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Preparation And Characterization Of Simvastatin Nanosuspension By Homogenization Method

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Abstract: The main aim of the study was to formulate and characterize nanosuspension of simvastatin (poorly soluble drug) by high pressure homogenization method to improve its dissolution characteristics and therapeutic activity. The prepared nanosuspensions were evaluated for DSC, Zeta potential analysis, SEM, solubility, *in-vito drug* release studies and *in-vivo* pharmacodynamic studies. DSC curves obtained confirms the transfer of drug crystalline form to amorphous form. Solubility studies and *in-vitro* drug release studies shows that the prepared nanosuspension has increased solubility and dissolution rate compared to pure drug. The *in-vivo* pharmacological studies shows that the nanosuspension of drug has increased anti hyperlipidemic activity compared to the pure drug. The technology is easy to scale up and requires less sophistication, the method can be extended to various poorly water soluble drugs.
Key Words: Simvastatin, Nanosuspension, Homogenization.

Introduction:

Poor solubility of drug substance has always been a challenging problem faced by pharmaceutical scientists and it is increased now because more than 40% of new chemical entities are poorly water soluble. One of the most persistent problems faced by drugs with poor aqueous solubility is that their oral delivery is frequently associated with implications of low bioavailability and lack of dose proportionality. There are number of technologies like solid dispersion, complexation, co-solvency, use of surfactants, etc., but they lack universal applicability to all drugs. A novel technology that can used to overcome problems associated with this method is nanosuspension, which is based on size reduction mechanism.

In the present research work an attempt was made to improve the solubility and dissolution rate of model drug simvastatin. Simvastatin is an hypolipidemic drug whose bioavailability is reported has less than 5%. Nanosuspension of simvastatin is prepared by high pressure homogenization method using PVP K-30 as stabilizer.

Materials And Methods:

Simvastatin was obtained as a gift sample from Microlabs, Hosur. All other chemicals and solvents used are of analytical grade.

Preparing Nanosuspension:

Simvastatin nanosuspension is prepared by high pressure homogenization method. Simvastatin powder (1% w/v) was dispersed in aqueous surfactant solution using magnetic stirrer. After drug dispersion first size reduction step is carried out using ultra turax T25 basic homogenizer at 9500 rpm for 10 min..Then obtained mixture is homogenized using micron lab 40 homogenizer (APV systems, Germany). The homogenization

steps includes first two steps with 100 bar pressure and next two cycles with 500 bar pressure as initial step. Finally the suspension is homogenized for 15 cycles with 1500 bar pressure to obtain nanosuspension.

Production Dry Nanoparticles:

The homogenized nanosuspension was freeze dried by using Virtis freeze dryer for increasing the shelf life of suspension and to study the dissolution behavior. 1% mannitol is added to the suspension at the time of lyophilization as a cryoprotectant. At first samples are kept in deep freezer at -70^{0}c overnight and kept in Virtis freeze dryer for 2 days at -50^{0}c at 2 millitorr.

Particle Size Analysis:

The particle size analysis was carried out using Microtac blue wave particle size analyzer. Before measurement the samples has to be diluted with de-ionized water to obtain a suitable concentration for measurement. The results obtained for particle size distributions were used to confirm the formation of nano-sized particles.

Saturation Solubility Studies:

Saturation solubility measurements were assayed through ultraviolet absorbance determination at 238 nm using shimadzu UV-Visible spectrophotometer. The saturation solubility studies were carried out for both the unprocessed pure drug and different batches of lyophilized nanosuspension. 10 mg of unprocessed pure drug and nanosuspension equivalent to 10 mg of simvastatin were weighed and separately introduced into 25 ml stoppered conical flask containing 10 ml distilled water. The flasks were sealed and placed in rotary shaker for 24 hrs at 37°C and equilibrated for 2 days. The samples were collected after the specified time interval, and it is filtered and analyzed. The diluted samples were analyzed using UV spectrophotometer at 238 nm.

Permeation studies:

Permeation study is carried out for both unprocessed drug and different batches of nanosuspension using cellulose nitrate membrane. The membrane is attached to the diffusion cell and then it is dipped in a beaker containing phosphate buffer pH 7.0. The pure drug sample and equivalent quantity of lyophilized suspension are weighed and placed in the different diffusion cells containing the specified quantity of buffer. The samples were withdrawn at specified time intervals for 1 hr and replaced with fresh buffer solution. Finally the samples are analyzed using UV spectrophotometer at 238 nm.

Differential Scanning Calorimetry:

The thermal properties of powder characterize the powder samples were analyzed by using differential scanning calorimeter. The 5 mg of sample is taken in the aluminum vial and kep sample is t in the instrument. The sample is then heated from 20°C to 200°C at 50mm of nitrogen atmosphere. Enthalpy changes (ΔH) were calculated from peak areas of samples to study the polymeric changes in formulations.

Zetapotential Analysis:

Zeta potential analysis of prepared nanosuspension formulation was carried out using Malvern Zetasizer (Malvern instruments). The samples were diluted with de-ionized water and conductivity is adjusted by addition of sodium chloride before measurement.

***In-Vitro* Drug Release Studies:**

The *in-vitro* release of simvastatin and the nanosuspension was carried out in USP dissolution test apparatus using paddle method at a rotation speed of 50 RPM. The dissolution profile of was carried out in freshly prepared acidic buffer (pH-1.2) and also in phosphate buffer (pH 7.0) containing 0.5% sodium lauryl sulphate. 10 mg of pure drug and nanosuspension equivalent to 10 mg of plain simvastatin was taken and placed in dissolution medium. The volume and temperature of dissolution medium were 900 ml and 37.0 ± 0.2°c, respectively. 5ml of samples were withdrawn at fixed time interval and were filtered. An equal volume of freshly prepared dissolution medium was replaced to maintain the sink condition. The filtered samples were analyzed at 238 nm using Shimadzu UV-Visible spectrophotometer.

Differential Scanning Calorimetry:

Figure I: Dsc Thermogram Of Simvastatin

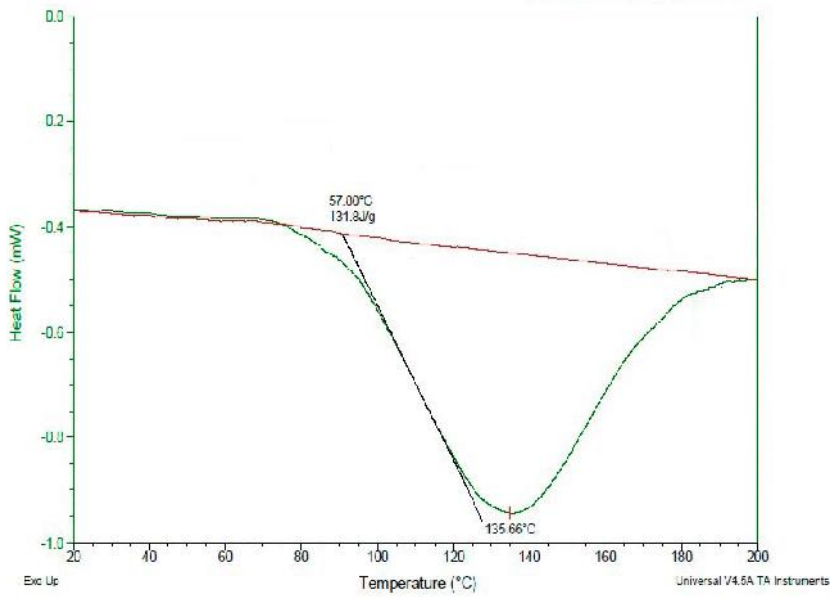


Figure II: Dsc Thermogram Of Homogenized Drug

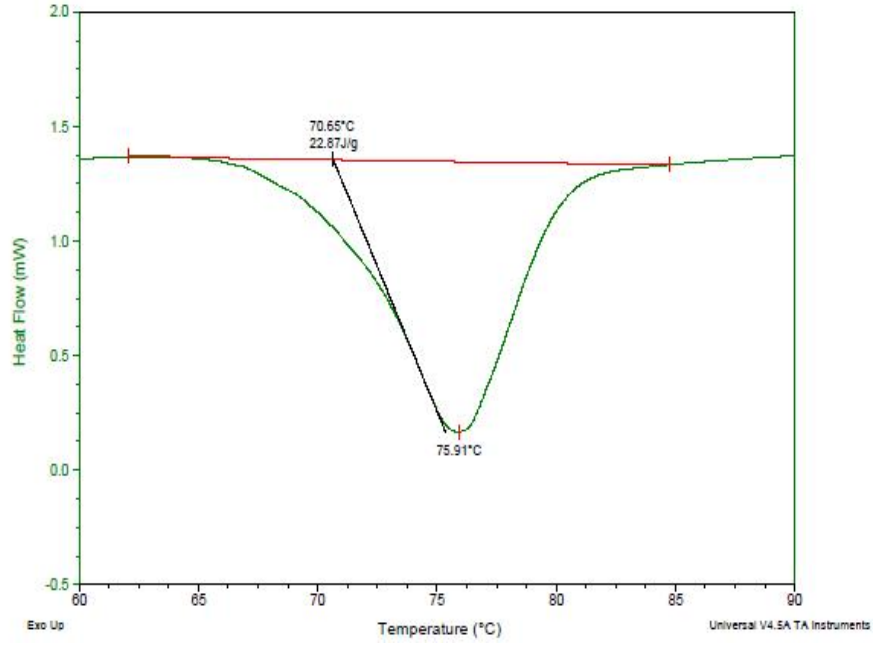
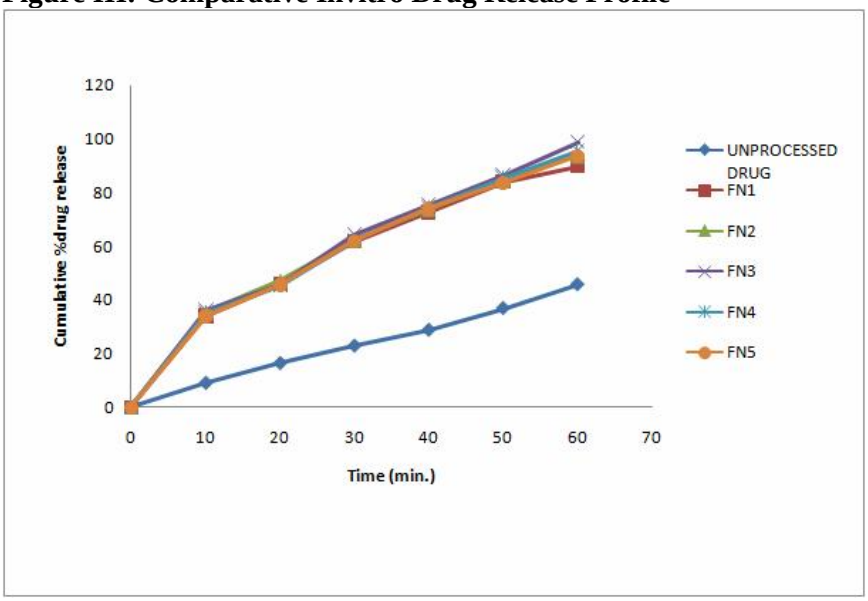


Table No-I: Results Of Particle Size, Solubility And Permeability Studies Of Formulation And Pure Drug

Sample	particle size (µm)	solubility (µg/ml)	Permeability(mg/ml/h)
Pure drug	31.49 ± 0.07	132	0.018
FN1	0.241 ± 0.06	329	0.042
FN2	0.244 ± 0.073	332	0.045
FN3	0.240 ± 0.012	357	0.051
FN4	0.240 ± 0.028	348	0.048
FN5	0.243 ± 0.030	330	0.046

Figure III: Comparative Invitro Drug Release Profile



Results Discussions:

The particle size distribution studies showed that all the formulation particle size was in the range of 240-244 nm and where as unprocessed drug shows 31.49 µm sizes. All the formulations having a particle size in the nanometer range and showing ideal surface morphology. The DSC of simvastatin shows an endothermic curve at its melting point 135.66°C (ΔH = 131.8 J/g) and the homogenized drug shows an endothermic peak at 75.91°C (ΔH = 22.87 J/g). The result indicates complete disappearance of melting endotherm of simvastatin which indicated the loss of drug crystallinity.

The saturation solubility studies indicating that nanosuspension showing maximum solubility compared to unprocessed drug which is due to the amorphous nature of drug after high pressure homogenization. The permeability studies was carried out by using cellulose nitrate membrane revealed that all the formulations having better membrane permeation compared to unprocessed drug, which shows increased release rate in the medium.

The zeta potential analysis value of prepared nanosuspension was found to be -37.1, which indicates that the formulations having good stability. *In-vitro* drug release data shows the increased dissolution rate of formulations compared to unprocessed drug. The formulations shows a maximum cumulative percentage drug release of 98.73% within 1 hr, where as the unprocessed drug having a maximum release of 45.90% only. This shows that the homogenized drug has better dissolution rate, solubility and permeability compared to unprocessed drug, this will increase the oral bioavailability and its *in-vivo* absorption rate. From this it can be concluded that the nanosuspension prepared by high pressure homogenization technique is a promising approach to enhance the bioavailability of the drug.

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