FORMULATION AND EVALUATION OF NANOSUSPENSION OF VALSARTAN

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ABSTRACT

Objective: The objective of the present research work was to formulate and evaluate Valsartan nanosuspension by nanoprecipitation ultra sonication method using different polymers to enhance solubility and bioavailability of the poorly water-soluble drug.

Methods: Formulation of nanosuspension of valsartan by nanoprecipitation technique was used. The nanosuspension formulations were prepared using different polymers such as hydroxyl propyl methyl cellulose E50, polyvinyl pyrollidone k-30, polyethene glycol 6000 and sodium lauryl sulphate was used as the surfactant.

Results: The formulation of nanosuspension was formed clear and no sedimentation was seen on further shaking. The nanosuspension formulations were Valsatan shows maximum solubility in HPMC as a non-volatile solvent. All the Preformulation parameters were evaluated such as organoleptic characterization of drug sample, melting point, pH, partition coefficient, identification of drug samples by using UV spectroscopy and FTIR analytical method, preparation of calibration curves, solubility studies of drug sample like qualitative, quantitative and pH dependent solubility of drug in different pH buffer solution. The viscosity of the dispersion medium was more in F10.895 mPa-s and F2 0.894 mPa-s than the other formulations. The particle size distribution of the nanosuspension with zeta potential found to be negative mv. Fourier transform infrared spectroscopy indicated that there was no possible interaction between drug and polymer.

Conclusion: From this study, it was concluded that in recent advances in novel drug delivery system aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance, one such approach is nanosuspension.

Keywords: Nanosuspension, Ultrasonocation, Nanoprecipitation, Solubility, Valsartan, Antihypertensive

INTRODUCTION

The objective of present research work is to enhance the aqueous solubility of the poorly water-soluble drug valsartan by using the nanosuspension technique by the simple and cost-effective method by using suitable solvents and stabilizers in various concentration [1]. Nanosuspensions consist of the weakly water-soluble drug with no matrix material suspended in the dispersion. These can be used to enhance the solubility of drugs that are poorly soluble in water. As a result of increased solubility, the rate of flooding of the active compound increases and the maximum plasma level is reached faster. This approach is helpful for molecules with poor solubility, poor permeability or both, which acquire a significant dispute for the formulators [2].

Valsartan is a new potent and orally active antihypertensive drug which selectivity act as angiotensin II antagonist acting on the AT1 receptor subtype. It is indicated for hypertension, heart failure and post-myocardial infarction [3]. The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility. The drug is having low aqueous solubility of about 0.0213 mg/ml. The drug is rapidly absorbed after oral administration having bioavailability is 23% [4]. This compound belongs to the class of organic compounds known as biphenyl tetrazoles and derivatives. These are organic compounds containing a biphenyl attached to a tetrazole. A carbon atom of the biphenyl moiety is boned to a carbon or the nitrogen atom of the tetrazole moiety. Other techniques are like liposomes, emulsions, microemulsion, solid dispersion and inclusion complexation using cyclodextrins show sensible achiever, but they lack in universal applicability to all drugs [5]. These techniques are not applicable for those drugs which are not soluble in aqueous and organic solvents. .Recent advances in novel drug delivery system aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance, one such approach is nanosuspension [6].

MATERIALS AND METHODS

Materials

Drug Valsartan was obtained as a gift sample from Cipla, Pithampur and hetero drugs, Hyderabad respectively. Hydroxypropyl methylcellulose was procured from LobaChemie Laboratory. Polyvinyl pyrrolidone k-30 and sodium lauryl sulphate was obtained from Hemedia. All other chemicals used in this study were of analytical grade.

Methods

Preformulation studies

Preformulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system.

Organoleptic properties

The pure drug sample was studied for their organoleptic properties like colour, odour, taste and crystallinity.

Melting point

In this method a small amount of drug was filled in a capillary tube open both the ends and it was placed along with thermometer in melting point apparatus (BTI-34 melting point apparatus, Mumbai, India).

pH value

0.1% solution was prepared in distilled water using the minimum amount of methanol and the pH of the solution was measured at 25±1 °C using pH meter (Global instruments pH meter, Delhi).

Partition coefficient

The partition coefficient study of valsartan was performed using n-octanol as the oil phase and phosphate buffer pH 7.4 as the aqueous

phase. The two phases were mixed in equal quantities (50 ml) by adding 20 mg of drug in a separating funnel and was saturated with each other at room temperature for 24 h. The saturated phases were separated by centrifugation. The two phases were separated and then analysed for respective drug contents. The partition coefficient measured by the given formula:

$$K_{0/w} = \frac{\text{Concentaration of drug in oil phase}}{\text{Concentration of drug in aqueous phase}}$$

Determination of λ_{max} by UV Spectrophotometer

The identification of drug was done by UV spectrophotometric by a simple quantitative method using Shimadzu Spectrophotometer UV-1800 (Shimadzu Corp., Japan).

50 mg of drug Valsartan has weighed accurately and transferred into a 50 ml volumetric flask and dissolved in methanol. The flask was shaken and volume was made up to the mark with methanol to give a solution of 1000 µg/ml. From this solution, 10 ml of solution was pipetted out and placed into 100 ml volumetric flask. The volume was made up to the mark with methanol to give a 100 µg/ml. A dilution of 20 µg/ml concentration was made from the above stock solution with the methanol and the resulting solution was scanned between the wavelength of 200 nm to 400 nm.

Preparation of calibration curve of valsartan

A standard stock solution of valsartan was prepared by dissolving 100 mg of drug in 100 ml of methanol (1000 µg/ml). From the above stock solution, 10 ml was taken and diluted up to 100 ml in 0.1 N NaOH (100 µg/ml). From the above solution 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8,0.9 and 1 ml was taken and diluted up to 10 ml with methanol to get series of solutions in concentration in range from 1to 10 µg/ml of valsartan. Absorbance was noted using UV-VIS Spectrophotometer at λ_{max} of 249 nm against a blank (0.1 N NaOH).

Solubility determination of valsartan

Qualitative solubility analysis: 10 mg drug in 10 ml solvent (aqueous/non-aqueous) taken in a conical flask. Different solvents were used for the solubility determination to determine the solubility of the drug. After shaking, the sample was examined for the presence of any undissolved suspended particles and clarity.

Quantitative solubility analysis: Dissolving excess amount of solute in 10 ml solvent in conical flask till a saturated solution was obtained. Different solvents were used for solubility determination like water, acetone, methanol, ethanol, for determination of solute dissolved in each solvent. These conical flasks were stoppered and agitated in thermostatically controlled orbital shaker at 25±1 °C. After 24 h equilibrium was attained and the sample was filtered through Whatman filter paper (No.1). The sample was analysed after dilution for the concentration of drug dissolved using UV-VIS spectrophotometer.

pH-dependent solubility

The solubility determination of valsartan was carried out in different pH solvents. The phosphate buffer of pH 1.2 to 10 was prepared in freshly boiled and cooled distilled water, and their pH was adjusted (±0.5). These solutions were filtered through Whatman filter paper (No.1) and kept in tightly closed glass bottles.

The drug was added in excess quantity to a series of screwcapped 15 ml glass vials containing 10 ml of phosphate buffer solutions of varying pH such as 1.2, 2.2, 4.6, 5.8, 7.4, 8, 9 and 10 until a saturated solution was obtained. The vials were mechanically shaken at room temperature for 24 h, in thermostatically controlled orbital shaker at 25±1 °C. These suspensions were filtered through Whatman filter paper. Aliquots of the filtrate obtained were diluted with distilled water and analysed using UV spectrophotometer at 249 nm against blank in case of valsartan.

Table1: Preformulation studies of valsartan

S. No.	Parameters	Observation	Result
1.	Organoleptic properties	Colour, odour, taste and crystallinity	White to off-white crystalline powder, odourless, tasteless
2.	Melting point	116-117 ° C	116±2 ° C
3.	pH value	Found to be weakly acidic in nature	3.5
4.	Partition coefficient	Lipophillic in nature	3.8
5.	Determination of max by UV spectrophotometer	Valsartan by UV analysis was carried out in 0.1 N NaoH as the drug was completely soluble in NaOH.	The spectrum was found to be maximum at λ_{max} 249 nm.
6.	Preparation of calibration curve of valsartan	Absorbance was noted using UV spectrophotometer of different concentration	Shows linear standard curve of valsartan
7.	Solubility studies	Qualitative solubility in which valsartan was soluble in methanol, ethanol, acetone, dichloromethane, 0.1 N NaOH, pH(7.4) phosphate buffer. Quantitatively drug was more soluble in ethanol and methanol.	Valsartan was freely soluble in methanol and ethanol. Quantitatively more soluble in methanol (2.76g/ml) and ethanol (2.15g/ml).
8.	pH-dependent solubility	Valsartan was carried out in different pH solvents (pH1.2 to 10).	The solubility of valsartan in water was 0.0213 mg/ml and in pH 10 was 1.150 mg/ml and hence solubility of valsartan in pH 10 was increased by 54 times.

Table 2: Composition of optimized formulations of nanosuspension of valsartan

Formulation code	Drug	Polymer HPMCE50PVPK30PEG6000	Surfactant (SLS)	Methanol	Water
F1	10 mg	20 mg	0.03	10 ml	50 ml
F2	10 mg	40 mg	0.02	10 ml	50 ml
F3	10 mg	60 mg	0.01	10 ml	50 ml
F4	10 mg	20 mg	0.03	10 ml	50 ml
F5	10 mg	40 mg	0.02	10 ml	50 ml
F6	10 mg	60 mg	0.01	10 ml	50 ml
F7	10 mg	20 mg	0.03	10 ml	50 ml
F8	10 mg	40 mg	0.02	10 ml	50 ml
F9	10 mg	60 mg	0.01	10 ml	50 ml

Preparation of nanosuspension of valsartan

The Valsartan nanosuspension was prepared by nanoprecipitation method. Firstly, 10 mg of drug is dissolved in a 50 ml of methanol. Then kept on a magnetic stirrer and this solution is then mixed with a miscible antisolvent system in the presence of surfactants. Rapid addition of drug solution into the antisolvent leads to sudden supersaturation of drug in the mixed solution forms ultrafine drug solids.

Fig. 1: Preparation of nanosuspension formulations

Characterization of optimized nanosuspension

Drug content

Drug content was determined by UV-Visible spectrophotometer at 249 nm. About 1 ml of nanosuspension preparation was taken and diluted with 0.1 N Hcl.

Redispersibility

Nanosuspension stored in vials was determined by titling the vial bottle up and down with hand till the sediment was uniformly dispersed in the aqueous phase and the no. of times tilted was noted.

Viscosity measurement

The viscosity of lipid-based formulations of several compositions can be measured at different shear rates at different temperatures using Brookfield type rotatory viscometer.

The sample room of the instrument must be maintained at 37% C by a thermo bath and the samples, for the measurement are to be immersed in it and found viscosity of the formulations.

Measurement of particle size and size distribution

The mean particle size and the width of particle size distribution called polydispersity index are determined by Photon Correlation Spectroscopy (PCS). Particle size and polydispersity index (PI) govern the saturated solubility; dissolution velocity and biological performance. The prepared nanosuspension of 100 µl was diluted to 5 ml with double distilled water and diluted dispersion was measured using Malvern zetasizer.

Zeta potential

For Zeta potential determination samples of formulations were diluted with water and placed in the electrophoretic cell. Each sample was measured 3 times at 25% C and average values were employed for measuring the response

Dissolution velocity and saturation solubility study

Adding the excess amount of sample to distilled water (2 ml) and the samples were subjected to shaking in screw-capped vials for 24 h. The sample was further taken in test tubes and centrifuged at 1000 rpm for 10 min. after the sample was filtered through a 0.22-micrometer membrane filter and the filtrate was diluted appropriately with distilled water and drug content was estimated in UV spectroscopy.

Fourier transform infrared spectroscopy

The drug-polymer compatibility was ascertained by subjecting the drug and polymer to Fourier transform infrared spectrometric study using FTIR-affinity-1S-Shimadzu, The samples were scanned in the spectral region between 4000 and 400 cm^{-1}. The solid material was placed onto the small crystal area, then the pressure arm was positioned over the crystal/sample area. Force was applied to the sample, pushing it onto the diamond surface. Transmittance was measured from wave number 4000 cm^{-1} to 400 cm^{-1}.

RESULTS AND DISCUSSION

A. Drug content

Drug content of various formulations are shown below in table1. The percentage of drug content in formulation1 and formulation2 was more as 96.677% and 97.543%.

Table 3: Drug content of various formulations

S. No.	Formulation code	% Drug content
1.	F1	96.677
2.	F2	97.543
3.	F3	94.432
4.	F4	95.667
5.	F5	94.632
6.	F6	90.345
7.	F7	96.535
8.	F8	92.675
9.	F9	94.576

B. Redispersibility

The redispersibility of various formulations was shown in table 2. The F2 and F1 formulation was best among all formulations. On shaking it may be easily redispersed.

C. Viscosity measurement

The viscosity measurement of different formulations was shown in table 3. The F2 shows 0.894 m Pa-s and F1 shows 0.895 m Pa-s respectively.

Table 4: Redispersibility of various formulations

Formulation code	Redispersibility
F1	Fast
F2	Very Fast
F3	Medium
F4	Fast
F5	Fast
F6	Fast
F7	Medium
F8	Fast
F9	Fast

Table 5: Viscosity measurement of different formulations

S. No.	Formulation code	The viscosity of the dispersion medium
1.	F1	0.895 mPa-s
2.	F2	0.894 mPa-s
3.	F3	0.892 mPa-s
4.	F4	0.890 mPa-s
5.	F5	0.879 mPa-s
6.	F6	0.875 mPa-s
7.	F7	0.874 mPa-s
8.	F8	0.872 mpa-s
9.	F9	0.870 mPa-s

D. Measurement of particle size and particle size distribution

The particle size and polydispersity index of formulation 1st and 2nd was shown in fig. 9 and fig 10. The particle size and the Polydispersity Index (PI) of the former drug particles were measured immediately after precipitation by dynamic laser light scattering (Zetasizer Ver. 6.11Malvern). The polydispersity index of F1 and F2 was found to be in the range of 4.194 and 230.81.
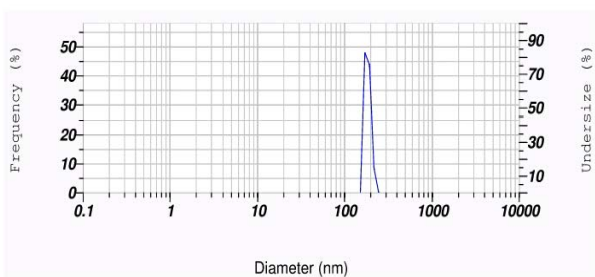

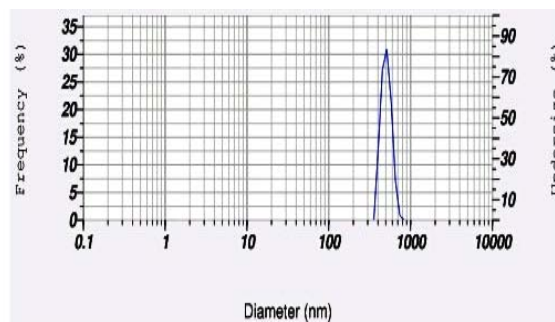**Fig. 1: Particle size and polydispersibility index of formulation2**

Fig. 2: Particle size and polydispersibility index of formulation1

E. Particle charge (Zeta potential)

The particle charge of formulation1 and formulation2 shows in fig. 2 and fig. 3. The zeta potential of the nanoparticles was found to be negative which may be due to the presence of terminal carboxylic groups. High potential values should be achieved to ensure a high-energy barrier and favour a good stability.
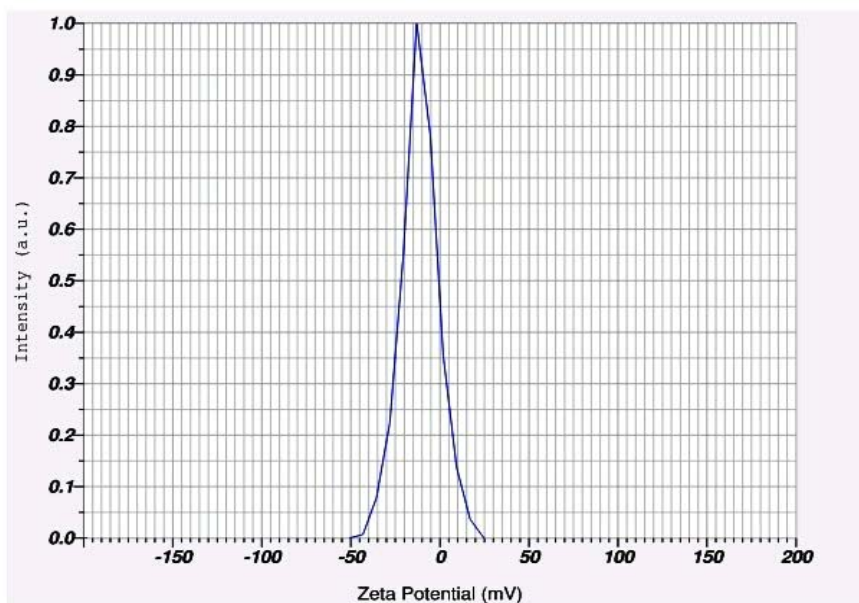

Fig. 2: Zeta potential of formulation1

F. Dissolution velocity and saturation solubility

The saturation solubility of different formulations was shown in table 4. Saturation solubility of an optimized batch of Nanosuspension was found to be 0.941 mg/ml and 0.772 mg/ml respectively. The improvement in saturation solubility is due to a reduction in particle size and subsequent increase in surface area.

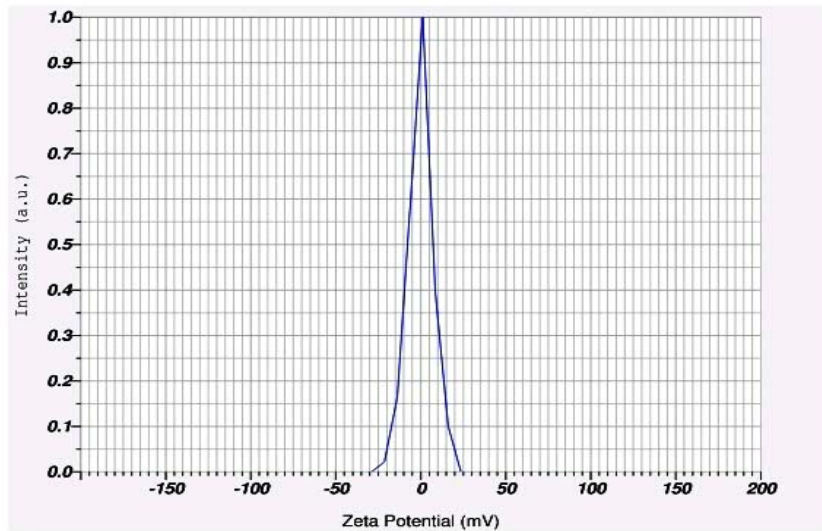So, it can be assumed that this increase in saturation solubility may improve bioavailability.

Fig. 3: Zeta potential of formulation2

Table 6: Saturation solubility of different formulation

S. No.	Formulation code	Saturation solubility in water mg/ml
1.	F1	0.772
2.	F2	0.941
3.	F3	0.620
4.	F4	0.537
5.	F5	0.526
6.	F6	0.442
7.	F7	0.507
8.	F8	0.432
9.	F9	0.650

G. FT-IR

The FTIR spectra of Valsartan with HPMC and FTIR spectra of Formulation1 shows in fig 3 and fig 4. The precipitated nanoparticles were comparable and the peaks of Valsartan in the physical mixture are of lower intensity than pure drug. The characteristic peak of N-H amide stretching, aromatic cyclic enes, CO group of acid, C=C aromatic, Carbonyl group, hydroxyl group, C-H bending (aromatic), C-C bending cm-1 which respectively were found to be intact in the physical mixture as well as the formulation which indicates the absence of HPMC and drug interactions.

Very less stretching or broadening of peaks of the drug was observed in mixture form.
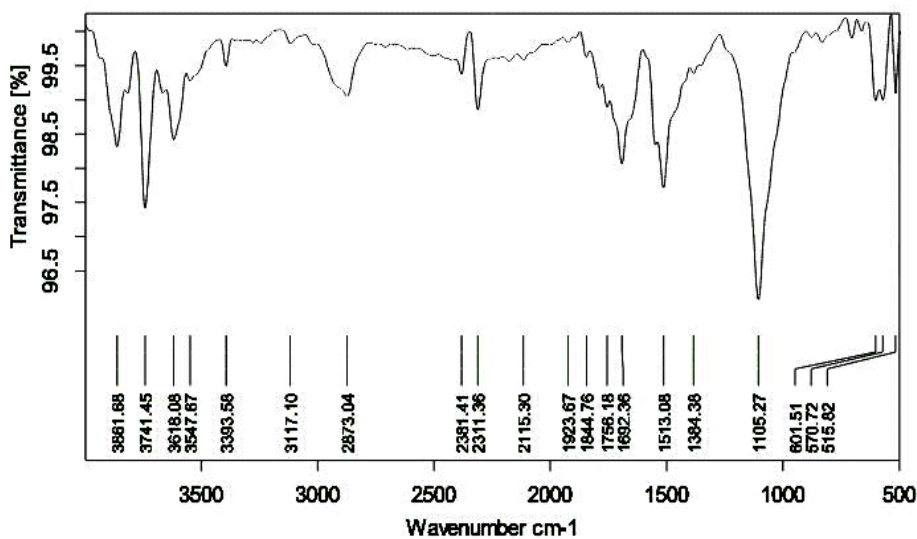

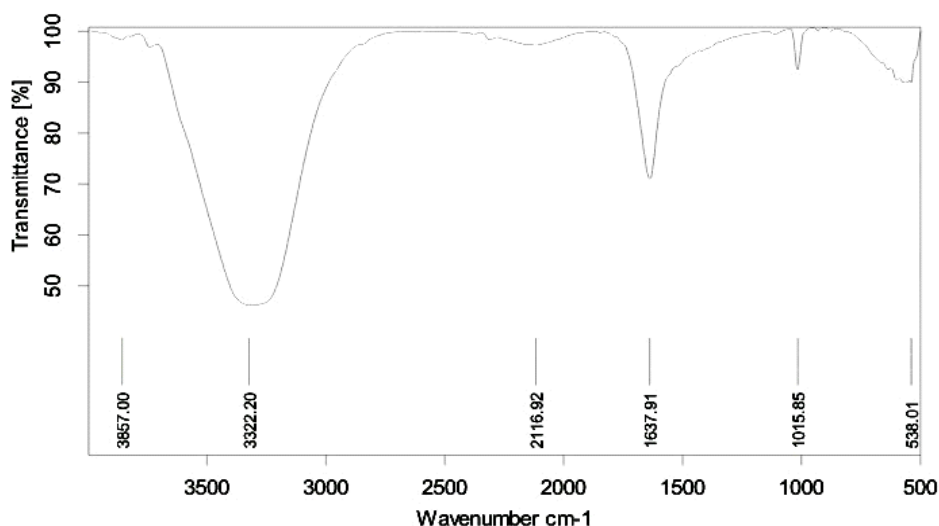**Fig. 4: FTIR Spectra of drug valsartan with polymer HPMC**

Fig.5: FTIR spectra of formulation1

Stability of formulated nanosuspension

The particle size of the formulations after 4 mo was observed. The formulations at 4 °c remained stable, whereas that at room temperature showed a slight increase in particle size. The stability studies of formulation F1 and F2 had been performed. A loose, thin layer of sediment was observed when nanosuspension was stored at room temperature for 1 mo. However, the sediment disappeared with slight handshaking. The average particle diameter was found to be 106.3 nm and 105.3 nm when the sample was stored at room temperature.

Table 7: Stability of formulated nanosuspension

Formulation code	Storage temperature conditions	Initial particle size	Particle size after 4 mo
F1	4 °C	108.4	104.4
	Room temp.		106.3
F2	4 ° C	105.6	102.5
	Room temp.		105.3

CONCLUSION

It was concluded that the nanoprecipitation with ultrasonication have potential to formulate homogeneous nanosuspensions with uniform sized stable nanoparticles of valsartan. It is a rapid and easy technique and nanoparticles were formed spontaneously. Nanoparticles were characterized by particle size distribution, zeta potential analysis, Fourier transform infrared spectroscopy. This method can be used to improve the therapeutic efficacy of poorly soluble drugs. The preparations were found to physically stable with HPMC as a stabiliser.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest

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