Preformulation Studies of Quetiapine Fumarate

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ABSTRACT

The objective of present study was to perform some of the important preformulation studies of quetiapine fumarate (QPF) to obtain the necessary information for the design of controlled drug delivery system. The aqueous stability, pH solubility and drug-excipient compatibility studies were evaluated at preformulation stage. The drug-excipient compatibility was evaluated by isothermal stress test method (IST), differential scanning calorimeter (DSC) and high-performance liquid chromatography (HPLC) were used as a tool to assess the compatibility of drug with the selected excipients. The compound was found to be stable in the studied pH conditions up to 24 h at 37 °C and the compound exhibited pH dependent solubility. On the basis of DSC and HPLC results, the drug was found to be compatible with gum kondagogu, chitosan, polyelectrolyte complex of gum kondagogu and chitosan, HPMC K100m, carbopol 934P, benecel® and A-tab®. Some degree of interaction was observed with magnesium stearate. Additional studies using fourier transform infrared spectroscopy and powder-X-ray diffractometry confirmed that QPF is compatible with magnesium stearate. The interaction observed in the DSC experiments could be due to solid-solid interaction but not due to incompatibility. The information gathered in preformulation studies would be very useful in the design of controlled drug delivery system.

Key words: Quetiapine fumarate, chitosan, gum kondagogu, polyelectrolyte complex, compatibility and preformulation

INTRODUCTION

Pharmaceutical preformulation is an important part of the drug development process. The information gathered about the molecules at preformulation stage would be very useful in making critical decisions in subsequent stages of development. Typical preformulation studies for solid dosage form include solubility, stability and drug-excipient compatibility. The routine drug-excipient interactions can be studied by two techniques i.e., differential scanning calorimeter (DSC) and quantitative assay after isothermal stress tests (IST) [2, 3]. The DSC can shows changes in the appearance, shift or disappearance of melting endotherm and exotherms, and/or variations in the corresponding enthalpies of reaction. The DSC allows the fast evaluation of possible incompatibilities; however, the interpretation of DSC results is not always easy. Hence, the DSC results must be interpreted carefully and some complementary techniques, such as fourier transform infrared (FTIR) spectroscopy, microscopy or powder X-ray powder diffractometry (pXRD) can be useful in avoiding misleading conclusions [4]. The IST involves storage of drug-excipient blends with or without moisture at high temperature to accelerate drug ageing and interaction with excipients. The normal duration of study could be around 3-4 weeks. The main downside of this approach is time consuming and requires quantitative analysis using HPLC. Ideally, by combining both the techniques i.e., DSC and IST helps in determining physical and chemical stability of drugs with the excipients [5].

Quetiapine (2-[2-(4-dibenzyl[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy] ethanol fumarate (2:1 salt)) is an atypical antipsychotic drug with a unique receptor-binding profile belonging to a new chemical class, the dibenzothiazepine derivatives. QPF is used in the treatment of schizophrenia or manic episodes receptor-binding profile belonging to a new chemical class, the dibenzothiazepine derivatives. QPF is administered once a daily, preferably in the evening, the recommended initial dose of 300 mg/day [6-8].

GKG (Cochlospermum gossypium), a tree exudate gum is a plant growing naturally in the forests of India. Basically it is a polymer of rhamnose, galacturonic acid, glucuronic acid, β-D-galactopyranose, α-D-glucose, β-D-glucose, galactose, arabinose, mannose and fructose, with sugar linkage of (1-2)-β-D-Gal p, (1-6)-β-D-Gal p, (1-4)-β-D-Glc p, 4-O-Me-α-D-Glc p A, (1-2)-α-L-Rha p and (1-4)-α-D-Gal p A, with average molecular weight of 7.23 x 105 to 8.25 x 105 g/mol determined by static light scattering method and berry plots [9-11]. GKG was found to be safe in 90 days sub-chronic toxicity study conducted in rats [12]. This gum is yet to be commercially exploited, as the physico-chemical properties of this gum are yet to be characterized. The polyelectrolyte complex (PEC) is formed by the electrostatic attractions between two oppositely charged polyelectrolytes mixed in aqueous solution. The PEC between chitosan and GKG was prepared by mixing two polymer solutions at the weight ratio of 1:10 at pH 5.0.

The objective of present study was to perform some of the important preformulation studies of QPF to obtain the necessary information for the design of controlled drug delivery system. To the best of our knowledge, there is no much literature precedence on drug-excipient compatibility for QPF. Hence, we have chosen QPF for our studies. The pH solubility, aqueous stability and drug-excipient compatibility studies were evaluated at preformulation stage. The solid state characterization of the compound was done by pXRD, DSC and TGA techniques and the compound was also characterized by FTIR spectroscopy. The drug-excipient compatibility was evaluated by IST method. The DSC and HPLC were used as a tool to assess the compatibility of drug with the selected excipients. The complementary techniques such as pXRD and FTIR spectroscopy were used to assist in the interpretation of DSC results, if needed. All the excipients used in the present study were commonly used excipients in solid dosage forms except GKG and PEC.

MATERIALS AND METHODS

Materials

QPF was received as a gift sample from Ajanta Pharma Ltd, Mumbai, India. The following excipients were purchased from commercial sources and used as such, lactose mono hydrate (Signet Chemical Corporation Pvt Ltd, Mumbai, India), carbopol 934P (Meggle, Germany), HPMC K100m (Signet Chemical Corporation Pvt Ltd, Mumbai, India), A-tab® (Dibasic calcium phosphate an-
hydrous, granular, Signet Chemical Corporation Pvt Ltd, Mumbai, India) magnesium stearate (Mallinckrodt, USA), benecel® (Signet Chemical Corporation Pvt Ltd, Mumbai, India), chitosan (Sigma-aldrich, India), gum kondagogu (grade-1, M/s. Girijan Co-operative Corporation, India). The HPLC grade solvents such as acetonitrile and methanol were purchased from Rankem, India and chemicals potassium dihydrogen orthophosphate GR and ammonium acetate GR were purchased from Loba Chemie, India.

**Methods**

**Structural identification by FTIR spectroscopy**

Infrared transmission spectra were obtained using a FTIR spectrophotometer (FTIR-8300, Shimadzu, Japan). Two percent (w/w) of the sample, with respect to a potassium bromide disk, was mixed with dry KBr. The mixture was ground into a fine powder using an agate mortar and then compressed into KBr disks in a hydraulic press at a pressure of 10,000 psi. The characteristic peaks were recorded in the wave number of 4000-500 cm⁻¹.

**Solid state characterization**

The solid state characterization was done by using pXRD, DSC and TGA techniques.

**pXRD**

Powder X-ray diffractometer, Rigaku (Dmax-2200), USA was used for diffraction studies. The studies were performed on the samples by exposing them to CuKα radiation (40KV, 30 mA) and scanned from 2 to 32°, 2θ at a step size of 0.03° and step time of 1.0 seconds.

**DSC**

Differential scanning calorimetric analysis was performed on TA Instruments Q 2000 DSC, USA. The temperature calibration was performed using indium. Samples were crimped in a standard aluminum pan and heated from 25 to 250 °C at a heating rate of 10 °C/min under constant purging of dry nitrogen. The TGA grade solvents such as acetonitrile and methanol were purchased from Rankem, India and chemicals potassium dihydrogen orthophosphate GR and ammonium acetate GR were purchased from Loba Chemie, India.

**TGA**

Thermal analysis was carried out on TA instrument Q 5000, USA. All thermo gravimetric analysis were performed with 5–6 mg of finely powdered samples in a platinum pan, under nitrogen atmosphere, and gas flowing at 25 mL/min. Samples were heated from 25 to 400 °C at a heating rate of 10 °C/min.

**High pressure liquid chromatographic assay**

Chromatography separation was performed on an Agilent 1200 liquid chromatography system. The instrument was equipped with a G1315D pump, a G1315D diode array detector variable UV/visible detector, a G1329 auto sampler injector, and Agilent chemstation chromatography workstation (Agilent, USA). The chromatography separations were carried out on Agilent eclipse plus C-8 (4.6 X 75 mm, 3.5 µm) column. The gradient mobile phase consists of 10 mM ammonium acetate and acetonitrile. The mobile phase components were filtered through 0.45µ membrane filter before use. Initially the run started with 100% aqueous solution and reached to 100% organic phase in 5 minutes, then 100% organic phase for 3 minutes followed by 100% aqueous phase in 2 minutes and stabilization for 4 minutes with 100% aqueous phase. The detection was monitored at 254 nm and the run time was 14 min. The flow rate was 1 mL/min and the volume of injection loop was 10 µL. Prior to the injection of the drug solution, the column was equilibrated for at least 30 min with the mobile phase flowing through the system. The column temperature was 40 °C and the auto sampler temperature was 10 °C.

**Aqueous stability studies**

The aqueous stability study was performed at 0.2 mg/mL in 0.1N HCl (pH 1.2), pH 7.4 (50 mM phosphate buffer) and at 0.025 mg/mL in pH 10.0 (50 mM carbonate buffer). The experiment was conducted at 37 °C for 24 h. The percent of drug remaining was reported relative to the initial peak area (t = 0 h) and the studies were performed in HPLC.

**Solubility studies**

The solubility studies were performed in the range of pH from 1.2 to 10.0 (50 mM buffer strength). Excess amount of drug was equilibrated in 2 mL of buffer and dispersion of the compound was ensured before equilibration. The slurry was equilibrated at 200 rpm on shaker bath for 24 h at room temperature. After equilibration, the slurry was filtered through 0.45 micron PVDF filters and the first 0.5 ml of filtrate was collected in scintillation vial. The filtrate was diluted suitably with methanol and the drug concentration was quantified by validated HPLC method with six point calibration curve.

**Drug-Excipient compatibility studies**

The commonly used excipients such as diluents, binders, controlled release polymers and lubricants were tested the present study. The drug to excipient ratio was 1:1 for all the excipients, except magnesium stearate where the ratio was 2:1. The drug samples and all the excipients were sieved through 60-mesh sieve.

**Isothermal stress testing**

The drug and different excipients of interest were weighed directly in 8 ml glass vials (n = 2) and the vials were mixed on a vortex mixer for 2 min. Approximately 10% w/w water was added to the drug-excipients blend and mixed further with glass capillary and capillary was left inside the vial to prevent any loss of material. All the vials were sealed using a teflon-lined screw cap. Three set of vials were prepared as per the procedure outlined above. One set of vials were control samples and stored at 2-8 °C. The second sets of samples were analyzed by
Figure 2: DSC profile of A) LMH, B) A-Tab, C) HPMC, D) GKG, E) Chitosan, F) PEC, G) Beneceul, H) Carbopol, and I) Magnesium stearate

DSC analysis of samples
The samples were weighed directly in the pierced DSC aluminum pan and scanned in the temperature range of 25–250 °C under constant purging of dry nitrogen at 30 mL/min. The heating rate was 10 °C/min and thermograms obtained were observed for any interaction. Before charging the samples, initial DSC thermograms were recorded and used as reference to evaluate the charged samples.

RESULTS AND DISCUSSION

FTIR Spectroscopy
The spectrum of QPF showed a strong absorption band at 3309 cm⁻¹ and the multiple peaks in the region of 3000 to 2700 cm⁻¹ is the indication of salt of secondary amine. The imine (C=N) stretching at 1597 cm⁻¹, α, β unsaturated acid of fumarate stretching at 1622 cm⁻¹, the C=C phenyl ring stretching at 1571 cm⁻¹ observed (figure 6).

Solid state characterization
The pXRD of QPF showed significant reflections in 2θ values at about 7.3, 9.2, 11.6, 13.3, 14.3, 14.7, 15.2, 15.8, 16.2, 16.6, 17.6, 19.0, 19.6, 20.2, 20.7, 21.0, 21.2, 21.7, 22.2, 23.2, 24.2, 24.6, 25.0, 25.5, 26.0, 27.0, 28.4, 28.6, 29.4, 30.5, 30.8, 31.5° (figure 5). The DSC (figure 3) of the QPF showed a sharp single melting endothermic event with the onset of 174.3 (ΔH: 126.6 J/g) and TGA (figure 1) didn’t show any significant weight loss before the melting of QPF. Based on the pXRD, DSC and TGA results, QPF was crystalline and this crystalline pattern was designated as Form-1 of QPF[13].

Aqueous stability studies
The stability study was conducted at the initial concentration of 0.2 mg/mL in pH 1.2, but at 7.4 and 10.2, the initial concentration was around 0.025 mg/mL due to poor solubility of compound at neutral and alkaline pH. The QPF was found to be stable in all the studied pH conditions i.e., pH 1.2, 7.4 and 10.0 up to 24 h.

Solubility studies
The QPF is weakly basic compound with two pKa values i.e., 3.3 and 6.8. The QPF showed pH dependent solubility; high solubility was observed at acidic pH and low solubility in the alkaline pH. The solubility of QPF at pH <4.0 was around 7-10 mg/mL and the significant drop in solubility was observed at pH >8.0 (0.10 mg/mL).

Drug Excipient compatibility studies
The drug excipient compatibility studies were performed with commonly used excipients i.e., diluents, binders, controlled release polymers and lubricants. The drug to excipient ratio was 1:1 for all the excipients, except magnesium stearate where the ratio was 2:1. The drug samples and all the excipients were sieved through 60-mesh sieve. The DSC overlay of all the excipients given in the figure 2. The melting endotherm of the drug was well preserved in majority of cases. However, there were slight changes in the peak shape with little broadening or shifting towards the lower temperature, which could be attributed due to the mixing process that lowers the purity of each component in the mixture [14]. The DSC and HPLC assay results are summarized in table 1.

Lactose Monohydrate (LMH)
The DSC thermogram of lactose showed a sharp endothermic peak at 145.4 °C due to loss of bound water[16], followed by its melting endotherm at around 220 °C (figure 2).
Figure 4: The DSC thermogram of charged sample of A) QPF-As such, B) QPF-LMH, C) QPF-GKG, D) QPF-Chitosan, E) QPF-PEC, F) QPF-HPMC, G) QPF-A-Tab, H) QPF-Benecel, I) QPF-Carbopol, and J) QPF-Magnesium stearate. The samples were stored at 50 °C for 4 weeks.

QPF-LMH Mixture
In the DSC trace of QPF–LMH mixture, the endothermic peak of QPF was well retained and there was no change in enthalpy value compared to initial sample (figure 3 and 4). The HPLC assay of QPF-LMH mixture after 4 weeks stored at 50 °C was 99.5% (table 1), suggested that there was no degradation of QPF. Thus, ruling out any incompatibility between QPF and LMH.

GKG
The GKG showed a broad endothermic at 109.4 °C, may be attributed to desorption of moisture (figure 2) (16).

QPF-GKG mixture
The shift in broad endothermic event of GKG from 109.4 to 93 °C was observed in the initial DSC traces of QPF-GKG mixture, however, the melting endothermic peak of QPF was appeared at same temperature i.e., at 173.6 °C (ΔH: 54.36 j/g) (figure 3). The DSC profile of QPF-GKG mixture after 4 week incubation at 50 °C, matched well with the initial DSC thermogram of QPF-GKG mixture (figure 4). The HPLC analysis of QPF-GKG mixture showed 98.65% assay (table 1) of QPF after 4 week study period indicated that there was no degradation of QPF. Based on the DSC and HPLC results, the QPF is compatible with GKG. The slight shift in the endothermic event of GKG to lower temperature could be due to solid-solid interaction of drug with GKG in the presence of moisture.

Chitosan
The DSC traces of chitosan showed a broad endothermic event at 95.4 °C could be due to loss of associated water molecules from the structure of chitosan (figure 2).

QPF-Chitosan Mixture
The melting endothermic peak of QPF was appeared at 173.6 °C (ΔH: 43.9 j/g) in the DSC traces of initial physical mixture of QPF-chitosan (figure 3). The endothermic peak of pure chitosan associated due to loss of bound water was also appeared in QPF–chitosan mixture. The DSC profile of charged sample was similar to initial physical mixture of QPF-chitosan (figure 4). The HPLC analysis of QPF-chitosan mixture showed 100.43 % assay of QPF (table 1).

Table: The HPLC assay and the DSC results of QPF in various drug-excipient mixtures

<table>
<thead>
<tr>
<th>Sample</th>
<th>Assay (% recovery)</th>
<th>DSC results of QPF in the sample</th>
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<tr>
<td></td>
<td>Initial sample</td>
<td>Charged sample</td>
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<tr>
<td></td>
<td>T_{onset} (°C)</td>
<td>ΔH (j/g)</td>
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<tr>
<td>QPF</td>
<td>99.5</td>
<td>101.2</td>
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<tr>
<td>QPF+LMH</td>
<td>98.7</td>
<td>97.6</td>
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<tr>
<td>QPF+GKG</td>
<td>98.0</td>
<td>99.4</td>
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<tr>
<td>QPF+HPMC</td>
<td>102.6</td>
<td>103.5</td>
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<tr>
<td>QPF+Carbopol</td>
<td>101.2</td>
<td>102.5</td>
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<tr>
<td>QPF+Benecel</td>
<td>100.2</td>
<td>101.5</td>
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<tr>
<td>QPF+PEC</td>
<td>97.4</td>
<td>98.6</td>
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<tr>
<td>QPF+Chitosan</td>
<td>99.2</td>
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<tr>
<td>QPF+PEC</td>
<td>101.0</td>
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<tr>
<td>QPF+GKG</td>
<td>99.4</td>
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Figure 5: The pXRD of A) Magnesium stearate, B) QPF and C) charged sample of QPF and magnesium stearate mixture
Figure 6: The FTIR spectra of A) Charged sample of QPF and magnesium stearate mixture, B) Magnesium stearate and C) QPF after 4 week study period indicated that there was no degradation of QPF. Based on the DSC and HPLC results, it can be concluded that QPF is compatible with chitosan.

PEC
The PEC was prepared from 10:1 weight ratio of GKG to chitosan at pH 5.0. The DSC traces of PEC showed a broad endothermic event at 109 °C, could be due to loss of water molecules associated with PEC (figure 2).

QPF-PEC Mixture
The melting endothermic peak of QPF was appeared at 173.8 °C (ΔH: 56 j/g) in the charged sample of QPF-PEC mixture and also broad endothermic event corresponds to PEC was also registered. The DSC profile of charged sample was same as that of initial mixture of QPF-PEC (figure 3 and 4). The assay of QPF was around 100.43% (table 1). Thus, QPF is compatible with PEC.

HPMC
A broad endothermic peak was recorded at 78 °C in the DSC thermogram of HPMC (figure 2).

QPF-HPMC Mixture
The melting endothermic peak of QPF was registered at 171.8 °C (ΔH: 49.5 j/g) in the DSC traces of initial mixture of QPF-HPMC. The endothermic peak at 78 °C, which was observed in case of pure HPMC, was present in QPF–HPMC mixture (figure 3). The DSC profile of QPF-HPMC mixture after 4 week incubation at 50 °C, well matched with the initial DSC thermogram of QPF-HPMC mixture (figure 4). The HPLC analysis of charged sample showed 103.56 % assay (table 1) of QPF. Based on the DSC and HPLC results, there was no incompatibility of QPF with HPMC.

A-tab
In the DSC scan of A-Tab, no peak was observed in the temperature range of 25–250 °C (figure 2).

QPF-A-tab mixture
The melting endothermic event of QPF was registered at 173.7 °C (ΔH: 51.6 j/g) in the DSC traces of initial physical mixture of QPF-A-tab (figure 3). The DSC profile of charged sample was similar to initial sample (figure 4). The melting endothermic peak of QPF was appeared at 173.8 °C (ΔH: 52.4 j/g) and the assay was 99.45% (table 1). Thus, ruled out the incompatibility of QPF with A-tab.

Benccel
A broad endothermic peak was registered at 73 °C in the DSC scan of pure benccel (figure 2).

QPF-Benccel mixture
The melting endothermic peak of QPF was registered at 171.6 °C (ΔH: 57.3 j/g) and the endothermic peak of benccel was slightly shifted from 73 to 63 °C in the DSC traces of initial physical mixture of QPF-benccel (figure 3). However, the DSC profile of charged sample was same as that of initial sample, indicates that there was no interaction of QPF with benccel (figure 4). The HPLC analysis of charged sample showed 101.56 % assay (table 1) of QPF.

Carbopol
A broad endothermic event was observed at 80°C in the DSC scan of carbopol (figure 2).

QPF-Carbopol mixture
The melting endothermic peak of QPF was registered at 172.7 °C (ΔH: 40 j/g) and also the endothermic peak of carbopol appeared at 80 °C (figure 3). The DSC profile of charged sample was same as that of initial sample, the HPLC analysis of charged sample (figure 4) showed 102.51% assay (table 1) of QPF. Thus there was no incompatibility between QPF and carbopol.

Magnesium stearate
The DSC trace of magnesium stearate showed three endothermic events at 77, 93 and 111 °C (figure 2).

QPF-Magnesium stearate mixture
The melting endothermic peak of QPF was shifted from 174.3 to 163.6 °C (ΔH: 75 j/g) and also broadening of peak was observed in the initial DSC traces of QPF-magnesium stearate mixture (figure 3). The DSC profile of QPF-magnesium stearate mixture after 4 week incubation at 50 °C, well matched with the initial DSC thermogram of QPF-magnesium stearate mixture. The melting endothermic peak was registered at 163.5 °C (ΔH: 77 j/g) and also the endothermic events corresponds to magnesium stearate (figure 4). The HPLC assay of QPF
in charged sample of QPF- magnesium stearate was 100.21% (table 1), indicated that there was no degradation of QPF. To address the shift in the melting point of the compound, the charged sample was further analyzed by pXRD and FTIR spectroscopy. All the crystalline peaks of QPF were appeared in the point of the compound, the charged sample was further analyzed by pXRD and FTIR spectroscopy. All the crystalline peaks of QPF were appeared in the pXRD of charged sample at 20 same as that of pure QPF (figure 5). So, the pXRD data indicated that there was no change in solid form of QPF. The FTIR spectroscopy data (figure 6) showed all the peaks correspond to QPF in the charged sample suggested that QPF is intact. The HPLC data indicated that there was no degradation of QPF and FTIR data also support the same. The DSC and pXRD data suggested that there was no physical interaction between QPF and magnesium stearate, the shift in melting endotherm of QPF in presence of magnesium stearate could be due to solid-solid interaction, but not necessarily an incompatibility.

CONCLUSIONS
As a part of research work on the development of controlled release formulations of QPF, the pH solubility, aqueous stability and drug-excipient compatibility studies were performed at preformulation stage. The DSC and HPLC were used as a technique to evaluate the compatibility of excipients with the drugs. The pH solubility studies revealed that QPF is highly soluble in the acidic pH and the solubility was decreased with increasing the pH. The shift in the melting endotherm of QPF towards lower temperature was observed in the DSC traces QPF-magnesium stearate mixture. The pXRD data of this mixture showed all the characteristic peaks of pure drugs at same 20 indicated that there was no evidence of physical instability. The HPLC analysis results of this mixture evident of chemical stability of QPF as the assay was within the acceptable range. Based on the DSC, pXRD and HPLC results, any possible pharmaceutical incompatibility between QPF and magnesium stearate was ruled out.

REFERENCES: