Enhancement Of Solubility And Dissolution Of Quetiapine By Recrystallization

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Quetiapine an antipsychotic agent, exhibits poor aqueous solubility, dissolution and flow properties. Thus, the aim of the present study was to improve the solubility and dissolution rate of Quetiapine through re-crystallization method by solution evaporation technique using ethanol. The prepared formulation containing different ratios of drug was evaluated for solubility and in-vitro dissolution. The prepared formulations were characterized by UV method. Dissolution profile of the prepared crystals was compared with its physical mixture and pure sample. In the presented investigation Quetiapine exhibited appreciable decrease in pH (4.3-5.8) recrystallized in 100%, 90%, 75% & 50% ethanol. The formation of crystalline structure is smaller in size as compared to 100%, 90%, & 75% ethanol. The decrease in pH indicates. Environment of more hydrogen atom during recrystallization stage Quetiapine exhibits increase in dissociation constant value around (10-12.05%) in 100%, 90%, 75% & 50% ethanol. The dissolution kinetics of Quetiapine decreased with addition of water in recrystallizing solvent. The study indicates the recrystalline solvent plays an importance role in designing of physiochemical properties of the drug.

Keywords:
Quetiapine, Solubility, Recrystallization, Dissolution, Ethanol.

ABSTRACT

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INTRODUCTION:

Crystallization:-

Crystallization is the process of forming a crystalline structure from a fluid or from materials dissolved in a fluid. (More rarely, crystals may be deposited directly from gas; see thin-film deposition and epitaxy.)

Crystallization is a complex and extensively-studied field, because depending on the conditions, a single fluid can solidify into many different possible forms.

Recrystallization

Recrystallization in the solid state is the change in the crystal structure of a substance that takes place upon heating or cooling, without a change in the state of aggregation. It is determined by the polymorphic (allotropic) transformations of the components forming the solid.

Recrystallization from solutions is a process involving the dissolution of a crystalline substance with the subsequent precipitation of its crystals from the solution. It is used to remove impurities from crystalline substances.

Three stages of recrystallization are distinguished: the primary stage, in which new, nondeformed crystallites are formed in the deformed material and grow by absorbing the deformed grains; the accumulative stage, in which the nondeformed grains grow at each other’s expense, as a result of which the average size of the grain increases; and secondary recrystallization, which differs from the accumulative stage in that only a few of the nondeformed grains have the capacity to grow. In the course of secondary recrystallization the structure is characterized by grains of different sizes.

Single Solvent Recrystallization: Single solvent recrystallization is the most basic and commonly used recrystallization method. An ideal solvent does NOT dissolve the solid at room temperature BUT dissolves the solid well in hot solvent.

Process:

1. Heat the solvent and add a minimum of the hot solvent to your crude product to dissolve it (dropwise addition).
2. Hot gravity filter the hot solution if impurities are present. If your solution is colored, use decolorizing charcoal and then hot gravity filter.
3. Allow the hot, clear solution to slowly cool to room temperature (or 0°C using an ice bath, if necessary). Use solubility tests to determine a suitable recrystallization solvent.
4. If crystallization does not occur, induce crystallization.
5. Collect crystals by vacuum filtration and wash the crystals using a minimal amount of cold solvent.
6. Allow the crystals to dry.

Two Solvent Recrystallization

Two solvent recrystallization is an alternative and very useful recrystallization method to single solvent recrystallization. The first solvent should dissolve your crude product very well at room temperature (or in hot solvent). The second solvent should NOT dissolve your crude product at room temperature or in hot solvent.

Process:

1. Use solubility tests to determine a suitable recrystallization solvent.
2. Heat the first solvent and add a minimum of the hot solvent to your crude product to dissolve it (dropwise addition).
3. Hot gravity filter the hot solution if impurities are present. If your solution is colored, use decolorizing charcoal and then hot gravity filter.
4. Add the second solvent slowly (with shaking) until the solution remains cloudy. Add one or two drops of the hot first solvent until the solution goes clear again.
5. Allow the hot, clear solution to slowly cool to room temperature (or 0 oC using an ice bath, if necessary). If crystallization does not occur, induce crystallization.

6. Collect crystals by vacuum filtration and wash the crystals using a minimal amount of cold solvent.

7. Allow the crystals to dry. \[5-6\]

**Methods Of Crystallization**

**1. Solvent Evaporation:** Prepare a solution of the compound in a suitable solvent. Transfer the solution to a clean crystal growing dish and cover. The covering for the container should not be air tight. Place the container in a quiet out of the way place and let it evaporate. This method works best where there is enough material to saturate at least a few milliliters of solvent.

**2. Solvent Diffusion (Layering Technique):** This method also is good for mg amounts of materials which are sensitive to ambient laboratory conditions (air, moisture). Dissolve the solute in S1 and place in a test tube. Slowly dribble S2 into the tube by syringe so that S1 and S2 form discreet layers. This will be successful if the density of S2 < S1. The narrower the tube, the easier it is to build up the layer. Five millimeter NMR tubes are excellent vessels to use for this crystal growing technique. CH\textsubscript{2}Cl\textsubscript{2}/Et\textsubscript{2}O is a good solvent combination to try this method (if your compound is insoluble in ether).

**3. Sublimation:** The first way is to simply seal a sample under vacuum into a glass tube and placing the tube into an oven for a few days or weeks. Larger crystals tend to grow at the expense of smaller ones. If it doesn't work raise the temperature of the oven or tube furnace can be used. \[7-8\]

**MATERIAL & METHOD**

The bulk drug of olanzapine was procured zyprexa from Sun Pharma Pvt Ltd. and reagent and solvent such as alcohol and acetone used for the study of were analytical grade.

**Preparation Of Calibration Curve**

**Formula for distilled water solution (1000ml)**

50mg of drug was taken in 50ml of volumetric flask to dissolve it. Sonicate it for 15 minutes and makeup the volume up to 50ml with distilled water solution i.e. stock solution (1mg/ml). 10ml of stock solution was diluted up to 100ml with distilled water solution i.e. working stock solution (100μg/ml). The 1-10ml of working stock solution was diluted up to 10ml with distilled water solution to get the 10-100μg/ml concentration of dilutions respectively. The absorbance of all the dilution was measured by UV Spectrophotometer at desired λ\textsubscript{max}. Calibration curve was plotted between concentration and absorbance; correlation coefficient value was determined. \[13\]

**Preparation Of Crystals**

Crystals were prepared by solvent evaporation method. The drug solution (supersaturated) was prepared in a suitable solvent (100%, 90%, 75% &50%) acetone dist water & ethanol. The solution was transferred in a clean petridish and cover. The covering for the container should not be air tight. The container was kept in a quiet place out of the reach and allowed to evaporate. \[14\]

**Characterization Of Drugs And Crystals**

**pH:** Firstly the pH meter was calibrated with buffer solutions at pH 4.0, 7.0 & 9.0. The 10 mg sample was dissolved in 5ml distilled water and then pH electrode was dipped and observed pH of the sample. \[15\]

**Melting Point:** The sample was filled in capillary tube and attached to a thermometer with a thread, then immersed in the thiele tube containing paraffin liquid. The thiel’s tube was heated at the bottom side and the temperature ranges at which the sample melts was observed. During heating, the point at which melting was observed and the
temperature constant is the melting point of the sample.\cite{16}

**Solubility:** Determined by shake flask method. The small amount of the sample was dissolved in the minimum amount of suitable solvent, then store for 3days in incubator. After 3days the minimum amount of solution was withdrawn and diluted, then absorbance was taken by UV Spectrophotometer at specific absorbance maxima of the drug.\cite{17}

**Dissolution:** The dissolution studies were carried out by using Paddle apparatus USP Type-2 dissolution apparatus. Dissolution was performed in 50mg of sample and 450ml of 0.1N HCl solution at 75rpm and a temperature 37±0.5°C. 5ml solution were withdrawn at 15minutes intervals and then replaced with 5ml fresh 0.1N HCl solution and then withdrawn solutions were diluted, then absorbance was taken by UV Spectrophotometer at specific absorbance maxima of the drug.\cite{18}

**Dissociation Constant:** Determination of dissociation constant 10 ml of 0.5% w/v solution of drug in solvent (in which the drug is soluble like methanol) was pipette out to a flask. This was then titrate against 0.5N (HCl/NaOH according to the nature of drug) using methyl red as indicator to completed against standard 0.5N (HCl/NaOH) solution to 50% neutralization point pH of this half neutralized solution is recorded.\cite{19}

**Quetiapine Crystals**

*Figure 1.1 - crystals of quetiapine in 100% distilled water*

*Figure 1.2 - crystals of quetiapine in 100% ethanol*
Figure 1.3 – crystals of quetiapine in 90% ethanol

Figure 1.4 crystals of quetiapine in 75% ethanol

Figure 1.5 - crystals of quetiapine in 50% ethanol
Figure 2 - calibration curve of quetiapine

Quetiapine stock solution was prepared in distilled water, which was scanned from 200-400nm. λmax was obtained at 288nm. Concentrations varying from 10µg/ml - 100µg/ml solution were prepared as described for which absorbance readings were taken at 247nm. The same is presented in figure no. 2 which give \( R^2 = 0.999 \) with equation \( y = 0.021X + 0.368 \).

Table 1 – pH & Dissociation Constant of quetiapine & its recrystallized Crystals

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Drug/crystal</th>
<th>pH</th>
<th>Dissociation Constant (PKa value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Quetiapine</td>
<td>4.70</td>
<td>12.02</td>
</tr>
<tr>
<td>2.</td>
<td>Quetiapine Crystals in distill water 100%</td>
<td>5.30</td>
<td>11.02</td>
</tr>
<tr>
<td>3.</td>
<td>Crystals in ethanol 100%</td>
<td>5.00</td>
<td>11.00</td>
</tr>
<tr>
<td>4.</td>
<td>Crystals in ethanol 90%</td>
<td>5.30</td>
<td>10.05</td>
</tr>
<tr>
<td>5.</td>
<td>Crystals in ethanol 75%</td>
<td>5.20</td>
<td>09.05</td>
</tr>
<tr>
<td>6.</td>
<td>Crystals in ethanol 50%</td>
<td>4.80</td>
<td>08.06</td>
</tr>
</tbody>
</table>

The above table shows the pH of the drug & their crystals of quetiapine the pH of recrystallized crystals increased from 4.70 to maximum of 5.30 pH, When recrystallized in ethanol 100%. The increase was nearly constant as the amount of water was added. With 90% ethanol pH was 5.00, 75% pH was 5.30, 50% & with pH was5.20. The above table shows the pka value of the drug & their crystal the pka value of recrystallized crystals varied from 12.05 to maximum of 10.05 pka value. The decrease was gradually minimized as the amount of water in recrystallizing solvent was increased. With 90% ethanol pka value was 10.05, 75% pka value was 09.05, 50% 08.06 & distilled water dissociation constant was 11.02.
The melting point of quetiapine was in the range 173º-177ºC the melting point of recrystallized crystals in distilled water exhibited lower ranges. On crystallization from alcohol & with dilution of alcohol marginal decrease in melting point was observed than that of control.

The above graph shows in $t_{20} = 25\%$, $t_{40} = 25\%$, $t_{120} = 28\%$. After initial 25% release graph shows nearly constant release till the end of dissolution till 140min.
The above graph shows in $t_20 = 13\%$, $t_40 = 16\%$, $t_{120} = 40\%$. The graph shows nearly constant till 60 min then step increase to 100 min. The after 100 min it shows constant release.

**DISCUSSION**

Crystallization in pharmaceuticals offer modification of active ingredients to more desired forms with improve pharmaceutical parameters like change in habits and preparation of a metastable polymorphs for more better therapeutics.\(^{(11)}\) In cases certain polymorphs can be added which again change the pharmaceutical parameters and converse them into more preferred way. Characterization of these polymorphs is one of the most important criteria to be followed for properly identifying at difference and the similarities between the commercial active pharmaceutical ingredients.\(^{(12)}\) The supersaturation kinetics as well as the crystallization procedure plays the key role in procuring the desired type of crystal, even slight changes in supersaturation protocol can alter many other physicochemical properties of the drug materials.\(^{(9)}\)\(^{(10)}\)\(^{(8)}\) Recrystallization of quetiapine was prepared from 100%, 90%, 75% & 50% ethanol & distilled water. The formation of crystalline structure in 75% ethanol is smaller in size where as in 50% ethanol shape was changed as compared to their 100%, 90%, & 75% ethanol crystals. Quetiapine exhibited appreciable increased in pH around (2-12%) in distilled water and it also exhibit appreciable increase in pH around (6-12%) 100%, 90%, 75% & 50% ethanol. The increase in pH probably indicates involvent of hydrogen atom in formation of crystalline structure thereby increasing the pH of the system towards alkine nature. Similar changes their observed in melting point that is the decrease in melting point when compared to the control drugs. Decrease in melting point probably indicates formation of weaker bonds / lattice structure during recrystallization. Quetiapine exhibits decrease increase in dissociation constant value around (12.05-10.05%) in 100%, 90%, 75% & 50% ethanol & distilled water.

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