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Original Research Article

Formulation and Characterization of Gastroretentive microsphere of Quetiapine Fumerate

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Abstract:
Quetiapine fumarate, an atypical antipsychotic drug, was subjected to comprehensive preformulation studies to evaluate its physicochemical properties and suitability for gastroretentive drug delivery. The drug was identified as a white to off-white, odorless crystalline powder with a bitter taste. Solubility studies revealed slight solubility in water and better solubility in organic solvents, indicating the need for formulation strategies to enhance its bioavailability. The melting point (182–184 °C), low loss on drying (1.56%), linear calibration curve obeying Beer–Lambert's law, and characteristic FTIR peaks confirmed the identity, purity, and stability of Quetiapine fumarate. Gastroretentive microspheres loaded with Quetiapine fumarate were successfully prepared using the solvent evaporation technique by varying the ratios of HPMC and Eudragit RLPO. The prepared formulations (F1–F6) were evaluated for percentage yield, drug entrapment efficiency, buoyancy, floating lag time, particle size, zeta potential, and in-vitro drug release. Among all formulations, F3 emerged as the optimized formulation, exhibiting the highest percentage yield (86.65 ± 0.22%), drug entrapment efficiency (79.88 ± 0.15%), excellent buoyancy (85.6 ± 0.2%), and minimal floating lag time (60 ± 3 s). In-vitro drug release studies demonstrated a sustained release profile over 12 hours, following diffusion-controlled kinetics as indicated by Higuchi and Korsmeyer–Peppas models. Particle size and zeta potential analyses confirmed nanoscale size and good stability of the microspheres. Stability studies conducted as per ICH guidelines revealed no significant changes in physical appearance, drug content, or dissolution behavior. The optimized gastroretentive microspheres of Quetiapine fumarate showed promising characteristics for prolonged gastric retention and controlled drug release, suggesting their potential to enhance bioavailability, therapeutic efficacy, and patient compliance.
Keywords: Gastroretentive microspheres; Quetiapine fumarate; Solvent evaporation method; Controlled drug release; Buoyancy; Stability studies.

Introduction

Gastro retentive drug delivery systems

Gastro retentive drug delivery systems is a type of system which prolongs the residence of administered drug in the gastric region for several hours thereby the bioavailability and solubility of challenging drugs may get enhanced, and improves the patient compliance. Gastric emptying delaying conceptual mechanisms of mucoadhesion, flotation and sedimentation support the gastro retentive drug delivery systems (Streubel et al., 2003). Thereby gastro retentive drug delivery systems enhance

the absorption of drugs in the gastrointestinal tract drug by improving the contact time with the small intestinal mucosa. Gastric retention-based drug delivery systems in turn provide a newer therapeutic possibilities and substantial benefits for researchers. Gastro retentive drug delivery systems may reduce the drug wastage. Gastro retentive drug delivery systems offer a controlled drug delivery profile with effective plasma drug concentration, reduces dosing frequency and minimizing plasma fluctuations (Klausner et al., 2003).

Drugs suitable for gastro retentive drug delivery formulations include drugs that have low absorption in the lower part of the GIT, unstable, poorly soluble at alkaline pH, short half- life, and show local activity at the upper part of the intestine. Due to the sustained/controlled release effect gastro retentive drug delivery formulations minimizes the mucosal irritation which may provide a desired plasma drug concentration and prevent drug fluctuations without causing dose dumping. Unstable drugs can also be delivered by this approach (Pillay and Shinde, 2008). The various approaches utilized in gastro retentive drug delivery system includes extended gastric residence time, low-density (floating), high-density (sinking), expandable (swelling), and mucoadhesive systems.

The better understanding on the anatomy and physiology of the stomach (specifically proximal stomach- fundus and body; and the distal stomach- antrum and pylorus) plays a crucial role for the successful development of the gastro retentive dosage form. The critical factors which affect the gastro retentive drug delivery systems are size/ shape/density of gastro retentive formulations, caloric density, factors associated with patients etc. The passage through the pyloric antrum can be prevented by an increase in the size of the dosage form. The lower density of gastro retentive drug delivery formulations than that of gastric fluids favors the floating capacity of the gastro retentive formulations.

Basic physiology of Gastrointestinal Tract:

Anatomically the stomach is divided into three regions: Fundus, body and antrum (pylorus). The proximal part made of fundus and body act as reservoir for undigested materials whereas the antrum is the main site for mixing motions and act as pump from gastric emptying by propelling the actions. Gastric emptying occurs during fasting as well as feed state. The patent of motility is however distinct in 2 states. During fasting state an inter digestive series of electrical events takes place, which cycle both through stomach and intestine every 2 to 3 hours (Benchgaard and Ladefoged, 1978). This is called the interdigestive myoelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington, (1989).

1. Phase I (basal phase) lasts from 40 to 60 minutes with contractions.
2. Phase II (pre burst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progress the intensity and frequency also increase gradually.
3. Phase III (burst phase) last for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this walve that all the undigested material is swept out of the stomach down to the small intestine .it is also known as the house keeper wave.
4. Phase IV last for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1mm) which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage form are subjected to basically two complications

that of short gastric residence time and unpredictable gastric emptying rate.

Floating drug delivery systems

Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation.

Advantages of floating drug delivery:

1. **Enhanced Bioavailability:** The bio-availability of some drugs (e.g. riboflavin and levodopa) CR-GRDF is significantly enhanced in comparison to administration of non-GRDF CR polymeric formulations (Mathur and Verma, 2010).
2. **Enhanced First-Pass Biotransformation:** When the drug is presented to the metabolic enzymes (cytochrome P-450, in particular CYP-3A4) in a sustained manner, the pre-systemic metabolism of the tested compound may be considerably increased rather than by a bolus input.
3. **Sustained drug delivery/reduced frequency of Dosing:** The drugs having short biological half-life, a sustained and slow input from FDDS may result in a flip-flop pharmacokinetics and it reduces the dose frequency. This feature is associated with improved patient compliance and thus improves the therapy.
4. **Targeted therapy for local ailments in the upper GIT:** The prolonged and sustained administration of the drug from FDDS to the stomach may be useful for local therapy in the stomach.
5. **Reduced fluctuations of Drug concentration:** The fluctuations in plasma drug concentration are minimized, and concentration-dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index that makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.
6. **Reduced counter-activity of the Body:** Slow release of the drug into the body minimizes the counter activity leading to higher drug efficiency.
7. **Extended time over Critical (effective) concentration:** The sustained mode of administration enables extension of the time
8. **Improved Receptor activation selectivity:** FDDS reduces the drug concentration fluctuation over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.
9. **Minimized adverse activity at the Colon:** Retention of the drug in GRDF at stomach minimizes the amount of drugs that reaches the colon and hence prevents the degradation of drug that degraded in the colon.
10. **Site specific Drug Delivery:** A floating dosage form is a widely accepted approach especially for drugs which have limited absorption sites in upper small intestine (Hardenia et al., 2011; Chandel et al., 2012; Shah et al., 2009).

Microsphere

Medication activity can be enhanced by growing new medication conveyance framework, for example, the microsphere sedate conveyance framework. These frameworks stay in close contact with the ingestion tissue, the mucous layer, discharging the medication at the activity site prompting a bioavailability increment and both nearby and foundational impacts (Carvalho et al., 2010). The oral course of medication organization constitutes the most helpful and favored methods for sedate conveyance to foundational dissemination of body. However oral organization of the greater part of the medications in traditional measurements frames has here and now restrictions because of their failure to limit and confine the framework at gastro-intestinal tract.

Microspheres constitute an essential piece of these particulate medication conveyance frameworks by uprightness of their little size and

productive bearer limit. Microspheres are the bearer connected medication conveyance framework in which molecule estimate is ranges from 1-1000 μm extend in distance across having a center of medication and completely external layers of polymer as covering material. Be that as it may, the accomplishment of these microspheres is restricted because of their short habitation time at site of assimilation. It would, in this way be worthwhile to have implies for giving a private contact of the medication conveyance framework with the engrossing layer. Microspheres have focal points like proficient retention and upgraded bioavailability of the medications because of a high surface to volume proportion, a substantially more cozy contact with the bodily fluid layer and particular focusing of medications to the ingestion site (Parmar et al., 2010).

Microspheres incorporate microparticles and microcapsules (having a center of medication) of 1-1000μm in distance across and comprising either totally of a floating polymer or having an external covering of it, individually. Microspheres, as a rule, can possibly be utilized for focused and controlled discharge sedate conveyance; however, coupling of floating properties to microspheres has extra preferences e.g. effective assimilation and bioavailability of the medications because of high surface to volume proportion, a considerably more personal contact with the mucous layer, particular focusing of medications to the ingestion site.

Types of microspheres

Bioadhesive microspheres

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water-soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bioadhesion. The term “bioadhesion” describes materials that bind to biological substrates’, such as mucosal members. Adhesion of Bioadhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of administration. This prolonged residence time can result in enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanospheres, liposomes, nanoparticles, etc., which modulates the release and absorption of the drug. Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity.

Magnetic microspheres

This kind of delivery system is very much important which localises the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. The different type are Therapeutic magnetic microspheres are used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system (Patel, 2010).

Radioactive microspheres

Radio emobilisation therapy microspheres sized 10-30 nm are of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumour of interest. So these radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are α emitters, β emitters, γ emitters (Yadav and Mote, 2008).

Mucoadhesive microspheres

Mucoadhesive microspheres which are of 1-1000mm in diameter and consisting either

entirely of a mucoadhesive polymer or having an outer coating of it and coupling of mucoadhesive properties to microspheres has additional advantages, e.g. efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions and antibodies, etc. on the surface of the microspheres. Mucoadhesive microspheres can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs (Chowdary et al., 2004).

Floating microspheres

In floating types, the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content, increases gastric residence and fluctuation in plasma concentration. It also reduces chances of striking and dose dumping and produces prolonged therapeutic effect. Drug (ketoprofen) given through this form (Najmuddin et al., 2010).

Polymers used in Floating Microspheres

A number of different substances both biodegradable as well as nonbiodegradable have been investigated for the preparation of microspheres; these materials include polymers of natural origin or synthetic origin and also semisynthetic substances. Microspheres can be prepared by using both hydrophilic and hydrophobic polymers.

- **Hydrophilic polymers**

These are including gelatin, agar, egg albumin, starch, chitosan, cellulose derivatives; HPMC, DEAE cellulose.

- **Hydrophobic polymers**

These are including ethyl cellulose, polylactic acid, PMMA, acrylic acid esters etc.

- **Biodegradable polymers**

These materials also slowly disappear from the site of administration; however, it occurs in response to a chemical reaction such as hydrolysis.

Example: Polylactic acid (PLA), poly glycolic acid (PGA), Polycaprolactone (PCL) and several generic classes such as the poly anhydrides and poly orthoesters.

- **Non-Biodegradable Hydrophobic Polymers**

These materials are inert in the environment of use, are eliminated or extracted intact from the site of administration.

Example: Polyethylene vinyl acetate (EVA), Polydimethyl siloxane (PDS), Polyether urethane (PEU), Ethyl cellulose (EC), Cellulose acetate (CA), Polyethylene (PE) and Polyvinyl chloride (PVC), Acrycoat, Eudragit S etc.

- **Hydrogels**

These polymers swell but do not dissolve when brought in contact with water. As with the hydrophobic polymers, hydrogels are inert, removed intact from the site of administration, and function by forming a rate limiting barrier to the transport and release of drugs.

Example: Polyhydroxy ethyl methyl acrylate (PHEMA), cross-linked poly vinyl alcohol (PVA), cross linked poly vinyl pyrrolidone (PVP), poly acryl amide etc.

- **Soluble polymers**

These are moderate molecular weight (less than 75,000 Daltons) uncross linked polymers that dissolve in water. The rate of dissolution decreases with increasing molecular weight. These materials can be used alone or in combination with hydrophobic polymers to provide devices that slowly erode over time.

Example: polyethylene glycol (PEG), uncross linked poly vinyl alcohol or poly vinyl pyrrolidone, hydroxyl propyl methyl cellulose (Methocel) and copolymers of methacrylic acid and acrylic acid methyl ester (Eudragit L) etc.

Evaluation of Floating Microsphere

Characterization of floating microspheres is an important phenomenon which helps in the evaluation of suitable drug delivery systems. Floating microspheres are characterized by following parameters:

- **Particle size analysis**

Particle size of floating microspheres is determined by using an optical microscopy and size istribution is carried out by sieving method. This is useful in the determination of mean particle size with the help of calibrated ocular micrometer.

- **Percentage yield**

Percentage yield of floating microspheres is calculated by dividing actual weight of product to total amount of all nonvolatile components that are used in the preparation of floating microspheres and is represented by following formula.

% Yield = actual wt. of floating microsphere / total wt. of exipient and drug * 100

- **Drug entrapment efficiency**

Estimation of drug content in floating microspheres can be carried out by dissolving the weighed amount of crushed microspheres in required quantity of 0.1 N HCl and analysed spectrophotometrically at a particular wavelength using the calibration curve. Each batch should be examined for drug content in a triplicate manner. The entrapment efficiency of floating microspheres is calculated by dividing the actual drug content by the theoretical drug content of Microspheres.

- **Surface morphology**

Surface characteristics of floating microspheres are analysed using a scanning electron microscopy. Samples are coated with gold dust under vacuum prior to observation. Cross sections should be made in order to observe the core and internal structure of the microspheres. These studies are useful in the examination of internal and external morphology of floating microspheres.

- **Swelling ratio**

Swelling property of floating microspheres is studied by soaking the known weight of microspheres at 37 ± 0.5°C in 0.1 N HCl or phosphate buffer pH 6.8 in a glass beaker for the required period of time. The microspheres are allowed to swell and removed at different time intervals.

- **In vitro drug release studies**

Release rate of drug from hollow floating microspheres is determined using USP dissolution apparatus type I or type II at 37± 0.5°C. The dissolution test is carried out using 900 mL of 0.1 N HCl dissolution medium at 100 rpm for the required period of time. At an appropriate interval, specific volume of aliquots are withdrawn and replaced with an equivalent volume of fresh dissolution medium to maintain the constant volume of dissolution medium. The sample solutions are filtered through Whatman filter paper and solutions are analysed using UV spectrophotometer.

- **Buoyancy studies**

In vitro floating tests can be performed in USP type II dissolution test apparatus by spreading the floating microspheres on a simulated gastric fluid (pH 1.2) containing the surfactant. The media is stirred at 100 rpm at 37± 0.5°C. After specific intervals of time, both the fraction of microspheres (floating and settled microspheres) is collected and buoyancy of the floating microspheres is determined by using formula. Where, Qf and Qs are the masses of floating and settled hollow microspheres, respectively.

Buoyancy % = Qf / Qf + Qs * 100

- **Hausner's ratio**

Hausner's ratio of floating microspheres is determined by comparing the tapped density to the fluff density using the equation.

Hausner's ratio = tapped density/fluffy density

Points of interest of microspheres drug delivery system

(1) Because of bond and personal contact, the definition remains longer at the conveyance site enhancing API bioavailability utilizing lower API fixations for infection treatment.
(2) The utilization of particular bioadhesive atoms takes into account conceivable focusing of specific locales or tissues, for instance the gastrointestinal (GI) tract.
(3) Increased home time joined with controlled API discharge may prompt lower organization recurrence.
(4) Offers an incredible course, for the fundamental conveyance of medications with high first-pass digestion, there by offering a more noteworthy bioavailability (Punitha and Girish, 2010).
(5) Additionally critical cost decreases might be accomplished and measurements related symptoms might be lessened because of API confinement at the sickness site (Gavin et al., 2009).
(6) Better patient consistence and comfort because of less incessant medication organization.
(7) Uniform and wide appropriation of medication all through the gastrointestinal tract which enhances the medication assimilation.
(8) Prolonged and maintained arrival of medication.
(9) Maintenance of restorative plasma tranquilize focus.
(10) Better processability (enhancing dissolvability, dispersibility, flowability).
(11) Increased wellbeing edge of high strength sedates because of better control of plasma levels.
(12) Reduction in change in unfaltering state levels and in this way better control of illness condition and decreased power of neighborhood or fundamental symptoms (Ganga, 2007).

Applications of microspheres

A portion of the uses of microspheres are depicted in detail as following: -

1. Controlled and supported discharge measurement shapes.
2. Microsphere can be utilized to plan enteric-covered measurement shapes, with the goal that the medicament will be specifically caught up in the digestive system instead of the stomach.
3. It has been utilized to shield drugs from natural dangers, for example, mugginess, light, oxygen or warmth. Microsphere does not yet give an ideal boundary to materials, which debase within the sight of oxygen, dampness or warmth, however an extraordinary level of insurance against these components can be given. For instance, vitamin A and K have been appeared to be shielded from dampness and oxygen through microsphere.
4. The partitions of incongruent substances, for instance, pharmaceutical eutectics have been accomplished by exemplification. This is where coordinate contact of materials realizes fluid development.

The security improvement of contradictory ibuprofen chlorpheniramine maleate blend is proficient by microencapsulating them two preceding blending.

5. Microsphere can be utilized to diminish the instability. A typified unstable substance can be put away for longer circumstances without considerable dissipation.
6. Microsphere has additionally been utilized to diminish potential peril of treatment of dangerous or harmful substances. The harmfulness happened because of treatment of fumigants; herbicides bug sprays and pesticides have been beneficially diminished after microencapsulation.
7. The hygroscopic properties of numerous center materials might be lessened by microsphere.
8. Numerous medications have been microencapsulated to lessen gastric aggravation (Meena et al., 2011; Ali, 2005).

9. Microsphere technique has additionally been proposed to get ready intrauterine preventative gadget.
10. Helpful attractive microspheres are utilized to convey chemotherapeutic specialist to liver tumor. Medications like proteins and peptides can likewise be focused through this framework. Mucoadhesive microspheres display a drawn-out living arrangement time at the site of use and causes hint contact with the assimilation site and delivers better remedial activity.

Review of Literature

Santhoshi et al., (2024) prepared and evaluated controlled release matrix tablet of Quetiapine Fumarate. All the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F5 formulation showed maximum % drug release i.e., 98.73 % in 24 hours hence it is considered as optimized formulation F5 which contains HPMC K4 M. It followed Zero order release mechanism.

Purkar and Surawase, (2024) formulated and evaluated of Quetiapine fumarate Extended-Release tablet by using 23 Factorial designs. The use Wet granulation process can be utilizing for manufacturing extended-release tablet utilizing polymer such as HPMC K100, HPMC K15 and Ethyl cellulose. The developed ER tablet using the wet granulation process. The developed extended-release tablet ranges in weight variation from 250-256mg. It was discovered that the friability 0.32 to 1.32%. The swelling index optimized batch was 85.01%. The drug optimised batch had a 98.94% in vitro release rate. A combination of HPMC K100, HPMC K15, and ethyl cellulose was effectively employed in the creation of Quetiapine fumarate extended-release matrix tablets. The examined extended-release matrix tablet produced optimal smooth blood levels of quetiapine fumarate for a full day and shown a strong in vitro and in vivo association.

Jain et al., (2023) improved bioavailability of Quetiapine fumarate by formulation into microemulsion. The Quetiapine fumarate micro emulsion was formulated by phase titration method using mixture of oleic acid as oil phase, tween-80 as surfactant, isopropyl alcohol as co-surfactant. Optimized ratio of tween 80: isopropyl alcohol was selected after developing pseudoternary phase diagrams for different ratio and microemulsions were prepared. The optimized formulation was evaluated for drop dilution test, dye solubility test, emulsifying time, pH, viscosity, drug content, diffusion study, stability studies. Emulsifying time of prepared microemulsion ranged from 27 to 38 seconds and drug content of prepared microemulsion ranged from 95.45 to 97.70 %. The % drug releases for formulations F1, F2, F3, F4 and F5 at the end of 7hr were found to be 93.454, 88.324, 79.625, 65.463, and 52.987 % respectively. The formulation containing oil and Smix in the ratio 9:1 (F1) was considered as an optimized formulation with lowest emulsifying time and highest drug release at the end of 7hr was found to be 27 second and 93.45 % respectively.

Pingale et al., (2021) created a reliable immediate-release tablet formulation of the antipsychotic Quetiapine Fumarate. Tablets are popular due to their low cost, packaging, and shipping, as well as their greater stability and virtual tamper resistance. Orally administered tablets with a faster disintegration time have a shorter absorption time and higher bioavailability. The goal of the study is to create a stable and physically and chemically compatible generic formulation for treating schizophrenia, as well as a pharmaceutically equivalent instant release tablet for individuals with mental illnesses like schizophrenia and bipolar disorder.

Sachan et al., (2020) designed, synthesized and evaluated the floating microsphere of muscle relaxant drug Thiocolchicoside. The surface morphology study by SEM indicated that microspheres were spherical with smooth surface. The prepared microspheres were

characterized by entrapment efficiency, particle size, and micromeritics properties. The drug must be delivered for a prolonged period and many medicines must be taken simultaneously in case of chronic patients. The Floating microspheres were shown to be effective for increasing the bioavailability. Among all formulations, F5 showed better drug release rate and buoyancy, which is considered as the best formulation. Stability studies show about less than 0.5 % of drug degrade in 60 days indicating relatively good stability study of the formulation. The Floating microspheres were shown to be effective for increasing the bioavailability of Thiocolchicoside in gastric region.

Patil et al., (2019) reviewed on bipolar disorder is psychological illness with periodic episodes of mania and depression. Schizophrenia is a complex mental disorder identified by delusions, hallucinations, disorganized behavior, impaired cognitive ability, disorganized speech and sudden change in personality. Quetiapine alone is successful for acute bipolar depression and the prevention of mania/hypomania switching.

Zhang et al., (2019) formulated with sustained release profiles is highly desired for the treatment of bipolar disorder (BD) to improve patient compliance by avoiding frequent dosing and stabilizing drug plasma concentration. Quetiapine fumarate hydrophilic matrix tablets (QFHMTs) were designed and developed in this study. This hydrophilic matrix was accomplished by the blended polymer systems composed of HPMC K100LV and HPMC K4M to achieve appropriate hydration rate and gel strength for sustained-release of QF. QFHMTs was optimized by single factor experiment and orthogonal test, and the reproducibility test was confirmed. The optimized QFHMTs showed 24-h sustained release profile.

Kandhula and Nippani, (2018) formulated intranasal mucoadhesive microemulsion with the view to provide faster onset of action and improved bioavailability. The exipients used were Oleic acid (oil), Tween 80 (surfactant), PEG400 (co surfactant) and chitosan (Mucoadhesive agent). The optimized formulation was evaluated for transparency, mucoadhesive strength, globule size (61.9 nm), zeta potential (-22.7 mV), PDI (0.13), % drug content, SEM analysis. Hence it can be concluded that the formulation with enhanced solubility can have potential of improving bioavailability of Quetiapine fumarate can be a better alternative than the available formulation.

Talele and Derle, (2018) prepared of self-nanoemulsifying drug delivery system (SNEDDS) of poorly water-soluble drug using Apelblat model for the development of self-nanoemulsifying drug delivery system (SNEDDS) solubility in surfactant, co-surfactant and in oil phase are considered as an important key to avoid phase separation and precipitation after dilution. The solubility of quetiapine fumarate was determined by the isothermal mechanical shaking method for its individual components in the temperature range from 305.15 to 330.15K was measured. The experimental mole fraction solubility of quetiapine was good correlated with calculated data by using modified Apelblat model. Prepared SNEDDS were evaluated in centrifugation, freeze-thaw cycle study, self-nanoemulsification efficiency test. Physicochemical properties of prepared SNEDDS including particle size, zeta potential, viscosity and refractive index were carried out. The equilibrium saturated and mole fraction solubility of Quetiapine fumarate was found to be high in tween80 than SNEDDS, Labrafac lipophile WL 1349 and capryol 90. Quetiapine fumarate equilibrium saturated solubility, as well as mole fraction solubility, was found to be increased with increase in temperature in SNEDDS as well as in its individual components Prepared SNEDDS was found to be highly stable at centrifugation, heating and cooling cycles and freeze-thaw cycles and shows no sign of precipitation after dilution in water. All physicochemical parameters were observed within specification including droplet size observed as 26.37 nm, polydispersity index 0.0970, zeta potential-14.69 and the refractive

index was observed as 1.458 which was nearer to the refractive index of water indicating the isotropic behavior of prepared SNEDDS.

Jat et al., (2018) Quercetin loaded microspheres were prepared using emulsion-solvent diffusion method. Particles so obtained were within the micrometer range (48.25 ± 2.01– 100.40 ± 3.01 µm for QM1 to QM10 batches). Fourier transform infrared spectra indicated no drug-polymer interaction whereas differential scanning calorimetry thermograms revealed the absence of crystalline drug in the drug-loaded microsphere formulation. Scanning electron micrographs showed that the fabricated microspheres were spherical in shape. Batch QM3 displayed 73% encapsulation efficiency with highest in vitro drug release rate (98%). Bioavailability studies showed that quercetin loaded Eudragit S100 microspheres were able to enhance the oral bioavailability of the drug. As per stability studies, the developed formulation was stable when tested under accelerated stability conditions. The fabricated quercetin-loaded Eudragit S100 microspheres were able to enhance the bioavailability of the drug in the serum of the animal model.

Porfire et al., (2017) formulated quetiapine fumarate sustained release matrix tablets using a QbD approach. The quality target product profile (QTPP) was defined after the pharmaceutical properties and kinetic release of the innovator product, Seroquel XR 200 mg. For the D-optimal experimental design, the level and ratio of matrix forming agents and the type of extra-granular diluent were chosen as independent inputs, which represented critical formulation factors. The critical quality attributes (CQAs) studied were the cumulative percentages of quetiapine released after certain time intervals. After the analysis of the experimental design, optimal formulas and the design space were defined. Optimal formulas demon-strated zero-order release kinetics and a dissolution profile similar to the innovator product, with f2 values of 74.53 and 83.74. It was concluded that the QbD approach allowed fast development of sustained release tablets with similar dis-solution behavior as the innovator product.

Venkateswarlu et al., (2017) prepared quetiapine fumarate (QF) extended-release tablets by direct compression method using natural polymers like xanthan gum (XG), guar gum (GG) and karaya gum (KG). Microcrystalline cellulose PH 102 (MCC PH 102) was used as a diluent. Powder blends showed acceptable flow properties and the results obtained from post compression parameters like weight variation, content uniformity and friability were complied with the pharmacopoeial limits. The dissolution study was performed by USP dissolution apparatus (paddle method) using 0.1 N HCl and pH 6.8 phosphate buffers. It was observed from the in vitro drug release studies, formulation F3 showed desired retardation time of 24 h with the optimum drug release of 97.3%. It was noted from the results, as the concentration of polymer increases, the drug release rate was decreased in case of the polymers like XG and KG, but not in the case of GG.

Phulzalke et al., (2016) formulated directly compressible orodispersible tablets of quetiapine fumarate by sublimation method with a view to enhance patient compliance. A full 32 factorial design was used to investigate the effect of two variables viz., concentration of Indion 414 and camphor. Indion 414 (3-5 % w/w) was used as superdisintegrant and camphor (5-15 % w/w) as subliming agent. The tablets were evaluated for thickness, weight variation, hardness, friability, content uniformity, wetting time, porosity, in vitro disintegration time and in vitro drug release. In vitro dissolution profile revealed faster and maximum drug from formulation F3. SEM study show formation of pores on tablet surface after sublimation of the sublimating agent, thus providing a sufficiently porous structure. This permitted the selection of a batch of tablets with desired disintegration time and im- proved dissolution rate after oral administration. The F3 batch containing the Indion 414 (5%) and Camphor (5%) w/w of total formulation weight had shown good the

disintegration time of 18.66 seconds and with improved dissolution rate and desirable friability.

Gubbala et al., (2016) prepared solid dosage form for quetiapine nanoparticles in order to increase the saturation solubility, rate of dissolution so that the oral bioavailability is enhanced. Quetiapine fumarate is a BCS class II drug, hence its oral bioavailability is dissolution limited. To enhance the oral bioavailability a nanoparticle formulation of QF was prepared by using high pressure homogenization. The nanosuspension prepared was converted into dry powder by using spray drying. The nanosuspension and spray dried nanoparticles are characterized for particle size, polydispersity index, zeta potential, saturation solubility, drug content, dissolution rate, solid state characterization such as X- ray diffraction (XRD), Differential scanning calorimetry (DSC), infrared (IR), scanning electron microscopy (SEM), transmission electron microscopy (TEM). The spray dried nanoparticles were blended with excipients to convert into solid dosage form such as tablets. The compressed tablets were evaluated for physical parameters, assay and dissolution was compared with the commercial QF formulation. Solid state characterization data showed loss of drug crystallinity after homogenization. The novel dosage form has shown significant increase in the rate of dissolution when compared to microparticle formulation in discriminating medium.

Pandey et al., (2016) formulated and characterized of floating microspheres using nateglinide as a model drug for the management of type-2 diabetes mellitus. Floating microspheres were prepared by oil-in-water emulsion solvent evaporation technique using ethyl cellulose and eudragit S-100 as release retarding polymers. The floating microspheres were evaluated for percentage yield (%), particle size, drug content, drug entrapment efficiency, in-vitro floating ability and in-vitro drug release studies. The surface morphology of prepared microspheres was characterized by scanning electron microscopy. The microspheres were found to be spherical in shape and porous in nature. Compatibility studies were performed by fourier transform infrared (FTIR) technique. The prepared microspheres showed prolonged drug release of 12 h and remain buoyant for more than 12h. In-vitro release kinetics were studied in different release kinetics models like zero order, first order, higuchi and korsmeyer peppas model and the best fit model was found to be higuchi plot with release exponent n value less than 0.89.

Saxena and Kitawat, (2015) formulations microspheres of ketoprofen were prepared by emulsion-solvent evaporation method using a mixture of HPMC and Ethyl Cellulose was dissolved in 50ml of acetone to form a homogenous polymers solution. The prepared ketoprofen microspheres were discrete and free flowing and indicated that the concentration of polymer, stirring rate significantly influenced the formation of microspheres and ketoprofen entrapment while concentration of the polymer has a significant positive impact on ketoprofen release over a period of 12 hours and the stirring rate have minimal effect on the drug release. Microspheres revealed the absence of drug-polymer interactions. Scanning electron microscopy study revealed that the microspheres were spherical and porous in nature.

Bharathi et al., (2014) formulated a sustained release (SR) matrix tablet of Quetiapine fumarate. Quetiapine fumarate and polymer compatibility studies were performed using Fourier transform infrared spectroscopy (FT-IR) and Differential scanning calorimetry (DSC). The pre-compression mixture formulation was evaluated for flow ability and compressibility. The tablets were prepared by direct compression method. The effect of concentration and type of polymers, type of diluent on in-vitro drug release and release kinetics was studied extensively. FT-IR and DSC studies revealed no interaction between Quetiapine fumarate and polymers. Flow ability and compressibility study of pre-compression powder formulation showed that these formulations were within the theoretical range for processing into tablet dosage form. In-

vitro drug release studies exhibited that the drug release was sustained up to 12 h for SR matrix tablets prepared with both Guar gum and Tara gum but Guar gum showed better sustained action with good percent drug release when compared with Tara gum.

Narala and Veerabrahma, (2013) improved oral bioavailability of quetiapine fumarate by incorporating in solid lipid nanoparticles (SLN). Six quetiapine fumarate SLN formulations were developed using three different lipids by hot homogenisation followed by ultrasonication. The drug excipient compatibility was studied by differential scanning calorimetry (DSC). Stable quetiapine fumarate SLNs having a mean particle size of 200– 250 nm with entrapment efficiency varying in between 80% and 92% were developed. The physical stability of optimized formulation F3 was checked at room temperature for 2 months. Comparative bioavailability studies were conducted in male Wistar rats after oral administration of quetiapine fumarate suspension and SLN formulation. The relative bioavailability of quetiapine fumarate from optimized SLN preparation was increased by 3.71 times when compared with the reference quetiapine fumarate suspension. The obtained results are indicative of SLNs as potential lipid carriers for improving the bioavailability of quetiapine fumarate by minimizing first-pass metabolism.

Kothamasu et al., (2013) designed and evaluated of extended-release film-coated matrix tablets of Quetiapine Fumarate to treat schizophrenia using different polymers mainly Carboxy methyl ethyl cellulose and Ethyl cellulose in combination by wet granulation method. The tablets were subjected to thickness, weight variation test, drug content, hardness, friability, in vitro and in vivo release studies. The film coated tablet formulations of various batches (50 mg, 150mg, 200 mg, 300mg and 400 mg) showed acceptable physicochemical properties. Optimized formulations were selected from each batch was based on the evaluation parameters and drug release kinetics. The FTIR & DSC studies indicated absence of any interaction between Quetiapine Fumarate and polymers. The optimized formulations follow zero order release kinetics and showed non-Fickian (anomalous) release, coupled diffusion, and polymer matrix relaxation, $0.45 < n < 0.89$. The innovator product Seroquel XR tablets in different strengths shown to be followed first order release kinetics. From the release kinetic study, it can be concluded that the drug release pattern of optimized formulations was controlled manner for 24 hours. The optimized formulation of C6 (200mg) was evaluated for its bioavailability compared with pure drug as reference standard. In vivo studies were carried out for 200mg tablets and the values of Cmax and tmax clearly indicated that the drug release was controlled and maintained constant plasma concentration upto 24 hours after oral administration in comparison with pure drug.

Lohan et al., (2013) improved their brain availability, solid lipid nanoparticles (SLN) loaded with Quetiapine fumarate or hemifumarate were prepared using glyceryl monostearate (GMS), poloxamer 407 and hydrogenated soya phosphatidylcholine (HSPC). They were characterized for physical characteristics like particle size, polydispersity (PDI), shape and entrapment efficiency (EE). Formulation and process parameters were optimized based on particle size, PDI and EE. SLNs with a mean particle size of 101.1 nm were obtained for quetiapine fumarate and 93.6 nm for quetiapine hemifumarate. In vitro drug release study showed the release followed Higuchi kinetics model for both the formulations. In vivo studies showed a significant increase in the percentage of drug reaching the brain when administered in the form of SLN's as compared to the respective drug solutions and the increase was greater in case of quetiapine hemifumarate salt.

Chand and Maulik, (2013) evaluated of microspheres containing Duloxetine hydrochloride. The particle size of microspheres analyzed by optical microscopic method, was affected by concentrations of ethyl cellulose.

When drug to polymer ratio was increased from 1:1 to 1:5, the proportion of larger particles formed became higher, which may be due to increase in viscosity of the solvent with increase in polymer to drug ratio. Larger microspheres showed greater drug loading. The low entrapment efficiency may be due to solubility of the drug in the solvent; the drug may be migrated to the processing medium during extraction and evaporation process of solvents.

Sony and Jain, (2013) floating microspheres of flupirtine maleate were prepared with the help of ethyl cellulose, hydroxypropyl methyl cellulose polymer & tween 80 as a surfactant with ethanol, dicholromethane as solvents. Different formulations were characterized in terms of buoyancy study, particle size, SEM, entrapment efficiency and release kinetic.

Kaliaperumal et al., (2012) quetiapine fumarate oral sustained release tablets were formulated using this polysaccharide. Dissolution of the developed tablets with 25% polysaccharide content showed a better release profile than the other batches (5–20%) at the end of 12 h. The strong matrix complex has low solubility in water, it does not dissolve rapidly and the drug continues to diffuse through the gel layer at a consistent rate. Drug release from the matrix tablets follows matrix type except F-4 and F-5 which follow first order and Hix.crow type. The bioavailability study was carried out using healthy male New Zealand white rabbits that show the AUC(0–inf) value for developed SR tablets is 1.44 times higher than the reference thus, indicating more efficient and sustained drug delivery capable of maintaining plasma drug levels better.

Potu et al., (2012) evaluated buccoadhesive Quetiapine Fumarate (QF) tablets, which is extensively metabolised by liver. Buccoadhesive tablets of QF were prepared using HPMC K4M, HPMC K15M and combination of carbopol and HPC as mucoadhesive polymers by direct compression method. Sodium deoxycholate was added to formulation to improve the permeation of drug. The formulations were tested for bioadhesion strength, ex vivo residence time, swelling time and in vitro dissolution studies and ex vivo permeation studies. Optimized formulation (F3) showed 92% in vitro release in 8 h and 67% permeation of drug through porcine buccal mucosa and followed fickian release mechanism with zero order kinetics. FTIR studies of optimized formulation showed no evidence of interaction between the drug and polymers. In vivo mucoadhesive behaviour of optimized formulation was performed and subjective parameters were evaluated.

Sahu and Rana, (2010) prepared sustained release matrix tablets of quetiapine fumarate using different polymers viz. Hydroxy propyl methyl cellulose (HPMC) and PVP K30. Varying ratios of drug and polymer like were selected for the study. After fixing the ratio of drug and polymer for control the release of drug upto desired time, the release rates were modulated by combination of two different rates controlling material and triplemixture of two different rate controlling material. After evaluation of physical properties of tablet, the in vitro release study was performed in 0.1 N HCl pH 1.2 for 2 hrs and in phosphate buffer pH 6.8 up to 12 hrs. The effect of polymer concentration and polymer blend concentration were studied. Dissolution data was analysed by Higuchi expression. It was observed that matrix tablets contained polymer blend of HPMC/PVP K30 were successfully sustained the release of drug up to 12 hrs. Among all the formulations, formulation QFSRT/08 which contains 60% HPMC K15M and 06% ofPVP K30 release the drug which follow Higuchi kinetics via, swelling, diffusion and erosion and the release profile of formulation QFSRT/08 was comparable with the prepared batch products. Stability studies (40±2ºC/75±5%RH) for 6 months indicated that quetiapine fumarate was stable in the matrix tablets.

Aim and Objective

Gastroretentive microspheres are an advanced drug delivery system designed to prolong the retention time of a drug in the stomach, enhancing its bioavailability and therapeutic

efficacy. These microspheres are small, spherical particles that float or adhere to the gastric mucosa, ensuring localized and sustained drug release in the stomach. This system is particularly beneficial for drugs with a narrow absorption window in the upper gastrointestinal tract, drugs that are unstable in the intestinal or colonic environment, or those that exhibit better solubility in acidic pH.

The aim of this study is to formulate and evaluate gastroretentive microspheres of Quetiapine fumarate, a widely used antipsychotic medication, to enhance its bioavailability and therapeutic efficacy. The primary objective is to develop a controlled drug delivery system that prolongs the gastric residence time of Quetiapine fumarate, ensuring consistent and sustained drug release over an extended period. This approach aims to improve patient compliance by reducing the dosing frequency, minimizing potential side effects, and optimizing the therapeutic outcomes. The study evaluates the physicochemical properties, drug entrapment efficiency, in vitro release characteristics, and stability of the prepared microspheres, ultimately contributing to the advancement of gastroretentive drug delivery systems.

Plan of Work

1. Literature survey
2. Preformulation study
    - Organoleptic properties
    - Solubility analysis
    - Melting point
    - UV Spectrophotometric analysis
    - FTIR spectroscopy
3. Formulation and preparation of gastroretentive microspheres
4. Evaluation of gastroretentive microspheres
    - Percentage yields
    - Drug entrapment efficiency
    - Measurement of mean particle size
    - Determination of zeta potential
    - Shape and surface characterization by scanning electron microscopy
    - In-vitro release studies
    - Stability studies
5. Results and discussion
6. Summary and conclusion
7. References

Drug and Excipient Profile

Drug profile

Quetiapine fumarate

Initially approved by the FDA in 1997, quetiapine is a second-generation atypical antipsychotic used in schizophrenia, major depression, and bipolar disorder. Quetiapine demonstrates a high level of therapeutic efficacy and low risk of adverse effects during long-term treatment. It is well-tolerated and a suitable option for some patients with high sensitivity to other drugs, such as Clozapine and Olanzapine. Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

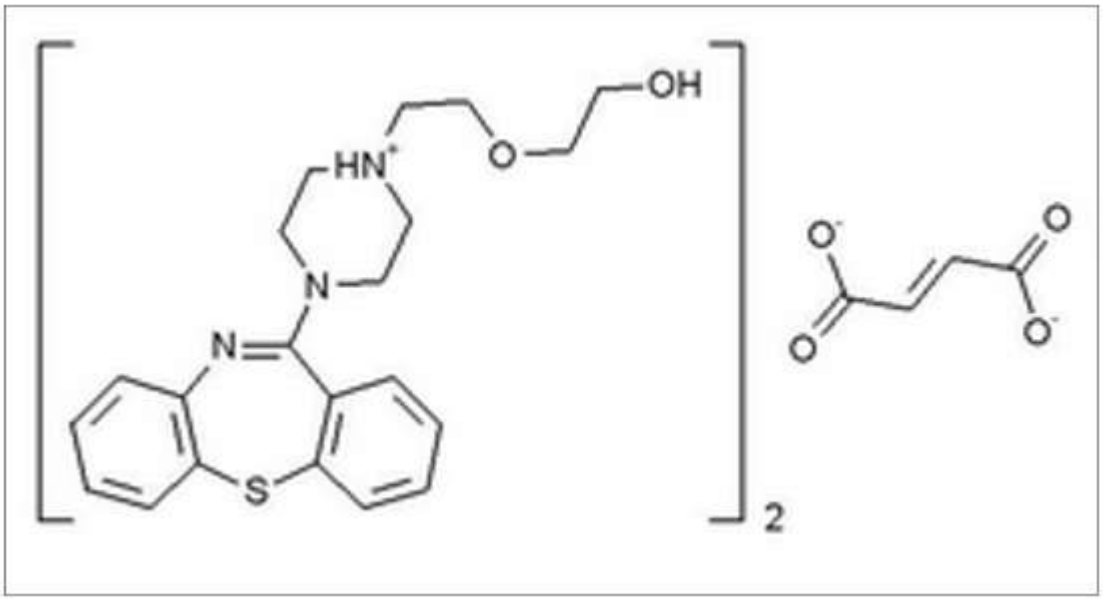


Figure 5.1: Structure of Quetiapine fumarate

Mol. Weight: 883.1

Chemical Formula: C46H54N6O8S2

IUPAC Name: 2-[2-(4-benzo[b][1,4]benzothiazepin-6-ylpiperazin-1-yl)ethoxy]ethanol;but-2-enedioic acid.

Pharmacology

Indication: Quetiapine is used in the symptomatic treatment of schizophrenia. In addition, it may be used for the management of acute manic or mixed episodes in patients with bipolar I disorder, as a monotherapy or combined with other drugs. It may be used to manage depressive episodes in bipolar disorder. In addition to the above indications, quetiapine is used in combination with antidepressant drugs for the treatment of major depression.

Some off-label uses for this drug include the management of post-traumatic stress disorder (PTSD), generalized anxiety disorder, and psychosis associated with Parkinson's disease.

Pharmacodynamics: Quetiapine improves the positive and negative symptoms of schizophrenia and major depression by acting on various neurotransmitter receptors, such as the serotonin and dopamine receptors. In bipolar disorder, it improves both depressive and manic symptoms.

Quetiapine can cause suicidal thinking or behavior in children and adolescents and should not be given to children under 10 years of age. It is important to monitor for suicidality if this drug is given to younger patients. In addition, this drug is not indicated for the treatment of psychosis related to dementia due to an increased death rate in elderly patients taking this drug.

Mechanism of action: Although the mechanism of action of quetiapine is not fully understood, several proposed mechanisms exist. In schizophrenia, its actions could occur from the antagonism of dopamine type 2 (D2) and serotonin 2A (5HT2A) receptors. In bipolar depression and major depression, quetiapine's actions may be attributed to the binding of this drug or its metabolite to the norepinephrine transporter. Additional effects of quetiapine, including somnolence, orthostatic hypotension, and anticholinergic effects, may result from the antagonism of H1 receptors, adrenergic α1 receptors, and muscarinic M1 receptors, respectively.

Absorption: Quetiapine is rapidly and well absorbed after administration of an oral dose. Steady-state is achieved within 48 hours. Peak plasma concentrations are achieved within

1.5 hours. The bioavailability of a tablet is 100%. The steady-state Cmax of quetiapine in Han Chinese patients with schizophrenia after a 300 mg oral dose of the extended released formulation was approximately 467 ng/mL and the AUC at steady-state was 5094 ng·h/mL. Absorption of quetiapine is affected by food, with Cmax increased by 25% and AUC increased by 15%.

Metabolism: The metabolism of quetiapine occurs mainly in the liver. Sulfoxidation and oxidation are the main metabolic pathways of this drug. According to in vitro studies, cytochrome P450 3A4 metabolizes quetiapine to an inactive sulfoxide metabolite and also participates in the metabolism of its active metabolite, N-desalkyl quetiapine. CYP2D6 also regulates the metabolism of quetiapine. In one study, three metabolites of N-desalkylquetiapine were identified. Two of the metabolites were identified as N-desalkylquetiapine sulfoxide and 7-hydroxy-N-desalkylquetiapine. CYP2D6 has been found to be responsible for metabolism of quetiapine to 7-hydroxy-N-desalkylquetiapine, a pharmacologically active metabolite. Individual differences in CYP2D6 metabolism may be present, which may affect the concentrations of the active metabolite.

Half-life: The average terminal half-life of quetiapine is about 6-7 hours.

Uses

This medication is used to treat certain mental/mood conditions (such as schizophrenia, bipolar disorder, sudden episodes of mania or depression associated with bipolar disorder). Quetiapine is known as an anti-psychotic drug (atypical type).

Side effects

- mood or behavior changes,
- constipation,
- stomach pain,
- upset stomach,
- nausea,
- vomiting,
- drowsiness,
- dizziness,
- lightheadedness

Excipient profile

Eudragit S100

Physical and Chemical Properties of Eudragit S100

Eudragit s 100 is anionic copolymer based on methacrylic acid and methyl methacrylate.

Non-proprietary name: Acidum methacrylicum et methylis methacrylas polymerisatum 1: 2 (BP)

Chemical/IUPAC name: poly (methacrylic-acid-co-methyl methacrylate) 1:2.

Molecular formula and weight: C8H12O4= mol/g 172.18

Description: it is a solid substance in form of a white powder with a faint characteristic odour.

Degree of deacetylation of industrial eudragit: >130

Viscosity: EUDRAGIT® L 100: 60 - 120 mPa. s EUDRAGIT® S 100: 50 - 200 mPa. s

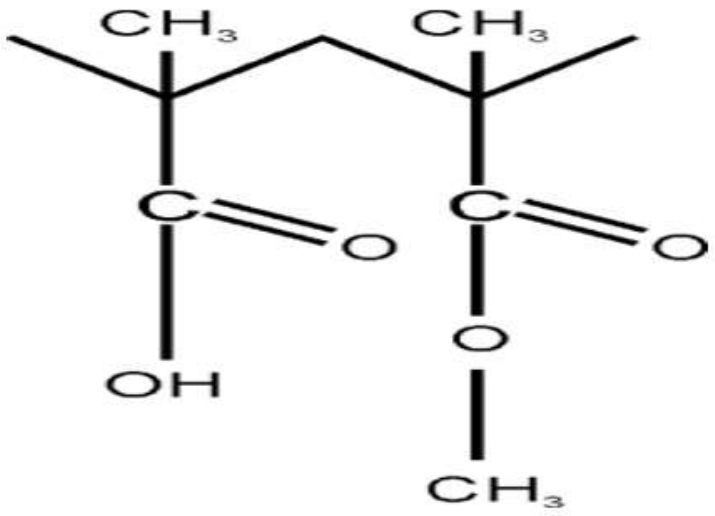


Figure 5.2: Structure of Eudragit S100

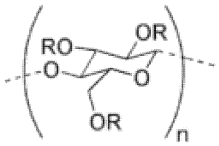
Solubility: 1 g of EUDRAGIT® L 100 or EUDRAGIT® S 100 dissolves in 7 g methanol, ethanol, in aqueous isopropyl alcohol and acetone (containing approx. 3 % water), as well as in 1 N sodium hydroxide to give clear to cloudy solutions. EUDRAGIT® L 100 and EUDRAGIT® S 100 are practically insoluble in ethyl acetate, methylene chloride, petroleum ether and water.

Functional category: Film former; tablet binder; tablet diluents.

Incompatibilities: Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. For example, coagulation may be caused by soluble electrolytes, pH changes, some organic solvents, and extremes of temperature; Interactions between polymethacrylates and some drugs can occur, although solid polymethacrylates and organic solutions are generally more compatible than aqueous dispersions.

Stability and Storage: Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 30°C.

Hydroxy propyl methyl cellulose

Name	**HPMC**
Structure	 R = H or CH_3 or $CH_2CH(OH)CH_3$
Properties	1. Hypromellose is a solid 2. Slightly off-white Powder 3. It's a Nontoxic Ingredient 4. Semisynthetic polymer
Uses	1. Pharmaceutical 2. Cosmetics 3. Detergents & cleaning 4. Excipient/tableting ingredient

	5. Used in Ophthalmic applications 6. Used as construction material

Hypromellose, short for hydroxylpropyl methylcellulose (HPMC), is a semisynthetic, dormant, viscoelastic polymer utilized as an ophthalmic oil, and additionally an excipient and controlled-conveyance segment in oral medicaments, found in an assortment of business items. As a nourishment added substance, hypromellose is an emulsifier, thickening and suspending operator, and another option to creature gelatin. Its Codex Alimentarius code (E number) is E464. It is by and large perceived as sheltered by the FDA.

Chemistry

Hypromellose is a strong, and is a marginally grayish to beige powder in appearance and might be shaped into granules. The compound structures colloids when broken down in water. This non-harmful fixing is flammable and can respond vivaciously with oxidizing specialists.

Hypromellose in a watery arrangement, not at all like methylcellulose, displays a warm gelation property. That is, the point at which the arrangement warms up to a basic temperature, the arrangement coagulates into a non-flowable however semi-adaptable mass. Normally, this basic (hardening) temperature is conversely identified with both the arrangement centralization of HPMC and the convergence of the methoxy gather inside the HPMC atom (which thusly relies upon both the level of substitution of the methoxy gathering and the molar substitution. That is, the higher the convergence of the methoxy gathering, the lower the basic temperature. The firmness/consistency of the subsequent mass, be that as it may, is specifically identified with the convergence of the methoxy gathering (the higher the focus, the more thick or less adaptable the subsequent mass.

Uses

- Oral, ophthalmic & topical pharmaceutical formulations.
- Emulsifier, suspending agent and stabilizing agent in topical gels & ointments.
- As a protective colloid, it can prevent droplets & particles from coalescing or agglomerating, thus inhibiting the formation of sediments.
- Used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses.
- It also widely used in cosmetics & food product.

Preformulation Study

Material used in investigation

Materials which are used in the investigation are listed in Table 6.1.

Table 6.1: Materials used for formulation development of gastroretentive microspheres

Sr. No.	Chemicals	Supplier
1.	Quetiapine fumarate	(Gift sample from Bioplus Life Science,Bangalore)
2.	Eudragit S100	LobaChemie Pvt. Ltd. Mumbai
3.	HPMC	LobaChemie Pvt. Ltd. Mumbai
4.	Methanol	Qualigens Fine Chemicals, Mumbai
5.	Ethanol	Qualigens Fine Chemicals, Mumbai
6.	Chloroform	Qualigens Fine Chemicals, Mumbai
7.	Hydrochloric acid (HCl)	RFCL Ltd. Mumbai

Instruments Used in Investigation

Instruments that can be used in the investigation are listed in Table 6.2.

Table 6.2: Instruments used for the preparation and evaluation of gastroretentive microspheres

Sr. No.	Instrument / Apparatus	Supplier
1.	UV -Visible Spectrophotometer	Labindia 3000+ Mumbai
2.	Fourier Transform Infra-Red Spectroscopy	Brucker, Alpha, Germany
3.	pH Meter	Electronic India
4.	Electronic Balance	Winsor, India
5.	Melting Point Apparatus	Chemline CL-725
6.	Hot Air Oven	Electronic India
7.	Sonicator	Electronic India
8.	Dissolution Testing Apparatus	Labindia DS- 8000 Mumbai

Preformulation studies

Preformulation studies were evolved in 1950 & early 1960. Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced. Preformulation investigations are designed to deliver all necessary data especially physicochemical, physico-mechanical and bio pharmaceutical properties of drug substances, excipients and packaging materials (Albert and Serjeant, 1984; Yalkowiski and Roseman, 1981).

Preformulation during drug discovery

Apart from helping formulation development, preformulation studies also help in lead identification during drug discovery phase. A new chemical entity should possess optimal biopharmaceutical properties to become a drug molecule. Mere possession of potency and selectivity does not ensure 'drug ability'. Preformulation studies help in assessing the 'drug ability' of a molecule. Preformulation can thus be considered as critical decision-making tool during both–drug discovery and development phase. A comprehensive understanding of physicochemical properties and its effect on biological performance, allows selection of potential lead molecules and in identification of drug delivery challenges.

Objectives

- To develop the elegant dosage forms (stable, effective & safe}
- It is important to have an understanding of the physical description of a drug substance before dosage form development.
- It is 1ststep in rational development of a dosage form of a drug subt before dosage form development.

Goals

- To establish the physico-chemical parameters of new drug substance.
- To establish the physical characteristics.
- To establish the compatibility with the common excipient.
- To choose the correct form of a drug substance.

Preformulation characteristics

Organoleptic properties:

Organoleptic properties of the drug substance are very important for designing the dosage form. The colour, odour and tests of the drug are characterized. Oganoleptic properties of drug were determined by direct observation of drug sample under optical microscope for its appearance color and crystal morphology.

Table 6.3: Organoleptic characteristics of Quetiapine fumarate

S. No.	Sensory characters	Result
1.	Appearance	White to off-white crystalline powder

2.	Taste	Bitter
3.	Odor	Odorless

An organoleptic property of Quetiapine fumarate was found to be white to off-white crystalline powder, bitter in taste.

Solubility Analysis:

An important physical-chemical property of a drug substance is solubility, especially aqueous solubility (Indian pharmacopeia, 2007). A drug must possess some aqueous solubility for therapeutic efficacy in the physiological pH range of 1 to 8.

Solubility is expressed in terms of maximum volume or mass of the solute that dissolve in a given volume or mass of a solvent. Pharmacopoeias give solubility's in terms of the number of parts by volume of solvent required to dissolve one part by weight of a solid, or one part by volume of a liquid. The solubility of Quetiapine fumarate was determined in various common solvents. The solubility in various aqueous and non-aqueous media is summarized in table 6.5. For the determination of solubility of Quetiapine fumarate in various solvents that were methanol, ethanol, chloroform and distilled water etc. 5mg of Quetiapine fumarate was added to 10 ml of each solvent in a test tube and shaken for few minutes at room temperature (21.0 ± 1.5°C). Note the solubility of the drug in various solvents.

Table 6.4: IP Index

Descriptive term	**Parts of solute required for** **Parts of solute**
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
slightly soluble	From 100 to1000
Very slightly soluble	From 1000 to 10000
Practically insoluble	10000 or more

Table 6.5: Solubility determination of Quetiapine fumarate in various solvent

S. No.	**Solvent**	**Solubility**
1.	Water	Slightly Soluble
2.	Ethanol	Soluble
3.	Methanol	Soluble
4.	0.1N HCl	Sparingly Soluble
5.	0.1N NaOH	Sparingly Soluble
6.	Chloroform	Soluble

Solubility of Quetiapine fumarate was examined that soluble in methanol and ethanol and chloroform, sparingly soluble in 0.1 N HCl and 0.1N NaOH, slightly soluble in water.

Loss on drying (%)

Loss on drying (LOD) is the loss of weight expressed as percentage w/w resulting from water and volatile matter of any kind that can be driven off under specified conditions (European Pharmacopoeia, 2004). Loss on drying is directly measured by IR moisture balance. Firstly, calibrated the instrument by knob, then taken 5 grams of sample (powder) and fixed the temperature at 100°C to 105°C for 15 minutes and constant reading, and fixed the knob and check percent moisture.

$$\text{Loss on drying (\%)} = \frac{\text{initial weight of sample - weight of sample after drying x 100}}{\text{Initial weight of sample}}$$

Table 6.6: Loss of drying of drug sample

S. No.	Initial weight	Final weight after 15 minutes	% loss of drying	Avg. % loss of drying
1.	5gm	4.92 gm	1.67 %	
2.	5gm	4.91 gm	1.82 %	1.56±0.26 %
3.	5gm	4.94 gm	1.2 %	

Loss on drying of Quetiapine fumarate was found to be1.56±0.26 %.

Melting point

Melting point of Quetiapine fumarate was determined using open capillary method by melting point apparatus containing castor oil.

Procedure for determine melting point:

Fine powder of the drug was filled in glass capillary tube which was sealed at one end. The capillary tube was tied to the thermometer and thermometer was kept in theils tube apparatus and then slowly increased the temperature of the apparatus and recorded the temperature at which drug was completely melted. The observed melting point of the drug was compared with melting point given in literature.

Results: The melting point of Quetiapine fumarate was found to be 182-184°C.

Determination of UV-visible absorption maxima of Quetiapine fumarate:

Preparation of calibration curve of Quetiapine fumarate in 0.1 N HCl: 10mg of Quetiapine fumarate was engaged in 10ml volumetric flask and dissolved upto 10ml with methanol to contribute the concentration of 1000 □g/ml. 1ml of beyond was diluted to 10ml with 0.1 N HCl to give concentration of 100□g/ml. From the beyond stock solution, aliquots of 0.5, 1.0, 1.5, 2.0 and 2.5 ml were shifted to 10 ml volumetric flasks and made up to the mark with 0.1 N HCl. This solution was perused in UV-Visible Spectrophotometer. The absorbance of these solutions was restrained at 244nm and a graph of concentration versus absorbance was plotted.

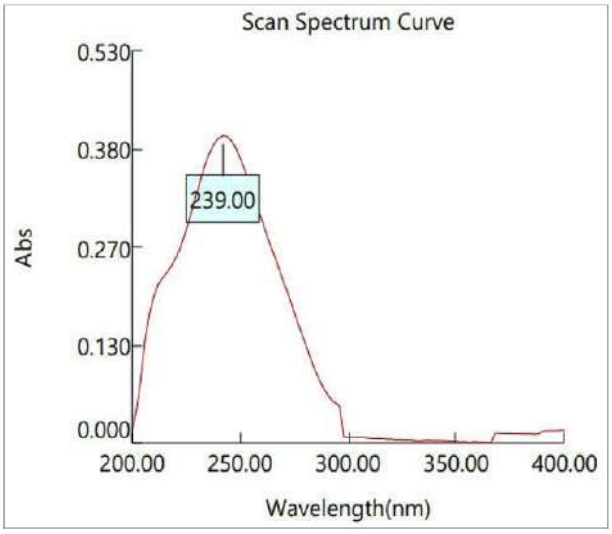


Figure 6.1: Determination of λ_{max} of Quetiapine fumarate

Table 6.7: Calibration curve of Quetiapine fumarate

S. No.	Concentration (µg/ml)	Mean absorbance
1.	5	0.121
2.	10	0.248
3.	15	0.395
4.	20	0.502
5.	25	0.623

All values are expressed in S.D (n=3)

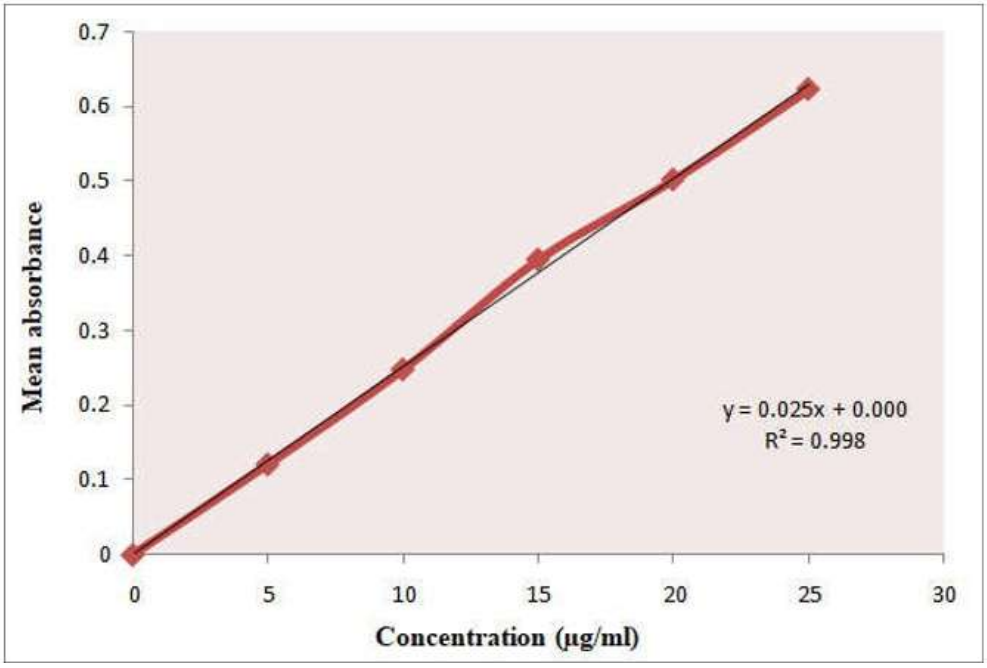


Figure 6.2: Calibration curve of Quetiapine fumarate

FTIR spectroscopy of Quetiapine fumarate:

The purity of pure drug was determined by I.R. Approximately 10 mg of Quetiapine fumarate was triturated with 100 mg of dried potassium bromide (KBr) in agatte mortar. Pellet was prepared by using KBr press pellet method. Pellet was scanned between the ranges of 400 to 2000 cm-1 with background correction. The spectrum was recorded and major peaks were determined.

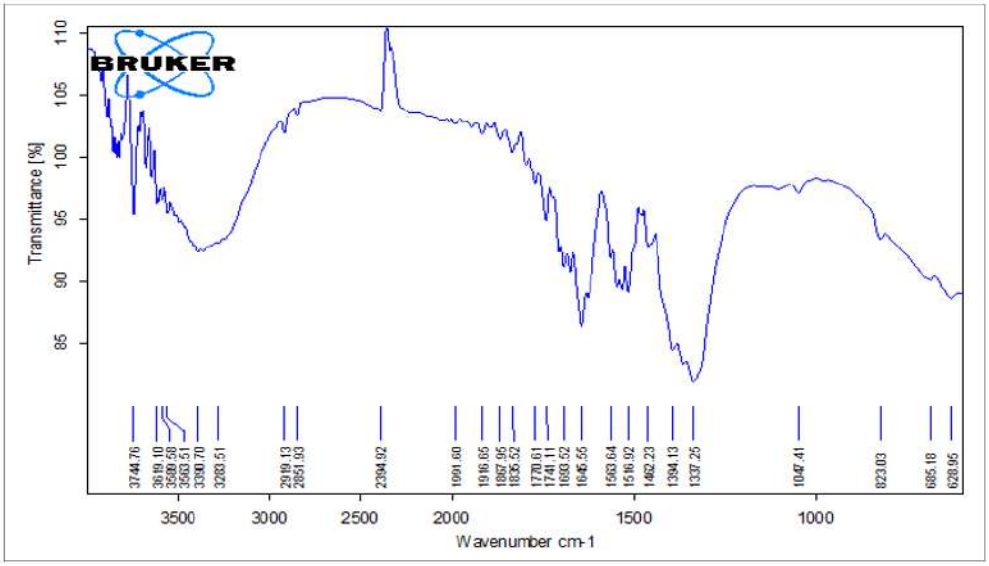


Figure 6.3: FTIR spectra of Quetiapine fumarate

Preparation and Characterization

Preparation of gastroretentive microspheres of Quetiapine fumarate

Gastroretentive microspheres loaded with Quetiapine fumarate were prepared using solvent- evaporation method using HPMC and Eudragit RLPO in different ratio table 7.1 (Rajinikanth et al., (2008). Drug and polymer in proportion of drug and polymers were dissolved in 1:2 mixture of solvent system of ethanol and dichloromethane. This clear solution was poured slowly in a thin stream into the aqueous solution of 1% polyvinyl alcohol. The emulsion was continuously stirred for 3 h at a speed of 500 rpm at 27±2°C. The floating microspheres were collected by decantation, while the non-floating microspheres were discarded. The microspheres were dried overnight at 40±2°C and stored in desicator.

Table 7.1: Formulations of the gastroretentive microspheres

S. No.	rmulation Code	Quetiapine fumarate (mg)	HPMC (mg)	Eudragit RLPO (mg)	Eudragit RSPO (mg)
1.	F1	25	150	25	-
2.	F2	25	150	50	-
3.	F3	25	150	75	-
4.	F4	25	150	-	25
5.	F5	25	150	-	50
6.	F6	25	150	-	75

HPMC: Provides swelling and matrix formation for drug release control and buoyancy.

Eudragit RLPO: Enhances initial drug release and contributes to microsphere buoyancy.

Eudragit RSPO: Controls the sustained release of the drug and maintains the structural integrity of the microspheres.

Ethanol: Used for dissolving hydrophilic polymers (like HPMC) and the drug. It also aids in the rapid evaporation process and helps form a uniform dispersion.

Dichloromethane (DCM): Used for dissolving hydrophobic polymers (like Eudragit RLPO and RSPO). It helps form a stable emulsion and ensures proper microsphere formation through controlled solvent evaporation.

Evaluation of microspheres

Percentage Yield

The prepared microspheres with a size range of 1µm to 1000µm were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres (Patel et al., 2006).

$$\% \text{ Yield } = \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} x\ 100$$

Drug Entrapment

The various formulations of the Floating microspheres were subjected for drug content. 10 mg of Floating microspheres from all batches were accurately weighed and crushed (Harsha, 2012). The powder of microspheres was dissolved in 10 ml 0.1 N HCl and centrifuge at 1000 rpm. This supernatant solution is than filtered through whatmann filter paper No. 44. After filtration, from this solution 0.1 ml was taken out and diluted up to 10 ml with 0.1 N HCl. The percentage drug entrapment was calculated using calibration curve method.

Floating behavior: Ten milligrams of the floating microspheres were placed in 0.1 N HCl (100 mL). The mixture was stirred at 100 rpm in a magnetic stirrer. After 10 h, the layer of buoyant microsphere was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in desiccators until a constant weight was obtained (Harsha, 2012). Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

$$\text{Percent buoyancy} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} x\ 100$$

Measurement of mean particle size

The mean size of the microspheres was determined by Photo Correlation Spectroscopy (PCS) on a submicron particle size analyzer (Malvern Instruments) at a scattering angle of 90°. A sample (0.5mg) of the microspheres suspended in 5 ml of distilled water was used for the measurement (Srivastava et al., 2005).

Determination of zeta potential

The zeta potential of the drug-loaded microspheres was measured on a zeta sizer (Malvern Instruments) by determining the electrophoretic mobility in a micro electrophoresis flow cell (Srivastava et al., 2005). All the samples were measured in water at 25°C in triplicate.

Shape and surface characterization of microspheres by scanning electron microscopy (SEM)

From the formulated batches of microspheres, formulations (F3) which showed an appropriate balance between the percentage releases were examined for surface morphology and shape using scanning electron microscope Jeol Japan 6000. Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator (Barhate et al., 2009). The acceleration voltage was set at 10KV during scanning. Microphotographs were taken on different magnification and higher magnification (200X) was used for surface morphology.

In-vitro release studies

The in vitro drug release rate from Floating microspheres was carried out using the USP type II (Electro Lab.) dissolution paddle assembly (Barhate et al., 2009). A weighed amount of floating microspheres equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCI (pH=1.2) maintained at 37 ± 0.5°C and stirred at 55rpm. One ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. The collected samples analyzed spectrophotometrically at 239 nm to determine the concentration of drug present in the dissolution medium.

Drug release kinetic data analysis

Several kinetic models have been proposed to describe the release characteristics of a drug from matrix. The following three equations are commonly used, because of their simplicity and applicability. Equation 1, the zero-order model equation (Plotted as cumulative percentage of drug released vs time); Equation 2, Higuchi's square-root equation (Plotted as cumulative percentage of drug released vs square root of time); and Equation 3, the Korsemeyer-Peppas equation (Plotted as Log cumulative percentage of drug released vs Log time).

To study the release kinetics of Quetiapine fumarate from the Floating microspheres the release data was fitted to these equations

1. **Zero order equation:** When a graph of the cumulative percentage of the drug released from the matrix against time is plotted, zero order release is linear in such a plot, indicating that the release rate is independent of concentration.

$$Q_t = k_0.t \text{……..} (1)$$

Where Q_t is the percentage of drug released at time t and k_0 is the release rate constant;

2. **First order equation:**

$$\text{In } (100\text{-}Q_t) = \text{In } 100\text{- } k_I.t \text{……}(2)$$

Where kI is the release rate constant;

3. **Higuchi's equation:**

$$Q_t = k^H.t^{1/2} \text{……}(3)$$

Where K_H is the Higuchi release rate constant

4. **Korsemeyer-Peppas:**

The curves plotted may have different slopes, and hence it becomes difficult to exactly pin-point which curve follows perfect zero order release kinetics. Therefore, to confirm the kinetics of drug release, data were also analyzed using Korsemeyer's equation.

$$Q_t/Q_\infty = k_{KP}.t^n$$

Where Q_t/ Q_∞ is the fraction of drug released at time t, k_{KP}a constant compromising the structural and geometric characteristics of the device and n is the release exponent.

The slope of the linear curve gives the 'n' value. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. The value of 'n' gives an indication of the release mechanism. When n = 1, the release rate is independent of time (typical zero order release / case II transport); n = 0.5 for Fickian release (diffusion/ case I transport); and when $0.5 < n < 1$, anomalous (non-Fickian or coupled diffusion/ relaxation) are implicated. Lastly, when $n > 1.0$ super case II transport is apparent. 'n' is the slope value of log Mt/M∞ versus log time curve.

Stability studies for optimized formulation

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a re-test period for the drug substance or a shelf life for drug product and recommended storage conditions. In general, a drug substance should be evaluated under storage condition (with appropriate tolerances) that test its thermal stability and if applicable, its sensitivity to moisture. Three types of storage conditions are used i.e. long term, Accelerated and where appropriate, Intermediate.

Table 7.2: General guideline for stability study

Study	Storage conditions	Minimum time period covered by data at submission
Long term	25±2°C/60±5% RH or 30±2°C/65±5% RH	12 months
Intermediate	30±2°C/65±5% RH	6 months
Accelerated	40±2°C/75±5% RH	6 months

Table 7.3: Sampling Intervals

Storage conditions	Sampling intervals
Real time storage 30°C/75% RH	0, 3, 6, 9, 12, 18, 24, 36, 48, 60, months
Accelerated 40°C/75% RH	0, 1, 3, 6 months

Results and Discussion

Evaluation of Quetiapine fumarate microspheres

Percentage Yield

The percentage yield of gastroretentive microspheres loaded with Quetiapine fumarate provides critical insight into the efficiency and effectiveness of the formulation process. This metric represents the amount of product recovered after the preparation process in relation to the theoretical yield, serving as a key indicator of process efficiency. The observed percentage yields for the six formulations ranged from 71.12% for F6 to 86.65% for F3, highlighting some variability among the different formulations. Several factors contribute to this variation, including the specific polymer composition, the solvent evaporation process, and the stability of the emulsion formed during preparation.

Formulations F1 and F2, which showed yields of 74.65% and 74.45%, respectively, exhibited relatively consistent recovery rates, suggesting that the ratio of HPMC to Eudragit RLPO in these formulations is conducive to efficient microsphere formation. Both polymers play complementary roles in forming stable microspheres, with HPMC being hydrophilic and Eudragit RLPO being hydrophobic. These formulations benefit from the balanced interaction between these polymers, leading to satisfactory yield values. In contrast, Formulation F3, with a higher yield of 86.65%, may have benefited from a higher proportion of Eudragit RLPO, which is a more hydrophobic polymer, potentially promoting better microsphere formation and higher encapsulation efficiency. This formulation's higher yield indicates that this specific polymer ratio leads to a more stable emulsion and better product recovery.

Formulation F4, which yielded 79.85%, contained a combination of HPMC and Eudragit RSPO. The addition of Eudragit RSPO, a more rigid polymer compared to Eudragit RLPO, may have helped enhance the microsphere matrix, leading to a higher yield compared to F1 and F2. Formulations F5 and F6, with yields of 77.32% and 71.12%, respectively, show a slight decrease in yield, with F6 achieving the lowest. The decreased yield in F5 and F6 can be attributed to the higher concentration of Eudragit RSPO, which might have affected the emulsion's stability and the solvent evaporation process. Eudragit RSPO, being a more rigid polymer, could have influenced the consistency and formation of microspheres, potentially causing some material loss during the preparation and drying processes.

Table 8.1: Percentage yield for different formulation

S. No.	Formulation	Percentage Yield
1.	F1	74.65±0.15
2.	F2	74.45±0.32
3.	F3	86.65±0.22
4.	F4	79.85±0.15
5.	F5	77.32±0.38
6.	F6	71.12±0.44

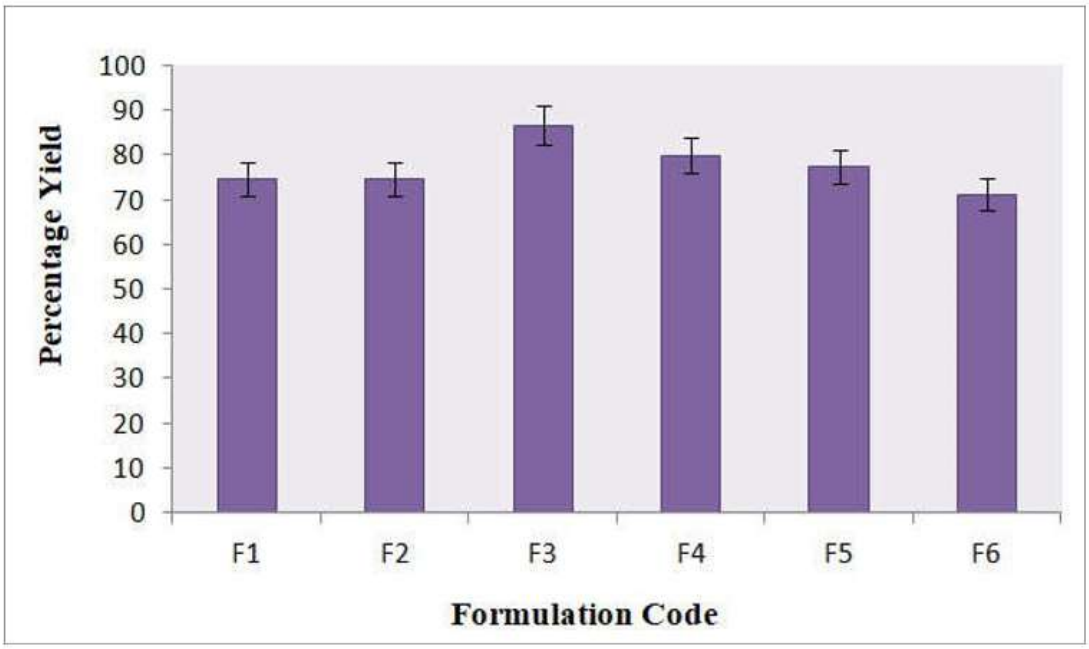


Figure 8.1: Percentage yield for different formulation

Drug Entrapment

The drug entrapment efficiency of the gastroretentive microspheres loaded with Quetiapine fumarate is a crucial factor in determining the effectiveness of the formulation in delivering the active pharmaceutical ingredient (API) over an extended period. This parameter indicates the proportion of the total drug that is successfully encapsulated within the microsphere matrix as opposed to being lost during the preparation process. The drug entrapment percentages for the six formulations ranged from 69.85% (F6) to 79.88% (F3), indicating varying levels of encapsulation efficiency among the formulations.

Formulations F1 and F2 demonstrated drug entrapment efficiencies of 69.98% and 70.25%, respectively, which were relatively consistent. These formulations incorporated a balance of HPMC and Eudragit RLPO, suggesting that this combination of polymers is effective at encapsulating a significant portion of the drug within the microspheres. The moderate drug entrapment observed in F1 and F2 may indicate that while the formulation allows for effective entrapment, there might be slight losses due to the process conditions or the proportion of the polymers used. HPMC, being a hydrophilic polymer, facilitates the formation of a matrix that is capable of retaining a good amount of the drug, but the addition of Eudragit RLPO could have affected the overall drug loading due to its hydrophobic nature.

Formulation F3 showed the highest drug entrapment efficiency at 79.88%. This higher value could be attributed to the increased amount of Eudragit RLPO in the formulation. The more hydrophobic nature of Eudragit RLPO likely improved the entrapment of Quetiapine fumarate by reducing the leaching or migration of the drug into the external medium during the preparation and drying stages. The increased drug-polymer interaction in F3, potentially aided by the polymer's film-forming characteristics, results in higher encapsulation efficiency. This suggests that a higher concentration of Eudragit RLPO, while maintaining a balance with HPMC, can enhance drug retention within the microsphere matrix.

Formulation F4, with a drug entrapment efficiency of 73.32%, also showed a reasonable drug loading capacity. This formulation included Eudragit RSPO, which is a more rigid polymer compared to Eudragit RLPO. The

presence of Eudragit RSPO could have contributed to a more stable matrix, allowing for efficient drug entrapment. The drug entrapment efficiency in F4 is slightly lower than in F3, possibly due to the slightly different matrix characteristics imparted by Eudragit RSPO. Despite this, the formulation still exhibited a relatively high drug entrapment percentage.

Formulations F5 and F6 exhibited drug entrapment efficiencies of 74.45% and 69.85%, respectively. These formulations contained increasing concentrations of Eudragit RSPO. The decrease in drug entrapment observed in F6, with the lowest value, might be due to the higher concentration of Eudragit RSPO, which could have caused the matrix to become too rigid, limiting the ability of the microspheres to encapsulate the drug effectively. The slightly lower entrapment in F5 and F6 could also be attributed to the processing conditions or the solubility behavior of the drug in the chosen solvent system.

Table 8.2: Drug Entrapment for Different formulations

S. No.	Formulation	Drug entrapment (% w/w) of prepared microsphere
1.	F1	69.98±0.45
2.	F2	70.25±0.32
3.	F3	79.88±0.15
4.	F4	73.32±0.36
5.	F5	74.45±0.18
6.	F6	69.85±0.22

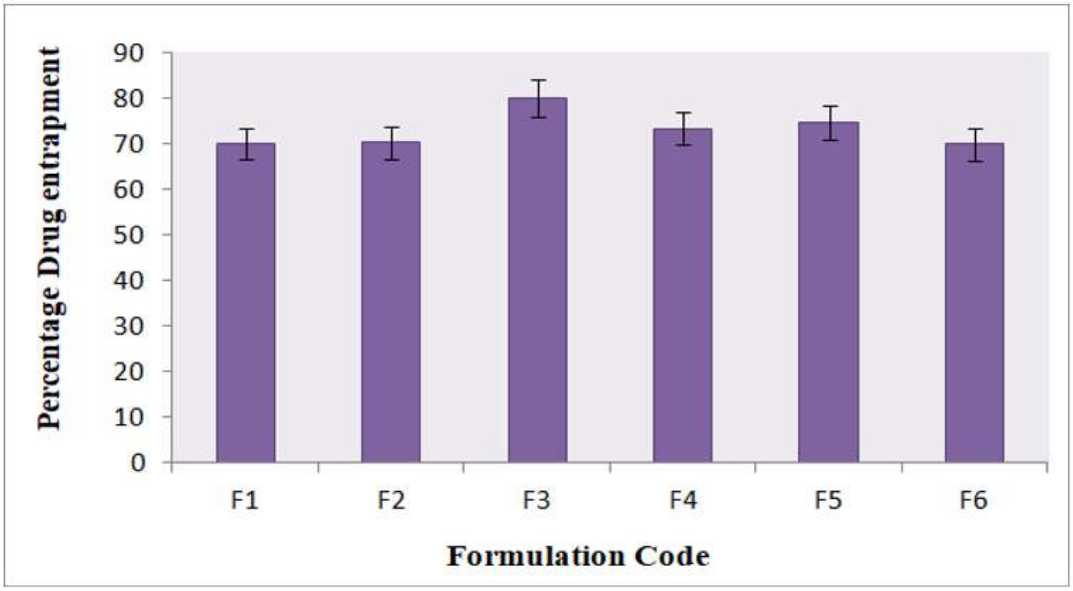


Figure 8.2: Drug entrapment for different formulation

Percentage Buoyancy and floating lag time of floating microsphere

The floating lag time and percentage buoyancy are essential characteristics of gastroretentive microspheres, as they directly influence the ability of the microspheres to remain in the stomach for prolonged periods, thus enhancing the drug's bioavailability and therapeutic efficacy. The floating lag time refers to the time taken for the microspheres to initially float on

the surface of the medium after being introduced, while the percentage buoyancy indicates the proportion of microspheres that remain afloat during the test.

The floating lag time results varied across the formulations, ranging from 60 seconds (F3) to 88 seconds (F4). The formulation F3 showed the shortest floating lag time of 60±3 seconds, which can be attributed to the higher concentration of Eudragit RLPO. Eudragit RLPO, being a hydrophobic polymer, tends to impart buoyancy to the microspheres, allowing them to float quickly upon contact with the gastric fluid. This rapid buoyancy suggests that the microspheres in F3 can quickly reach the desired floating state, which is favorable for gastroretentive drug delivery systems.

Formulations F1, F2, F5, and F6 exhibited intermediate floating lag times, ranging from 68 seconds to 75 seconds. These formulations balanced the amounts of HPMC and either Eudragit RLPO or RSPO, producing a moderate lag time that might indicate a compromise between matrix rigidity and buoyancy. The presence of HPMC, a hydrophilic polymer, contributes to the formation of a gel layer that absorbs water, helping to initiate buoyancy. However, the variation in lag time may be influenced by the specific ratios of polymers used in each formulation.

The percentage buoyancy results ranged from 68.5% (F2) to 85.6% (F3), demonstrating that the formulations exhibited good buoyancy, but with varying degrees of efficiency. Formulation F3 showed the highest buoyancy at 85.6±0.2%, likely due to the higher proportion of Eudragit RLPO, which significantly enhances the floating capacity of the microspheres. The hydrophobic nature of Eudragit RLPO prevents rapid disintegration in gastric fluid, promoting the buoyancy of the microspheres and allowing them to remain afloat for extended periods. This high buoyancy is desirable for gastroretentive systems, as it ensures the microspheres stay in the stomach for prolonged drug release.

Formulation F4, which had a moderate buoyancy of 78.8±0.3%, also showed good floating properties, though it was lower than F3. This can be attributed to the use of Eudragit RSPO, which is more rigid and less likely to swell as quickly in gastric fluid, resulting in a slightly lower buoyancy compared to F3. However, the formulation still demonstrated favorable buoyancy and remained afloat for a substantial amount of time, making it suitable for gastroretentive drug delivery.

Formulations F1, F2, F5, and F6 exhibited buoyancy values ranging from 68.5% to 71.2%. Although these formulations showed lower buoyancy than F3 and F4, they still possessed sufficient floating ability to retain the drug in the stomach. The combination of HPMC with either Eudragit RLPO or RSPO in these formulations may not have achieved the same level of floating ability as F3 but still contributed to a reasonable buoyancy.

The results of floating lag time and percentage buoyancy provide important insights into the effectiveness of different formulations for gastroretentive drug delivery. Formulation F3, which contained the highest amount of Eudragit RLPO, exhibited the shortest floating lag time and the highest percentage buoyancy, making it the most favorable for prolonged gastric retention.

Table 8.3: Percentage Buoyancy and floating lag time of floating microsphere

Formulation	Floating Lag Time (Sec.)	Percentage Buoyancy
F1	68±5	71.2±0.6
F2	74±8	68.5±0.5
F3	60±3	85.6±0.2
F4	88±4	78.8±0.3
F5	75±6	71.1±0.4
F6	73±3	69.9±0.7

The maximum percentage yield, drug entrapment, percentage buoyancy and floating lag time was found to be formulation F3 in floating microsphere. The optimized formulation of both batches subjected to further studies.

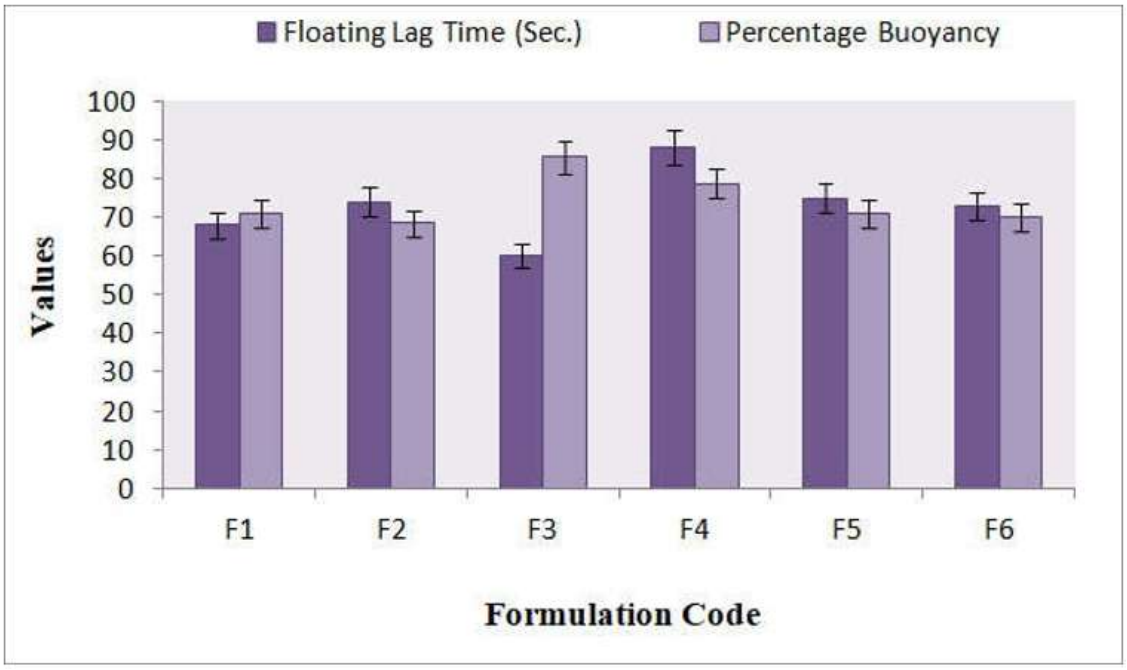


Figure 8.3: Floating lag time and percentage buoyancy for different formulation

Particle size analysis

The mean size of the microspheres was determined by photo correlation spectroscopy (PCS) on a submicron particle size analyzer (Malvern particle size analyzer) at a scattering angle of 90°. A sample (0.5mg) of the microspheres suspended in 5 ml of distilled water was used for the measurement. The results of measurement of mean particle size of optimized formulation F3 of floating microsphere was found to be 210.32 nm.

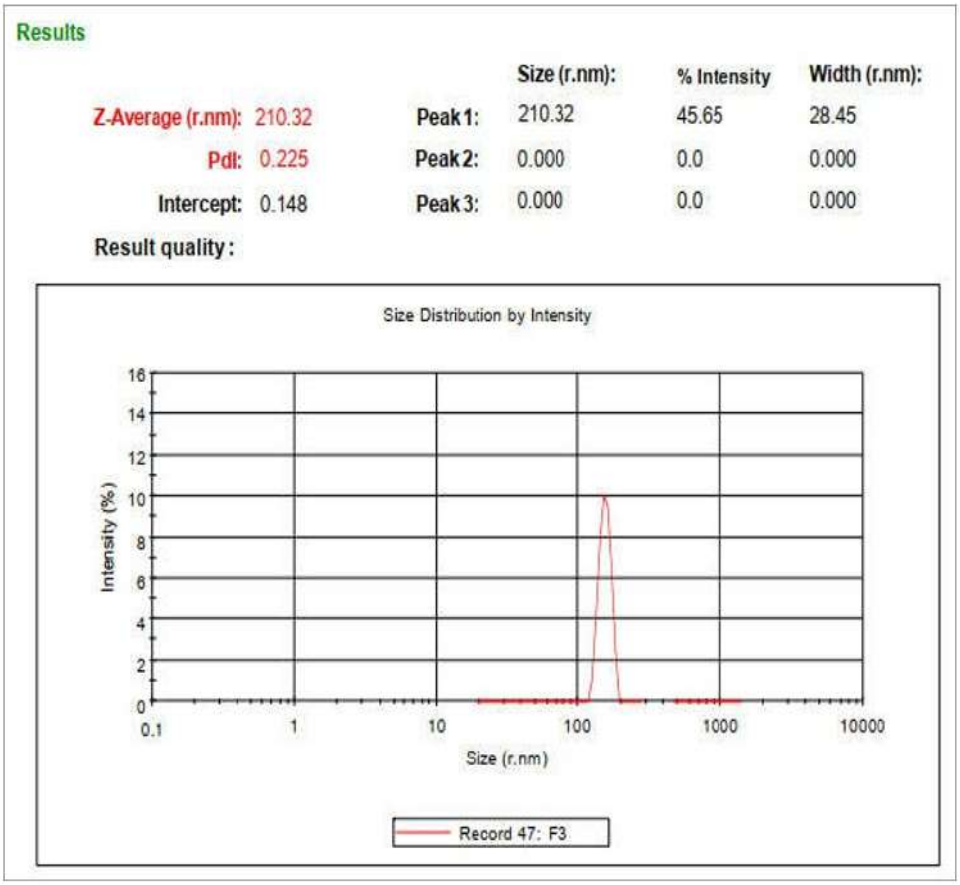


Figure 8.4: Particle size data of optimized microsphere formulation F3

Zeta Potential

The zeta potential of the drug-loaded microspheres was measured on a zeta sizer (Malvern Instruments) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25°C in triplicate. Results of zeta potential of optimized formulation F3 of floating microsphere was found -38.20 mV.

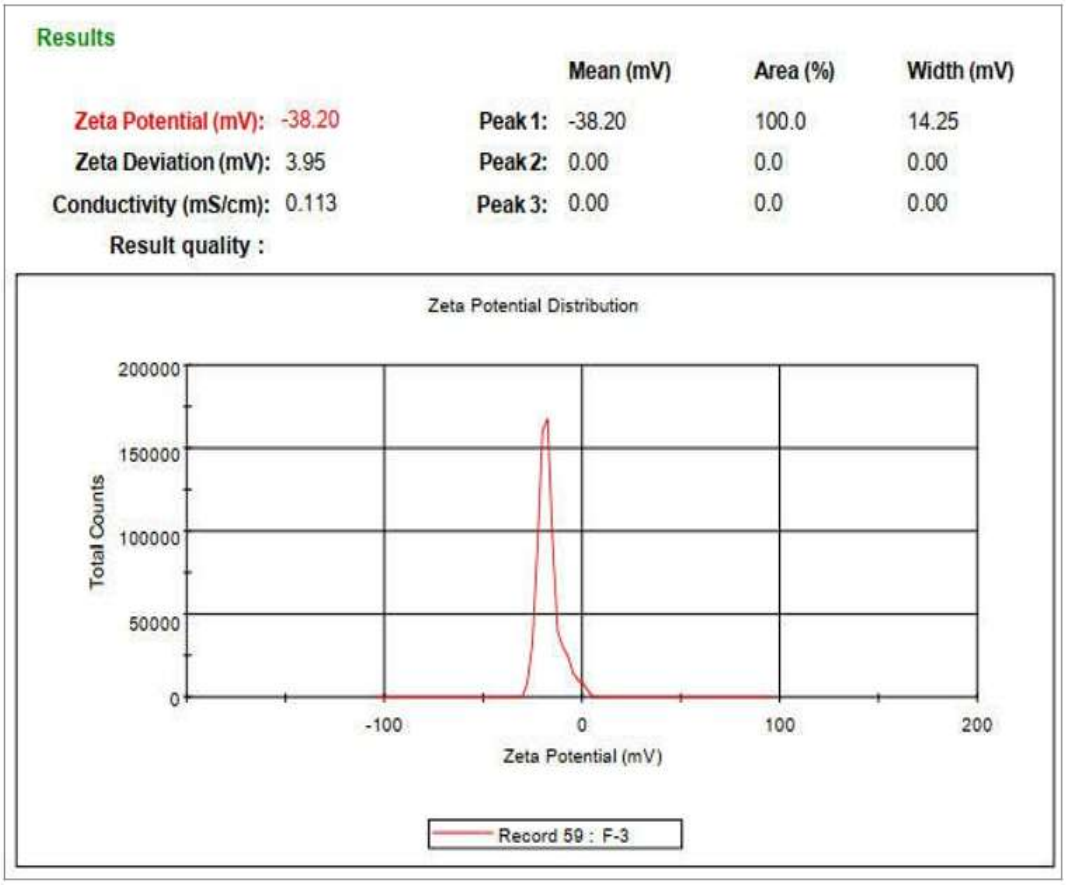


Figure 8.5: Zeta potential data of floating microsphere F3

Shape and Surface Characterization of Microspheres by Scanning Electron Microscopy (SEM)

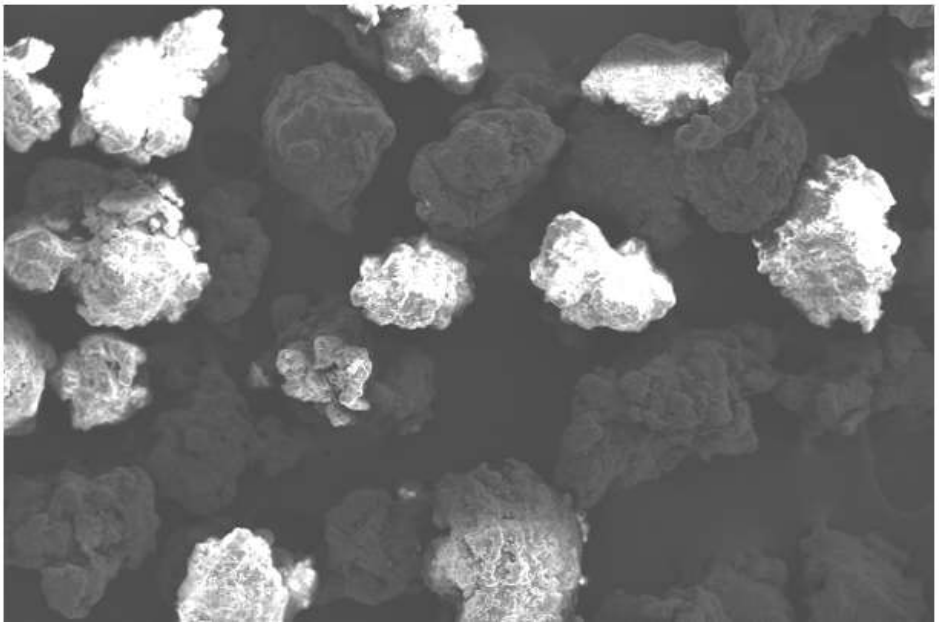


Figure 8.6: Graph of scanning electron microscopy (SEM) of optimized formulation F3

In vitro drug release study of Quetiapine fumarate loaded microsphere

Table 8.4: Release Study data of formulation F1-F6

Time (Hrs)	% of Drug Release						
	F1	F2	F3	F4	F5	F6	Marketed Formulation (Quetiapine fumarate 25mg Tablet)
0.5	35.65	30.45	26.65	32.25	34.42	35.45	35.65
1	56.33	45.65	39.98	45.65	49.98	48.85	65.65
2	65.54	53.32	45.65	43.32	55.65	53.32	99.12
4	76.65	65.45	61.14	65.58	69.98	65.56	
6	89.92	76.65	73.32	73.32	75.65	73.32	
8	98.85	88.98	85.65	85.65	89.98	85.65	
10	99.12	99.85	95.65	98.85	98.89	98.85	
12	99.45	99.92	99.12	99.12	99.12	99.12	

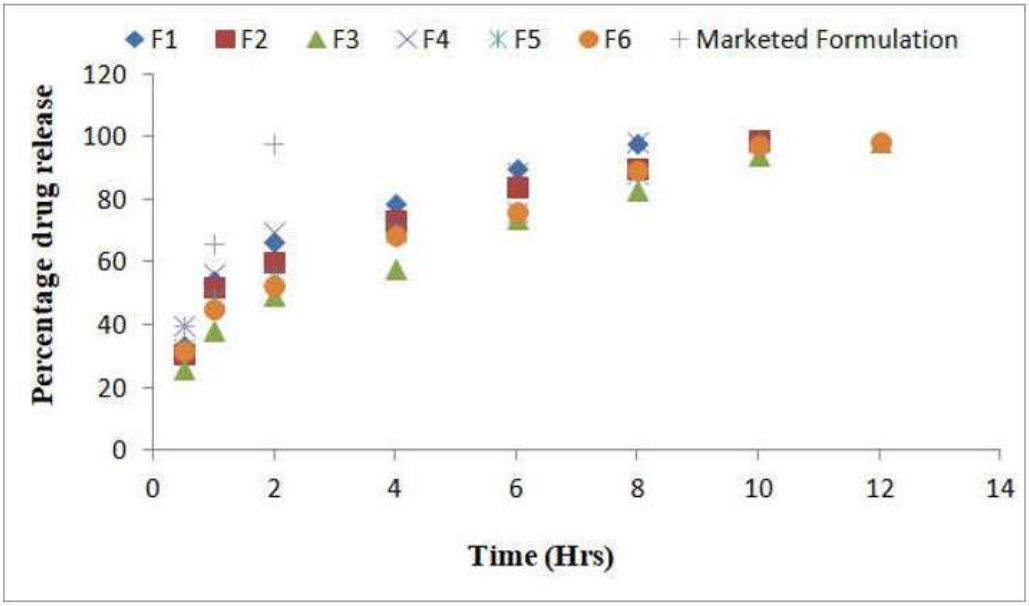


Figure 8.7: Graph of release study of formulation F1-F6

Table 8.5: Release Kinetics of optimized formulation of microsphere F3

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative % Drug Release	Log Cumulative % Drug Released	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	26.65	1.426	73.35	1.865
1	1.000	0.000	39.98	1.602	60.02	1.778
2	1.414	0.301	45.65	1.659	54.35	1.735
4	2.000	0.602	61.14	1.786	38.86	1.590
6	2.449	0.778	73.32	1.865	26.68	1.426
8	2.828	0.903	85.65	1.933	14.35	1.157
10	3.162	1.000	95.65	1.981	4.35	0.638
12	3.464	1.079	99.12	1.996	0.88	-0.056

Zero order release kinetics of optimized formulations

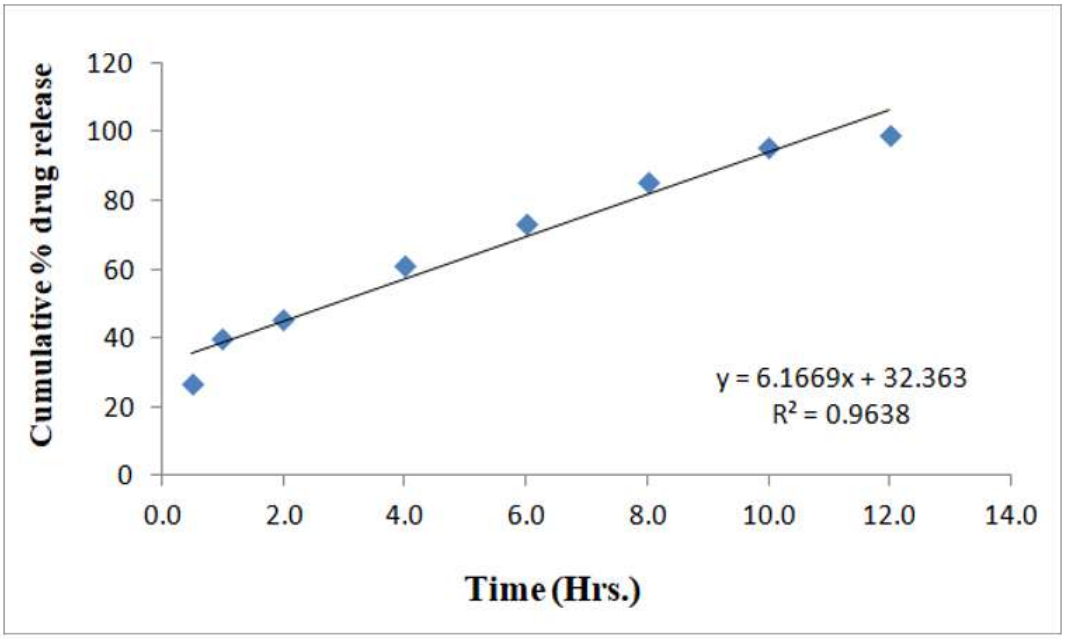


Figure 8.8: Zero order release kinetics graph of optimized formulations

First order release kinetics of optimized formulations

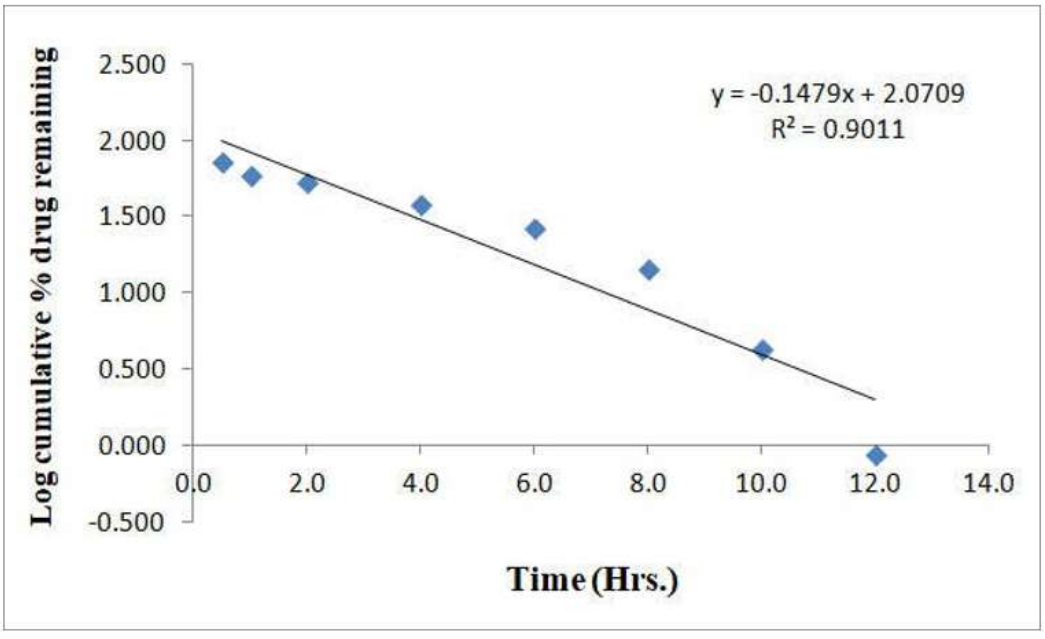


Figure 8.9: First order release kinetics graph of optimized formulations

Higuchi release kinetics of optimized formulations

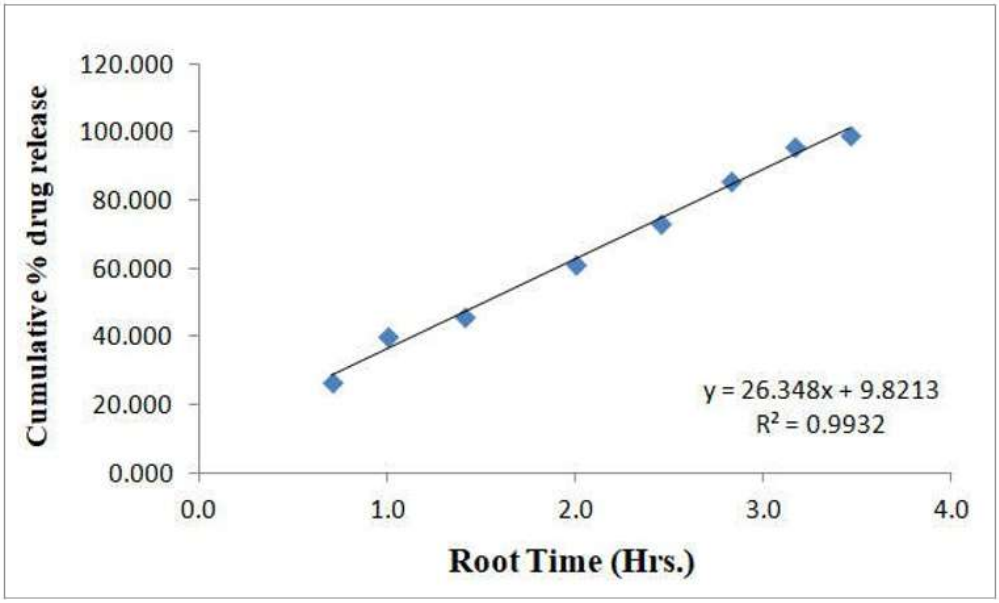


Figure 8.10: Higuchi release kinetics graph of optimized formulations

Korsmeyer peppas release kinetics of optimized formulations

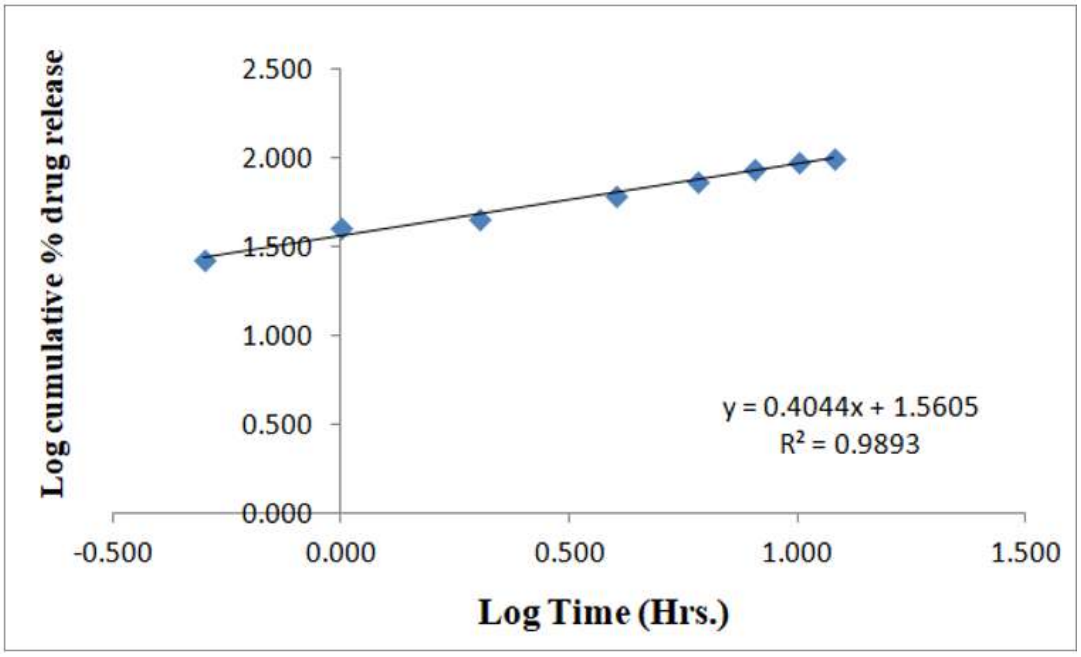


Figure 8.11: Graph of korsmeyer peppas release kinetics of optimized formulations

Table 8.6: Comparative study of regression coefficient of optimized Formulation F3

Release Kinetics	Zero order	First order	Higuchi	Korsmeyer peppas
R^2	0.9638	0.9011	0.9932	0.9893

The optimized formulation F3 appears to be well-suited for controlled and sustained release of Quetiapine fumarate, with its release kinetics primarily following the Higuchi model. These findings support the use of this formulation for gastroretentive drug delivery, where a controlled and prolonged release of the drug is essential for maximizing therapeutic effects.

Stability studies of final formulation

According to ICH guidelines, 3 months accelerated stability study at 40±2°C and 75±5% RH optimized formulations (F3) was carried out. It showed negligible change over time for parameters like appearance, drug content, dissolution and assay etc., No significant difference observed in the drug content between initial and formulations stored at 40±2°c & 75±5% RH for 3 months.

Summary and Conclusion

The organoleptic characteristics of Quetiapine fumarate reveal important sensory properties that can influence its formulation and administration. The drug is described as a white to off-white crystalline powder, which suggests a high level of purity. It has a bitter taste, a common trait for many pharmaceutical compounds, which may necessitate taste-masking strategies in oral formulations. Additionally, Quetiapine fumarate is odorless, which is advantageous for incorporation into dosage forms such as tablets or capsules, where the odor might otherwise affect the overall sensory experience.

In terms of solubility, Quetiapine fumarate exhibits varying degrees of solubility in different solvents, which is important for both its formulation and bioavailability. It is slightly soluble in water, which could pose challenges for its dissolution in the gastrointestinal tract and may necessitate strategies to improve its solubility. The drug is soluble in ethanol, methanol, chloroform, and has sparing solubility in both 0.1N HCl and 0.1N NaOH, indicating that it can dissolve in both acidic and slightly alkaline conditions, which are relevant to its performance in the stomach and small intestine. This solubility profile can guide formulation approaches to enhance the drug's absorption.

The loss of drying analysis revealed a minimal moisture content, with an average loss of drying of 1.56%, suggesting that Quetiapine fumarate is stable and free from excess moisture that could affect its integrity and shelf life. The melting point of the drug was found to be between 182-184°C, which further confirms its high purity, as impurities typically lower and broaden the melting point range. This characteristic is essential for ensuring that the drug maintains its desired physical form during storage and use.

A calibration curve generated for Quetiapine fumarate demonstrated a linear relationship between concentration and absorbance, confirming that the drug follows Beer's Law. This makes it suitable for quantitative analysis, and the data obtained can be used for accurately determining the concentration of Quetiapine fumarate in solution for applications such as drug release studies and quality control tests. Finally, the FTIR spectroscopy of Quetiapine fumarate provided detailed information about the functional groups and chemical bonds present in the drug, further confirming its identity and purity.

The preparation of gastroretentive microspheres loaded with Quetiapine fumarate was successfully achieved using the solvent-evaporation method. Various formulations, F1 to F6, were prepared by varying the ratio of HPMC (hydroxypropyl methylcellulose) and

Eudragit RLPO, with the goal of enhancing the drug's gastroretentive properties. The formulations were characterized for key parameters such as percentage yield, drug entrapment, buoyancy, floating lag time, particle size, zeta potential, and in-vitro drug release.

The percentage yield of the microspheres varied across the formulations, with F3 showing the highest yield (86.65±0.22%), indicating the optimal combination of polymers for the preparation process. Drug entrapment was also relatively high, particularly in formulation F3 (79.88±0.15%), indicating good loading

capacity. These results suggest that the formulation can effectively encapsulate Quetiapine fumarate within the microspheres, ensuring its sustained release over time.

The buoyancy and floating lag time of the microspheres were crucial in determining their ability to remain in the stomach for extended periods. Formulation F3 exhibited the best buoyancy (85.6±0.2%) and the shortest floating lag time (60±3 sec), making it the most promising formulation for gastroretentive drug delivery. These characteristics are vital for enhancing the bioavailability of Quetiapine fumarate by prolonging its gastric residence time and ensuring more efficient absorption in the gastrointestinal tract.

The optimized formulation, F3, demonstrated excellent in-vitro drug release profiles, with a sustained and controlled release over 12 hours. The release data were analyzed using different kinetic models, and the formulation exhibited a good fit to the Higuchi and Korsmeyer-Peppas models (R^2=0.9932 and 0.9893, respectively), indicating that drug release followed diffusion-controlled mechanisms. This sustained release behavior is desirable for Quetiapine fumarate, as it allows for prolonged therapeutic effects, improving patient compliance and minimizing side effects associated with fluctuating drug concentrations.

Particle size analysis of the optimized formulation (F3) revealed a mean size of 210.32 nm, indicating the formulation's suitability for controlled release. Zeta potential analysis further confirmed the stability of the microspheres, with a value of -38.20 mV, suggesting that the particles were sufficiently stable and unlikely to aggregate.

The stability study, conducted as per ICH guidelines, indicated that formulation F3 was stable under accelerated conditions (40±2°C and 75±5% RH) for 3 months, with no significant changes in appearance, drug content, or dissolution profile. This result further affirms the stability of the microspheres and their potential for long-term storage and use.

In conclusion, the prepared gastroretentive microspheres of Quetiapine fumarate (F3) demonstrated excellent physical and chemical characteristics, including high drug entrapment efficiency, desirable buoyancy, a controlled and sustained release profile, and good stability under accelerated conditions. These findings suggest that formulation F3 is a promising candidate for improving the therapeutic efficacy of Quetiapine fumarate through a controlled, gastroretentive drug delivery system, offering potential benefits such as enhanced bioavailability, prolonged therapeutic action, and improved patient compliance.

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