FORMULATION AND EVALUATION OF SOLID DISPERSION OF TADALAFIL

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RESEARCH ARTICLE

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ABSTRACT

Tadalafil is used for the treatment of the erectile dysfunction (ED) and pulmonary arterial hypertension. It is having low aqueous solubility thus it shows poor bioavailability of about 28% by after oral administration. To improve its solubility and dissolution profile solid dispersions (SDPs) of Tadalafil was prepared by physical mixing and solvent evaporation method using polyvinyl pyrollidone-K30 (PVP-30) as a hydrophilic polymeric carrier in different proportions with respect to drug (drug to polymer ratio 1:1 to 1:5). Drug and polymer compatibility studies were performed using FTIR study. The best suitable ratio and method was selected on the basis of enhanced aqueous solubility of drugs. Further selected SDPs were evaluated for various parameters like DSC analysis, percentage yield, percent drug content, saturation solubility, percent drug dissolution and stability studies. FTIR study indicated no incompatibility between Tadalafil and PVP-K30. SDPs prepared with drug to polymer ratio 1:3 and solvent evaporation method was found to be best as they shown significant increased (up to 10 fold) in aqueous solubility in comparison with that of others. DSC study also suggested the depression in the crystalline nature of Tadalafil. Selected SDPs exhibited good stability up to 3 months at 25 ± 2°C /60 ± 5% RH. Based on the results it can be concluded that, SDPs shown remarkable increase in the aqueous solubility and dissolution of Tadalafil and it may improve oral bioavailability of drug as compared with plain drug.

Keywords: Tadalafil, Solubility, Solid Dispersion (SDP), Bioavailability.

INTRODUCTION

Tadalafil is a potent and selective phosphodiesterase-5 inhibitor used for the treatment of erectile dysfunction and pulmonary arterial hypertension and is approved by the FDA. (1) It is a water insoluble drug and it shows bioavailability of about 28% by oral route. (2) Many chemical approaches can be used for improving dissolution and bioavailability such as salt formation and preparation of a pro-drug. Moreover, these types of approaches have the major disadvantage of performing clinical trials as the resultant product represents a new chemical entity. (3) Whereas, to overcome the difficulties associated with poor water solubility of drugs SDP formulations can also be prepared by mixing drug with a carrier polymer through melting or dissolution in solvents. SDPs are the molecular dispersion of poorly water soluble drugs with hydrophilic polymeric carriers, which promote rapid release and dissolution of drugs. (4) The most commonly used hydrophilic carriers for solid dispersions include PEG, PVP, colloidal silicon dioxide and lipids such as polyglycolized glycerides. (5) SDPs may be prepared by different techniques such as by using organic solvents and by dissolving the active substance in another suitable dissolution medium. Solvent evaporation method includes dissolution of physical mixture of the drug substance and the carrier in a common organic solvent followed by evaporation of the solvent. (6)

MATERIAL AND METHODS

Materials

Tadalafil was obtained as a gift sample from Shagun Pharma, Indore (M.P.). PVP-K30, Ethanol and all other chemicals were purchased from Loba chemicals, Mumbai.

Methods

Determination of λmax of Tadalafil by UV spectroscopy

Absorbance maxima or λmax of Tadalafil was determined by scanning its 100µg/ml solutions in ethanolic distilled water (2:8 ratio) at wavelength range of 200-400nm against blank solution on spectrum mode of double beam UV visible spectrophotometer (UV1800, Shimadzu, Japan). (7)

Preparation of calibration plot of Tadalafil

Calibration curve of Tadalafil was plotted in triplicate by preparing its standard solution in phosphate buffer pH 6.8 separately to obtain various dilutions of 2, 4, 6, 8 & 10µg/ml in standard volumetric flasks. These solutions were scanned in double beam UV visible spectrophotometer (UV1800, Shimadzu, Japan) at 281.5nm against blank and absorbance values were noted. The linear relationship was observed for the range of 2-10µg/ml and correlation coefficient was calculated. (8)

FTIR analysis

FTIR spectrum of Tadalafil, PVP-K30 and physical mixture of Tadalafil with PVP-K30 were separately recorded using FTIR spectrophotometer (FTIR-84008, Shimadzu, Japan) to study the chances of any interaction between drug and polymer. KBr pellets for sampling purposes were prepared by mixing 9mg of above mentioned sample with 300mg of KBr. Prepared samples were scanned over the wavelength range of 4000 to 400cm^{-1} to record the spectrums and were analyzed for compatibility and incompatibility. (9)

PREPARATION OF SDPs

To enhance the aqueous solubility, SDP of Tadalafil was prepared by applying physical mixing and solvent evaporation method using PVP-K30 as hydrophilic polymeric carrier. The best combinations and method was selected on the basis of enhancement in aqueous solubility of drugs and further these were evaluated for various parameters.

Preparation of SDP of drugs by physical mixing

SDP of Tadalafil was prepared by physical mixing method using PVP-K30 as hydrophilic polymeric carrier in ratio (drug: polymer) of 1:1, 1:2, 1:3, 1:4. and 1:5. Accurately weighed amount of Tadalafil and PVP-K30 was mixed in a glass mortar by trituration and then resultant mixture was passed through sieve no. 44. Prepared mixtures were stored in desiccator until used for further studies. (10,11)

Preparation of SDP of drugs by solvent evaporation method

SDP of Tadalafil was prepared by solvent evaporation method using PVP-K30 as hydrophilic polymeric carrier in ratio (drug: polymer) of 1:1, 1:2, 1:3, 1:4 and 1:5. Weighed amount of Tadalafil and PVP-K30 was dissolved in 10ml of ethanol in a beaker to get a clear solution and was further stirred continuously at 40^{0}C until complete solvent gets evaporated to obtain solid mass. Then solid mass was passed through the sieve no. 44 and stored in a desiccator until used for further studies. (11-13)

EVALUATION OF SDPs

Percentage yield

It is calculated to identify the efficiency of the method of preparation. The percentage practical yield of SDP of Tadalafil prepared with solvent evaporation method was determined by using the following equation (13):

Percentage yield = Practical mass (SDP) / Theoretical mass (drug + carrier) × 100

Percent drug content

Accurately weighed quantity of SDP of Tadalafil (equivalent of 10mg of drug) was separately dissolved in ethanol. The solutions were then filtered, diluted suitably and scanned in double beam UV visible spectrophotometer (UV1800, Shimadzu, Japan) at 281.5nm to determine percent drug content using the following equation. (14)

% Drug content = Practical drug content / Theoretical drug content x 100

Determination of saturation solubility

Saturation solubility of SDP of Tadalafil was determined in triplicate using saturation solubility method. Excess amount of SDP was added to 10ml of phosphate buffer pH 6.8 in a glass vials. The content of vials was mixed

vigorously for 30 minutes and further solutions were shaken mechanically to equilibrate. After 72 hours content of each vial was centrifuged for 10 minutes at 2500 rpm. The supernatant of each vial was filtered through 0.45µ membrane filter and then filtrate was diluted suitably with solvent separately. The concentration of Tadalafil was analyzed by double beam UV visible spectrophotometer (UV1800, Shimadzu, Japan) at 281.5nm against blank. (15)

Percent drug dissolution study

Percent drug dissolution study of selected SDP of Tadalafil was performed using USP paddle type apparatus in phosphate buffer pH 6.8 as dissolution medium. SDPs (equivalent to 10 mg of drug) were added to 300 ml of dissolution medium at 37.0 ± 0.5°C and stirred at 50rpm up to 12 minutes. Sample of 5ml was collected at 0, 2, 4, 6, 8, 10 & 12 minutes and equal volume of fresh medium was added to maintain the volume of dissolution medium. Samples were filtered using membrane filter, diluted suitably and analyzed by double beam UV visible spectrophotometer (UV1800, Shimadzu, Japan) at specified wavelength of drugs against blank. (14,16)

Stability study

Stability study for selected SDP of Tadalafil was performed at 25 ± 2°C /60 ± 5% RH for 90 days. Samples were collected on 0, 30, 60 and 90 days and were analyzed on the basis of determination of drug content. (17)

DSC Analysis

To identify the thermal behavior and crystallinity, DSC analysis of the Tadalafil, PVP-K30 and SDP of Tadalafil were separately recorded using a DSC (DSC-60, Shimadzu, Japan) at a heating rate of 10°C/minutes in the range of 3-400°C under inert nitrogen environment at a flow rate of 40ml/minutes. Samples (2-3 mg) were put in aluminum sampling pan against empty aluminum pan as reference standard and DSC Thermograms were recorded and studied. (9)

RESULTS AND DISCUSSION

Determination of λmax of Tadalafil by UV spectroscopy

UV spectrum of Tadalafil presenting the λmax of drug is shown in figure-1 and λmax was found to be at 281.5nm.

Figure 1: UV spectrum of Tadalafil

Preparation of calibration plot of Tadalafil

Calibration plot of Tadalafil in phosphate buffer pH 6.8 indicating the R^2 value is shown in figure-2 and R^2 value was found to be 0.999 which revealed the linearity.

FTIR analysis

FTIR spectrum of Tadalafil, PVP-K30 and physical mixture of Tadalafil and PVP-K30 are shown in figure- 3, 4 & 5 respectively. FTIR spectrums of physical mixture of Tadalafil and PVP-K30 showed the major peaks of both the components (drug and polymer) when compared with that of FTIR spectrum of pure form of the components. There were no incompatibility or interactions found between drug and PVP-K30 in their SDP forms.

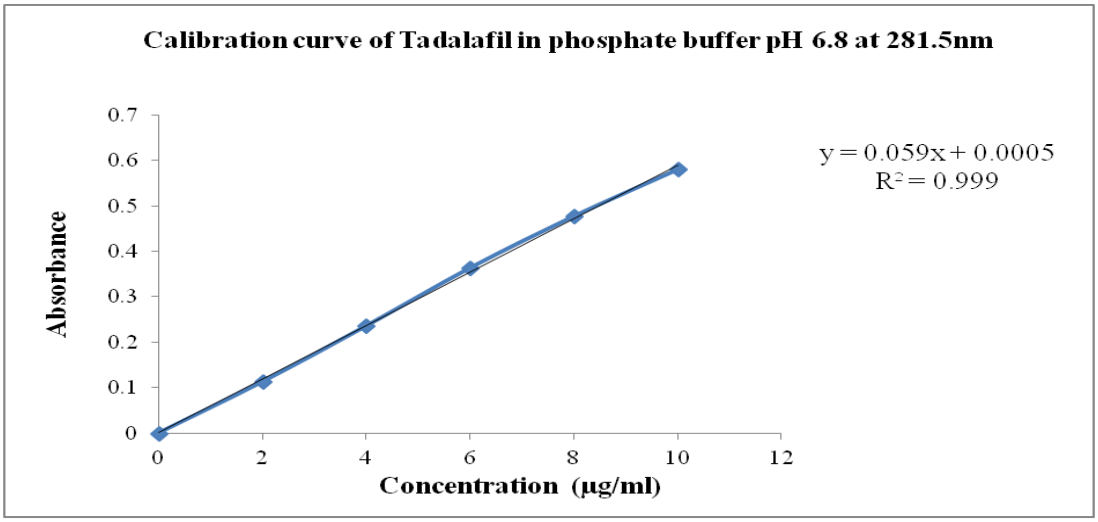

Figure 2: Calibration plot of Tadalafil in phosphate buffer pH 6.8 at 281.5nm

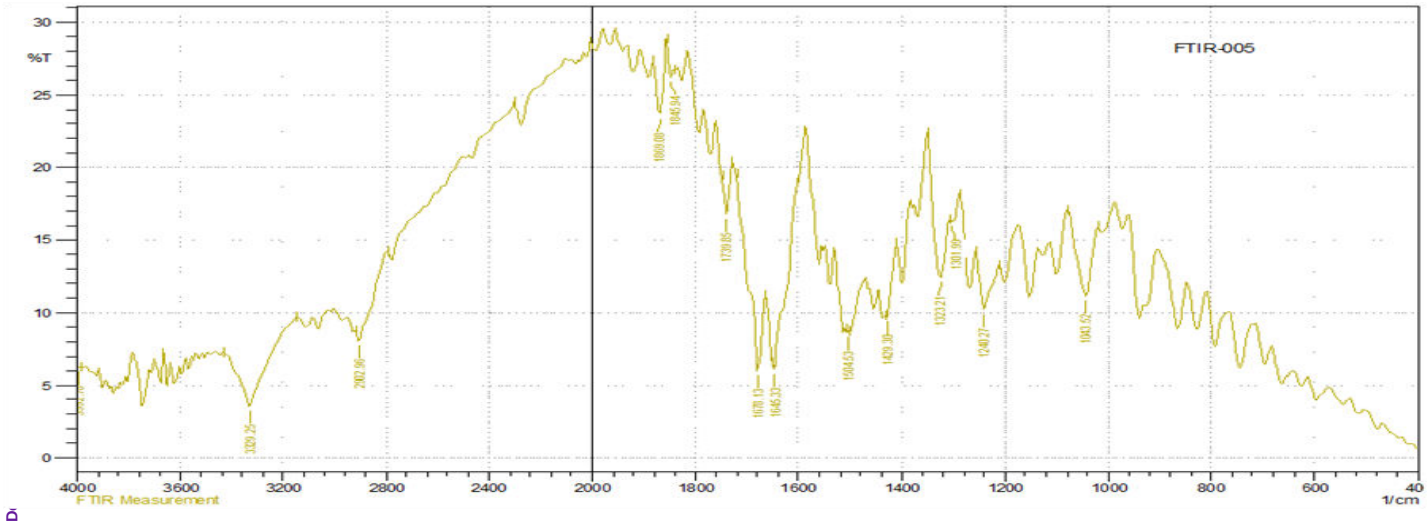

Figure 3: FTIR spectrum of Tadalafil

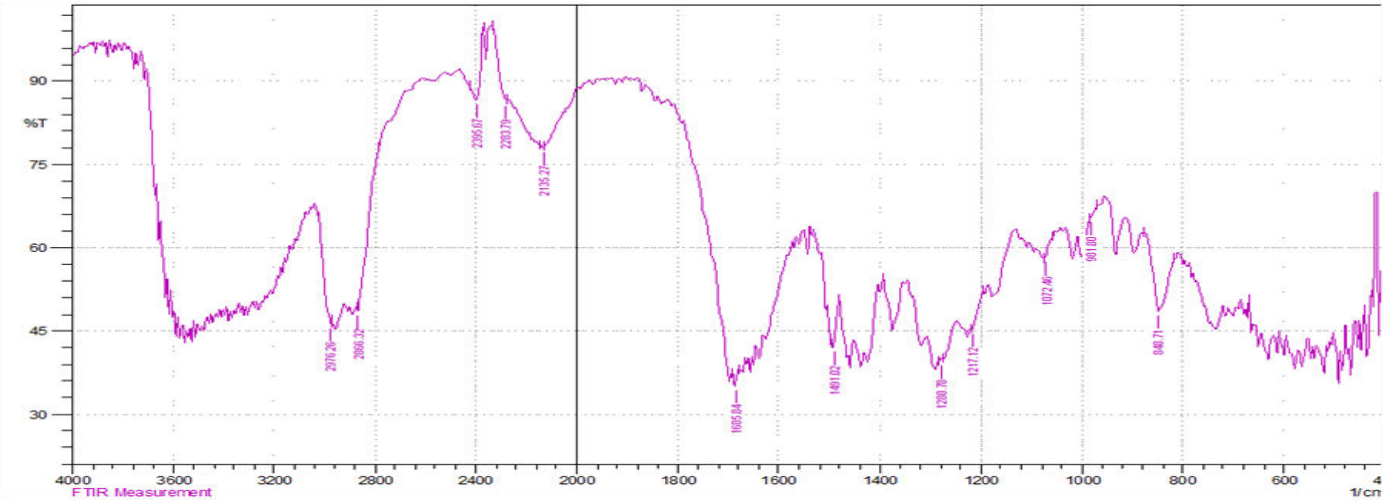

Figure 4: FTIR spectrum of PVP-K30

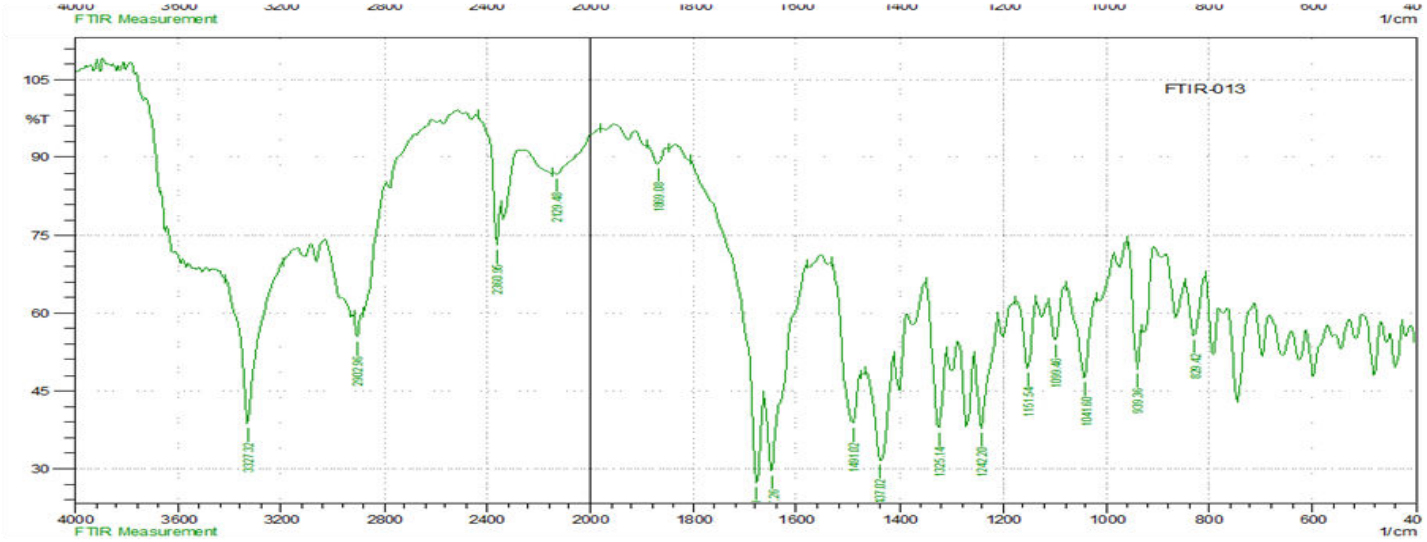

Figure 5: FTIR spectrum of physical mixture of Tadalafil and PVP-K30

Preparation of SDPs

SDPs were prepared successfully with both the methods to find out the best suitable combination in terms of enhancement of aqueous solubility of drugs in comparison with their pure form. Observations of saturation solubility studies of SDPs of Tadalafil are shown in table-1 and table-2 for physical mixing and solvent evaporation method respectively.

Results revealed the maximum increase in the aqueous solubility by both the methods for drug: polymer ratio of 1:3 in comparison with 1:1 & 1:2. Whereas, SDPs had not shown any significant increase in the solubility of Tadalafil on further increasing drug: polymer ratio up to 1:4 and 1:5 in comparison with drug: polymer ratio of 1:3 for both methods.

But, SDPs prepared with solvent evaporation method had shown significant increase in the aqueous solubility as compared with that of SDPs prepared with physical mixing and pure form of Tadalafil. Thus SDPs which were prepared with drug to polymer ratio of 1:3 using solvent evaporation method found to be best and selected for the further studies and characterization.

Table 1: Observation of SDPs prepared by physical mixture (n=6)

S. No.	Drug	Polymer	Drug : Polymer ratio	Solubility in phosphate buffer pH 6.8 (Average mg/ml ± SD)
1	Tadalafil	PVP-K30	1:1	0.142 ± 0.011
2	Tadalafil	PVP-K30	1:2	0.325 ± 0.014
3	Tadalafil	PVP-K30	1:3	0.592 ± 0.018
4	Tadalafil	PVP-K30	1:4	0.594 ± 0.013
5	Tadalafil	PVP-K30	1:5	0.595 ± 0.019

Table 2: Observation of SDPs prepared by solvent evaporation method (n=6)

S. No.	Drug	Polymer	Drug : Polymer ratio	Solubility in Phosphate buffer pH 6.8 (Average mg/ml ± SD)
1	Tadalafil	PVP-K30	1:1	0.161 ± 0.014

2	Tadalafil	PVP-K30	1:2	0.392 ± 0.011
3	Tadalafil	PVP-K30	1:3	0.647 ± 0.017
4	Tadalafil	PVP-K30	1:4	0.649 ± 0.015
5	Tadalafil	PVP-K30	1:5	0.652 ± 0.018

Evaluation of SDP

Data of determination of percentage yield, percentage drug content and saturation solubility of SDPs are shown in table-3. Results of percentage yield showed significantly increased yield with increase in the concentration of polymer up to 1:3 ratio. It revealed more than 98.84 % percentage practical yield for selected SDPs.

Percent drug content of SDP was found to be approximately 98.97 % for selected SDPs.

Results showed significantly increased percent drug content with increase in the concentration of polymer up to 1:3 ratio. It also indicated the uniformity of content among the SDPs of Tadalafil.

Result of saturation solubility study revealed approximately 10 fold increased in the aqueous solubility of Tadalafil in their SDP form up to 1: 3 ratio in comparison with that of pure Tadalafil and it also revealed remarkable decrease in crystallinity of Tadalafil in molecular dispersion form with PVP-K30.

Table 3: Results of evaluation parameters of SDPs (n=6)

S. No.	Tadalafil : PVP-K30 ratio	% Practical Yield (Average % ± SD)	% Drug content (Average % ± SD)	Solubility in phosphate buffer pH 6.8 (mg/ml) ± SD
1	1:1	96.35 ± 1.19	96.41 ± 0.56	0.161 ± 0.014
2	1:2	97.91 ± 1.45	97.13 ± 0.61	0.392 ± 0.011
3	1:3	98.84 ± 1.12	98.97 ± 0.82	0.647 ± 0.017
4	1:4	98.86 ± 1.41	98.98 ± 0.97	0.649 ± 0.015
5	1:5	98.89 ± 1.73	98.98 ± 0.94	0.652 ± 0.018

Percent drug dissolution studies

The percent drug dissolution data of selected SDP of Tadalafil are shown in table-4 and figure-6. Percentage drug dissolution of selected SDP of Tadalafil was found to be 95.96 ± 1.15%. It suggested rapid and almost complete dissolution of Tadalafil up to 12 minutes in their SDP form with PVP-K30.

Table 4: Data of percent dissolution studies of selected SDP of drugs (n=6)

S. No.	Time (minutes)	Percent drug dissolution (Average % ± SD) Tadalafil SDP
1	0	0
2	2	28.57 ± 1.13
3	4	40.13 ± 1.03
4	6	57.34 ± 1.17
5	8	73.92 ± 1.14
6	10	84.45 ± 1.19
7	12	95.96 ± 1.15

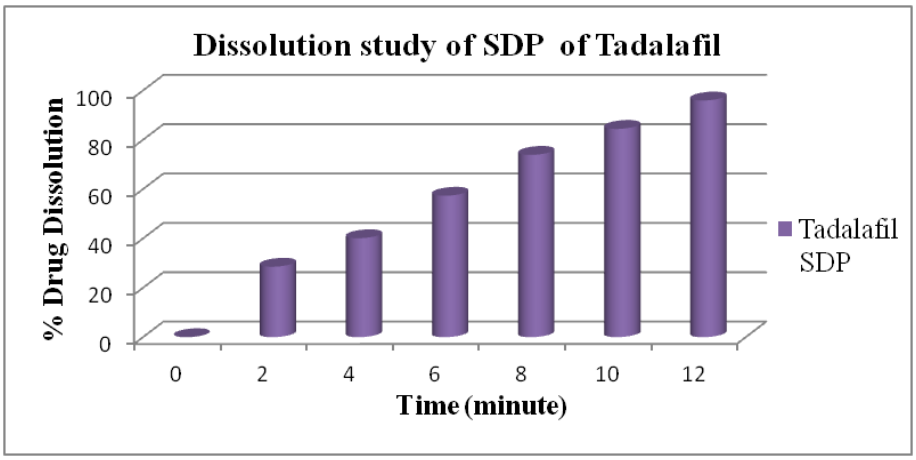

Figure 6: Graphical representation of percent dissolution studies of selected SDP of drugs

Stability study

Stability study data of selected SDP of Tadalafil are shown in Table-5. Based on the results of periodic drug content determination there was no significant signs of instability found up to 90 days of the study for SDPs of Tadalafil and it suggested the good stability of Tadalafil in their SDP form.

Table 5: Data of stability studies of selected SDP of Tadalafil (n=6)

Sampling Time	Percent drug content (Average % ± SD)
Initial	98.97 ± 0.82
After 30 days	98.75 ± 1.09
After 60 days	98.68 ± 1.10
After 90 days	98.61 ± 1.11

DSC analysis

DSC Thermogram of Tadalafil, PVP-K30 and SDP of Tadalafil are shown in figure- 7, 8 & 9 respectively. DSC Thermogram of Tadalafil showed the sharp endothermic peak at 305.20^{0}C indicated the melting point of Tadalafil and the high intensity of peak also suggested its crystalline behavior. DSC Thermogram of PVP-K30 showed the broad endothermic peak at 92.34^{0}C indicated the melting point of PVP-K30 and broader peak suggested its highly amorphous nature. DSC Thermogram of SDP of Tadalafil showed one endothermic peak at 67.75^{0}C and showed the absence of crystalline peak of Tadalafil in comparison with Thermogram of pure Tadalafil. It suggested the reduced crystallinity of drug in the molecular dispersion form with PVP-K30.

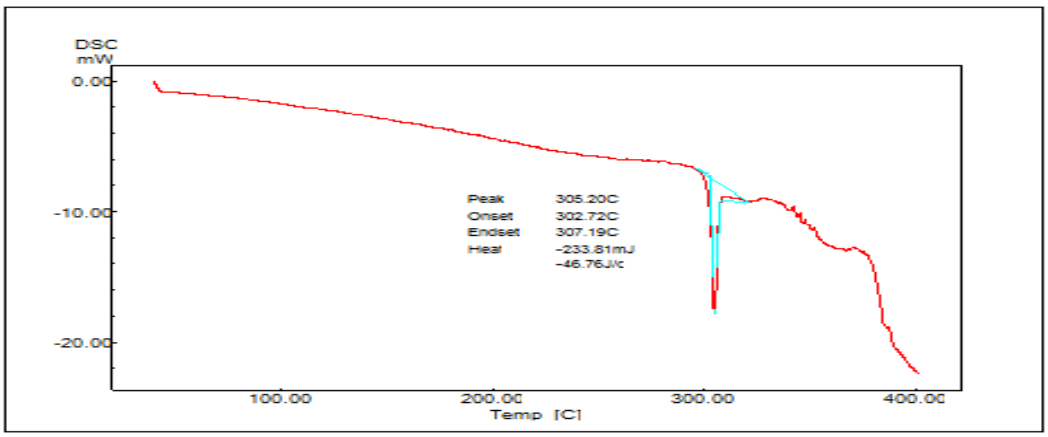

Figure 7: DSC Thermogram of Tadalafil

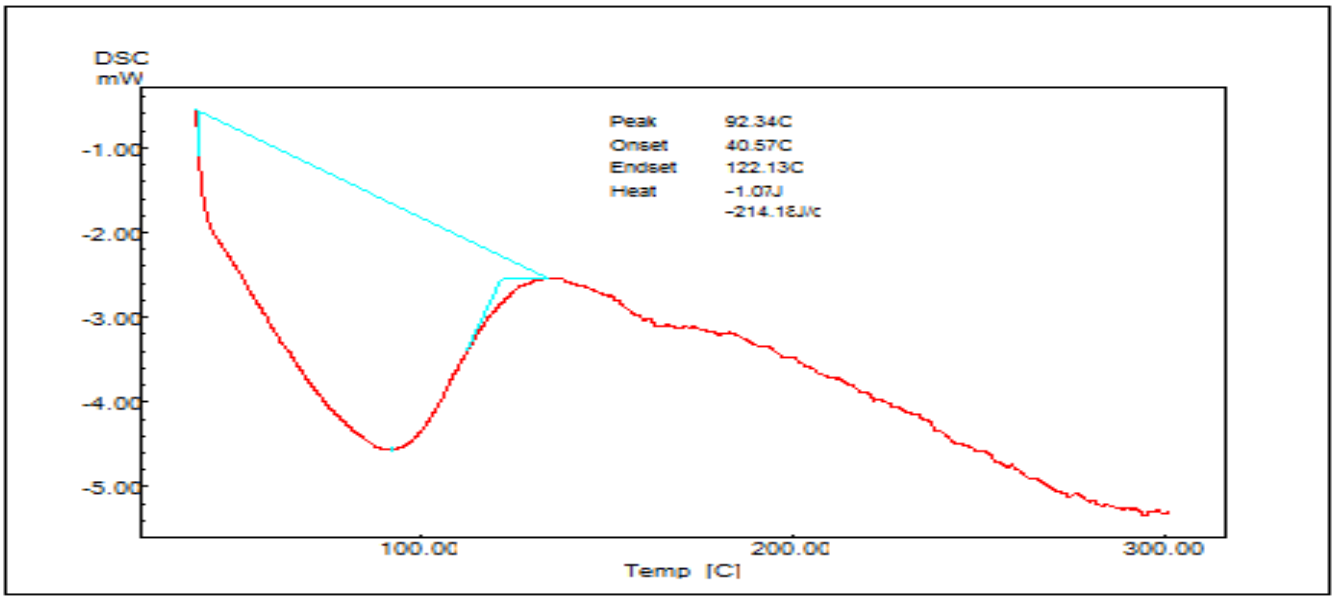

Figure 8: DSC Thermogram of PVP-K30

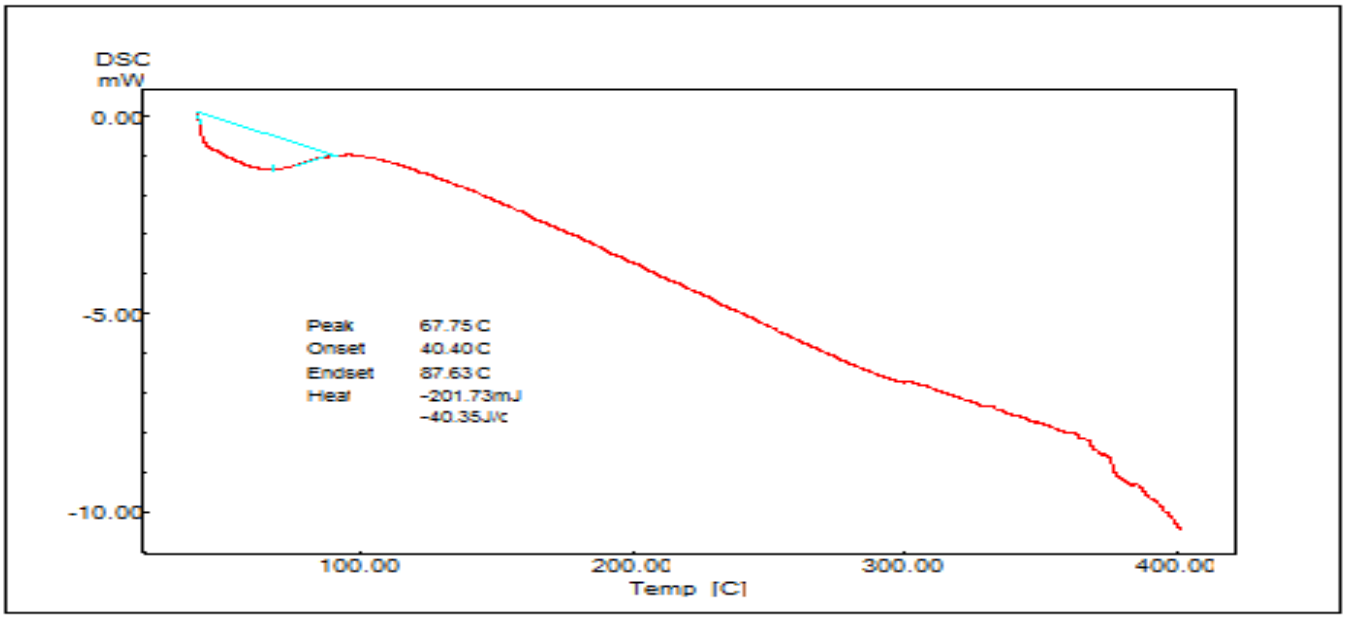

Figure 9: DSC Thermogram of SDP of Tadalafil

CONCLUSION

Best solid dispersion form of Tadalafil was prepared by solvent evaporation method using PVP-K30 up to 1:3 ratio. FTIR study revealed compatibility of Tadalafil with PVP-K30. DSC study also suggested the significant decrease in the crystalline nature of the drug. Moreover, selected SDPs were also found to be stable up to 3 months of the study. Based on the results, it can be concluded that SDPs shown remarkable increase in the aqueous solubility and dissolution of Tadalafil and it may improve oral bioavailability of drug as compared with plain Tadalafil.

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CONFILCTS OF INTEREST

The authors declare that there are no conflicts of interest.

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