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PREPARATION & EVALUATION OF VALSARTAN NANOPARTICLES

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ABSTRACT

Valsartan belongs to BCS class II drugs (low aqueous solubility and high permeability), hence the oral absorption (20-30%) of the drug is dissolution rate limited. Improvement of dissolution velocity of Valsartan is desired so as to improve its bioavailability. The objective of the present research is to improve the dissolution rate of the drug adopting the concept of nanonization. Simple mixing and probe sonication were employed to prepare nanocrystals using 3 polymers namely Polyvinyl pyrrolidone (PVP K30), polyvinyl alcohol (PVA), polyethylene glycol (PEG 400) as stabilizers. Nanoparticles were characterized by FT-IR, SEM, assay, dissolution & micromeritics studies. Finally simple mixing was considered as best method compared to probe sonication method, in which PEG 400 is the best polymer as stabilizer to enhance the dissolution of Valsartan at 1 : 0.5 (Valsartan: PEG 400) concentration ratio.

KEYWORDS: Valsartan, nanoparticles, simple mixing, probe sonication.

INTRODUCTION[1,2]

Almost more than 90% drugs are orally administered. Drug absorption, sufficient & reproducible bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on solubility of that compound in aqueous medium. More than 90% of drugs are approved since 1995 have poor solubility. It is estimated that 40% of active new chemical entities (NCEs) identified in combinatorial screening programs employed by many pharmaceutical companies are poorly water soluble. Drug absorption, sufficient and reproducible bioavailability and/or pharmacokinetic profile in humans are recognized today as one of the major challenges in oral delivery of new drug substances. Valsartan is a non-peptide, orally active and specific angiotensin II antagonist used to treat hypertension, is a low aqueous soluble and high permeable drug belongs to BCS Class II. Hence, the oral absorption of the drug is dissolution rate limited. Improvement of dissolution velocity of Valsartan is desired so as to improve its bioavailability. The objective of the present research is to improve the dissolution rate of the drug adopting the concept of nanonization. The bottom up approach is followed to fabricate drug nanocrystals in an attempt to improvise Valsartan dissolution rate. The specific objectives are 1) to fabricate Valsartan carrier free nanocrystals 2) to screen various polymeric stabilizers to optimally stabilize the nanocrystals 3) to optimize the level of polymeric stabilizers 4) to carry out in vitro dissolution studies to assess the dissolution rate enhancement 5) to assess the physicochemical characteristics of the nanocrystals by instrumental methods of analysis like SEM, DSC, FT IR and particle size analysis 6) to suggest optimized nanocrystals technology for Valsartan.

MATERIALS

Valsartan and all other excipients and chemicals were gifted by SK Health Care Formulations Pvt Ltd, Bolaram, Hyderabad.

METHODS[3,4,5]

PREFORMULATION STUDIES

General Appearance

General appearance is the physical test to identify the compound, which was carried out to identify the Valsartan.

Infra red spectroscopy

The IR absorption spectrum of Valsartan was determined by FTIR spectrophotometer using KBr dispersion method. The IR spectrum of the obtained sample of fabricated nanoparticles was compared with the standard IR spectra of the pure drug. FTIR spectra help to confirm the identity of the drug and detect the interaction of the drug with polymers was carried out to check compatibility between drug and polymer.

Preparation of standard graph of Valsartan

Preparation of 1% Sodium lauryl solution

Accurately measured amount of 10 gm of sodium lauryl sulphate was added to 1000ml of distilled water to make 1% of sodium lauryl solution.

Preparation of standard graph in 1% SLS Solution

10 mg of Valsartan was taken in a 1000 ml of volumetric flask and dissolved in 1000ml of water containing 10 gm of sodium lauryl solution. From the stock 2, 4 6, 8ml was taken separately and made upto10 ml with 1% SLS solution to produce 2, 4 6, 8µg/ml respectively. When this solution was scanned in the UV range i.e. from 200nm to 800nm λ_{max} was found to be 249 nm for Valsartan in 1% SLS as a blank in UV-Visible Spectrophotometer (Libra- Biochrome). The absorbance of these solutions was measured at 249 nm and a graph of concentration versus absorbance was plotted.

METHOD OF PREPARATION

Valsartan drug nanocrystals were prepared by Anti-solvent precipitation method and different types of polymers were used.

Simple mixing

Valsartan nanoparticles were prepared by using solvent/anti-solvent precipitation technique as an effective technology in preparation of nano-drugs. 1gm of drug of Valsartan was completely dissolved in 8ml of water miscible solvent. Methanol is used as solvent. 0.1%, 0.3%, 0.5% polymer solution was prepared. This polymer solution was added to drug solution individually at rate of 0.6 to 0.8 ml per minute with the help of a burette simultaneously kept under stirring at 400-500 rpm by magnetic stirrer and temperature was maintained at 10˚c by using ice bath. Precipitation of solid drug particles occurred immediately upon mixing. The precipitated nanoparticles were dried at for 24 hrs.

Table 1: Simple Mixer Conditions.

S. No.	Parameters	Limits
1.	Magnetic stirrer speed	400-500rpm
2.	Temperature	10°c
3.	Anti-solvent addition	0.6-0.8ml/minute

Table 2: Preparation of Valsartan Nano Particles.

Polymer	Drug: Polymer ratio	Formulation Code
PVPK30	1:0.1	A1
	1:0.3	A2
	1:0.5	A3
PVA	1:0.1	A4
	1:0.3	A5
	1:0.5	A6
PEG-400	1:0.1	A7
	1:0.3	A8
	1:0.5	A9

Probe sonication

Valsartan nanoparticles were prepared by using solvent/anti-solvent precipitation technique as an effective technology in preparation of nano-drugs. 1gm of drug of Valsartan was completely dissolved in 8ml of methanol and 0.1%, 0.3%, 0.5% polymer solutions were prepared. This polymer solution was added to drug solution individually at rate of 0.6 to 0.8 ml per minute with the help of a burette simultaneously kept under probe sonicator The ultrasonic energy can be introduced simply by dipping a probe sonicator in a vessel kept under stirring for mixing a solvent with an anti solvent and temperature was maintained at 10˚c by using ice bath. Precipitation of solid drug particles occurred immediately upon mixing. The precipitated nanoparticles were dried at for 24 hrs.

Table 3: Probe Sonication Conditions.

S.No.	Parameters	Limits
1.	Amplitude	60
2.	Temperature	10°c
3.	Anti-solvent addition	0.6-0.8ml/minute
4.	Pulse-on time	00:00:05
5.	Pulse –off time	00:00:10
6.	Process-Time	00:02:00

Table 4: Preparation of Valsartan Nano Particles (probe sonication).

Polymer	Drug: Polymer ratio	Formulation Code
PVPK30	1:0.1	A10
	1:0.3	A11
	1:0.5	A12
PVA	1:0.1	A13
	1:0.3	A14
	1:0.5	A15
PEG-400	1:0.1	A16
	1:0.3	A17
	1:0.5	A18

CHARACTERIZATION OF NANOPARTICLES

Assay

10 mg equivalent Valsartan nanoparticles were weighed accurately and dissolved in 10 ml of methanol as working standard and from this different dilutions were prepared using 1% sodium lauryl sulfate solution and analysed using UV-Spectrophotometer at 249 nm for drug content.

Dissolution Test

The in vitro dissolution studies were carried out using USP Type II (paddle type) dissolution apparatus. The dissolution media used was 900 ml of 1% sodium lauryl sulfate (SLS) solution in distilled water. The studies were carried out for 60 minutes. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37±0.05°C. Basket rotation was adjusted to 50 rpm. At definite intervals, 5 ml samples were withdrawn and analyzed UV-Spectrophotometrically at 249 nm for the drug release. At each time of withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask to maintain the sink condition.

FT-IR Spectroscopy

Infrared (IR) spectral matching studies are employed to detect any possible interaction between drugs and the polymers or excipients. In the present, the compatibility between the drug Valsartan with different polymers and were evaluated with help of FT-IR (PERKIN ELMER FT-I Insf. USA). The samples were scanned from 4000 to 400 cm $^{-1}$in FT-IR spectrophotometer. Similarly the IR spectra of all the individual drug and prepared nanocrystals were also recorded. Physical appearance of the samples and appearance or disappearances of peaks in the spectra were observed to access any possible physical and chemical interaction.

Scanning Electron Microscopy (SEM)

Scanning electron microscopy was used to characterize the particle morphology of the unprocessed drug as well as the fabricated drug nanoparticles. A small fraction of each drug powder sample was fixed on a double-sided conductive carbon tape and sputter-coated with 5 nm of a Pt–Pd alloy. Micrographs were obtained on a Zeiss DSM 982 Field Emission Gun Scanning Electron Microscope (Carl Zeiss AG, Germany).

Micromeritic properties

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose (θ). It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force.

The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose (θ) was calculated using the following formula.

$$\tan \theta = h/r$$

Where; θ = angle of repose h= height of cone r= radius of the cone base

Angle of repose less than 30° shows the free flowing of the material.

Bulk density

Density is defined as weight per unit volume. Bulk density ρb, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm³. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together.

One gram powder blend introduced into a dry 5ml cylinder, without compacting. The powder was carefully levelled without compacting and the unsettled apparent volume, $v_{\circ}$, was read. The bulk density was calculated using the formula.

$$\rho_b = M/V_{\circ}$$

Where; ρ_b = apparent bulk density M= Weight of sample $v_{\circ}$= apparent volume of powder.

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides a fixed drop of 14±2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped 500 times initially followed by an additional tap of 750 times until the difference between succeeding measurement is less than 2% and then tapped volume, v_r was measured, to the nearest graduated unit. The tapped density was calculated, in gm per ml, using the formula.

$$\rho_{tap} = M/V_r$$

Where; ρ_{tap}= tapped density M=weight of sample V_r= tapped volume of powder.

Carr's Index

The compressibility index is a measure of the propensity of nano-particles to be compressed and the flow ability of the nano-particles. It is determined from the bulk and tapped densities using the following formulas.

$$\text{Carr's index} = [(\rho_{tap}-\rho_b)/\rho_{tap}] \times 100$$

Where; ρ_b=bulk density ρ_{tap}=tapped density.

Hausner's ratio

It is the ratio of tapped density and bulk density. Hausner's found that this ratio was related to antiparticle friction and as such, could be used to predict powder flow properties. Generally value less than 1.25 indicates good flow properties, which equivalent to 20% of Carr's index.

Particle size distribution

The size of drug nanoparticles was measured immediately after precipitation by dynamic laser light scattering (Nanoparticle size analyzer, Malvern). Before analysis, the drug suspension was diluted by purified water to 0.2mg/ml. Graphic mean size (Mz) & calculated surface area (Cs) were used to interpret the results of particle size analysis.

RESULTS

PREFORMULATION STUDIES

Characterization of Active pharmaceutical ingredients were performed

In preformulation studies, characterization of API (appearance, identification test by FTIR, assay.) was performed and it was found that all are within the range specified in the pharmacopoeia.

Table 5: Characterization of active pharmaceutical ingredient.

Description	Specifications	Observations
Appearance	White Crystalline powder	White
Identification	FTIR	Complies
Assay	Not less than 99.0% w/w and not more than 101.0% w/w of Valsartan	Above 99.97 %w/w

Calibration Curve of Valsartan

Table 6: Standard graph of Valsartan.

S.No	Concentration (µg/ml)	Absorbance
1	5	0.059
2	10	0.110
3	15	0.171
4	20	0.228
5	25	0.284

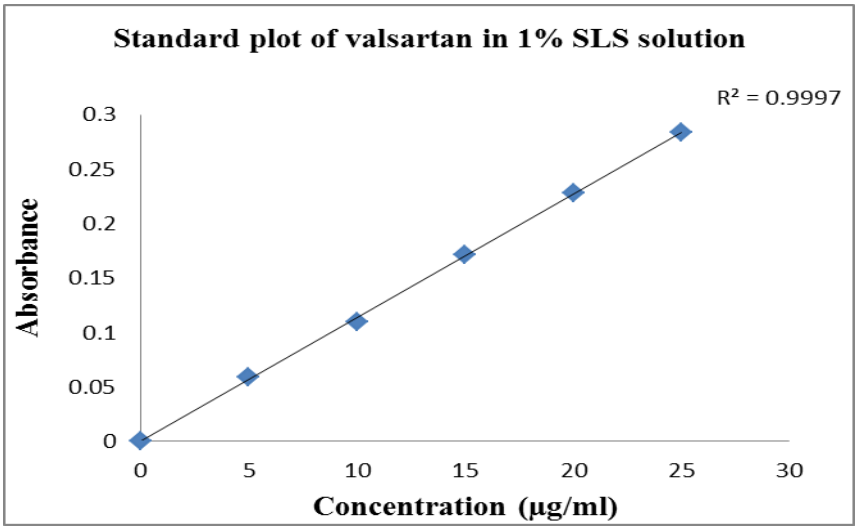

Figure 1: Standard graph of Valsartan.

Analytical method was suitable for the analysis of Valsartan or Valsartan nanoparticles using UV-Spectrophotometer, obeying Beer-Lambert's law at the concentration range between 1-5µg/ml in 1% SLS solution at the wavelength of 249 nm.

Assay(%)

Table 7: Assay data for all the Valsartan Nanoparticles.

Formulation Code	Assay(%)		Formulation Code	Assay(%)
Drug	99.24		A10	99.26
A1	99.08		A11	99.38
A2	99.40		A12	99.40
A3	99.36		A13	99.22
A4	99.28		A14	99.32
A5	99.24		A15	99.26
A6	99.34		A16	99.38
A7	99.32		A17	99.24
A8	99.18		A18	99.32
A9	99.42			

The assay results were observed between 99-100, which are within the range as specified in the Pharmacopoeia values.

***In - vitro* dissolution studies**

Table 8: In vitro dissolution studies for A1, A2 & A3 (PVP K30) Nanoparticles by simple mixing.

Sample time	Cumulative drug release (%)		
	A1 (0.1%)	A2 (0.3%)	A3 (0.5%)
10	16.11	21.06	25.56
20	21.23	26.39	28.84
30	27.20	32.46	36.75
45	30.75	41.03	45.5
60	33.37	44.40	53.25

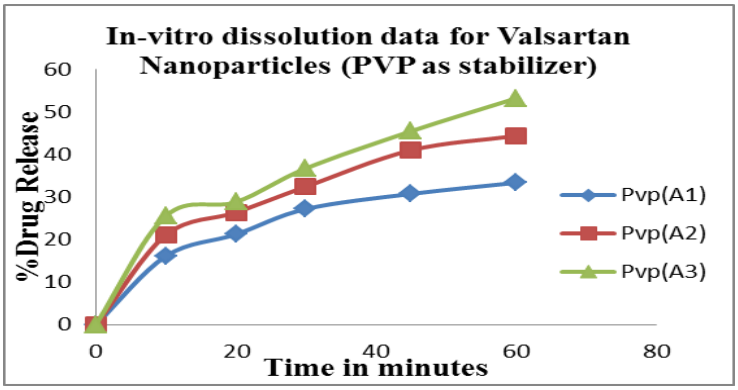

Figure 2: In vitro dissolution studies for A1, A2 & A3 (PVP) Nanoparticles.

Table 9: In vitro dissolution studies for A4, A5 & A6 (PVA) Nanoparticles by simple mixing.

± Sample time	Cumulative drug release (%)		
	A4 (0.1%)	A5 (0.3%)	A6 (0.5%)
10	17.10	22.25	24
20	22.57	26.02	27.33
30	29.58	33.36	35.78
45	31.57	52.46	56.28
60	36.23	55.95	58.49

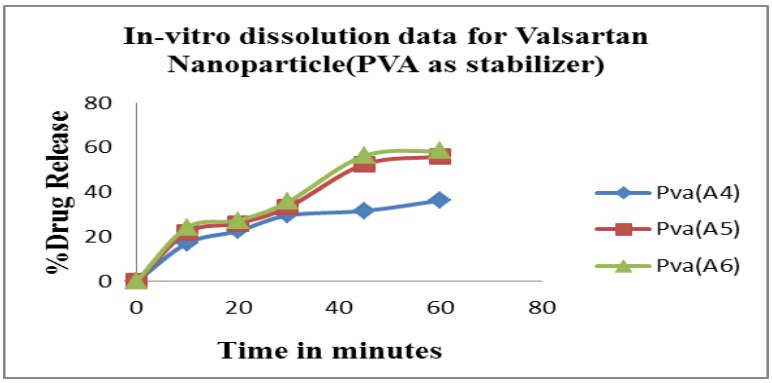

Figure 3: In vitro dissolution studies for A4, A5 & A6 (PVA) Nanoparticles.

Table 10: In vitro dissolution studies for A7, A8 & A9 (PEG 400) Nanoparticles by simple mixing.

Sample time	Cumulative drug release (%)		
	A7 (0.1%)	A8 (0.3%)	A9 (0.5%)
10	29.79	38.7	39.69
20	32.92	42.96	43.87
30	38.14	47.16	48.61
45	40.78	52.19	54.19
60	52.08	61.83	64.92

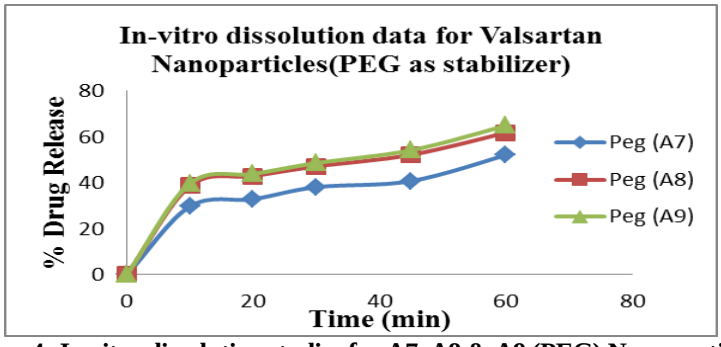

Figure 4: In vitro dissolution studies for A7, A8 & A9 (PEG) Nanoparticles.

Table 11: In vitro dissolution studies for A10, A11 & A12 (PVP) Nanoparticles of Probe Sonication.

Sample time	Cumulative drug release (%)		
	A10 (0.1%)	A11 (0.3%)	A12 (0.5%)
10	12.72	18.31	22.50
20	20.3	21.5±	25.42
30	25.76	26.93	32.93
45	29.84	30.05	40.58
60	32.12	38.04	44.19

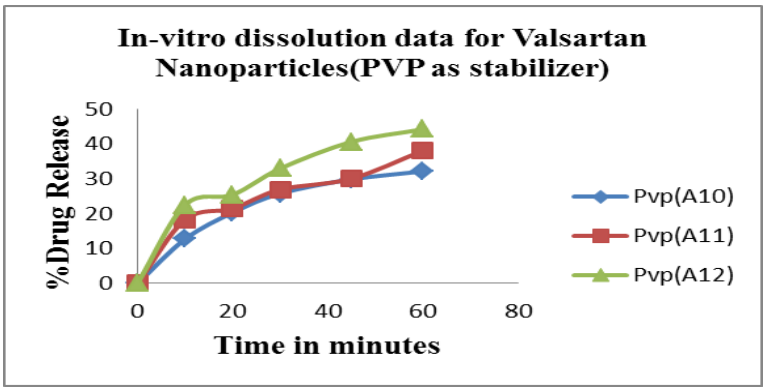

Figure 5: In vitro dissolution studies for A10, A11& A12 (PVP) Nanoparticles.

Table 12: In vitro dissolution studies for A13, A14 & A15 (PVA) Nanoparticles of Probe Sonication.

Sample time	Cumulative drug release (%)		
	A13 (0.1%)	A14 (0.3%)	A15 (0.5%)
10	17.87	21.23	20.97
20	20.30	25.48	26.55
30	28.06	32.15	33.05
45	32.65	38.78	42.23
60	35.52	42.39	45.70

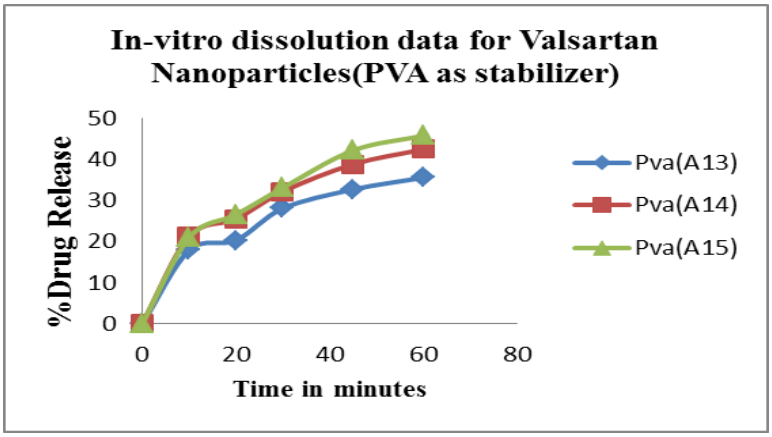

Figure 6: In vitro dissolution studies for A13, A14& A15 (PVA) Nanoparticles.

Table 13: In vitro dissolution studies for A16, A17 & A18 (PEG) Nanoparticles of Probe Sonication.

Sample time	Cumulative drug release (%)		
	A16 (0.1%)	A17 (0.3%)	A18 (0.5%)
10	28.08	30.6	31.13
20	29.85	33.65	37.79
30	34.61	39.06	40.97
45	42.54	47.82	51.01
60	49.52	54.92	56.79

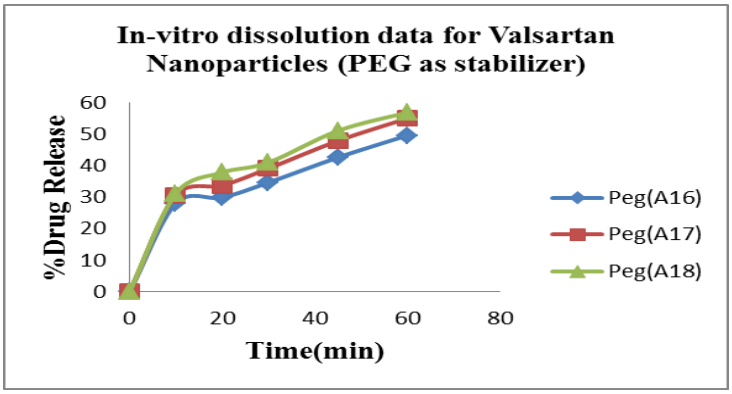

Figure 7: In vitro dissolution studies for A16, A17 & A18 (PEG) Nanoparticles.

Table 14: In vitro dissolution studies for Valsartan.

Sample time	Cumulative drug release (%)
10	9.45
20	12.20
30	19.91
45	20.56
60	21.76

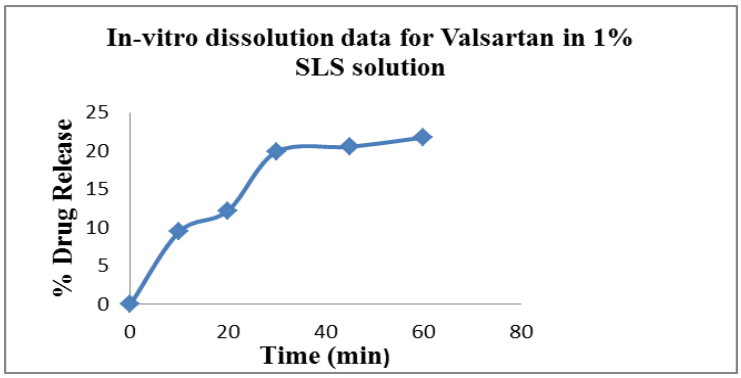

Figure 8: In vitro dissolution studies for Valsartan.

Table 15: Comparsion of Drug with prepared nanoparticles.

Time (Minutes)	Drug	PVP K30(A3)	PVA(A6)	PEG(A9)
10	9.45	25.56	24.23	39.69
20	12.20	28.84	27.33	43.87
30	19.91	36.75	35.78	48.61
45	20.56	45.5	56.28	54.19
60	21.76	53.25	58.49	64.92

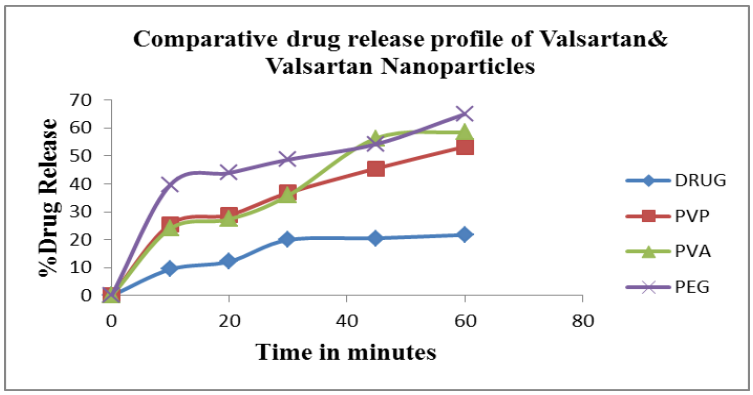

Figure 9: Comparative drug release profile of Valsartan & Valsartan nanoparticles.

The studies revealed improved dissolution of Valsartan through the process of nanonization carried out in presence of various stabilizers. Among the stabilizers studied in this investigation, PEG was found most efficient which lead to highest dissolution (PEGA9; 64.92 ± 0.64%). The performance of stabilizers with respect to dissolution of Valsartan nanocrystals is as follows; PEG>PVA>PVP (Table). The particle size of the engineered nanocrystals also followed the same order. Hence, the extent of improvement in dissolution is directly related to the extent of reduction in particle size. Reduction in particle size results in greater effective surface area available for dissolution of drug. Hence, the increased surface area and solubility enhanced dissolution velocity of drug from the fabricated nanoparticles.

The assessment of morphology of the particles using SEM indicated slab like crystals in raw Valsartan. It is evident from the SEM study that the crystal engineering process to obtain nanocrystals significantly altered the shape and size of Valsartan particles. Though spherical shaped particles are often desired, irregular shaped particles were found in our study.

FT-IR Studies

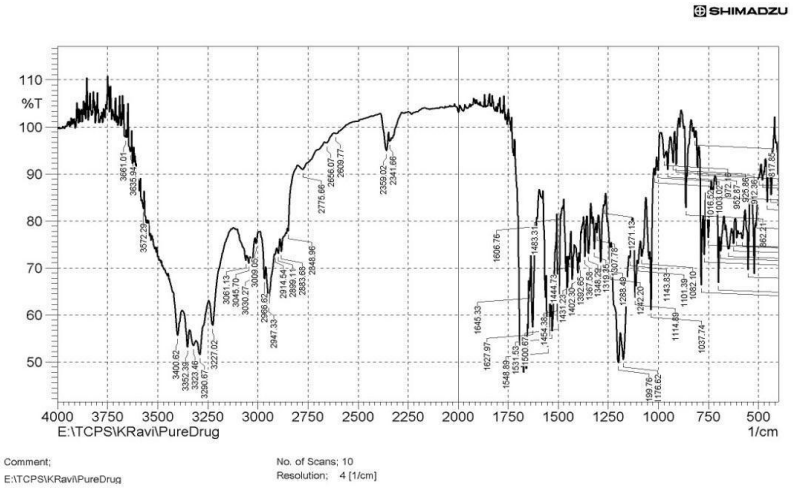

Figure 10: IR spectra of PVPK30 (A3) Nanocrystals.

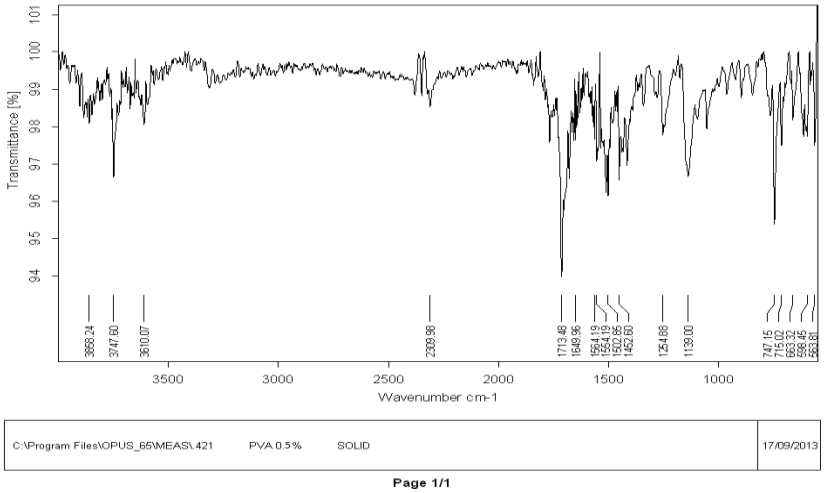

Figure 11: IR spectra of PVA (A6) Nanocrystals.

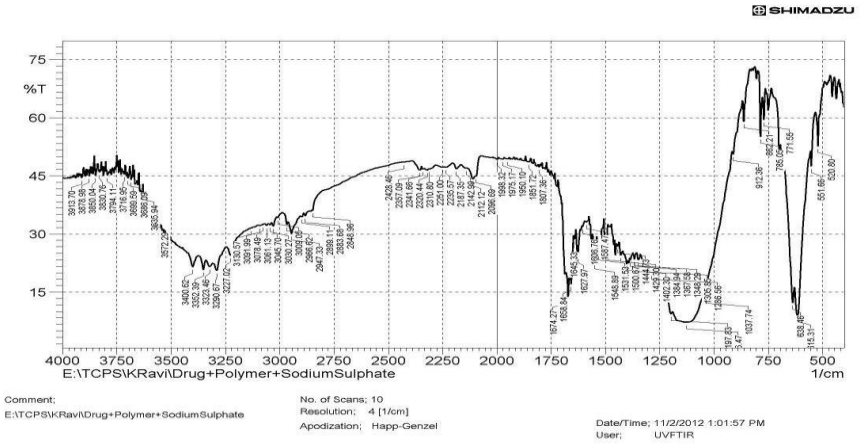

Figure 12: IR spectra of PEG400 (A9) Nanoparticles.

An FT-infrared (FT-IR) spectroscopy study was carried out to check the compatibility between the Valsartan and the prepared Valsartan nanocrystals.

The IR spectrum of Valsartan drug was compared with the IR spectrum of prepared nanocrystals. Valsartan and precipitated nanoparticles exhibit same IR spectrum. This demonstrates that the chemical structure of the drug is not changed before and after the decreasing of particles size.

Scanning Electron Microscopy (SEM) Studies

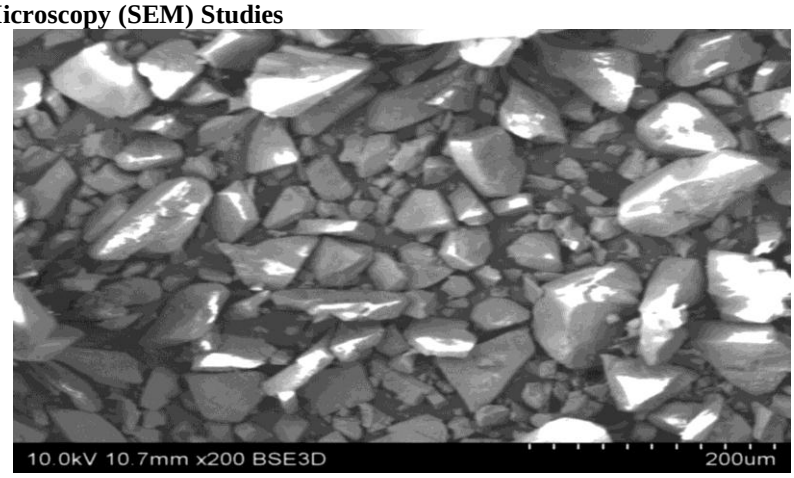

Figure 13: Scanning Electron Microscopy(SEM) of Valsartan.

Figure 14: Scanning Electron Microscopy(SEM) of PVP(K30) (A3) Nanoparticles.

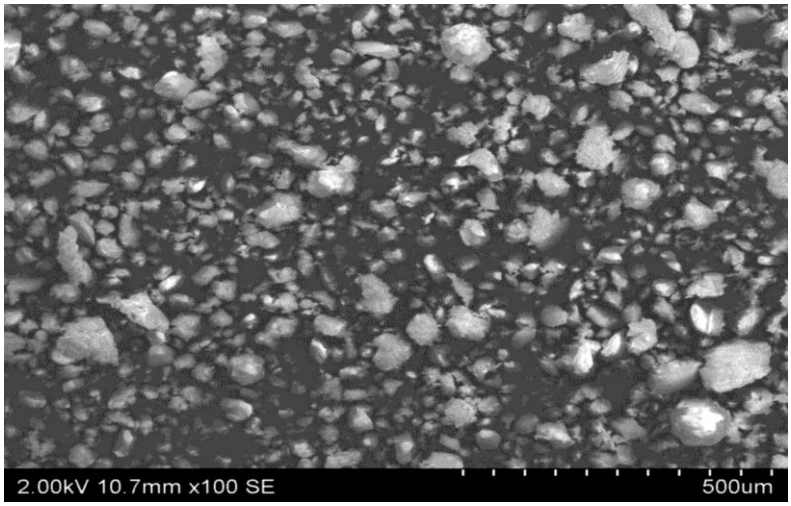

Figure 15: Scanning Electron Microscopy(SEM) of PVA (A6) Nanoparticles.

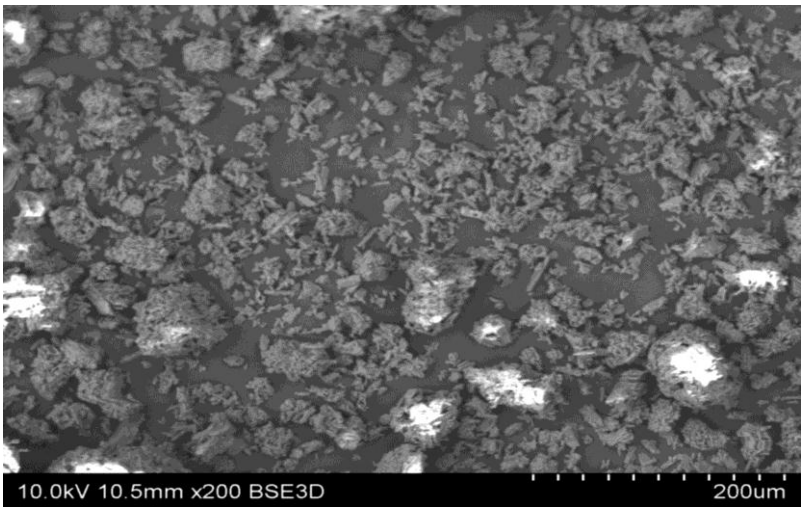

Figure 16: Scanning Electron Microscopy(SEM) of PEG400(A9) Nanoparticles.

The assessment of morphology of the particles using SEM indicated slab like crystals in raw Valsartan. It is evident from the SEM study that the crystal engineering process to obtain nanocrystals significantly altered the shape and size of Valsartan particles. Though spherical shaped particles are often desired, irregular shaped particles were found in our study.

Evaluation of physical properties

Table 16: Micromeritic properties of Valsartan & Valsartan Nanoparticles.

Formulation Code	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Hausner's Ratio	Angle of Repose(^{o})
Drug	0.54	0.73	27.38	1.37	31°06'
A1	0.44	0.52	16.3	1.21	16°04'
A2	0.16	0.20	20.0	1.25	22°01'
A3	0.44	0.53	16.9	1.20	18°05'
A4	0.42	0.52	19.5	1.24	24°02'
A5	0.16	0.19	16.5	1.18	19°04'
A6	0.43	0.52	17.3	1.17	18°06'
A7	0.24	0.49	17.8	1.25	23°05'
A8	0.19	0.26	19.1	1.17	21°03
A9	0.41	0.29	15.2	1.18	20°04'
A10	0.34	0.32	14.2	1.19	16°06'
A11	0.44	0.34	20.2	1.19	23°01'
A12	0.42	0.48	18.2	1.22	25°04'
A13	0.42	0.49	17.7	1.23	27°02'

A14	0.46	0.53	14.2	1.24	22°01'
A15	0.47	0.54	14.6	1.25	23°02'
A16	0.42	0.45	18.9	1.21	20°01'
A17	0.41	0.48	15.8	1.22	25°01'
A18	0.44	0.52	16.7	1.20	23°04'

Micrometric Properties

Angle of repose

Table 16 shows the results obtained for angle of repose for all the preparations. The values were found to be in the range 16°04'to 27°02'. The angle of repose of drug was found to be 31°06'. All the preparations showed angle of repose below 30°, which indicate excellent flow compared to pure drug.

Bulk density

The bulk density and tapped bulk density for all the preparations varied from 0.16 gm/cm^3 to 0.52 gm/cm^3 respectively. The values obtained lies within the acceptable range and no large differences found between bulk density and tapped bulk density. These results help in calculating the % compressibility of the powder. The values are depicted in table 16.

Compressibility index/ Carr's index

The percentage compressibility of powder mix was determined by the equation given for Carr's consolidation index. The percentage compressibility for all the preparations lies within the range of 14.8-20.0 which indicates that the flow is good. The percentage compressibility for drug was found to be 27.38 which indicate that the flow is poor. The values depicted in table 16.

Hausner's ratio

The Hausner's ratio was determined by the data of bulk density and tapped density. The Hausner's ratio for all the preparations lies within the range of 1.17 to 1.25, which indicates flow is excellent The Hausner's ratio for drug was found to be 1.37 which indicates flow is poor. The values depicted in the table 16.

Particle size analysis

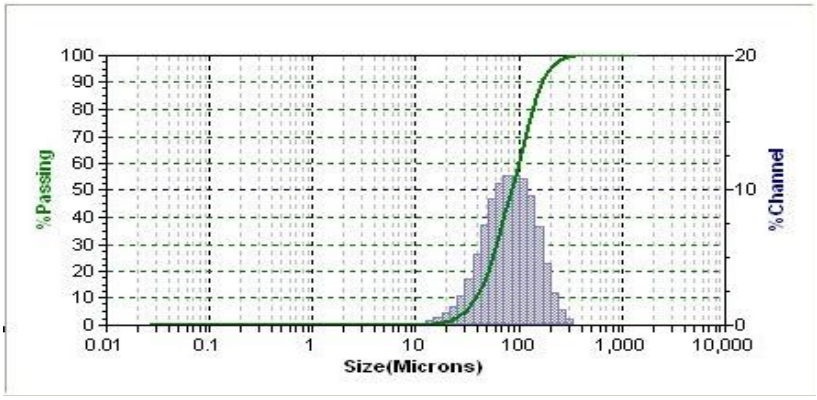

Figure 17: Particle size analysis of Valsartan.

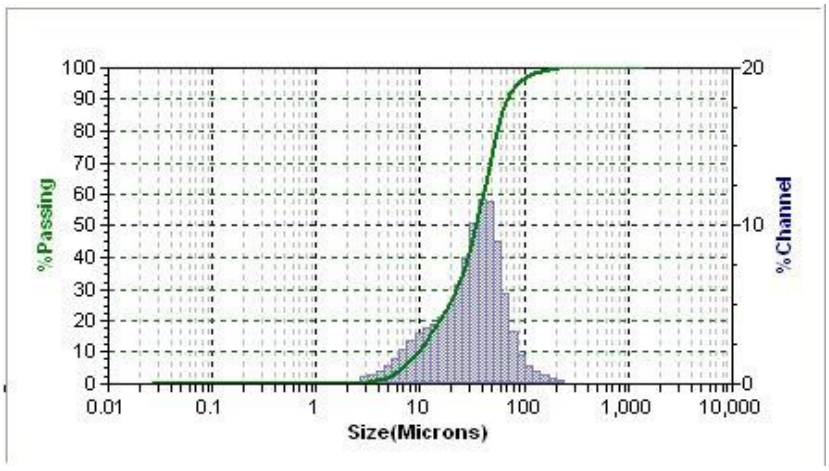

Figure 18: Particle size analysis of PVPK30 (A3) Nanoparticles.

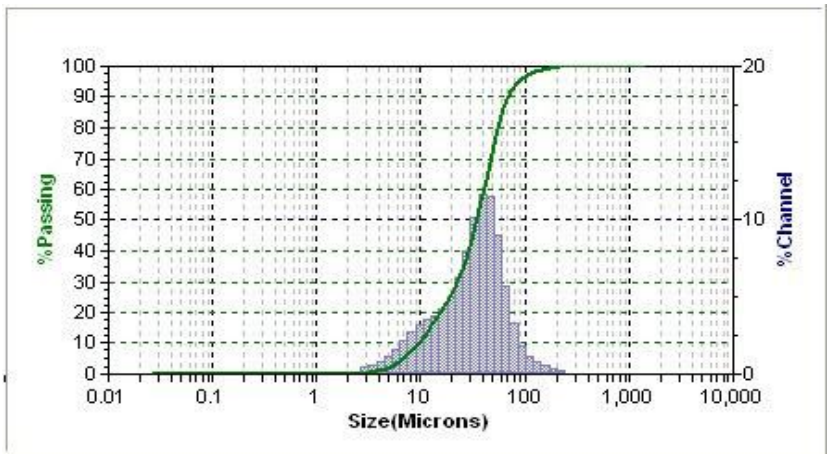

Figure 19: Particle size analysis of PVA (A6) Nanoparticles.

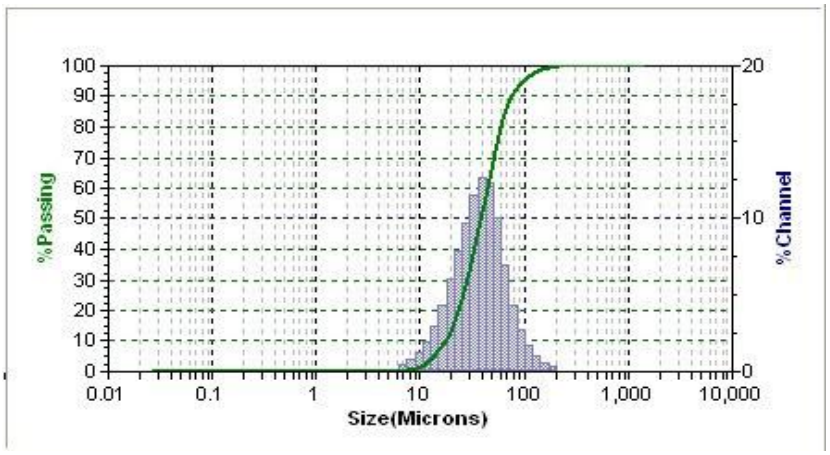

Figure 20: Particle size analysis of PEG 400 (A9) Nanoparticles.

Table 17: Particle Size Analysis.

Formulation Code	Graphical mean values(M_Z)	Calculated surface area(C_S)
DRUG	92.73	2.70
PVP(A3)	41.34	4.1
PVA(A6)	40.63	4.5
PEG(A9)	35.45	5.2

The particle size analysis for the raw Valsartan and fabricated nanoparticles using various stabilizers revealed that presence of stabilizer influenced the particle size., Graphic mean (Mz) & calculated surface area (Cs) were used to interpret the results of particle size analysis. Graphic Mean provides a less coarse-particle weighted mean particle size than mean diameter of the volume distribution. While it includes the median value, it can provide a different and possibly better control value since both small particles and large particles are included in the calculation. Smaller graphic mean (Mz) values indicating smaller particles were found when PEG (35.45 nm) was used as stabilizer. The Mz value for the raw Valsartan was found maximum (92.73 nm) indicating bigger particles. The concentration of polymeric stabilizer found to influence the particle size. Increasing the concentration of most of the studied polymers from 0.1 to 0.5% decreased the particle size.

Polymeric stabilizers help in preventing growth and stabilize the particles essentially by the same way as of surfactants, i.e. adsorption at the solid–liquid interface and reduction of the interfacial tension leading to an increased rate of nucleation. Moreover, polymers also get accumulated in the hydrodynamic layer between the particles and hinder their collision and subsequent growth. During the crystal formation stage, adsorption of polymers on the particles further helps in stabilization by providing static hindrance. In the present investigation, the particle size of all the fabricated nanocrystals were found significantly less compared to raw drug and indicating excellent stabilization of nanoparticles.

Calculated surface area (Cs) is an indication of specific surface area. The Cs values were found to increase when stabilizers are used. The value was found maximum with PEG (5.2) stabilizer indicating smaller particles.

DISCUSSION

The Study was undertaken with an aim to improve the dissolution rate of the drug adopting the concept of nanonization., Valsartan nanocrystals were prepared using a very simple bottom up approach and various polymeric stabilizers like PEG400, PVP and PVAk30were used to inhibit crystal growth and aggregation.

Valsartan fabricated nano crystals were prepared by using different polymeric stabilizers (PVAk30, PVP and PEG 400) in varying composition by Simple Mixing& Probe sonication. Invitro drug release studies were performed for prepared nano crystals. From the dissolution studies, it was found that, PEG was found most efficient which lead to highest dissolution (PEGA9; 64.92 ± 0.64%). The performance of stabilizers with respect to dissolution of Valsartan nanocrystals is as follows; PEG400>PVA>PVPk30.

Physicochemical characteristics of the nanocrystals by instrumental methods of analysis like SEM, DSC, FT IR and particle size analysis were performed.

FTIR revealed that no change in chemical structure of drug after preparation of nano crystals & The DSC studies have been performed for the pure drug and drug nanoparticles. It is observed that the sharp melting endothermic peak in Valsartan is at and for the prepared drug nanoparticles has a sharp endothermic melting peak is observed at due to reduced crystalline lattice energy of the prepared.

The assessment of morphology of the particles using SEM indicated slab like crystals in raw Valsartan. It is evident from the SEM study that the crystal engineering process to obtain nanocrystals significantly altered the shape and size of Valsartan particles. Though spherical shaped particles are often desired, irregular shaped particles were found in our study.

Micrometric Properties of pure drug &prepared nano crystals were performed, it was found that the angle of repose of drug was found to be 31°06'. All the preparations showed angle of repose below 30°, which indicate excellent flow compared to pure drug. The percentage compressibility for all the preparations lies within the range of 14.8-20.0 which indicates that the flow is good. The percentage compressibility for drug was found to be 27.38 which indicate that the flow is poor. The Hausner's ratio for all the preparations lies within the range of 1.17 to 1.25, which indicates flow is excellent the Hausner's ratio for drug was found to be 1.37 which indicates flow is poor.

The particle size analysis for the raw Valsartan and fabricated nanoparticles using various stabilizers revealed that presence of stabilizer influenced the particle size., Graphic mean (Mz) & calculated surface area (Cs) were used to interpret the results of particle size analysis. Smaller graphic mean (Mz) values indicating smaller particles were found when PEG400was used as stabilizer (Table). The Mz value for the raw Valsartan was found maximum (92.73 nm) indicating bigger particles. The concentration of polymeric stabilizer found to influence the particle size. Increasing the concentration of most of the studied polymers from 0.1 to 0.5% decreased the particle size. Calculated surface area (Cs) is an indication of specific surface area. The Cs values were found to increase when stabilizers are used. The value was found maximum with PEG stabilizer indicating smaller particles.

Preclinical investigation using Wistar rats revealed statistically significant improvement of efficacy of fabricated nanocrystals (PVAk30 and PEG400) in terms of percentage inhibition of paw oedema induced by carrageenan challenge indicating enhanced bioavailability through improved dissolution of Valsartan nanocrystals.

CONCLUSION

In this study, Valsartan nanoparticles were prepared using a very simple bottom up approach and various polymeric stabilizers like PVPk30, PVA and PEG400 were used to inhibit crystal growth and aggregation. The performance of stabilizers with respect to dissolution of Valsartan nanocrystals is as follows; PEG400>PVA>PVPk30 The particle size of the engineered nanocrystals also followed the same order. Hence, the extent of improvement in dissolution is directly related to the extent of reduction in particle size. Reduction in particle size results in greater effective surface area available for dissolution of drug. Finally, simple mixing process was shown better dissolution enhancement compared to probe sonication technique. A9 formulation can be considered as final formulation, because of its high dissolution profile.

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REFERENCES

1. Prajapati Maheshkumar, GS Shantha Kumar, Divakar Goli, Maulik P Talsania, Hardik shah, Design, Development of Nanoparticles of Poorly Soluble Valsartan, World Jr. Pharmacy and Ph. Sci, 2013; 2(6): 5737-5749.
2. B. Parmar, S. Mandal, K. C. Petkar, L. D. Patel and K. K. Sawant, Valsartan Loaded Solid Lipid Nanoparticles, Inter. J. Of Pharm. Sci & Nano. Tech, 2011; 4(3): 1483-1490.
3. Mansour mansouri, Hamid Reza Pouretedal, Vida Vosoughi, Preparation & Characterization of Ibuprofen Nanoparticles by Solvent/Antisolvent

Precipitation, The Open Conference Proceedings J., 2011; 2: 88-94.
4. Mansour mansouri, Hamid Reza Pouretedal, Vida Vosoughi, Preparation of Clarithromycin Nanoparticles by Solvent/Antisolvent Precipitation technique, Int. J Pharm. Sci. Res, 2008; 5: 472-474.
5. S. Dalvi, R. Dave, Controlling Particle size of a poorly water drug using Ultrasound and stabilizers in antisolvent precipitation technique, Inter. J. Of Pharm. Sci & Res., 2009; 48: 7581-7593.