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# FORMULATION, DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE GASTRO-RETENTIVE DRUG DELIVERY SYSTEM FOR QUETIAPINE FUMARATE

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**ABSTRACT:**

This study aimed to formulate, develop, and evaluate sustained-release gastro-retentive drug delivery systems for Quetiapine Fumarate (QF). The pre-formulation study involved determining the drug's organoleptic properties, melting point (173.33±0.58°C to 176.00±1.00°C), and UV absorbance maxima (248nm). Method validation confirmed the UV spectroscopic method's accuracy, precision, ruggedness, and robustness, with recovery percentages ranging from 99.152% to 100.031% and %RSD under 1%. Solubility studies revealed QF's solubility in water, methanol, ethanol, 0.1N HCl, and phosphate buffer pH 6.8. The partition coefficient in an n-octanol/water mixture was determined. QF-loaded microspheres were prepared using the solvent diffusion evaporation method, with various parameters screened for optimization. Evaluation showed microspheres with physical appearances ranging from nearly spherical to uniform, with percentage yields ranging from 80.565% to 96.859%. In-vitro drug release profiles exhibited a biphasic pattern, with an initial burst release followed by sustained release. In-vivo pharmacokinetic studies and stability assessments over time further characterized the developed formulation.

**Keywords:** Pre-formulation study, microspheres, Quetiapine Fumarate, partition coefficient, Gastro-retentive drug delivery, sustained release, pharmacokinetic studies, Drug release kinetics, Antipsychotic drugs.

## Introduction:

Managing psychiatric disorders, particularly those requiring antipsychotic medications, presents notable challenges due to the intricate pharmacokinetics and dosing schedules linked with

conventional drug delivery systems. To counter these hurdles, there's been increasing interest in crafting innovative drug delivery platforms tailored to antipsychotic drugs, featuring sustained release and gastro-retentive properties. This review article offers a thorough examination of the design and evolution of sustained-release gastro-retentive drug delivery systems for antipsychotic medications, with the aim of boosting therapeutic effectiveness, refining drug availability, and promoting patient compliance.

Psychiatric disorders like schizophrenia and bipolar disorder often require long-term treatment with antipsychotic medications. However, conventional drug delivery systems face challenges like poor solubility and variable absorption, leading to inconsistent dosing and patient non-adherence. To overcome these issues, sustained-release gastro-retentive drug delivery systems have emerged, offering prolonged drug release and improved bioavailability. This review explores the development and applications of such systems, aiming to enhance therapeutic efficacy and patient compliance. Despite their promise, current treatments for schizophrenia have limitations, highlighting the need for innovative solutions to improve patient outcomes.

Due to the limited understanding of schizophrenia's causes, treatment primarily focuses on symptom management with antipsychotic drugs. These medications, commonly used to treat schizophrenia, are also employed for other conditions like brain damage and mania. Most antipsychotics block dopamine receptors, with some affecting serotonin receptors as well. However, current medications have drawbacks, prompting the need for new therapeutic approaches requiring a deeper understanding of the disorder's mechanisms.

First-generation antipsychotics block dopamine receptors but can lead to various side effects. They include phenothiazines and butyrophenones, each with different potencies and side effect profiles. Second-generation antipsychotics, like clozapine, offer improved efficacy and fewer side effects compared to first-generation drugs. Third-generation antipsychotics, such as aripiprazole, act differently on dopamine receptors, providing alternative treatment options.

This review will explore sustained-release gastro-retentive drug delivery systems for antipsychotics, discussing formulation techniques and potential benefits such as improved adherence and reduced side effects. By understanding advancements in this field, researchers and clinicians can innovate psychiatric pharmacotherapy to better address clinical needs and enhance patient outcomes.

## Material and Methods

### Quetiapine Fumarate

Quetiapine fumarate, a second-generation (atypical) antipsychotic, finds its mainstay in treating schizophrenia and bipolar disorder. By antagonizing key neurotransmitter receptors like dopamine D2 and serotonin 5-HT2 in the brain, it orchestrates a delicate balance in neurotransmitter activity. This versatile medication extends its therapeutic reach to major depressive disorder as well, when used adjunctively with antidepressants. Absorbed efficiently through oral intake, quetiapine fumarate swiftly reaches peak plasma concentrations, typically within 1.5 to 2.5 hours. Its journey through the body involves hepatic metabolism, primarily via enzymes like CYP3A4 and CYP2D6, generating several metabolites. With an elimination half-life ranging from 6 to 7 hours, steady-state plasma concentrations stabilize within 1 to 2 days of consistent dosing.

Despite its efficacy, quetiapine fumarate is not without its share of side effects, ranging from sedation and dizziness to metabolic disturbances like hyperglycemia and dyslipidemia. Rare but serious adverse effects, such as neuroleptic malignant syndrome and tardive dyskinesia, underscore the importance of vigilant monitoring during treatment. Contraindications include known hypersensitivity and caution is advised in certain populations like the elderly and those with cardiovascular disease.

In the realm of drug delivery, various methods offer avenues to tailor dosage forms for optimized therapeutic outcomes. Direct compression and encapsulation techniques form the backbone of tablet and capsule formulations, respectively. Hot melt extrusion, employing mucoadhesive polymers, emerges as a promising strategy, enhancing adhesion to the gastric mucosa. These methods, adaptable to the drug's properties and desired release profile, open doors for personalized gastro retentive dosage forms. Combination approaches further amplify gastric retention, refining drug delivery for diverse therapeutic needs.

**Formulation Development:**

Pre formulation Study

**Organoleptic Properties:**

The color, odor, and taste of quetiapine fumarate assessed visually. A small amount of the drug was sprinkled onto a piece of butter paper and observed under a slit lamp to determine its color. Odor was determined by smelling a small amount of the drug on a fingertip.

**Melting Point:**

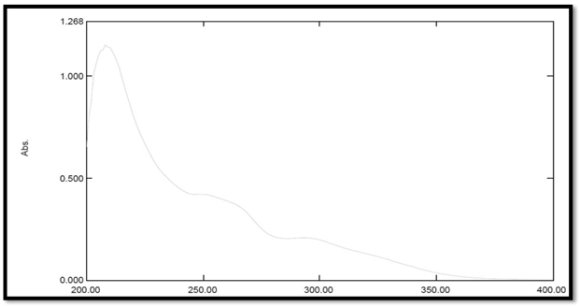
The visual observation confirmed Quetiapine Fumarate appeared as white to off white powder in bulk form.

Melting Point Determination

The capillary tube method employed to determine the melting point of the quetiapine fumarate through the melting point apparatus. The observation confirmed the melting point of the quetiapine fumarate was in the range of 173.33±0.58°C to 176.00±1.00°C close to the reference value 172-176°C as mentioned in the previous literature.

**Determination of Absorbance Maxima of Quetiapine Fumarate using UV Spectroscopy:**

The UV method development of the quetiapine fumarate was executed in the methanol solvent. The working solution concentration 10µg/ml of Quetiapine Fumarate was prepared in methanol and scanned between 200-400nm using the UV spectroscopy. The UV spectrum demonstrated absorption maxima 248nm wavelength similar to the absorbance maxima 248nm indicated in previous literature.




UV spectrum of Quetiapine Fumarate solution concentration 10µg/ml in methanol.

**Method Validation:**

Linearity: Standard calibration curves were prepared in methanol within a concentration range of 2-20µg/ml using the stock solution. Various volumes of the stock solution were diluted to achieve concentrations ranging from 2 to 20µg/ml. UV spectra of these solutions were recorded, and absorbance values at characteristic wavelengths were noted. The linearity curve constructed by plotting concentration versus absorbance, and the equation was determined

**Standard calibration curve of Quetiapine Fumarate**

| **Concentration (µg/ml)** | **Absorbance** | **Absorbance** | **Absorbance** | **Mean Absorbance** | **STD** |
|---|---|---|---|---|---|
| 2 | 0.083 | 0.084 | 0.084 | 0.084 | 0.001 |
| 4 | 0.168 | 0.168 | 0.17 | 0.169 | 0.001 |
| 6 | 0.245 | 0.249 | 0.248 | 0.247 | 0.002 |
| 8 | 0.329 | 0.333 | 0.335 | 0.332 | 0.003 |
| 10 | 0.418 | 0.42 | 0.426 | 0.421 | 0.004 |
| 12 | 0.495 | 0.499 | 0.5 | 0.498 | 0.003 |
| 14 | 0.567 | 0.57 | 0.576 | 0.571 | 0.005 |
| 16 | 0.65 | 0.651 | 0.653 | 0.651 | 0.002 |
| 18 | 0.734 | 0.739 | 0.74 | 0.738 | 0.003 |
| 20 | 0.809 | 0.805 | 0.813 | 0.809 | 0.004 |
| 22 | 0.889 | 0.892 | 0.897 | 0.893 | 0.004 |

Accuracy: For the current method, accuracy parameters assessed by evaluating the percentage recovery of quetiapine fumarate at three distinct levels 80%, 100%, and 120% of the nominal analytical values of 10µg/ml. The technique proved to be very precise and appropriate for its intended usage, according to recovery tests. Recovery percentages were 99.411% to 100.031% at 80%, 98.883% to 99.876% at 100%, and 99.152% to 99.979% at 120%. The

Average recoveries at three levels were 99.514%, 99.462%, and 99.635%, respectively. The results showed that the %RSD for each level was under 1%. The percentage recovery and percentage RSD data confirmed the proposed method exhibited an adequate degree of accuracy for quetiapine fumarate.

| **Level of addition** | **Conc.(µg/ml)** | **% Recovery** | **Mean % Recovery** | **SD** | **%RSD** |
|---|---|---|---|---|---|
| **80%** | 8 | 100.031 | 99.514 | 0.474 | **0.476** |
| | 8 | 99.100 | | | |
| | 8 | 99.411 | | | |
| **100%** | 10 | 99.876 | 99.462 | 0.517 | **0.519** |
| | 10 | 99.628 | | | |
| | 10 | 98.883 | | | |
| **120%** | 12 | 99.979 | 99.635 | 0.430 | **0.432** |
| | 12 | 99.773 | | | |
| | 12 | 99.152 | | | |

**Precision**: Precision assessed for repeatability and inter-day precision. Repeatability evaluated by analyzing the 100% level solution (10µg/ml) six times within the same day. Inter-day precision involved analyzing solutions at 80%, 100%, and 120% levels (8, 10, and 12µg/ml) on six different days. Percentage recovery was determined for each analysis.

**Ruggedness:** Ruggedness was determined by analyzing the 100% level solution (10µg/ml) by two different analysts. Percentage recovery calculated based on absorbance values obtained from UV spectra.

**Robustness**: Robustness evaluated by assessing the effect of small variations in absorbance maxima (±1nm) on the percentage recovery of quetiapine fumarate. Solutions were prepared and analyzed at wavelengths of 247nm, 248nm, and 249nm, and percentage recovery was determined.

**Solubility:** Quetiapine fumarate's solubility tested in water, methanol, ethanol, 0.1N HCl, and phosphate buffer pH 6.8 using the shake flask method. After 24 hours of agitation, samples centrifuged, and absorbance measured by UV spectroscopy to calculate solubility.

**Partition Coefficient:** The partition coefficient of quetiapine fumarate was determined in an n-octanol/water mixture via the shake-flask method. After agitation, the mixture left to settle overnight, and layers were collected, centrifuged, and analyzed by UV spectroscopy to determine the partition coefficient.

**Method of preparation of Quetiapine Fumarate loaded gastro retentive microspheres**

Quetiapine Fumarate loaded gastro retentive microspheres were prepared using the solvent diffusion evaporation method. The drug-polymer organic phase created by dissolving a specific amount of the drug and polymer in a 1:1v/v mixture of dichloromethane and butanol (5ml). Simultaneously, the aqueous phase was prepared by dissolving polyvinyl alcohol stabilizer in 100ml of water under continuous stirring at 100rpm. The clear organic phase then emulsified in the aqueous phase under continuous stirring at 800rpm and room temperature for 3 hours, using a three-blade mechanical stirrer to remove the organic solvent. After stirring, the microsphere-containing mixture filtered and washed twice with 10ml of distilled water. The collected microspheres, air-dried, transferred to a mesh screen, labeled, and stored for further use.

Drug polymer organic solution aqueous stabilizer solution

**Screening of formulation and process parameters**

The impact of different parameters, including polymer type, polymer amount, solvent volume, stabilizer amount, and stirring speed, was examined. The drug-loaded microspheres then subjected to various characterization tests, including assessment of physical appearance, percentage drug entrapment, yield, drug loading, particle size, floating ability percentage, and micrometric properties.

**Composition of microsphere containing various polymers**

| Formulation code | Amount of Drug (mg) | Amount of Eudragit S 100 (mg) | Ethyl cellulose (mg) | Amount of HPMC K4M (mg) | Amount of HPMC E5 (mg) | Solvent (Butanol: DCM) | Amount of PVA (%w/v) |
|---|---|---|---|---|---|---|---|
| A1 | 100 | 300 | - | - | - | 1.0:1.0 | 0.1 |
| A2 | 100 | - | 300 | - | - | 1.0:1.0 | 0.1 |
| A3 | 100 | 300 | - | 10 | - | 1.0:1.0 | 0.1 |
| A4 | 100 | 300 | - | - | 10 | 1.0:1.0 | 0.1 |
| A5 | 100 | - | 300 | 10 | - | 1.0:1.0 | 0.1 |
| A6 | 100 | - | 300 | - | 10 | 1.0:1.0 | 0.1 |

**Characterization parameter**

**Physical appearance**

Physical appearance evaluation involves the visual observation of the all prepared microsphere formulation for their color, uniformity, and aggregation.

| **Formulation code** | **Physical appearance** |
|---|---|
| DA1 | Nearly spherical particles |
| DA2 | Nearly spherical particles |
| DA3 | Aggregation of particles |
| DA4 | Spherical uniform particles |
| DA5 | Spherical uniform particles |
| DA6 | Nearly spherical particles |

**Percentage yield**

The dried microsphere employed to determine the percentage yield of the all prepared microsphere formulation. The percentage yield of the prepared microsphere was determined using the below equation.

Percentage drug release of the pure drug and optimized microsphere formulation DA14 in drug release medium phosphate buffer pH 6.8.

| **Formulation code** | **Percentage yield (%)** |
|---|---|
| DA1 | 90.871±±0.860 |
| DA2 | 92.983±0.439 |
| DA3 | 80.565±0.580 |
| DA4 | 92.286±0.273 |
| DA5 | 96.859±0.173 |
| DA6 | 89.311±0.498 |

***In-vitro* drug release study**

The *in-vitro* drug release profile demonstrated that the pure drug releases the drug in an immediate manner in one phase while the microsphere formulation releases the quetiapine fumarates in a biphasic manner. Initially, the microsphere displayed a burst effect, releasing the drug adsorbed around the surface of the microsphere, and later the microsphere released the drug in the sustained. The preliminary quick release in both instances attributed to wall integrity being lost during microsphere formation or following particle drying. It could also be the result of drug distribution around the surface or in the surface layer, which made them readily available for release during the first release phase.

Once the drug that had been absorbed by the surface released completely, the release process continued to be relatively slow and prolonged because the drugs released from the microspheres

through the walls of the particles in the following order: solvent penetration, polymer gelation, drug solubilization in solvent, and drug molecules diffusing through the polymeric microsphere matrix. Additionally, the quantity of drug released from the microsphere controlled by mixing polymers, such as (HPMC E5), in Eudragit-S100. The sustained release of the drugs from the microspheres ascribed to their interlocalization within the polymeric network. Moreover, GI fluid would dissolve finely dispersed, highly surface-area micronized drug particles far more quickly than micronized powder or tablet dose forms, making them available for absorption, Incorporation.

**Regression coefficient value of the all drug release kinetic model**

| **S.No.** | **Model** | **Regression coefficient** | **Slope** |
|---|---|---|---|
| 1 | Zero | 0.8857 | 4.2711 |
| 2 | First | 0.8344 | -0.0899 |
| 3 | Higuchi | 0.9631 | 24.876 |
| 4 | Korsmeyer peppas | 0.9892 | 0.7123 |

***In-vivo* pharmacokinetic study**

**Preparation of standard calibration curve in plasma**

Linear calibration curve of Quetiapine Fumarate in plasma was prepared in concentration ranges of 1-6µg/ml (1, 2, 3, 4, 5, and 6µg/ml). The linear regression equation for Quetiapine Fumarate was found to be Y= 0.80092+1927.20 with correlation coefficient greater than 0.999. In this equation 80092 is the slope and 1927.20 is the Y-intercept (a point of the Y- coordinate where a given line intersects the Y-axis) at which X is equal to zero. It defines the elevation of the line.

Standard calibration curve of the Quetiapine Fumarate in plasma

| **Con. (µg/ml)** | **Area** |
|---|---|
| 1 | 80065.67±3.51 |
| 2 | 162356.34±3.21 |
| 3 | 245364±2.08 |
| 4 | 323124±2.65 |
| 5 | 400026±3.61 |
| 6 | 482554±2.89 |

**Stability study**

Stability study of the formulation Quetiapine fumarate was performed at 2-8$^{o}$C and 25$^{o}$C/60%RH. The effect of the storage condition over the performed of the drug loaded microsphere was determined by evaluating its characteristics parameters like physical appearance, percentage drug entrapment, percentage drug loading, particle size and percentage buoyancy.

**Characterization parameters at one month**

Sample was withdrawn at one month and characterized for the physical appearance, percentage drug entrapment, percentage drug loading, particle size and percentage buoyancy.

| **Time interval** | **Storage condition** | | | | | |
|---|---|---|---|---|---|---|
| | **2-8°C** | | | **25°C/60%RH** | | |
| | **Physical appearance** | **Particle size (µm)** | **Percentage Buoyancy (%)** | **Physical appearance** | **Particle size (µm)** | **Percentage Buoyancy (%)** |
| 0th month | Spherical uniform particles | 105.81±0.297 | 94.567±0.565 | Spherical uniform particles | 105.81±0.297 | 94.567±0.565 |
| 1st month | Spherical uniform particles | 105.470±0.198 | 94.483±0.551 | Spherical uniform particles | 106.250±0.276 | 94.467±0.601 |

**Conclusion:**

In conclusion, the formulation, development, and evaluation of sustained-release gastro-retentive drug delivery systems for Quetiapine Fumarate (QF) yielded promising results. The study demonstrated the successful preparation of QF-loaded microspheres using the solvent diffusion evaporation method, with optimized parameters enhancing formulation characteristics. The in-vitro drug release profiles exhibited a desirable biphasic pattern, indicating both immediate and sustained release, which is advantageous for achieving therapeutic efficacy. Moreover, in-vivo pharmacokinetic studies and stability assessments validated the effectiveness and stability of the developed formulation. Overall, this research underscores the potential of gastro-retentive drug delivery systems to improve drug delivery, offering opportunities for enhanced therapeutic outcomes and patient compliance in the treatment of various conditions. Further studies and clinical trials are warranted to explore the full potential of these formulations in clinical settings.

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