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FORMULATION DEVELOPMENT AND CHARACTERIZATION OF MICROSPHERES OF QUETIAPINE FUMERATE

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ABSTRACT

The aim of present work is to formulate the microspheres of anti-psychotic drug Quetiapine fumerate using the chitosan to enhance its bioavailability and sustain its action and evaluate by various parameters. Quetiapine is a dibenzothiazapine derivative belongs to the atypical antipsychotic category. It is used in the treatment of schizophrenia as well as for the treatment of acute manic episodes associated with bipolar I disorder. Reported side effects of QF are Somnolence, dizziness, dry mouth, abdominal pain, anorexia, constipation, and dyspepsia after oral therapy. Since this drug is usually taken for long period so patient compliances are also very important. The plasma half-life of the drug is 6 hours and oral bioavailability is only 9% which makes frequent dosing necessary to maintain the therapeutic blood level of the drug for long term treatment. Therefore, controlled release microspheres of QF were prepared to give its sustaining release action. The micro particles drug delivery system is a physical approach to alter and improve the pharmacokinetic and pharmacodynamics properties of various types of drug molecules. They have been used in vivo to protect the drug entity in the systemic circulation, restrict access of the drug to the chosen sites and to deliver the drug at a controlled and sustained rate to the site of action with enhanced therapeutic benefit, while minimizing side effects. The drug polymer ratio and the ratio of emulsifier influenced the % yield, drug loading, particle size, entrapment efficiency and drug release behavior of drug. Quetiapine fumerate microspheres were prepared successfully by using the ionic- gelation emulsification method. Prepared microspheres showed good % yield and drug loading. Encapsulation efficiency of microspheres was good for all formulations. Quetiapine fumerate is an antipsychotic drug of atypical neuroleptics. It is used in the treatment of schizophrenia and bipolar disorders. Polymers chitosan and Eudragit were selected on the basis of their coating property and non-toxicity. The result of the finding showed excellent controlled release. Result from present study concluded that quetiapine fumerate microspheres in combination with chitosan and eudragit produced smooth, flexible micospheres. Further, result of the drug content within the formulation was in the range of 33.08±0.03 to 88.30±0.02. The cumulative percent drug releases in 24 hours were found to be 88.30% in *in-vitro* drug release. An increase in drug polymer ratio was found to helpful in entrapment increase and to control the release of drug and the Eudragit S – 100 coating retard the release of drug to the enteric pH and make formulation targeted delivery system.

KEYWORDS: Quetiapine fumerate, Dibenzothiazapine Derivative, Antipsychotic, Polymers chitosan.

• INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. During the past decade a new era of science and technology has emerged in pharmaceutical research aimed at the development of novel or advance drug delivery systems. For human health novel delivery system, common concerns exist in area of cost-efficient treatment, patient compliance, optimum drug delivery and bioavailability. Ideally controlled drug release entails carefully programming the output of a chemical from a physiochemical system such that drug release can be activated on demand (James W., et al) The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics

to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were generated. These new strategies, often called drug delivery systems (DDS), are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology.

To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development. Among drug carriers one can name soluble polymers, microparticles made of insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles. The carriers can be made slowly degradable, stimuli-reactive (e.g., pH- or temperature-sensitive), and even targeted (e.g., by conjugating them with specific antibodies against certain characteristic components of the area of interest). Targeting is the ability to direct the drug-loaded system to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release: (i) passive and (ii) active targeting. An example of passive targeting is the preferential accumulation of chemotherapeutic agents in solid tumors as a result of the enhanced vascular permeability of tumor tissues compared with healthy tissue. A strategy that could allow active targeting involves the surface functionalization of drug carriers with ligands that are selectively recognized by receptors on the surface of the cells of interest. Since ligand–receptor interactions can be highly selective, this could allow a more precise targeting of the site of interest. An ideal drug delivery system is one which provides the drug only when and where it is needed, and in the minimum dose level required to elicit the desired therapeutic effects**.**

The aim of developing any drug delivery system (DDS) is to achieve a safe and effective drug concentration in body tissues. Traditional drug delivery systems (TDDSs) are characterized by rapid and unrestrained drug release kinetics, usually leading to abrupt increase of drug concentration in body tissues followed by a similar decrease. A number of controlled- release drug delivery systems have been developed and some are already commercialized. These include, for example, transdermal nitroglycerin delivery systems for the prevention of angina and oral osmotic pump devices for the delivery of a variety of therapeutic agents.

Recent development in polymeric delivery systems for the controlled release of therapeutic agents has demonstrated that these systems not only can improve drug stability both in vitro and in vivo by protecting labile drugs from harmful conditions in the body, but also can increase residence time at the application site and enhance the activity duration of short half - life drugs. Therefore, compounds which otherwise would have to be discarded due to stability and bioavailability problems may be rendered useful through a proper choice of polymeric delivery system.

- **1.1 Microspheres: Microparticulate System**

1.1.1 Introduction

The last two decades there has been a remarkable improvement in the field of novel drug delivery systems. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microsphere, Nanoparticles, Liposome, etc, which modulates the release and absorption characteristics of the drug. Microspheres constitute an important part of this particulate drug delivery system by virtue of their small size and efficient carrier characteristics. Microspheres are the colloidal drug delivery system. Microspheres are characteristically free powders consisting of proteins/synthetic polymers that are biodegradable in nature and ideally having a particle size less than 200 µm.

- **1.1.2 Materials used in preparation of microsphere**

Materials used in preparation of microspheres used usually are polymers. They are classified as follows:-

POLYMERS	
Synthetic Polymers	**Natural polymers**
a. Non-biodegradable polymers- e.g. Poly methyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers **b. Biodegradable polymers**- e.g. Lactides, Glycolides & their co polymers, Poly alkyl cyano acrylates, Poly anhydrides	**a. Proteins:** Albumin6, Gelatin7, and Collagen **b. Carbohydrates:** Agarose, Carrageenan, Chitosan, Starch8 **c. Chemically modified carbohydrates:-** Poly dextran, Poly starch

In case of non-biodegradable drug carriers, when administered parenterally, the carrier remaining in the body after the drug is completely released poses possibility of carrier toxicity over a long period of time.

Biodegradable carriers which degrade in the body to non-toxic degradation products do not pose the problem of carrier toxicity and are more suited for parenteral applications.

1.1.3 Criteria for preparation of microsphere (Vyas and khar) P reparation of microspheres should satisfy certain criteria:

- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation after synthesis with a clinically acceptable shelf life.
- Controlled particle size and dispersability in aqueous vehicles for injection.
- Release of active reagent with a good control over a wide time scale.
- Biocompatibility with a controllable biodegradability and Susceptibility to chemical modification

1.2 Disease Profile

Schizophrenia is a neuro-developmental psychiatric disorder with etiology spanning both genetic and environmental factors. It affects 1% of the population and ranks among the top 10 causes of disability worldwide. It is a severe form of mental illness affecting about 7 per thousand of the adult population, mostly in the age group 15-35 years. Though the incidence is low (3-10,000), the prevalence is high due to chronicity.

The core features of schizophrenia include "positive," "negative," "cognitive," and "affective" symptoms. The positive symptoms (e.g., agitation, delusions, hallucinations and grossly disorganized behaviour) are easily identified, are more likely to lead to hospitalization, and have been used as main determinants of illness outcome. The negative and cognitive symptoms, although less florid, are usually much more pernicious. While positive symptoms are most amenable to treatment, there is no effective treatment available for "negative" and "cognitive" symptoms. Increased and decreased dopamine transmission in the subcortical meso-limbic and meso- cortical systems is closely linked to the "positive" and "negative" symptoms of schizophrenia, respectively. Important roles have also been found for serotonin and acetylcholine, both of which are closely linked to dopamine. An abnormality in glutamate functioning involving N-methyl-D-aspartic acid as well as other receptor subtypes may underlie the dopamine dysfunction observed in schizophrenia. (Mattoo S.K. et al., 2011). According to WHO, Schizophrenia affects about 24 million people worldwide. It is a treatable disorder, treatment being more effective in its initial stages. More than 50% of persons with schizophrenia are not receiving appropriate care. 90% of people with untreated schizophrenia are in developing countries. Care of persons with schizophrenia can be provided at community level, with active family and community involvement.

There are effective interventions (pharmacological and psychosocial) available and the cost of treatment of a person suffering from chronic schizophrenia is about US$2 per month; the earlier the treatment is initiated, the more effective it will be. However, the majority of the persons with chronic schizophrenia do not receive treatment, which contributes to the chronicity. Antipsychotics are useful in all types of functional psychosis, especially schizophrenia. Various types of antipsychotic drugs and neuroleptics have been used in the treatment of psychosis. (Tripathi K.D., 2008)

- Phenothizines– Chlorpromazine, triflupromazine, thioridazine, trifluperazine, fluphenazine
- Butyrophenones- haloperidol, trifluperidol, penfluridol
- Thioxanthines- Flupenthixol
- Others heterocyclics- pimozide, loxapine
- Atypical neuroleptics- clozapine, olanzapine, quetiapine, aripiprazole, ziprasidone, risperidone.

1.3 Drug Profile

The selected antipsychotic drug, quitiapine fumerate is a dibenzothiazepine derivative, is an atypical antipsychotic with demonstrated efficacy in acute schizophrenia. It is indicated for the treatment of schizophrenia as well as for the treatment of acute manic episodes associated with bipolar I disorder. It has a relatively broad receptor binding profile. It has major affinity to cerebral serotonergic (5HT2A), histaminergic (H1), and dopaminergic D1 and D2 receptors, moderate affinity to α1- und α2-adrenergic receptors, and minor affinity to muscarinergic M1 receptors; it demonstrates a substantial selectivity for the limbic system. Model drug also has an antagonistic effect on the histamine H1 receptor. (Spellmann.I. et al., 2007).

2. MATERIALS

In the preparation of microsphere of quetiapine fumerate, ionic gelation method of microsphere preparation was used and the materials used in the preparation of microspheres are as follows:-

Drug: Quetiapine fumerate was bought from bull chemicals, Hydrabad.

2.1 METHODOLOGY

- **Preformulation studies**

Preformulation study is a stage of development during which the physicochemical properties of drug substance are characterized. Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physicochemical properties of a new drug substance alone and when combined with the excipients, to generate data useful to the formulator in developing safe, stable, potent, bioavailable and efficacious dosage form, which can be mass produced.

The goals of Preformulation studies are

- To establish the physicochemical parameter of new

drug substances.
- To establish the kinetic rate profile.
- To establish physical characteristics.
- To establish compatibility with the common excipients.

Hence, the following parameters were selected for the Preformulation studies for the pure drug.

2.2 Identification of drug and polymers

The drug sample quetiapine fumerate was obtained as a gift sample from Aurobindo pharmaceuticals, Hyderabad. Purity of quetiapine fumerate and polymers was determined by Infrared studies, Standard calibration curve and solubility studies.

- **Estimation of absorbance of QF by U.V. Spectrophotometer**

In order to determine λ max for QF, standard stock solution of Quetiapine fumerate (10 mg/ml) in phosphate buffer 7.4 was prepared and scanned for absorbance in between 400-200 nm by using U.V spectrometer (Jasco V-630). The peak was found 216.6 nm. (Figure 4)

- **Determination of solubility of quetaipine fumerate**

Solubility analysis was done to select suitable solvents/solvent systems to dissolve the drug, polymer as well as various excipients used for the formulation of microspheres. A saturated solution of QF was prepared in different solvent systems and then drug concentration was measured in these solvents system by using U.V Spectrometer at 334.5 nm. (Table 4) The experiment was performed in triplicate (n=3).

- **Melting point determination**

Melting point of QF was determined by using Thiele's tube apparatus. Melting point of a drug sample is a first indication of purity of the sample. The presence of relatively small amount of impurity can be detected by a lowering as well as widening in the melting point. The experiment was performed in triplicate (n=3).

- **Determination of Partition co-efficient of drug**

The partition coefficient is the ratio of unionized drug distributed between the organic and aqueous phase at equilibrium. For a drug delivery system, lipophilic/hydrophilic balance has been shown to be a contributing factor for rate and extent of drug absorption. The measurement of drug lipophilicity and its ability to cross the lipoidal cell membrane is determined by oil/water partition coefficient in system such as n-octanol/water and n-octanol/buffer.

- **Determination of Partition coefficient**

The partition coefficient was performed using n-octanol as oil phase and phosphate buffer pH 7.4 as aqueous phase. The two phases were mixed in equal quantity and 10 mg of weighed amount of drug was added. Then, these were saturated on a mechanical shaker for 2 hours. The saturated phases were separated by separating funnel and equal volume of both phases n-octanol and phosphate buffer were taken in a conical flask and then analyzed for respective drug controls.

The partition coefficient of drug $P_{O/W}$ was calculated by the following formula:

$$\frac{Po}{w} = C\,(oil)/C\,(water)\ \text{Equilibrium}$$

- **Differential scanning calorimetry**

In order to determine the physical state of drug, i.e. amorphous or crystalline, before and after final formulation and to evaluate any possible drug-polymer, drug-other components interaction, DSC examination was conducted for the optimized formulation, pure drug, the polymer, the coupling agents using a DSC instrument. Samples of 2-6 mg were placed in aluminum pans and sealed. The probes were heated from 25 ^{0}C to 400 ^{0}C at a rate of 100 C/min under nitrogen atmosphere.

2.3 Standard curve of Quetiapine fumerate

- **Standard curve of QF in phosphate buffer pH 7.4**

Phosphate buffer pH 7.4 was prepared by method as mentioned in Indian pharmacopoeia.

Standard solution of QF was prepared by dissolving the 100 mg of drug in 100ml of phosphate buffer in a 100 ml volumetric flask which makes the concentration of 1000µg/ml. Then 10 ml of this solution was transferred in to 100ml volumetric flask and make the volume 100 ml with phosphate buffer resulting in conc. of 100µg/ml. From this solution the aliquots of 0.2 to 2.0 ml were withdrawn into a series of 10 ml volumetric flask and volume was made up to 10ml with phosphate buffer pH7.4 to prepare the standard solution containing the 2.0 µg/ml to 20 µg/ml of drug. These solutions were analyzed spectrophotometrically. The absorbance of each sample was noted at 254 nm. Calibration curve were plotted between absorbance and concentration of drug, expressed in µg/ml. These standard curves were linearly regressed and statistical parameters related to it were derived. Shown in table and graph.

- **Standard curve of QF in 0.1N HCl**

Standard solution of QF was prepared by dissolving accurately weighed 100mg of drug in100ml of 0.1N HCl. The drug was dissolved by gentle shaking. Then further dilutions were prepared to make stock solution of 100 µg/ml conc. Solution of appropriate concentration was made by dilution of stock solution with 0.1N HCl. The calibration curve standards contained 2-20µg/ml of drug. These solutions were analyzed spectrophotometrically. The absorbance of each sample was noted at 216.6 nm. Calibration curve were plotted between absorbance and concentration of drug, expressed in µg/ml. These standard curves were linearly regressed and statistical parameters related to it were derived.

2.4 Method of Preparation

Cross linked Chitosan microspheres were prepared using ionic-gelation emulsion method employing a suitable

cross linker. In this Tripolyphosphate (TPP) is used as a cross linker. Chitosan solution (4% w/v) was prepared in 5% aqueous acetic acid solution in which the drug was previously dissolved and dispersed in liquid paraffin containing span 80 (1% w/v). The dispersion was stirred using a specially fabricated stainless steel half- moon paddle stirrer and Tripolyphosphate (TPP) saturated aqueous solution (1 ml to 3 ml) was added with stirring.

The stirring was continued further 4hr, then microspheres were centrifuged, washed two times with hexane to remove oily phase from the solution and acetone and dried in vacuum desiccators for 48 hrs.

Emulsion preparation for microsphere formulation

Table 2.1: Composition of different formulations.

Batch Code	Chitosan (%w/v)	TPP (%w/v)	Span 80 (%w/v)
M1	4	6	1
M2	4	12	1
M3	4	18	1
M4	5	6	1
M5	5	12	1
M6	5	18	1
M7	6	6	1
M8	6	12	1
M9	6	18	1

2.4.1 Determination of drug entrapment, Drug loading and % yield

- **Drug entrapment**

The capture efficiency of the microspheres or the percent entrapment was determined by suspending in methanol. After 24 hours, the solution was filtered and filtrate was analyzed for drug content and diluted to appropriate dilutions for determination of entrapment efficiency using following formula:

$$\text{Entrapment efficiency (\%)} = \frac{(actual\ content)}{t\square eoritical\ content} X100$$

- **Drug loading (%)**

The active components are loaded over the microspheres principally using two methods, i.e. during the preparation of microsphere or after the formation of microspheres by incubating them with the drug. The total drug loading is calculated by following formula:

$$\text{Drug loading (\%)} = \frac{Weig\square t\ of\ Drug}{Weig\square t\ of\ Microparticles} X100$$

- **Yield (%)**

Yield (%) of microspheres is determined by using following formula:

$$\text{Yield (\%)} = \frac{Weig\square t\ of\ \text{Microparticles}}{Total\ expected\ weig\square t\ of\ drug\ \&\ polymer} X100$$

- **Particle size analysis**

Determination of average particle size of QF microspheres was carried out by optical microscopy in which stage micrometer was employed. A minute quantity of microspheres was spread on a clean glass slide and average size of 100 microspheres was determined in each batch. The experiment was performed in triplicate (n=3).

- **Zeta potential**

Zeta potential was measured by using Zeta potentiometer (Zeta 3.0+ meter, USA). Sample was filled into the cell,

electrodes are inserted, placed under the microscope, and connected them to Zeta meter 3.0+ Unit. Electrodes energized and the colloids watched to move across a grid in the microscope eyepiece. Track one by simply pressing a track button and holding it down while the colloid traverses the grid. When the track button is released, the zeta-meter 3.0+ instantly calculates and displays the colloids zeta potential.

- **Scanning electron microscope**

For determination of surface characteristics all the microspheres were coated uniformly with gold palladium by using sputter coater for 5 to 7 minutes, after fixing the sample in individual steps. All samples of microspheres were then randomly examined for surface morphology by using scanning electron microsphere (Leo 435VT) at different magnification ranges.

2.4.2 Micromeretic properties

- **Angle of repose**

Angle of repose is calculated to check the flow property of microspheres. Angle of repose of different formulations was measured according to fixed funnel method using following formula:

$$\text{Angle of Repose } (\Theta) = \tan^{-1}\frac{2h}{d}$$

The experiment was performed in triplicate (n=3).

Flow property and Corresponding standard values for Angle of repose

Flow property	Angle of repose (degree)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very Poor	56-65
Very, very Poor	66<

- **Density & Tapped density**

Bulk density was measured by using 10ml graduated cylinder the simple work poured in cylinder and tapped mechanically 100 times then tapped volume was noted and bulk and tapped density were calculated. The experiment was performed in triplicate (n=3).

- **Hausner ratio**

Hausner ratio of microspheres was calculated according to following equation. The experiment was performed in triplicate (n=3).

Flow property and Corresponding standard values for Hausner ratio

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Flow property	Hausner ratio
Excellent	1.00-1.11
Good	1.12-1.18
Fair	1.19-1.25
Passable	1.26-1.34
Poor	1.35-1.45
Very Poor	1.46-1.59
Very, very Poor	1.60<

- **Carr index**

Carr index value of microspheres was calculated according to following equation.
The experiment was performed in triplicate (n=3).

$$\text{Carr index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} 100$$

Flow property and Corresponding standard values for Carr's index

Flow property	Carr's index
Excellent	≤ 10
Good	11-15
Fair	16-20
Passable	21-25
Poor	26-31
Very Poor	32-37
Very, very Poor	38<

2.4.3 *In-vitro* drug dissolution analysis

In-vitro dissolution studies were carried out on the microspheres at 37±0.5c at 100 rpm using USP dissolution apparatus-II. The in-vitro dissolution studies were performed in different pH, pH 1.2, i.e simulated gastric fluid pH and pH 6.8 i.e simulated intestinal fluid pH. An accurately weighed sample 100mg Quetiapine Fumerate microspheres were suspended in dissolution media consisting of 900 ml of 0.1 N HCl. Dissolution was done for 2 hours. At the end of 2 hrs, 25.92 g of di-sodium hydrogen phosphate & 10.305 g potassium dihydrogen phosphate was added to make pH 6.8 and dissolution was performed up to 24 hours. 5 ml sample was withdrawn at each hour interval and replaced with the same volume of test medium withdrawn samples were estimated for QF concentration at 216.6 nm in U.V spectrophotometer Finally, the drug content was determined from calibration curve of QF to determine release pattern. The experiment was performed in triplicate (n=3).

- **Data Analysis**

The values of result were expressed in mean ±S.D. One way ANOVA (Analysis of Variance) was performed for studying the statistical significance using Minitab 15 software. Values of P< 0.05 were considered to be significant.

3. RESULTS AND DISCUSSION

3.1 Preformulation studies

The following Preformulation studies were

performed for the identification and compatibility of the drug and polymer.

Table 3.1: Interpretation of FTIR of Quetiapine.

Functional group	Peak scan cm^{-1}
-OH stretching	3750
Ar-H stretching	3080
C-H stretching	2880
Ar-C=C stretching	2380
C-N stretching	1600
C-H bending	1340
-C-O-C group	1030

Table 3.2: Interpretation of FTIR of Chitosan.

S. No	Peak(cm^2)	Functional group
1	3455-3445	Stretching of O-H
2	2923-2867	Stretching of C-H bonds
3	1653	Stretching of C=O bonds
4	1414-1401	Carboxymethyl group

FTIR spectra of the drug, polymer predicted that it was not showing any type of incompatibility. The major peaks were also observed in the formulation.

3.1.1 Partition coefficient

Partition coefficient of drug in n-octanol/ phosphate buffer pH 7.4 was found to be 2.7 which indicated that the drug was lipophilic in nature.

3.1.2 Melting point

Melting point of the drug was found to be 170˚C.

3.1.3 Solubility Analysis

Solubility analysis was done to select suitable solvents/ solvent systems to dissolve the drug, polymer as well as various excipients used for the formulation of microspheres. A saturated solution of drug was prepared in different solvent systems and then drug concentration was measured in these solvents system by using U.V Spectrometer at 216.6 nm. Data observed was matched with standard.

Table 3.3: Solubility Analysis.

S.No.	Solvent	Inference
1.	Water	Soluble
2.	Ethanol	Freely soluble
3.	Methanol	Freely soluble
4.	Acetone	Partial soluble
5.	0.1N HCl	Freely soluble
6.	NaOH	Precipitate formed
7.	Dichloromethane	Precipitate formed

3.1.4 Determination of absorption maxima (λmax)

An order to determine λ max for QF, standard stock solution of drug (10 mg/ml) in phosphate buffer 7.4 was prepared and scanned for absorbance in between 400-200 nm by using U.V spectrometer. λmax of Quetiapine fumerate was found to be 216.6 nm.

3.1.5 Standard curve of Quetiapine fumerate

Table 3.4 showing the calibration curve of Quetiapine fumerate in phosphate buffer pH 7.4 with regression coefficient value 0.999. The *in-vitro* drug release was calculated from this calibration curve. Table 3.5 showing the calibration curve of Quetiapine fumerate in 0.1 N HCl with regression coefficient value 0.998. The relation of drug concentration and absorbance was found to be linear in the curve. The curve obey's Beer's law in the concentration range of 2.0 to 20.0 µg/ml.

Table-3.4: Calibration curve of Quetiapine in phosphate buffer pH 7.4.

S.No.	Concentration (µg/ml)	Absorbance
1.	2	0.076
2.	4	0.0139
3.	6	0.202
4.	8	0.267
5.	10	0.329
6.	12	0.386
7.	14	0.449
8.	16	0.511

Table- 3.5: Calibration curve of Quetiapine in 0.1N HCl.

S.No.	Concentration (µg/ml)	Absorbance
1.	2	0.0544
2.	4	0.1203
3.	6	0.1886
4.	8	0.2525
5.	10	0.3254
6.	12	0.3638
7.	14	0.4107
8.	16	0.4823

- **Zeta potential**

Zeta potential was measured by using Zeta potentiometer (Zeta 3.0+ meter, USA). Zeta potential of microspheres was found in range -32.9 to -42.9 which indicate that all formulations are moderately stable. Jain S.D. 2010 prepared microsphere of tinidazole with different polymer ratio and concluded the stable charged microsphere when analysed by zeta potentiometer. In this present study zeta potential was found to be in stable range.

Table 3.6: Zeta potential.

S. No	Formulation code	Zeta potential(mV)
1	M1	-34.6
2	M2	-32.9
3	M3	-43.1
4	M4	-42.9
5	M5	-36.6
6	M6	-34.7
7	M7	-39.2
8	M8	-32.9
9	M9	-36.8

3.1.6 Drug loading, Entrapment efficiency and percentage yield of Quetiapine Fumerate formulation

It was observed that as the polymer ratio increases the % yield also increase. The low % yield in some formulations may be due to microsphere lost during washing process. The % yield was varying from 67-84%. 84% is best one in M9. Drug loading also increases as the polymer concentration increase and the emulsifier concentration have reverse effect on drug loading. The drug loading was varying from 20.28%-33.26% (Table 3.7)

Table 3.7: Drug loading (%), Entrapment efficiency (%) and percentage yield of mesalamine formulation.

S. No	Formulation	% Yield	Drug loading (%)	Entrapment efficiency (%)
1	M1	67.50	33.26	51.85
2	M2	65.49	32.11	47.30
3	M3	63.99	30.42	43.72
4	M4	76.15	25.39	68.08
5	M5	75.89	25.16	67.23
6	M6	72.44	23.41	61.95
7	M7	84.94	21.52	82.27
8	M8	81.03	20.33	76.58
9	M9	78.91	20.28	73.27

Entrapment efficiency also increases as the polymer concentration increase and the emulsifier concentration have reverse effect on Entrapment efficiency. The entrapment efficiency was varying from 43.72%-82.27% (Table 10) Jain V. et al, 2012 prepared formulations with different polymer ratio and concluded the increase in entrapment efficiency, % yield and drug loading with increase in polymer ratio. In this present study the entrapment efficiency, % yield and drug loading of microspheres were found to significantly increase with increasing polymer ratio ($P<0.05$) However increasing emulsifier concentration showed non-significant results in entrapment efficiency, % yield and drug loading of polymers ($P>0.05$).

3.1.7 Micromeretic properties

3.1.8 Angle of repose

All formulation showed angle of repose from 11.65 – 16.29 i.e less than 30, which showed good flowing properties of prepared microspheres (Table 3.8)

Table 3.8: Angle of repose, Bulk density and tapped density of mesalamine formulations.

Formulation codes	Angle of repose		Bulk density		Tapped density	
	Mean	S.D (±)	Mean	S.D (±)	Mean	S.D (±)
M1	16.29	0.68	0.418	0.004	0.542	0.006
M2	16.16	0.65	0.386	0.003	0.428	0.004
M3	15.52	0.63	0.327	0.004	0.405	0.004
M4	13.65	0.54	0.315	0.001	0.396	0.006
M5	13.85	0.59	0.329	0.007	0.412	0.003
M6	14.34	0.53	0.386	0.002	0.432	0.001
M7	11.65	0.61	0.273	0.005	0.342	0.001
M8	11.98	0.59	0.286	0.003	0.365	0.003
M9	12.34	0.52	0.295	0.003	0.379	0.006

3.1.9 Bulk density and tapped density

Bulk density and tapped density of prepared microspheres were found from 0.273-0.418 and 0.342-0.542 respectively, which showed good packability. (Table 3.8) and Kumar N.N. et al, 2011 prepared microsphere with different polymer ratio and concluded decrease in Angle of repose, bulk density and tapped density with increase in polymer ratio. In this present study the values of Angle of repose, bulk density and tapped density were significantly decreased with increasing polymer ratio ($P<0.05$) However increase emulsifier concentration showed non significant results in Angle of repose, bulk density and tapped density ($P>0.05$).

3.1.10 Carr's index

Carr's index range from 6.72 – 22.16% and formulation m9 shows excellent compressibility. (Table 3.9)

3.1.11 Hausner's ratio

Hausner's ratio varied from 1.10 – 1.29, which showed the good flow properties of all formulations. (Table 3.9)

Table 3.9: Carr's index, Hausner's ratio and Particle size of formulations.

Formulation codes	Carr's index		Hausner's Ratio		Particle Size(μm)	
	Mean	S.D. (±)	Mean	S.D. (±)	Mean	S.D. (±)
M1	6.72	0.43	1.29	0.30	72.21	1.93
M2	8.75	0.42	1.10	0.28	65.22	0.94
M3	19.25	0.39	1.23	0.31	61.22	1.28
M4	20.45	0.53	1.22	0.27	80.02	1.80
M5	20.34	0.56	1.25	0.27	74.15	0.84
M6	20.28	0.39	1.31	0.26	72.05	1.12
M7	20.17	0.41	1.34	0.30	98.91	1.20
M8	21.64	0.41	1.27	0.29	93.41	1.43
M9	22.16	0.55	1.28	0.27	90.41	1.83

Kumar N.N. et al, 2011 prepared formulations with different polymer ratio and concluded irregular carr's index and hausner's ratio. In this present study there was significant difference in carr's index and hausner's ratio with increasing polymer ratio ($P<0.05$), However increasing emulsifier concentration showed non-significant results in carr's index and hausner's ratio ($P>0.05$).

3.1.12 Particle size

The particle size of Quetiapine fumerate microspheres was influenced by the concentration of polymer and emulsifier. The size increased with increase in polymer concentration and decreased with increase in emulsifier concentration. The size of microspheres ranges from 61.22-90.41μm. (Table 3.9).

Yellanki S.K. et al, 2010, Jain. V et al, 2012 and Kumar N.N. et al, 2011 prepared formulations with different polymer ratio and concluded the increase in particle size with increasing in polymer ratio. In this present study the particle size was found significantly increased with increase in polymer ratio ($P<0.05$), However increasing emulsifier concentration showed non-significant results in particle size ($P>0.05$).

3.3 Drug release

Quetiapine fumerate microspheres were studied for 24 hrs for drug release behavior, i.e in simulated gastric fluid (1.2 HCl) for 3 hrs and in simulated intestinal fluid (6.8 PBS) up to 24 hr**s** The comparison of formulation with different drug polymer ratio and different concentration of emulsifier was done to identify the best formulation which shows sustained release up to 24 hrs. The rate of release was clearly affected by increasing the ratio of polymer and concentration of emulsifier as the release rate was successfully controlled by using high polymer ratio. The best release formulation was found **M9** (Table 3.10). *In vitro* dissolution study was conducted to understand *in-vitro* drug release profile of formulations with different drug polymer ratio and emulsifier concentration. Release profile of uncoated and coated microspheres was also carried out. The purpose of this formulation was to avoid release of drug in gastric and upper intestinal region but to release the drug slowly in the lower part of the intestine maximizing drug concentration in the colon. Accordingly, the in-vitro drug release study was conducted in pH change method as per USP protocol.

Table 3.10: *In vitro* release of drug from different formulations.

Time (Hrs)	pH	% Drug Release								
		M1	M2	M3	M4	M5	M6	M7	M8	M9
0		0	0	0	0	0	0	0	0	0
1	**1.2**	0.68	0.52	0.49	0.33	0.28	0.24	0.19	0.16	0.13
2	**HCl**	3.80	3.66	3.05	2.40	2.10	2.09	1.78	1.59	1.34
3		09.86	09.01	06.59	06.99	04.59	03.96	02.91	1.820	1.103
4		20.19	18.95	13.81	10.13	10.01	09.56	08.45	07.09	06.81
5		31.52	28.90	19.38	17.98	17.42	15.39	13.44	12.81	10.15
6	**6.8**	45.18	42.65	36.12	29.12	30.46	28.20	24.68	22.15	19.96
8	**PBS**	59.80	51.39	49.33	38.99	37.12	35.11	32.81	29.06	26.38
12		76.53	63.95	60.01	59.30	58.08	56.78	38.01	36.11	29.89
24		88.30	79.05	76.40	70.02	68.90	67.30	43.60	38.10	33.80

The coating of eudragit was found to be useful in sustained release of drug from polymers Yellanki S.K. et al, 2010, Jain .V et al, 2012 and Kumar N.N. et al, 2011 Kumar S.M., et al, 2010 prepared formulation with different polymer ratio and concluded a significant retardation in release of drug when polymer is increased. In the present study the retardation in drug release was also found to be significant with increasing polymer ratio ($P<0.05$). However, increase in emulsifier concentration in the formulations showed non-significant results in the drug release rate ($P>0.05$).

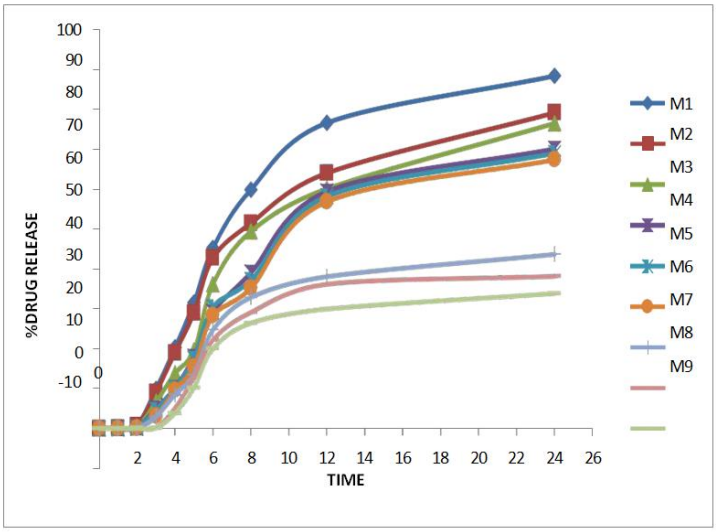

Figure 3.1: Graph representing release of drug in different formulations.

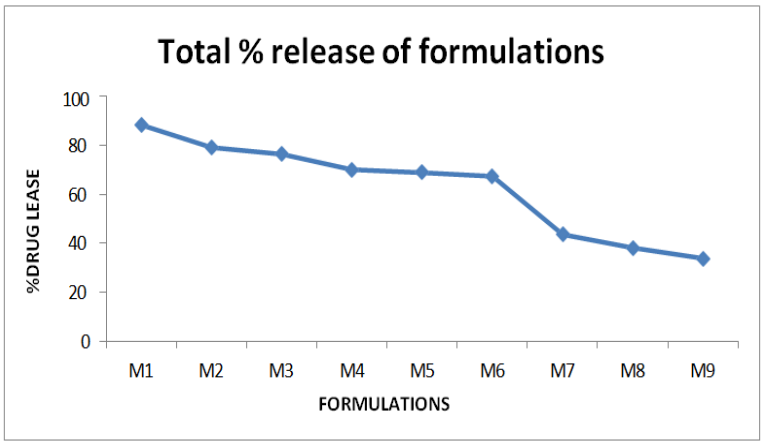

Figure 3.2: Graph representing the total % release of drug in different formulations.

- **SUMMERY**

The microparticles drug delivery system is a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. They have been used in vivo to protect the drug entity in the systemic circulation, restrict access of the drug to the chosen sites and to deliver the drug at a controlled and sustained rate to the site of action with enhanced therapeutic benefit, while minimizing side effects. The drug polymer ratio and the ratio of emulsifier influenced the % yield, drug loading, particle size, entrapment efficiency and drug release behavior of drug. Quetiapine fumerate microspheres were prepared successfully by using the ionic- gelation emulsification method. Prepared microspheres showed good % yield and drug loading. Encapsulation efficiency of microspheres was good for all formulations.Quetiapine fumerate is an antipsychotic drug of atypical neuroleptics. It is used in the treatment of schizophrenia and bipolar disorders. Polymers chitosan and Eudragit were selected on the basis of their coating property and non toxicity. The result of the finding showed excellent controlled release. Result from present study concluded that quetiapine fumerate microspheres in combination with chitosan and eudragit produced smooth, flexible micospheres. Further, result of the drug content within the formulation was in the range of 33.08±0.03 to 88.30±0.02. The cumulative percent drug releases in 24 hours were found to be 88.30% in *in-vitro* drug release. An increase in drug polymer ratio was found to helpful in entrapment increase and to control the release of drug and the Eudragit S – 100 coating retard the release of drug to the enteric pH and make formulation targeted delivery system.

- **Future Prospects**

The results of present study indicate the potential of microparticulate system to sustain the release as compared to conventional formulations in treatment and management of atypical neuroleptic patients. The formulated microspheres may further be corporate in a suitable dosage form such as capsule, tablet, suspension etc. to increase convenience of patient. Further in-vivo studies will have to be performed with the best formulation to correlate with in-vitro release data for the development of suitable dosage form.

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