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'ANTISOLVENT SONOCRYSTALISATION OF ATORVASTATIN: EFFECT OF ULTRASOUND ON PHYSIOCHEMICAL PROPERTIES'

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Abstract

In this research, influence the physicochemical properties were improved utilising ultrasound (US) and the Antisolvent sonocrystallization technology (ASC) of Atorvastatin Calcium (AC). The study is carried out to optimize the small particles of AC along with the stabilizers like poloxamer188 and polyvinyl pyrrolidone K-30 (PVP) in the concentration of 0.04% and US amplitude of 102% for different time intervals such as 5min, 10min and 15min in the antisolvent solution at 37° C. The application of ultrasonication effect resulted in a decrease in particle size, up to 1 to 4µm of both the batches A3 and B3, where the particle size of pure drug was found to be 15.92 µm. The rate and extent of dissolution were enhanced significantly almost 99.07% drug was released from batch A3 and 89.77% drug was released from batch B3, as compared with pure drug (AC) 32.5%. Saturation solubility of both the batches A3 and B3 was increased, two times than the pure drug (AC) after giving ultrasound Effect. Presence of characteristic peaks of AC in FTIR spectra's of prepared; might confirm that there is no interaction between drug and polymer. From DSC and XRD data it is clearly manifested that crystallinity of AC has reduced with increase in sonication time. Fast dissolving tablets of optimized batch were prepared by using super disintegrant crosscarmellose (Ac-Di-Sol). Prepared fast dissolving tablet of optimized batch had shown superior dissolution profile than that of marketed tablet. The result of accelerated stability study concludes the prepared fast dissolving tablet was stable enough at 45ºC/ 75% RH for three months. Therefore Ultrasonication is an interesting technique to increase solubility of drugs with poor water solubility which was successfully developed for engineering small particles of Atorvastatin.

Key words: Antisolvent sonocrystallization, Atorvastatin, Poloxamer 188, PVP K-30, physicochemical properties, Dissolution, DOE, fast dissolving tablet.

Introduction

Sonocrystallization

Sonocrystallization method is used to enhance the solubility of poorly soluble drug. Ultrasound (US) using the antisolvent sonocrystallization technique (ASC) was used to improve the physicochemical properties of poorly water-soluble drug. Ultra-sonication significantly influences the crystallization process as the resulting intensified micro-streaming enhances the mass transfer and increases the diffusion coefficient between the solvent and the antisolvent, leading to high levels of super saturation.

The interfacial tension may also be influenced by the United States, according to reports. Furthermore, localised high pressure and subsequent rapid local cooling rates have a significant impact on supersaturation. The growth rate of certain crystal faces can be increased or decreased, resulting in a change in crystal habit. Ultrasound irradiation is well known for causing acoustic streaming, micro streaming, and highly localised temperature and pressure changes within a fluid, with these effects providing significant benefits to crystallisation processes when using a sonotrode..

During the crystallisation process, ultrasound energy has been used to induce nucleation at moderate supersaturation, or as a final treatment to achieve deagglomeration and the desired crystal habit. These effects provide significant benefits to the crystallisation process, such as rapid induction of primary nucleation, crystal size reduction, agglomeration inhibition, and crystal size distribution manipulation.

Ultrasound has been widely applied in cleaning materials, cell disruption, organic synthesis, substance crystallization, bioactive compound extraction and food extraction. Ultrasound, on the other hand, is frequently employed in multidisciplinary disciplines. The solid dissolution rate is dictated by an accelerated rate of mass transfer in a solid–liquid system under ultrasonic action, hence using sonication during the mixing of drug and carrier in the creation of solid dispersions could speed up the drug dissolution process.

The application of US in various crystallising processes is a non-destructive and relatively repeatable technique to optimise end product attributes such as crystal size and habit.

The nucleation induction time and metastable zone width are both greatly lowered, indicating that US allows nucleation to proceed at much lower supersaturation conditions. Furthermore, particle aggregation is greatly reduced. US can be used instead of a seed crystal to improve the purity of the powder.

Characteristics of sonocrystallization

- The presence of US waves has been found to alter the nucleation of solid crystals from a variety of liquids ranging from organic fluids to metals.
- The use of ultrasound not only causes nucleation, but it also improves repeatability.
- The induction time between the establishment of supersaturation and the commencement of nucleation and crystallisation is also shortened by US on nucleation.
- Sonocrystallization has a variety of characteristics that are unique to the US wave, including (a) faster primary nucleation, (b) more easy nucleation in materials, (c) secondary nucleation initiation, and (d) the creation of smaller, more uniform crystals.
- Under some conditions, ultrasound has been proven to have a considerable impact on the reduction of agglomeration.

Effects of ultrasound on crystallization

Now a day, the use of ultrasound wave in the antisolvent crystallization has been increased drastically to produce the smaller size crystals with uniform in morphology. The influence of an ultrasonic wave on particle size can be studied by changing three basic parameters: ultrasound addition time, ultrasonic power intensity,

and the time at which the sonication is applied. The particle size is generally observed to decrease as the ultrasonic power input is increased. This phenomenon is due to an increase in the erosion impact on the surface of big crystals as ultrasonic power increases, allowing crystals to agglomerate. The other parameter, sonication time is also responsible to decrease the particle size to a certain extent. Prolong sonication time provides more persisting cavitation bubbles and increases the probability of collision between the particles. When the collision occurs, it generates the large number of nuclei and causes the subsequent reduction in particle size. When sonication is delivered to a solution at the beginning of crystallisation, when crystal development is about to begin, ultrasound can also cause particle size reduction. The presence of an ultrasonic wave during crystallisation has the most significant effect of reducing both the nucleation induction time and the metastable zone width. As a result, ultrasound may influence the rate of nucleation and crystal development, as well as the size of each particle.

Physical US effects (which enable mixing-homogenization) and chemical US effects (which occur from radical production through cavitation) both influence crystallisation by altering the major variables involved in this physical process (namely, induction period, supersaturation concentration and metastable zone width). These effects vary in strength with the nature of the US source and its location; also, their influence is a function of the particular medium to which this form of energy is applied.

Why use Sonocrystllization?

- The use of ultrasound provides a non-invasive way of improving crystal properties and process control.
- Non-invasive means no added chemicals or additional mechanical treatment – maintain a sterile closed loop in seeded processes.
- By controlling the nucleation event and therefore the crystal size and crystal size distribution, yield, purity, habit and product handling (including filtration) may be improved.
- Avoidance of encrustation.
- Manufacture better quality products and improved productivity.

Materials and methods

Materials

Atorvastatin calcium were supplied by glenmark Mumbai. Croscarmellose sodium, Sodium stearate, Microcrystalline Cellulose were supplied from Loba chemie Mumbai and all other chemicals were used from Research lab fine chem.Industries, Mumbai.

Methods

Preformulation studies:

The first step in the rationale development of any pharmaceutical dosage form of a new drug is preformulation. Because a preformulation study focuses on the new compound's physicochemical qualities that can influence medication performance and the development of an effective dosage form. Simply put, these preformulation studies show that there are no significant barriers to the development of the compounds.

In the present research work following preformulation studies had performed on Atorvastatin Calcium:

Organoleptic properties:

This includes testing of properties like color, taste, odor etc. Observations are mentioned in table.

Melting point determination:

Melting point of AC had determined by open capillary tube method using Thieles tube apparatus and also by performing DSC analysis.

Determination of crystalline nature:

Crystalline nature of AC is determined by taking its SEM micrographs.

Spectroscopic analysis:

Determination of λmax:

Stock solution of 1000 ppm was prepared by adding 10mg of pure AC in 10mL of methanol. This contained 1000 µg/ml (Stock I). From that 1mLof stock solution had taken and suitably diluted with methanol, water, pH 6.8, 7.4 phosphate buffers respectively to make 100 ppm (Stock II). From that withdrawal 1 ml and diluted up to 10 with methanol, water, pH 6.8, 7.4 phosphate buffer solution to make 10 ppm. The solution was then filtered and its UV spectrum was recorded in the wavelength range 200 - 400 nm.

Preparation of calibration curve for Atorvastatin Calcium:

Stock solution of 1000ppm was prepared by adding 10mg of AC in 10mL of methanol. This contained 1000 µg/ml (Stock I) from that withdrawal 1 ml and further diluted with solutions of methanol, water, pH 6.8, 7.4 phosphate buffers respectively to get 100 µg/ml (Stock II). From that withdraw a sample and diluted in such away that making solution 2-20ppm (Stock III). At 246 nm, the solutions were filtered and spectrophotometrically analysed.Calibration curve of AC was also obtained in the distilled water and phosphate buffer (pH 6.8, 7.4) by replacing methanol with respective solvent.

Determination of saturation solubility of Atorvastatin Calcium:

The solubility of AC was determined in distilled water. In a 10mL volumetric flask, a known excess quantity of AC was added to 10mL of the above solutions. The volumetric flask was then shaken for 48 hours with a mechanical shaker. After that, the samples were filtered, diluted appropriately, and spectrophotometrically examined at 246 nm.

Evaluation:

Percent yield:

The percentage yield of batches A1, A2, and A3 as well as batches B1, B2, and B3 was calculated using the weight of the end product after drying in relation to the initial total weight of the AC using the formula below.

Practical yield ×100

Percentage yield= /Therotical yield

Drug content determination of prepared batches:

Dissolving dry produced powder batches A1, A2, and A3, as well as batch B1, B2, and batch B3, yielded the drug content. In 10 ml of methanol, it's equivalent to 10 mg of AC. The solution was filtered using Whatman filter paper, diluted appropriately, and spectrophotometrically analysed at 246 nm. In triplicate, each sample was prepared and evaluated.

Determination of saturation solubility of pure drug (AC) and prepared batches:

Saturation solubility of pure drug (AC) and prepared powder (batch A1, A2 and A3 and batch B1, B2 and batch B3) was performed by using water as solvent. In a volumetric flask, known excess amounts of different formulations and pure medication were introduced to 25 ml of water separately. For 48 hours, samples were

shaken with a mechanical shaker. After that, the samples were filtered using Whatman filter paper, diluted appropriately, and UV spectrophotometrically measured at 246 nm.

Particle size analysis of pure drug (AC) and prepared batches:

Particle size analysis of pure drug (AC) and prepared powder (batch A1, A2 and A3 and batch B1, B2 and batch B3) was performed by using electron microscope. Firstly powder of prepared batches were spread on glass slide and covered with cover slip and examined under microscope. All measurements were carried out in triplicate.

Dissolution studies of pure drug (AC) and prepared batches:

The paddle method was used to release the drug from pure drug and prepared powder batches using a USP Type II device (Electrolab). According to USFDA guidelines, these samples were placed in dissolution tubes containing 900 ml dissolving medium (pH 6.8) and tested at 75 rpm at 37oC. 10 mg of AC and an equivalent amount of prepared powder were added separately to vessels containing dissolution media, and 5 ml of sample was withdrawn at different time intervals of 5, 10, 15, 20, 25, 30, and the volume of dissolution medium was adjusted with the same dissolution medium to maintain the sink condition. The material was filtered using whatman paper and UV spectrophotometry at 246 nm was used to evaluate it. The dissolving trials were done in triplicate and the % amount of drug was determined.

Fourier transforms infrared spectroscopy (FTIR):

FTIR spectrometer was used to collect infrared spectra of pure medication and produced powder batches (Cary 630 FTIR, Agilent technologies, United States). About 3-4mg sample was directly placed on the stage of spectrometer and scanned from 4000-400 cm1.

Powder X - Ray diffraction (PXRD): The physical state of AC in the different samples was evaluated by X-ray powder diffraction (PXRD). Diffraction pattern were analyzed with a Miniflex II X- ray diffractometer (Rigaku Co. Tokyo, Japan.), Standard runs were carried out using a voltage of 56 kV, a current of 182 mA and a scanning rate of 2º min-1 over a 2-θ angle range of 5-50º.

Differential scanning calorimetry (DSC):

DSC studies were carried out to see how ultrasonication and stabilisers affected the inner structure of AC and to confirm the XRD crystallinity result. A DSC study was carried out using a Pyris 6 DSC with Pyris6 software from Perkin Elmer Pvt. Ltd. 3-5 mg sample was loaded in to aluminums pan and it was crimped. A sample and reference pan was placed in the heating chamber. Parameters like weight, heating range, nitrogen flow were set in to the software. A pan was heated from 30-300℃ and endotherm was recorded.

Scanning electron microscopy (SEM):

SEM was used to examine the surface morphology of the drug and the formed powder (SEM-JEOL-JSM-6360). A sample was adhered on a metallic stub with gold-sputtered double-sided adhesive tape. The micrographs were viewed at X150, X500, X2000, X5000, and X10000 magnifications using a scanning electron microscope with a 16.00 kV acceleration voltage.

Thin layer chromatography (TLC):

Mostly TLC is used for the identification of compound and determines the impurities of drug. The reaction mixture is also examined by TLC to access whether is complete or incomplete. A sample was spotted on the TLC plate and TLC plates are transferred in to the mobile phase allow the run for the sample, and activate the plate in the iodine chamber and spots are determined and RF value was calculated.

Formulation of AC fast dissolving tablet:

Nine batches of different formulations were prepared, every batch having AC and talc in same quantity, where as others ingredients such ascrosscarmellose sodium, microcrystalline sodium,sodium saccharin and Sodium stearatewere mixed with differentratiis. The resultant powder blend was then compressedunder constant pressure using multi-punch rotary tableting machine into 100 mg tablets, each containing a total of 40mg Atorvastatin.

Evaluation of powder blend

The powder blend was evaluated for flow properties as follows:

Angle of repose:

The funnel method was used to determine the angle of repose of the powder blend. In a funnel, 5 mg of carefully weighed powder blends were placed. The funnel was adjusted to a height of 2 cm above the tip of the funnel that meets the powder blend heap. The powder mixtures were allowed to pour freely onto the surface through the funnel. The powder cone's diameter was measured, and the angle of repose was determined. The results were mentioned in table 7.20

$$\Theta = \tan^{-1}(h/r)$$

Where, h and r are the h, eight and radius of the cone

Bulk density

Bulk density is defined as the mass of the powder divided by the bulk volume, and is measured in grammes per cubic metre. 5 gm of powder mix from each formulation was accurately weighed into a measuring cylinder, and the starting volume of powder blend in the measuring cylinder was documented, and this was computed using the formula below.

The mean ± standard deviation values of bulk density were calculated.

Bulk density=Mass of powder/Bulk volume

Tapped density:

The ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder blend for 100 times. The tapped density was calculated by using following formula. The mean ± standard deviation values of tapped density were calculated.

Tapped density= Mass of powder/Tapped volume

Hausners Ratio:

Hausners Ratio is the tapped density of the powder divided by the bulk density of the powder.

Hausners Ratio = Tapped density /Bulk density

Compressibility index:

Compressibility index were calculated by using following formula.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

Evaluation of prepared fast dissolving tablets:

Weight variation test:

Weighing 20 tablets individually, computing the average weight, and comparing the individual tablet weights to the average were all part of the USP weight variation test. If no more than two tablets are outside the % limit and no tablet differs by more than twice the percentage limit, the tablets pass the USP test.

Friability:

The pills were weighed and placed in the Roche friabilator test device, where they were subjected to rolling and repeated shocks caused by free falls. The tablets were de-dusted and re-weighted after 100 revolutions. The percentage loss in weight of the tablets was used to determine their friability. The % weight loss should be less than 0.5 to 1% the total weight of tablets.

Hardness:

The Pfizer hardness tester was used to determine the hardness. Between the retaining anvil and a piston coupled to a direct force reading gauge, the tablet is squeezed. The dial indicator remained at the reading where the tablet broke, and by pressing a reset button, it was reset to zero.

Dimensions:

A verniercaliper was used to measure the thickness and diameter of the tablets. The average values were computed using five pills from each formulation.

Disintegration test:

To test the disintegration time, one tablet was placed in the each tube of the USP disintegration apparatus and the basket rack was positioned in a one liter beaker of 0.1N HCL, at 37ºC +2ºC. The basket assembly housing the tablets is then moved up and down by a motor-driven device at a rate of 28 to 32 cycles per minute.

Tablet Assay:

Five tablets were accurately weighed and finely powdered. A quantity equivalent to 10 mg of AC was transferred to a 100 mL volumetric flask; 50 mL of methanol was added and shaken for 30 min to dissolve the drug. The solution was then filtered and suitably diluted with methanol. The drug content was determined spectrophotometrically at 246nm.

Comparative in vitro dissolution profile of prepared fast dissolving

Tablet and marketed tablets of AC:

The dissolution tests of prepared fast dissolving tablet of AC and the marketed tablets of AC were performed using the United States Pharmacopoeia (USP) dissolution apparatus II at 75 rpm. The dissolution studies were conducted in triplicate and the mean values were plotted versus time.

Similarity and differential factor:

This test was performed to compare the release pattern of prepared tablet/dissolution profile of tablet. For this study we were used 6 tablet of test(prepared batches) and 6 reference tablets (Marketed tablet Atocor 40 mg) and checked out how much they are similar or differential from each other.

Experimental Design

The design of experiments (DOE) is a method for determining the relationship between factors affecting a process and the process' output. To put it another way, it's utilised to discover cause-and-effect relationships.

Stability study

Physical stability study of prepared fast dissolving tablets:

The tablets were stored at 45ºC temperature and 75% relative humidity for 3 months in stability chamber and the effect of storage conditions on the tablet were studied by measuring in vitro drug release.

Results and Discussion

Preformulation studies:

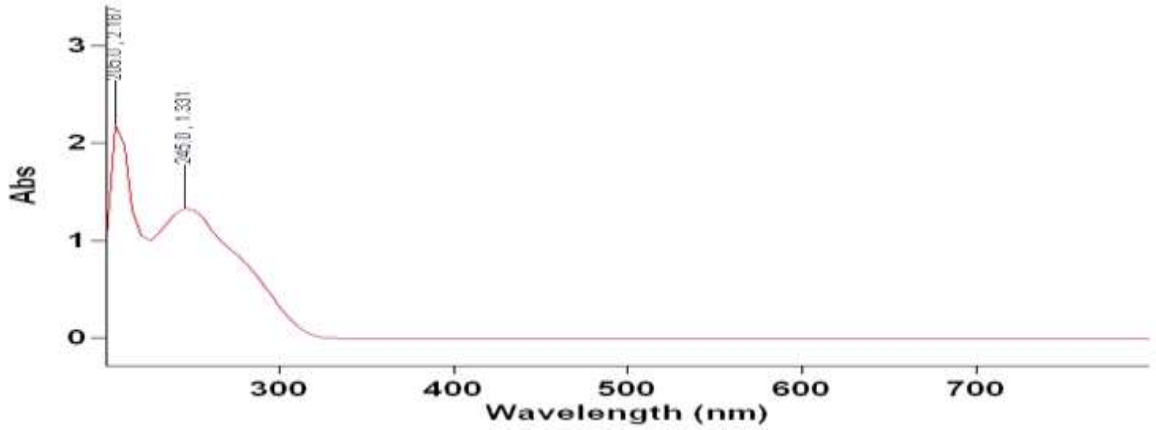
Pure drug AC was characterized and identified by organoleptic properties, physical nature, melting point, and solubility. Results are enlisted in Table No.1

Tests	Observation
Description	A white powder
Taste	Bitter
Odour	Odourless
Nature	Crystalline
Melting point	175-178°C
Solubility	Freely soluble in methanol

Determination of λ max:

For the determination of maximum absorption (λmax) of AC, methanolsolution of AC was scanned from 200 to 400 nm and it was determined at 245,0 nm shown in fig no 1.

Figure 1 UV absorption spectrum of AC in Methanol



Experimental study

Stirring effect:

Firstly pure drug divided in to two batches batch A (AC + PVP K30) and batch B (AC + Poloxamer) ratio 1:0.04w/w. Then different Stirring effect given to the Batch A and batch B. When the stirring time is 10 min average particle size were found. Increase the stirring time up to 30 min the particle size does not changes obviously. However the stirring time increasedup to 60 min the particle size dramatically decreased. With the stirring time prolonged up to 90 min, the average or no in particle size of drug further decreased. It can be determined that stirring for 60 minutes reduces particle size. Particle growth can explain the phenomenon of particle size increasing with stirring time.Therefore stirring for 60 min is believed as an optimum condition to obtain a small particle.

Effect of ultrasound on AC:

Ultrasonication effect given to the pure AC in two different batches batch A consist AC + PVP K30 and batch B consist AC + Poloxamer, ratio 1:0.04. US amplitude of 101% and US parameters like US duration5min, 10min, 15min. which is considered as batch A1,A2,A3 & B1,B2,B3 with different solvent antisolvent ratio (1:1 and 1:3). US duration 5,10 and 20 min,They could not give good results. But when US duration increases up to 15 min were sufficient enough to prevent localized supersaturation. Therefore, further experiments were carried out at US amplitude of 101% and duration of 15 min. was used for all experiments in this study.

Particle size analysis:

The application of ultrasonication effect resulted in a decrease in particle size, up to 1 to 4µm of both the batches A3 and B3, where the particle size of pure drug was found to be 15.92 µm. Microscopic images of pure AC, batch A3 and

B3 shown in figure no 2

Atorvastatin calcium. A3. B3

In vitro Dissolution studies of AC and all prepared batches:

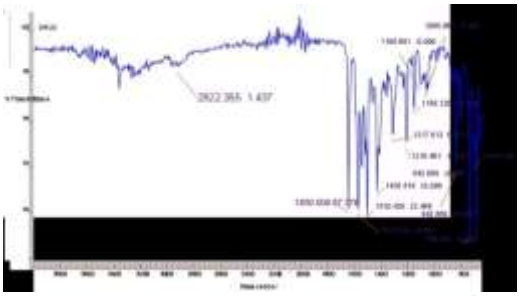
In vitro dissolution study of AC and all the prepared batches were performed in the pH 6.8 phosphate buffer. It is observed that batches prepared by antisolvent sonocrystallization method showed greater drug release than the pure AC. This due to decrease crystallinity nature of pure AC and formation of reduced particle size of pure drug. The results are discussed in Table no 23

Time (min)	Pure drug % drug release	A1 % drug release	A2 % drug release	A3 % drug release	B1 % drug release	B2 % drug release	B3 %drug release
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5	20.93+ 0.01	25.98+0.08 3	44.65+.04 1	71.72+0.08 2	23.98+0.4 1	32.65+0.2 8	69.72+0.3 5
10	22.53+0. 015	28.30+0.03 5	47.74+69	73.24+0.05 9	26.03+0.3 4	37.44+0.2 3	72.24+0.1 9
15	26.78+0. 043	33.88+0.01 6	52.94+0.3 1	87.980.91	29.88+0.2 8	42.94+0.3 9	76.98+0.2 4
20	28.86+0. 091	39.10+0.40	57.89+0.0 8	91.52+0.87	33.10+0.1 6	49.89+0.1 7	80.52+091 3
25	30.61+0. 71	45.91+0.61	60.68+0.7 2	94.75+0.01 8	38.91+0.2 5	53.68+0.2 2	83.15+022
30	32.05+0. 92	50.54+0.78	65.28+0.4 7	99.07+0.54	43.77+0.2 9	57.28+0.1 5	86.77+0.2 7

Physicochemical characterization:

Interpretation of FTIR spectrum of AC:

FTIR spectrum shows the fundamental peaks corresponding to chemical nature of the drug. The FTIR study of AC was performed to identify its chemical stability and purity.FTIR Spectra of pure drug, Batch A3 and B3 was shown in fig. No3



AC.

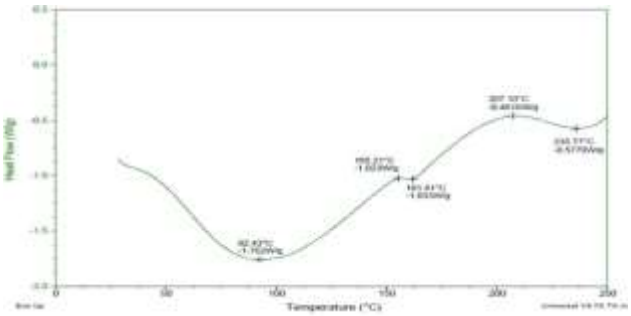
A3

B3

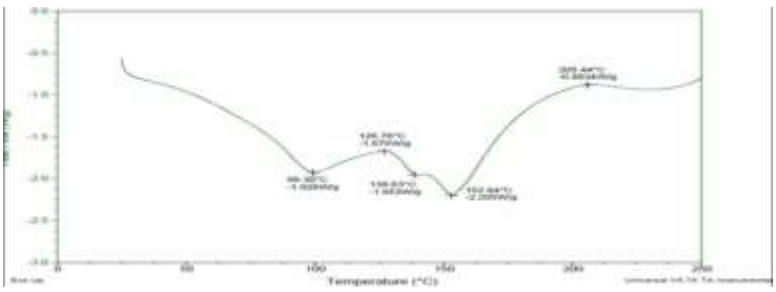
Differential scanning calorimetry (DSC):

DSC thermogram over the temperature range 10-300ºC. The DSC thermogram of AC exhibited a sharp exothermic peak at 152.84ºC corresponding to its crystallinity and melting point. This indicates AC is completely crystalline in nature. DSC thermogram OF Batch A3 showed changes in the melting point recording 161.61ºC and batch B3 showed changes in melting point at 148.48°C.Changes in melting point indicate the changes in Crystallinity state to partially amorphous form and smaller particle size of Atorvastatin Calcium after the giving effect of ultrasonication with the presence of stabilizers (PVP K 30, Poloxamer 188).DSC graphs was

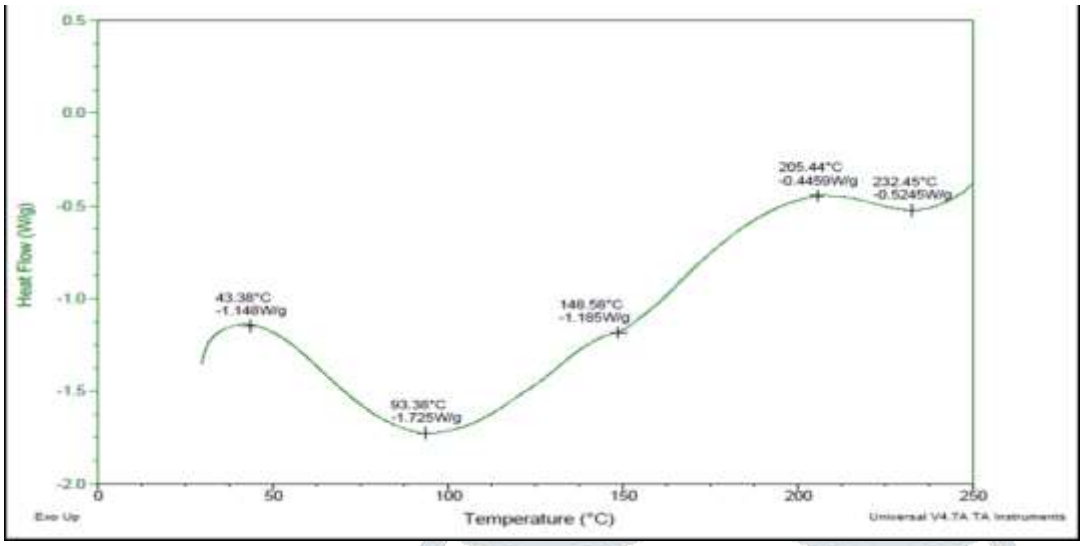
shown in figure no. 4



AC



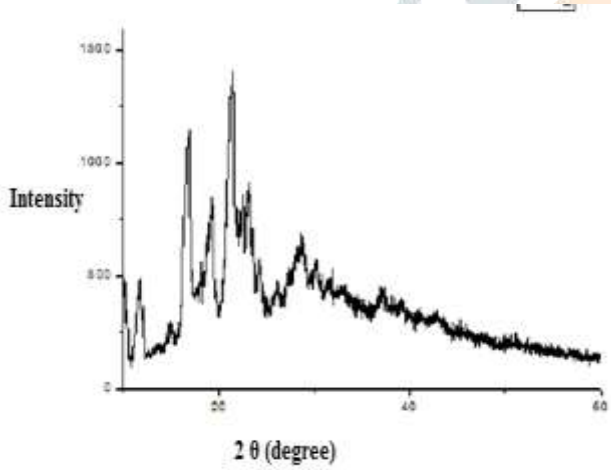
A3

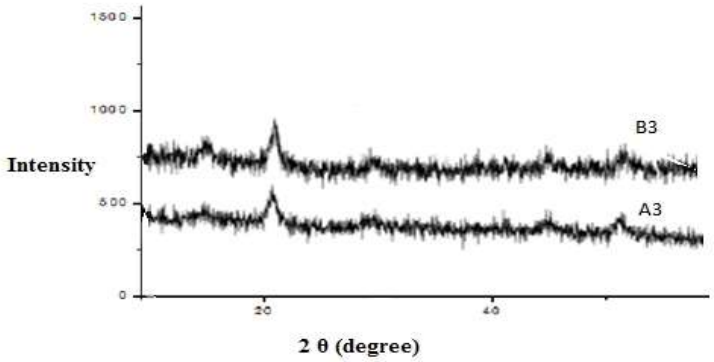


B3

Powder X - Ray diffraction (PXRD):

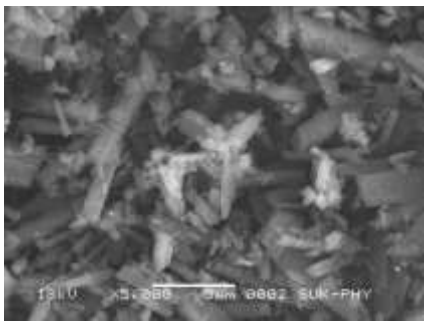
The X-ray diffraction patter of AC shows the intensity peak at 5000, 7500, 12000, 14000,suggesting that AC is purely crystalline in nature. Where as, The X-ray diffraction patter of prepared batches A3 and B3 shows the changes in the peak intensity compare to the peak of the pure drug, that indicate formation of smaller form of AC. Therefore batch A3 has selected for further morphological characterization. PXRD graphs shown in figure no 5



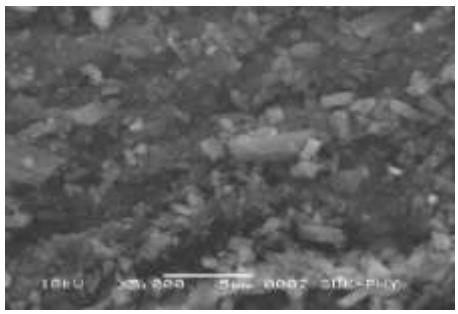


Scanning electron microscopy (SEM):

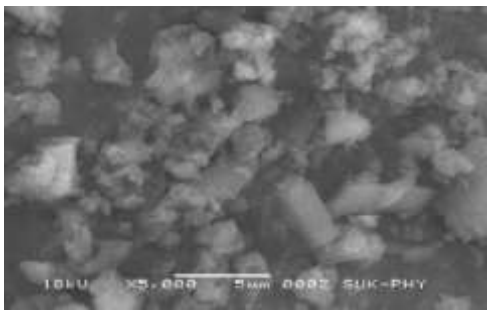
The SEM micrograph of pure AC revealed irregular shape crystals of AC with rough surfaces (Image A). SEM image of prepared powder (batch A3, B3) observed in the form of hollow spherical particles (Image B, C) and not a single crystal of AC has observed.SEM graphs shown in figure no 6.



AC



A3



B3

Experimental design:

Box - Behnken design

A traditional approach to developing a formulation is to change one variable at time. By this method it is difficult them to develop an optimized formulation, as the method reveal nothing about interaction among the variables. When using the classic step-by-step technique, the use of experimental design allows for the simultaneous testing of a large number of elements and eliminates the need for a large number of separate runs. Box – Behnken design were used to optimize the concentrations (low, medium, high) of crosscarmellose, microcrystalline cellulose and sodium stearate. Systematic optimization procedures are carried out by selecting an objective function, identifying the most essential or contributing elements, and using response surface methodology to investigate the relationship between response and factors. The result batches are discussed in Table no.3

Pareto chart-ANOVA

The Pareto chart developed by software used to investigate the standardized effect of the independent variables and their interaction on the dependent variables as disintegration time (Y1) and hardness (Y2) which depicts the main effect of the independent variables and interactions with their relative non-significance on Y1 and Y2. Result were shown in figure no.7

The results of ANOVA demonstrate that the model was significant for all the dependent variables shown in the table. Regression analysis was carried out to determine the regression co-efficient. All the independent variables were found to be significant for all response variables. The quadratic model was found to be non-significant Y1 and Y2. The linear model was found to be non-significant for Y1. So, the above result indicates that both the factors play an important role in formulation of tablet containing AC.

Run order	X1 Crosscarmellose	X2 Microcrystalline cellulose	X3 Sodium Stearate	Y1 Disintegration Time(sec	Y2 Hardness (kg/cm2)
1	1	0	1	22±0.6	4.8±0.2
2	-1	0	-1	12±0.5	4.1+0.3
3	0	0	0	25+0.8	5.2+0.4
4	-1	0	1	22±0.6	4.5+0.8
5	-1	-1	0	57±0.4	4.8+0.6
6	0	-1	-1	32+0.7	4.9+0.4
7	0	0	0	09+0.1	5.1+0.7
8	1	0	-1	56+0.3	4.2+0.6
9	0	1	1	38+0.7	4.4+0.6

Table no.3 Box Behnken experimental design for independent factor and dependent response Where, X1, X2, X3= Independent variables an AZd Y1, Y2 = Dependent Variables.

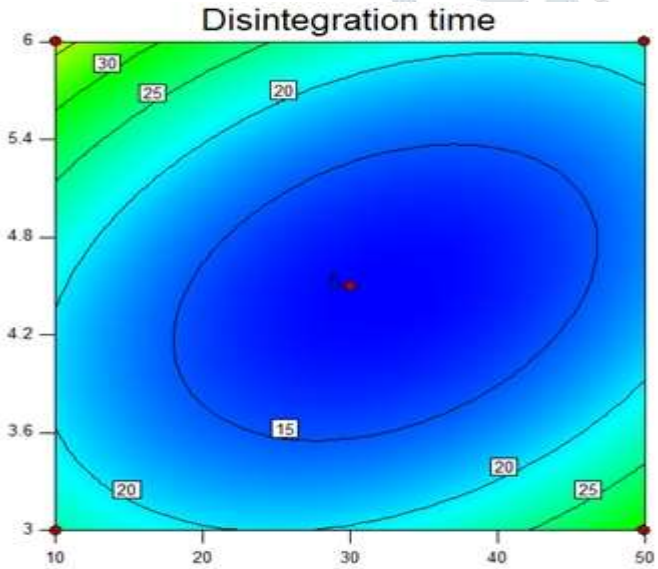
Figure no. 7. Pareto chart ANOVA showing effect and interaction on disintegration time and hardness

Contour Plot

Two dimensional (2D) contour plots are presented in fig.no.8and 9which are very useful to study the interaction effect of the factor on the responses. These type of plots are useful in study of the effects of two factors on the response at one time and plots and all the presented, the third factor was kept at a constant level. All the relationships among the three variables are linear upto certain rang the effect of X1, X2 and X3 with their non-interaction on disintegration time at a fixed level. The plots were found to be linear upto 25% indicating a linear relationship between X1 and X2. Similarly, all the values were reminded dependent variables. It was determined from the contour plot that an optimum value of disintegration time could be obtained with X1 level range from 30 to 25% and X2 at 4.8 to 5%. It is an evident from the contour plot that the higher level of X1, X2, X3favours the formulation.

Response Surface Plot

A response surface (3D) plot depicts the potential link between three variables graphically. The response (z) variable is represented by a smooth surface (3D) plot, which is generated by plotting two independent variables on the x and y axes. 3D surface plots, like contour plots, are useful for determining response values in a more exact manner. Response surface (3D) plots are presented in figure no.10 and 11



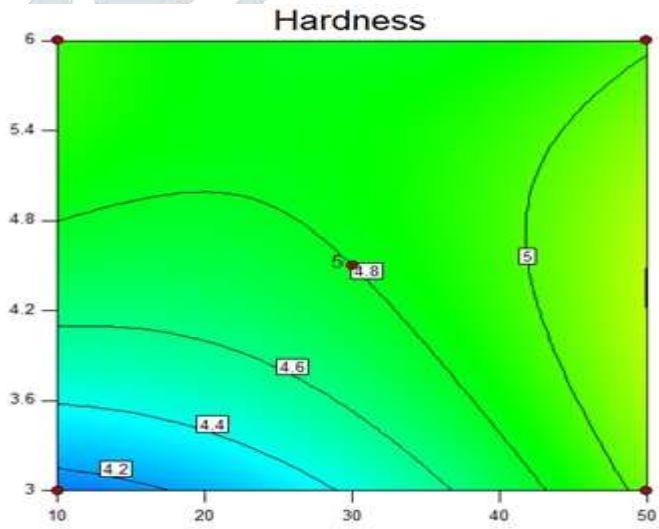
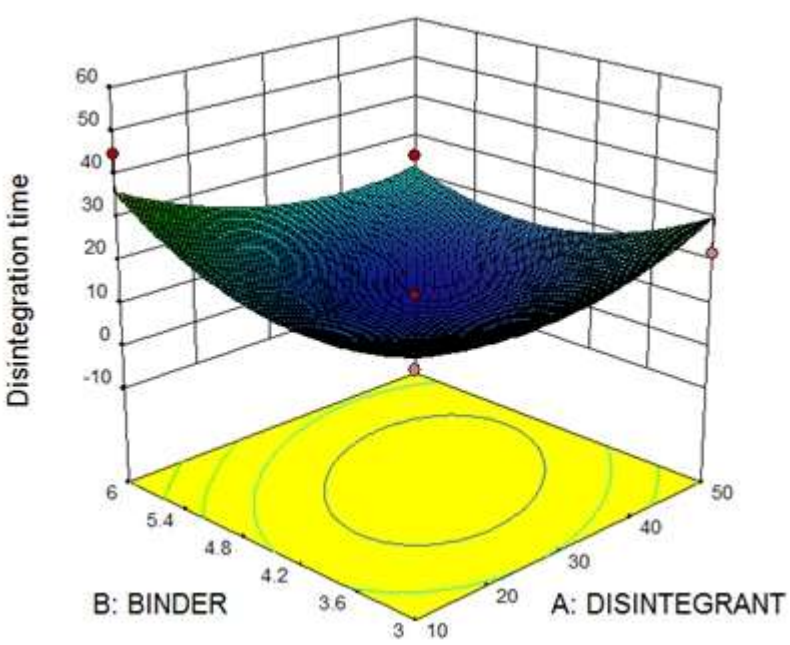


Figure.8Contour plot showing effect on disintegration time Figure.9 Contour plot showing effect on hardness



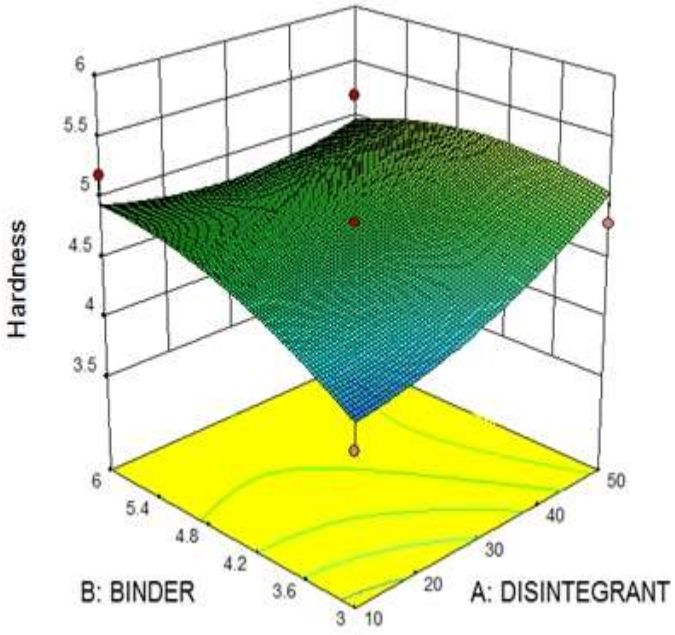


Fig..10 3D surface plot showing effect on disintegration time.Fig.11 3D Surface Plot graph showing effect on hardness

Precompression properties;

The tablet blend's angle of repose was found to be 26. The angle of repose was determined to be less than 26, indicating good flow properties. The bulk density and tapped density values were both less than one, indicating that the tablet blend had good flow qualities. Similarly the percentage compressibility (Carrs Index) value was less than 10% and Hausner ratio shows normal level. Table 4 Precompression properties of tablet blend

Sr. No.	Precompression properties	
1	Angle of Repose(θ)	26
2	Bulk Density(gm/cm3)	0.13
3	Tapped Density(gm/cm3)	0.82
4	Hausners ratio	1.08
5	Carr's index	9.78

Table no. 5 Evaluation of fast dissolving tablet

Properties	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hardness (kg/cm2)	**4.8**	4.1	**5.2**	**4.5**	**4.8**	**4.9**	**5.1**	**4.2**	**4.4**
Disintegration time (s)	**22**	**12**	**25**	**22**	**57**	**32**	**12**	**56**	**38**
Friability (%)	**0.45**	0.61	**0.39**	**0.52**	**0.34**	**0.36**	**0.25**	**4.58**	**0.47**

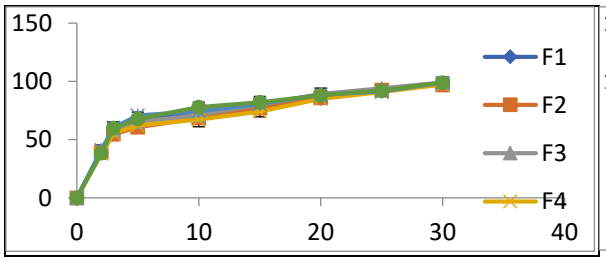
Table no. 6 Properties of F7 batch tablets

Sr. no	Tablet properties
Hardness (kg/cm2)	5.1+0.068
Friability (%)	0.25+0.023
Disintegration time(sec)	28.37+0.87
Thickness(mm)	2.7+0.04
Diameter(mm)	2.9+0.058

Similarity and differential factor

This test was performed to compare the release pattern of prepared tablet/ dissolution profile of two batches of tablet. This study was carried out using 6 tablet of test (prepared batches) and 6 of reference (marketed tablet, Atocor 40 mg).

Parameters	Standard value	Obtained value
Differential factor(f1)	0-15	0.018
Similarity factor(f2)	50-100	98.62



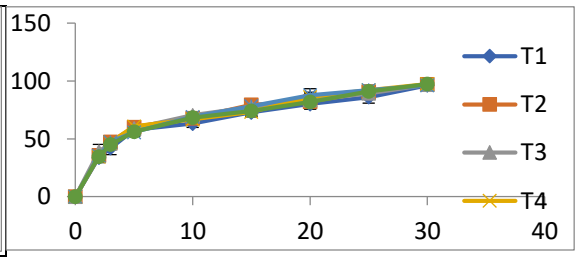


Fig. No. 12 Dissolution profile of prepared fast dissolving tablet of batch F7 Fig no.13 Dissolution profile of marketed tablet (Atocor 10 mg)

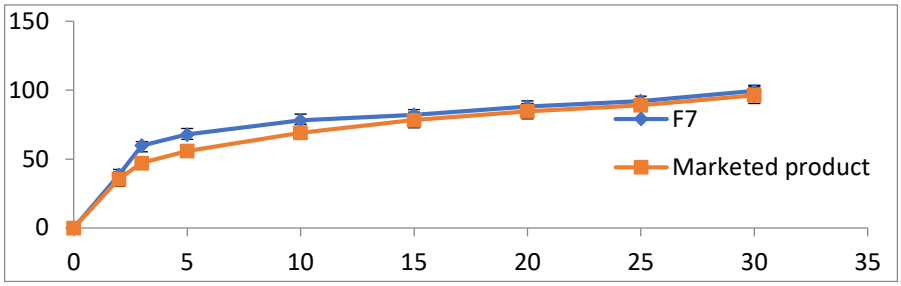


Fig no. 14 Dissolution study of prepared tablet F7 and marketed product (Atocor) 10 mg

Stability study

Stability study of optimized batch carried out as per ICH guidelines for safe, stable and effective of dosage forms, at temperature 40oC /75% RH.

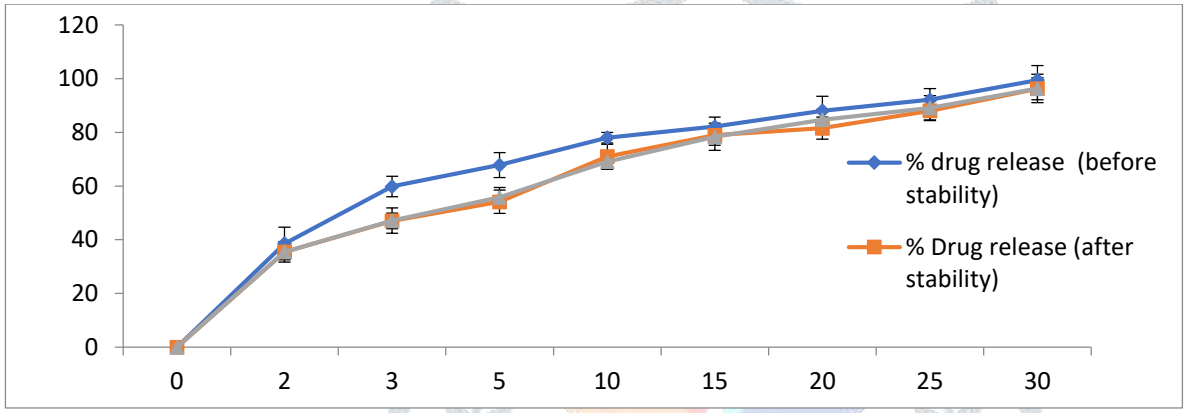


Fig no. 15Drug release profile of optimized formulation batch pre-stability, post-stability, marketed product

Conclusion

This study aimed at improving the solubility, dissolution rate and dissolution extent of AC. Antisolvent sonocrystallization technique was successfully developed for engineering small particles of AC the particles were almost spherical with smooth surfaces and particle size of less than 2 μm. The solubility of the ASC powders has slightly increased to the increase in surface area. The US power has significantly improved the dissolution rate and extent of the slightly water-soluble drug, AC. The results show that the antisolvent sonocrystallization method is a non-destructive technique and that the powder didn't undergo structural modification. In addition, the Flowability and the compressibility were improved. Thus, from the above conclusion it is summarized that reduction of particle size of AC by Antisolvent sonocrystallization method and formulation and evaluation of fast dissolving tablet of AC was successfully prepared by using direct compression method.

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