FORMULATION AND EVALUATION OF QUETIAPINE FUMARATE EXTENDED RELEASE TABLETS

Dissertation Submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32

In partial fulfillment of the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

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CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION AND EVALUATION OF QUETIAPINE FUMARATE EXTENDED RELASE TABLETS"** was carried out by **TAMILSELVAN.P. (REG.NO:261711454),** under the guidance of **Dr. D.KUMARASAMYRAJA,**M.Pharm.,Ph.D**.,** Professor in the Department of Pharmaceutics, PGP College of Pharmaceutical Science and Research Institute, Namakkal-637 207, Affiliated to The Tamilnadu Dr. M.G.R Medical University, Chennai - 32.

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DECLARATION

We hereby declare that the matter embodied in the dissertation entitled **"FORMULATION AND EVALUATION OF QUETIAPINE FUMARATE EXTENDED RELASE TABLETS"**is a bonafide and genuine research work carried by us under the guidance of **Dr. D.KUMARASAMYRAJA,**M.Pharm.,Ph.D**.,** Professor, Department of Pharmaceutics, PGP College of Pharmaceutical Science & Research Institute, NH-7, Karur Main Road, Namakkal-637207.

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ACKNOWLEDGEMENT

Gratitude is one of the least articulate of emotions especially when it is deep. Words are not enough to express my gratitude towards the people who stood behind me during my project work.

The highest appreciation is not to utter words but to live by them. Wewill be indebted throughout our life to our guide, **Dr. D.KUMARASAMYRAJA,**M.Pharm.,Ph.D., Professor, Department of Pharmaceutics, PGP College Pharmaceutical of Science and Research Institute, Namakkal-637 207 whose guidance, invaluable encouragement, innovative ideas and quest of knowledge beyond present frontiers, enabled me to accomplish this thesis with zest and zeal. We are extremely grateful for his infallible determination, untiring patience and emotional strength that he instilled in us.

We are highly grateful to **Prof. Dr. G. ARUNACHALAM**, M.Pharm., Ph.D.,FIC., Principal, PGP College of Pharmaceutical Science and Research Institute, Namakkal-637 207 for providing all the facilities for this project work and for his constant encouragement given throughout the work.

We express our sincere thanks to our honorable chairman **Dr.PALANI G. PERIASAMY,** M.A.,M.A., Ph.D., (USA), Vice Chairman **Mrs.VISALAKSHI PERIASAMY.,**B.B.A.,and **Mr.M.GANAPATHI**, IFS® Correspondent, PGP Group of Educational Institutions, Namakkal–637 207 for providing the all necessary facilities.

We are highly obliged to our respected **Dr.M.ALAGARRAJA.**M.Pharm,Ph.D.,Professor cum Vice Principal, Department of Pharmaceutical Analysis, **Dr.A.CHANDRAN**,M.Pharm,Ph.D., Department of Pharmaceutical Chemistry**,** and **Mr.D.SAKTHIVEL,**M.Pharm., Ph.D., Department of Pharmaceutics, and PGP College of Pharmaceutical Science and Research Institute, Namakkal–637 207, who have a profound influence in shaping my orientation for research.

It is our privilege to express our sincere thanks to **Mr.R.BALAN, MA.,MLIS**., Librarian PGP College of Pharmaceutical Science and Research Institute, Namakkal–637 207 for providing the library facilities and co-operation to complete this work.

Also express our sincere thanks to Lab Assistants **Mr.J.RAMESH,MA.,B.Ed., Mr. K.T. SHIVANESAN, M.Sc., B.Ed.,** and **Mr. S. MANIKANDAN M.Com.,** PGP College of Pharmaceutical Science and Research Institute, Namakkal–637 207 for their timely help.

We find ourselves lacking in words to express our deepest sense of gratitude towards our beloved parents for their unconditional support, encouragement and motivation. It's all because of their belief and the optimism that they instilled in us that we have been able to complete this work successfully.

By

TAMILSELVAN.P

CERFICATE OF APPROVAL

The foregoing thesis entitled **"FORMULATION AND EVALUATION OF QUETIAPINE FUMARATE EXTENDED RELASE TABLETS"** is hereby approved as creditable study of research topic and has been presented in satisfactory manner to warrant its acceptance as prerequisite to the degree for which it has been submitted.

(INTERNAL EXAMINER) (EXTERNAL EXAMINER)

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CHAPTER NO: 1

INTRODUCTION

1. TABLETS:

Definition: Tablets are tamperproof solid unit dosage forms containing medicament or mixture of medicaments and excipients compressed or moulded into solid cylindrical shape having either flat or convex surfaces.

1.1. Properties of tablets:

The attributes of an acceptable tablet are as follows:

- The tablet must be sufficiently strong and resistant to shock, abrasion, should withstand handling during manufacturing, packing, shipping, and use. Hardness and friability tests measure this property
- Tablet must be uniform in weight and in drug content of the individual tablet. This is measured by the weight variation and content uniformity tests
- The drug content of the tablet must be bioavailable. This property is measured by the dissolution test. Accurate bioavailability can be obtained from the drug levels in the blood after its administration
- Tablets must be elegant in appearance, characteristic shape, colour and other markings necessary to identify the product
- Tablets must retain all these functional attributes which include drug stability and efficacy

1.2 Types and classes of tablets:

Tablets are classified by their route of administration or function, by the type of drug delivery system they represent within that route, by their form and method of manufacture.
Tablets ingested orally

1. Compressed tablets (CT)
2. Multiple compressed tablets (MCT)
    a. Layered tablets and Bi-layer tablets
    b. Compression coated tablets

3. Repeat action tablets
4. Delayed action and enteric coated tablets
5. Sugar and chocolate coated tablets
6. Film coated tablets
7. Air suspension coated tablets
8. Chewable tablets
9. Dispersible tablets

Tablets used in oral cavity

1. Buccal tablets
2. Sublingual tablets
3. Troches, Lozenges and dental cones

Tablets used to prepare solution

1. Effervescent tablets
2. Dispensing tablets (DT)
3. Hypodermic tablets (HT)
4. Tablet triturates (TT)

The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration that is, the drug delivery system should delivery system should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment.

2. ORAL DRUG DELIVERY SYSTEM:

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamics effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms. [1]

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized" . Several types of modified-release drug products are recognized:

1. Extended-release drug products. A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release and long-acting drug products.

2. Delayed-release drug products. A dosage form that releases a discrete portion or portions of drug, at a time or at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

3. Targeted-release drug products. A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate- or extended-release characteristics.

2.1 Oral controlled release drug delivery system

Oral ingestion is traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is very little control over release of drug. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses, which in most situations, often results in constantly changing, unpredictable and often sub or supra therapeutic plasma concentrations leaving the marked side effects.[2,3]

Oral controlled release drug delivery is a system that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action.

An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled release (CR) delivery system provides a uniform concentration or amount of the drug at the absorption site and thus, after absorption allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.

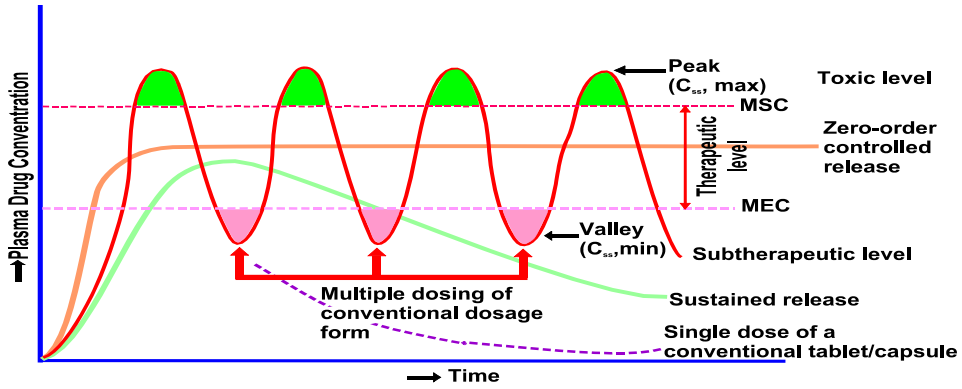


Fig. 1 - A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations.

(MSC = maximum safe concentration, MEC = minimum effective concentration).

3. SELECTION OF DRUG CANDIDATE FOR EXTENDED RELEASE DOSAGE FORMS[5]

The design of extended release delivery system is subjected to several variables of considerable importance. Among these, the properties of the drug, the route of drug delivery, and the disease being treated and length of the therapy have major importance . The following physico-chemical and biological factors have to be considered before selection.

3.1 Physicochemical factors

- Aqueous solubility
- Partition coefficient
- Drug stability
- Protein binding
- Molecular size and Diffusivity

3.2 Biological factors

- Absorption
- Distribution

•Elimination

•Biological half-life and Duration of action

•Side effects and Margin of safety

•Dose size

•Disease state

3.3. Characteristics of drugs suitable for formulation as extended release products

1. Exhibit moderate rates of absorption and excretion.
2. Uniform absorption throughout the gastrointestinal tract.
3. Administered in relatively small doses.
4. Possess good margin of safety.
5. Used for treatment of chronic therapy.

3.4.Characteristics of drugs unsuitable for formulation as extended Release Products

1. Not effectively absorbed in the lower intestine (Riboflavin).
2. Absorbed and excreted rapidly i.e. short biological half lives, less than one hour (Penicillin G, Furosemide).
3. Long biological half lives greater than 12 hours (Diazepam, Phenytoin).
4. Large doses required, 1gm (Sulphonamides)
5. Drugs with low therapeutic index (Phenobarbital, Digoxin).
6. Precise dosage titrated to individuals required (Anticoagulants)
7. No clear advantage for prolonged release formulation (Griseofulvin)

3.5. Types of oral controlled release drug delivery systems

A number of techniques are used to achieve controlled release of drugs via the oral cavity. The majority of the oral controlled release systems relay on dissolution, diffusion or a combination of both mechanisms to generate slow release of drug.

- Dissolution controlled release systems
- Diffusion controlled release systems
- Diffusion and dissolution systems
- Osmotically controlled release systems
- Gastro retentive drug delivery systems
- Electrically stimulated release devices
- Ion-exchange resins

4. DRUG RELEASE KINETICS - MODEL FITTING OF THE DISSOLUTION DATA: [8, 9]

4.1 Drug Release Kinetics:

Whenever a new solid dosage form is developed or produced, it is necessary to ensure that drug dissolution occurs in an appropriate manner. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, tor Q=f (t). Some analytical definitions of the Q (t) function are commonly used, such as Zero order, First order, Higuchi and Korsmeyer–Peppas models.

Table no.1: Drug Release Kinetics

Kinetic Model	Relation	Systems Following the Model
First order	$\ln Q_t = \ln Q_o + K_t$(release is proportional to amount of drug remaining)	Water-soluble drugs in porous matrix
Zero order	$f_t = K_o t$ (independent of drug concentration)	Transdermal systems Osmotic systems
Higuchi	$f_t = K_H t^{1/2}$ (proportional to square root of time)	Matrix formulations
Peppas–Korsmeyer	$M_t / M_\alpha = K_s t^2$	Erodible isometric matrices

f_t = fraction of dose released at time‘t’;

K_H, K_o, and K_s = release rate constants characteristic to respective models;

Q_o = the drug amount remaining to be released at zero hour;

Q_t = the drug amount remaining to be released at time ‘t’;

M_t = initial amount of drug present in the matrix at time‘t’,

M_α = amount of drug released at time ‘α’.

4.2 Mechanisms of drug release

To find out the drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix, first 60% drug release data can be fitted in Korsmeyer–Peppas model which is often used to describe the drug release behaviour from polymeric systems when the mechanism is not well-known or when more than one type of release phenomena is involved.

$$\text{Log } (M_t / M_\infty) = \text{Log } K_{KP} + n \text{ Log } t$$

Where, $M_t$is the amount of drug release at time *t*, M_∞ is the amount of drug release after infinite time; K_{KP} is a release rate constant incorporating structural and geometrical characteristics of the tablet, and *n* is the release exponent indicative of the mechanism of drug release.

Table no.2: Diffusion Exponent and Solute Release Mechanism for Cylindrical Shape

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

5. DOSE DETERMINATION OF EXTENDED-RELEASE DOSAGE FORMS[16]

In general, the total dose required (D_{tot}) in an extended-release dosage form is the sum of the maintenance dose (D_m) and the initial dose (D_I) released immediately to provide a therapeutic blood level.

$$D_{tot} = D_I + D_m$$

In practice, D_m (mg) is released over a period of time and is equal to the product of t_d (the duration of drug release) and the zero-order rate k_r^0 (mg/hr). Therefore

$$D_{tot} = D_I + k_r^0 t_d$$

or simply

$$D_{tot} = D_I + C_p Cl_T \tau$$

Where C_p = required therapeutic concentration of drug

τ = dosing interval

Cl_T = clearance of the drug

For many sustained-release drug products, there is no built-in loading dose (ie, $D_I = 0$). Therefore, the dose needed to maintain a therapeutic concentration for τ hours is

$$D_{tot} = C_p Cl_T \tau$$

6. DISEASE PROFILE

6.1 Schizophrenia is a mental disorder characterized by a breakdown of thought processes and by a deficit of typical emotional responses.[10] Common symptoms include auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking, and it is accompanied by significant social or occupational dysfunction. The onset of symptoms typically occurs in young adulthood, with a global lifetime prevalence of about 0.3–0.7%.[11] Diagnosis is based on observed behavior and the patient's reported experiences.

Genetics, early environment, neurobiology, and psychological and social processes appear to be important contributory factors; some recreational and prescription drugs appear to cause or worsen symptoms. Current research is focused on the role of neurobiology, although no single isolated organic cause has been found. The many possible combinations of symptoms have triggered debate about whether the diagnosis represents a single disorder or a number of discrete syndromes. Despite the etymology of the term from the Greek roots *skhizein* ("to split") and *phrēn, phren*-("mind"), schizophrenia does not imply a "split personality", or "multiple personality disorder" (which is known these days asdissociative identity disorder)—a condition with which it is often confused in public perception.[12] Rather, the term means a "splitting of mental functions", because of the symptomatic presentation of the illness.[13]

The mainstay of treatment is antipsychotic medication, which primarily suppresses dopamine (andsometimes serotonin) receptor activity.Psychotherapy and vocational and social rehabilitation are also important in treatment. In more serious cases—where there is risk to self and others—involuntary hospitalization may be necessary, although hospital stays are now shorter and less frequent than they once were.[14]

The disorder is thought mainly to affect cognition, but it also usually contributes to chronic problems with behavior and emotion. People with schizophrenia are likely to have additional (comorbid) conditions, including major depression and anxiety disorders; the lifetime occurrence ofsubstance use disorder is almost 50%.[15] Social problems, such as long-term unemployment, poverty, and homelessness are common. The averagelife expectancy of people with the disorder is 12 to 15 years less than those without, the result of increased physical health problems and a highersuicide rate (about 5%).[11, 16]

Management

The primary treatment of schizophrenia is antipsychotic medications, often in combination with psychological and social supports.[11]

Medication

The first-line psychiatric treatment for schizophrenia is antipsychotic medication,[22] which can reduce the positive symptoms of psychosis in about 7–14 days. Antipsychotics, however, fail to significantly ameliorate the negative symptoms and cognitive dysfunction.[28][29] Long term use decreases the risk of relapse.[30]

The choice of which antipsychotic to use is based on benefits, risks, and costs.[11] It is debatable whether, as a class, typical or atypical antipsychotics are better.[31][32] Both have equal drop-out and symptom relapse rates when typicals are used at low to moderate dosages.[33] There is a good response in 40–50%, a partial response in 30–40%, and treatment resistance (failure of symptoms to respond satisfactorily after six weeks to two or three different antipsychotics) in 20% of people.[28] Clozapine is an effective treatment for those who respond poorly to other drugs, but it has the potentially serious side effect of agranulocytosis (lowered white blood cell count) in less than 4% of patients.[11][12][34]

With respect to side effects typical antipsychotics are associated with a higher rate of extra pyramidal while atypicals are associated with considerable weight gain, diabetes and risk of metabolic syndrome.[33] While atypicals have fewer extrapyramidal side effects these differences are modest.[35] Some atypicals such as quetiapine and risperidone are associated

with a higher risk of death compared to the typical antipsychotic perphenazine, while clozapine is associated with the lowest risk of death.[45] It remains unclear whether the newer antipsychotics reduce the chances of developing neuroleptic malignant syndrome, a rare but serious neurological disorder.[37]

For people who are unwilling or unable to take medication regularly, long-acting depot preparations of antipsychotics may be used to achieve control.[38] They reduce the risk of relapse to a greater degree than oral medications.[30] When used in combination with psychosocial interventions they may improve long-term adherence to treatment.[38]

6.2 Bipolar disorder

Bipolar disorder or **bipolar affective disorder** (historically known as **manic–depressive disorder** or **manic depression**) is a psychiatric diagnosis for a mood disorder. Individuals with bipolar disorder experience episodes of a frenzied state known as mania (or hypomania), typically alternating with episodes of depression.

At the lower levels of mania, such as hypomania, individuals appear energetic and excitable and may in fact be highly productive. At a higher level, individuals begin to behave erratically and impulsively, often making poor decisions due to unrealistic ideas about the future, and may have great difficulty with sleep. At the highest level, individuals can experience very distorted beliefs about the world known as psychosis. Individuals who experience manic episodes also commonly experience depressive episodes; some experience a mixed state in which features of both mania and depression are present at the same time. Manic and depressive episodes typically last from a few days to several months and can be interspersed by periods of "normal" mood.

Current research suggests that about 4% of people experience some of the characteristic symptoms at some point in their life. Prevalence is similar in men and women and, broadly, across different cultures and ethnic groups. Genetic factors contribute substantially to the likelihood of developing bipolar disorder, and environmental factors are also implicated. Bipolar disorder is often treated with mood stabilizing medications andpsychotherapy. In serious cases, in which there is a risk of harm to oneself or others, involuntary commitment may be used. These cases generally involve severe manic episodes with dangerous behavior or depressive episodes with suicidal ideation. There are widespread problems with social stigma, stereotypes, and prejudice against individuals with a

diagnosis of bipolar disorder. People with bipolar disorder exhibiting psychotic symptoms can sometimes be misdiagnosed as having schizophrenia.

The current term bipolar disorder is of fairly recent origin and refers to the cycling between high and low episodes (poles). The term "manic–depressive illness" or psychosis was coined by German psychiatrist Emil Kraepelin in the late nineteenth century, originally referring to all kinds of mood disorder. German psychiatrist Karl Leonhard split the classification in 1957, employing the terms unipolar disorder (major depressive disorder) and bipolar disorder.

Management

There are a number of pharmacological and psychotherapeutic techniques used to treat bipolar disorder. Individuals may use self-help and pursuerecovery.

Hospitalization may be required especially with the manic episodes present in bipolar I. This can be voluntary or (if mental health legislation allows and varying state-to-state regulations in the USA) involuntary (called civil or involuntary commitment). Long-term inpatient stays are now less common due to deinstitutionalization, although these can still occur.[14] Following (or in lieu of) a hospital admission, support services available can include drop-in centers, visits from members of a community mental health team or Assertive Community Treatment team, supported employment and patient-led support groups, intensive outpatient programs. These are sometimes referred to partial-inpatient programs.[26]

Medication

Medications used to treat bipolar disorder are known as mood stabilizers; these work by reversing manic or depressive episodes and preventing relapses.[66] The first known and "gold standard" mood stabilizer is lithium, which is effective in treating acute manic episodes,[67] and preventing relapses, more so for manic than for depressive episodes.[68] Treatment with lithium carbonate has been strongly linked to a reduced risk of suicide, self-harm, and death in people with bipolar disorder.[69] Initially used as an anticonvulsant, sodium valproate has become a commonly prescribed treatment, and is effective in treating manic episodes.[70] Three other anticonvulsants are used in the treatment of bipolar disorder. Carbamazepinebecame widely used to treat bipolar disorder in the late 1980s and early 1990s, but was displaced by sodium valproate in the 1990s. Carbamazepine is effective in treating manic episodes, with some evidence it has greater benefit in rapid-cycling bipolar disorder, or those with more psychotic manic symptoms or a more

schizoaffective clinical picture. It is less effective in preventing relapse than lithium.[71] Lamotrigine has been shown to have some efficacy in treating bipolar depression, and this benefit is greatest in more severe depression.[72] It has also been shown to have some benefit in preventing further episodes, though there are concerns about the studies done, and is of no benefit in rapid cycling disorder.[73] The effectiveness of topiramate is unknown.[74] Depending on the severity of the case, anti-convulsants may be used in combination with lithium-based products or on their own.[74]

Atypical antipsychotics have been found to be effective in managing mania associated with bipolar disorder.[75] Olanzapine is effective in preventing relapses, although the evidence is not as solid as for lithium.[76] Antidepressants have not been found to be of any benefit over that found with mood stabilizers.[75]

Short courses of benzodiazepines may be used as adjunct to medications until mood stabilizing become effective.[77]Omega 3 fatty acids, in addition to normal pharmacological treatment, may have beneficial effects on depressive symptoms, although studies have been scarce and of variable quality.[78]

7. Atypical antipsychotic

The **atypical antipsychotics** (AAP) (also known as **second generation antipsychotics**) are a group of antipsychotic tranquilizing drugs used to treat psychiatric conditions. Some atypical antipsychotics are FDA approved for use in the treatment of schizophrenia. Some carry FDA approvedindications for acute mania, bipolar depression, psychotic agitation, bipolar maintenance, and other indications. Both generations of medication tend to block receptors in the brain's dopamine pathways, but atypicals at the time of marketing were claimed to differ from typical antipsychotics in that they are less likely to cause extrapyramidal motorcontrol disabilities inpatients, which include unsteady Parkinson's disease-type movements, bodyrigidity and involuntary tremors.[80] More recent research has demonstrated the side effect profile of these drugs is similar to older drugs, causing the leading medical journal The Lancet to write in its editorial "the time has come to abandon the terms first-generation and second-generation antipsychotics, as they do not merit this distinction." [81]

During the course of treatment atypical antipsychotics are associated with the following benefits: higher rate of responders, efficiency in patients with refractory disease,

lower risk of suicides, better functional capacity and an improved quality of life.[82] However, there has been considerable debate about whether second-generation antipsychotic drugs are better than first-generation antipsychotic drugs.[83] Although atypical antipsychotics are thought to be safer than typical antipsychotics, they still have severe side effects, including tardive dyskinesia, a serious movement disorder,neuroleptic malignant syndrome, and increased risk of stroke, sudden cardiac death, blood clots, and diabetes. Significant weight gain may also occur.

Medical uses

Atypical antipsychotics are typically used to treat schizophrenia or bipolar disorder.[83] They are also frequently used for agitation associated with dementia, anxiety disorder, and obsessive-compulsive disorder.[84] Some agents showing some benefits for these uses but are associated with significant rates of adverse events.[26] In dementia they should only be considered after other treatments have failed and if the person in question is at either risk to themselves or others.[28]

Schizophrenia

The first-line psychiatric treatment for schizophrenia is antipsychotic medication,[106] which can reduce the positive symptoms of psychosis in about 8–15 days. Antipsychotics, however, fail to significantly improve the negative symptoms and cognitive dysfunction.[11][31]

The choice of which antipsychotic to use is based on benefits, risks, and costs.[33] It is debatable whether, as a class, typical or atypical antipsychotics are better.[12] Both have equal drop-out and symptom relapse rates when typicals are used at low to moderate dosages.[85] There is a good response in 40–50%, a partial response in 30–40%, and treatment resistance (failure of symptoms to respond satisfactorily after six weeks to two of three different antipsychotics) in 20% of people.[11] Clozapine is an effective treatment for those who respond poorly to other drugs, but it has the potentially serious side effect of agranulocytosis (lowered white blood cell count) in 1–4%.[33][86][87]

Effectiveness

There has been considerable debate about whether second-generation antipsychotic drugs are more effective than first-generation antipsychotic drugs.[82] It has been suggested that there is no validity to the term "second-generation antipsychotic drugs" and that the drugs that currently occupy this category are not identical to each other in mechanism,

efficacy, and side-effect profiles, the second-generation drugs have no special atypical characteristics that separate them from the typical, or first-generation, antipsychotics. As a group they are no more efficacious, do not improve specific symptoms, have no clearly different side-effect profiles than the first-generation antipsychotics, and are less cost effective. The spurious invention of the atypicals can now be regarded as invention only, cleverly manipulated by the drug industry for marketing purposes and only now being exposed.[88]

7.1. List of atypical antipsychotics

The following are approved and marketed antipsychotic drugs in various parts of the world:

Table no.3: List of Atypical Antipsychotic drugs

S.NO	DRUG	COMPANY NAME
1	Amisulpride	Solian
2.	Aripiprazole	Ability
3.	Asenapine	Saphris
4.	Blonanserin	Lonasen
5.	Perospirone	Lullan
6.	Quetiapine	Seroquel

CHAPTER NO: 2

REVIEW OF LITERATURE

Madhusudhan P *et al.*, 2010 stated that extended release formulations make the drug available over prolonged period after oral administration. The extended release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. By incorporating the dose for 24 hours into one tablet/capsule from which the drug is released slowly. This formulation helps to avoid the side effects associated with low and high concentrations. The ideal drug delivery system should show a constant zero-order release rate and maintain the constant plasma concentrations.

Minkwitz M *et al.*, 2010 after an extensive study conveyed that, Immediate-release of quetiapine fumarate (Quetiapine IR) is a well-established, effective, atypical antipsychotic treatment for patients with schizophrenia, having shown efficacy across a broad range of symptoms (positive, negative, cognitive, and affective). The recommended initial dose of quetiapine IR is 25 mg twice daily, with increases in total daily dose of25–50 mg divided into two or three daily doses on days 2 and3, as tolerated, to a daily dose range of 300–400 mg, given in two or three doses, by day 4. When dose adjustment is required, increases or decreases of 25–50 mg divided twice daily are recommended. It has also been reported that a more rapid titration can provide safe and effective treatment. Extended-release quetiapine fumarate (quetiapine XR) is a once-daily formulation, developed to provide patients and physicians with a more convenient dosing regimen and a simpler dose initiation so patients can reach the recommended therapeutic dose range (400–800 mg/d) by day 2–3 of treatment. Quetiapine XR is effective and generally well tolerated in patients with schizophrenia or bipolar disorder, and is currently approved for the treatment of schizophrenia, acute manic and mixed episodes associated with bipolar I disorder, and acute treatment of depressive episodes associated with bipolar disorder in the United States and several other countries around the world. Beyond acute treatment, quetiapine XR is approved for relapse prevention in patients with stable schizophrenia.

Goodwin GM *et al.*, 2009 suggested thatatypical antipsychotics are currently considered to be first-line treatments for schizophrenia. A key advantage of the atypical antipsychotics over the conventional antipsychotics is that, as a class, they are better

tolerated, in particular with regard to their reduced propensity for extra pyramidal symptoms (EPSs).

The FDA approval of quetiapine XR for acute mania/mixed episode was based on a study by **Cutler *et al.*, 2009**.This randomized, multicenter, double-blind, parallel-group, placebo-controlled study included a total of 308 subjects with bipolar I with or without history of rapid cycling who were in acute manic or mixed episodes. Subjects recruited were18 to 65 years of age with a Young Mania Rating Scale (YMRS)of >= 20, and Clinical Global Impression-Bipolar-Severity of Illness (CGI-BP-S) overall score of >= 4. All subjects were hospitalized for at least 4 days at the beginning of the study. One hundred and forty-nine subjects were randomized to receive quetiapine XR initiated at 300 mg at the first day and increased to 600 mg the following day. The target flexible daily dose ranged from 400 to 600 mg. The primary outcome measure was change of YMRS total score after3 weeks of randomization. Secondary outcomes included YMRS remission rate (YMRS < 12), response rate (>=50%reduction in YMRS score) as well as changes in CGI-BP-Sand CGI-BP-change (CGI-BP-C).At the end of the study, subjects on quetiapine XR showed a statistically significant decline in total YMRS scores compared to placebo (–14.34 vs –10.52, $P < 0.001$).Among subjects on quetiapine XR, 55.0% showed response and 41.6% remission compared to only 33.3% and 27.7%on placebo ($P < 0.001$ and $P = 0.006$).

Figueroa *et al.*, 2009 compared pharmacokinetic profiles of quetiapine XR and quetiapine immediate release (IR) in patients with schizophrenia, and schizoaffective and bipolar disorder. In this open-label randomized, crossover trial, all 28 subjects received quetiapine IR 150 mg twice a day and quetiapine XR 300 mg daily over 4-day treatment intervals. Over a 24-hour dosing interval, Cmax of quetiapine XR was 13% less than quetiapine IR (495.3 vs568.1 ng/ml, 90% confidence interval [CI] 0.77 to 0.99). Cmax was achieved in 5 hours with quetiapine XR compared to 2 hours with quetiapine IR. Morning trough quetiapine concentrations (Cmin) showed no difference between the XR and IR formulations with 95.3 ng/mL and 96.5 ng/mL, respectively, (90% CI 0.77 to 1.31).With similar AUC and oral clearance for both formulations of quetiapine, drug–drug interaction data of quetiapine XR can be extrapolated from the quetiapine IR studies. Quetiapine IR has a limited inhibitory effect on cytochromeP450 enzymes 1A2, 2DC, 2C19, 2D6 and 3A4 substrates. Its plasma concentration and clearance is affected by cytochrome3A4 inhibitors

and inducers. For example, ketoconazole slows quetiapine metabolism and thus increase its plasma concentration while phenytoin, carbamazepine andthioridazine lower it.

US FDA Prescribing information 2008 Quetiapine extended release (XR) is an atypical antipsychotic, belonging to what is generally referred to as second generation antipsychotics. Its active metabolite is N-desalkylquetiapine (norquetiapine).Quetiapine XR was approved in the United States in 2007for the acute treatment as well for maintenance therapy of schizophrenia in adult patients. In October 2008, it gained FDA approval as monotherapy for treatment for bipolar disorder-acute depressive episodes, and bipolar I disorder-acute manic or mixed episodes. It also has FDA approval as adjunct therapy with lithium or divalproex for bipolar I disorder acute manic or mixed episode and maintenance. Quetiapine XR is available in 50 mg, 150 mg, 200 mg, 300 mg and 400 mg prolonged release tablets.

B, Brecher *et al*., 2008 stated that, the use of atypical antipsychotics in the treatment of bipolar disorder is a current standard of care. The role of atypical antipsychotics in the treatment of acute mania, acute bipolar depression and maintenance treatment is well established. Quetiapine XR offers a longer-acting formulation with a potential role in maximizing adherence, but this needs a more focused assessment. Treatment non adherence among subjects with bipolar disorder is estimated be around 40% and is associated with substantial humanitarian and financial burdens. While a once-daily treatment is likely to improve adherence for individuals who forget to take medication twice daily, formulations that require an even less frequent administration and perhaps with routes other than oral (ie, long-acting injectable compounds) such as once-weekly or once every 1 to 3 months should be a subject of future research focus.

El-Khalili N, et al., 2008 stated that, In Major depressive disorder (MDD), extended release quetiapine fumarate (quetiapine XR) was effective as adjunct to antidepressant therapy in two large, double-blind, placebo-controlled studies and in a small (n=58) study in patients with MDD, comorbid anxiety symptoms, and residual depressive symptoms. An additional longer-term study evaluating the maintenance treatment of MDD found that quetiapine XR once-daily monotherapy significantly reduced the risk of relapse of depression. The primary hypothesis of the present study was that quetiapine XR 50 mg/day, 150 mg/day, and 300 mg/day would be more effective than placebo in reducing Montgomery-Åsberg Depression Rating Scale (MADRS) total score from randomization to Week 6.

Simon *et al*., 2008suggested that, extended-release quetiapine fumarate (quetiapine XR) offers a potential treatment option for GAD. While an augmentation study with a small sample size (6/11 patients completed) reported no additional benefit when quetiapine was added to paroxetine controlled release, other studies have reported positive efficacy results for quetiapine as either monotherapy or adjunct therapy in patients with GAD (Adson et al. 2004; Galynker et al. 2005; Katzman et al.2008). This study evaluated the efficacy and tolerability of quetiapine XR as once-daily monotherapy for GAD.

Weiden PJ *et al*., 2007 stated that**,** schizophrenia is a debilitating and isolating disease imposing a significant burden on the lives of those affected and its effective and particularly long-term, management remains a significant clinical challenge. Enduring symptomatic improvement is required to improve and maintain quality of life and day-to-day functioning, and to achieve reasonable patient expectations of daily living. To achieve these goals, successful pharmacological treatment should be individualized and should provide a good balance between efficacy and tolerability.

Grant BF *et al*., 2005 mentioned that,bipolar disorder is a life-long clinical illness characterized by the presence of cycling episodes of mania or hypomania and mostly episodes of depression. Men and women are equally affected across all ethnicities with an overall lifetime prevalence of about2%–3%.Treatment of bipolar disorder must also address: 1) acute intervention for manic or depressive episodes, 2) maintaining long term remission and 3) prevention of recurrence. However, a major challenge has been that different medications may have limited therapeutic benefit for the disorder's polarity of symptoms or only have specific efficacy in certain phases of the illness. Moreover, medications may treat acute symptoms but not necessarily offer long-term maintenance.

AM Raggi *et al*., 2003 mentioned that Quetiapine fumarate (QF) (bis [2-(2-[4-(dibenzo[b,f][1,4]thiazepin-11-yl)]ethoxy)ethanol] fumarate, a dibenzothiazepine derivative, is a recent antipsychotic drug with an atypical neuro pharmacological profile. Quetiapine is the antipsychotic that has the highest serotonin/dopamine binding ratio, being the serotonin type 2 (5- HT2)-receptor blocking effect about twice as strong as the dopamine D2-receptor blocking effect**.** Due to this binding pattern, quetiapine causes minimal extra pyramidal side effects. It is readily absorbed from the gastrointestinal track with oral bioavailability of about

83% and a plasma elimination half life ranging from 6- 7 hours. Administration of QF in the sustain release dosage form as once daily would be more desirable as this formulation is intended to be given to schizophrenic patients. The sustain release form would also control the mood for longer period of time by maintaining the plasma concentration of drug well above the therapeutic concentration. It appears as effective as the older antipsychotics producing side effects no worse than those encountered with standard antipsychotics.

Arvanitis LA *et al.*, 1997 suggested that schizophrenia is a chronic and disabling brain disease. It is a state of mental impairment marked by hallucinations. It is characterized by distorted perceptions of reality, hallucinations and illusions, delusions, disorder thinking, emotional expression. The main types of schizophrenia are paranoid schizophrenia, disorganized schizophrenia (hebephrenic schizophrenia), catatonic schizophrenia, residual schizophrenia schizoaffective disorder and undifferentiated schizophrenia.

Hamner MB *et al.*, 1996 mentioned that Quetiapine fumarate (2-(2-(4-dibenzo [b, f] [1, 4] thiazepine-11-yl-1 piperzinyl) ethoxy)ethanol) is an antagonist at serotonin 5-HT 1 and 5-HT 2, dopamine D 1 and D 2, histamine H1, and adrenergic alpha1 and alpha2 receptors. It is prescribed for the treatment of schizophrenia. It is a second generation antipsychotic.

Leon Lachman *et al.*, 1990 mentioned that Controlled and sustained release products provide an immediate release of drug that promptly reduces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a pre-determined period. Such a dosage form leads to the better management of the acute or chronic disease condition. The goal in designing sustained or controlled delivery systems is to reduce the frequency of dosing.

Ganesan *et al*, 2005 Was Studied to efficacy and tolerability data, the previously described trial by in which switching from other antipsychotics to quetiapine XR was evaluated, also assessed patient-reported outcomes through recording of Personal Evaluation of Transitions in Treatment (PETiT) scores (a self-administered patient questionnaire comprising 30 questions relating to perceived well being, adherence to treatment, tolerability, and satisfaction).At the end of the 12-week study, there was a significant improvement in PETiT total score in patients who switched to quetiapine XR; improvements were recorded irrespective of whether patients switched due to insufficient efficacy or tolerability. It is

important to consider the patients' opinions of their medication; therefore, future trials evaluating the use of quetiapine XR in patients with schizophrenia should incorporate patient-reported outcomes to provide further evidence for the benefits of the formulation.

CHAPTER NO: 3

AIM AND OBJECTIVE OF THE WORK

- Aim and objective of the project work is to develop a stable formulation of quetiapinefumarate extended release tablets
- Develop the bioequivalent product to SEROQUEL XR® (Quetiapine fumarate) tablets 200mg , which is the reference listed drug product (RLD) in orange book , FDA
- SEROQUEL XR® (Quetiapine fumarate)tablets 50/150/200/300/400mg are extended release tablet dosage forms available as film coated tablets for oral administration. The proposed generic product is also to be formulated as a tablet dosage form
- Based on the tablet weight of innovator product of all available strengths , it was concluded that available strengths are not dose proportional and pseudo-dose proportional to each other
- As 200mg strength is reference listed drug , bioequivalence is to be proved between generic (test) product and SEROQUEL XR®(Quetiapine fumarate) tablets 200mg (Under fasting and fed condition)

CHAPTER NO: 4

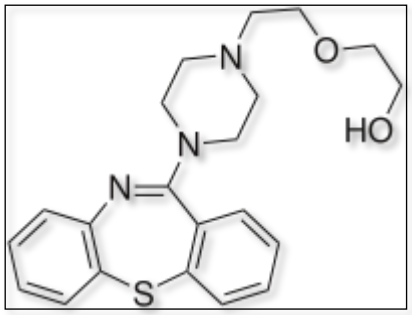
DRUG AND EXCIPIENT PROFILE

4.1 DRUG PROFILE:

Quetiapinefumarate is used for the treatment of schizophrenia as well as for the treatment of bipolar 1 disorder .

Chemical Structure and Nomenclature:

The chemical designation is 2[2-(4-dibenzo[b,f][1,4] thiazepin – 11 –yl – 1 piperazinyl) ethoxy]-ethanol fumarate (2:1) salt . It is present in tablets as the fumarate salt.



Molecular Formula: $C_{42}H_{50}N_6O_4S_2.C_4H_4O_4$.

Molecular Weight: 883.11 (fumarate salt)

TherapeuticCategory: anti-psychotic.

PHYSICO-CHEMICAL PROPERTIES:

Description: White to off-white crystalline powder.

Melting point: 174-176ºC

Solubility of drugs: Soluble in dimethylformamide and glacial acetic acid, sparingly soluble in methanol .

Partition co-efficient: Log P is 2.8

CLINICAL PHARMACOLOGY:

Mechanism of Action:

The mechanism of action quetiapinefumarate extended release tablets as with other drugs having efficacy in the treatment of schizophrenia, bipolar disorder and major depressive disorder (MDD), is unknown. However, it has proposed that the efficacy of quetiapinefumarate extended release tablets in schizophrenia is mediated through a combination of dopamine type2 (D2) and serotonin type2A (5HT2A) antagonism . The active metabolite , n-desalkylquetiapine (norquetiapine), has similar activity at D2 , but greater activity at 5HT2A receptors , than the parent drug quetiapinefumarate efficacy in bipolar depression and major depressive disorder (MDD) amy partly be explained by the high affinity and potent inhibitory effects that norquetiapine exhibits for the nor-epinephrine transport.

Antagonism at receptors other than dopamine and serotonin with similar (or) greater affinities may explain some of the other effects of quetiapine and norquetiapine antagonism at histamine H1 receptors may explain the somnolence, antagonism at muscarinic M, receptors may explain the anti-cholinergic effects.

PHARMACOKINETICS:

ABSORPTION:

Quetiapinefumerate reaches peak plasma concentration approximately 6hours following administration. Quetiapinefumerate extended release tablets dosed once daily at steady state has comparable bioavailability to an equivalent total daily dose of quetiapinefumerate administered in divided doses, twice daily. Quetiapine fumarate administered along with a high-fat meal (approximately 800 to 1000 calories) was found to produce statistically significant increase in the AUC of quetiapinefumerate extended release tablets (maximum AUC of 44% to 52% and 20% to 22% respectively) for the 50mg and 300mg. In comparison , a light meal (approximately 300 calories) had no significant effect on the Cmax or AUC of quetiapine .

DISTRIBUTION:

It is widely distributed throughout the body with an apparent volume of distribution of 10±4L/Kg . It is 83% bound to plasma proteins at therapeutic concentration . In-vitro, quetiapine did not affect the binding of warfarin or diazepam to human serum albumin . In turn , neither warfarin nor diazepam altered the binding of Quetiapine .

METABOLISM:

Highly metabolized by the liver via CYP3A4 is enzyme. Major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to parent acid metabolite ; both metabolites are inactive . Active metabolite is n-desalkylquetiapine.

ELIMINATION:

Mainly via hepatic metabolism ; less than 1% excreted as unchanged drug approximately 73% of dose recovered in urine and 20% in feces. The mean terminal half-life for immediate-release is 6 hours , for extended release is 7 hours , and n-desalkylquetiapine is 12 hours .

PHARMACOKINETIC PARAMETERS:

T max: 6 hours

Absolute bioavailability: 100%

Protein binding: 83%

Elimination half-life:7 hours

Volume of distribution: 10±4L/Kg

Linear/non-linear pharmacokinetics: The pharmacokinetics of quetiapine and n-desalkyl quetiapine are linear across the approved dosing range

Gender effect and food effect: There is no gender effect on pharmacokinetic of quetiapineand the bioavailability is marginally effected by administration with food, with C_{max} and AUC values is increased by 25 % and 15 % respectively.

INDICATION, DOSAGE AND ADMINISTRATION:

SCHIZOPHRENIA:

Quetiapine fumarate extended release tablets is indicated for the treatment of schizophrenia . The efficacy of quetiapine fumarate extended release tablets in schizophrenia was established in one 6 week and one maintenance trials in adults with schizophrenia as well by extrapolation from three-6-week trials in adults with schizophrenia treated with quetiapine .

Quetiapine fumarate extended release tablet should be administered once daily , preferably in the evening. The recommended initial dose is 300mg/day. Patients should be titrated within a dose range of 400mg/day to 800mg/day depending on the responses and tolerance of individual patient. Dose increases can be made at intervals as short as 1 day and in increments of upto 300mg/day. The safety of doses above 800mg/day has not been evaluated in chemical trials.

BIPOLAR DISORDER:

Quetiapine fumarate extended release tablets is indicatedfor the acute treatment of manic (or) mixed episodes associated with bipolar 1 disorder, both as monotherapy and as an adjunct to lithium (or) divalproex.

The effective of monotherapy for the maintenance treatment of bipolar disorder has not been systematically evaluated in controlled clinical trials usual dose for acute monotherapy (or) adjunct therapy (with lithium (or) divalproex).

The efficacy of quetiapinefumarate extended release tablets was established in one 8-week trial in adults with bipolar 1 (or) 2 disorder as well as extrapolation from two 8-week trials in adults with bipolar 1 (or) 2 disorder treated with quetiapine.

MONOTHERAPY:

Quetiapinefumarate extended release tablet should be administered once daily in the evening starting with 300mg on day 1 and 600mg on day 2 quetiapinefumarate extended release tablets can be adjusted between 400mg and 800mg beginning on day 3 depending on the response and tolerance of the individual patient.

ADJUNCTIVE TREATMENT OF MAJOR DEPRESSIVE DISORDER (MDD):

Quetiapine fumarate extended release tablets is indicated for use as adjunctive therapy to antidepressants for the treatment of MDD. The efficacy of quetiapine fumarate extended release tablets as adjunctive therapy to antidepressant in MDD was established in two 6-week trials in adults with MDD who had an inadequate response to anti-depressant treatment.

Quetiapine fumarate extended release tablet in a dose range of 150mg/day to 300mg/day was demonstrated to be effective as adjunctive therapy to antidepressant. Begin with 50mg once daily in the evening. on day 3 , the dose can be increased to 150mg once daily in the evening . there were dose-dependent increase in adverse reaction in the recommended dose range o 150mg/day. Doses above 300mg/day were not studied.

4.2 EXCIPIENT PROFILE:

1. **DIBASIC CALCIUM PHOSPHATE DEHYDRATE:**

It is widely used in tablet formulation both as an excipient and as a source of calcium and phosphorous in nutritional supplements. It is one of the more widely used materials , particularly in the nutritional/health food sector. It is also used in the pharmaceutical products because of its compaction properties and the flow properties of the coarse grade material.

2. **LACTOSE ANHYDROUS:**

It is widely used in direct compression tableting application and as a tablet and capsule and binder. It is also used with moisture-sensitive drug due to its low moisture content. It occurs as white to off-white crystalline particles (or) powder. It contains 70-80% anhydrous β-lactose and 20-30%anhydrous lactose.

3.CARBOXYMETHYL ETHYLCELLULOSE:

Carboxymethyl ethyl cellulose (CMEC) is a new excipient prepared by reacting carboxymethyl ethyl cellulose (CMC) with an etherifying agent such as an ethyl halide in the presence of a caustic alkali. CMEC has been employed in enteric protective coating. The fundamental physical property required for enteric protective coating films is that the films are not dissolved or disintegrated in gastric juice, but or promptly dissolved or disintegrated in gastric juice , but or promptly dissolved in intestinal juice.

Carboxymethyl ethyl cellulose used in the formulation development is pharmaceutical grade supplied by, Sanyo Chemical Industries Limited, Japan with brand name CMEC . This grade confirms to the requirements stated in the Japan monograph and it's not official in USP.Carboxymethylethylcellulose is mixed ether of carboxymethyl- and ethyl-cellulose. When dried , it contains not less than 8.9% and not more than 14.9% of carboxymethyl group (-CH_2COOH:59.04), and not less than 32.5% and not more than 43.0% of ethoxy group (-OCH_2H_5:45.06).

DESCRIPTION :

Carboxymethylethylcellulose occurs as white to yellowish white, odourless and tasteless powder or granules. It is practically insoluble in water and in ethanol.

IDENTIFICATION:

1.To 0.01g of carboxymethylethylcellulose and 1ml of water and 2ml of anthrone TS, and shake. A green colour develops, and gradually changes to dark green.

2.To 0.01g of carboxymethylethylcellulose in a small test tube add 2 drops of a solution of benzoyl peroxide 75% in water in acetone (1 in 10), evaporate on a water bath to dryness, fix a glass rod with chromotropic acid TS on its lower end in the small test tube with a cork stopper, and heat in an oil bath at 125ºC for 5 to 6 minutes. The chromotropic acid TS acquires a red-purple colour.

3. Dissolve 1g of carboxymethylethylcellulose in 20ml of dilute sodium hydroxide TS, and shake with 1ml of cupric sulphate TS. A light blue, flocculent precipitate is formed.

4. Dissolve 1g of carboxymethylethylcellulose in 50ml of a mixture of methanol and dichloromethane(1:1) with shaking, apply 0.5ml of the solution thinly on an optic plate, evaporate the solvent with hot air to make a film, and determine the infrared absorption spectrum as directed under the infrared spectrophotometry. It exhibits absorption at the wave nimbers of about 2980cm^{-1}, 2880cm^{-1}, 1760cm^{-1}, and 1112cm^{-1}.

VISCOSITY:

To 10.00g of carboxymethylethylcellulose, previously dried, add 90.0g of a mixture of methanol and dichloromethane (50% each in ratio by weight), stopper the vessel, dissolve by continuous shaking for 40minutes, and perform the test under the viscosity. The viscosity is 20-70mm^2/S.

PURITY:

1. **Clarity and colour of solution**-Dissolve 1.0g of carboxymethylethylcellulose in 10ml of a mixture of methanol and dichloromethane(1:1): the solution is clear and colourless to light yellow. Even if a turbidity is produced, it is not thicker than the following control solution.
   Control solution: Mix 2.0ml of 0.05mol/l sulphuric acid VS, 1ml of dilute hydrochloric acid, 45ml of water and 2ml of barium chloride TS, allow the mixture to stand for 10minutes, and shake.

2. **Chloride –** Dissolve 0.1g of carboxymethylethylcellulose in 40ml of 0.2mol/l sodium hydroxide TS, add 1 drop of phenolphthalein TS, and add dropwise dilute nitric acid with vigorous stirring until the red colour disappears. Add 20ml of dilute nitric acid with stirring. Continue heating on a water bath with stirring until the gelatinous precipitate becomes granular, cool, and centrifuge. Collect the supernatant liquid, wash the precipitate with three 20ml portions of water, centrifuging each time, to the combined supernatant liquid and washing add water to make 200ml, and filter. Perform the test with 50ml of filtrate. Prepare the control solution as follows: to 0.50ml of 0.01mol/l hydrochloric acid VS add 10ml of 0.2mol/l sodium hydroxide TS, 7ml of dilute nitric acid and water to make 50ml (not more than 0.071%).

3. **Sulfate-** To 0.5g of carboxymethylethylcellulose add 30ml of hot water, stir well, heat on a water bath for 10 minutes, filter by decantation while hot, wash the

residue well with hot water, combine the washing with the filtrate,cool,add water to make 100ml, and use this solution as the sample solution. Prepare the control solution as follows:to 0.40ml of 0.005mol/l sulphuric acid VS add 1ml of dilute hydrochloric and water to make 50ml(not more than 0.096%).

4. **Heavy metals –** Proceed with 2.0g of carboxymethylethylcellulose according to Method 2, and perform the test. Prepare the control solution with 2.0ml of standard lead solution(not more than 10ppm).
5. **Arsenic –** To 1.0g of carboxymethylethylcellulose in a porcelain crucible add 10ml of a solution of magnesium nitrate in ethanol(95) (1 in 10), fire the ethanol(95) to burn, and heat gradually to incinerate. After cooling, to the residue add 3ml of hydrochloric acid, dissolve by heating on a water bath, and perform the test with this solution using Apparatus B(not more than 2 ppm).
6. **Loss on drying-**Not more than 5.0 %(1g, 105ºC, 1 hour)
7. **Residue on ignition-**Not more than 0.5 %(1g).

PROCESS FOR PREPARING CARBOXYMETHYLETHYLCELLULOSE SUITABLE FOR ENTERIC COATING

Carboxymethylethylcellulose (CMEC) is prepared by reacting carboxymethylcellulose(CMC) with an etherifying agent such as an ethyl halide in the presence of a caustic alkali. It is known, as disclosed in U.S.Pat.No.4,250305, that when a phase transfer catalyst is employed in the reaction, one of the reaction substrates is solubilized in another phase, that is, the reaction system is made more homogeneous, where not only poor reproducibility of ethylation owing to heterogeneous reaction in conventional process is overcome, but also CMEC of high quality having a uniform distribution of ethoxy substituent group is obtained.

Carboxymethylethylcellulose has been employed in enteric protective coating. The fundamental physics property required for enteric protective coating films is that the films are not dissolved or disintegrated in gastric juice, but are promptly dissolved in intestinal juice.

Carboxymethylethylcellulose has a better hydrolysis resistance than cellulose acetate phthalate used conventionally as an enteric coating materials, but still causes change during preparation steps or storage, thus forming a gel material insoluble in a solvent used for preparing an enteric coating solution, lowering the film-forming property, producing cracks in coating films, or lowering the enteric property. The reason is considered to be that ester linkage such as a lactone is produced by heating under acidic condition.

Coating procedure of carboxymethylethylcellulose can be conducted in the form of an organic solvent solution, but an aqueous coating liquid is desired from the viewpoint of economy in process step such as recovery of a solvent and the safety. Dispersion of CMEC into fine particles and dispersing the fine particles into water with a plasticizer, dispersing agent, etc.

There is provided a process for preparing carboxymethylethylcellulose suitable for enteric coating which comprises:

1.Adding an alkali metal hydroxide to a dispersion of carboxy methyl cellulose in an organic solvent and subjecting the dispersion to a reaction with an ethyl halide in the presence of a presence of a phase transfer catalyst to produce carboxymethyethylcellulose, said carboxymethyl cellulose having a degree of substitution of carboxymethyl group of 0.2 to 1.2, and said organic solvent being substantially immiscible with an aqueous solution of the alkali metal hydroxide and capable of dissolving the ethyl halide.

2.Dissolving carboxymethylethylcellulose in an aqueous solution of a basic compound selected from the group consisting of ammonia, a water-soluble amine and an alkali metal hydroxide, and subjecting the resulting solution to depolymerisation in the presence of a peroxide.

3.Neutralizing the resulting basic solution of the depolymerized carboxy methyl ethyl cellulose with an acidic substance in the presence of an alkyl alcohol having 1 to 3 carbon atoms or acetone to form a hydrogel to dehydration with agitation at a temperature not lower than the temperature at which dehydration occurs, followed by isolation and washing with water.

4.Drying the wet carboxymethylethylcellulose. If desired the wet carboxy methyl ethyl cellulose may be pulverized in the wet state to particles having an average particle size of not more than 100µm, preferably not more than 40µm before drying.

4.MICROCRYSTALLINE CELLULOSE:

It is purified , partially depolymerised cellulose that occurs as a white odourless,tasteless,crystalline powder composed of porous particles.

5.MAGNESIUM STEARATE:

It is a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate.

6.TALC:

Talc is amineral composed ofhydrated magnesium silicate with the chemical formula H2Mg3(SiO3)4 or Mg3Si4O10 (OH) 2. In loose form, it is the widely used substance known as talcum powder. It occurs as foliated to fibrous masses, and in an exceptionally rare crystal form. It has a perfect basal cleavage and the folia are non-elastic, although slightly flexible. It is the softest known mineral and listed as 1 on the Mohs hardness scale. It can be easily scratched by a fingernail. It is also sectile (can be cut with a knife). It has a specific gravity of 2.5–2.8, a clear or dusty luster, and is translucent to opaque. Talc is not soluble in water, but it is slightly soluble in dilutemineral acids. Its colour ranges from white to grey or green and it has a distinctly greasy feel. Its streak is white.

7.ISOPROPYL ALCOHOL:

Isopropyl alcohol is a common name for a chemical compound with the molecular formula C3H8O. It is a colourless, flammable chemical compound with a strong odour. It is the simplest example of a secondary alcohol, where the alcohol carbon is attached to two other carbons sometimes shown as (CH3)2CHOH. It is a structural isomer of propanol.

8.OPADRY YELLOW:

Ferric oxide yellow is available as a fine red powder. Sicovit red 30E172 grade of ferric oxide yellow is selected as a colorants in the formulation of Aripiprazole tablets and is produced from BASF. In addition to the tests specified in the USP/NF monographs, appropriate controls on the raw materials. The colour depends on the particle size and shape and the amount of combined water.

CHAPTER NO: 5

CHARACTERZATION OF INNOVATOR

INNOVATOR: SEROQUEL XR® (QUETIAPINE FUMARATE) TABLETS

STRENGTHS: 50mg, 150mg, 200mg, 300mg&400mg.

MANUFACTURED BY: AstraZeneca pharmaceuticals

5.1 PHYSICAL CHARACTERIZATION:

Table no:4 Physical Characterization of Seroquel XR®50 and 150 mg Tablets

PARAMETERS	50mg	150mg
Description	Peach, film coated capsule-shaped, biconvex , intagliated tablet with 'XR 50' on one side and plain on other side	White, film coated, capsule shaped, intagliated tablet with 'XR 150' on one side and plain on other side.
Manufactured and Distributed By	AstraZeneca Pvt .Itd	AstraZeneca Pvt .Itd
Shelf Life	3 years	3 years
Average Mass of Tablets (mg)	520	580
Colour	Peach	White
Diameter (mm)	6.64	6.68
Shape	Capsule	Capsule
Coated/Uncotted	Coated	Coated
Thickness(mm)	5.14-5.18	5.52-5.58
Hardness(Kp)	24.5-25.5	24.0-24.9
Inactive Ingredients	Microcrystalline cellulose, sodium citrate, lactose monohydrate, magnesium stearate, hypromellose. **FILM COATING:** Hypromellose,	Microcrystalline cellulose, sodium citrate, lactose monohydrate, magnesium stearate, hypromellose **FILM COATING:** Hypromellose,

	polyethylene glycol 400, titanium. In addition yellow iron oxide(50mg)	polyethylene glycol 400, titanium. In addition yellow iron oxide(150mg)
Label Claim	Each tablet contains 58mg of quetiapine fumarate equivalent to 50mg quetiapine.	Each tablet contain 173mg of quetiapinefumarate equivalent to 150mg Quetiapine
Pack	HDPE contains of 60's count	HDPE contains of 60's count
Storage Conditions	59ºF to 86ºF(15ºC to 30ºC)	59ºF to 86ºF(15ºC to 30ºC)
Pharmacopoeial Status	Both, drug substance and drug product not official in USP/BP/EUROPEAN PHARMACOPOEIAS	Both, drug substance and drug product not official in USP/BP/EUROPEAN PHARMACOPOEIAS

Table no: 5 Physical Characterization of Seroquel XR® 200mg, 300mg, and 400mg Tablets

PARAMETERS	200mg	300mg	400mg
Descreption	Yellow, film coated, capsule shaped, biconvex, intagliated tablet with 'XR 200'on one side and plain on other side.	Pale yellow, film coated, capsule shaped, biconvex, intagliated tablet with 'XR 300'on one side and plain on other side.	Peach, film coated, capsule shaped, biconvex, intagliated tablet with 'XR 400'on one side and plain on other side.
Manufactured and Distributed By	AstraZeneca Pvt.Itd	AstraZeneca Pvt.Itd	AstraZeneca Pvt.Itd
Shelf Life	3 years	3 years	3 years
Average Mass of Tablets (mg)	615	820	910
Colour	Yellow colour	pale yellow	White colour

Diameter (mm)	6.67	7.73	**7.77**
Shape	Capsule shape	Capsule shape	Capsule shape
Coated/Uncotted	Coated tablets	Coated tablets	Coated tablets
Thickness(mm)	5.78-5.82	6.05-6.10	6.70-6.75
Hardness(Kp)	25.5-26.1	24-24.5	31-31.6
Inactive Ingredients	Microcrystalline cellulose, sodium citrate, lactose monohydrate, magnesium stearate, hypromellose **FILM COATING:** Hypromellose, polyethylene glycol 400, titanium. In addition yellow iron oxide(200mg)	Microcrystalline cellulose, sodium citrate, lactose monohydrate, magnesium stearate, hypromellose **FILM COATING:** Hypromellose, polyethylene glycol 400, titanium. In addition yellow iron oxide(300mg)	Microcrystalline cellulose, sodium citrate, lactose monohydrate, magnesium stearate, hypromellose **FILM COATING**: Hypromellose, polyethylene glycol 400, titanium. In addition yellow iron oxide(400mg)
Label Claim	Each tablet contains 230mg of quetiapine fumarate to 200mg quetiapine	Each tablet contains 345mg of quetiapine equivalent to 300mg quetiapine	Each tablet contains 461mg of quetiapine equivalent to 400mg quetiapine
Pack	HDPE container of 60's count	HDPE container of 60's count	HDPE container of 60's count
Storage Conditions	59ºFto 86ºF(15ºC to 30ºC)	59ºFto 86ºF(15ºC to 30ºC)	59ºFto 86ºF(15ºC to 30ºC)
Pharmacopoeial Status	Both,drugsubstance and drug product not officialin USP/BP/EUROPEAN PHARMACOPOEIAS	Both, drugsubstance and drug product not official in USP/BP/EUROPEAN PHARMACOPOEIAS	Both, drugsubstance and drug product not official in USP/BP/EUROPEAN PHARMACOPOEIAS

5.2 CHEMICAL CHARACTERIZATION

DISSOLUTION STUDIES ON INNOVATOR PRODUCT: Innovator tablet were evaluated for dissolution profiles in 750ml of 0.1N HCL for 2 hours followed by addition 250ml of 0.2M sodium phosphate buffer to afford a pH of 6.2. USP type-2 (paddle) apparatus is used for the study. The apparatus was agitated for 100 rpm at room temperature (37º±2ºC) and the data is presented below:

TABLE NO: 6 Dissolution Profile of Seroquel XR®50mg (Quetiapine Fumarate) Extended Release Tablet

TIME (HOUR)	UNIT-1	UNIT-2	UNIT-3	UNIT-4	UNIT-5	UNIT-6	MEAN % DRUG RELEASE
1	29	29	29	28	28	28	28
2	48	47	49	49	48	45	48
4	57	56	57	56	54	51	55
6	66	68	67	62	63	59	64
8	77	77	78	71	70	72	74
16	99	100	97	94	99	92	97

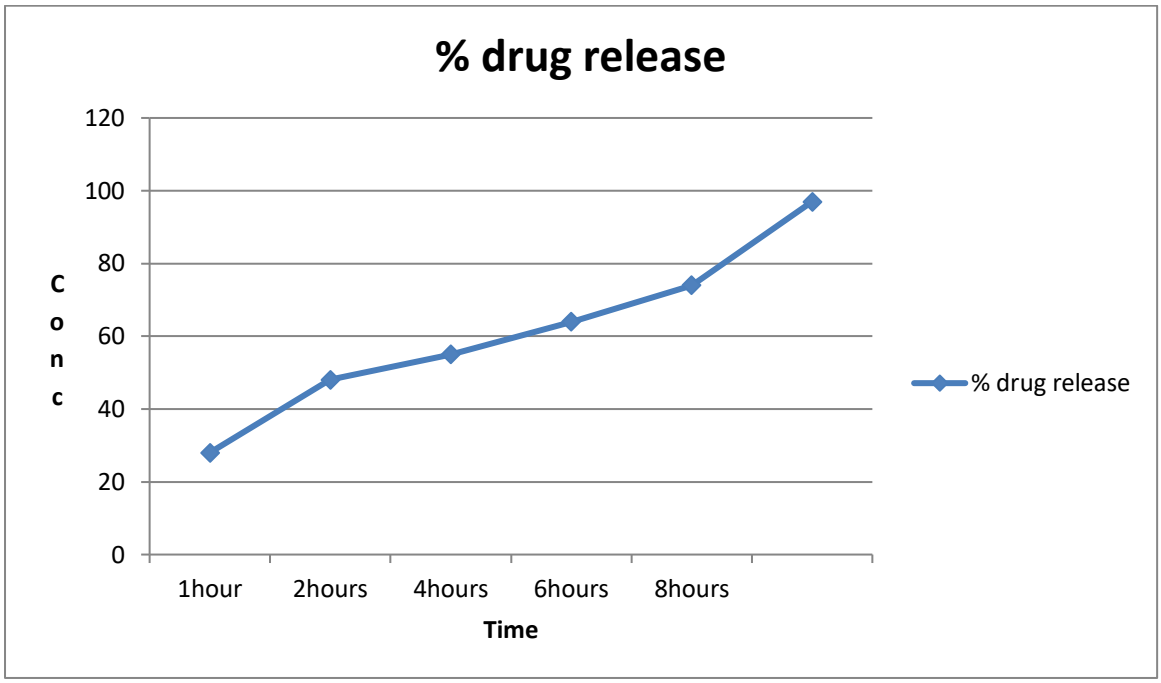


Figure no: 2 Dissolution Profile of Seroquel XR®50mg (Quetiapine Fumarate) Extended Release Tablet

CONCLUSION:

The innovator product showed 48% of drug release within 2 hours in 0.1N HCL and 97% of drug release within 16 hours in 0.1N HCL followed by 0.2M sodium phosphate buffer to afford a pH of 6.2.

Table no: 7 Dissolution Profile of Seroquel XR® 150mg (Quetiapine Fumarate) Extended Release Tablets

TIME (hour)	Unit -1	Unit -2	Unit -3	Unit -4	Unit -5	Unit -6	Mean % drug release
1	22	28	23	32	23	28	26
2	36	48	39	41	40	42	41
4	40	58	42	45	45	46	46
6	51	68	51	54	54	59	57
8	62	79	59	66	66	73	69
10	**74**	**88**	**70**	**76**	**76**	**90**	**81**
12	**86**	**93**	**81**	**84**	**84**	**101**	**90**
14	**93**	**104**	**90**	**92**	**92**	**107**	**93**
16	**101**	**106**	**98**	**98**	**100**	**107**	**103**

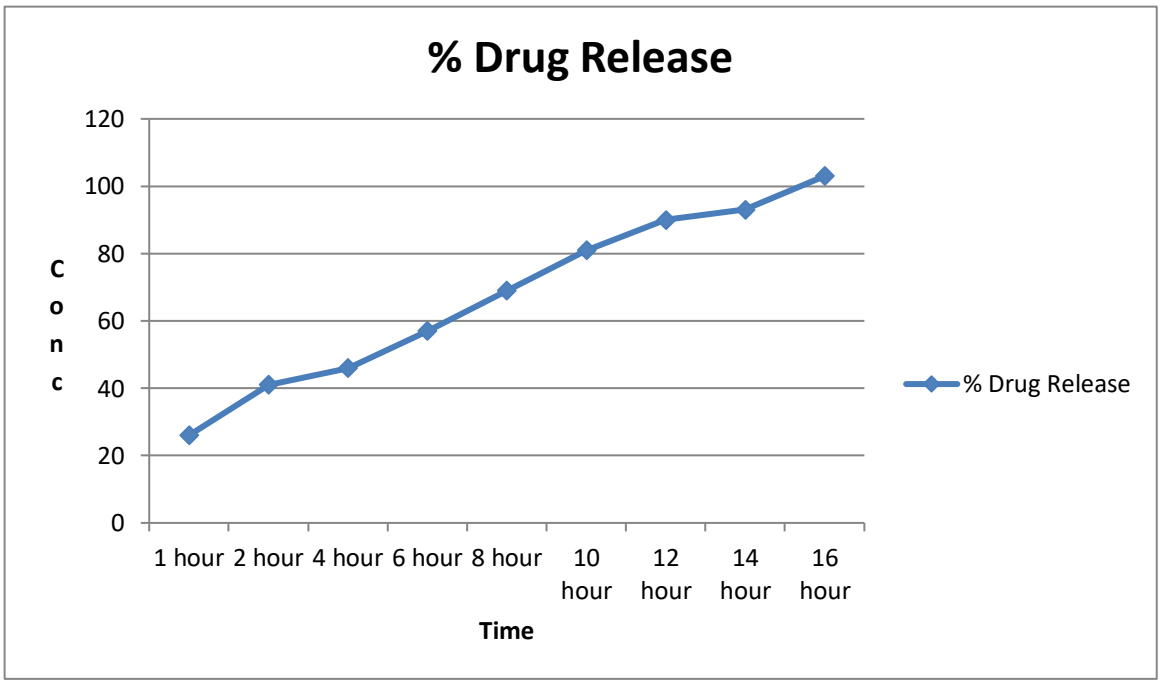


Figure no: 3- Dissolution Profile of Seroquel XR® 150mg (Quetiapine Fumarate) Extended Release Tablet

CONCLUSION:

It showed 41% of drug release in 2hours and 103% of drug release in 16hours.

Table no: 8 Dissolution Profile of Seroquel XR® 200mg (Quetiapine Fumarate) Extended Release Tablets

TIME (hour)	Unit -1	Unit -2	Unit -3	Unit -4	Unit -5	Unit -6	Mean % drug release
1	23	24	23	20	24	21	22
2	39	43	39	36	41	37	34
4	44	47	47	39	48	41	45
6	51	60	57	50	63	51	55
8	66	71	66	59	73	60	66
10	75	79	74	69	77	69	74
12	83	88	81	78	87	77	84
14	86	91	90	86	89	82	87
16	91	92	97	88	93	88	90

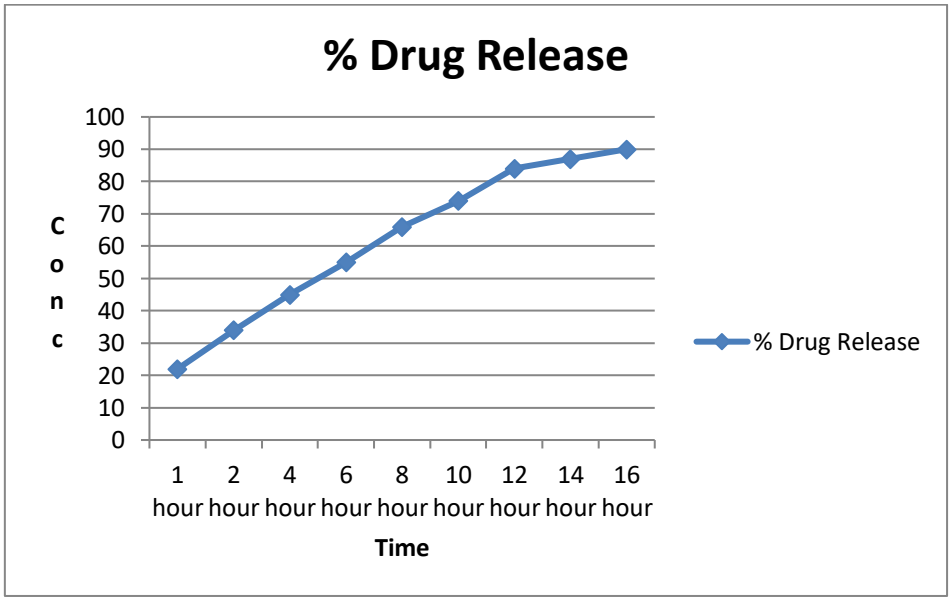


Figure no: 4 Dissolution Profile of Seroquel XR® 200mg (Quetiapine Fumarate) Extended Release Tablet

CONCLUSION:

It showed 39% of drug release in 2 hours and 90% of drug release in 16 hours.

Table no: 9 Dissolution Profile of Seroquel XR®300mg (Quetiapine Fumarate) Extended Release Tablets

TIME (hour)	Unit -1	Unit -2	Unit -3	Unit -4	Unit -5	Unit -6	Mean % drug release
1	27	25	24	25	29	23	26
2	47	45	40	40	49	40	44
4	55	50	44	45	57	47	50
6	70	63	56	59	70	60	63
8	83	71	67	71	80	70	74
10	96	82	80	83	91	83	86
12	100	95	89	89	100	98	95
14	102	105	102	100	104	98	102
16	103	107	104	101	106	106	104

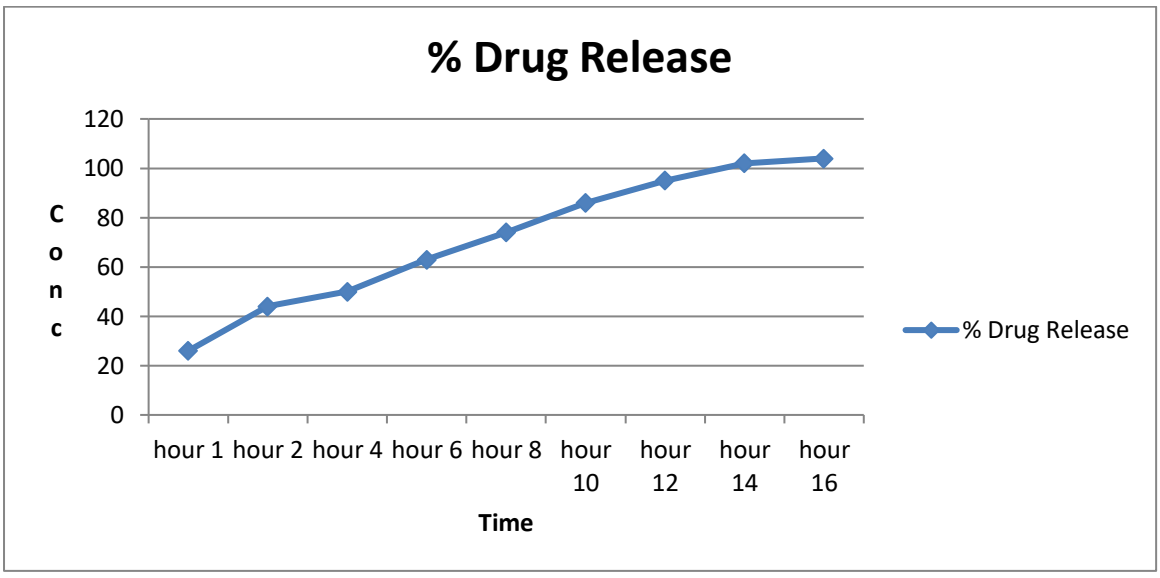


Figure no: 5 Dissolution Profile of Seroquel XR® 300mg (Quetiapine Fumarate) Extended Release Tablet

CONCLUSION:

It showed 44% of drug release in 2 hours and 104% of drug release in 16 hours.

Table no: 10 Dissolution Profile of Seroquel XR® 400mg (Quetiapine Fumarate) Extended Release Tablets

TIME (hour)	Unit -1	Unit -2	Unit -3	Unit -4	Unit -5	Unit -6	Mean % drug release
1	14	17	16	21	17	18	18
2	17	26	30	27	29	31	27
4	38	44	40	41	50	41	42
6	49	51	51	55	72	48	54
8	61	72	71	75	80	66	71
12	79	94	84	88	93	90	89
16	95	98	100	93	100	101	97

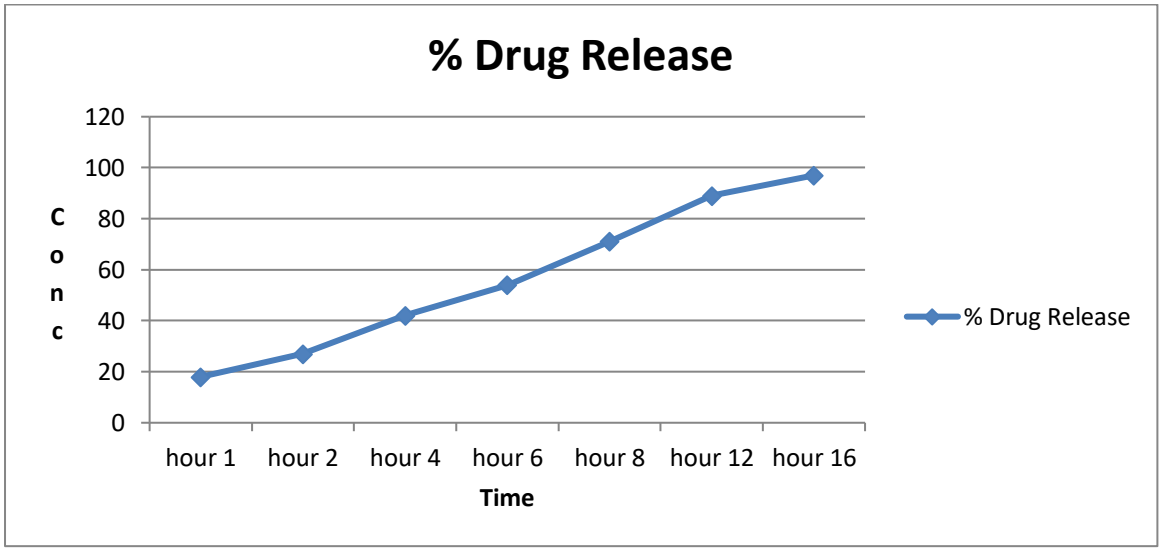


Figure no: 6 Dissolution Profile of Seroquel XR® 400mg (Quetiapine Fumarate) Extended Release Tablets

CONCLUSION:

It showed 27% of drug release in 2 hours and 97% of drug release in 16 hours.

CHAPTER NO: 6

PREFORMULATION STUDIES OF ACTIVE PHARMACEUTICAL INGREDIENTS

Quetiapine fumarate is Manufactured by Hetero Drug Limited (Bulk Unit-3), Jeedimetla Hyderabad, Andhra Pradesh, India.

1.Description: It was observed that the active pharmaceutical ingredient is white to off-white in colour.

2.Solubility: Solubility of quetiapine fumarate was evaluated in the following medias and solubility in mg/ml is presented in the below table.

Table no: 11 pH – Solubility Profile of Quetiapine Fumarate

MEDIA/BUFFER	SOLUBILITY (mg/ml)	SOLUBILITY (mg/250ml)	APPROXIMATE VOLUME OF SOLVENT IN ml/gm SOLUTE	SOLUBILITY CRITERIA
0.1N HCL	49.298	12074.5	20.70479	Sparingly Soluble
0.01N HCL	8.544	2136	117.04119	Slightly Soluble
pH 4.5 Acetate buffer	3.051	762.75	327.76138	Slightly Soluble
pH 6.8 Phosphate buffer	0.804	201	1243.781	Very Slightly Soluble
pH 7.2 Phosphate buffer	0.441	110.75	2267.5736	Very Slightly Soluble
pH 8.0 Phosphate buffer	0.542	135.5	1845.018	Very Slightly Soluble
Purified water	1.6676	416.9	599.6641	Slightly Soluble

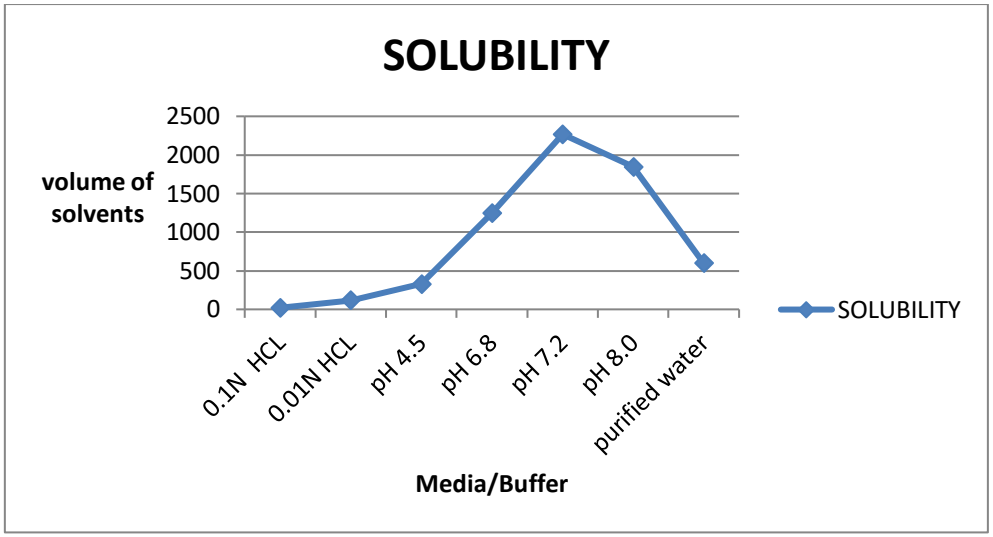


Figure no: 7 pH- Solubility Profile of Quetiapine Fumarate.

CONCLUSION:

Quetiapinefumarate is slightly soluble in purified water , 0.01N Hcl and pH 4.5 acetate buffer , very slightly soluble in pH 6.8 phosphate buffer , sparingly soluble in 0.1N Hcl . Hence it has been observed that quetiapinefumarate exhibits poor solubility across the range of pH 1.0 to 8.0.

3. Compatibility Studies:

The objective of drug excipients compatibility studies is to select compatible excipients (in active raw materials) with active pharmaceutical ingredients based on acceptable related substance (impurity profile) level by stressing (direct exposure) the binary mixture (direct excipient) at 40ºc (75% RH and 60ºc) for 4 week. To study the compatibility of quetiapine fumarate with inactive ingredients, the binary mixtures were prepared and resulting blends were packed in a self-sealpolyethylene bag without seal and in a glass vial with perforated seal & were stressed at 40ºc/75%RH and 60ºc respectively for 4 weeks and were evaluated for physical and chemical stability. The observation of the same is presented in the table below.

Table no: 12 Physical Compatibility of Quetiapine Fumarate with Excipients

S.NO	INITIAL	40ºC/75%RH (4 WEEKS)	60ºC/75%RH (4 WEEKS)
API+Dibasic Calcium Phospate Dihydrate	White to white off	NCC	NCC
API+Lactose Anhydrate	White to white off	NCC	NCC
API+Carboxy Methylethyl Cellulose	White to white off	NCC	NCC
API+Microcrystalline Cellulose	White to white off	NCC	NCC
API+Magenesium Stearate	White to white off	NCC	NCC
API+ Opadry Yellow	Light yellow colour	NCC	NCC
API+Opadry Pink	Light pink colour	NCC	NCC
API+Opadry White	White colour	NCC	NCC
API	White to white off	NCC	NCC

NCC: No Characteristic Change

CONCLUSION:

There was no significant changes in the description of active drug substance and above excipients after 4 weeks of direct exposure to 40ºc/75%RH and 60ºc/75%RH.

CHAPTER NO: 7

DRUG PRODUCT DEVELOPMENT

7.1 SELECTIONS AND FUNCTIONS OF INGREDIENTS

1. Active Pharmaceutical Ingredients:

Quetiapinefumarate is used as active ingredients for the product development.

2. Inactive Pharmaceutical Ingredients:

Based on the preformulation studies , patent evaluation , literature search and innovators product composition , following excipients were selected for the development of stable Quetiapinefumarate extended release tablet 200mg.

Table no: 13 Inactive pharmaceutical ingredients and its uses

INGREDIENTS	USE
Dibasic calcium phosphate dehydrate	Diluent
Anhydrous lactose	Diluent
Carboxymethyethyl cellulose	Rate controlling polymer
Microcrystalline cellulose	Diluent
Magnesium stearate	Lubricant
Opadry yellow	Colourant
Talc	Lubricant
Isopropyl alcohol	Solvent

7.2 SELECTION OF PROCESS:

Poor in flow and compressibility , direct compression was not choosen for quetiapine fumarate.

GRANULATION:

In order to ensure uniform distribution of drug substance in dosage units and to get free flowing and compressible granules . Wet granulation process was selected for the manufacturing of quetiapinefumarate extended release tablet 200mg. High shear granulation using rapid mix granulator was preferred as granulation process for preparation of quetiapinefumarate extended release tablet 200mg .

DEVELOPMENT OF QUETIAPINE FUMARATE EXTENDED RELEASE TABLETS-200MG BY WET GRANULATION APPROACH USING HIGH SHEAR RAPID MIX GRANULATOR (RMG):

As reference listed drug (RLD) strength is 200mg , initial product developed trails were taken on 200mg only . The following excipients were taken to optimize the concentration of inactive ingredients like diluent , rate controlling polymer , lubricant and compressed tablets were evaluated for tablet compression parameter and finally coated using opadry yellow . The coated tablets were evaluated for dissolution profiles for a period of 24 hours.

7.3 TRAILS:

The trail batch was executed with proposed excipients and evaluated for compression and coating parameters .

Table no: 14-Optimization of working formulas for various formulation drugs

COMPOSITION	**QUETIAPINE FUMARATE EXTENDED RELEASE TABLETS 200mg**									
1.DRY MIX	Trail -001	Trail -002	Trail -003	Trail -004	Trail -005	Trail -006	Trail -007	Trail -008	Trail -009	Trail -010
1.Quetiapine fumarate	230.4	230.4	230.4	230.4	230.4	230.4	230.4	230.4	230.4	230.4
2.Dibasic calcium phosphate	79.6	89.6	84.6	109.6	119.6	119.6	129.6	114.6	----	164.6
3.Lactose anhydrous	60	60	60	60	60	60	60	60	164.6	----
4.Carboxymethyl ethylcellulose	60	60	60	40	40	30	20	35	35	35
5.Talc	-----	-----	5	5	5	5	5	5	5	5
2.GRANULATION										
6.Carboxymethyl ethylcellulose	35	25	25	20	10	20	20	20	30	20
7.Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
3.EXTRA GRANULAR PORTION										
8.Magnesium stearate	5	5	5	5	5	5	5	5	5	5
Core tablet	470	470	470	470	470	470	470	470	470	470
4.FILM COATING(18%W/W)										
9.Opadry yellow	18 gms	18 gms	18 gms	18 gms	18 gms	18 gms	18 gms	18 gms	18 gms	18 gms
10.Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

BRIEF MANUFACTURING PROCESS:

1. SIFTING :

Step 1: Quetiapine fumarate and dibasic calcium phosphate dehydrate was sifted together through mesh # 30

Step 2:Anhydrous lactose and carboxymethyl ethyl cellulose was sifted together through mesh # 30

Step 3: All the above materials was sifted through mesh # 30

2. GRANULATION SOLUTION PREPARATION:

Step 4: Required quantity of isopropyl alcohol and purified water was taken in a s.s vessel container.

3. DRY MIXING:

Step 5: The material of quetiapine fumarate , dibasic calcium phosphate dehydrate , anhydrous lactose and carboxymethyl ethyl cellulose was loaded into rapid mixer granulator and mixed for 10 minutes with impeller at slow speed and choppered off . The amperage reading of impeller motor was recorded.

4. WET GRANULATION:

Step 6: Granulating solution of isopropyl alcohol and purified water was added to the dry mix material of quetiapinefumarate , dibasic calcium phosphate dehydrate , anhydrous lactose and carboxymethyl ethyl cellulose over a period of 3 to 5 minutes while mixing the impeller at fast speed and chopper off and the amperage reading of impeller motor was recorded.

Step 7: Based on granulation consistency , additional quantity of isopropyl alcohol and purified water was added over a period of 1 to 3 minutes with impeller at fast speed and chopper off and the amperage reading of impeller motors was recorded.

Step 8: The wet mass over a period of 1 to 3 minutes was kneaded with impeller and chopper at fast speed and the amperage readings of impeller and chopper was recorded.

Step 9: The wet mass was discharged into fluid bed dryer bowl through co-mill fitted with 8.0mm screen.

5. DRYING:

Step 10: The wet mass of above mixture was dried at an inlet air temperature of 60±5ºc in a fluid bed dryer till to get LOD in between 0.2 to 0.7 litres w/w at 105ºc in automode by using suitable moisture analyser.

6.SIFTING AND MILLING:

Step 11: The dried granules of the above mixture was sifted through mesh # 25 and mill the retention using the suitable mill with 1.0mm screen at slow speed / knives forward direction.

Step 12: The milled granules of above mixture was sifted through mesh # 25 and mill the retentions using suitable mill equipped with 1.0mm screen at slow speed / knives forward directions and ensure all granules pass through mesh # 25.

Step 13: The above process was repeated if required till the granules passed through mesh # 25.

7.EXTRA GRANULAR MATERIAL SIFTING:

Step 14: Micro crystalline cellulose was siftedthrough mesh # 40

Step 15: Magnesium stearate was sifted through mesh # 60

8.PRE-LUBRICATION:

Step 16: Dried granules of the above mixture(step 13) was loaded into a suitable blender and sifted microcrystalline cellulose was added to the above mixture and blended for 10 minutes.

9.LUBRICATION:

Step 17: The above mixture was lubricated with sifted magnesium stearate for 5 minutes.

10.COMPRESSION:

Step 18: Tooling :

15.70 ×6.00mm , modified capsule shape deep concave punch embossed with ‘J’ on lower punch and ‘70’ on upper punch was used for compression of blend mixture.

11. FILM COATING:

Step 19:Required quantity of isopropyl alcohol and purified water was taken in a s.s container equipped with a propeller stirrer

Step 20: Carboxymethyl ethyl cellulose was added slowly to the above solution while stirring , the speed of stirrer was increased if necessary. Formation of excessive foam during stirring was avoided. Stirring was continued for 30-40minutes until clear solution was obtained.

Step 21: Opadry yellow was added slowly to the above solution while stirring . The speed of stirrer was increased if necessary. Formation of excessive foam during stirring was avoided. Stirring was continued for 30-45 minutes until a smooth homogeneous suspension was obtained . The dispersion was kept under constant agitation at slow speed during the entire coating process

Table no: 15 Coating parameters and its ranges

PARAMETERS	RANGE
Pan speed	1-8 RPM
Spray type	Continuous
Spray rate	15-50gm/gun/min
Atomized air pressure	5±2kg/cm²
Tablet bed temperature	50±5ºc
% Weight gain/tablet	4±0.75%w/w(3.25%w/w-4.75%w/w)

Step 22: Core tablets was transferred into coating pan, the tablets was warmed while jogging the pan until the tablet bed temperature reaches approximately 50±5ºc

Step 23: Coating suspension was sprayed on to the coating pan and the weight gain of the tablets was recorded. The coating was continued till the percentage weight gain was 4.0±0.75%w/w of the core tablet weight

13. The manufacturing process for trails (003,004,005,006,007,008) was similar to the above trails (001,002).Along with anhydrous lactose and carboxymethyl ethylcellulose,**talc** was included in **step 2**.Instead of Rapid Mix

Granulator(RMG) , **Fluidised Bed Processor(FBP)** have been used for effective mixing in **step 5**.

14. The manufacturing process for these trails is also similar to the above mentioned trails(001-008). The only change which was taken in step 1 of **trail-009,**dibasic calcium phosphate was not included and in step 1 of **trail-010,** lactose anhydrous was excluded. Remaining procedures were same as that of earlier trails.

15.PACKAGING:

Step 24: The approved tablets was packed as per current approved master packaging card.

7.4 EVALUATION PARAMETERS:

Tablet evaluation in extended release dosage forms may be divided conveniently into following categories.

Organoleptic properties:

Many pharmaceutical tablets use colour as a vital of rapid identification and consumer acceptance. The colour of a product must be uniform within a single tablet is generally referred to as “mottling”, from tablet to tablet, and form lot to lot non uniformity of colouring not only lacks esthetic appeal but also could be associated by the consumer with non-uniformity of content and general poor quality of the product.

Weight variation test:

Weight variation test was done by weighing 20 tablets individually, by using analytical balance. Calculating the average weight and comparing the individual tablet weight to the average weight.

The weight of not more than 2 tablets must not deviate from the average weight and no tablets deviate by double the percentage.

Tablet thickness:

Thickness was determined for 5 preweighed tablets of each batch using a digital vernier scale and the average thickness was determined in mm. The tablet thickness should be controlled within a +5 % variation of a standard.

Tablet hardness:

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

Friability:

Friability is an important factor in tablet formulation to ensure that the tablet can stay intact and withhold its form from any outside force of pressure. It can be calculated by using the following formula.

$$\%friability = 100 \times \frac{(W_o - W_f)}{W_o}$$

Wo-is the original weight of the tablets,

Wf- is the final weight of the tablets after the collection is put through the friabilator. Friability below 0.8% is usually considered satisfactory.

In vitro disintegration test:

The test was carried out on 6 tablets using Tablet disintegration tester. Distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in seconds taken for complete disintegration of the tablet with no paltable mass remaining in the apparatus was measured.

In vitro dissolution test:

Dissolution means the process by which solid substance enters in the solvent to yield solution. It is controlled by the affinity between the solid substance and the solvent is a process in which a solid substance solubilises in a given solvent that is transfer from the solid surface to the liquid phase.

MEDIUM: pH – 4.8 sodium citrate buffer followed by pH -6.6 sodium phosphate buffer.

VOLUME: 1000ml

APPARATUS: # 20 Mesh basket

SPEED: 200 RPM

TEMPERATURE: 37ºc±0.5ºc

PROFILE: 1 hour, 2 hours, 4 hours in pH-4.8 sodium citrate buffer and 6 hours, 8 hours, 10 hours, 12 hours, 16 hours, 20 hours and 24 hours in pH-6.6 sodium phosphate buffer

Table no: 16 Different types of chemicals and reagents and its grades

CHEMICALS AND REAGENTS	GRADES
Potassium dihydrogen orthophosphate	AR grade
Tri ethylamine	AR grade
Sodium citrate monobasic	AR grade
Sodium di hydrogen orthophosphate monohydrate	AR grade
Sodium hydroxide	AR grade
Potassium hydroxide	AR grade
Acetonitrile	HPLC grade
Methanol	HPLC grade
Water	MILLI-Q grade

PREPARATION OF SODIUM CITRATE BUFFER pH 4.8:

10.7g of sodium citrate monobasic and 1.6g of sodium hydroxide was weighed and transferred into a beaker containing 1000ml of water and was mixed.

PREPARATION OF 0.05M SODIUM PHOSPHATE BUFFER:

6.9gm of sodium di hydrogen phosphate monohydrate and 18.4gms of sodium hydroxide was weighed and transferred into a beaker containing 1000ml of water and was mixed.

PREPARATION OF 5N SODIUM HYDROXIDE SOLUTION:

20gms of sodium hydroxide pellets was weighed and transferred into a 100ml volumetric flask, it was dissolved and diluted to required volume with water.

PREPARATION OF BLANK SOLUTION (DILUENT):

900ml of pH-4.8 sodium citrate buffer and 100ml of 0.05M sodium phosphate buffer was mixed. pH of the solution to 6.6±0.05 with 5N sodium hydroxide solution was adjusted, the volume of 5N sodium hydroxide solution was consumed and noted.

PREPARATION OF 5% POTASSIUM HYDROXIDE SOLUTION:

5gms of potassium hydroxide pellets was weighed and transferred into a 100ml volumetric flask. It was dissolved and diluted torequired volume with water.

PREPARATION OF BUFFER pH 7.0:

3.4gms of potassium dihydrogen orthophosphate was weighed and transferred into a beaker containing 1000ml of water , 1ml of tri ethylamine was added and mixed. The pH of the solution to 7.0 ±0.05 with 5% 0.22µ membrane filter was adjusted.

PREPARATION OF MOBILE PHASE:

A degassed mixture of buffer pH 7.0 and acetonitrile in the ratio of 55.45%v/v was prepared.

CHROMATOGRAPHIC CONDITIONS:

Column: Water × Bridge (18,150 × 4.6 mm, 35µm or equivalent)

Flow rate: 1.2ml/min

Detection: 225nm

Injection volume: 20µl

Column temperature: 40ºc

Run time: 10minutes

PREPARATION OF STANDARD SOLUTION:

5.8mg of quetiapine hemifumarate working standard was weighed and transferred into a 100ml volumetric flask, 20ml of methanol sonicate was added to dissolve.Volume was diluted with diluent and was mixed.

5ml of above solution was transferred into a 50ml volumetric flask, volume was diluted with diluent and was mixed.

PREPARATION OF SAMPLE SOLUTION:

900ml of pH-4.8 sodium citrate buffer was transferred into each of the six dissolution vessels. The parameters was settled as mentioned in method and the apparatus was started and runs for 5 hours. 100ml of 0.05M sodium phosphate buffer was added after 5 hours, volume of 5N sodium hydroxide was also added consumed for adjusting pH for blank and the dissolution was continued for specified time. 10ml of the samples was withdrawn from each dissolution vessel at prescribed time points. The liquid withdrawn was replaced with equal volumes of dissolution medium maintained at 37±0.5ºc. A portion of the solution was filtered through 0.45µm membrane filter and first few ml of the filtrate was discarded.

FOR 50mg TABLETS:

Use the solution as such.

FOR 150mg TABLETS:

3ml of sample solution was transferred into a 10ml volumetric flask, volume was diluted with diluent and was mixed.

FOR 200mg TABLETS:

5ml sample solution was transferred into 20ml volumetric flask, volume was diluted with diluent and was mixed.

FOR 300mg TABLETS:

4ml sample solution was transferred into 25ml volumetric flask, volume was diluted with diluent and was mixed.

FOR 400mg TABLETS:

3ml sample solution was transferred into 25ml volumetric flask, volume was diluted with diluent and was mixed.

PROCEDURE:

The column was equilibriumed with mobile phase for not less than 30minutes at a flow rate of 1.2ml/min. Separately 20µl of standard solution(five injections) and sample solution was injected into the chromatographic system. The chromatogram was recorded and the peak response was measured.

EVALUATION OF SYSTEM SUITABILITY PARAMETERS:

The column efficiency as determined for the quetiapine peak from standard solution was not less than 2000 theoretical plates and the tailing factors for the Same peak was not more than 2.0. The %RSD of the peak area of quetiapine obtained from fine replicate injections of standard solution was not more than 2.0. The retention time for quetiapine fumarate peak was about 5minutes.

CALCULATION:

FOR 200mg TABLETS: (Trail -001 to Trail-010)

For pH 4.8 BUFFER:

$At/As \times Ws/100 \times 5/60 \times 900/1 \times 20/5 \times p/100 \times 100/L \times 767.02/883.11$

$=96/100 \times 480/100 \times 5/60 \times 900/1 \times 20/5 \times 100/100 \times 100/ \quad 767.02/883.11$

FOR pH 6.6 BUFFER:

At/As × Ws/100 × 5/60 × 1000/1 × 20/5 × p/100 × 100/L × 767.02/883.11

Where,

At = area of quetiapinefumarate peak in sample solution

As = average area of quetiapinefumarate peak obtained from fine replicate injections of standard solutions.

Ws = weight ofquetiapinefumarate working standard taken in mg

P = % purity ofquetiapinefumarate working standard used (on as basis)

L = label claim of quetiapine fumarate , in mg

Stability Studies:

Selected formulation were subjected to stability studies as per ICH guidelines at 30°C/ 65 % RH and 40°C / 75% RH for 6 months. Sample were taken and analyzed at time interval of 15 days for 6 months.

Table no: 17 Stability studies for the selected formulation

S.NO	STUDY	STORAGE CONDITION	MINIMUM TIME PERIOD
1	Long term	25ºC+ 2ºC/60 %RH+ 5ºC (or) 30C+2ºC/ 65%RH+5%RH	12 months
2	Intermediate	30ºC+2ºC/65%RH+5%RH	6 months
3	Accelerated	40ºC +2ºC / 75% RH +5 % RH	6 months

Parameters like Assay, water content, related substance (impurity profile) and dissolution studies were carried out for the best formulation trail-008 as per in house specification of Hetero Lab, Unit-III, Hyderabad in analytical R&D department. Only 3 months of stability studies was over and the study is under progressing for the remaining period.

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RESULTS AND DISCUSSION

Yellow to pale yellow , modified capsule shaped biconvex coated tablet embossed with 'J' on one side and '70' on other side was obtained. Weight build up was found to be 4.0±0.75%w/w (3.25%w/w-4.75%w/w).

Results of post-compression parameter for Trail-008 batch

Table no: 18 Evaluation parameters and its range

PARAMETERS	RANGE
Organoleptic properties	Pale yellow , biconvex capsule shaped
Weight of individual tablets(mg)	480.00mg±5.0%(456.000-504.000mg)
Weight of 10 tablets (gm.)	4.800gm±4%(4.608-4.992)
Hardness (Kp)	17.0-27.0Kp
Thickness (mm)	4.70-5.60mm
Friability (% w/w)	Not more than 1.0%
Disintegration time	30 minutes

Table no: 18 depicts results of post-compression parameter for Trail-008 batch. Remaining formulation failed to show the satisfactory results.

Dissolution studies

MEDIA:

pH 4.8 sodium citrate buffer (900ml) followed by pH 6.6 sodium phosphate buffers (100ml)

Table no: 19 Dissolution Studies for Trail-001 and Trail-002 batches

Time(hours)	Innovator	Trail -001	Trail -002
2	20	9	8
4	41	21	19
6	61	35	33
8	72	58	50
10	83	64	65
12	92	68	69
16	96	72	75
20	96	89	90
24	98	96	96

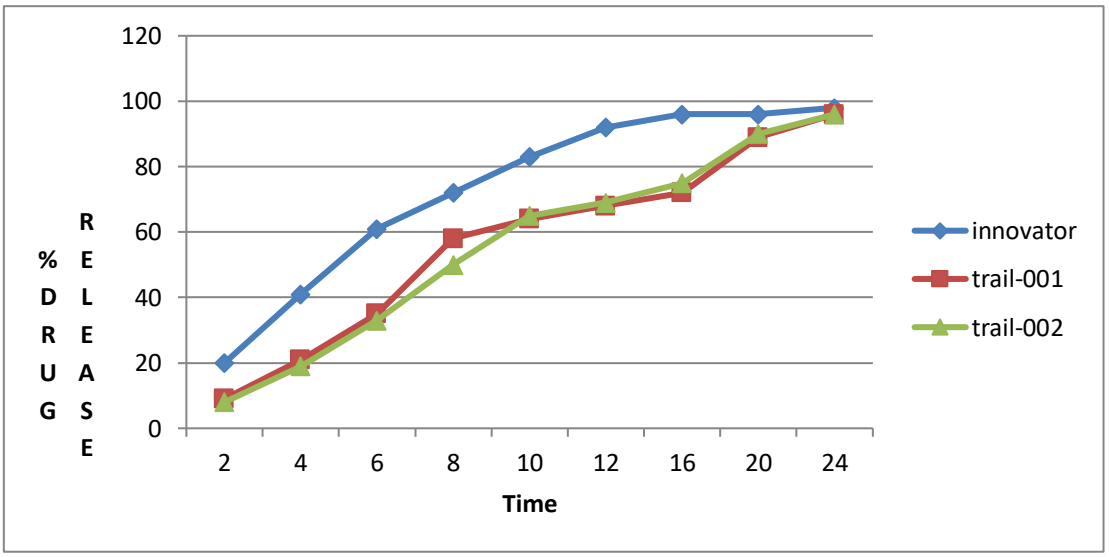

Figure no: 8 Dissolution Studies for Trail-001 and Trail-002 batches

DISCUSSION:

• The compression parameters of test products were found to be unsatisfactory

• The test product was evaluated for dissolution profiles in 900ml of pH 4.8 sodium citrate buffer followed by 100ml of pH 6.6 sodium phosphate buffer and it was compared to the dissolution profiles of innovator product, it was found that the rate of drug release profile of both test (trail-001,trail-002) were lower than the innovator product

• The rate of drug release was lowered in both the trails due to non-uniformity in granulation process . To get the uniform granules, next trails have been carried out with fluidised bed processor (FBP)

Table no: 20 Dissolution Studies for Trail-003 to Trail-008 batches

TIME (HRS)	INNOVATOR	TRAIL-003	TRAIL-004	TRAIL-005	TRAIL-006	TRAIL-007	TRAIL-008
2	20	11	14	18	17	15	19
4	41	25	29	29	27	32	37
6	61	45	47	45	49	51	57
8	72	59	55	64	57	67	69
10	83	77	79	89	80	88	81
12	92	89	87	91	87	92	93
16	96	91	92	94	90	94	94
20	96	93	94	98	92	97	96
24	98	93	96	99	96	99	99

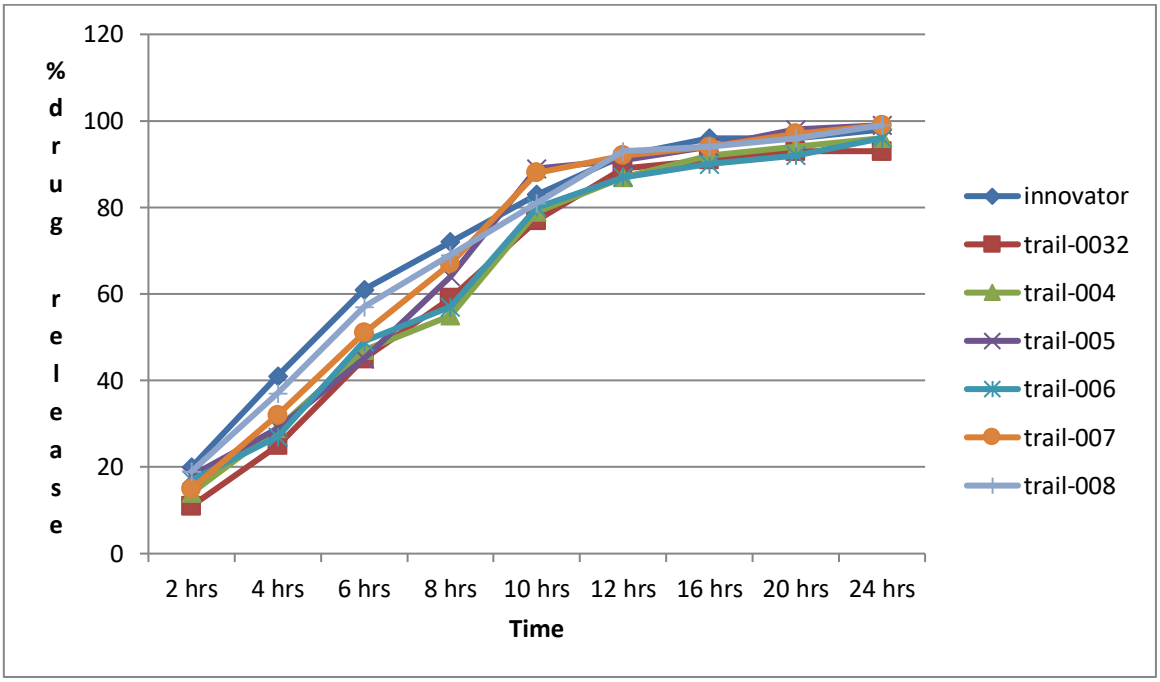

Figure no: 9 Dissolution Studies for Trail-003 to Trail-008 batches

DISCUSSION:

- The compression parameter of test product were found to be satisfactory
- These trails were taken in the fluidised bed processor instead of rapid mix granulator for uniform granulation
- The talc was added to avoid the stickness in fluidised bed processor
- The test products (trail-003,004,005,006,007,008) was evaluated for dissolution profiles in 900ml of pH 4.8 sodium citrate buffer followed by 100ml of pH 6.6 sodium phosphate buffer and it was compared to the dissolution profiles of innovator product, it was found that the rate of drug release profile of test (trail-003,004and006) were lower than the innovator product. And rate of release of drug profile of test (trail-005,007and008) were higher than the innovator product
- In trail-003,the rate of drug release is decreased than the innovator , so it was decided to decrease the quantity of drug release controlling polymer (carboxymethylethylcellulose) in both dry mix and granulation
- In trail-004, the rate of drug release is decreased than the innovator. So it was decided to decrease the rate controlling polymer in granulation stage and not in dry mix
- Accordingly trail-005 were taken using Fluidised Bed Processor (FBP), rate of drug release were higher than that of the innovator product
- In trail-006, it was decided to take up the batch with decrease in concentration of carboxymethyl ethyl cellulose in dry mix and increased in the granulation stage. The rate of drug release was decreased when compared to the innovator
- Again ,trail-007 was taken with equal concentration of carboxymethyl ethyl cellulose in both dry mix and granulation stage . Further the release profile got increased when compared to the innovator
- In trail-008, further incorporation of carboxymethyl ethyl cellulose in dry mix and the same concentration of rate controlling polymer was maintained as that of in trail-007 in granulation stage. Drug release profile got increased and matches with the innovator in all aspects, Hence it was considered to the best formulation of all trails.

Table no: 21 Dissolution Studies for Trail-009 and Trail-010 batches

TIME(HRS)	INNOVATOR	TRAIL-009	TRAIL-010
2 hrs	20	32	14
4 hrs	41	50	26
6 hrs	61	59	45
8 hrs	72	60	52
10 hrs	83	85	82
12 hrs	92	93	94
16 hrs	96	93	95
20 hrs	96	95	96
24 hrs	98	96	97

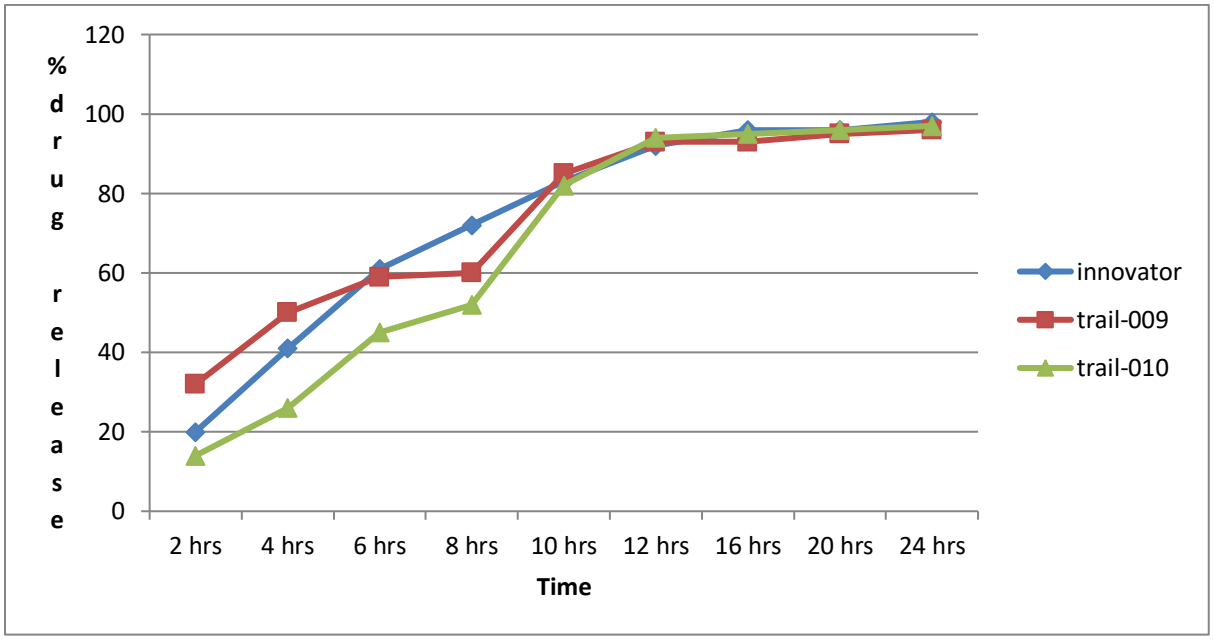

Figure no: 10 Dissolution Studies for Trail-009 and Trail-010 batches

DISCUSSION:

• The compression parameter of test product were found to be satisfactory

• These trails were taken in the fluidised bed processor instead of rapid mix granulator for uniform granulation

• The talc was added to avoid the stickness in fluidised bed processor

• The rate of drug release profile is decreased in trail – 009 when compared to the innovator product due to the absence of dibasic calcium phosphate and also increases in the concentration of rate controlling polymer (carboxymethyl ethyl cellulose) in granulation stage

• Even after by maintaining constant rate controlling polymer , the rate of drug release profile is decreased in trail-010 when compared to the innovator product due to the absence of lactose anhydrous (supertab)

SUMMARY OF STABILITY STUDIES:

RELATED SUBSTANCES:

There was no significant changes in the levels of known and unknown impurities between initial and 6 months stability loaded product

ASSAY,DISSOLUTION AND WATER CONTENT:

There was no significant difference in all the values between initial and 3 months stability samples.

DISCUSSION:

From the above stability data, it was clear that there were no significant changes in the physical and chemical parameters of quetiapinefumarate extended release tablet 200mg in both bottle and blister packs during the stability studies at intermediate (30ºC+2ºC/65%RH+5%RH) and accelerated conditions (40±2ºC/75±5%RH) during 3 months period. Hence the qualitative composition of trail-008 has been proposed as best to take up further batches.

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CONCLUSION

- Present work focuses on development of Extended Release Tablet of Quetiapinefumarate
- Quetiapinefumarate is an antipsychotic drug and is used for schizophrenia and bipolar disorder
- In the market it is available as SEROQUEL XR® (Quetiapinefumarate) tablets
- It is available in different strengths like 50mg,150mg,200mg,300mg and 400mg
- In this work , Quetiapinefumarate extended release tablet 200mg (which is the reference listed drug product (RLD) in orange book , FDA) was formulated by wet granulation method
- Totally 10 formulation trails were carried out
- Among all the formulations, trail-008 was found to be satisfactory. Hence on the basis of compression parameter results and in vitro release data, it can be concluded as best formulation
- The optimized formula was subjected to stability studies as per ICH guidelines
- There was no significant changes observed in stability studies after 3 months and hence trail-008 has been considered to take up further batches.

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BIBILOGRAPHY

1. Leon Shargel, Susanna Pong, Andrew B.C., Applied Biopharmaceutics and Pharmacokinetics, Modified Release Drug Products, Fifth Edition, CBS Publishers & Distributers, New Delhi, 2004, Pg 515,526,534-535.

2. Chien Y.W. Encyclopedia of Pharmaceutical Technology: Controlled and Modulated Release Drug Delivery Systems, 3rd ed., Varghese Publishing House, Mumbai, 1992, Pgs 281-313.

3. J. R. Robinson, S. P. Eriksen, Theoretical Formulation of Sustained Release Dosage Forms, J Pharm Sci, 1966; Volume 4, Issue 3, Pg: 243-253

4. Gilbert S. Banker, Christopher T. Rhodes, Modern Pharmaceutics: Sustained and Controlled Release Drug Delivery Systems, Fourth Edition, 2002, Pg 505-513

5. Leon Lachman, The Theory and Practice of Industrial Pharmacy: Sustained Release Dosage Forms, Third Edition, 1987, pgs 430-431

6. http://www.pharmainfo.net/reviews/floating-drug-delivery-systemsan-approach-gastro-retention
7. http://www.initium.demon.co.uk/relfick.htm
8. Korsmeyer RW, Gurny R, Doelker E, Buri P. Peppas NA. Mechanisms of Solute Release from Porous Hydrophilic Polymers, Int J Pharm, 1983; 15(2): Pgs 25–35.

9. Alfred Martin, Textbook of Physical Pharmacy, Fifth edition, Lippincott Williams and Wilkins, 1983; Pgs 285 – 289

10. “Schizophrenia", Concise Medical Dictionary. Oxford University Press, 2010. Oxford Reference Online. Maastricht University Library. 29 June 2010.

11. Van Os J, Kapur. S, Schizophrenia. Lancet. 2009;374(9690):635–45.
12. Picchioni MM, Murray RM., Schizophrenia. BMJ. 2007; 335 (7610):915.
13. Baucum, Don, Hauppauge, Psychology, 2nd Ed., Barron's., N.Y.,2006; Pg. 182.
14. Becker T, Kilian R. Psychiatric services for people with severe mental illness across Western Europe: what can be generalized from current knowledge about differences in

provision, costs and outcomes of mental health care? Acta Psychiatrica Scandinavica Supplement. 2006; 113(429):9–16.

15. Buckley PF, Miller BJ, Lehrer DS, Castle DJ. Psychiatric comorbidities and schizophrenia. Schizophr Bull. 2009; 35(2):383–402.
16. http://jop.sagepub.com/content/24/4_suppl/81.full.pdf+html
17. Carson VB, W.B. Saunders, Mental Health Nursing: The nurse-patient journey, Springer *Publishing* Company, 2000; Pg. 638.
18. Schizophrenia. Wiley-Blackwell, Blackwell Publishing Company, 2nd ed., 2003; Pg. 21, 481.
19. Brunet-Gouet E, Decety J. Social brain dysfunctions in schizophrenia: A review of neuroimaging studies. Psychiatry Res. 2006; 148(2–3):75–92.
20. Ungvari GS, Caroff SN, Gerevich J. The catatonia conundrum: evidence of psychomotor phenomena as a symptom dimension in psychotic disorders. Schizophr Bull. 2010;36(2):231–8.
21. Addington J, Cadenhead KS, Cannon TD, et al., North American prodrome longitudinal study: a collaborative multisite approach to prodromal schizophrenia research. Schizophrenia Bulletin. 2007;33(3):665–72.
22. Cullen KR, Kumra S, Regan J et al., Atypical Antipsychotics for Treatment of Schizophrenia Spectrum Disorders. Psychiatric Times. 2008; 25(3), Pg 66-70.
23. Amminger GP, Leicester S, Yung AR, et al., Early onset of symptoms predicts conversion to non-affective psychosis in ultra-high risk individuals. Schizophrenia Research. 2006;84(1):67–76.
24. Parnas J, Jorgensen A. Pre-morbid psychopathology in schizophrenia spectrum. British Journal of Psychiatry. 1989;115:623–7.
25. Coyle, Joseph ,"The Neurochemistry of Schizophrenia". In Siegal, George J; Albers, R. Wayne; Brady, Scott T et al. Basic Neurochemistry: Molecular, Cellular and Medical Aspects, Chapter 54: (7^{th} Ed.). Burlington, MA: Elsevier Academic Press.(2006). Pg. 876.
26. McGurk SR, Mueser KT, Feldman K, Wolfe R, PascarisA. Cognitive training for supported employment: 2–3 year outcomes of a randomized controlled trial.. American Journal of Psychiatry. 2007;164(3):437–41.
27. Gorczynski P, Faulkner G. Exercise therapy for schizophrenia. Cochrane Database Syst Rev. 2010;(5), Pg 236-243

28. Smith T, Weston C, Lieberman J. Schizophrenia (maintenance treatment). Am Fam Physician. 2010;82(4):338–9.
29. Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, "Just the Facts": What we know in 2008 part 1: Overview. Schizophrenia Research. 2008; 100(1–3):4–19.
30. Leucht S, Tardy M, Komossa K, et al., Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. The Lancet. 2012; 379(9831):2063–71.
31. Kane JM, Correll CU. Pharmacologic treatment of schizophrenia. Dialogues ClinNeurosci. 2010; 12(3):345–57.
32. Satterthwaite et al., Antipsychotics in Adults with Schizophrenia: Comparative Effectiveness of First-Generation Versus Second-Generation Medications: A Systematic Review and Meta-analysis. Annals of internal medicine. Aug 14, 2012 ;42(4):233–246.
33. Schultz SH, North SW, Shields CG. Schizophrenia: a review. Am Fam Physician. 2007;75(12):1821–9.
34. Essali A, Al-Haj Haasan N, Li C, Rathbone J. Clozapine versus typical neuroleptic medication for schizophrenia.Cochrane Database Syst Rev. 2009; 36(1):48–70.
35. Tandon R, Belmaker RH, Gattaz WF, et al., World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. Schizophr. Res.2008; 100(1–3):20–38.
36. Chwastiak LA, Tek C. The unchanging mortality gap for people with schizophrenia. The Lancet. 2009; 374(9690):590–2.
37. Ananth J, Parameswaran S, Gunatilake S, Burgoyne K, Sidhom T. Neuroleptic malignant syndrome and atypical antipsychotic drugs. Journal of Clinical Psychiatry. 2004;65(4):464–70.
38. McEvoy JP. Risks versus benefits of different types of long-acting injectable antipsychotics. J Clin Psychiatry. 2006; 67 Suppl 5:15–8.
39. Pharoah F, Mari J, Rathbone J, Wong W. Family intervention for schizophrenia. Cochrane Database Syst Rev. 2010; 38(2):48–55.
40. Medalia A, Choi J. Cognitive remediation in schizophrenia.. Neuropsychology Rev. 2009;19(3):353–364.
41. Dixon LB, Dickerson F, Bellack AS, et al., The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. Schizophr. Bull. 2010;36(1):48–70.

42. Lynch D, Laws KR, McKenna PJ. Cognitive behavioural therapy for major psychiatric disorder: does it really work? A meta-analytical review of well-controlled trials. Psychol. Med. 2010; 40(1):9–24.
43. Jones C, Cormac I, Silveira da MotaNeto JI, Campbell C. Cognitive behaviour therapy for schizophrenia. Cochrane Database Syst Rev. 2004; (4):32-36.
44. Ruddy R, Milnes D. Art therapy for schizophrenia or schizophrenia-like illnesses. Cochrane Database Syst Rev. 2005; (4):11-23.
45. Ruddy RA, Dent-Brown K. Drama therapy for schizophrenia or schizophrenia-like illnesses.. Cochrane Database Syst Rev. 2007; (1):65-78.
46. Bowden, C. L. "Strategies to reduce misdiagnosis of bipolar depression". Psychiatric services (Washington, D.C.), 2001; 52 (1): 51–55.
47. Muzina, DJ; Kemp, DE; McIntyre, RS. "Differentiating bipolar disorders from major depressive disorders: treatment implications". Annals of clinical psychiatry: official journal of the American Academy of Clinical Psychiatrists. (2007 Oct–Dec); 19 (4): 305–12.
48. Mayo Clinic staff. "Bipolar disorder: Tests and diagnosis". 2010; 22(07):19-21.
49. Diagnostic and Statistical Manual of Mental Disorders-IV 1994, Pg. 357.
50. Dean, k; Walsh E, Morgan C, et al. "Aggressive behaviour at first contact with services: findings from the AESOP First Episode Psychosis Study". Psychological Medicine, 2007; 37, Pg: 547–57.
51. Altman, E. G, Hedeker, D, Peterson, J. L, Davis, J. M. "The Altman Self-Rating Mania Scale". Biological Psychiatry, 1997; 42 (10): 948–955.
52. Young, R. C.; Biggs, J. T.; Ziegler, V. E.; Meyer, D. A. "A rating scale for mania: Reliability, validity and sensitivity". The British journal of psychiatry: the journal of mental science. 1978; 133: 429–435.
53. Furukawa, T. A."Assessment of mood: Guides for clinicians". Journal of Psychosomatic Research, 2010; 68 (6): 581–589.
54. Mansell, W.; Pedley, R. "The ascent into mania: A review of psychological processes associated with the development of manic symptoms". Clinical Psychology Review. 2008; 28 (3): 494–520.
55. "Hypomania and Mania Symptoms in Bipolar Disorder". WebMD.com. January 10, 2010.

56. Bipolar Disorder: NIH Publication No. 95-3679". U.S. National Institutes of Health. September 1995.
57. "Bipolar II Disorder Symptoms and Signs". Web M.D. 2010-12-06.
58. "Practice Guideline for the Treatment of Patients With Bipolar Disorder Second Edition". APA Practice Guidelines for the Treatment of Psychiatric Disorders: Comprehensive Guidelines and Guideline Watches 1. 2006.
59. Goldman E. "Severe Anxiety, Agitation are Warning Signals of Suicide in Bipolar Patients". ClinPsychiatr News, 1999; 25(5):236-242.
60. Srivastava, S.; Ketter, T. A. "The Link Between Bipolar Disorders and Creativity: Evidence from Personality and Temperament Studies". Current Psychiatry Reports. 2010; 12(6): 522–530.
61. Andreoli, T. E. "Molecular aspects of endocrinology". Hospital practice. Office Ed., 1989; 24 (8): 11–12.
62. Perugi, G.; Ghaemi, S. N.; Akiskal, H. "Diagnostic and Clinical Management Approaches to Bipolar Depression, Bipolar II and Their Comorbidities". Bipolar Psychopharmacotherapy. 2006; 16(3): Pg 193.
63. Picardi, A. "Rating scales in bipolar disorder". Current Opinion in Psychiatry. 2009; 22 (1): 42–49.
64. Zaretsky, A. E.; Rizvi, S.; Parikh, S. V. "How well do psychosocial interventions work in bipolar disorder? "Canadian journal of psychiatry. Revue canadienne de psychiatrie. 2007; 52 (1): 14–21.
65. Havens, L. L.; Ghaemi, S. N. "Existential despair and bipolar disorder: The therapeutic alliance as a mood stabilizer". American journal of psychotherapy. 2005; 59 (2): 137–147.
66. Bauer, M. S.; Mitchner, L. "What is a "mood stabilizer"? An evidence-based response". The American Journal of Psychiatry. 2004; 161 (1): 3–18.
67. Poolsup, N.; Li Wan Po, A.; De Oliveira, I. R. "Systematic overview of lithium treatment in acute mania".Journal of clinical pharmacy and therapeutics. 2000; 25 (2): 139–156.
68. Geddes, J. R.; Burgess, S.; Hawton, K.; Jamison, K.; Goodwin, G. M. "Long-term lithium therapy for bipolar disorder: Systematic review and meta-analysis of randomized controlled trials". The American Journal of Psychiatry. 2004; 161 (2): 217–222.
69. Cipriani, A.; Pretty, H.; Hawton, K.; Geddes, J. R. "Lithium in the Prevention of Suicidal Behavior and All-Cause Mortality in Patients with Mood Disorders: A Systematic

Review of Randomized Trials". American Journal of Psychiatry. 2005; 162 (10): 1805–1819.

70. MacRitchie, K.; Geddes, J.; Scott, J.; Haslam, D. R.; Silva De Lima, M.; Goodwin, Valproate for acute mood episodes in bipolar disorder. In Reid, Keith. "Cochrane Database of Systematic Reviews". Cochrane database of systematic reviews (Online) (1):1698-1732
71. Post, R. M.; Ketter, T. A.; Uhde, T.; Ballenger, J. C. "Thirty years of clinical experience with carbamazepine in the treatment of bipolar illness: Principles and practice". CNS Drugs. 2007; 21 (1): 47–71.
72. Geddes, J. R.; Calabrese, J. R.; Goodwin, G. M. "Lamotrigine for treatment of bipolar depression: Independent meta-analysis and meta-regression of individual patient data from five randomised trials". The British Journal of Psychiatry. 2008; 194 (1): 4–9.
73. Van Der Loos, M. L.; Kölling, P.; Knoppert-Van Der Klein, E. A.; Nolen, W. A. "Lamotrigine in the treatment of bipolar disorder, a review". Tijdschriftvoorpsychiatrie. 2007; 49 (2): 95–103.
74. Vasudev, K.; MacRitchie, K.; Geddes, J.; Watson, S.; Young, A. H. (2006). Topiramate for acute affective episodes in bipolar disorder. In Young, Allan H. "Cochrane Database of Systematic Reviews". Cochrane database of systematic reviews (Online) (1): CD003384.
75. El-Mallakh, R.; Elmaadawi, A.; Loganathan, M.; Lohano, K.; Gao, Y. (2010). "Bipolar Disorder: An Update".Postgraduate Medicine 122 (4): 24–31.
76. Cipriani, A.; Rendell, J. M.; Geddes, J. (2009). Olanzapine in long-term treatment for bipolar disorder. In Cipriani, Andrea. "Cochrane Database of Systematic Reviews".Cochrane database of systematic reviews (Online) (1): CD004367.
77. "Benzodiazepines for Bipolar Disorder". WebMD.com.13 February 2013.
78. Montgomery, P.; Richardson, A. J. (2008). Omega-3 fatty acids for bipolar disorder. In Montgomery, Paul. "Cochrane Database of Systematic Reviews". Cochrane database of systematic reviews (Online) (2).
79. Culpepper, L. (2007) A Roadmap to Key Pharmacologic Principles in Using Antipsychotics, Primary Care Companion To The Journal of Association of Medicine and Psychiatry 9(6): Pg. 444–454.
80. Tyler. P and Kendall. T. The Lancet, 2008; 373(9657): Pages 4 – 5.
81. Horacek, J., Bubenikova-Valeova, V., Kopecek, M., Palenicek, T., Dockery, C., Mohr, P. &Höschl, C. Mechanism of Action of Atypical Antipsychotic Drugs and the

Neurobiology of Schizophrenia, CNS Drugs, 2006; 20(5) 389–405 Retrieved from Psychology and Behavioral Sciences Collection database.

82. Stefan Leucht, Caroline Corves, Dieter Arbter, Rolf R Engel, Chunbo Li, John M Davis. "Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis". The Lancet. (January 3, 2009). Pg. 31–41.
83. Maher, AR; Maglione, M, Bagley, S, Suttorp, M, Hu, JH, Ewing, B, Wang, Z, Timmer, M, Sultzer, D, Shekelle, PG (2011 Sep 28). "Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis.".JAMA: the Journal of the American Medical Association 306 (12): 1359–69.
84. American Geriatrics Society 2012 Beers Criteria Update Expert, Panel (2012 Apr). "American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults" Journal of the American Geriatrics Society 60 (4): 616–31.
85. Wahlbeck K, Cheine MV, Essali A. Clozapine versus typical neuroleptic medication for schizophrenia. The Cochrane Database of Systematic Reviews. 2007; (2):CD000059.
86. Peter Tyrer and Tim Kendall. "The spurious advance of antipsychotic drug therapy". The Lancet. (January 3, 2009). Pg 373.
87. Robert Whitaker "Anatomy of an Epidemic". First Edition, Published by Crown. 2010 Pg. 303.
88. Kabinoff, G.S., Toalson, P.A., Masur Healey, K., McGuire, H.C. & Hay, D.P. (2003) Metabolic Issues with Atypical Antipsychotics in Primary Care: Dispelling the Myths, Primary Care Companion To The Journal of Association of Medicine and Psychiatry 5(1) 6–14.
89. Dirk Ziskoven. Does antipsychotic treatment increase the risk of internistic complications in pyschotic patients? Manual of Clinical Neurosciences; 2003 (5) 1134-48.