatable chamber with a drug a reservoir (which may be a drug-loaded polymeric matrix) and encasing it in a gelatin capsule. Upon oral administration, the capsule dissolves, releasing both the drug reservoir and the inflatable chamber, which then inflates and retains the drug in the gastric fluid.

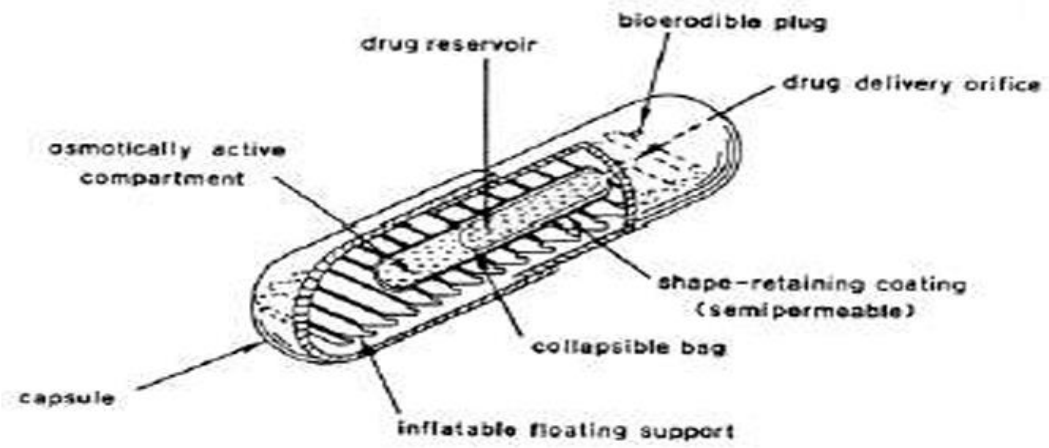

Figure 8: Inflatable Gastrointestinal Delivery System

1.7 FACTORS INFLUENCING GASTRIC RETENTION TIME OF DOSAGE FORMS

1. **Impact of Dosage Form Density**

   The density of a dosage form significantly influences its gastric emptying rate and its positioning within the stomach. Dosage forms with a density lower than that of the gastric contents tend to float to the upper part of the stomach, while those with a higher density settle at the bottom. This positional difference can affect the system's proximity to the pylorus. For a dosage form to demonstrate floating properties, its density needs to be less than 1.0 gm/cm^3.

2. **Influence of Shape and Size**

   The shape and size of dosage forms play a crucial role in the design of indigestible single-unit solid dosage forms. The gastric residence time of non-floating dosage forms varies widely and is significantly influenced by their size, which can range from large to small units. Generally, larger dosage forms tend to have longer gastric residence times. The retention time of dosage forms, referred to as Gastric Retention Time (GRT), can be influenced by the size of the dosage form.

   Larger dosage forms may take longer to pass through the pyloric antrum into the intestines. Dosage forms with diameters greater than 7.5 mm tend to have improved gastric residence time compared to those with diameters around 9.9 mm. Shapes such as rings and tetrahedrons generally offer better gastric retention compared to other configurations.

3. **Food intake and its nature**

   The presence and nature of food intake significantly impact the GRT of dosage forms. Factors like food viscosity, volume, caloric content, and feeding frequency can affect how long a dosage form remains in the stomach. Typically, having food in the gastrointestinal tract enhances the GRT of dosage forms, which can lead to improved drug absorption by extending the time the drug spends at the absorption site. Additionally, higher acidity and caloric value of food can slow gastric emptying time, further enhancing the retention of dosage forms.

4. **Effect of gender, posture and age**

   Differences in gastric emptying rates are also observed between genders and age groups. Generally, females experience slower gastric emptying compared to males. Posture does not significantly impact GRT when comparing upright, ambulatory, and supine states. However, elderly individuals tend to have slower gastric emptying rates.

1.8 APPLICATIONS

The following are applications of Gastroprotective Drug Delivery Systems (GRDDS):

1. **Enhanced Bioavailability**

   Gastroprotective dosage forms (GRDF) such as those containing riboflavin show improved bioavailability compared to non-GRDF polymeric formulations. Various processes related to drug absorption and gastrointestinal transit act together to affect the drug absorption rate.

2. **Sustained Drug Frequency of Dosing Delivery/Reduced**

   For drugs with a short biological half-life, sustained and slow release from GRDF improves pharmacokinetic profiles and reduces dosing frequency. This enhances patient compliance and improves overall therapy.

3. **Targeted Therapy for Local Ailments in the Upper GIT**

   Prolonged and sustained drug administration from GRDF can provide targeted therapy to the stomach and small intestine. This ensures therapeutic drug concentrations locally while maintaining minimal systemic concentrations post-absorption and distribution.

4. **Reduced Concentration Fluctuations of Drug**

   Continuous drug intake following GRDF administration maintains blood-drug concentrations within a narrower range compared to immediate-release forms. This reduces fluctuations in drug effects and minimizes adverse effects caused by higher concentrations.

5. **Site-Specific Drug Delivery**

   For drugs with limited absorption sites in the upper small intestine, a floating dosage form can be used. Controlled and slow drug release to the stomach achieves local therapeutic levels and limits systemic exposure. This approach reduces side effects in the bloodstream and decreases dosing frequency due to prolonged gastric retention.

1.9 Microspheres are small, free-flowing, spherical particles with a size range typically between **1–1000 µm**, made from **natural or synthetic polymers**, used mainly as **controlled and targeted drug delivery systems**.

Types of Microspheres

1. **Bio adhesive microspheres** – adhere to mucosal surfaces (e.g., buccal, nasal, ocular).
2. **Biodegradable microspheres** – prepared using polymers like **PLGA, chitosan, gelatin**.
3. **Magnetic microspheres** – targeted delivery using an external magnetic field.
4. **Floating microspheres** – gastro-retentive systems for prolonged gastric residence.

5. **Radioactive microspheres** – used in cancer therapy (e.g., liver tumours).

Materials Used

Natural polymers: Chitosan, alginate, gelatin, albumin

Synthetic polymers: PLGA, PLA, PMMA, ethyl cellulose

Methods of Preparation

1. Solvent evaporation
2. Emulsion–solvent extraction
3. Spray drying
4. Ionic gelation
5. Phase separation (coacervation)
6. Single & double emulsion techniques

Characterization of Microspheres

- Particle size & morphology: Optical microscopy, SEM
- Entrapment efficiency (%)
- Drug loading
- Surface charge (zeta potential)
- In-vitro drug release studies
- **FT-IR, DSC, XRD** (drug–polymer interaction)

Stability studies

Advantages

- Controlled and sustained drug release
- Reduced dosing frequency
- Improved bioavailability
- Targeted drug delivery
- Reduced side effects

Limitations

- High production cost
- Use of organic solvents
- Scale-up difficulties
- Possible burst release

Applications

- **Cancer therapy**
- **Antibiotics & antifungals**
- **Vaccines**
- **Hormones & proteins**

- **Ocular and nasal delivery**

CHAPTER 2

LITERATURE REVIEW

Singh et al.2018 dealt with current mechanical degrees of progress of FDDS including approved development frameworks and propelled things, and their focal centres and future potential for oral controlled solution transport was assessed.

Dave et al.2018 dealt with gastroprotective pharmaceutical improvement procedure of ranitidine hydrochloride. Guar gum, xanthan gum, and hydroxypropyl methylcellulose were looked into for gel-forming properties. Sodium bicarbonate was entwined as gas-creation administrators. The effects of citrus centre and stearic perilous on cure release profile and skimming properties were analysed. These studies demonstrate that best conceivable kind disposition between release rate enhancer and release rate retardant can make pharmaceutical isolating profile like speculative disintegrating profile.

Soppimath et al.2019 tended to quickly physiology of gastric discharging framework concerning floating arrangement development structures. As of late, multiarticulate drug-development frameworks are utilized as bit of oral transport of solutions. One of methods toward this objective is to build up drifting microspheres to broaden gastric bolster time.

Baumgartner et al.2019 prepared floating grid tablets with high measurements of openly dissolvable drugs. Tablets containing HPMC, drug and diverse added substances are packed. Tablet piece and mechanical quality have more noteworthy impact on floating properties and medication discharge. With consolidation of gas creating specialists, other than ideal floating time of 30 seconds and span of gliding > 8 hr, medication discharge was additionally expanded.

Shimpi et al.2020 prepare Gelucire43/01 purpose of outline multi-unit drifting frameworks of particularly water-dissolvable medication diltiazem HCl. Pretty just around 65% to 80% arrangement was released over 6 hours with beginning vivacious release from surface. Surface topography, HSPM, DSC examination of made examples exhibited stage change of Gelucire. The stage change in like way recognized first extension in game plan release. Considering everything, hydrophobic lipid, Gelucire 43/01, can be considered as genuine conveyor for structure of multi-unit floating remedy advancement diagram of by and large water-dissolvable solutions, for event, diltiazem HCl.

Stochwell et al. 2020 defined and assessed floating gel framework. Lightness was accomplished via carbon dioxide gas and its resulting entanglement into gel system. Sodium alginate, which experiences gelation in acidic conditions and in vicinity of calcium, was utilized. It was assessed in vitro as managed discharge floating gel framework.

Igani et al.2020 planned measurements structure with particular density under one as twofold layer-maintained discharge packed hydrophilic grid to accomplish reproducible floatation of tablet. Carbon dioxide was caught into gelled hydrocolloids. The gastric maintenance of HBS measurement structure was discovered to be essentially more than that of non-floating dose structure.

Sheth et al. 2021 made regulated discharge hydrodynamically adjusted holders which, upon contact with gastric liquid got and kept up mass thickness of under one and stayed light in liquid and remained so until generously large portion of dynamic fixings are discharged. The percent Chlordiazepoxide discharge from cases into reflected gastric liquid (pH 1.2) following 1,2,3.7 hours were 39,61, 100 % only.

Sangekar et al. 2021 researched impact of sustenance and particular gravity on gastric upkeep time of skimming and non-floating tablet purposes of enthusiasm utilizing gama scintigraphy as bit of people. No affiliation was found between gastric home time and particular gravity of estimation structure.

Nakamichi et al.2021 coordinated floating estimation structure made out of nicardipine hydrochloride (NH) and hydroxypropyl methylcellulose acidic ruinous determination succinate (enteric polymer) was readied utilizing twin-screw extruder. By fulfilling position of high-weight sink fragments energetic region of kick dish outlet, and by controlling barrel temperature, he found himself organized to set up puffed estimation structure with little and uniform pores. It was found that porosity and pore purge transversely over could be controlled by fluctuating measure of calcium phosphate dihydrate. In shaking test, puffed estimation's structure was found to have surprising skimming point of confinement and mechanical quality in hurting system (JP First Fluid, pH 1.2). The separating profile of NH was controlled by measure of wheat starch. In separating test utilizing JP Second Fluid (pH 6.8), splendid breaking down of NH and loss of delicacy were viewed.

Fabregas et al. 2022 planned long-acting acid neutralizer pieces with gliding properties. It contained substance solvent in water at impartial pH. The plan brought about gastric regularization for epigastric agony and queasiness.

Mazer et al.2022 watched intragastric conduct and ingestion active of ordinary and gliding changed discharge container of iseradipine under fasted and encouraged conditions. Vicinity or unlucky deficiency of nourishment as opposed to lightness was main determinant of gastric living arrangement time of case. The medication discharge and retention were all more by intragastric association with lipid period of dinner.

Inouye et al.2022 arranged light supported discharge granules of Prednisolone utilizing "H" or "L" evaluations of chitosan. The granules were instantly light in both acidic and nonpartisan liquids. Supported medication assimilation from these arrangements was seen in beagle canines.

Kawashima et al.2023 coordinated void microspheres (microballons) stacked with pharmaceutical in their outside polymer shell by novel emulsion dissolvable dispersing strategy. The ethanol: dichloromethane arrangement of pharmaceutical (ibuprofen) what's more, acrylic polymer was poured that were thermally controlled at 40C. The gas stage made in scattered polymer globule by spread of dichloromethane confined and inside pit in microballons of polymer. The flowability and packability of resultant microballons were

portrayed by and large property and arrangement discharge rate were doubtlessly lessened relying on polymer fixation at pH 6.8.

Franz et al. 2023 arranged supported discharge bilayer light coasting measurement's structure containing Misoprostol, one layer is medication discharge layer and other is light or floating layer. The measurements' structure gave broadened gastric maintenance so that whole medication is discharged in stomach more than expanded period. The gliding layer incorporated polymer i.e., which has property of gelling and which on contact with gastric liquids, hydrates and structures thick boundary. This measurement's structure is light on gastric liquid for up to more or less 13 hours. Desai et al.16 had added to no compressed controlled release skimming tablets of Theophylline using agar and mineral oil. Tablets were made by scrambling medication/mineral oil mix in warm agar methodology, resultant mix was filled tablet molds which on cooling and air-draying surrounded floatable CR tablets. The light mineral oil was boss for floating property of tablet since for the most part high measure of course of action (75%) and low measure of agar (2%) were used into arrangement.

Du Quing et al.2023 figured numerous units floating managed discharge granules of aminophylline and assessed. They have reported that expanding amount of cetyl liquor and octadecanol could builds granules gliding capacity in vitro. Increased convergence of ethyl cellulose postponed medication discharge rate

Whitehead et al.2024 prepared gliding alginate globules from alginate arrangement containing either broke up or suspending Amoxycillin. Medication discharge study demonstrates that globules arranged with medication in arrangement gave some maintained discharge characters and these were enhanced by expansion of amylase. The dots held their lightness were amylase and amoxicillin were consolidated.

Abubakr et al.2024 arranged captopril floating and/or bio cement tablets utilizing two evaluations of HPMC (400 and 15000 cps.). He looked at two traditional tablets; discharge from coasting tablets was clearly drawn out. A 24 hours-controlled discharge measurement structure for captopril was accomplished. Tablet hardness was discovered deciding element with respect to lightness of tablets

Shoufeng et al.2024 addresses bona fide trial setup and information examination utilizing reaction surface framework. A focal composite box-Wilson game plan for controlled passage of calcium was utilized with three definition variables like HPMC stacking, Citric ruinous stacking and magnesium stearate stacking. Supported discharge drifting development of calcium with augmented bioavailability was master.

Farouk et al.2024 built up programmable controlled discharge medication transport framework. The contraption as non-edible oral case was design to used regularly worked geometric watch that keeps gadget skimming in stomach and keep it from encountering straggling leftovers of GIT. Different consistency appraisals of HPMC were utilized as model separating metrics. Zero requesting discharge could be kept up for period taking off between 5 to 20 days going before geometric impediment was activated off.

Talwar et al.2025 arranged gastroprotective oral medication conveyance framework basically included very permeable lattice having medication, gas creating segment, sugar, discharge controlling specialists and alternatively spheronising operators. The pharmaceutical detailing either as pellets, globules, granules or cases

was held in stomach while specifically conveying medication at gastric level or upper piece of small digestive tract for developed time of time.

Joseph et al.2025 made drifting sort estimations structure (FDF) of piroxicam in void polycarbonate (PC) microspheres fit for coasting on reenacted gastric and intestinal fluids was composed by dissolvable vanishing system. Joining efficiencies of more than 95% were expert for epitome. In vitro area of piroxicam from PC microspheres into imitated gastric fluid at 37 C exhibited no principal burst impact. The whole released connected with time for around 8 h after which near to no was found to be released up to 24 h. In intestinal fluid, release was snappier and enthusiastic and at high solution payloads, aggregate release came to more than 90% in around 8 h. In vivo assessment of particular estimations sorts of piroxicam, for event, free pharmaceutical, arrangement exemplified microspheres and microspheres nearby stacking estimation of free cure in rabbits showed assorted fixing in plasma centre time twist proposing enterohepatic transport of medicaments.

CHAPTER 3

AIM AND OBJECTIVE

3.1 Ranitidine HCl

Class: H_2 receptor antagonist (reduces stomach acid).

Why used in floating drug tablets:

Ranitidine is **often used as a model drug** in research on floating (gastroprotective) tablets, **not** as an excipient.

Ranitidine has a **short half-life (2–3 hours)**.

It is **absorbed mainly in the stomach and upper small intestine**.

Floating drug systems help the tablet **stay longer in the stomach**, improving **bioavailability** and **therapeutic effect**.

3.2. Glipizide

Class: Oral antidiabetic (sulfonylurea).

Why used in floating drug tablets:

Glipizide has a **narrow absorption window** (absorbed mainly in the upper part of the GI tract).

It has a **short biological half-life (2–4 hours)**.

Floating or gastroprotective formulations help to **extend its gastric residence time**, maintaining therapeutic levels longer and reducing dosing frequency.

It's used because **sustained, controlled release in the stomach** improves its pharmacokinetic profile.

1. **Preformulation study**
2. **Drug excipient interaction study**
3. **Preparation of floating microspheres**
4. **Evaluation of powder blend**
5. **Evaluation of microspheres**
6. **In Vitro dissolution studies**

7. **In vitro buoyancy studies**
8. **Kinetic modelling of drug release**

CHAPTER 4

MATERIALS AND METHODS

Table 4.1: Formulation table of Ranitidine HCL.

Ingredient	Role	Quantity (mg)			
		F1	F2	F3	F4
Ranitidine HCl	API	150	150	150	150
Ethyl Cellulose	Rate-controlling polymer	450	455	460	465
Polyvinyl Alcohol (PVA)	Emulsifying agent	100 (1% w/v aqueous phase)	100	100	100
Dichloromethane	Organic solvent	q.s.	q. s	q. s	q. s
Distilled Water	Continuous phase	q.s.	q. s	. s	q. s

Table 4.2: Formulation table of Glipizide.

Ingredient	Role	Quantity (mg) F1	F2	F3	F4
Glipizide	API	50	50	50	50
PLGA (50:50)	Biodegradable polymer	150	155	160	165
Polyvinyl Alcohol (PVA)	Stabilizer	100 (1% w/v aqueous phase)	100	100	100
Dichloromethane / Acetone	Organic solvent	q.s.	q. s	q. s	q. s
Distilled Water	Continuous phase	q.s.	q. s	q. s	q. s

4.2. Preformulation study

4.2.1 Organoleptic Properties

Table 4.3: Organoleptic Properties of Ranitidine HCl and Glipizide

Parameter	Ranitidine HCl	Glipizide
Colour	White to pale yellow	White
Odor	Odourless	Odourless
Taste	Bitter	Slightly bitter
Appearance	Crystalline powder	Crystalline powder

4.2.2: Solubility Analysis

Procedure: Excess drug was added to 10 mL solvent, shaken for 24 h at 25 °C, filtered, and analysed spectrophotometrically.

Table 4.4: Solubility analysis of Ranitidine HCl and Glipizide

Solvent	Ranitidine HCl	Glipizide
Water	Soluble	Slightly soluble
Methanol	Soluble	Soluble
Ethanol	Sparingly soluble	Soluble
Dichloromethane	Insoluble	Slightly soluble
Phosphate buffer pH 7.4	Soluble	Slightly soluble

Inference

Ranitidine HCl → Hydrophilic drug and Glipizide → Poorly water-soluble drug.

4.2.3: Determination of Melting Point

Procedure: Capillary tube method using melting point apparatus.

Table 4.5: Melting point of Ranitidine HCl and Glipizide.

Drug	Melting Point
Ranitidine HCl	134–140 °C
Glipizide	208–210 °C

4.2.4 Calibration curve of Ranitidine HCL

According to Beer–Lambert Law, absorbance is directly proportional to concentration.

A = mC + b

A = Absorbance

C = Concentration of Ranitidine HCl (µg/mL)

m = Slope of calibration curve

b = Intercept

λ max ≈ 313 nm in UV spectrophotometry

Linearity range: 2–20 µg/mL

Correlation coefficient (R^2): ≈ 0·999

Procedure

Prepare standard solutions of **Ranitidine HCl** (2–20 µg/mL).

Measure absorbance at **313 nm**.

Plot **Concentration vs Absorbance**.

Perform **linear regression** to obtain **A = mC + b**.

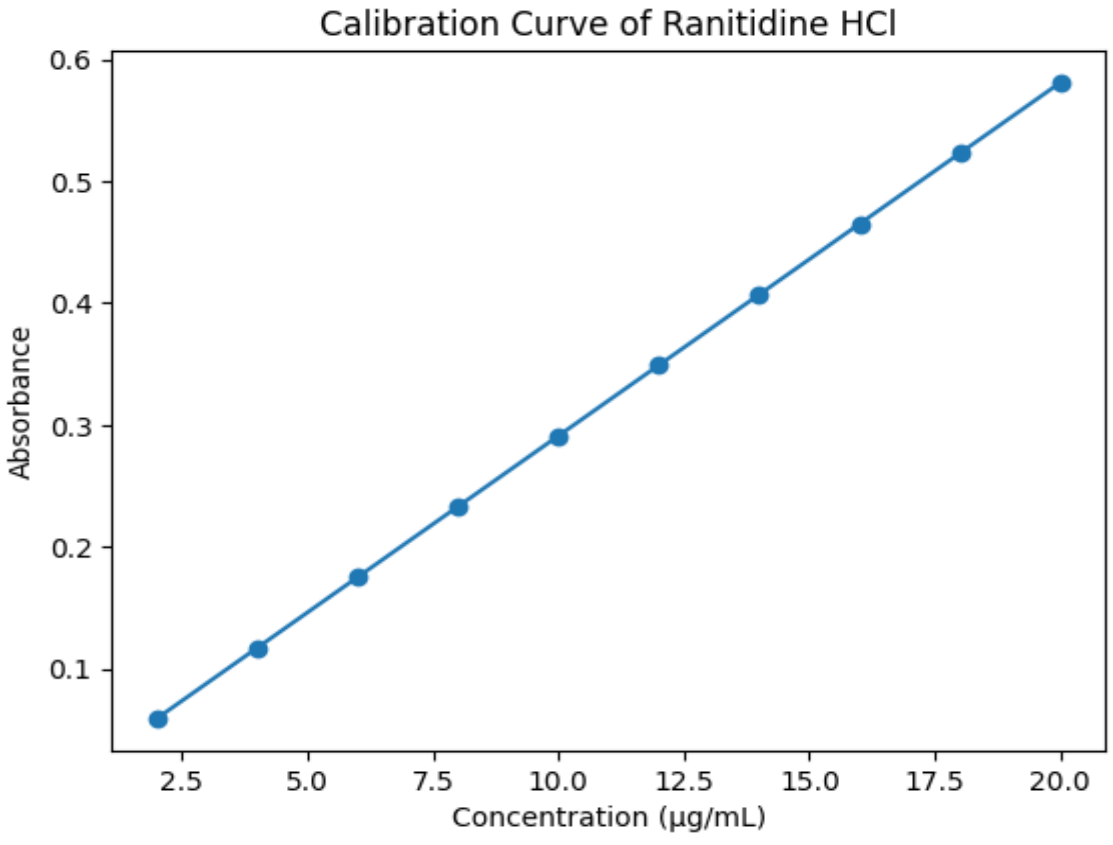

Figure 4.1: Calibration graph for Ranitidine Hydrochloride

From the graph, the regression equation is:

$$A = 0.029C + 0.001$$

Where:

A = Absorbance

C = Concentration (µg/mL)

0.029 = Slope

0.001 = Intercept

Table 4.6: Calibration Table of Ranitidine HCL.

S.NO	Concentration(µg/ml)	Absorbance(nm)
1.	2	0.059
2.	4	0.117
3.	6	0.175
4.	8	0.233
5.	10	0.291
6.	12	0.349
7.	14	0.407
8.	16	0.465
9.	18	0.523
10.	20	0.581

4.2.5 Calibration curve of Glipizide

According to **Beer–Lambert Law**, absorbance is directly proportional to concentration.

$$A = 0.041C + 0.002$$

Where:

A = Absorbance

C = Concentration of Glipizide (µg/mL)

0.041 = Slope

0.002 = Intercept

λmax: ~275 nm

Linearity range: 2–20 µg/mL

Correlation coefficient (R^2): ≈ 0·999

Procedure

Prepare standard solutions of **Glipizide** (2–20 µg/mL)

Measure absorbance at **275 nm**.

Plot **Concentration vs Absorbance**.

Perform **linear regression** to obtain **A = mC + b**.

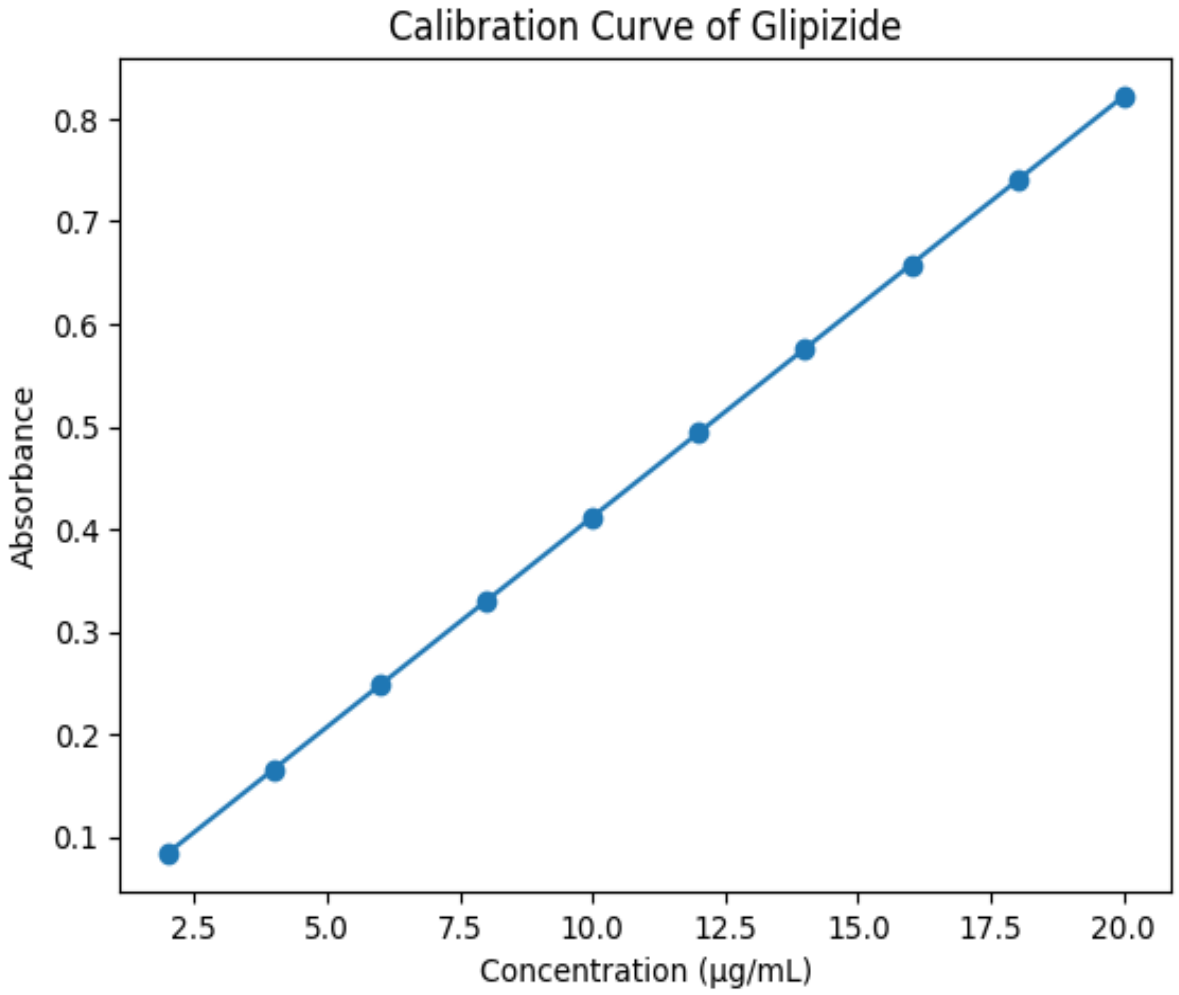

Figure 4.2: Calibration graph for Glipizide

Table 4.7: Calibration Table of Glipizide HCL.

S.NO	Concentration(µg/ml)	Absorbance(nm)
1.	2	0.084
2.	4	0.166
3.	6	0.248
4.	8	0.330
5.	10	0.412
6.	12	0.494
7.	14	0.576
8.	16	0.658
9.	18	0.740
10.	20	0.822

4.2.6 IR OF Ranitidine HCL

Table 4.8: IR data of Ranitidine HCl

S.NO	**Wave number**	**Functional group**
1.	3400–3300	**N–H stretching**
2.	3050	**Aromatic C–H stretch**
3.	2950	**Aliphatic C–H stretch**
4.	1640	**C=N stretching**
5.	1580	**C=C stretching**
6.	1460	**CH_2 bending**
7.	1350	**C–N stretching**
8.	1240	**C–N / C–O stretch**
9.	1050	**C–N stretching**
10.	820	**Aromatic C–H bending**

The IR spectrum confirms the presence of:

- Secondary amine (–NH–)
- Imine group (C=N)
- Aromatic/heterocyclic ring
- Aliphatic chains
- C–N functional groups

These peaks help in confirming the identity and structural integrity of ranitidine during pharmaceutical analysis.

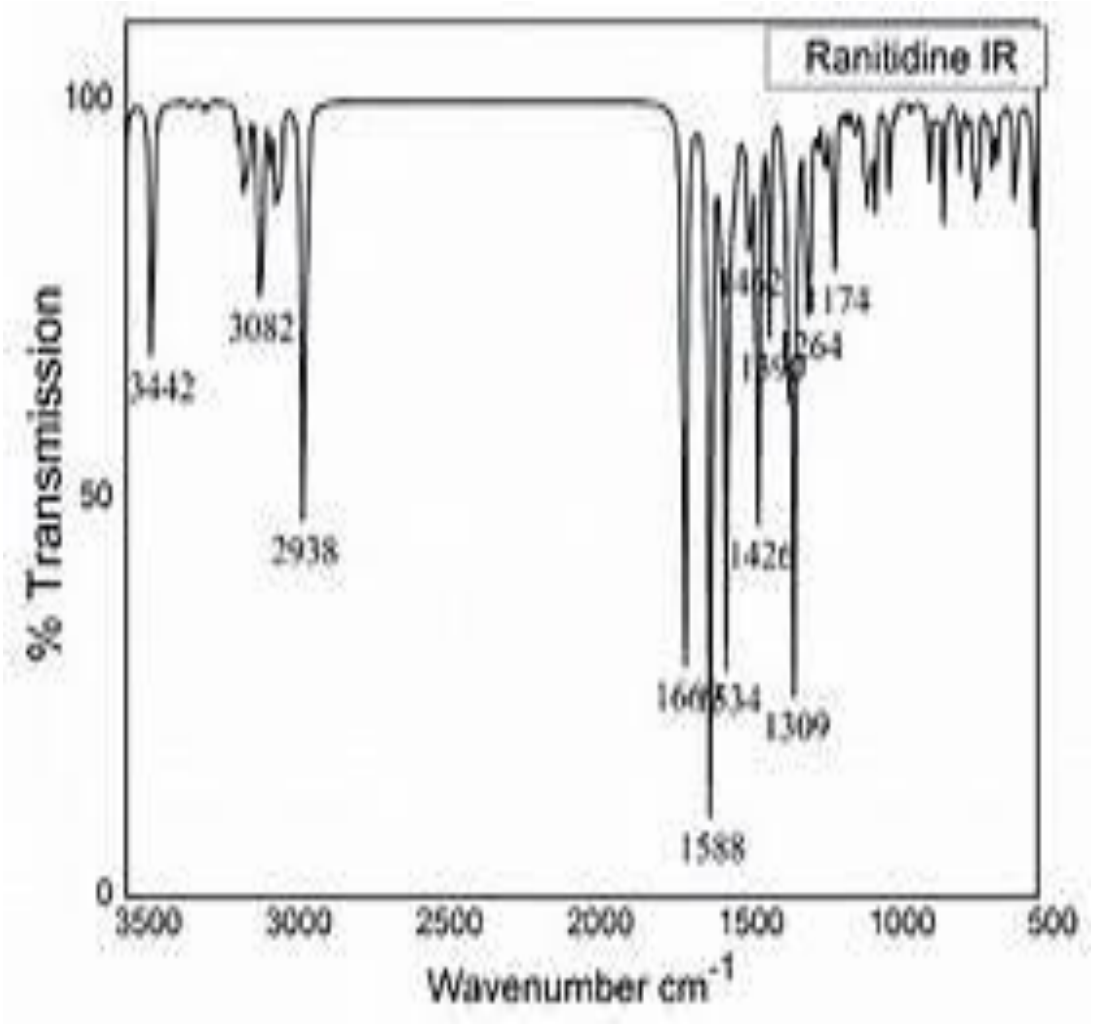

Figure 4.3: IR of Ranitidine HCL

4.2.7 IR of Glipizide

Table 4.9: IR data of Glipizide

S.NO	Wave number	Functional group
1.	3350–3200	**N–H stretching**
2.	2960	**C–H stretching**
3.	1680	**C=O stretching**
4.	1600	**C=C stretching**
5.	1340	**S=O stretching (asymmetric)**
6.	1160	**S=O stretching (symmetric)**
7.	1090	**C–N stretching**
8.	830	**C–H bending**
9.	750	**Aromatic ring bending**

The IR spectrum confirms the presence of:

- Sulfonylurea group (–SO_2–NH–CO–NH–)
- Carbonyl group (C=O)
- Sulfonyl group (S=O)
- Aromatic benzene ring
- Aliphatic C–H chains

These peaks are commonly used for identification and characterization of glipizide during pharmaceutical analysis (FTIR studies).

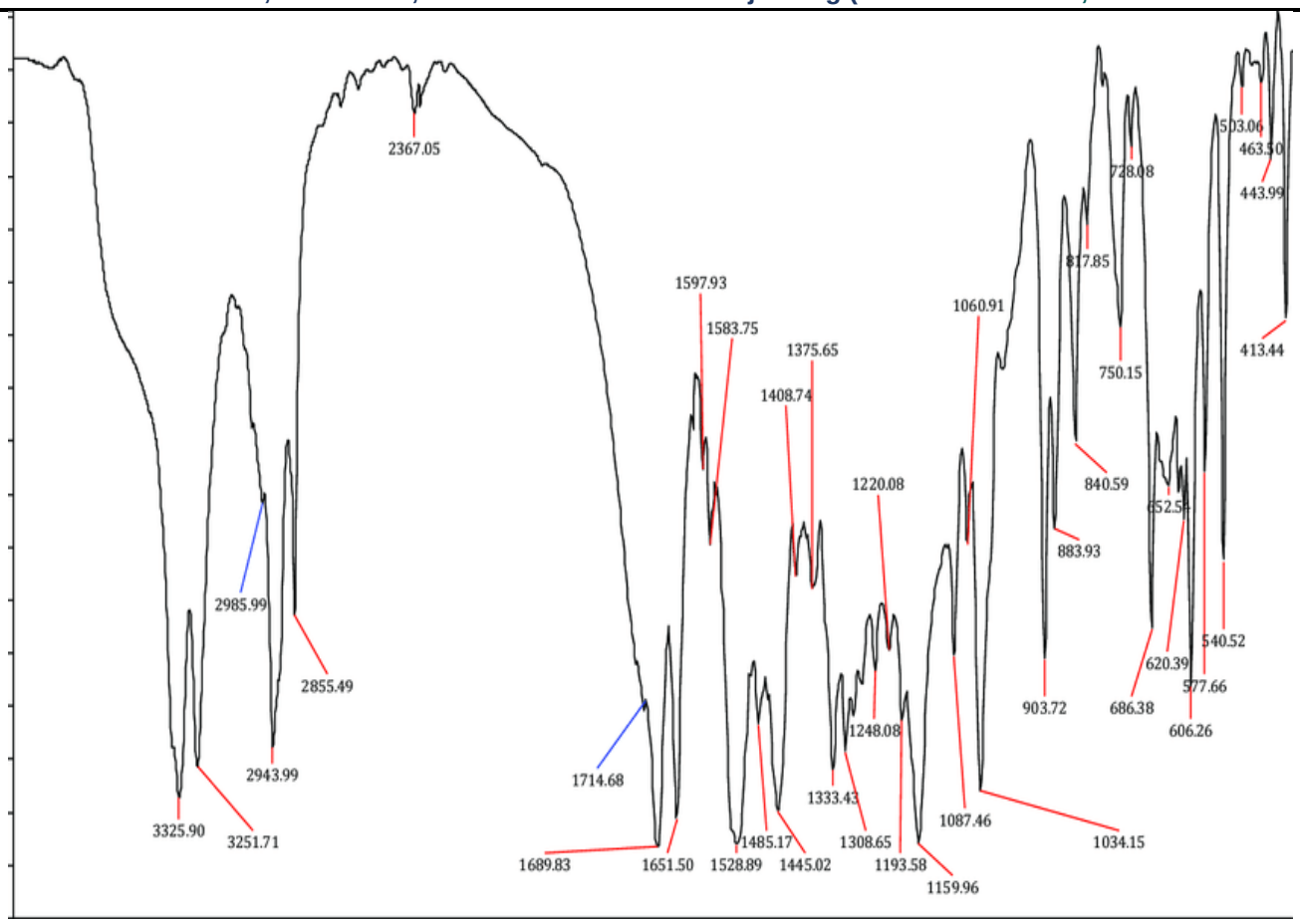

Figure 4.4: IR of Glipizide

CHAPTER 5

RESULT AND DISUSSION

5.1 Materials Required

1. Drug: Ranitidine HCl / Glipizide
2. Polymer: **Ethyl cellulose / HPMC / Eudragit RS100**
3. Solvent: **Ethanol or Dichloromethane (DCM)**
4. Surfactant: **Polyvinyl alcohol (PVA)**
5. Distilled water
6. Magnetic stirrer
7. Beaker and mechanical stirrer
8. Whatman filter paper
9. Oven or desiccator

5.2 Procedure

Preparation of Floating Microspheres of Ranitidine hydrochloride and Glipizide by the Solvent Evaporation Method

Step 1: Preparation of Organic Phase

1. Accurately weigh the **drug (Ranitidine HCl or Glipizide)**.
2. Dissolve the drug in a mixture of **ethanol and dichloromethane**.
3. Add the required amount of **polymer (ethyl cellulose or HPMC)** into the solution.
4. Stir the solution until a **clear polymer–drug solution** is obtained.

Step 2: Preparation of Aqueous Phase

1. Prepare **0.5–1% w/v Polyvinyl Alcohol (PVA)** solution in distilled water.
2. This acts as a **stabilizing agent** for microsphere formation.

Step 3: Emulsification

1. The **organic phase** is slowly added into the **aqueous PVA solution**.
2. Stir the mixture using a **mechanical stirrer at 800–1200 rpm**.
3. Continue stirring for **1–2 hours**.

During stirring:

- The solvent evaporates.
- Polymer solidifies.
- **Floating microspheres are formed.**

Step 4: Solvent Evaporation

1. Continue stirring until **complete evaporation of organic solvent** occurs.
2. Microspheres will form and **float due to hollow internal structure**.

Step 5: Collection of Microspheres

1. Separate microspheres by **filtration or decantation**.
2. Wash with **distilled water** to remove residual surfactant.

Step 6: Drying

1. Dry the microspheres in **hot air oven at 40–45°C for 12–24 hours**.
2. Store in a **desiccator** until further evaluation.

5.3 Micromeritic properties

Angle of repose: The angle of repose of different formulations was measured according to fixed funnel standing method (n = 3) θ = tan-1h / r where θ is the angle of repose, r is the radius, and h is the height.

Table 5.1: Angle of repose of Ranitidine HCl and Glipizide.

S.NO	FORMULATIONS	ANGLE OF REPOSE
1.	F1	32
2.	F2	22
3.	F3	24
4.	F4	36

5.4 Scanning electron microscopy (S.E.M) of Ranitidine HCL and Glipizide.

To determine the texture, particle size distribution, surface topography, and to examine the morphology of the sectioned or fractured surface S.E.M has been utilized. SEM is the most frequently used method to distinguish drug delivery systems and ease of operation. SEM studies were carried out by using a JEOL JSM T- 330A scanning microscope (Japan). Dry Ranitidine Hcl and Glipizide floating microspheres were placed on an electron microscope brass stub and coated within an ion sputter. The random scanning of the stub is used for talking the image of Ranitidine Hcl and Glipizide floating microspheres.

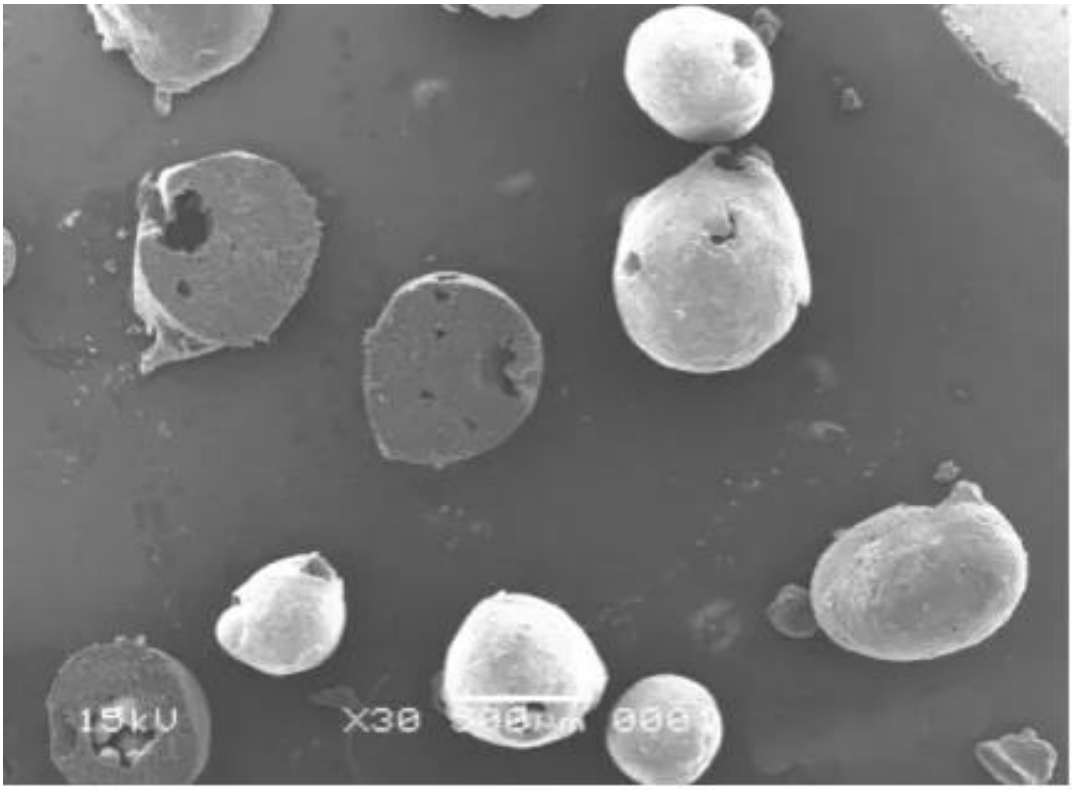

Figure 5.1: Scanning electron microscopy of Ranitidine HCl.

5.5 Particle size analysis

Determination of average particle size of Ranitidine HCl, floating microspheres was carried out by optical microscopy in which stage micrometre was retained. A small quantity of Ranitidine HCl floating microspheres was laid out on a clean glass slide and an average size of Ranitidine HCl and Glipizide floating microspheres was determined in each batch.

Table 5.2: Average diameter of Ranitidine HCL and Glipizide floating microspheres

S.NO	FORMULATION	AVERAGE PARTICLE SIZE (µm
1.	F1	74.43
2.	F2	82.78
3.	F3	57.10
4.	F4	70.12

5.6 Buoyancy percentage

1. Place microspheres in **0.1 N HCl (pH 1.2)** at **37°C**.
2. Record the **time taken for microspheres to rise to the surface**.

Result:

The polymer concentration increases the buoyancy time increases.

Table 5.3: Buoyancy % of Ranitidine and Glipizide floating microspheres.

S.NO	FORMULATION	% BUOYANCY
1.	F1	69.42
2.	F2	73.20
3.	F3	59.54
4.	F4	72.81

5.7 Percentage of Drug Entrapment Efficiency

Entrapment efficiency increases with an increase in polymer concentration. From the results, it can be inferred that there is a proper distribution of Ranitidine HCL in the microspheres and the deviation is within the acceptable limits. A maximum of 88.60% drug entrapment efficiency was obtained in the Ranitidine HCL floating microspheres which were prepared by using Ethyl cellulose and PLGA. A maximum of 82.22% drug entrapment efficiency was obtained in the Ranitidine HCL and Glipizide floating microspheres which were prepared by using Ethylcellulose. It was further observed that the drug entrapment was proportional to the Ranitidine HCL: polymer ratio and size of the Ranitidine HCl floating microspheres. By increasing the polymer concentration, the encapsulation efficiency was increased.

Table 5.4: % Buoyancy of Ranitidine HCl and Glipizide floating microspheres.

S.NO	FORMULATION	% BUOYANCY
1.	F1	69.42
2.	F2	73.20
3.	F3	59.54
4.	F4	72.81

Table 5.5: Drug entrapment efficiency % of Ranitidine HCl and Glipizide floating microspheres.

S.NO	FORMULATION	DRUG ENTRAPMENT EFFECIENCY
1.	F1	67%
2.	F2	78%
3.	F3	83%
4.	F4	69%

5.8 In-vitro dissolution studies of Ranitidine HCl and Glipizide Floating Microspheres

- **Procedure:** Accurately weigh floating microspheres equivalent to 150 mg of ranitidine HCl.
- Place the microspheres in the dissolution vessel containing 900 mL of 0.1 N HCl.
- Rotate the paddle at 50–100 rpm.
- Maintain the temperature at 37 ± 0.5°C throughout the experiment.
- Withdraw 5 mL sample at predetermined time intervals (0.5, 1, 2, 3, 4, 6, 8, 10, 12 hours).
- Replace with equal volume of fresh dissolution medium to maintain sink conditions.
- Filter the samples using Whatman filter paper.
- Measure absorbance using a UV-spectrophotometer at λmax ≈ 314 nm.
- Calculate the percentage cumulative drug release using the calibration curve.

Cumulative Drug Release (%) =Total amount of drug Amount of drug released×100

Table 5.6: Dissolution Data table of Ranitidine HCl and Glipizide floating microspheres.

S.NO	F3 TIME(HOUR)	% DRUG RELEASED
1.	0.5	12%
2.	1	28%
3.	2	43%
4.	4	51%
5.	6	59%
6.	8	67%
7.	10	73%
8.	12	82%

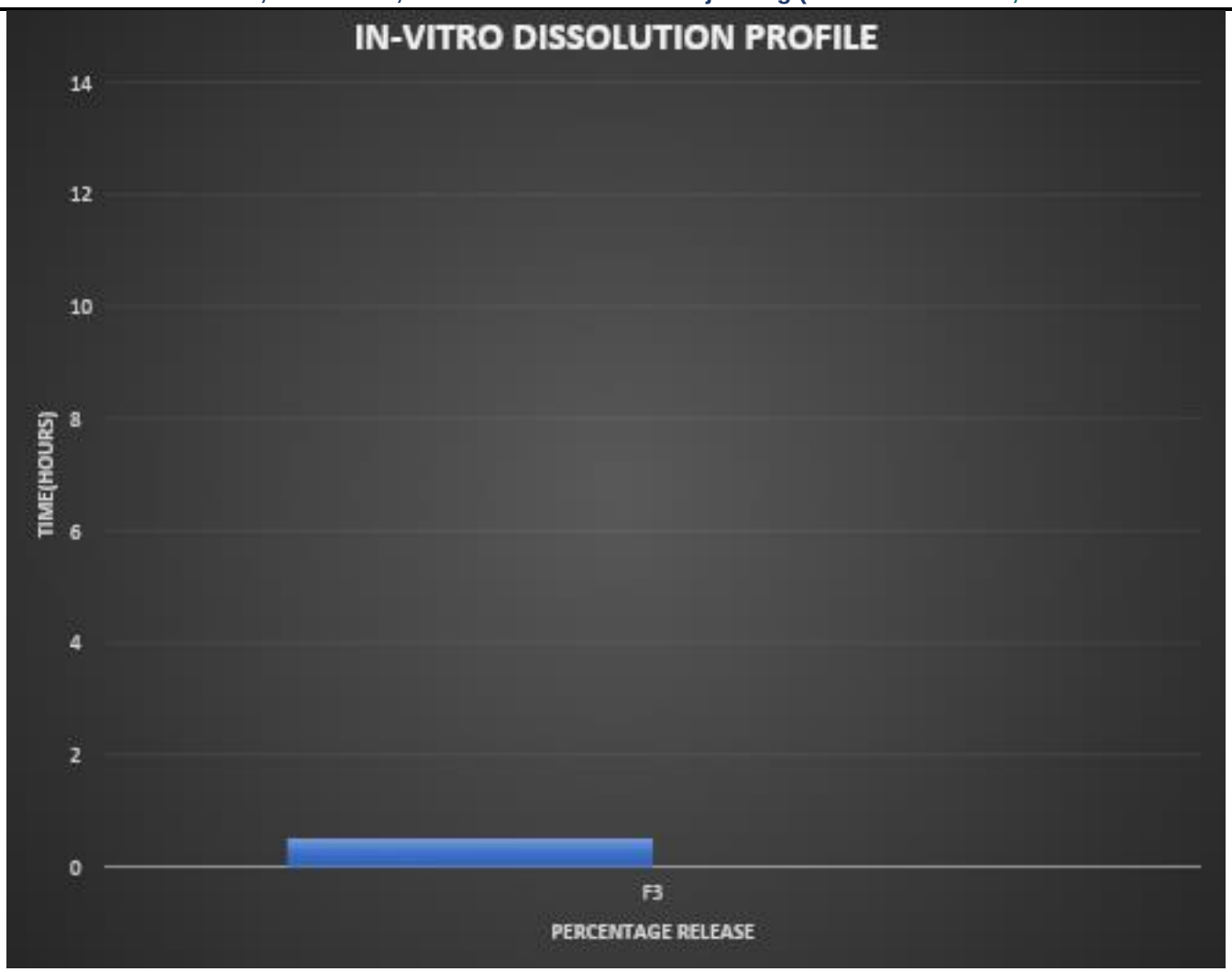

Figure 5.2: In-vitro Dissolution Profile of Ranitidine HCl and Glipizide floating microspheres (F3).

5.9 Kinetic modals for Ranitidine HCl and Glipizide Microspheres

For Ranitidine HCl microspheres and Glipizide microspheres, the drug release kinetics are usually analysed using standard mathematical models applied to dissolution data. The most common models used in microsphere studies are:

- **Zero-order kinetics**
- **First-order kinetics**
- **Higuchi diffusion model**
- **Korsmeyer–Peppas model**
- **Hixson–Crowell model**

These models help determine drug release mechanism (diffusion, erosion, or swelling). [OBJ]

Kinetic Models for Ranitidine HCl and Glipizide Microspheres

1. Zero-Order Kinetics

Zero-order kinetics describes a system where the drug release rate is constant and independent of drug concentration.

Equation

$Q_t = Q_0 + K_0 t$

Were

Q_t = amount of drug released at time t

Q0=Initial amount of drug

Ko=zero order rate constant

Graph: It shows graph between cumulative percentage drug release VS time.

Interpretation: Its straight line indicates control drug release.

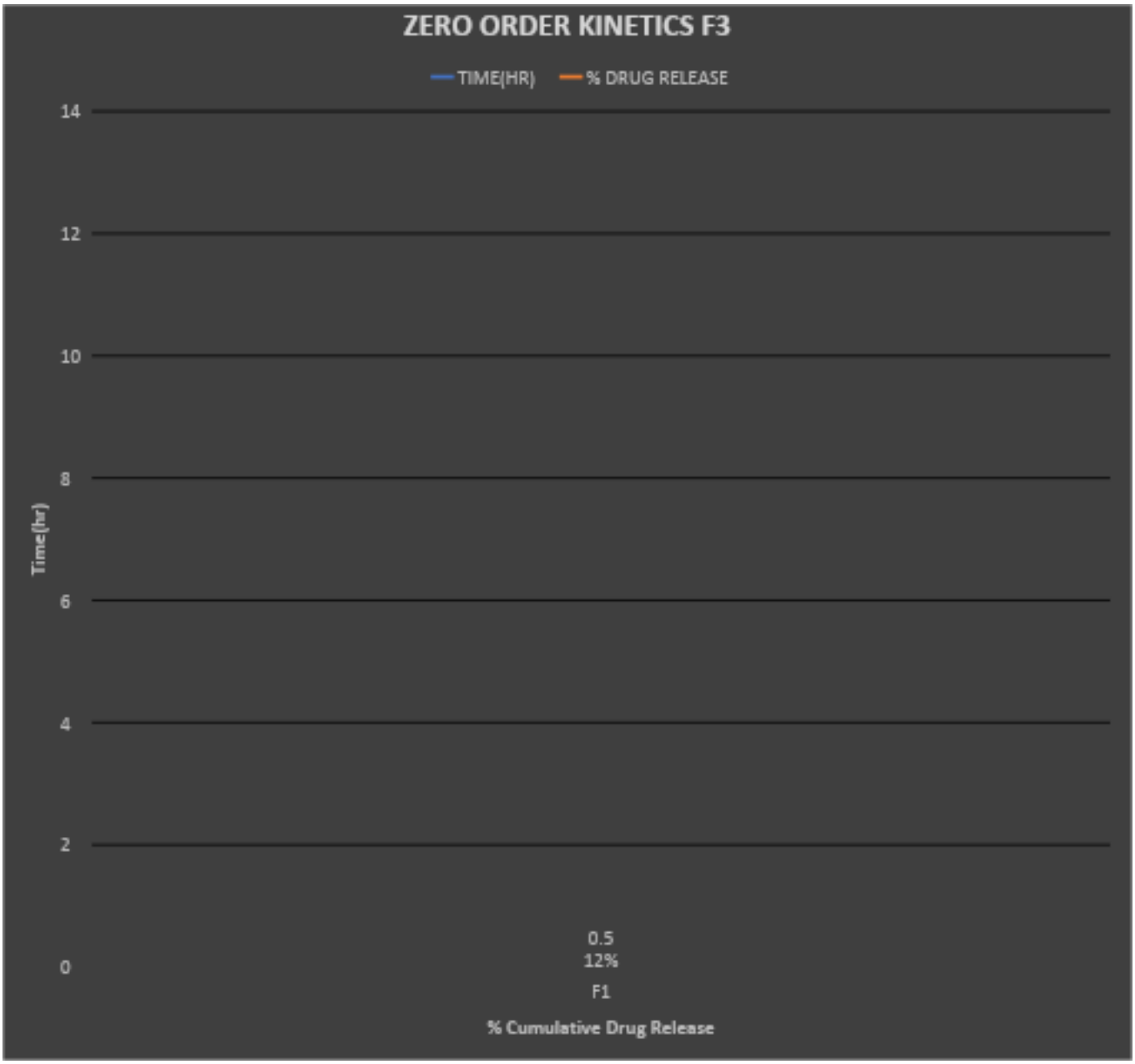

Figure 5.3: Zero order kinetics of F3

2. First-Order Kinetics

In first-order kinetics, drug release rate depends on the remaining drug concentration in the dosage form.

Equation

\Log (Q_0 - Q_t) = \log Q_0 - \frac {K_1 t} {2.303}

Were

K_1 = first-order rate constant

Graph: Log % drug remaining vs time

Interpretation: Release rate decreases with time

Table 5.7: First order release kinetics data

S.NO	TIME	% RELEASE(Q)	% REMAINING (100-Q)	LOG (100-Q)
1.	0.5	12	88	1.944
2.	1	28	72	1.857
3.	2	43	57	1.756
4.	4	51	49	1.690
5.	6	59	41	1.613
6.	8	67	33	1.519
7.	10	73	27	1.431
8.	12	82	18	1.255

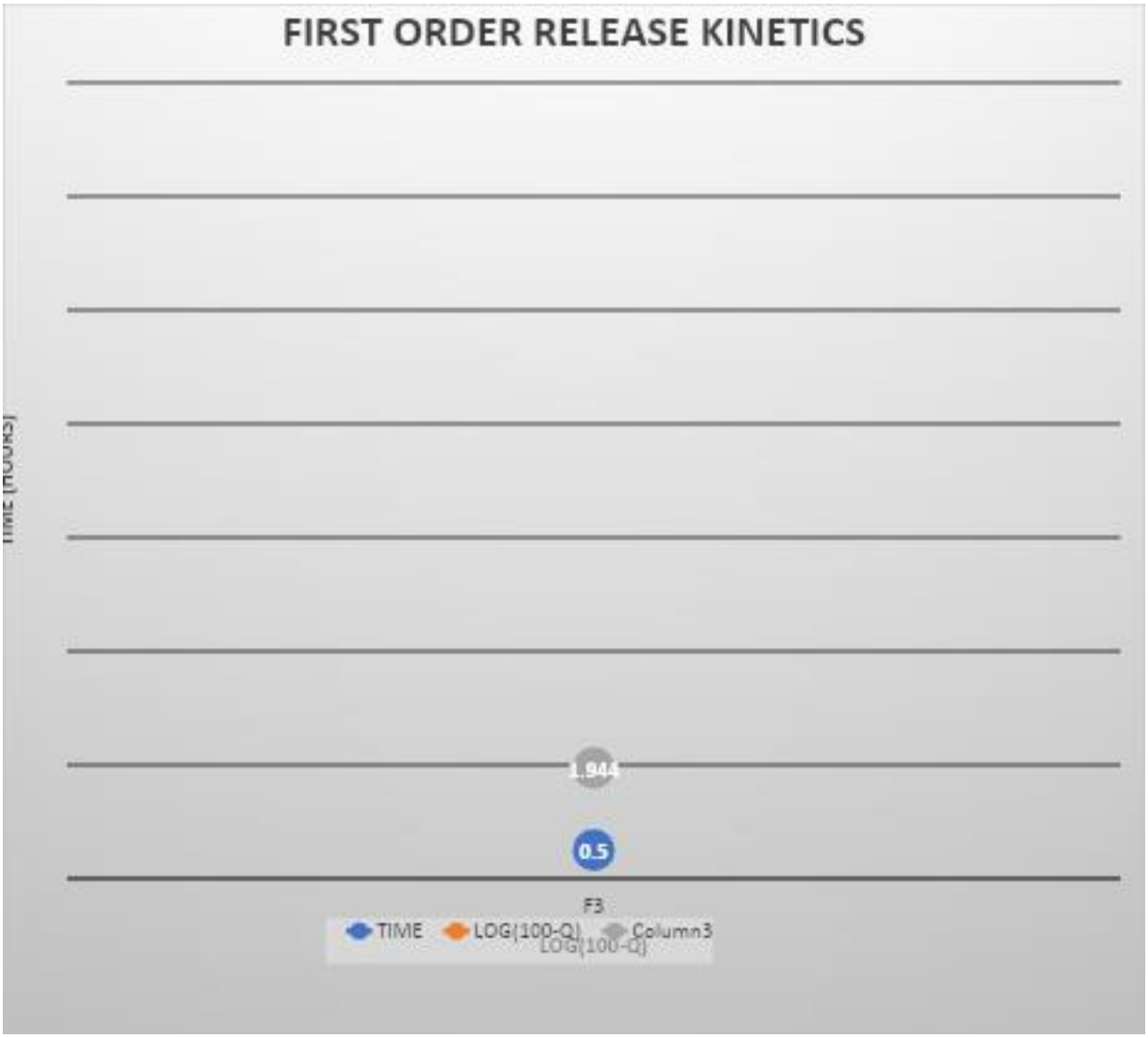

Figure 5.4: First order kinetics of F3

3. Higuchi Model

The Higuchi model describes drug release by diffusion from a polymer matrix system.

Equation

$Q = K_H t^{1/2}$

Where

Q = cumulative amount of drug released
K_H = Higuchi constant

Graph: *Cumulative % drug release vs √ time*

Interpretation: Indicates diffusion-controlled release from microspheres and frequently observed in polymer-based microspheres.

Table 5.8: Higuchi model release kinetics data

S.NO	**TIME(HOURS)**	√ *Time*	**% RELEASE**
1.	0.5	0.70	12
2.	1	1.00	28
3.	2	1.414	43
4.	4	2.00	51
5.	6	2.449	59
6.	8	2.828	67
7.	10	3.162	73
8.	12	3.464	82

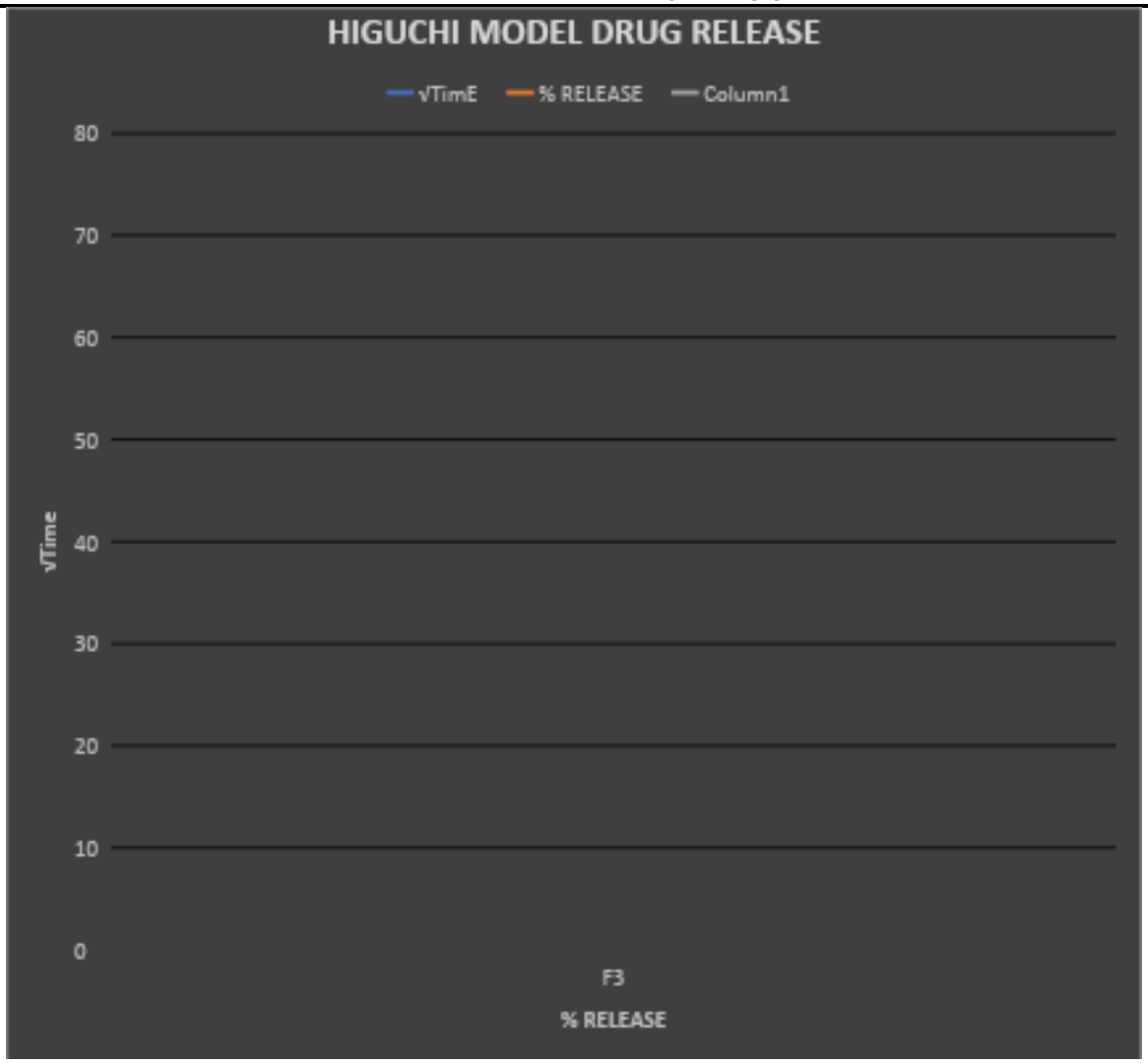

Figure 5.5: Higuchi model kinetics of F3.

4. Korsmeyer–Peppas Model

It is used when the drug release mechanism is complex or not well known.

Equation

\Frac {Mt} {M_\infty} = K t^n

Where

M_t/M_\infty = fraction of drug released
K = release constant
n = release exponent

Table 5.10: Interpretation of n

N VALUE	MECHANISM
$n \leq 0.45$	Fickian diffusion
0.45–0.89	Non-Fickian diffusion
0.89	Case II transport
>0.89	Super Case II transport

Table 5.11: Korsmeyer–Peppas Model release kinetics data

S.NO	TIME	LOG (TIME)	% RELEASE	LOG(Q)
1.	0.5	-0.301	12	1.079
2.	1	0.000	28	1.447
3.	2	0.301	43	1.633
4.	4	0.602	51	1.708
5.	6	0.778	59	1.771
6.	8	0.903	67	1.826
7.	10	1.000	73	1.863
8.	12	1.079	82	1.914

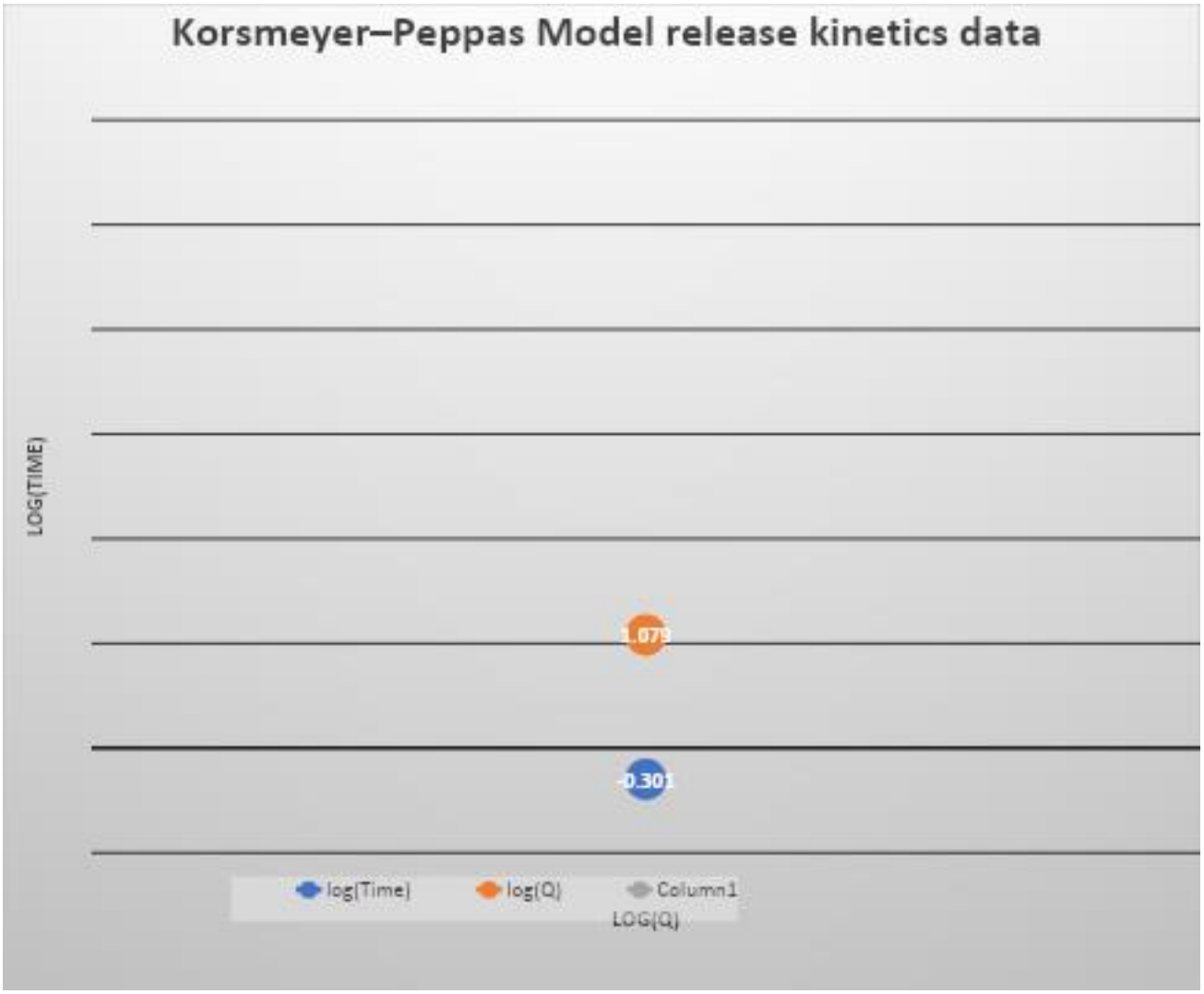

Figure 5.12: Korsmeyer–Peppas Model release kinetics data of F3.

5.Hixson–Crowell Model

It is Used when drug release occurs due to change in particle size and surface area.

Equation

Q_0^ {1/3} - Q_t^ {1/3} = K_{HC} t

Graph: Cube root of % drug remaining vs time

Interpretation: Indicates erosion or dissolution of microspheres

Table 5.13: Typical Result Pattern for Microspheres

Model	**Mechanism**	**Graph**
Zero order	Constant release	% Release vs Time
First order	Concentration dependent	log % remaining vs Time
Higuchi	Diffusion	% Release vs √ Time
Koresmeyer-peppas	Diffusion + polymer relaxation	Log % Release vs Log Time
Hixson -=Crowell	Surface erosion	Cube root plot

Table 5.14: Hixson–Crowell Model Data Release Kinetics

S.NO	**TIME**	**% REMAINING**	**CUBE ROOT (100-Q)**
1.	0.5	88	4.447
2.	1	72	4.160
3.	2	57	3.848
4.	4	49	3.684
5.	6	41	3.448
6.	8	33	3.207
7.	10	27	3.000
8.	12	18	2.620

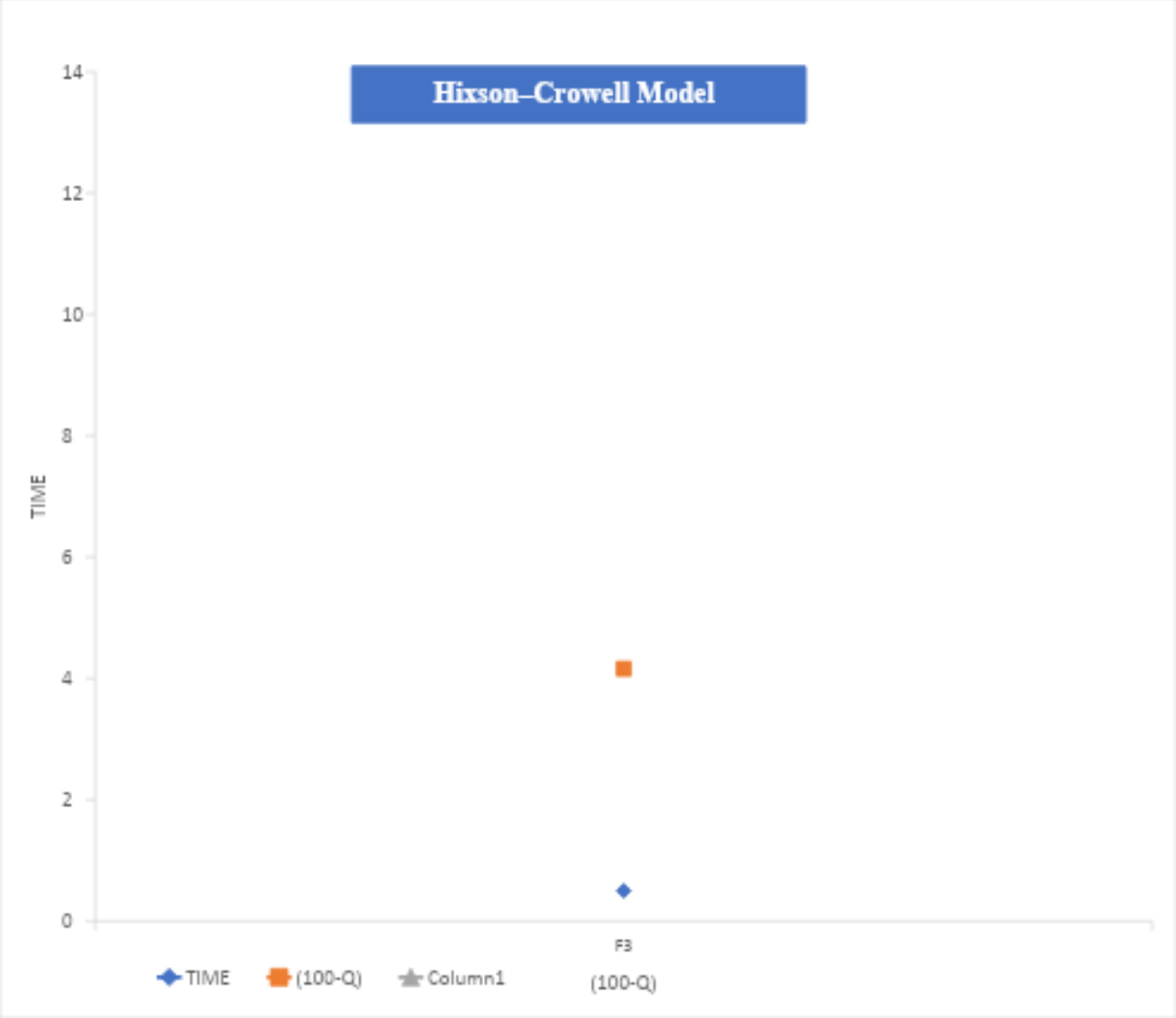

Figure 5.13: Hixson -Crowell Model release kinetics data of F3.

CHAPTER 6

Conclusion

The concept of formulating floating microspheres containing Ranitidine HCL and Glipizide offers a suitable, practical approach to achieve a prolonged therapeutic effect by continuously releasing the medication over an extended period of time. Floating microspheres of Ranitidine HCL and Glipizide were prepared successfully by emulsion solvent evaporation method using the different concentrations of individual polymers like HPMC K15 M, and EC utilizing prolonging its gastric retention thus improving the oral bioavailability of the drug. It would be faster and more economical to alter beneficially the properties of the existing drugs than developing new drug entities hence this formulation will be boon to novel drug dosage forms.

The coefficient of determination indicated that the release data were best fitted with zero-order kinetics. Higuchi equation explains the diffusion-controlled release mechanism. The diffusion exponent ‘n’ values of the Korsmeyer-Peppas model were found to be in the range of 0.5 to 1 for the RPS floating microspheres prepared with PLGA and EC indicating Non-Fickian of the drug through RPS floating microspheres.

The total four formulations were prepared (F1, F2, F3 and F4), out of which F3 was considered best. The readings were as follows:

Angle of repose:24

Particle size analysis :57.10 um

Buoyancy percentage:59.14%

Drug Entrapment Effeciency:83%

In-Vitro Drug Release: 82%

CHAPTER 7

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