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Research

ENHANCEMENT OF SOLUBILITY OF QUETIAPINE FUMARATE BY LIQUISOLID COMPACTS TECHNIQUE

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Abstract

Pharmaceutical researchers' remains uncertain about enhancing the water solubility and dissolution of medications, the objective of this study was to ascertain whether the liquisolid compact formulation of the BCS class II medications Quetiapine Fumarate could enhance its solubility and consequently its dissolution rate to make the Liquisolid compact a number of non volatile solvents were used. Liquisolid preparation made with non volatile solvent labrafac and peccol have shown promising results. Quetiapine Fumarate liquisolid tablets made from peccol or labara dissolve better than other LS formulations, it was found that the best formulations of Quetiapine Fumarate had a hardness of 2.8kg/cm2 a drug release of 99.58%after 10mins, and an angle of repose of 23.24°C obtained, the results for the designed product made with LS compacts technology showed quick release when compared to the pure medication.

Keywords: Quetiapine Fumarate, Liquisolid, Solubility

INTRODUCTION

Therapeutic effectiveness of a drug depends up on the bioavailability which is dependent on the solubility of drug molecules. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown.1 Poorly water soluble drugs will be inherently released at a slow rate owing to their limited solubility within the GI contents.

A great number of new, and possibly, beneficial chemical entities do not reach the public merely because of their poor oral bioavailability due to inadequate dissolution. For drugs belonging to class II (poor water solubility and high permeability) dissolution rate is often the rate determining step in the drug absorption the

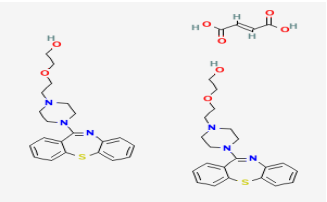
challenge for poorly water soluble drugs is to enhance the rate of dissolution. This in turn subsequently improves absorption and bioavailability and the liquisolid technique as described by Spire as is a novel concept, where a liquid maybe transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is included into the porous carrier material. An inert, preferably water-miscible organic solvent system with high boiling point such as liquid polyethylene glycols, propylene glycol, or glycerin is most excellent fitting as liquid vehicles.

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are: Physical Modifications, Particle size reduction, Micronization, Nano suspensions Modification of the crystal habit, Polymorphs, Pseudo polymorphs (including solvates) Drug dispersion in carriers, Eutectic mixtures, Solid dispersions Solid solution Complexation, Solubilization by surfactants Micro emulsions,

It was developed to determine Ψ values and involves steps such as preparing carrier coating material admixture systems,61 preparing several uniform liquid/powder admixtures to tablet, determining average hardness, measuring of average liquid content of crushed tablets, as well as determining plasticity, sponge index and Ψ value and Lf. Advantages of Liquisolid Compacts: Huge number of Bio-Pharmaceutical classification class II drugs with high permeability, slightly or very slightly water soluble and practically insoluble liquids and solid drugs canbe formulated into liquisolid systems.

Materials and Methods: Quetiapine Fumarate was obtained as a gift sample from Hetero Drugs (Pvt. Ltd), Hyderabad, India. Peceol & Labrafac were purchased from Gattefosse, Mumbai,Maharashtra., India. Microcrystalline Cellulose, Aerosil, Talc, Dicalcium Phosphate were purchased from S.D. Fine Chem. Ltd. Mumbai., India.All additional chemicals, reagents, and solvents used were of analytical grade.

Drug Profiles: Quetiapine Fumarate Chemical nature White crystalline powder is a dibenzothiazepine atypical antipsychotic that mediates its action by serotonergic 5-T1A and 5-HT2 receptors antagonism and partly by dopamine D2 antagonism. Molecular Formula C25H29N3O6S, Molecular weight 441.54, Melting point 174-176° C, Solubility 0.0403 mg/Ml



Quetiapine Fumarate Liquisolid Compacts: Preformulation Studies: General Description: The appearance, colour and odor of the drug was observed and noted. Melting Point Determination: Melting point of the drug was determined by Capillary method. Fine powder of the drug was filled in the capillary tube (previously sealed at one end). The capillary tube was inserted in the sample holder of melting point apparatus and a thermometer was placed in the apparatus. The temperature at which the powder melted was noted. Determination of Absorption Maxima: Accurately weighed 100 mg of Q was dissolved in 10 ml of methanol; volume was made up to 100 ml with 0.1N HCl to get stock solution of 1mg/ml. From this 10 ml solution was transferred into a 100 ml volumetric flask, volume was made up to 100 ml with 0.1N HCl which was considered as second stock solution. curve 0.2, 0.4, 0.6, 0.8, and 1.0 ml of the second stock solution was transferred into a series of 10 ml volumetric flask and volume was made up to 10 ml with 0.1N HCl to get 2, 4, 6, 8 and 10 µg/ml solution. Absorbance of 10 µg/ml was subjected for scanning at 200 to 400nm UV range using UV-spectrophotometer (PG Instruments-T60). Linearity of Quetiapine Fumarate: For the preparation of linearity curve 0.2, 0.4, 0.6, 0.8, and 1.0 ml of the second stock solution was transferred into a series of 10 ml volumetric flask and volume was made up to 10 ml with 0.1N HCl to get 2, 4, 6, 8 and 10 µg/ml solution. The optical density values of the resulting solutions were measured at 283 nm using-spectrophotometer (PG Instruments-T60).E. Solubility Studies Solubility studies for Quetiapine Fumarate were performed by using various solvents. Excess amount of Quetiapine Fumarate was added in 10 ml of selected non-volatile liquid solvents to form a supersaturated solution in a glass vial. The mixtures were vortexed for 15 minutes to facilitate the mixing of drug and non-volatile solvent. The mixtures were kept in a shaker incubator at 25° C for 48h to achieve equilibrium. The samples were centrifuged at 5000 rpm for 30 min to sediment in solubilized drugs. Filtered solution was appropriately diluted with methanol, and UV absorbencies were measured at 283 nm wavelength. Concentration of dissolved drug was determined using standard equation.F. Measuring Angle of Slide (θ) Angle

of slide is used as a measure of flow properties of powders. Determination of angle of slide is done by weighing the required quantity of carrier material and placing it at one end of the metal plate having a polished surface. The end is gradually raised till the plate becomes angular to the horizontal at which powderis about to slide. This angle is known as the angle of slide.

Steps Involved in Determination of Angle of Slide,Measuring Flowable Liquid Retention Potential (φ):Increasing amount of selected solvent was added and mixed well with 10 gm of each of material (carrier and coating respectively) and angle of slide was determined using the above mentioned procedure. The corresponding Phi-value was calculated from the following equation Φ– value = Wt. of liquid/Wt. of solid, Measuring Liquid Load Factor (Lf), On the basis of Phi-value of optimized carrier and coating material the liquid load, factor (Lf) and quantities of carrier and coating materials were calculated using formula Lf = φCA + φCQ (1/R), Drug-

Excipient Compatability By FT-IR spectroscopy helps to determine any chemical interaction between drug and excipients used in formulation. The FTIR spectra for Quetiapine Fumarate and optimized powder mixture for liquisolid preparations were obtained using Bruker II Alpha spectrophotometer in the range of 4000– 400 cm− 1 pressure.

Formulation Development of Quetiapine Fumarate: A. Preparation of Powder for Liquisolid Tablets Initial trials of Liquisolid tablets were done with the calculated values of Avicel112 and Aerosil 200. PVP K 30 was selected as the binder and Sodium starch glycolate was used as a disintegrants, DCP was used a diluent and the tablets were compressed using 8 mm punches to an average weight of 250 mg. Based on the observations of these initial trials, it was concluded that of all the Excipients used, Avicel 112 and Aerosil 200 were found to be the main factors influencing tablet properties like flow, hardness, and friability. Hence, these two factors were selected for the design of Formulation of Liquisolid Tablets of Quetiapine Fumarate.

Evaluation of Quetiapine Fumarate Liquisolid Tablets:

A. Thickness: The thickness was measured using vernier callipers. Five tablets from each batch were used and average values were calculated.

B. Hardness: The hardness of the tablets was determined using Monsanto hardness tester. Six tablets from each formulation were tested for hardness. It is expressed in kg/cm2

C. Friability: The test was performed using Roche friabilator (Electrolab). Twenty tablets were weighed and placed in the drum of the friabilator. The tablets were allowed to revolve, fall from height of six inches for 4 min. Then tablets were de-dusted and re-weighed.

D. Disintegration Time: The disintegration time of the tablets was measured in distilled water (37 ± 2° C), using disintegration test apparatus (Electrolab, India) with disk. Five tablets from each formulation were tested for the disintegration time.

E. Drug Content The QPF content in different liquisolid tablet formulations was determined by accurately weighing 20 tablets of each formula individually. Each tablet was then crushed and a quantity of powder equivalent to 10 mg of QPF was dissolved in 100 ml methanol. 1 ml of this solution was diluted to 10 ml with methanol and measured spectrophotometrically at λmax of 283 nm.

F. In-Vitro Drug Release Study: The release of Quetiapine Fumarate from the prepared composition was performed using a USP type II (Paddle) apparatus at a rotation speed of 50 RPM in 900 ml of 0.1N. HCl (pH 1.2) at 37° C ± 0.5° C according to USP Monograph of Quetiapine Fumarate. Samples are taken at predetermined time intervals and filled with fresh dissolution medium to maintain a constant volume. The sample is filtered and analyzed spectrophotometrically at 295 nm. All formulations were performed in triplicate. Stability Studies: The stability study is an indicative method for determination of durability of quality and quantity of therapeutic agents with the passes of time under the influence of various atmospheric conditions such as temperature, humidity, light and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions at 40° C ± 2° C/75% RH ± 5% RH. Stability studies were conducted towards 3 batches of optimized for 3 months using Newtronic StabilityChamber-NLWH327SI. Samples were withdrawn after 3rd month and were analyzed, and results are tabulated. Differential Scanning Calorimetry: Thermal analysis of Optimized Formulation was performed using thermal analyzer (Shimadzu DSC-60) Temperature axis and cell constant were calibrated by utilizing indium (In).

Formulation Development of Quetiapine Fumarate

Preparation of Powder for Liquisolid Tablets: Initial trials of Liquisolid tablets were done with the calculated values of Avicel 112 and Aerosil 200. PVP K 30 was selected as the binder and Sodium starch glycolate was used as a disintegrant, DCP was used a diluent and the tablets were compressed using 8 mm punches to an average weight of 250 mg. Based on the observations of these initial trials, it was concluded that of all the

excipients used, Avicel 112 and Aerosil 200 were found to be the main factors influencing tablet properties like flow, hardness, and friability. Hence, these two factors were selected for the design.

Table 4: Formulation of Liquisolid Tablets of Quetiapine Fumarate:

Ingredients (mg)	QPF1	QPF2	QPF3	QPF4	QPF5	QPF6	QPF7	QPF8	QPF9
Quetiapine Fumarate	50	50	50	50	50	50	50	50	50
Labrafac	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Avicel 112	100	130	70	70	70	100	130	130	100
Aerosil 200	3.5	9.5	9.5	6.5	3.5	9.5	6.5	3.5	6.5
Sodium starch glycolate	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
PVP K- 30	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Dicalcium phosphate	66.44	30.44	90.44	93.44	96.5	60.44	33.44	36.44	63.44
Magnesium	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	250	250	250	250	250	250	250	250	250

Liquisolid tablets of were prepared each containing 50 mg of drug. QPF was dispersed in Peceol. Avicel 112 and Aerosil 200 were added to the above mixture under continuous mixing in a mortar. Finally, Sodium starch glycolate as superdisintegrants, PVP K- 30 as binder and Dicalcium phosphate as filler were mixed and the mixture was blended for a period of 10 minutes.

A. **Evaluation of Powder Blend:** The blends of all formulations were evaluated for angle of repose which is indicative of flow properties.
B. **Compression of Powder Blend into Tablets:** To the above blend, Magnesium Stearate and Talc were added, and the blend was compressed using 8 mm round flat punches in a single punch tablet press. Liquisolid tablets of QPF were successfully prepared and were used for further evaluation studies. Conventional Formulation was prepared with all the ingredients excluding non-volatile solvent mentioned in formulation Table 6.

Evaluation of Quetiapine Fumarate Liquisolid Tablets

A. Thickness: The thickness was measured using vernier callipers. Five tablets from each batch were used and average values were calculated.
B. Hardness: The hardness of the tablets was determined using Monsanto hardness tester. Six tablets from each formulation were tested for hardness. It is expressed in kg/cm^2.
C. Friability: The test was performed using Roche friabilator (Electrolab). Twenty tablets were weighed and placed in the drum of the friabilator. The tablets were allowed to revolve, fall from height of six inches for 4 min. Then tablets were de-dusted and re-weighed.
D. **Disintegration Time:** The disintegration time of the tablets was measured in distilled water (37 ± 2°C) using disintegration test apparatus (Electrolab, India) with disk. Five tablets from each formulation were tested for the disintegration time.
E. **Drug Content:** The QPF content in different Liquisolid tablet formulations was determined by accurately weighing 20 tablets of each formula individually. Each tablet was then crushed and a quantity of powder equivalent to 10 mg of QPF was dissolved in 100 ml methanol. 1 ml of this solution was diluted to 10 ml with methanol and measured spectrophotometrically at λmax of 283 nm.
F. **In-Vitro Drug Release Study:** The *in-vitro* release of Quetiapine Fumarate from the prepared composition was performed using a USP type II (Paddle) apparatus at a rotation speed of 50 RPM in 900 ml of 0.1N. HCl (pH 1.2) at 37°C ± 0.5°C according to USP Monograph of Quetiapine Fumarate. Samples are taken at predetermined time intervals and filled with fresh dissolution medium to maintain a constant volume. The sample is filtered and analyzed spectrophotometrically at 295 nm. All formulations were performed in triplicate.

Stability Studies: The stability study is an indicative method for determination of durability of quality and quantity of therapeutic agents with the passes of time under the influence of various atmospheric conditions such as temperature, humidity, light and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions at 40°C ± 2°C/75% RH ± 5% RH. Stability studies were conducted towards 3 batches of optimized for 3 months using Newtronic Stability Chamber-NLWH327SI. Samples were withdrawn after 3rd month and were analysed, and results are tabulated.

RESULT AND DISCUSSION

Quetiapine Fumarate Liquisolid Compacts

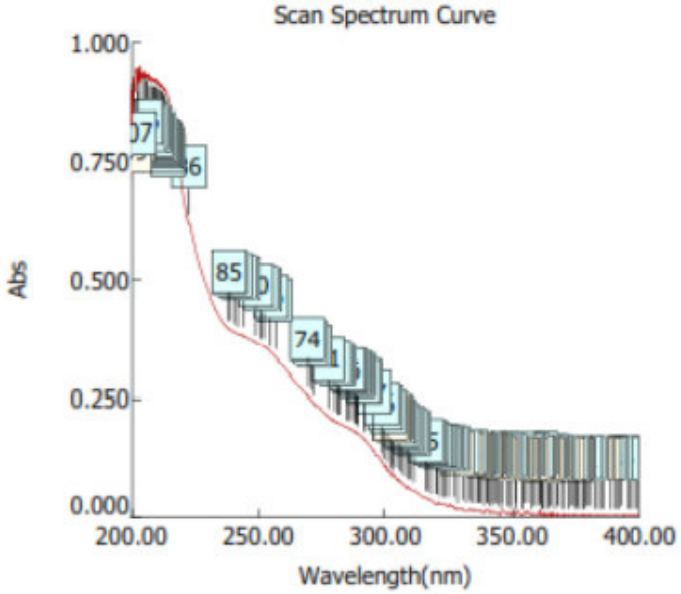
Pre-formulation Studies

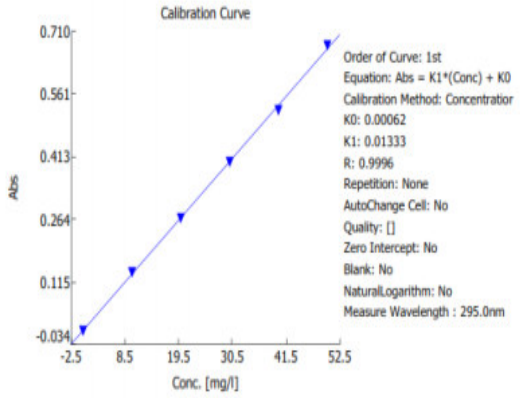
A. **General Description:** Quetiapine Fumarate is an odorless yellow crystalline powder, having a bitter taste.

B. **Melting Point Determination:** Melting point of QPF was found to be 174°C which was in accordance with reported melting point, 171-178°C.

C. Determination of Absorption Maxima

Standard graph of Quetiapine Fumarate was constructed using concentration 10,20,30,40,50 (µg/ml) in 0.1N HCL. It is evident from the figure 1&2 that the graph is linear with regression coefficient value of R^2=0.9996and slope=0.01333 at λmaxof 295nm.





ID	Type	Conc [mg/l]	Abs	295.00 nm
Blank	Standard	0.0	0.000	0.000
Quetapine Fumarate	Standard	10.0	0.138	0.138
Quetapine fumarate	Standard	20.0	0.267	0.267
Quetapine fumarate	Standard	30.0	0.400	0.400
Quetapine fumarate	Standard	40.0	0.522	0.522
Quetapine fumarate	Standard	50.0	0.676	0.676

SUMMARY

Quetiapine Fumarate is an odorless yellow crystalline powder, having a bitter taste.Melting point of QPF was found to be 174°C which was in accordance with reported melting point, 171-178°C. Standard graph of Quetiapine Fumarate was constructed using concentration 10,20,30,40,50 (µg/ml) in 0.1N HCL. It is evident from the figure 1&2 that the graph is linear with regression coefficient value of R^2 = 0.9996 and slope = 0.01333 at λ max of 295nm. In the liquisolid formulation non-volatile liquid solvent is optimized for the high drug

solubility in solvent. The solubility in various non-volatile solvents is given in Table. The table shows that solubility of Quetiapine in Labrafac is highest in comparison with other solvents. Labrafac undergoes more hydrophobic interactions and cause the drug to solubilize. Thus, Labrafac was selected to be the suitable solvent for preparing liquisolid formulation of Quetiapine Fumarate, The Phi-value corresponding to an angle of slide of 33° was recorded as the flowable liquid retention potential of carrier and coating material. The Phi- values for carrier and coating material have been abbreviated as φCA and φCO respectively. The carrier and coating material with maximum liquid retention potential have been selected as optimum. Higher the φ value at angle of slide 33° is considered as better carrier material and coating material. θ and φ values of various carrier material and coating materials are shown in Table 10 and Figure 5 & 6. Avicel 112 and Aerosil 200 were found to have the highest phi value i.e. 0.712 and 2.01 respectively. Hence Avicel 112 and Aerosil 200 were selected as an optimum carrier and coating materials respectively for the Quetiapine liquisolid formulation. IR spectrum of quetiapine Fumarate shows a broad peak at 3312.64 cm^{-1} may be due to O-H stretching, 2895.12 cm^{-1} C-H stretching, 2139.56 cm^{-1} may be due to aromatic C=C stretching, 1636 cm^{-1} may be due to C-N, 1334.28 cm^{-1} maybe due to C-H bending. 1068.87 cm^{-1} may be due to –C-O-C group. 832.42 cm^{-1} may be due to substituted benzene ring. From IR Spectra interpretation of drug was done with individual excipients and formulation mixture and observed that there is no appreciable change in the positions of the characteristic bands. Since there is no change in the nature and position of the bands in the formulation, it can be concluded that the drug maintains its identity without going any chemical interaction with the excipients used.

Powder blend was evaluated for angle of repose and compressed tablets were evaluated for thickness, hardness, friability, disintegration, and drug content. Results are reported in table. As shown in Table, Angle of repose of the formulations varied from 25.34° to 29.38°. Average weight of tablet was found in the range of 118.26-130.30mg, results indicate that tablet weight was found within the specified limits of USP recommendation with a deviation of ±10%. Thickness of liquisolid tablet was found to be in the range of 2.85 to 4.27 mm. It was observed that as the concentration of Avicel 112 and Aerosil 200 changes thickness varies. Avicel 112 has large surface area and porous nature, adsorbs high loads of oils or water and can be mechanically compacted into high quality tablets. Hardness of liquisolid tablet was found to be in the range of 2.8 to 3.4 kg/cm2 respectively. Avicel 112 is superior in compressibility. Avicel 112 makes hard tablets at low compression force and in addition, improves the hardness of other filler and binder excipients. Avicel 112 with combination of Primojel and Dicalcium phosphate here improves the hardness and increases the bulk of tablet. But concentration of Dicalcium phosphate is same in all trials so there is no individual effect of Dicalcium Phosphate here on hardness. Increase in hardness and compression pressure did not affect the disintegration time and as well as friability. This indicates that as the concentration of Avicel 112 increases hardness of liquisolid tablet increases. Friability of tablets was found to be below 1% which is acceptable. Disintegration time of liquisolid tablets were in the range of 28- 84 secs. Drug content of all liquisolid tablets were found to be in between acceptable range. The percent drug release from DPY liquisolid tablet of batches QPF1 to QPF9 is shown in Figure & Table. Conventional formulation showed a release of 31.32 % after 10 minutes and 58.45 % after 30 minutes. The % drug release after 10 minutes from all the batches was found to be in the range of 78.56 % to 99.58 % . The batch QPF8 showed the highest drug release 99.58% at 10 minutes when compared to all other batches and Conventional formulation. The obtained results of in vitro drug release showed a relationship between the carrier to coating material ratio and the in vitro release of DPY from liquisolid tablets. An increase in the R-value results in an enhanced release rate as there is higher quantity of Avicel 112 and low quantity of Aerosil 200. This is associated with enhanced wicking, disintegration and thus, enhanced drug release showed by batch QPF8. If high amounts of Aerosil 200 are used, which means that the R-value is low, the liquisolid formulation is overloaded with liquid formulation due to a high liquid load factor. In such cases, even though drug diffusion out of the primary particles may be rapid, oversaturation might occur resulting in local precipitation/ recrystallization of the drug and thus slows down release rates. Of all the formulations, the highest % drug release was from QPF8 which was 99.58 % at 10 minutes whereas % drug release of Conventional formulation at 10 minutes was 31.32 %. This suggests that liquisolid technology has enhanced the solubility and dissolution of DPY.

The formulations were loaded for stability as per ICH guidelines into stability chambers which were maintained at 40°C ± 2°C/75% RH ± 5% RH. Stability studies were conducted for 3 months. Samples were withdrawn at 1 month, 2 months and 3 months. Third month samples were analysed for optimized formulation and results are tabulated.

It is evident from the table, there were no physical changes observed throughout the stability study for the selected optimized formulation.

CONCLUSION

The Quetiapine Liquisolid compacts were developed and optimised based on evaluation parameters. The drug content, in vitro dissolution and stability stduiesof the improved formulation (QPF8) were all within acceptable ranges. Thus, it can be stated that the formulation can be further studied for assessment of pharmacokinetic parameters. Liquidolif compacts is considered to be a potential method for delivering medications for the enhancement of solubility of poorly soluble drugs.

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