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Current Strategies of Quetiapine Fumarate Delivery in Management of Bipolar Disorder and Schizophrenia

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Abstract

Bipolar disorder is psychological illness with periodic episodes of mania and depression. Schizophrenia is a complex mental disorder identified by delusions, hallucinations, disorganized behavior, impaired cognitive ability, disorganized speech and sudden change in personality. In both the diseases quetiapine fumarate (QF) drug is worth important in today's scenario. This review gives complete QF drug profile along with mechanism of action. Quetiapine alone is successful for acute bipolar depression and the prevention of mania/hypomania switching. Literature survey section of this review gives information about quetiapine in different dosage form. By this review one can explore the scale up of quetiapine fumarate not only with immediate release and sustained release dosage form but also with novel drug delivery system like solid lipid nanoparticle and nanostructured lipid carrier.

Keywords: Bipolar disorder, Delusions, Hallucinations, Schizophrenia, Quetiapine fumarate

Introduction

Approximately 2-4% of the general population suffers from bipolar I, bipolar II [1]. In 2015, an estimated 17,000 people in world died by schizophrenia. In both the diseases quetiapine fumarate (QF) drug is worth important in today's scenario. It is available in traditional dosage form, by this review we want to explore different dosage form for QF.

Bipolar disorder (manic depression) is psychological illness with periodic episodes of mania and depression. Patient with bipolar disorder feels major changes in sleep, energy, thinking, behavior and highs and lows as two ‘poles’ of mood, so the name ‘bipolar disorder’. In between those poles, patient feels normal.

Sometimes patient with bipolar disorder feels over excitement and confidence (manic episode) along with irritability, reckless decision-making, hallucinations. The term ‘Hypomania’ describes milder symptoms of mania without delusions or hallucinations. Sometimes
A patient with bipolar disorder feels very sad or depressed (depressive episode).

Pathophysiology of bipolar disorder includes G protein subunits abnormality. There are elevated levels of the stimulatory G protein (Gαs) and post-receptor stimulated adenylyl cyclase activity [2-4]. Protein kinase C activity [5] and intracellular Ca2+ levels in platelets, lymphocytes and neutrophils also increases in bipolar disorder [6].

Symptoms of (highs) behavior include excessive excitement, sudden changes of mood, restlessness, less concentration, less need for sleep. Symptoms of (lows) behavior include sadness, loss of energy, feelings of worthlessness, uncontrollable crying, need more sleep, changes in appetite and thoughts of suicide [7]. Genes, brain changes, and stress contribute to develop bipolar disorder mostly in late adolescence age. Women are more receptive than men for ‘rapid cycling’ of mood episodes.

**What is bipolar I and bipolar II disorder?**

Diagnosis of bipolar disorder is crucial task for psychiatrist. Close friends and family member can help the psychiatrist to distinguish bipolar disorder from other psychological disorders that causes change in thinking, mood and behavior (Table 1).

<table>
<thead>
<tr>
<th>Table 1: Bipolar I and Bipolar II disorder.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bipolar I</strong></td>
</tr>
<tr>
<td>Patient has episodes of mania and depression</td>
</tr>
<tr>
<td>Patients are not in neutral state or functions normally.</td>
</tr>
<tr>
<td>Bipolar I is mainly associated with mania.</td>
</tr>
<tr>
<td>Symptoms are talkativeness, increased grandiloquence, less need for sleep, increased in energy level, racing thoughts and poor attention</td>
</tr>
</tbody>
</table>

Treatment for bipolar disorder includes drugs such as carbamazepine, lamotrigine, lithium or valproate. Sometimes drugs such as olanzapine, quetiapine, lurasidone and cariprazine and antidepressants are also used. Combinations of above mood stabilizers and antipsychotic drugs are often used along with patient counseling [9].

**Schizophrenia**

Schizophrenia is a complex mental disorder identified by delusions, hallucinations, impaired cognitive ability [10,11], disorganized speech [12], and sudden change in personality and behavior [13]. Pathophysiology include over or deficiency dopamine, serotonin and glutamate, with imbalance in levels of aspartate, glycine and gamma-aminobutyric acid.

Positive symptoms of schizophrenia include repetition of certain motions again and again (stereotypies), moving or talking for a while (catatonia). Negative symptoms include talking in a low voice, expressionless face, stick to an activity. Cognitive symptoms include difficulty in making decisions and less attention [13].

Etiology of schizophrenia includes obstetric difficulties such as bleeding, infections, excessive stress during pregnancy, gestational diabetes, emergency cesarean, deprived of oxygen condition, fetal disturbances during the second trimester and low birth weight [14,15,16].

Schizophrenia can be diagnosed through careful examination of patient’s duration of illness, time of delusions or hallucinations and severity of symptoms [13,17].

Treatment includes first-line monotherapy with second generation antipsychotic drugs. Next step consists of monotherapy with either other first or second generation antipsychotics antipsychotic drugs. Still no response next step is clozapine monotherapy, if agranulocytosis occurs, clozapine must be discontinued and start with combination therapy of clozapine with first and second generation antipsychotic drugs or electroconvulsive therapy. Still treatment shows no response then monotherapy with first generation antipsychotic drugs along with second generation antipsychotics that has not been tried should be given. Final stage consists of combination therapy of first, second generation antipsychotics, electroconvulsive therapy and/or a mood stabilizer [18].

**Quetiapine fumarate (QF)**

The combination therapy of olanzapine and fluoxetine was the first treatment which receive regulatory approval in the US for bipolar I depression. Quetiapine was the second medication to be approved for this indication. Doses of quetiapine such as 300 mg and 600 mg once daily at bedtime was effective for bipolar I and bipolar II depression [19].
QF is a second-generation atypical antipsychotic drug, marketed as immediate release tablets (IR) or extended release (XR) tablets. QF is a dibenzothiazepine derivative with biopharmaceutical classification system (BCS) class II drug. Quetiapine and quetiapine XR are approved for schizophrenia, and bipolar disorder in the UK and US. In US quetiapine alone or combination of lithium/valproate semisodium was approved. Quetiapine XR along with antidepressants is also approved in the UK and US as combination therapy in patients with major depressive disorder who have not showed response to quetiapine monotherapy [20]. Presently, quetiapine is also suggested as front-line treatment for acute bipolar depression [21,22].

Pharmacokinetic profile

The therapeutic dose of quetiapine show linear kinetics with half-life of about 7 hours and low oral bioavailability (7-9%) due to high first-pass metabolism. The Tmax is 5 hours for XR and 2 hours for IR. Quetiapine XR tablet required to take once daily as high plasma levels are sustained, as opposed to IR required to take at least two times daily.

Quetiapine is metabolized by liver and only 1% excreted unaltered in the urine. In the cytochrome P450 system quetiapine reacts with isoenzymes CYP 3A4 to produce N-desalkyl quetiapine or norquetiapineas key metabolite. Insignificant metabolism occurs through CYP2D6 into 7-hydroxy quetiapine which is inactive metabolite. Both quetiapine and norquetiapine involves for the broad spectrum activity due to action on dopaminergic, serotonergic and noradrenergic receptor [23].

Pharmacodynamic profile

Quetiapine is an antagonist at serotonin 5-hydroxytryptamine 5-HT1A (prefrontal cortex of brain), D2(dopamine), H1(histamine), α1 and α2(adrenergic) receptors. Quetiapine has ability to occupy about 30% of D2 receptors at therapeutic doses. According to ‘kiss and run’ hypothesis, quetiapine has fast dissociation from D2 receptors due to which higher doses of quetiapine required to induce its antipsychotic effect. Quetiapine has high attraction for 5-HT2A than for D2 receptors. Norquetiapine has 5HT7, 5HT2C and α2 antagonism, 5HT1A agonism and is also a Noradrenaline Reuptake Inhibitor (NRI) which brings about antidepressant action [19,20,24] (Figure 1).

Figure 1: Mechanism of action of Quetiapine fumarate.
5-HT1A , 5HT2A and 5HT2C -Types of serotonin 5-hydroxytryptamine receptor,D2- Dopamine receptor, H1 - Histamine receptors, α1 and α2–Types of adrenergic receptors, NRI- Noradrenaline Reuptake Inhibitor.

Due to high affinity for 5HT1A receptors, norquetiapine increases serotonergic transfer of impulses by the raphe neurons in brain and fluctuate 5HT performance in the limbic and cortical regions and in the hippocampus, it stimulate neuron regeneration by increase in the release of brain-derived neurotrophic factor.

Adverse effects

Quetiapine and norquetiapine causes sedation, hypnosis, increased appetite and weight gain due to action on H1 receptors. Quetiapine and norquetiapine causes blockage of alpha 1 which produces orthostatic hypotension. Norquetiapinedue to strong antagonism at muscarinic (M1, M3, M5) receptors causes dry mouth, urine accumulation, pupillary dilatation, increase in intraocular pressure, hypothermia, hyperglycemia and diabetes [23].

Dosage

Table 2 showed FDA-approved doses for quetiapine IR and quetiapine ER. Adjustments in doses can be made, depending on clinical response and tolerability of the patient [25,26,27].

Classical mood stabilizer has less efficacy and narrow therapeutic index in intense manic, mixed episodes of bipolar disorder . In contrast, QF was superior in management of intense manic and mixed episodes as monotherapy or adjunctive to classical mood stabilizers for bipolar depression with low side effect. Brand names
for QF are showed in table 3 [28].

**Literature survey**

Exhaustive literature survey was carried out using different research, published reports pertaining to QF through different databases like Google scholar, Science direct, Pub med central, Scopus etc. Information regarding QF was collected by using different keyword such as SNEDDS, SMEDDS, SLN, etc. on above mentioned databases. Most of the information was derived from various reports published between years 2011 to 2018.

Panzade P. et al. formulated directly compressible orodispersible tablets containing QF as drug. Orodispersible tablets were prepared by sublimation method. Full factorial design (32) was used to study the effect of concentration of Indion 414 (superdisintegrant) and concentration of camphor (subliming agent). Different batches were formulated with varying concentration of Indion 414 (3-5% w/w) and camphor (5-15 % w/w). The evaluation test such as thickness, weight variation, content uniformity, porosity, disintegration time and in vitro drug release was carried. The formulation F3 was selected as optimized batch due to less disintegration time, greater drug release. The formulation with 5% w/w of each Indion 414 and camphor was optimized. The disintegration time was 18.66 seconds. Scanning electron microscopy (SEM) of tablet, before and after sublimation showed presence of pores on surface. Differential scanning colorimetric (DSC) showed no excipient incompatibility. Stability studies showed no remarkable changes in drug content and in vitro disintegration time. Thus Indion 414 and

<table>
<thead>
<tr>
<th>FDA approved indications</th>
<th>Quetiapine IR (Dose mg/day and year of approval)</th>
<th>Quetiapine ER (Dose mg/day and year of approval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia Adults</td>
<td>150-750 BID /TID and 1997</td>
<td>400-800 and 2007</td>
</tr>
<tr>
<td>Adolescents (13-17 years)</td>
<td>400-800 BID</td>
<td>Not approved</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar mania, adults</td>
<td>400-800 BID as monotherapy/ adjunct and 2003</td>
<td>400-800 once a day as monotherapy/ adjunct and 2008</td>
</tr>
</tbody>
</table>

**Table 2: FDA-approved indications.**

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Dose of drug</th>
<th>Manufactured by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qmax Tablet</td>
<td>25 mg and 100 mg</td>
<td>ACI Limited</td>
</tr>
<tr>
<td>Qpine Tablet</td>
<td>25 mg and 100 mg</td>
<td>Sanofi Bangladesh LTD</td>
</tr>
<tr>
<td>Quetimax Tablet</td>
<td>25 mg</td>
<td>Novartis (Bangladesh) Ltd.</td>
</tr>
<tr>
<td>Quetinil Tablet</td>
<td>25 mg and 100 mg</td>
<td>Albion Pharmaceuticals Ltd.</td>
</tr>
<tr>
<td>Quiet Tablet</td>
<td>25 mg and 100 mg</td>
<td>Incepta Pharmaceuticals Limited</td>
</tr>
<tr>
<td>Quiet Tablet (Extended Release)</td>
<td>50 mg</td>
<td>Incepta Pharmaceuticals Limited</td>
</tr>
<tr>
<td>Qutap Tablet</td>
<td>25 mg and 100 mg</td>
<td>Healthcare Pharmaceuticals Ltd.</td>
</tr>
<tr>
<td>Qutipin Tablet</td>
<td>25 mg and 100 mg</td>
<td>Sun Pharmaceutical (Bangladesh) Limited</td>
</tr>
<tr>
<td>Qutipin SR Tablet (Sustained Release)</td>
<td>50 mg, 200 mg and 300 mg</td>
<td>Sun Pharmaceutical (Bangladesh) Limited</td>
</tr>
<tr>
<td>Seroquet Tablet</td>
<td>25 mg and 100 mg</td>
<td>UnimedUnihealth MFG. Ltd.</td>
</tr>
<tr>
<td>Seroquet ER Tablet (Extended Release)</td>
<td>50 mg</td>
<td>UnimedUnihealth MFG. Ltd.</td>
</tr>
<tr>
<td>Sizofree Tablet</td>
<td>25 mg and 100 mg</td>
<td>Eskayef Bangladesh Ltd.</td>
</tr>
<tr>
<td>Tiapine Tablet</td>
<td>25 mg and 100 mg</td>
<td>General Pharmaceuticals Ltd.</td>
</tr>
<tr>
<td>Tiapine XR Tablet (Extended Release)</td>
<td>50 mg and 200 mg</td>
<td>General Pharmaceuticals Ltd.</td>
</tr>
<tr>
<td>Toliken Tablet</td>
<td>25 mg and 100 mg</td>
<td>Delta Pharma Limited</td>
</tr>
</tbody>
</table>

**Table 3: Available brand names for quetiapine fumarate.**
camphor have significant effect on dependant responses. Hence, using experimental design optimum formulation can be developed in shorter time. Sublimation would be an effective approach for the development of ODTs [29].

Porfire A et al. developed sustained release quetiapine tablets by applying quality by design approach. D-optimal design was used for formulation of various batches. The level and ratio of matrix forming agents and type of diluents were chosen as independent variable. The dependent variables were the cumulative % of drug release and time intervals. Optimized formulation showed zero order release and a dissolution profile same as to the standard product (Seroquel XR200 mg), with similarity factor values f2 of 74.53 and 83.74. Thus sustained release tablets were developed successfully by using the quality by design approach [30].

Murthy RR et al. prepared solid lipid nanoparticles (SLN) containing QF and hemifumarate. Glycerol monostearate (solid lipid), poloxamer 407 (surfactant) and soya lecithin (stabilizers) were used as excipient. SLNs were prepared by using a hot melt emulsification high-pressure homogenization method. SLNs were evaluated by particle size, polydispersity and entrapment efficiency. SLNs of quetiapine hemifumarate and QF with particle size of 101.1 nm and 93.6 nm and 101.1 nm were obtained respectively. In vitro drug release study showed Higuchi model as best fitted model for both QF and quetiapine hemifumarate SLNs. These studies showed a remarkable increase in quetiapine hemifumarate drug in brain in case of SLN as compared to the respective drug solutions [31].

Rao NGR et al. prepared QF fast disintegrating tablets by using direct compression method. Solvent evaporation method was used to prepare QF and eudragit E100 complex. The QF was reduced and masked after forming complex with eudragit EPO in distinct ratios. Taste evaluation was carried out on human volunteers. Crospovidone showed better drug release as compared with other superdisintegrants. The results concluded that drug's bitter taste was masked with enhanced dissolution [32].

Sevukarajan M et al. prepared QF hydrogel with chitosan, Sodium alginate and different ratios of Hydroxy propyl methyl cellulose HPMC to achieve controlled release formulation. The formulations were evaluated for SEM, swelling index, and entrapment efficiency (EF) and in-vitro dissolution. Drug EF and water uptake capacity of hydrogel beads increased with increase in %and grade of HPMC (K100, K15 and K4). Drug release was reduced as the polymer concentration was increased. Formulation F4 showed good in-vitro dissolution profile. Thus it conclude that controlled drug delivery systems were formulated successfully with polymeric network [33].

Talele SG et al. designed self nanoemulsifying drug delivery system (SNEDDS) for QF. SNEDDS was optimized by using test such as particle size, zeta potential and drug release by using response surface methodology. Labrafac lipophile WL, tween 80, capryol 90 was used as oil, surfactant, and cosurfactant respectively. Pseudoternary phase diagrams of oil, surfactant or co surfactant, and water were constructed. A optimized formulation with 0.57 ml of tween 80, 0.19 ml labrafac lipophile WL and 0.30 ml of capryol 90 was prepared [34].

Vadlamudi HC et al. formulated quetiapine self microemulsifying drug delivery system formulation. Solubility of drug was taken in oils, surfactants and cosurfactants. Pseudoternary phase diagram was plotted. Optimized liquid self microemulsifying drug delivery systems (SMEDDS) were converted into solid SMEDDS by adsorption and melt granulation method. Batches were tested for micromeritic properties, drug release, stability and antipsychotic activity for amphetamine induced stereotypy and swimming normalization test. Solid self microemulsifying drug delivery system showed good micromeritics properties, 96% of drug release and drug content of 80 to 90%. Formulation O13 showed 1.2 years of shelf life and showed better antipsychotic activity [35].

Shah B et al. prepared QF microemulsion with and without chitosan. QF microemulsion and chitosan microemulsion was evaluated for globule size, pH and viscosity. Chitosan microemulsion with particle size of 35.31 ± 1.71 nm showed highest ex-vivo nasal diffusion (78.26 ± 3.29%) in 8 hours with no sign of damage of skin. By using intranasal route the result showed, 2.7 and 3.8 folds higher bioavailability with chitosan microemulsion compared to QF microemulsion and drug solution respectively [36].

Pokharkar V et al. formulated QF nanoemulsion for intranasal delivery. The different HLBs of Emalex LWIS 10, PEG 400 and transcotol P were used as co-surfactants, capmul MCM was used as a oil, tween 80 was used as a surfactant and water as vehicle. Pseudoternary-phase diagrams were plotted. Prepared nanoemulsion was tested for globule size, in vitro dissolution, transmission
electron microscope and brain-targeting efficiency. Optimized nanoemulsion formulation showed globule size of 144 ± 0.5 nm and twofold increase in drug release as compared with drug. In vivo study was performed on rats. The intranasal administration of QF loaded nanoemulsion showed shorter Tmax compared to intravenous administration [37].

Veerabrahma K et al. developed SLN using three different lipids such as glyceryl trimyristate, glyceryl tristearate and glyceryl monostearate. SLN were prepared by hot homogenization and then ultrasonication method. DSC was used to study drug excipient compatibility. Optimized formulation F3 showed particle size of 200-250 nm with varying entrapment efficiency in range between 80% - 92%. The physical stability was carried out at room temperature after two months. In vivo studies were performed in male wistar rats showed increase in relative bioavailability of QF by 3.71 times as compared with the reference drug suspension [38].

Elmenoufy GA et al. compared the efficacy of QF and QF-loaded SLN (QFSLN). Schizophrenia was induced to rats was by intraperitoneal ketamine injection for 1 week. To estimate the antipsychotic effect of QF, a low dose (LD) of 10 mg/kg and a high dose (HD) of 30 mg/kg were orally administrated to two groups of rats (designated L.QF and H.QF) for 3 weeks (2 weeks without ketamine injection; the last week with ketamine). Two other groups of rats were administered equivalent low and high doses of QF in its SLN form orally for 3 weeks, after 1 hour of ketamine injection. QFSLN treatment showed enhanced effect over QF in a dose dependent manner with minimal side effects in schizophrenic rats [39].

Upadhyay P et al. QF simple and liposomal dispersion were prepared in simulated nasal fluid pH 6.8, characterized and compared for diffusion through sheep nasal mucosa by ex vivo% drug diffusion within 6 h. After 6 h liposomal dispersion showed 32.61 ± 1.70 and the simple dispersion showed 27.56 ± 1.33 for % drug diffusion. It was found that diffusion coefficient for liposomal dispersion was higher than simple dispersion. Liposomal dispersion showed Hopfenberg model and non-Fickian super case II anomalous transport and simple dispersion showed Higuchi model and Fickian diffusion mechanism. Results of in vivo, ciliotoxicity, and gamma scintigraphy studies on mice confirmed liposome appropriate for taking through nasal route for brain delivery [40].

Conclusions

This systematic review underlines the effectiveness of quetiapine monotherapy for bipolar I and II disorder and schizophrenia. Quetiapine fumarate may have a protective effect on man treatment of mania. In nutshell this review gives idea about detail information about quetiapine fumarate along with literature survey of different dosage forms of quetiapine fumarate. Quetiapine fumarate is ideal candidate for development for novel drug delivery system such as nanostructured lipid carrier, more studies in these areas are required. The lower risk of headache in quetiapine treated patients with acute bipolar depression should require study. The evidence for the use of quetiapine combined with mood stabilizers in child and adolescents with acute bipolar depression is very small to support the clinical practice.

Declarations

Conflict of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

Authors' contributions

All authors contributed to the preparation of the manuscript.

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