IJPSR (2014), Vol. 5, Issue 3 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 27 June, 2013; received in revised form, 26 December, 2013; accepted, 07 February, 2013; published 01 March, 2014

PREPARATION & PHYSICOCHEMICAL CHARACTERIZATION OF POORLY WATER SOLUBLE DRUG BY USING SPRAY DRYING AND SOLVENT EVAPORATION METHODS

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Keywords:

Solid dispersion, Spray drying, Solvent evaporation, PVP K30, Aerosil carrier

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ABSTRACT: Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of hydrophobic drugs. The various preparation techniques for solid dispersion and compiles some of the recent technology transfers. This research article investigates enhancement of the dissolution profile of atorvastatin using solid dispersion with PVP. The article also describes the preparation of fast-dissolving atorvastatin by using water soluble polymer. Polyvinyl pyrrolidone (PVP K-30) was selected and solid dispersions were prepared by the method of spray drying and solvent evaporation. Dissolution studies using the USP paddle method were performed for solid dispersions of atorvastatin. Infrared (IR) spectroscopy, differential scanning calorimetry (DSC), and x-ray diffractometry (XRD) were performed to identify the physicochemical interaction between drug and carrier, hence its effect on dissolution. Dissolution of atorvastatin improved significantly in solid dispersion products. Thus, the solid dispersion technique can be successfully used for improvement of dissolution of atorvastatin.

INTRODUCTION: Most of the new chemical entities (NCE) under development these days are intended to be used as a solid dosage form that originate an effective and reproducible *in vivo* plasma concentration after oral administration [1-3]. In fact, most NCEs are poorly water soluble drugs, not well-absorbed after oral administration [4-5], which can detract from the drug's inherent efficacy [6-8]. Consequently, if these drugs are not completely released in this gastrointestinal area, they will have a low bioavailability [9, 11].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(3).1035-44

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(3).1035-44

Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs [6, 12, 13]. Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. By improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce side effects [9, 12, 14–16].

Solid dispersions are one of the most successful strategies to improve drug release of poorly soluble drugs. These can be defined as molecular mixtures of poorly water soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties. The use of solid dispersion technologies to improve the dissolution, characteristics of poorly water-soluble drugs and in turn their oral bioavailability.

Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water-soluble drugs. Other methods, such as salt formation, complexation with cyclodextrins, solubilization of drugs in solvent(s), and particle size reduction have also been utilized to improve dissolution properties of poorly water-soluble drugs; however, there are substantial limitations with each of these techniques.

On the other hand, formulation of drugs as solid dispersions offers a variety of processing and excipients options that allow for flexibility when formulating oral delivery systems for poorly water soluble drugs. Much of the research that has been reported on solid dispersion technologies involves drugs that are poorly water-soluble and highly permeable to biological membranes as with these drugs dissolution is the rate limiting step to absorption.

The spray dry technique has been an important and widely applied technique in the pharmaceutical and biochemical fields [24, 25].

For fabricating micro-particulate systems, the spray dry can be applicable to both heat resistant and heat sensitive drugs both water soluble and water insoluble drugs. This technique is also applicable to both hydrophilic and hydrophobic polymers. It is a one stage continuous process, which produces dry powders, granules or agglomerates from drug-excipients solutions and/or suspensions. This technique can be adaptable in an industrial scale, which is superior to most of other fabrication procedures being only good for laboratory-scale operation.

Furthermore, the polymeric microsphere drug delivery systems produced by this technology have a potential to provide new types of administered routes, such as oral dosage forms, targeting systems to organs and tissues and long acting parenteral biodegradable systems. The objectives of the present study were therefore, to develop a solid dispersion of atorvastatin by spray drying, using Aerosil 200 as water-soluble solid carrier. The spray dried powders were investigated and correlated to solid state characterization of the powders performed by Scanning Electron Microscope (SEM), Differential Scanning Calorimetry (DSC) and X-ray powder diffraction and *in vitro* dissolution study.

MATERIALS AND METHODS: Atorvastatin was a generous gift from Lupin Pharmaceutical Industries Ltd., (Mumbai, India). PVPK30, aerosol 200, were purchased by Research Fine Pvt. Ltd. (Mumbai, India). All other chemicals and solvents were of analytical grade.

Preparation of Solid Dispersions (SDs): Atorvastatin either alone or in combination with PVP (1:1.1:2 parts by weight) was dissolved in sufficient amount methanol, to clear solution proposed quantity of AEROSIL200 (Table I), was slowly added to obtain uniform suspension.

1. **Spray drying** was carried out using laboratory scale spray dryer (LU-20Advanced Model, Labultima, Mumbai, India), under the following set of conditions: inlet temperature 100^{o}C, outlet temperature, 60^{o}C, feed rate–6 ml/min, atomization air pressure 2kg cm/2)and aspiration pressure (_200 mm WC)

2. **Solvent evaporation** was carried out by; accurately weighed quantity of Atorvastatin was dissolved in completely in a minimum quantity of methanol in to a 100ml round bottom flask. Accurately weighed quantity of hydrophilic polymer was dispersed in a drug solution with shaking; resulted batches are designated. Methanol was allowed evaporate completely under vacuum in rotary evaporator at a constant temperature and speed of 60^{o}C and 80 rpm respectively. Collect the free flowing powder was vacuum dried for 24 hr.

TABLE 1 VARIOUS SOLID DISPERSION BATCHES WITH DIFFERENT RATIOS PREPARED BY SPRAY DRYING & SOLVENT EVAPORATION

Type of formulation	Atorvastatin (mg)	PVP K30 (mg)	Aerosil 200 (mg)
Batch-I	1	2	1
Batch-II	1	4	1
Batch-III	1	6	1

Evaluation of Solid dispersion: Powder is evaluated for the following parameters.

1. **Drug content:** Samples of each complexes were assayed by dissolving weighed amounts (100mg) of phosphate buffer PH 7.4. The solution is filtered, diluted and drug content was determined spectrophotometrically at 246 nm.

2. **Infrared spectroscopy:** Infrared spectroscopy was performed on FTIR. All the complexes prepared by solid dispersion method were analyzed by FTIR. The resulting mixture was analyzed in range 400 to 4000nm was selected.

3. **Crystallographic Investigation:**

   a. **Powder X-ray crystallography:** The powder X-ray diffraction patterns were recorded using an X-ray Diffractometer (pw 1729, Philips, Netherland). The samples were analyzed in the 2θ range of 5 to 60^o. The range and the chart speed were 2×10^3 CPS and 10mm/2θ, respectively.

4. **Differential Scanning Calorimetry (DSC):** A DSC study was carried out using Differential Scanning Calorimeter. Sample was hermetically sealed in aluminum pans and heated at constant rate of 5^0.c/mi over temp range of 40-200̊ c/min .Inert atmosphere was maintained by purging nitrogen gas at flow rate of 20ml/min.

5. **Dissolution Study**: The *in vitro* dissolution behaviors of the solid dispersion prepared by solid dispersion method were compared with those of pure drug. The dissolution rate studies were performed according to USP dissolution apparatus type II. Dissolution study was performed in pH 7.4 phosphate buffer. The solid dispersion was placed in 900ml of dissolution media.

   The stirring speed was 50rpm, and the temperature was maintained at $37^oC\pm0.5^oC$. The samples were withdrawn at 15, 30 and 45 and up to 120 min, and replenished with fresh dissolution media. The samples were filtered and analyzed by spectrophotometer at 246nm.

RESULT AND DISCUSSION:

Evaluation of solid dispersions of atorvastatin:

Percentage drug content of various solid dispersions of Atorvastatin: In the preparation of solid dispersion, hydrophilic polymer (PVP K30), single type of adsorbent (aerosil) was used in different concentration. The drug content of different batches of solid dispersion is shown in table.

TABLE 2: SOLVENT EVAPORATION METHOD

Batch No.	Drug content (%±SD)
BATCH 1	69.24±0.30
BATCH 2	65.29±0.071
BATCH 3	72.40±0.011

TABLE 3: SPRAY DRYING METHOD

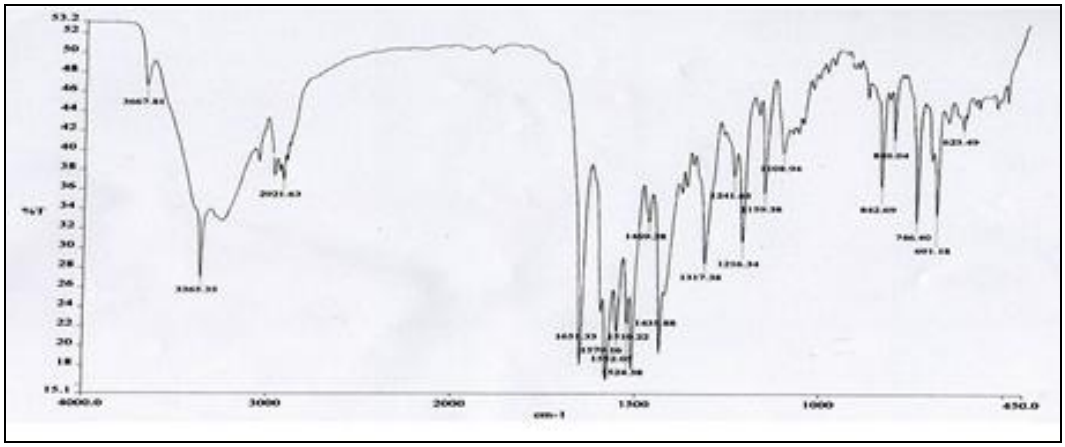
Batch No.	Drug content (%±SD)
BATCH A	85.45±0.43
BATCH B	66.45±0.12
BATCH C	97.86±0.72

In this study, the results showed that the drug content of the solid dispersions of Atorvastatin prepared were up to 97.86 % and 72.40% for spray drying and solvent evaporation method respectively which containing the mainly PVPK-30, due their highly hydrophilic in nature and using porous adsorbent carrier (Aerosil 200).

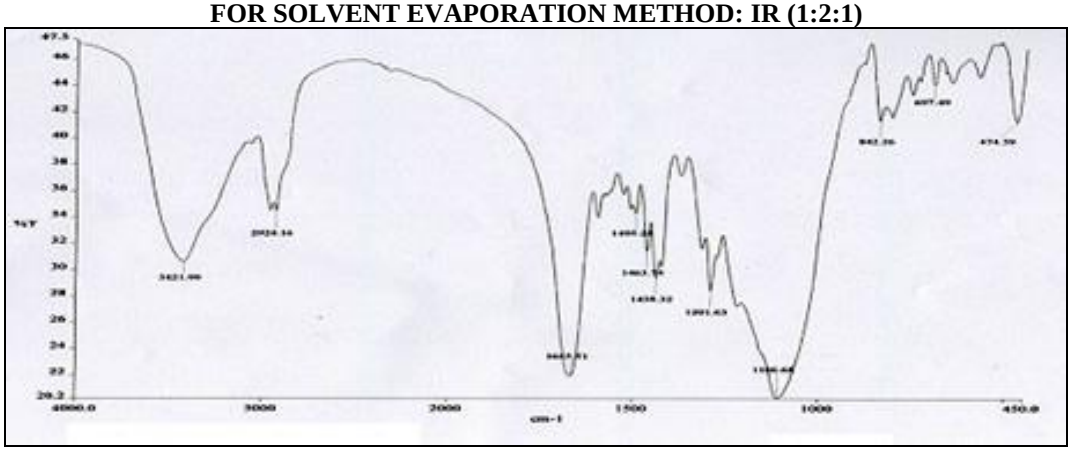
Infra-red Spectroscopy (IR) [1, 4, 11]: The intermolecular interaction of complex system was established by FTIR. IR Spectrum of pure atorvastatin presented characteristics peak of free O-H stretching vibration at -3553 cm^{-1}, C-H stretching vibration at 2921 cm^{-1}. A stretching vibration of carbonyl functional group appeared at wave number 1699 cm^{-1}.

Spray drying showed significant broadening of peaks in the region 1107 cm^{-1} while solvent evaporation shows at 1105 cm^{-1}. It may attribute to intermolecular hydrogen bonding. This solid dispersion methods presented possibility of hydrogen bonding between atorvastatin and PVP due to PVP has two groups =N, =O that can potentially form hydrogen bond with drug.

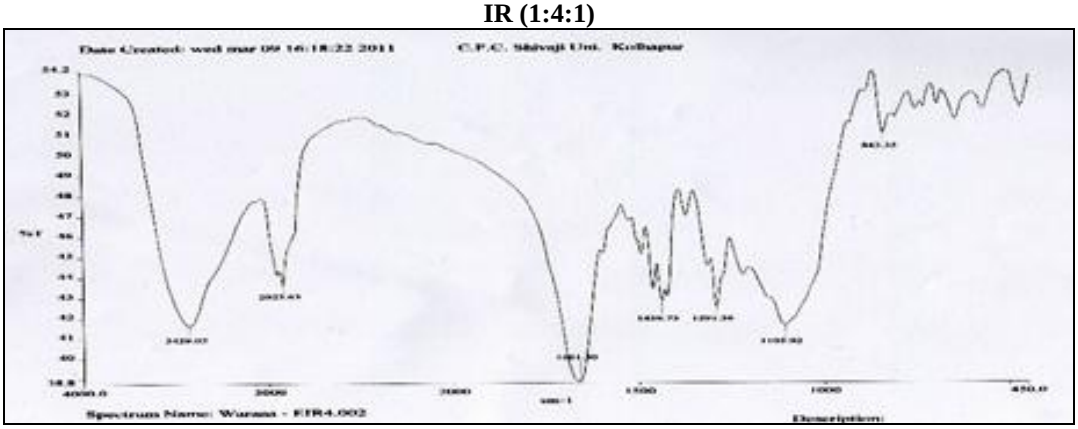
BATCH: PURE DRUG



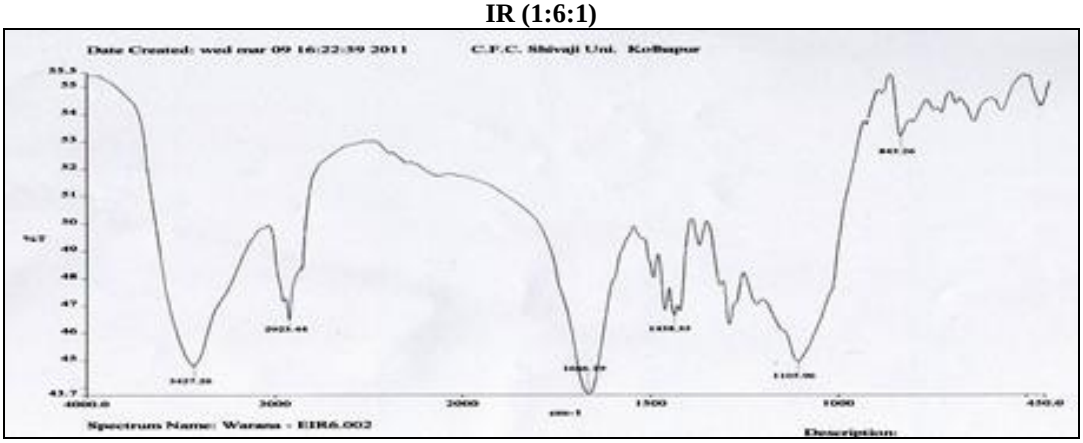
FOR SOLVENT EVAPORATION METHOD: IR (1:2:1)



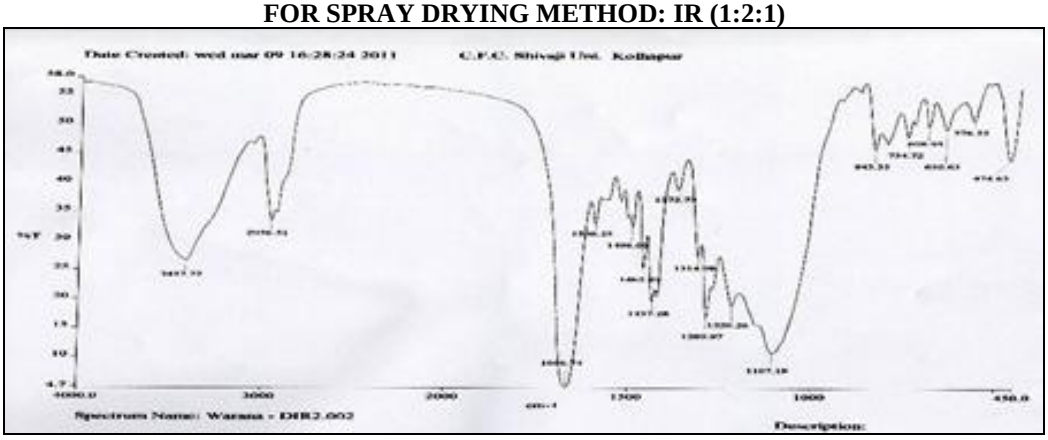
IR (1:4:1)



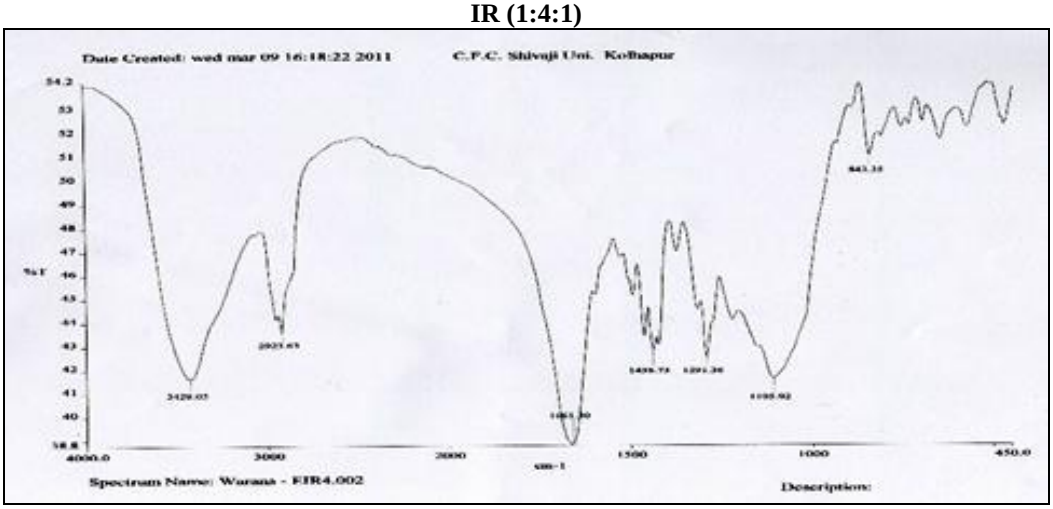
IR (1:6:1)



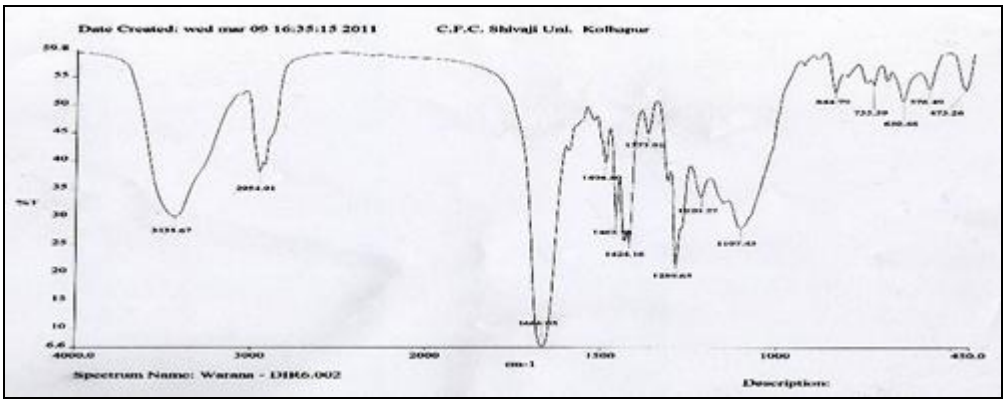
FOR SPRAY DRYING METHOD: IR (1:2:1)



IR (1:4:1)



IR (1:6:1)

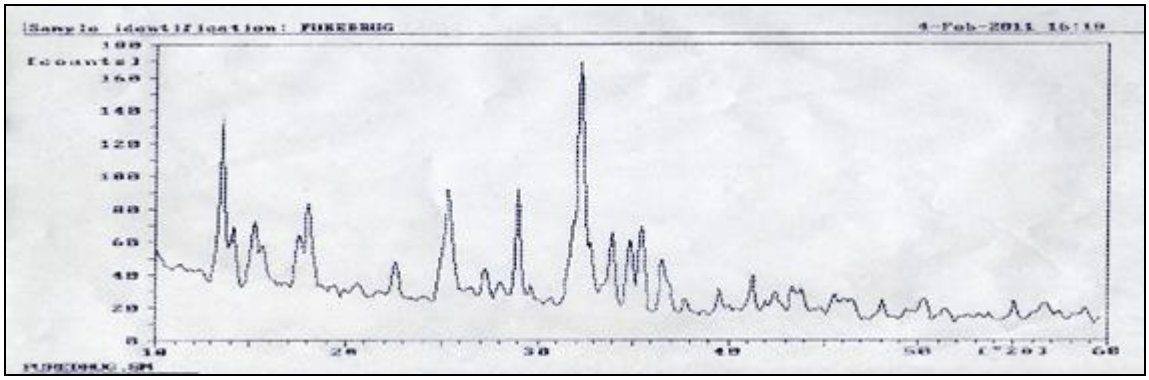


XRD Studies [1, 4, 11, 14]: XRD could be used to study any change in crystalline of drug in amorphous form, which could be of the mechanism responsible for improvement of dissolution. Characteristic sharp peak of atorvastatin were observed when it was in pure form Atorvastatin is present in a crystalline form with characteristic diffraction peak appearing at 2θ are 13.565 to 58.795 etc. When in solid dispersion methods for both solvent evaporation and spray drying technique characteristic peak of drug disappeared with significant elevation of diffractogram on different ratios, characteristics hump of amorphous form was observed. In PVP solid dispersion absence of characteristics peak of drug indicated formation of amorphous with PVP of drug, this because characteristics property of PVP is form amorphous solid to amorphous complex form.

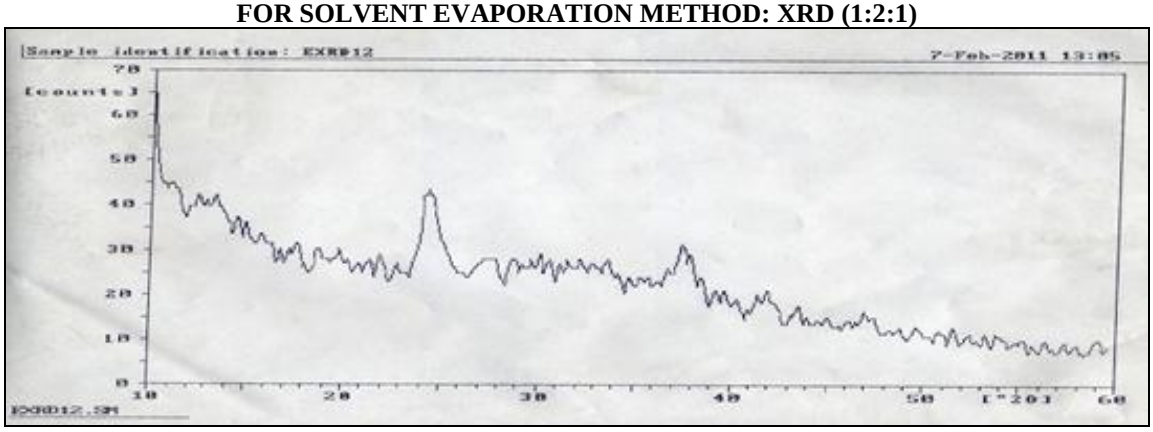
Reduction crystalline may be explained the higher drug release of PVP solid dispersion. Characteristic property of Aerosil is to form amorphous solid

complexes which also influence on reduction of crystalline also in PVP carriers ratio absence of any diffraction peak corresponding to drug indicated that atorvastatin is in amorphous form.

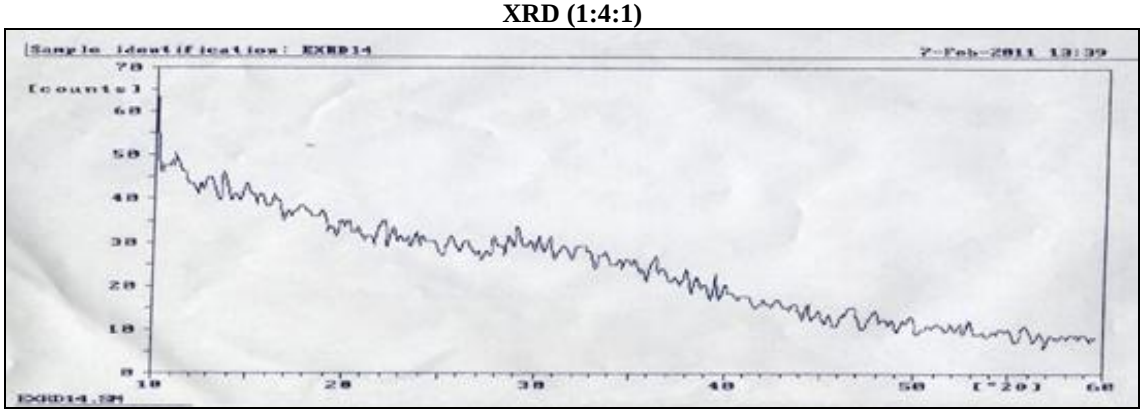
BATCH= PURE DRUG



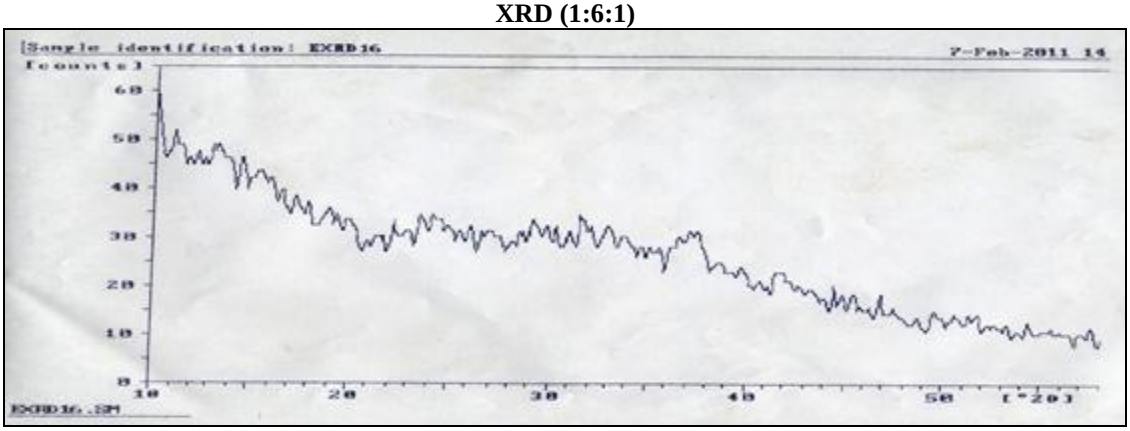
FOR SOLVENT EVAPORATION METHOD: XRD (1:2:1)



XRD (1:4:1)

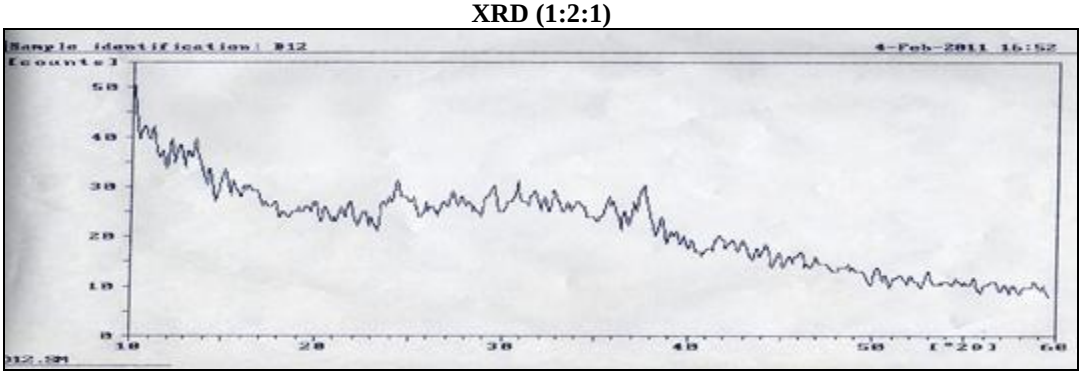


XRD (1:6:1)

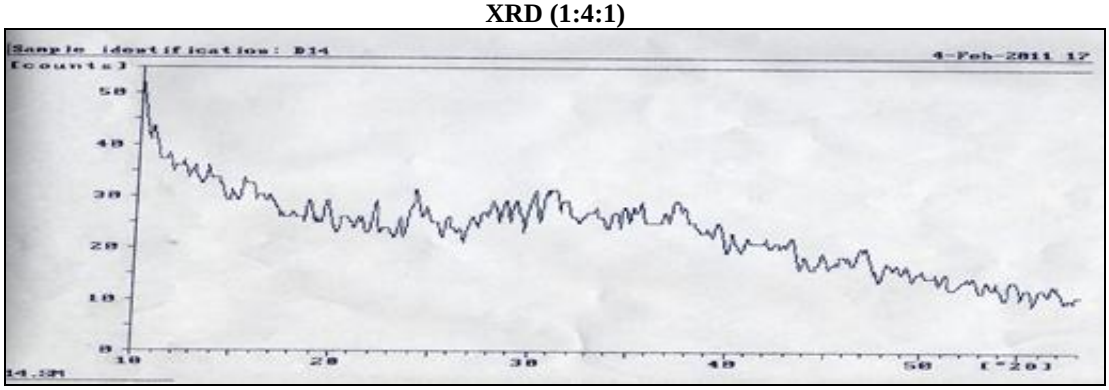


FOR SPRAY DRYING:-

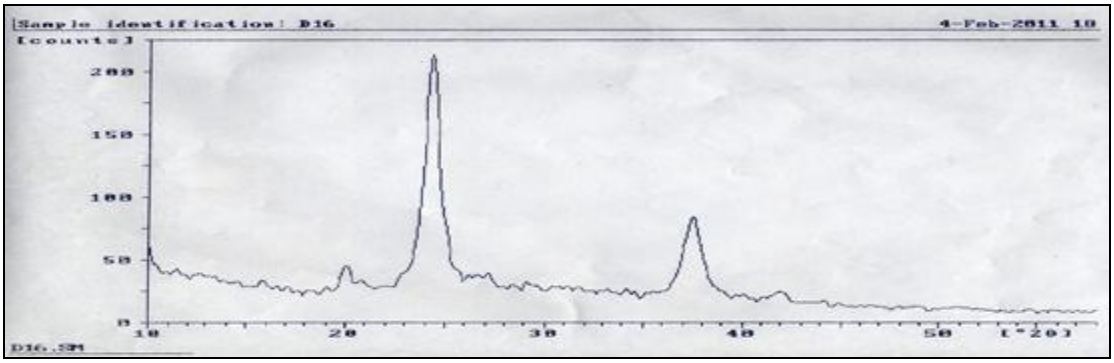
XRD (1:2:1)



XRD (1:4:1)

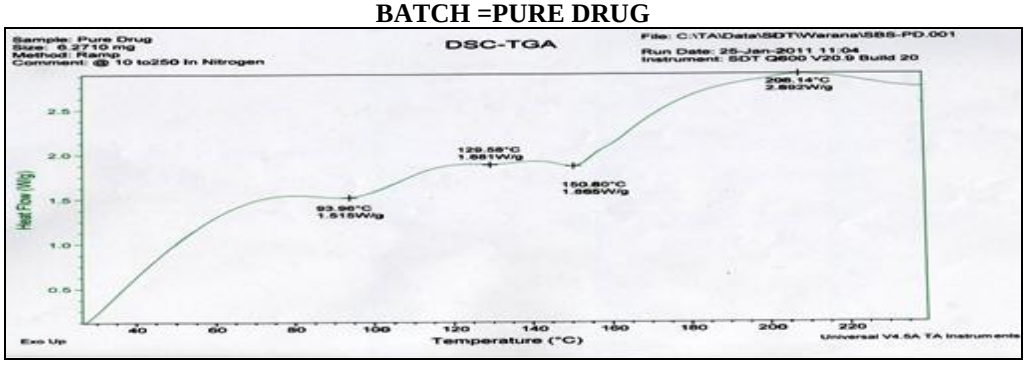


XRD (1:6:1)



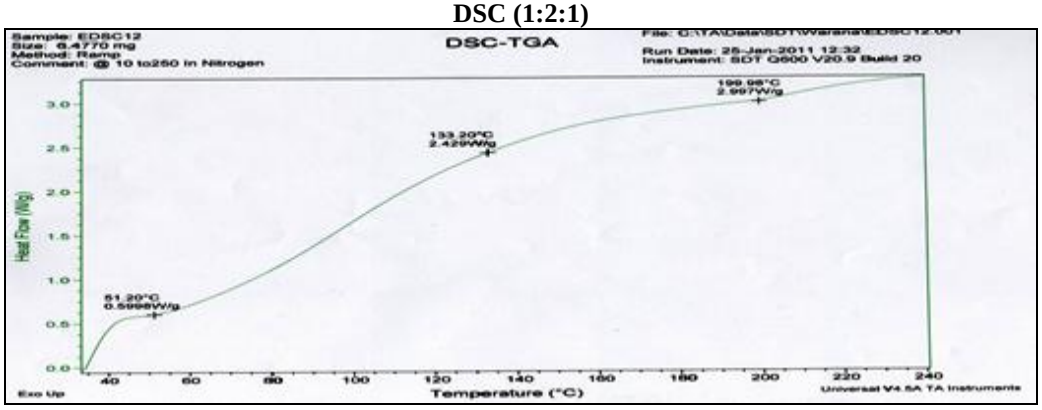
DSC Studies [1, 4, 11, 14]: Pure crystalline atoravastatin was characterized by single sharp peak melting endotherm at 173.7℃during DSC. DSC scan a broad endoderm ranging from 80 to 120℃ was observed, because of the presence of residual moisture in PVP.In solvent evaporated as well as spray dried PVP due to loss of water from PVP and complete absence of drug peak at 173℃.This complete absence atorvastatin peak indicate that atorvastatin present amophous inside the PVP matrix.

BATCH =PURE DRUG

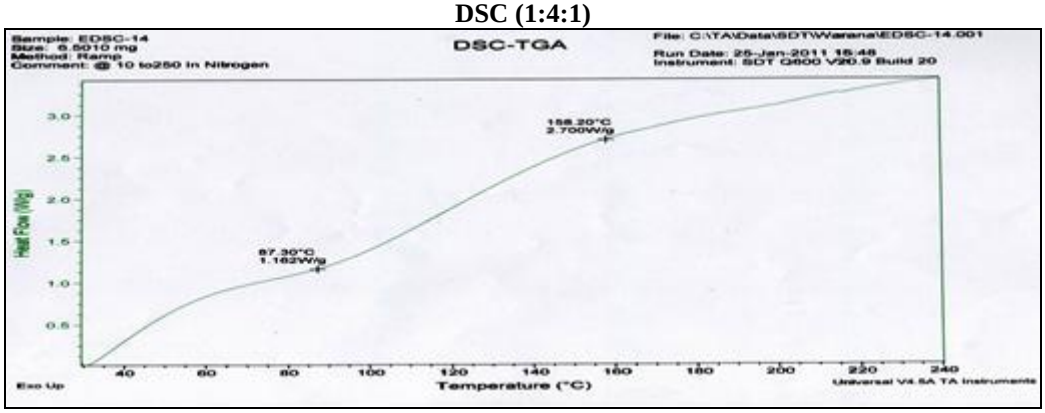


FOR SOLVENT EVAPORATION METHOD:-

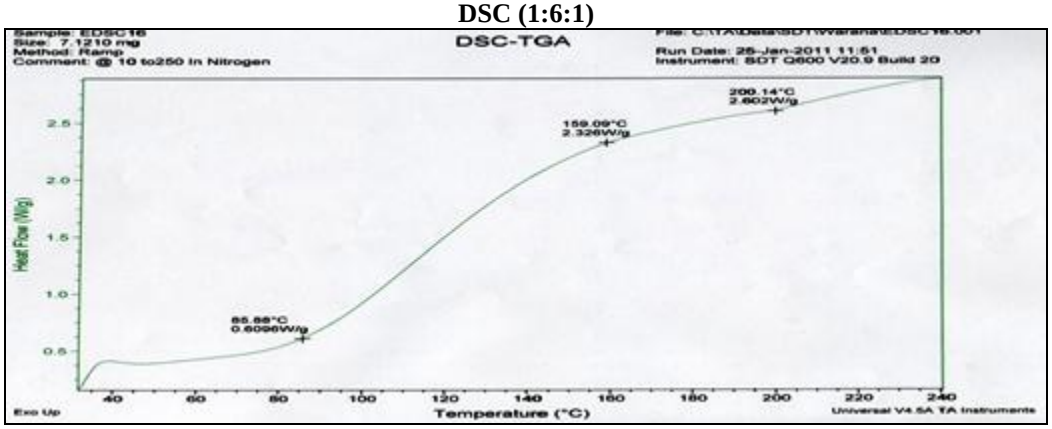
DSC (1:2:1)



DSC (1:4:1)

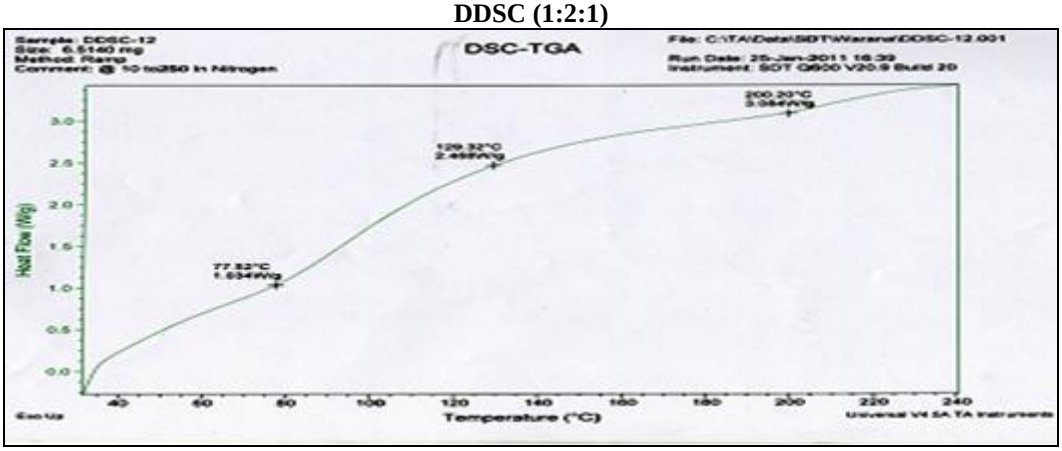


DSC (1:6:1)

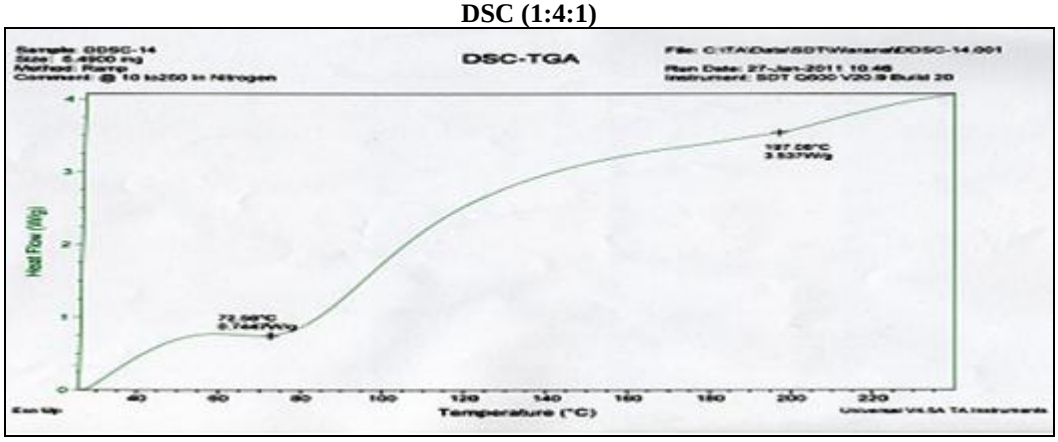


FOR SPRAY DRYING:-

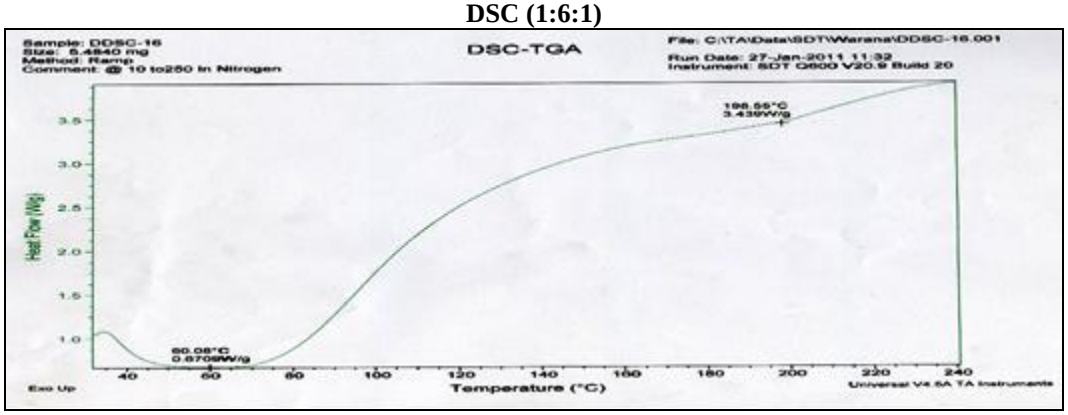
DDSC (1:2:1)



DSC (1:4:1)



DSC (1:6:1)



Dissolution studies:

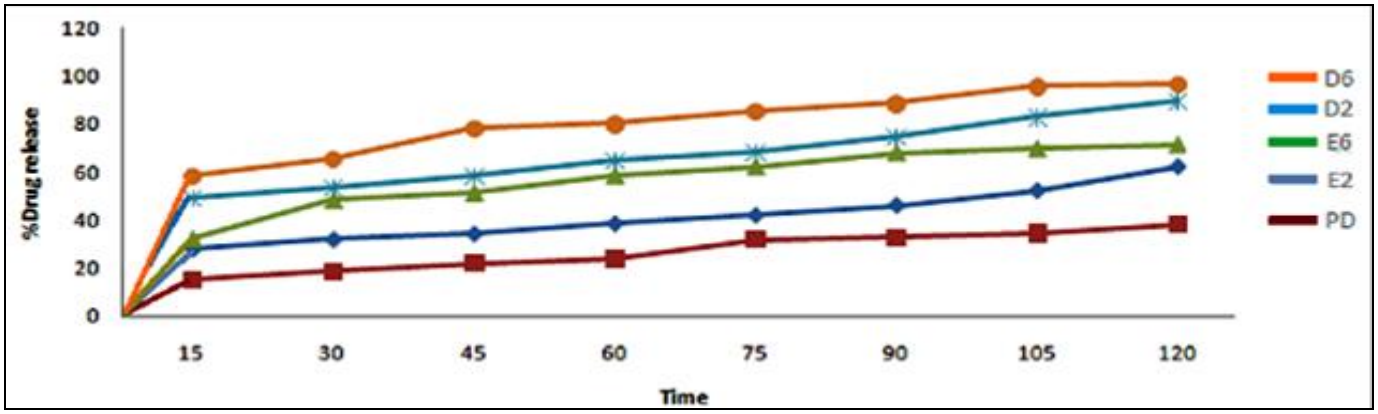


FIG. 9: DISSOLUTION STUDIES (SPRAY DRYING D6-(1:6:1), D2-(1:2:1), SOLVENT EVAPORATION E6-(1:6:1), E2- (1:2:1), PD-PURE DRUG) PD – E2 – E6 – D2 – D6

In spray drying D6 (1:6:1) presented highest release, approximately increased in the amount of drug release from spray drying followed by solvent evaporation with pure drug Atorvastatin. This improved drug release could be attributed to presence form of Atorvastatin as confirmed XRD, IR, and DSC. Atorvastatin characterized by (90%) drug release within 120 min in phosphate buffer 7.4. This could be attributed to the improved wettability of drug particles by physical presence of hydrophilic amorphous adsorbent.

Improved dissolution attributed to decreased of the drug, improved wetting and solubilizing effects of carriers (PVP K30), significant reduction in drug particle size reduction and increased dissolution rate.

SUMMARY AND CONCLUSION: Study concluded that the dissolution rate of Atorvastatin significantly enhanced by use of carrier and adsorbent by solid dispersion methods. During initial characterization, PXRD and dissolution

confirmed the presence of less crystalline of Atorvastatin in drug complexes. IR spectrum has shown formation of hydrogen bonding in the solid dispersion of Atorvastatin system correlated with the crystalline of atorvastatin to amorphous form. Thus, present study demonstrated high potential of solid dispersion methods for obtaining large surface area and amorphicity of drug.

ACKNOWLEDGEMENTS: Authors are grateful thanks to Shivaji University, Kolhapur, for allowing the X-ray Diffraction and Differential Scanning Calorimetric studies.

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How to cite this article:
Shinde SS, Shete AS, Patil MV, Salunkhe S and Indapure D: Preparation & physicochemical characterization of poorly water soluble drug by using Spray drying and solvent evaporation methods. *Int J Pharm Sci Res* 2014; 5(3): 1035-44.doi: 10.13040/IJPSR.0975-8232.5(3).1035-44