"Formulation and evaluation of nanosuspension of valsartan''

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ABSTRACT

Valsartan is a new potent and orally active solubilization which selectivity act as angiotensin II antagonist acting on the AT1 receptor subtype. It is indicated for hypertension, heart failure and post-myocardial infarction It is a poorly aqueous soluble drug (BCS Class II), and is being selected for the enhancement of solubility and bioavailability.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 0.0213mg/ml.The drug is rapidly absorbed after oral administration having bioavailability is 23%.This compound belongs to the class of organic compounds known as biphenyltetrazoles 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.There are many conventional methods for increasing the solubility of poorly soluble drugs, which include micronization, solubilization using co-solvents, salt form, surfactant dispersions, precipitation technique, and oily solution.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. These techniques are not applicable for those drugs which are not soluble in aqueous and organic solvents.

Keyword: *Nanosuspension, valsartan, solubilization, Hpertension*

INTRODUCTION

NANOSUSPENSION :

A pharmaceutical nano suspension is defined as "very finely single solid drug particles in an aqueous vehicle, stabilized by surfactants, for both oral and topical use or parental and pulmonary administration, as well as decreased particle size, leading to an increased dissolution rate and therefore enhanced better bio-availability".[1]

A nano suspension is a sub-micron colloidal dispersion of drug particles which are stabilized by surfactants. The particle size allocation of the solid particles in nano- suspensions have been frequently less than one micron with standard particle size ranging between 200 to 600 nm. In nano-suspension techniques, the drug is maintained in the requisite crystalline state with reduced particle size, foremost to increased dissolution rate and therefore enhanced bio-availability. An increase in the dissolution speed of micronized particles (particle size < 10 μm) is associated to an increase in the surface area and as a result the dissolution velocity. Nano-sized particles can increase solution speed and diffusion solubility because of the vapor pressure effect. In addition, the diffusional space on the shell of the drug nanoparticles is decreased, thus leading to an increased concentration grade. The increases in surface area and concentration gradient lead to a much more prominent increase in the dissolution velocity as compared to a micronized product. Moreover, the saturation solubility is

increased as well. Another possible description for the increased saturation solubility is the formation of high energy surfaces when disrupting the more or less ultimate drug microcrystal's to nanoparticles.

Nanosuspensions consist of the weakly water-soluble drug with no matrix material suspended in 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. The reduced particle size renders the possibility of intravenous administration of poorly soluble drugs without any blockage of the blood capillaries. The suspensions can also be lyophilized into a solid matrix. Apart from these advantages, it also has advantages of liquid formulations over others.[

Materials and Methods:

MATERIALS

Drug sample Valsartan was obtained as a gift samples from Cipla, Pithampur and Hetero Drugs, Hyderabad respectively

Materials and company name

S.No	Material	Company
1.	Valsartan	Gift sample from cipla,Pithampur
2.	Hydroxypropylmethyl cellulose	Loba Chemie
3.	Polyvinyl pyrolidone-K30	Himedia
4.	Polyethylene glycol-6000	Central Drug House Laboratory
5.	Sodium lauryl sulfate	Himedia
6.	Methanol	Rankem
7.	n-Octanol	Oxford Laboratory
8.	Hydrochloric Acid	Rankem

Firstly, the drug is dissolved in a suitable solvent. This solution is then mixed with a miscible antisolvent system in the presence of surfactants. Rapid addition of drug solution in to the antisolvent leads to sudden supersaturation of drug in the mixed solution forms ultafine drug solids.

PREFORMULATION STUDY

1. Identification of drug

A. Organoleptic properties

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

B. Melting Point

Melting point determination of drug was performed using melting point apparatus (BTI-34 melting point apparatus, Mumbai, India). In this method small amount of drug was filled in capillary tube open from both ends and it was placed along with thermometer in melting point apparatus. The temperature was noted when the drug completely melted.

C. pH value

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

D. 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 (50ml) by adding 20 mg of drug in a separating funnel and was saturated with each other at room temperature for 24 hrs. The saturated phases were separated by centrifugation. The two phases were separated and was then analyzed for respective drug contents. The partition coefficient of drug (K o/w) was calculated using the following formula:

The partition coefficient was measured by the given formula:

Ko/w =Coil/Cwater

E. Determination of λmax by UV Spectrophotometer

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

50 mg of drug valsartan was 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 upto 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 resuting solution was scanned between wavelength ranges of 200nm to 400 nm. [37]

F. FTIR spectrometry

The IR analysis of the sample was carried out for qualitative compound identification. In ATR (Attenuated Total Reflectance), the solid material is placed onto the small crystal area. In this instrument IRAffinity-1, (Shimadzu, Japan) diamond being the preferred choice for most applications because of its robustness and durability. After solid has been placed on the crystal area, the pressure arm is positioned over the crystal/sample area. Force is applied to the sample, pushing it onto the diamond surface. Transmittance was measured from wave number 4000 cm-1 to 400-1 using Happ-Gensel apodization.

G. Preparation of Caliberation Curve of Valsartan

Standard stock solution of Valsartan was prepared by dissolving 100mg of drug in 100ml of methanol (1000µg/ml). From the above stock solution 10 ml was taken and diluted upto 100ml in 0.1 N NaOH (100µg/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 10ml with methanol to get series of solutions in concentration range from 1 to 10 µg/ml of Valsartan. Absorbance was noted using UV-VIS Spectrophotometer at λmax of 249 nm against blank (0.1 N NaOH).

H. Qualitative Solubility determination

- Qualitative Solubility

Qualitative solubility analysis for Valsartan was done by dissolving 10mg of drug in 10 ml of solvent (aqueous/ nonaqueous) taken in conical flask. Different solvents were used for the solubility determination like distilled water, acetone, ethanol, methanol, chloroform etc. to determine the solubility of drug. After shaking, the sample was examined for the presence of any undissolved suspended particles and clarity.

- Quantitative solubility study

Quantitative solubility analysis for Valsartan was done by taking 10ml solvent and dissolving excess amount of solute in solvent taken in conical flask till saturated solution was obtained. Different solvents were used for solubility determination like water, acetone, chloroform, methanol, ethanol, for determination of solute dissolved in each solvent. These conical flasks were stoppered and agitated in thermostatically controlled orbital shaker (Tanco, Pitampura, New Delhi, India) at 25±1°C. After 24hrs equilibrium was attained and the sample was filtered through Whatman filter paper (No.1). The sample was analyzed after suitable dilution for the

concentration of drug dissolved using UV-VIS spectrophotometer. The experiment was conducted in triplicate and the average value was noted.

I. pH Dependent Solubility of Valsartan

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 screw capped 15ml glass vials containing 10ml of phosphate buffer solutions of varying pH such as pH 1.2, 2.2, 4.6, 5.8, 7.4, 8, 9 and 10 until saturated solution was obtained. The vials were mechanically shaken at room temperature for 24 hrs, in thermostatically controlled orbital shaker (Tanco, Pithampura, Delhi) at 25±1°C. These suspensions were filtered through Whatman filter paper (No.1). Aliquots of filtrate obtained were diluted with distilled water and analyzed using UV spectrophotometer at 249 nm against blank in case of Valsartan. The solubility study was carried out in triplicate and observation was noted.

RESULT & DISCUSSION

RESULTS

A.Organoleptic properties

The drug was studied for their organoleptic properties like colour, odour, taste , crystallinity and observation was recorded in table 8.

Table 8: Organoleptic properties of drug.

Parameter	Valsartan
Colour and Physical appearance	white to off-white crystalline powder
Odor	odorless
Taste	tasteless

B.Melting point

The melting point of the drug was in the reported range indicating that the drug sample was pure.

Table 9: Melting point of Valsartan

Drug	Observed	Reference
Valsartan	116±2°C	116-117°C

C. pH value

The pH of drug Valsartan was found to be 3.5 indicating weakly acidic in nature.

Table 10: pH value of Valsartan

Drug	Value
Valsartan	3.5

The logP value of Valsartan was found to be in the range of 2.5 to 4 indicating the lipophilic nature of drugs and the value was reported in table 10.

D. Partition coefficient

The partition coefficient value of valsartan was found and illustrate in table11.

Table 11: Partition coefficient value of Valsartan

Drug	Observed	Reference
Valsartan	3.8	3.68-5.27

E. UV Spectroscopic Characterization

UV spectroscopic analysis for the drug sample was performed and the maximum absorption i.e. λmax of Valsartan was observed at 249nm.Valsartan UV analysis was carried out in 0.1 N NaOH as the drug is completely soluble in NaOH.

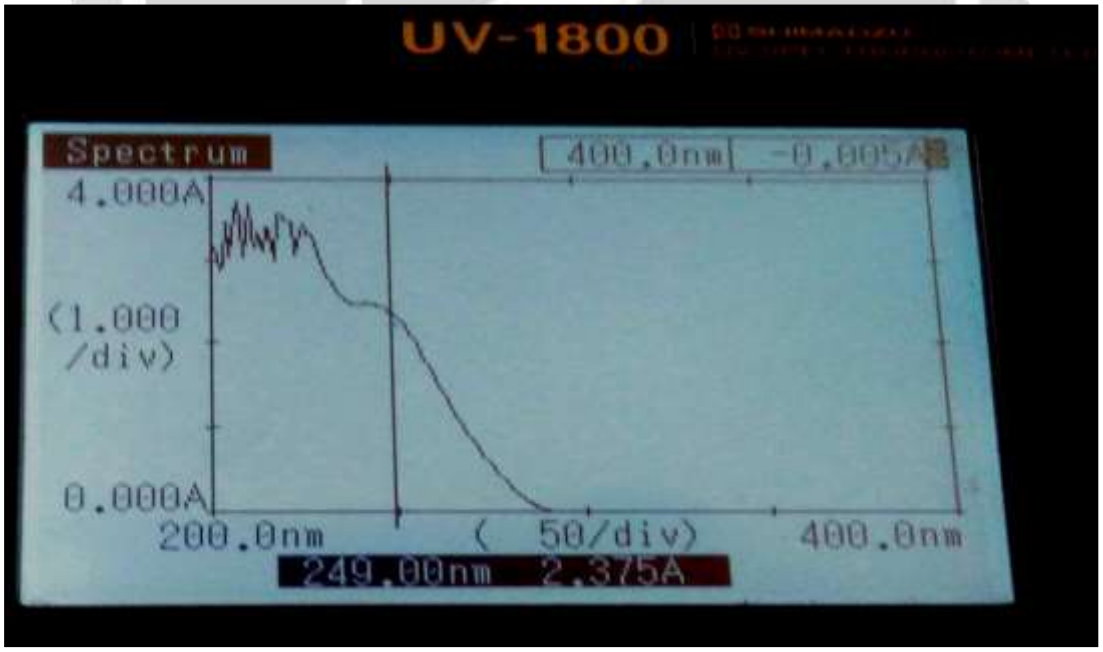


Fig.6 UV Spectra of Valsartan at 249 nm

F. FTIR spectrometry

The IR Spectra of sample of Valsartan was shown in fig. The characteristic peaks attributable to various functional groups present in the molecule of drug was assigned to establish the identity of drug sample of Valsartan in Table 12.

Table 12: Characteristic FT-IR Absorption peaks of Valsartan

Functional Group	Absorption Frequency in Wave no.(cm^{-1})
N-H amide Stretching	3566.38
Aromatic cyclic enes	2962.66
CO group of acid	1732.08
C=C aromatic	1456.26
Carbonyl group	1409.96
Hydroxyl group	1271.09
C-H bending (aromatic)	810.10
C-C bending	758.02

All the peaks values were found to be near the standard values to confirm the purity of the drug molecules.

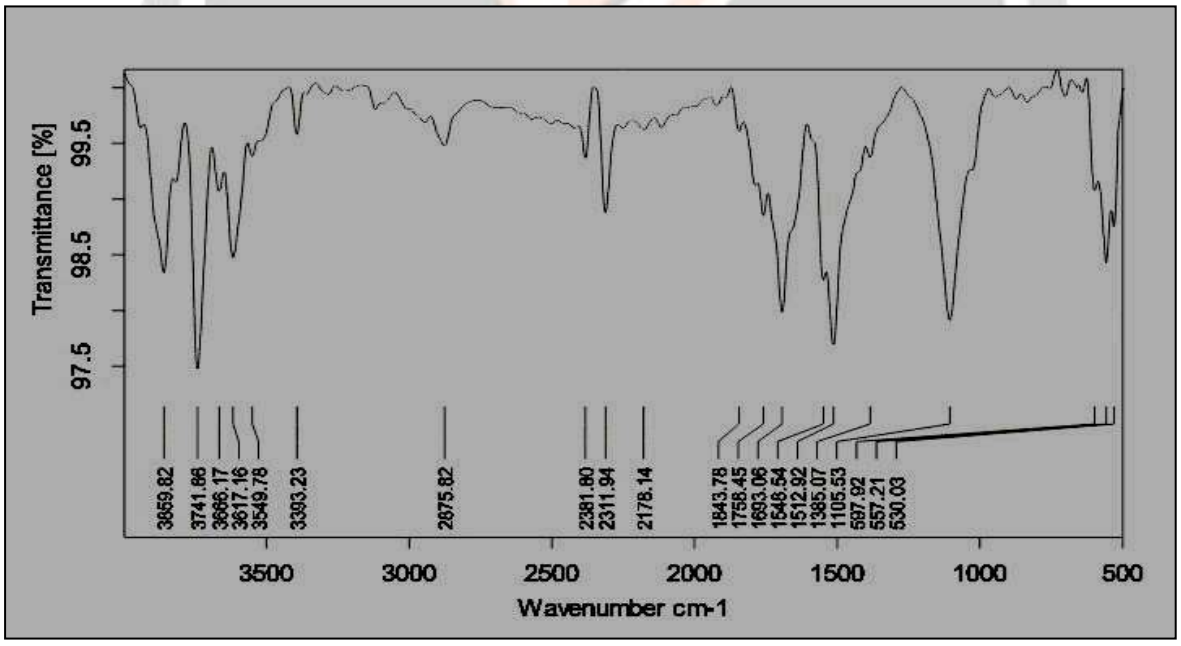


Fig.7 FTIR Spectra of drug sample Valsartan

G.Preparation of calibration curve of Valsartan in 0.1 N NaOH (λmax 249nm)

Calibration curve in of Valsartan was plotted using NaOH at λmax of 249 nm and the readings were shown in table 8. Figure 4 depicts the linear standard curve of Valsartan including the graph equation.

Table 13: Calibration curve of Valsartan in 0.1N NaOH (λmax 249nm)

Concentration (µg/ml)	Absorbance
0	0
1	0.230
2	0.486
3	0.761
4	0.985
5	1.203
6	1.353
7	1.600
8	1.846
9	2.006
10	2.215

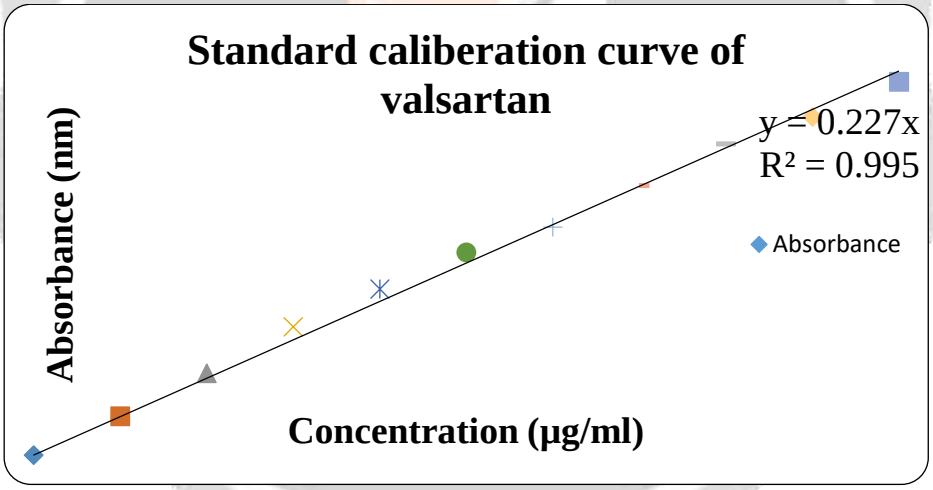


Fig.8: Caliberation curve of Valsartan at 249 nm

H. Solubility studies of drugs

- **Qualitative solubility study**

Qualitative solubility analysis for valsartan was done by dissolving 10mg of drug in 10 ml of solvent. Different solvents were used for the solubility determination like distilled water, acetone, ethanol, methanol, NaOH and chloroform to determine the solubility of drug.

Table 14:The qualitative solubility of Valsartan in different solvents

S.No.	Solvent	Result
1.	Water	Practically insoluble
2.	Methanol	Freely soluble
3.	Ethanol	Freely soluble
4.	Chloroform	Soluble
5.	Acetone	Soluble
6.	Ethyl acetate	Soluble
7.	Dichloromethane	Soluble
8.	0.1 N NaOH	Soluble
9.	0.1 N Hcl	Practically insoluble
10.	pH 7.4 phosphate buffer	Soluble

Valsartan was found to be soluble in ethanol, methanol, chloroform, acetone, dichloromethane, ethyl acetate, 0.1 N NaOH and 7.4 pH phosphate buffer.

- **Quantitative solubility study**
  Quantitative analysis for valsartan was done by dissolving 10mg of drug in 10 ml of solvent. Different solvents were used for the solubility determination like distilled water, acetone, ethanol, methanol, NaOH and chloroform to determine the solubility of drug.

Table 15: The quantitative solubility of valsartan in different solvents

S.No	Solvent	Solubility of Valsartan
1.	Water	0.0213mg/ml
2.	Ethanol	2.15 g/ml
3.	Methanol	2.76 g/ml
4.	7.4pH phosphate buffer	0.962 mg/ml
5.	Ethyl acetate	55.72 mg/ml
6.	Chloroform	67.84 mg/ml
7.	Dichloromethane	36.11 mg/ml
8.	Acetone	45.16 mg/ml

Average of three determinations

The quantitative solubility of Valsartan determined in different solvents and the results was illustrated in table 15. Valsartan was found to be more soluble in ethanol and methanol.

I. pH dependent solubility study

The pH dependent solubility of Valsartan in phosphate buffers ranging from pH 1.2 to 10 were shown in Table. Valsartan was found to be more soluble at higher pH indicating acidic nature of drug.

Measurement of particle size and particle size distribution

The particle size and polydispersity index of formulation 1st and 2nd was shown in fig 9 and10.

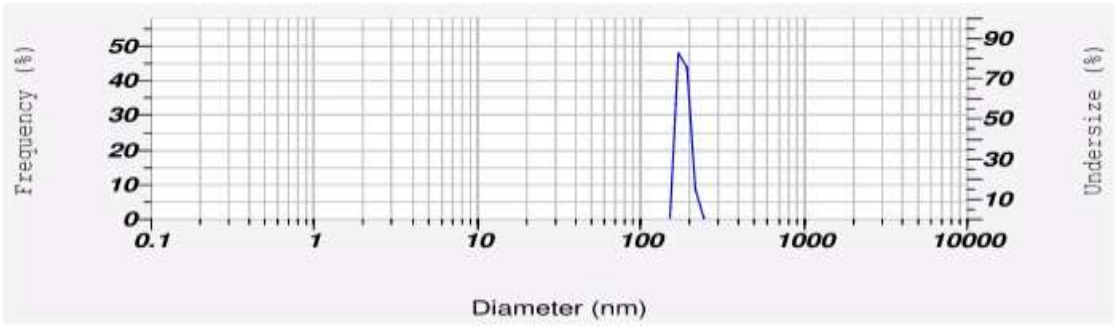


Fig.9: Particle size and polydispersibility index of formulation1

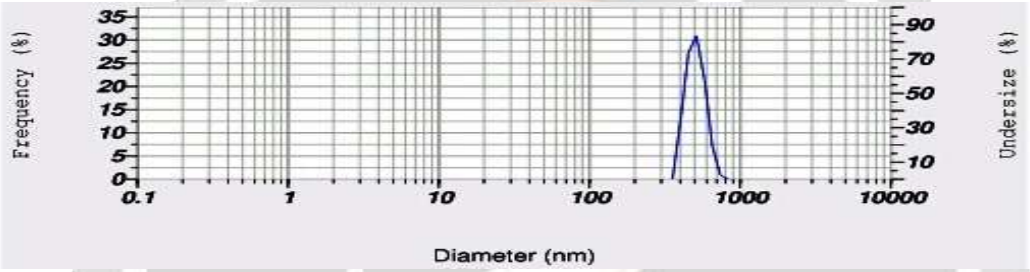


Fig.10:Particle size and polydispersibility index of formulation2

E.Particle charge (Zeta Potential)

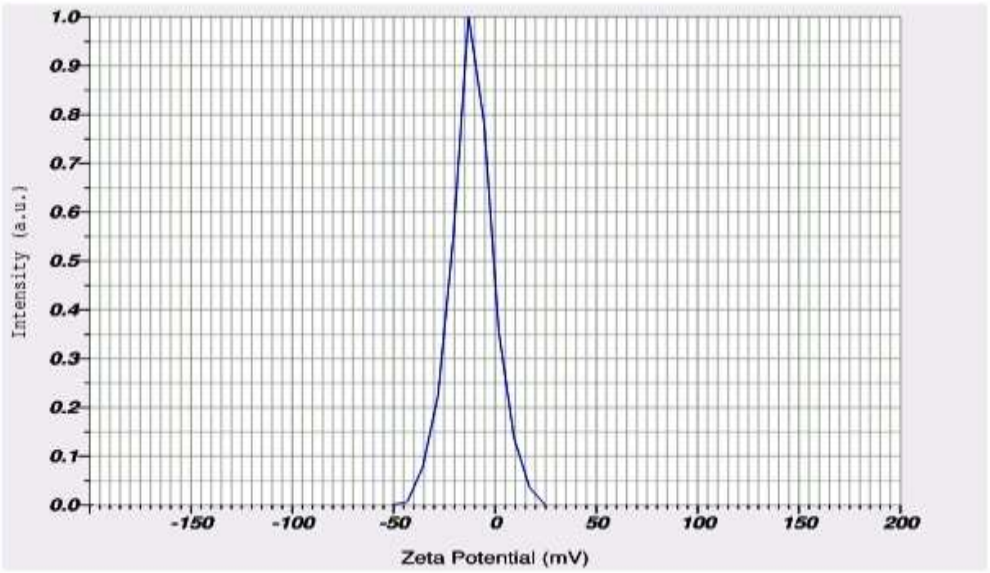


Fig.11: Zeta potential of Formulation1

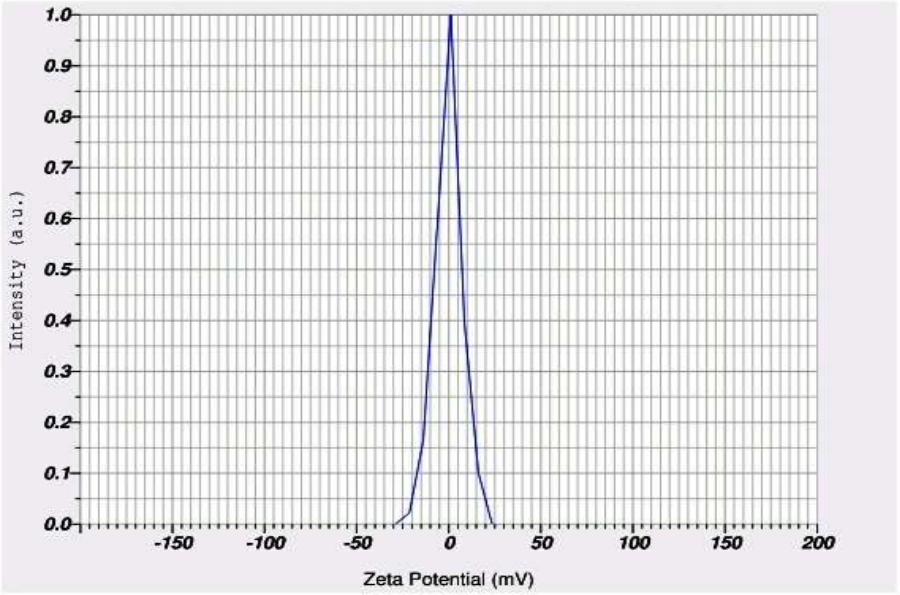


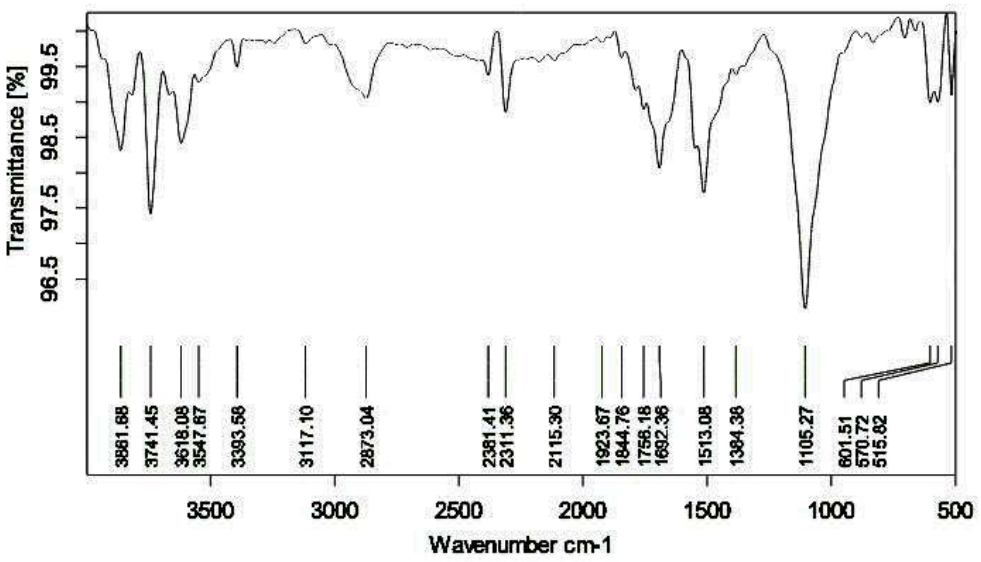
Fig. 12: Zeta potential of Formulation2

F. Dissolution velocity and Saturation solubility

The saturation solubility of different formulations was shown in table 21.

Table 21: 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

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