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Solid Dispersion- A way to Enhance Solubility of Quetiapine Fumarate

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ABSTRACT

Quetiapine Fumarate is a antipsychotic agent indicated for treatment of Schizophrenia and Bipolar disorder. Quetiapine Fumarate is BCS Class II drug which is poorly water soluble and may show dissolution limited absorption. Hence to improve dissolution rate and bioavailability, Solid dispersion of Quetiapine Fumarate by Solvent Evaporation method were prepared using 1:1, 1:2, 1:3, 1:4 and 1:5 ratios of Quetiapine Fumarate and Polyvinyl Pyrrolidone K30(PVP K30). The solid dispersion (SD) was characterized for physical appearance, solubility, FTIR, DSC, XRD studies and in vitro dissolution studies. FTIR study revealed that there was no drug-carrier chemical interaction in Solid dispersion. DSC studies revealed that, the peak observed for the melting of Quetiapine Fumarate is found to be absent in SD with PVP K30 carrier. XRD studies suggested that there has been a large change in the nature of Quetiapine Fumarate in the solid dispersion. Solubility of Quetiapine Fumarate from SD increased in distilled water. The drug content was found to be high and uniformly distributed in the formulation. The in vitro dissolution studies were carried using USP type II (paddle) type dissolution apparatus. The prepared Solid dispersion showed marked increase in the dissolution rate of Quetiapine Fumarate than that of pure drug. The Solid dispersion with PVP K30 (1:5) by Solvent evaporation method showed faster dissolution rate as compared to other Solid dispersions. It is concluded that dissolution of the Quetiapine Fumarate could be improved by the Solid dispersion.

Keywords: Quetiapine Fumarate, bioavailability, Solid dispersion, dissolution.

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INTRODUCTION

The term Solid Dispersion defined as the dispersion of one or more active ingredient (hydrophobic) in an inert carrier or matrix (hydrophilic) at solid state prepared by melting (fusion), solvent or melting solvent method. The term 'Solid dispersion' refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, as amorphous particles (clusters) or as crystalline particles. The term 'Solid dispersion' has been utilized usually with a view to enhance oral bioavailability and solubility of poorly water soluble drug. [1-4]

Increase in solubility for poorly soluble drug is very important approach for increasing the dissolution of drug thereby improving its bioavailability. Solid dispersion is a technique through which solubility of poorly water soluble drug can be markedly increase by using suitable hydrophilic polymer. Different methods of Solid Dispersion are available of which Solvent Evaporation method is selected as it is easy to formulate as well as easy to commercialize. Solid dispersion increases the porosity of drug thereby improving its wetting property and thus increases the dissolution of drug.

Quetiapine was BCS Class IV drug having low solubility and low permeability so to solve this problem Fumarate salt was prepared which increase the permeability of Quetiapine but solubility remains the same. Thus Quetiapine was converted to Quetiapine Fumarate which is a BCS Class II drug used for treatment of schizophrenia having low solubility and high permeability thus make it suitable candidate for formulating as solid dispersion. As it is poorly soluble in water thus solid dispersion improves its dissolution property resulting improvement in its bioavailability. The solubility of such drug can be increase by using hydrophilic polymer having low melting point, high water solubility, high glass transition point and soluble in common solvent with drug. So Povidone which is hydrophilic polymer having melting point lower than quetiapine fumarate and thus selected as carrier for solid dispersion.

Quetiapine fumarate shows pH dependent solubility-It is highly soluble in acidic environment, moderately soluble in water and in basic environment. Quetiapine fumarate is gastric irritant in nature, so to prevent release in stomach, Enteric coating is required so that it get release in intestine.

The rationale for coating pharmaceutical dosage form such as capsule is;

- To minimize irritation of oesophagus and stomach.

- Minimize inactivation in stomach.
- Improve drug effectiveness.
- Improve patient compliance e.g. easier to swallow, masks unpleasant taste.
- Increased Bioavailability.
- Formulation Stability.

MATERIALS AND METHOD

Material

Quetiapine Fumarate is obtain as gift sample from Torrent Pharmaceutical Ltd., Ahmedabad. Poly vinyl Pyrollidone K30 is obtain from Balaji Drugs, Mumbai. Methanol is obtain from Priya Enterprise, Vapi. Magnesium Stearate is obtain from West Coast Laboratories, Mumbai. Talc is obtain from Loba Chemie Pvt.Ltd. Colorcoat EC4W-D is obtain from Coral Pharma Chem, Ahmedabad.

Method:

Preparation of Physical mixtures:

Five physical mixtures (P.M.) of different proportions of Quetiapine Fumarate with PVP K30 were prepared in the ratios of 1:1, 1:2, 1:3, 1:4 and 1:5 w/w. The required amounts of PVP K30 and Quetiapine Fumarate were weighed and mixed thoroughly by light mixing in a glass mortar. The mixture was sieved and the powder fraction corresponding to mesh size less than 60 was collected for further investigation.

Preparation of Solid dispersions:

Different ratios of Quetiapine Fumarate with PVP K30 of 1:1, 1:2, 1:3, 1:4 and 1:5 w/w were accurately weighed. The solid dispersions were prepared by solvent evaporation method using the Methanol as a solvent. The solvent was evaporated on a water bath at 45°C. After complete evaporation, the solid mass was further dried in vacuum desiccator for 12 h. The dried solid mass was pulverized with a mortar and pestle and then sieved. The solid dispersions of 60–200 mesh were used in the experiment.

Preparation of Enteric Coating of Capsule

Colorcoat EC4W-D (Enteric coated polymer) was added slowly into a vessel containing distilled water with continuous stirring. The solution was stirred for 45 min. Then it is filtered through Whatman filter paper. Then the hard gelatin capsule filled with optimized solid dispersion was enterically coated with resulting filtrate of colorcoat EC4W-D solution by using Pan coater.

Table 1.Formula for formulating Enteric Coated Capsule

Sr No.	Ingredients	Quantity
1.	Solid Dispersion	Equivalent to 100 mg of Quetiapine Fumarate
2.	Magnesium Stearate	2%
3.	Talc	2%

Evaluation of Solid dispersions:

Assay:

- **Preparation of Standard Solution:**

Quetiapine Fumarate 10 mg was weighed accurately and transferred to 10 ml volumetric flask. It was dissolved in methanol AR grade and volume was made to 10 ml with methanol. From this stock solution (1000 µg/ml) 1 ml solution was removed and diluted to 10 ml with Phosphate buffer (pH-6.8) to get the solution of 100 µg/ml. 2 ml from this solution was taken and further diluted to 10 ml with Phosphate buffer (pH-6.8) to obtain the solution of final concentration 20 µg/ml. Absorbance of resulting solutions was measured on UV spectrophotometer at 291.5 nm.

- **Preparation of Sample Solution:**

Solid dispersion equivalent to 10 mg Quetiapine Fumarate was weighed accurately and transferred to 10 ml volumetric flask. It was dissolved in methanol

AR grade and volume was made to 10 ml with methanol. From this stock solution (1000 µg/ml) 1 ml solution was removed and diluted to 10 ml with Phosphate buffer (pH-6.8) to get the solution of 100 µg/ml. 2 ml from this solution was taken and further diluted to 10 ml with Phosphate buffer (pH-6.8) to obtain the solution of final concentration 20 µg/ml. Absorbance of resulting solutions was measured on UV spectrophotometer at 291.5 nm.

Assay was calculated by using equation:

$$\text{Assay (\% w/w)} = \frac{\text{Sample absorbance}}{\text{Standard absorbance}} \times 100$$

Determination of Saturation Solubility:

The shake flask method was used to determine saturation solubility of prepared solid dispersions in distilled water and Phosphate buffer (pH-6.8). Excess quantities of solid dispersions were added in 10 ml distilled water and Phosphate buffer (pH-6.8) which is then incubated in orbital shaker at room temperature. Solutions were filtered through Whatman filter paper. Absorbance of resulting solutions was measured on UV spectrophotometer at 290 nm and 291.5nm.

Saturation solubility was then calculated by putting measured absorbance value in calibration curve equation for distilled water.

In vitro Dissolution studies (Phosphate buffer (pH-6.8):

In vitro dissolution studies were performed for all the formulation combinations in duplicate using USP Dissolution Apparatus II (paddle type). An accurately weighed sample of solid dispersions (equivalent to 100 mg Quetiapine Fumarate) was placed into 900 ml of Phosphate buffer (pH-6.8), maintained at a temperature of 37ºC ± 0.5ºC and stirred at a speed of 50 rpm. At different time intervals, a 10 ml aliquot of the sample was withdrawn and the volume was replaced with an equivalent amount of plain dissolution medium kept at 37ºC. The collected samples were filtered and analyzed at λ_{max} 291.5 nm using a UV visible spectrophotometer against Phosphate buffer (pH-6.8) taken as blank.

Optimization of Solid Dispersion

By considering results obtained from Assay, Saturation solubility studies and in-vitro dissolution studies, the best optimum ratio of S.D. were confirmed.

Evaluation of Optimized Solid Dispersion

DSC Studies

The thermal behaviour of optimized solid dispersion was determined using 2910 modulated DSC, thermal analyst 2000 TA instrument, at a heating rate of 10°C/min and temperature range of 50-300°C, for sample size 2-5 mg. All samples used for DSC were comprised of following specifications complex containing equivalent amount of drug was heated under inert Argon gas flowing at 35 cc/min in a temperature range of 50°C- 300°C using oxidation method at a scanning speed of 10°C/ min.

XRD Studies

The XRD pattern of optimized solid dispersion was recorded using high power powder x-ray diffractometer (Ru-200B, Pune, India) with Cu as target filter having a voltage/current of 40 KV/50 mA at a scan speed of 4 deg/min. The samples were analyzed at 2θ angle range of 2 to 45. Step time was 0.5 second and time of acquisition was 1 hour.

Solvent Residual Test

The residual solvent test is a test to determine the amount of residual organic solvents in pharmaceuticals by using gas chromatography to monitor adherence to the limits which are advised for the safety of patients by "Guideline for Residual solvents: ICH Harmonized Tripartite guideline."

The solvent residual test of optimized solid dispersion was carried out by Gas chromatography using FID (Flame ionization detector) from which peak of optimized solid dispersion was obtained which determine the amount of residual organic solvent.

Formulation Development of Optimized Solid Dispersion

Optimized solid dispersion was further formulated into capsule dosage form using following excipients.(**table 1)**

The resulting powder blend was evaluated for flow parameters. The powder blends equivalent to the 100 mg of drug was filled in Hard Gelatin Capsule, which was then enterically coated with Colorcoat EC4W-D. Capsule blend was evaluated for various parameters.

- Coating pan size – 36″ with around 4-6 artificial baffles
- Coating pan RPM – 8-12
- Air Pressure – 2.5-3.5 kg/cm^2
- Bed temperature – 38-40º C
- Inlet Air temperature – 60-65º C

Evaluation of Powder Blend(5)

- Following are the evaluation of capsule blend
    - Bulk Density
    - Tapped Density
    - Angle of Repose

Evaluation of Enteric Coated Capsule

The capsules were evaluated for following test parameters.

1. Weight Variation
2. Assay
3. Disintegration Time
4. Dissolution study

Weight Variation[6]

To perform this test 20 units were individually weighed at random and average weight was determined. Not more than 2 of the individual mass deviate from the average weight.

Assay:

Preparation of Standard Solution:

Quetiapine Fumarate 10 mg was weighed accurately and transferred to 10 ml volumetric flask. It was dissolved in methanol AR grade and volume was made to 10 ml with methanol. From this

stock solution (1000 µg/ml) 1 ml solution was removed and diluted to 10 ml with Phosphate buffer (pH-6.8) to get the solution of 100 µg/ml. 2 ml from this solution was taken and further diluted to 10 ml with Phosphate buffer (pH-6.8) to obtain the solution of final concentration 20 µg/ml. Absorbance of resulting solutions was measured on UV spectrophotometer at 291.5 nm.

Preparation of Sample Solution:

Capsule blend equivalent to 10 mg Quetiapine Fumarate was weighed accurately and transferred to 10 ml volumetric flask. It was dissolved in methanol AR grade and volume was made to 10 ml with methanol and sonicated for 10 min. From this stock solution (1000 µg/ml) 1 ml solution was removed and diluted to 10 ml with Phosphate buffer (pH-6.8) to get the solution of 100 µg/ml. 2 ml from this solution was taken and further diluted to 10 ml with Phosphate buffer (pH-6.8) to obtain the solution of final concentration 20 µg/ml. Absorbance of resulting solutions was measured on UV spectrophotometer at 291.5 nm.

Disintegration time:

Place one dosage unit in each of the six tubes of the basket and add a disk upon it. Operate the apparatus using water as immersion fluid maintained at 37± 2˚C. Note down the time required to disintegrate all contents except fragments from the capsule shell.

Dissolution Study:

For any formulation drug release from the dosage form is the foremost parameter to be measured. Drug release is evaluated by the in-vitro dissolution test apparatus. The dissolution test for each formulation was performed in duplicate using the dissolution test apparatus (Electrolab TDT-06 T USP standard). The dissolution test was carried out by using 900 ml 0.1N HCl (pH-1.2) for 2 hours then it is replaced by 900 ml Phosphate buffer (pH-6.8) as dissolution medium. The test was performed using USP type II apparatus at 50 rpm and maintaining the temperature at 37 ± 0.5 ^{0}C. Aliquots of 10 ml were periodically withdrawn and the volume was replaced with fresh dissolution medium. The aliquots were filtered, suitably diluted and finally analyzed spectrophotometrically at 208.5 nm, 291.5 nm for 0.1N HCl (pH-1.2) and Phosphate buffer (pH-6.8) respectively.

Stability Studies

Based on the results of evaluations, optimized solid dispersions with PVPK 30 prepared by Solvent Evaporation Method was subjected to stability studies at 40°C and 75 % relative humidity for 15 days period.

The preparations were evaluated for –

- Assay

- Dissolution studies

RESULTS AND DISCUSSION

Evaluation of Solid Dispersion:

Assay:

The drug content of prepared solid dispersion with PVP K30 was found to be in the range of 98.72 to 99.69 % w/w. The drug content values are shown in Table No.18. Satisfactory reproducibility of results was observed when repeating the assay. Low values of Relative standard deviation (% RSD) i.e. < 1.5 in respect of drug content indicate uniform drug distribution and application of all the three methods for the preparation of solid dispersions with high content uniformity.(table 2)

Table 2. Assay values of prepared SDs with PVPK 30

Sr. No.	Method of Preparation of SDs	D:P Ratio	Assay with PVP K30
1	Solvent Evaporation Method	1:1	99.69 ± 0.26
		1:2	98.72 ± 0.46
		1:3	99.90 ± 0.42
		1:4	99.01 ± 0.72
		1:5	98.89 0.52

Determination of Saturation Solubility:

The saturation solubility values and their comparison are depicted graphically in figure 1 respectively.(Figure 1,2)

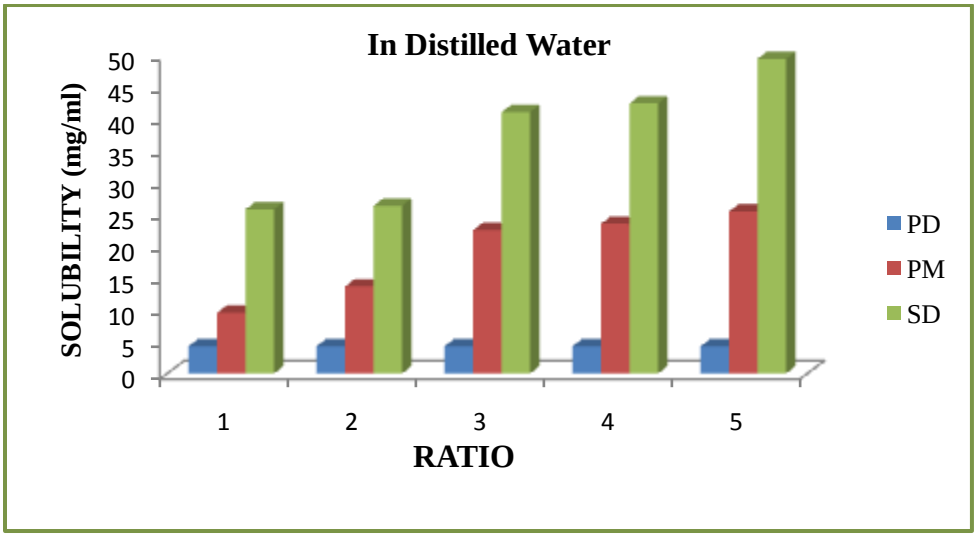

Figure.1 Comparison of Saturation Solubilities of PD, PM and Prepared SDs with PVP K 30 in Distilled water.

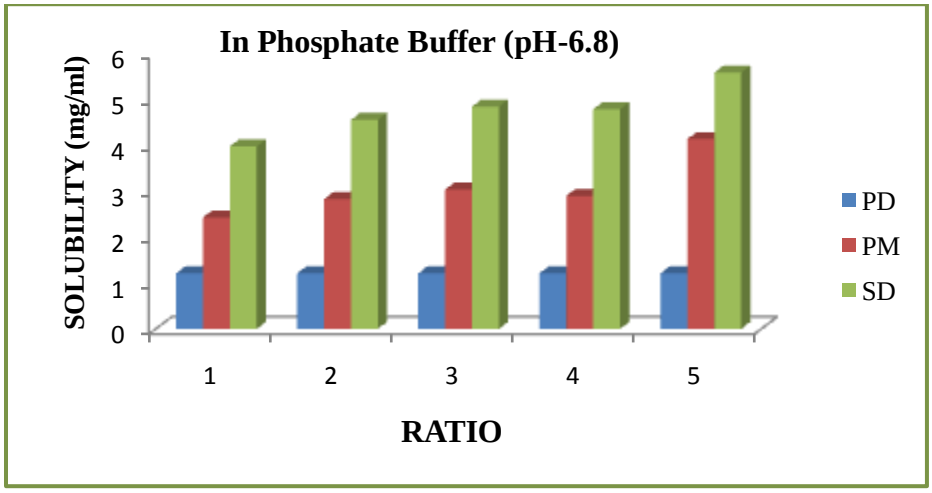

Figure.2 Comparison of Saturation Solubilities of PD, PM and Prepared SDs with PVP K 30 Phosphate buffer (pH-6.8)

In vitro Dissolution studies:

Dissolution studies were carried out to determine the drug release profile from formulations and its comparison with that of pure drug.

- **In vitro Dissolution studies in Phosphate buffer (pH-6.8)**
  - **Ratio- 1:1 figure 3**
  - **Ratio- 1:2 figure 4**
  - **Ratio- 1:3 figure 5**
  - **Ratio- 1:4 figure 6**
  - **Ratio- 1:5 figure 7**

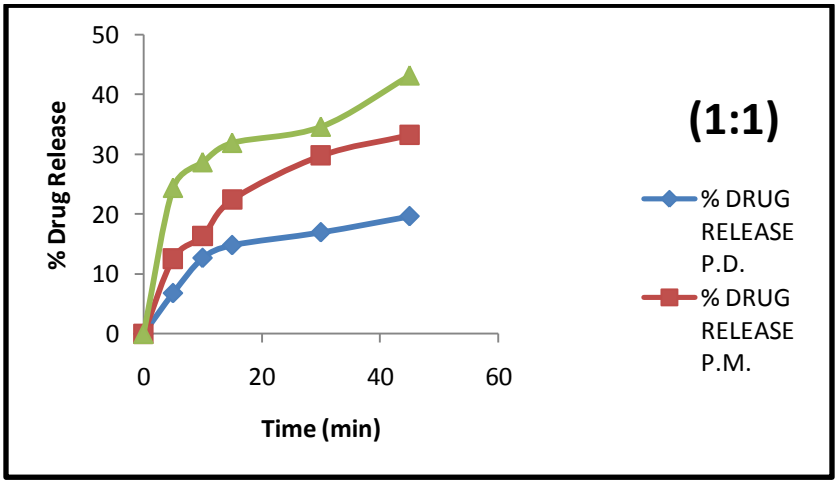

Figure. 3. % Drug Release for S.D. (1:1)

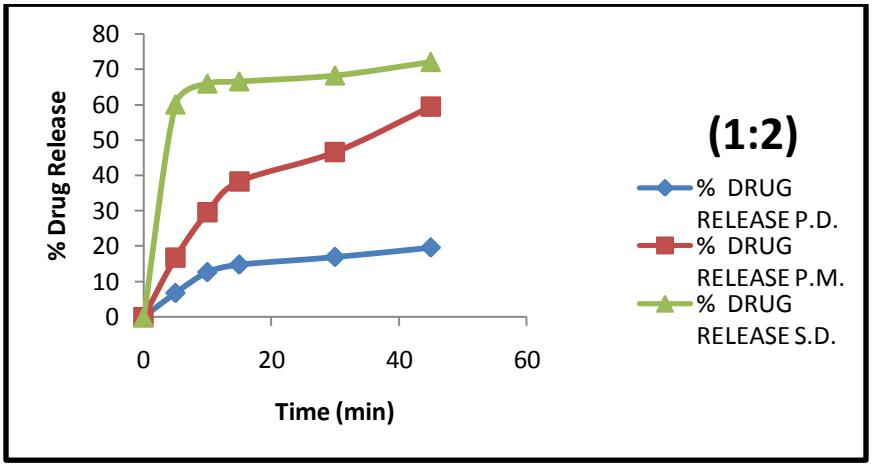

Figure 4.: % Drug Release for S.D. (1:2)

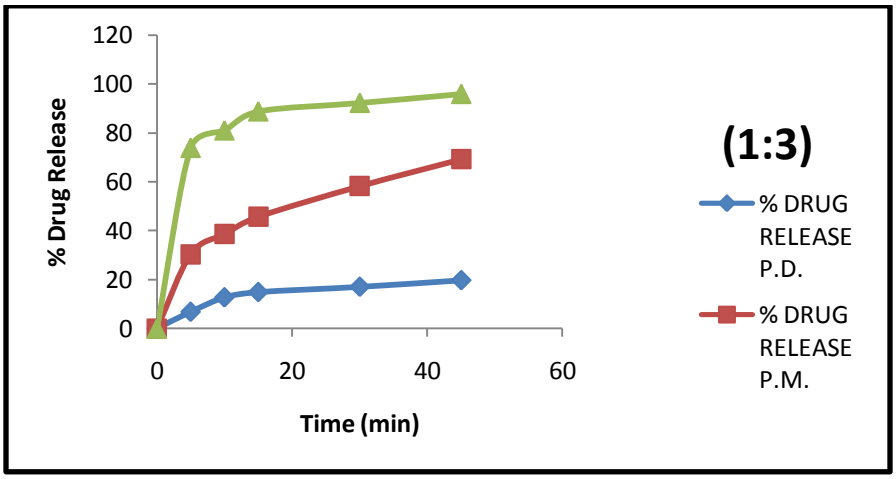

Figure 5. % Drug Release for S.D. (1:3)

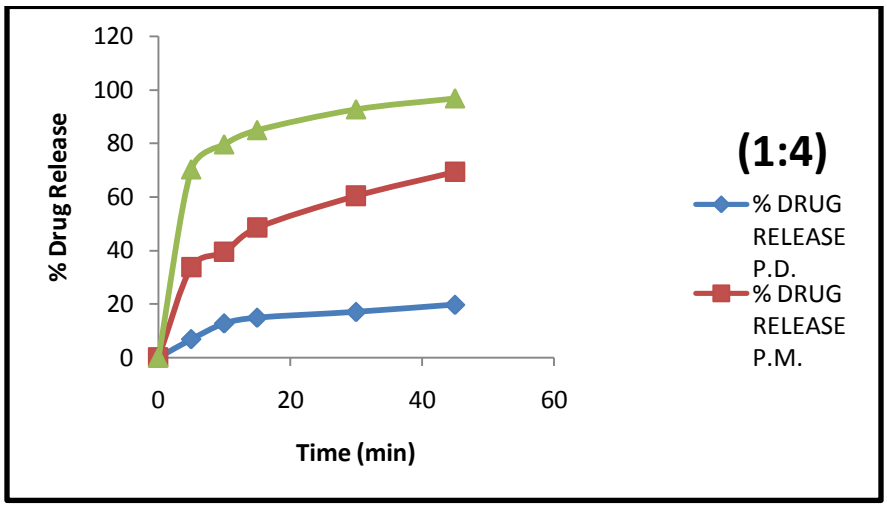

Figure 6. % Drug Release for S.D. (1:4)

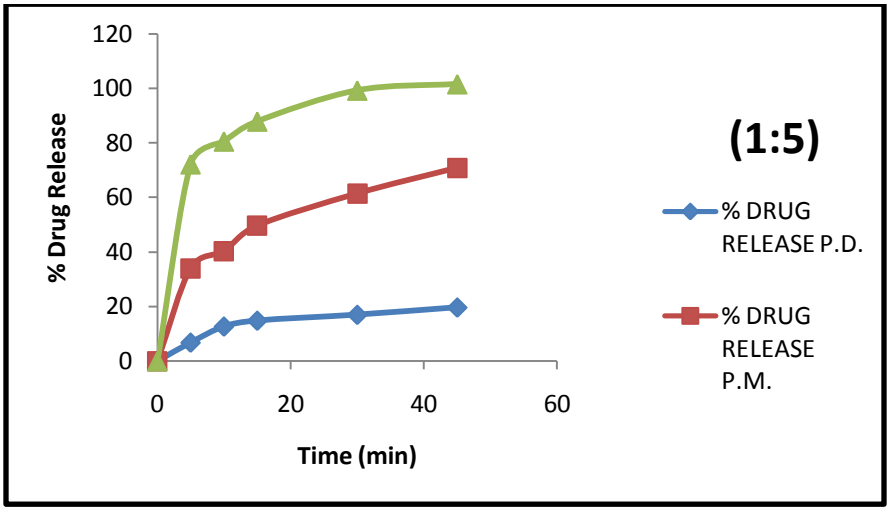

Figure 7. % Drug Release for S.D. (1:5)

Optimization of Solid Dispersion

By observing the results obtained from Saturation Solubility, 1:5 ratios showed drastic increase in solubility.

In vitro Dissolution studies in dissolution mediums showed marked increase in drug release as compared to PD and PM for 1:5 ratios. In USP and IP, Quetiapine Fumarate tablets are official. Dissolution test in USP and IP specifies drug release of NLT 70% within 45 min as acceptance criteria. Only SD (1:5) fit in acceptance criteria. So, if a formulation is developed from S.D. (1:5), it will show better solubility and comply with Pharmacopoeial requirement with respect to drug release.

Hence, by considering all above parameters, solid dispersions prepared for 1:5 ratios were taken as optimized Solid dispersions which were further formulated into suitable dosage form.

Evaluation of Optimized Solid Dispersion

DSC Studies

- DSC Thermogram of a) Quetiapine Fumarate (P.D.), b) Physical mixture (P.M.) and c) Optimized Solid Dispersion (S.D.) were shown in figure 8.
- DSC thermograms were recorded to study the thermal behaviour of the solid dispersions. DSC studies revealed that, sharp endothermic peak corresponding to melting point of Quetiapine fumarate can be observed at approximately 177.30°C and 72.43°C in the thermogram of pure drug and PM 1:5 respectively (Figure. 8 a, b). The peak observed for the melting of Quetiapine fumarate is found to be absent in SD with PVPK 30 carrier (Figure. 8, c). The complete disappearance of drug melting peak observed in the DSC thermogram of SD with PVPK 30 can be attributed to uniform drug dissolution in the carriers. No

significant difference can be found between the DSC thermograms of solid dispersions (1:5) prepared by Solvent Evaporation method for PVPK 30 suggesting similarity in their thermodynamic properties.

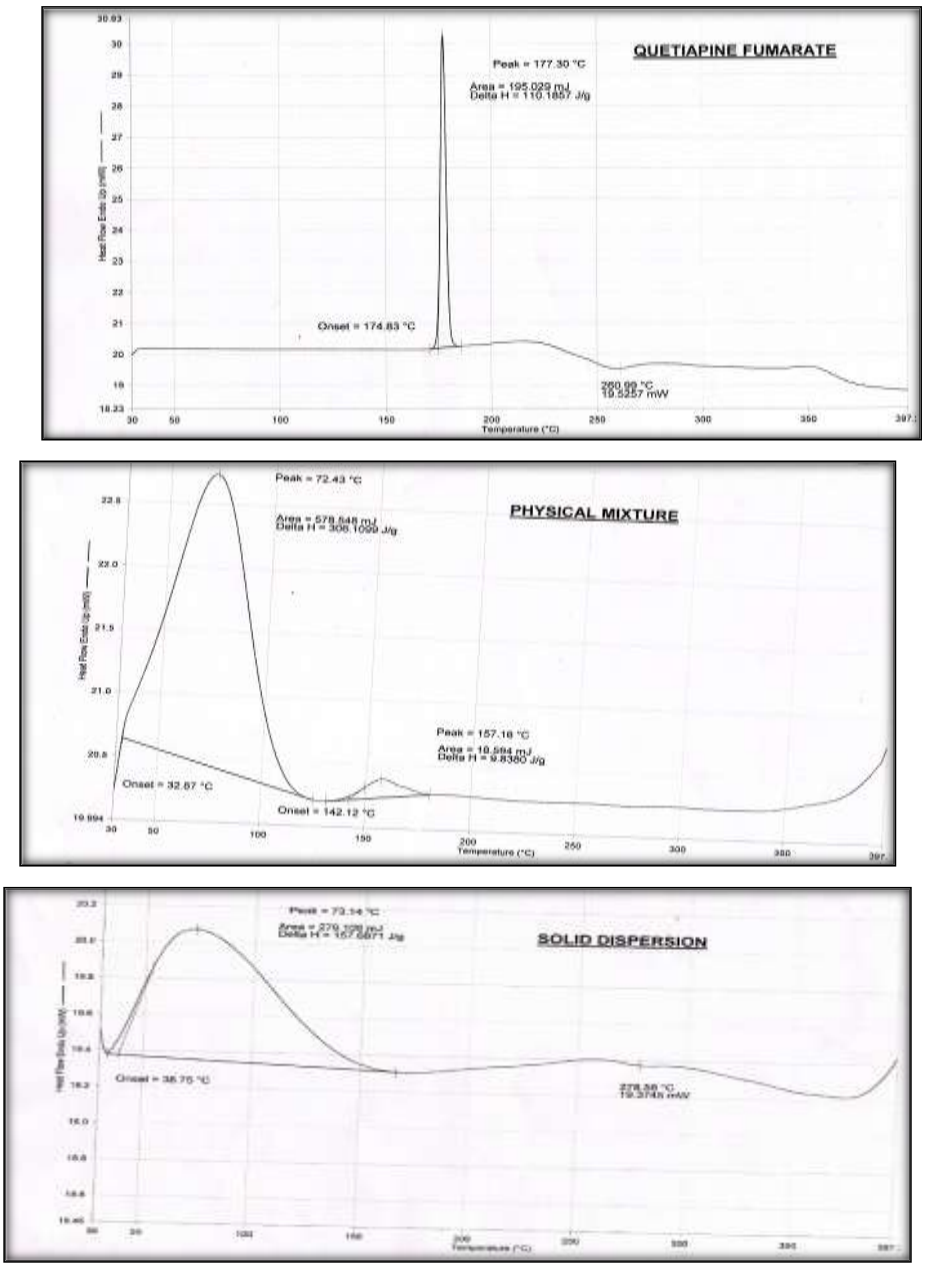

Figure 8. DSC Thermogram of Pure drug, Physical mixture and Optimized Solid Dispersion

XRD Studies

- XRD of A) Quetiapine Fumarate (P.D.), B) Physical mixture (P.M.) and C) Optimized Solid Dispersion (S.D.) were shown in figure 9

- From the figure 9 it was observed that there has been a large change in the nature of Quetiapine fumarate in the solid dispersions. It also indicates possibility of conversion of a large portion of Quetiapine fumarate to amorphous form in the solid dispersions.

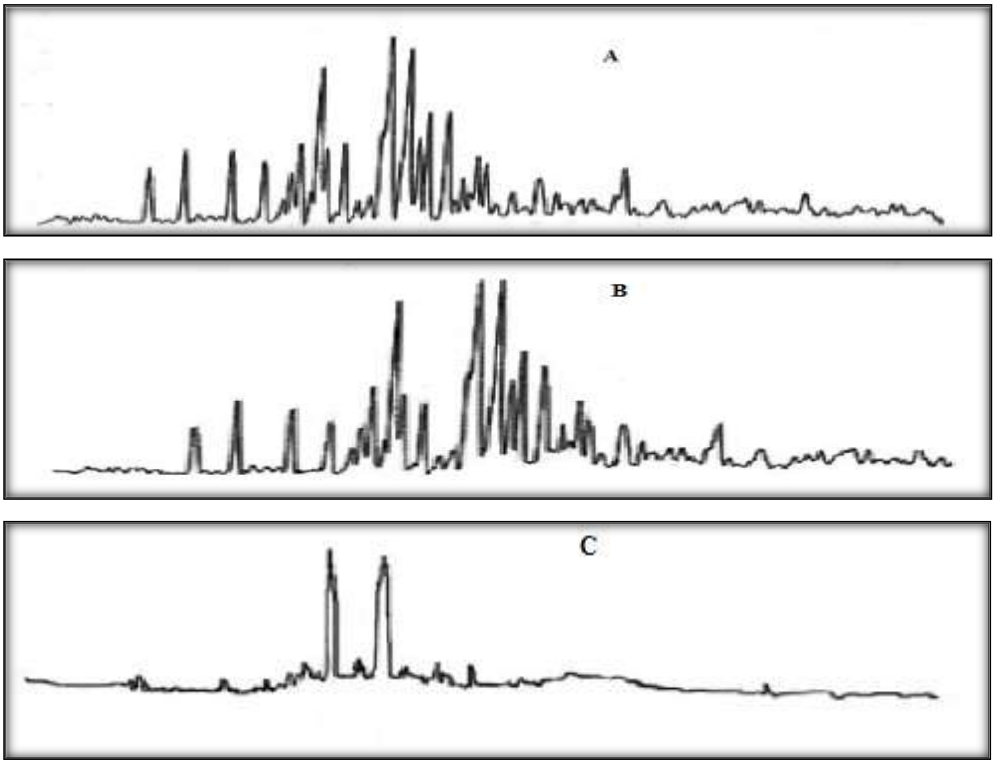

Figure 9. XRD of Pure drug, Physical mixture and Optimized Solid Dispersion

Solvent Residual Test

From the figure 10 and 11 it was observed that there was no peak of residual solvent found in optimized solid dispersion.

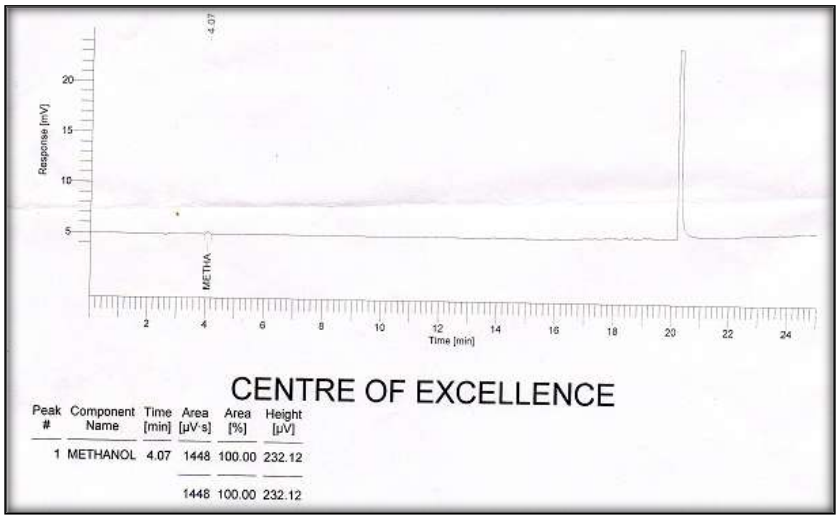

Figure. 10. Standard Peak of 10 ppm Methanol

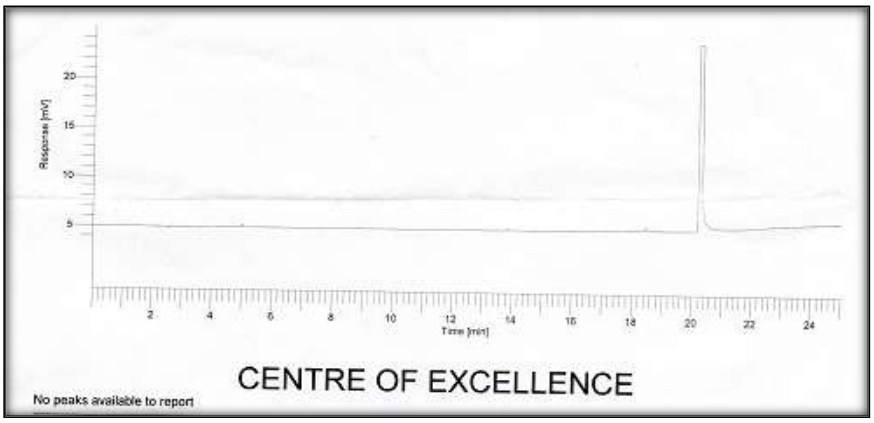

Figure11. Sample peak of Solid Dispersion

Formulation Development of Optimized Solid Dispersion and its Evaluation

Formulation of capsule dosage form of the optimized solid dispersion prepared by solvent evaporation method was undertaken by hand filling of hard gelatin capsule, which was enterically coated with Colorcoat EC4W-D. In this formulation, Quetiapine fumarate used as an active ingredient, PVP K30 as a hydrophilic polymer, magnesium stearate as a lubricant and talc as a glidant.

Evaluation of Powder Blend (table3)

Evaluation of Enteric coated Capsule

Weight variation (table 4)

The capsules weighing between 80 mg to 250 mg have the allowed limit of ± 7.5 % variation according to U. S. Pharmacopoeia. The capsules evaluated showed the weight variation within limit, and thus passed the test. The % standard deviation was found between 0 – 0.84 which is within the limit as per USP.

Table 3. Data for evaluation of powder blend

Sr No.	Evaluation Tests	Results
1.	Bulk Density (gm/ml)	0.47
2.	Tapped Density (gm/ml)	0.60
3.	Angle of Repose (θ)	40

Table 4.Weight variation of filled capsule

No. Of filled Capsule	Weight of Capsule (x)	% Standard Deviation
1	705	0.14
2	710	0.56
3	706	0
4	708	0.28
5	712	0.84
6	704	0.28
7	710	0.56

8	705	0.14
9	703	0.42
10	706	0
11	701	0.70
12	711	0.70
13	712	0.84
14	709	0.42
15	702	0.56
16	710	0.56
17	706	0
18	707	0.14
19	701	0.70
20	704	0.28

Assay

Assay were found to be 99.56 ± 0.42 which was within the limits specified by USP and hence, pass the test.

Disintegration Time

All the capsules showed disintegration within 2-2.5 min. and hence passes the test.

In-vitro Dissolution Study

Dissolution studies were carried out with 900 ml 0.1N HCl (pH-1.2) for 2 hours then it is replaced by 900 ml phosphate buffer (pH-6.8) to determine the drug release profile from formulation.(table 5 and figure 12)

Table 5. % Drug Release for Enteric coated capsule

Time (min)	% Drug Release
60	0
120	0
125	68.87
130	81.65
135	86.67
150	**99.44**
165	101.29

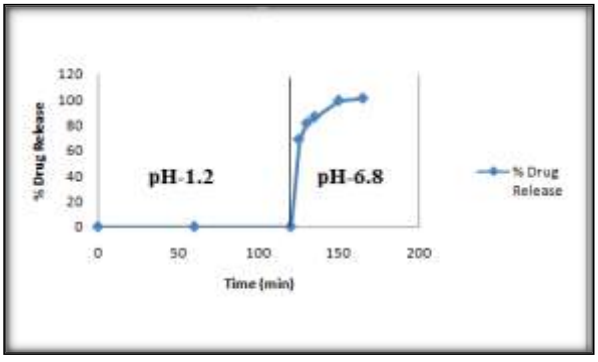

Figure 12. % Drug Release for Enteric coated capsule

Stability Studies

Optimized SD was subjected to accelerated stability studies for 15 days (40˚C and 75% RH). In order to predict the stability of optimized SD, following tests were carried out after 15 days.

CONCLUSION

From the findings of the study conducted, following conclusions can be drawn: Solid dispersion prepared with PVP K30 carrier showed improvement in the solubility as well as dissolution rate of Quetiapine Fumarate. Significant improvement in solubility was observed with 1:5 ratios (D: P). SD having Ratio 1:5 showed better saturation solubility and drug release as compared to PD, PM and other ratios. FTIR characterization indicated that there was no drug-carrier chemical interaction in the solid dispersions. DSC studies revealed that, the peak observed for the melting of Quetiapine Fumarate is found to be absent in SD with PVP K30 carrier. The complete disappearance of drug melting peak observed in the DSC thermo gram of SD with PVP K30 can be attributed to uniform drug dissolution in the carriers. XRD studies suggested that there has been a large change in the nature of Quetiapine Fumarate in the solid dispersions. It also indicates possibility of conversion of a large portion of Quetiapine Fumarate to amorphous form in the solid dispersions. Formulated capsule dosage form from optimized SD showed better drug release as compared to pure drug and Physical mixture. Hence by preparing SD of Quetiapine Fumarate its solubility will get increased. Thus, improved solubility may lead to better absorption and hence, ultimately, improved bioavailability. Hence, these SD if formulated into suitable oral dosage form, it will have acceptable dissolution profile along with other parameters. Thus, it can be scaled up and can have commercial acceptance.

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