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Dissolution Enhancement of Atorvastatin Calcium Trihydrate by Using *In situ* Micronization Technique

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ABSTRACT

The main principle of *in situ* salt formation has been utilized to enhance the dissolution and absorption rate of poorly water soluble drugs. Atorvastatin is a selective competitive inhibitor of HMG-COA reductase & the category of drug is anti hyperlipidemic. Atorvastatin shows maximum efficacy for reducing LDL-CH, because it promotes the atherosclerosis and other cardiovascular diseases. The intention of the present study is to improve the solubility of drug while formation of microcrystals. Five formulations of ACT containing varying concentrations of polymer (PVPK30) were designed. The microcrystals ACT were prepared by solvent change method. The prepared microcrystals were evaluated for Percentage crystal yield, Mean particle size, Percentage Drug content & *In vitro* dissolution studies and also they can be characterized by FT-IR, DSC, XRD & SEM. The *Invitro* dissolution studies revealed that out of five formulations, formulation F5 was found to be optimized which showed less particle size & the drug release was found 98.99% at 60min.

Keywords: *Insitu* micronization, Anti hyperlipidemic, Microcrystals, PVPK30, Solvent change method, Atorvastatin Calcium Trihydrate (ACT).

INTRODUCTION

Solubility has a crucial role in the success of a drug development. Compounds with low solubility not only cause problems for in vitro and in vivo assays, but also add significant burden to drug development. Drug discovery and drug development often have different solubility screening requirements and methodologies have been developed to meet the needs of these different stages. The solubility of a solute is the maximum quantity of solute that can dissolve in a definite quantity of solvent or quantity of solution at a specified temperature (D.M.Brahmankar *et al*., 2009).

In situ process has been utilized to enhance the dissolution and absorption rate of poorly water soluble drugs. Many of techniques are commonly used to improve dissolution and bioavailability of poorly water-soluble drugs, such as pH modification, use of surfactants, the formation of solid dispersions, complexation with cyclodextrins, co-solvent and hydrotroph formation, co-crystallization techniques. Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. It decrease cholesterol synthesis by competitively inhibits conversion of 3-hydroxy, 3-methyl,glutaryl coenzyme A to Mevalonate. Atorvastatin also reduces blood levels of triglycerides and slightly increases levels of HDL–cholesterol Atorvastatin is lowering the cholesterol or targeting levels of LDL (Gennaro AR. Remington *et al*., 2005).

The present investigation was to prepare and characterize microcrystals of Atorvastatin calcium trihydrate (ACT), a poorly water soluble drug employing *in situ* micronisation technique by rapid solvent change method to approach, enhance the solubility and dissolution rate and to optimize the solvent and anti-solvent ratio (v/v) using constant stabilizer concentration in the formulation of Atorvastatin calcium trihydrate

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microcrystals. The prepared microcrystals were evaluated for the percentage crystal yield, mean particle size, content uniformity & *in-vitro* dissolution studies of ACT microcrystals. To characterize the prepared microcrystals of the optimized formulation using various techniques they are DSC, PXRD, FT-IR & SEM.

MATERIALS AND METHODS

Materials

Atorvastatin calcium trihydrate (ACT) (med rich pharmaceuticals Ltd., Bangalore.), PVPk30, Methanol (A to Z pharmaceuticals).

Rapid solvent change method

First, an organic solution of the drug was prepared by dissolving 1.76 g of drug in 10 ml of methanol. Then measured quantity of aqueous solution containing 0.1% w/v of carrier (antisolvent to the drug solution) was added rapidly under stirring to the drug solution. This causes super saturation with respect to the drug and subsequent nucleation and crystal growth. The mixture was stirred for 60 min by using magnetic stirrer. The crystals were collected by filtration using whattman filter paper, followed by three consecutive washings with 10 ml of cold water to remove any non-adsorbed excipients and dried in an oven at 45^0C for 2 hrs. In this way, formulations from F_1-F_5 were prepared by changing the solvent to anti-solvent ratios (Rajesh A Keraliya *et al*., 2010).

Evaluation of Atorvastatin calcium trihydrate microcrystals

Percentage crystal yield

Percentage crystal yield was calculated to know about percent yield or efficiency of any method and thus its help in selection of appropriate method of formulation. The final weights of the prepared microcrystals were taken and percentage crystal yield was calculated (Bhumika Patel *et al*., 2012).

Mean particle size

The eye piece micrometer was calibrated by using a standard stage micrometer at 45X. Samples were taken and the suspension was prepared by using propylene glycol and the prepared suspension was mounted on a slide and placed on a mechanical stage. The size of particles was estimated with the help of eye piece micrometer. Around 50 particles were counted to estimate the true mean (Patrick J. Sinko *et al*., 2011).

Percentage drug content

Equivalent weight of prepared microcrystals containing 10 mg of drug were taken and transferred into 100 ml standard flask and volume was made up to 100 ml with methanol and suitably diluted. The absorbance of the solutions was measured at 246 nm (Patel Manish *et al*., 2009).

In vitro Dissolution Studies

In vitro dissolution studies of pure Atorvastatin calcium trihydrate and microcrystals were conducted with the USP type II apparatus (paddle type). The dissolution studies were performed using phosphate of pH 7.4 buffer as dissolution medium at 37±0.5°C with 75 rpm speed. Samples of each preparation equivalent to 80mg of drug were added into the dissolution medium. The sample of 1ml aliquots were withdrawn periodically (15, 30, 45 and 60 min). The withdrawn sample was replaced every time with same quantity of fresh dissolution medium. The filtered solutions were diluted suitably. Samples were analyzed for their drug content by using UV spectrophotometer at wavelength of 246 nm. Percent of ACT dissolved at various time intervals was calculated and plotted against time (Polli J.E *et al*., 1997).

Characterization of microcrystals

FT-IR Spectroscopy

Fourier Transform Infrared (FT-IR) spectral measurements for ACT, PVP K30, and their microcrystals were recorded using Thermo-IR 200 FTIR spectrophotometer. Potassium bromide pellet method was employed. The microcrystals were finely ground with KBr to prepare the pellets under a hydraulic pressure of 600 psi and background spectrum was collected under identical conditions. Each spectrum was derived from 16 single average scans collected in the range of 4000-400 cm^{-1} at the spectral resolution of 2 cm^{-1} (Brittain H *et al*., 2011).

DSC Thermal Analysis

Thermal analysis of ACT and their microcrystals were recorded with Netzsch DSC 200PC (Netzsche, Selb, German). The temperature axis and cell constant of DSC were previously calibrated with Indium. A heating rate of 5^0C/min was employed over a temperature range of 25-200^0C with nitrogen purging. The sample was weighed into an aluminum pan was used as reference (Kakumanu V *et al*., 2002).

X-Ray Diffraction Study (XRD)

X-Ray diffraction spectra of ACT, PVP K30 and their microcrystals were recorded on a Seifert 303, Germany X-Ray Diffractometer with Reflex software using Ni-filtered, CuKα-radiation, a voltage of 40 kV and a current of 25 mA. The instrument was operated in the continuous scan mode over a 2-θ range of 10 to 70° at step time of 0.5 seconds. The relative intensity I/I_0 and the inter-planar distance (d) corresponding to the 2-θ value were reported and compared (Hancock B *et al*., 1997)

Scanning Electron Microscopy (SEM)

Scanning electron micrographs of ACT microcrystals and pure drug powder were taken using a scanning electron microscope (Philips, Philips XL 30 ESEM, and Japan). Samples were fixed on an aluminum stub with conductive double-sided adhesive tape and coated with gold in an Argon atmosphere (50 Pa) at 50mA for 50 sec.

RESULTS AND DISCUSSION

Table.1 Composition of different formulations of ACT Microcrystals

S.No	Ingredients	Formulation Code				
		F1	F2	F3	F4	F5
1	ACT(g)	1.76	1.76	1.76	1.76	1.76
2	PVP K30(g)	0.2	0.3	0.4	0.5	0.6
3	Solvent volume (ml)	10	10	10	10	10
4	Anti-solvent volume(ml)	20	30	40	50	60

Table.2 Percentage practical yield of ACT microcrystals containing PVP K30

S. No	Formulation Code	% Practical yield
1	F1	88.2
2	F2	89.4
3	F3	91.2
4	F4	92.2
5	F5	95.5

Table.3 Mean particle size of ACT microcrystals Containing PVP K30

S. No	Formulation Code	Mean particle size (µm)
1	F1	19.05±0.12
2	F2	15.17+0.07
3	F3	17.21±0.22
4	F4	14.20±0.05
5	F5	11.26±0.01

Table.4 % Drug Content of ACT Microcrystals Containing PVP K30

S. No	Formulation Code	% Drug content
1	F1	95.03±0.07
2	F2	97.08±0.17
3	F3	98.66±0.23
4	F4	96.24±0.73
5	F5	97.53±0.22

Table.5 Dissolution data of microcrystals of ACT

S.No	Time (min)	% Cumulative drug release					
		Pure Drug	F1	F2	F3	F4	F5
1	15	13.76±0.26	48.99±0.25	46.85±0.12	49.56±0.001	51.78±0.25	54.18±0.11
2	30	27.11±0.08	72.50±0.14	62.56±0.22	67.25±0.31	73.55±0.21	79.84±0.04
3	45	41.73±0.15	82.26±0.46	70.32±0.12	76.45±0.07	86.11±0.05	90.22±0.01
4	60	51.52±0.03	89.90±0.71	81.89±0.29	84.62±0.32	93.66±0.05	98.99±0.43

Characterization of microcrystals: FT-IR Spectroscopy

Table.6 FT-IR data of ACT and ACT microcrystals

Functional group	Pure drug(cm^{-1})	F5 (cm^{-1})
C-H (Aromatic stretching)	3055.62	3058.51
C=C (Stretching)	1540.35	1543.24
N-H (Bending)	1626.19	1631.98
C-F (Alkyl halides stretching)	1058.08	1055.19
C-O (Alcohol stretching)	1215.30	1223.02
O-H (Alcohol Stretching)	3630.47	3635.30

Figure.1 Comparative % Cumulative drug release of ACT microcrystals

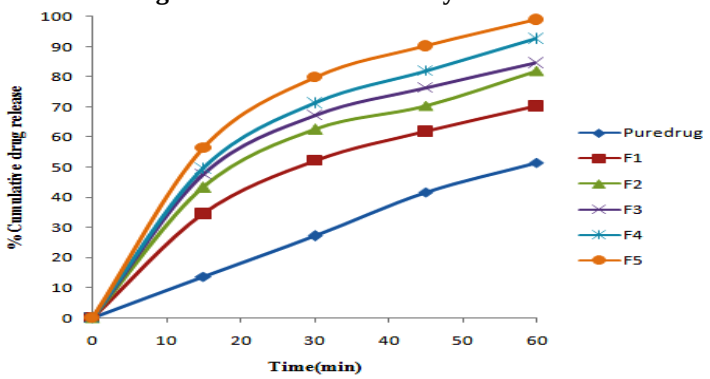
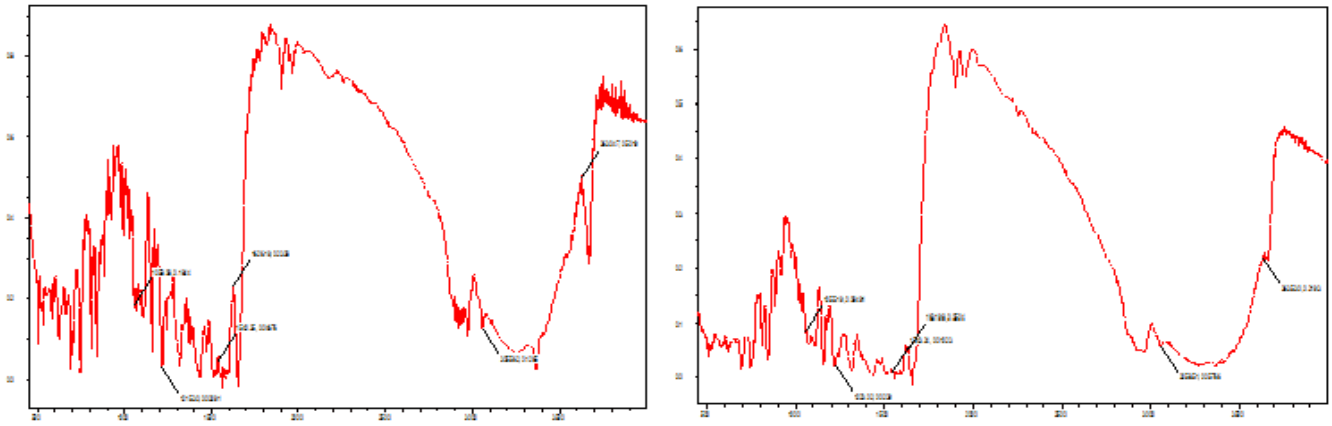
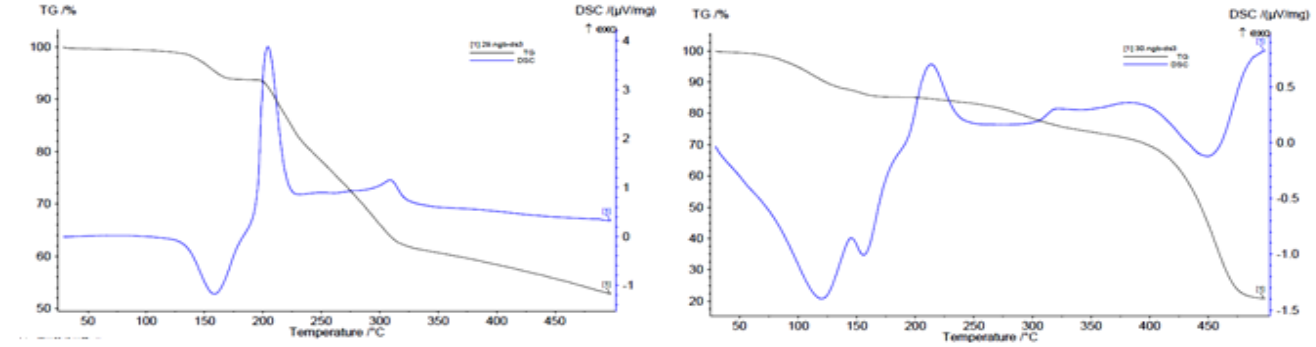


Figure.2 FT-IR spectras of ACT & F6



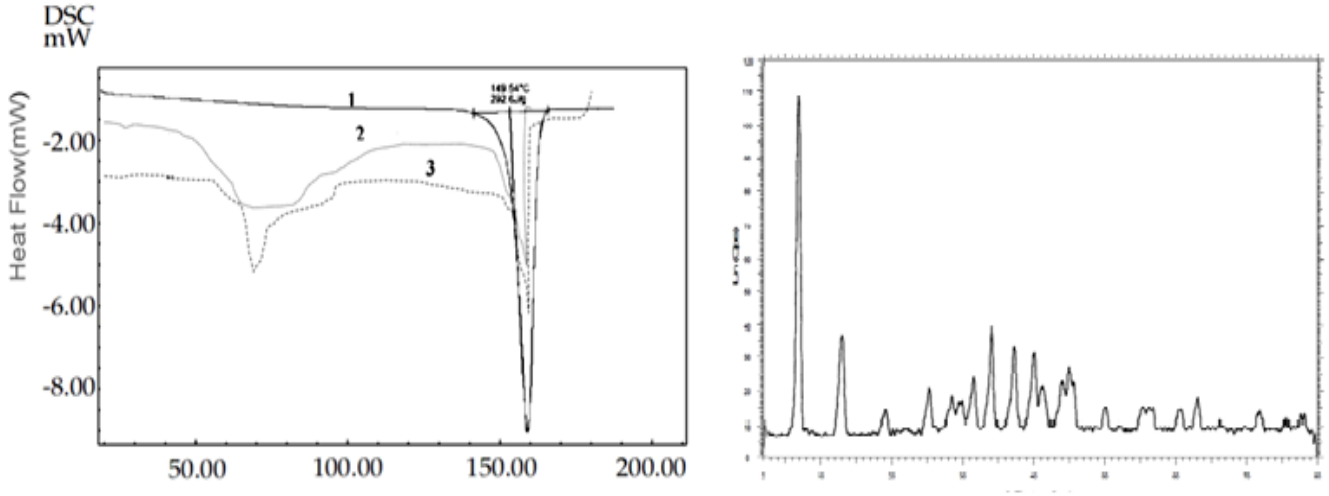
DSC Thermal Analysis

Figure.3 DSC of pure drug & F5



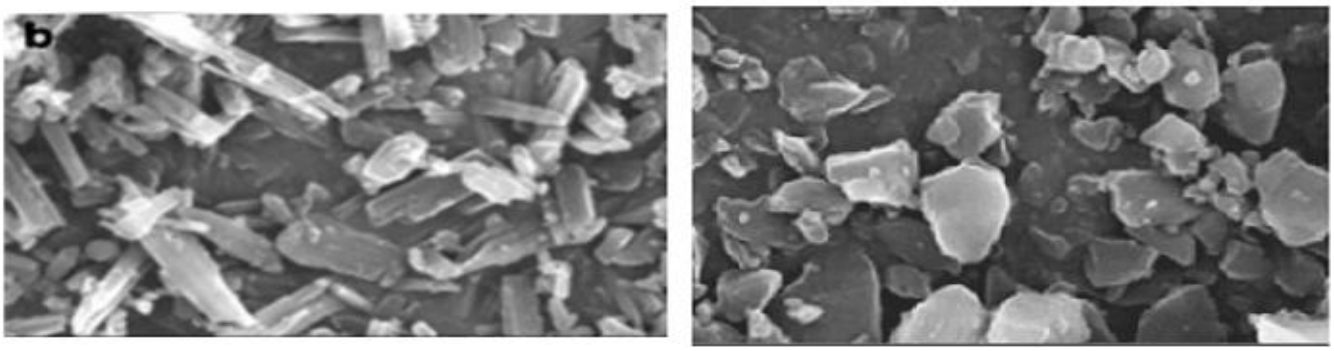
X-Ray Diffraction Study (XRD)

Figure.4 SEM of Pure Atorvastatin calcium trihydrate



Scanning Electron Microscopy (SEM)

Figure.5 SEM of Pure Atorvastatin calcium trihydrate & F5



CONCLUSION

Atorvastatin calcium trihydrate is a poorly water soluble drug, its solubility has been improved by preparing the microcrystals through rapid solvent change method & PVP K30 as hydrophilic stabilizing agent. Solvent ratio (methanol/water) and PVPK30 were optimum parameters for micro-crystallization of ACT. Microcrystals produced using PVPK30 showed narrow particle size distribution and change in the crystal habit from rod type to small plate type. The FTIR, DSC and XRD results showed no chemical interaction between the drug and the stabilizer, and crystalline habit modification has occurred in the microcrystals without any polymorphic changes. The XRD revealed that crystallinity was reduced significantly in microcrystals. The enhanced dissolution rates attributed to the reduction of the particle size, change in crystal habit, formation of hydrophilic surface and the increased wettability due to adsorption of PVPK30 and reduction in crystallinity of ACT during micro-crystallization. In conclusion, the mentioned technique is a promising tool for effective microcrystal formation during pharmaceutical development in order to increase dissolution rate of poorly water soluble active ingredient.

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