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Enhancement of Solubility and Dissolution of Olanzapine by Recrystallization

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ABSTRACT

Olanzapine, 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 Olanzapine through the re-crystallization method by solvent evaporation technique using acetone. The prepared formulation containing different ratios of a drug was evaluated for solubility and *in vitro* dissolution. The prepared formulations were characterized by UV method. The dissolution profile of the prepared crystals was compared with its physical mixture and pure sample. In the presented investigation olanzapine exhibited appreciable decrease in pH (8.5-7.6) recrystallized in 100%, 90%, 75% & 50% acetone. The formation of the crystalline structure is smaller in size as compared to 100%, 90%, & 75% acetone. The decrease in pH indicates. The environment of more hydrogen atom during recrystallization stage Olanzapine exhibits an increase in dissociation constant value around (10-12.05%) in 100%, 90%, 75% & 50% acetone. The dissolution kinetics of olanzapine decreased with the addition of water in a recrystallizing solvent. The study indicates the crystalline solvent plays an important role in designing of physiochemical properties of the drug.

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 the gas; see thin-film deposition and epitaxy.) [1]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. [2]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 [3]. 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 filters 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 0ºC using an ice bath if necessary1. 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. [4]

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 the 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 filters 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 0ºC 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 airtight. 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.

3. 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 discrete 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_2Cl_2/Et_2O 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 to raise the temperature of the oven or tube furnace can be used. [7-8]

MATERIALS AND METHODS:

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 were analytical grades.

PREPARATION OF CALIBRATION CURVE

The formula for distilled water solution (1000ml)

50mg of a drug was taken in 50ml of volumetric flask to dissolve it. Sonicate it for 15minutes and make up the volume up to 50ml with distilled water solution i.e. stock solution (1mg/ml). 10ml of the 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 a 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 λmax. A calibration curve was plotted between concentration and absorbance; correlation coefficient value was determined. [13]

PREPARATION OF CRYSTALS

Crystals were prepared by a 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 Petri dish and cover. The covering for the container should not be airtight. 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 the pH electrode was dipped and observed pH of the sample. [15]

MELTING POINT: The sample was filled in a capillary tube and attached to a thermometer with a thread, then immersed in the Thiele tube containing paraffin liquid. The Thiele 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. [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 the 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.[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 HCI solution at 75rpm and a temperature 37+0.5ºC. The 5ml solution was 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. The % drug release was calculated. [18]

DISSOCIATION CONSTANT: Determination of dissociation constant 10 ml of 0.5% w/v solution of drug in a solvent (in which the drug is soluble like methanol) was pipette out to a flask. This was then titrated against 0.5N (HCL/NaOH according to the nature of drug) using methyl red as an indicator to completed against standard 0.5N (HCL/NaOH) solution to 50% neutralization point pH of this half neutralized solution is recorded. [19]

RESULTS AND DISCUSSION:

RESULTS:

OLANZAPINE CRYSTALS

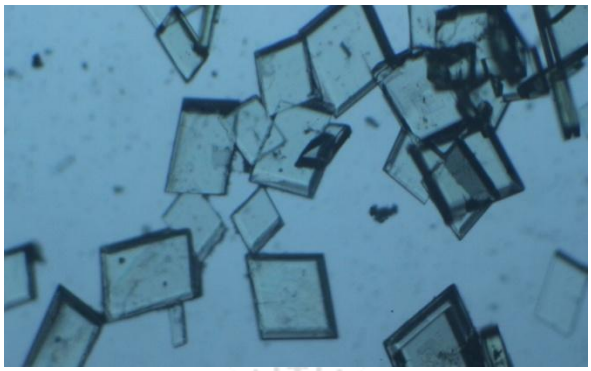

Figure 1: Crystals (100% Acetone) of Drugs (Prepared in Petri Dish)

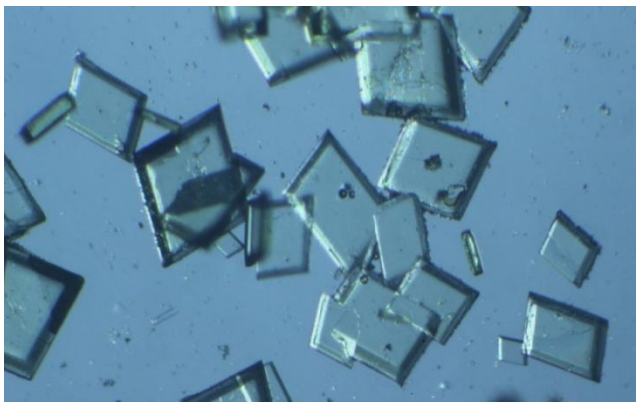

Figure 2: Crystals (90% Acetone) of Drugs (Prepared in Petri Dish)

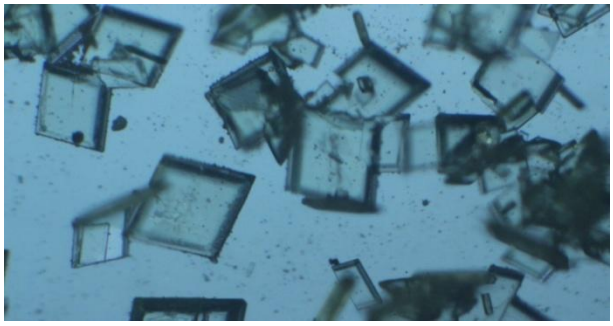

Figure 3: Crystals (75% Acetone) of Drugs (Prepared in Petri Dish)

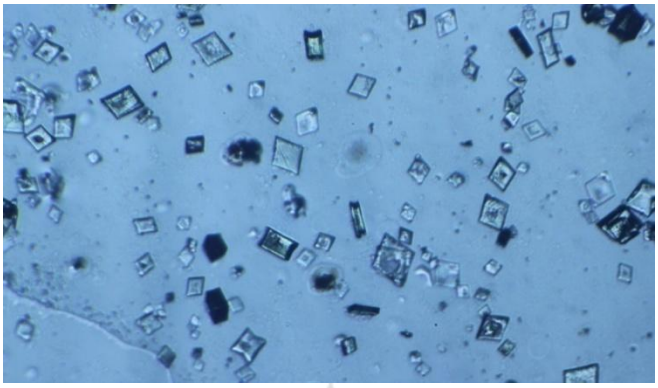

Figure 4: Crystals (50% Acetone) of Drugs (Prepared in Petri Dish)

CALIBRATION CURVE OF OLANZAPINE

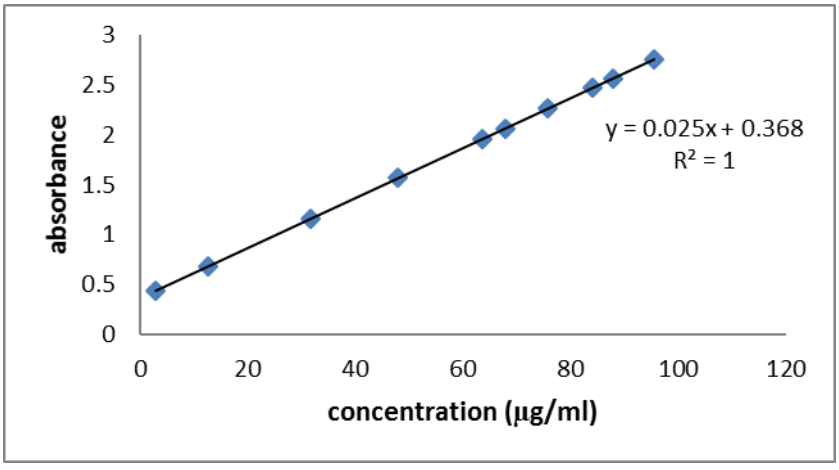

Figure 5: Calibration curve of olanzapine drug

Olanzapine stock solution was prepared in distilled water, which was scanned from 200-400nm. λ max was obtained at 247nm. Concentration varying from 10µg/ml - 100µg/ml solution was prepared as described in 5.1 for which absorbance readings were taken at

247nm. The same is presented in fig no. 6., which give R^2 = 1 with equation y = 0.025X + 0.368

pH and Dissociation Constant of Drug & Recrystallized Crystals

Table 1: pH % dissociation constant of drug and recrystallized crystal

	DISSOCIATION CONSTANT (PKa value)
OLANZAPINE	11
Crystal(100%)	12.05
Crystal(90%)	10.02
Crystal(75%)	12.03
Crystal(50%)	11.02

	p pH Pp
OLANZAPINE	8.50
Crystal (100%)	7.03
(90%)	7.70
(75%)	7.30
(50%)	7.60

The above table no: 1 shows the pH of the drug & their crystals of olanzapine the pH of recrystallized crystals decreased from 8.5 to maximum of 7.03 pH When recrystallized crystals in acetone 100 %. The decrease was gradually minimized as the amount of water was added. With 90% acetone pH was 7.70, 75% pH was 7.30 & with 50% pH was7.60.

The above table no: 1 shows the pka value of the drug & their crystal the pka value of recrystallized crystals varied from 10.02 to maximum of 12.05 pka value. The increase was gradually minimized as the amount of water was increased with 90% acetone pka value was 10.02, 75% pka value was 12.03 & with 50% dissociation constant was 11.02

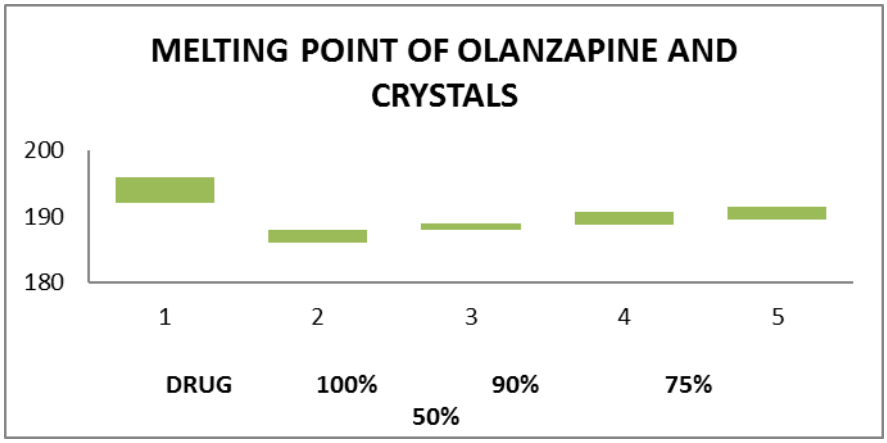

Figure 6: Melting point of olanzapine and crystals

The melting point of olanzapine was in the range 192º-196ºC the melting point of recrystallized crystals exhibited lower ranges. Recrystallized crystals show melting point 186º-188ºC linearly 3% lower than control. On addition of water to recrystallizing solvent linear increase in melting point was observed but still the melting point was lower than the commercial drug. Recrystallized crystals from 50% acetone yielded exhibited melting point of 189º-191ºC which was around 1.5% lower than control.

DISSOLUTION:

Dissolution of drug & recrystallized crystals.

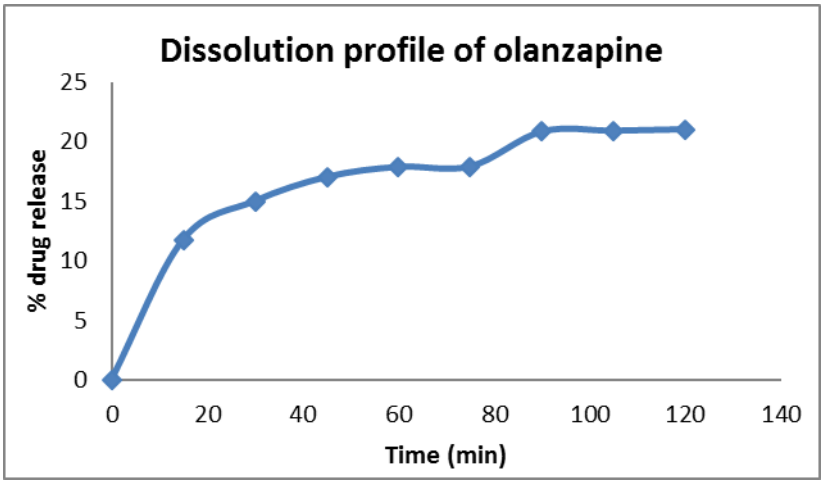

Figure 7: Dissolution profile of olanzapine

The above graph fig no: 7 shows in t_{20} = 12%, t_{40} = 15%, t_{120} = 20%. Drug release with time which was nearly constant after 100 min.

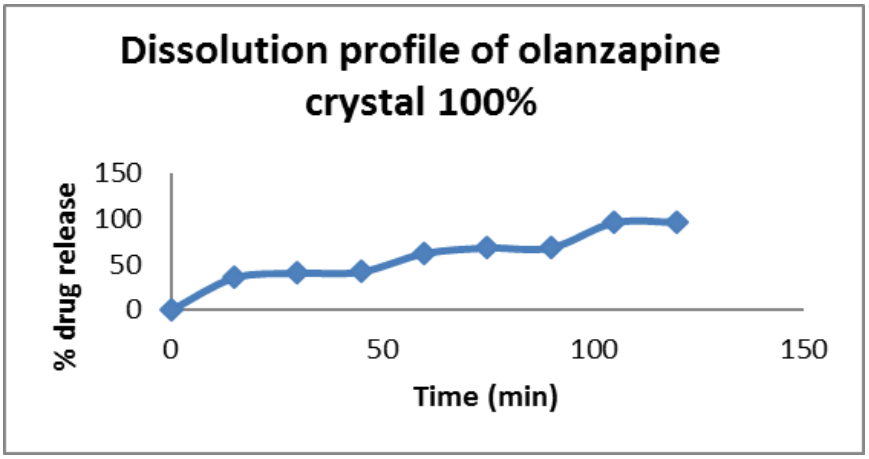

Figure 8: Dissolution profile of olanzapine crystal 100%

The drug release pattern from recrystallized olanzapine crystals from 100% acetone exhibited an initial 40% release at t_{20} which after 20 min again showed 40% release and again after 20 min 40% release till t_{120} min

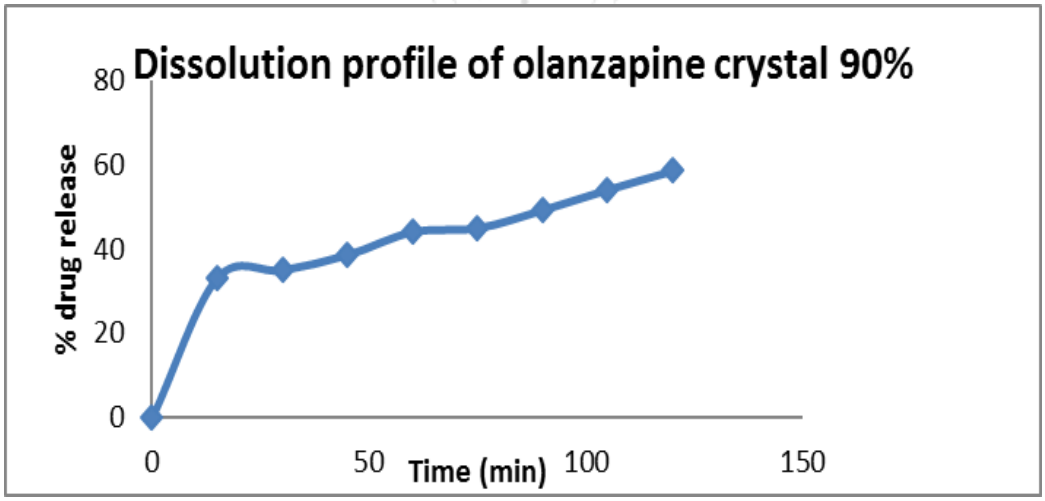

Figure 9: Dissolution profile of olanzapine crystal 90%

The above graph fig no: 9 shows in t_{20} = 35%, t_{40} = 38%, t_{120} = 60%. The graph shows the linearly increased in the dissolution profile of olanzapine after 20min.

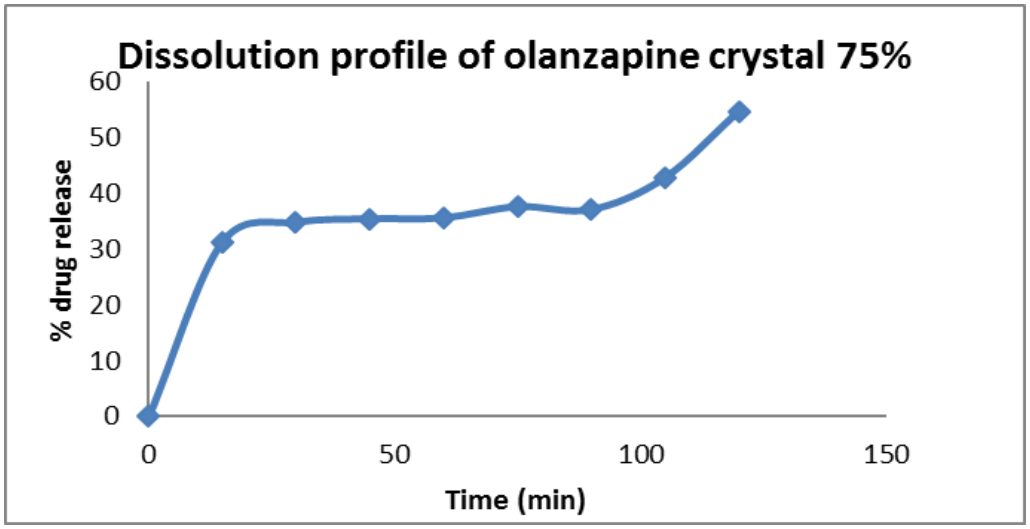

Figure 10: Dissolution profile of olanzapine crystal 75%

The above graph fig no: 10 shows in t_{20} = 30%, t_{40} = 35%, t_{120} = 55%. The graph shows the constant released till 100min then rapid increase was observed after 100min.

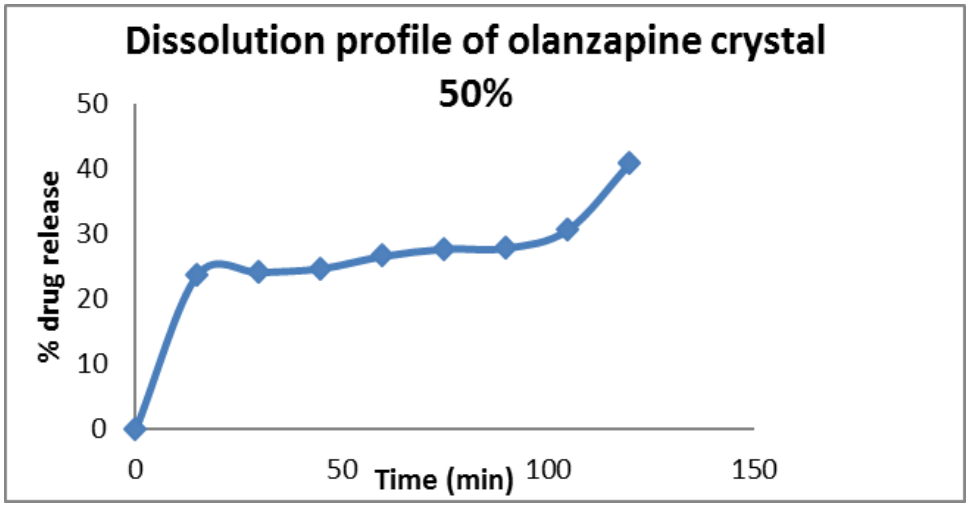

Figure 11: Dissolution profile of olanzapine crystal 50%20min

The above graph fig no: 11 shows in t_{20} = 25%, t_{40} = 25%, t_{120} = 40%. The graph shows nearly constant till 100min then rapidly increase after 100min.

DISCUSSION:

Crystallization in pharmaceuticals offers a modification of active ingredients to more desired forms by improving pharmaceutical parameters like the change in habits and preparation of metastable polymorphs for better therapeutics. [(11)] In cases, certain polymorphs can be added

which again change the pharmaceutical parameters and converse them into the more preferred way. Characterization of these polymorphs is one of the most important criteria to be followed for properly identifying at the 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 olanzapine was prepared from 100%, 90%, 75% & 50% acetone in Petri dishes. The formation of the crystalline structure is smaller in size as compared to 100%, 90%, & 75% acetone. In the presented investigation olanzapine exhibited appreciable decrease in pH (8.5-7.6) recrystallized in 100%, 90%, 75% & 50% acetone. Which was around 9 -17% in various cases. The decrease in pH indicates. The environment of more hydrogen atom during recrystallization stage Olanzapine exhibits an increase in dissociation constant value around (10-12.05%) in 100%, 90%, 75% & 50% acetone.

CONCLUSIONS:

The study indicates the recrystalline solvent plays & importance role in designing of physiochemical properties of the drug. The dissolution kinetics of olanzapine decreased with the addition of water in a recrystallizing solvent.

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