International Journal of Medicine and Pharmaceutical Research
CODEN (USA): IJCPNH | ISSN: 2321-2624
Journal Home Page: www.pharmaresearchlibrary.com/ijmpr

Development, Characterization and Solubility Enhancement of Valsartan using Nanotechnology

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A B S T R A C T

Background: Drug absorption from the gastro intestinal tract can be limited by various factors with the most common one being poor aqueous solubility and poor permeability of a drug molecule. Aim: The aim of the work is to enhance the solubility, dissolution rate and oral bio availability of poorly soluble drug Valsartan by formulating them into Nanosuspension with poloxamer as a stabilizing agent. **Methods:** Preformulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance with the goal of designing optimum drug delivery system. Preformulation yields basic knowledge necessary to develop suitable formulation. **Results:** The optimized Nanosuspensions were formulated as tablets and capsules to make the formulations stable and patient friendly. Valsartan Nanosuspensions were prepared by pearl milling technique using Zirconium beads as milling media and Poloxamer 407 as stabilizer. **Conclusion:** Based on its physicochemical and biopharmaceutical properties, Valsartan was selected as a drug candidates for developing Nanosuspension based formulations for improving the solubility and bioavailability by enhancing the rate and extent of dissolution.

Keywords: Biopharmaceutical properties, Pre formulation, Poloxamer 407, Valsartan, Nano suspensions.

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A R T I C L E H I S T O R Y: Received 20 December 2021, **Accepted** 10 Feb 2022, **Available Online** 16 March 2022

Citation: *G. Srivani, et al. Development, Characterization and Solubility Enhancement of Valsartan using Nanotechnology. Int. J. Med. Pharm. Res., 2022, 10(1): 24-30.*

CONTENTS

1. Introduction

Drug absorption requires that molecules be in solution at the absorption site. Dissolution of solid dosage forms in gastrointestinal fluids is a prerequisite to the delivery of a drug to the systemic circulation following oral administration. Dissolution depends in part on the solubility of drug substance in the surrounding medium. Fairly soluble drugs in gastrointestinal media exhibit complete oral absorption, and thus good bioavailability.

About 40% of drugs are not soluble in water in practice and therefore are slowly absorbed, which results in insufficient and uneven bioavailability and GI toxicity[1-6]. Thus, most exigent phase of drug development practice particularly for oral dosage forms is the enhancement of drug solubility thereby its oral bioavailability. Bioavailability refers to the amount of therapeutically active drug that approaches the systemic circulation and thus, is available at the site of action. There are numerous chemical molecules which experience low aqueous solubility problems. Although these molecules have prospective pharmacodynamics properties, they exhibit low bioavailability, which can be attributable to poor aqueous solubility and therefore, these molecules turn into abortive entities.

Factors Affecting Solubility:

Several factors affect solubility of a drug. The following are the factors that affect solubility are Particle Size, Temperature, Pressure, Nature of the solute and solvent, Molecular size, Polarity, Polymorphs.

Nanotechnology areas and applications:

Nanotechnology, being an interdisciplinary field, has three main extensively overlapping areas: Nanoelectronics, Nanomaterials and Nanobiotechnology which find applications in materials, electronics, environment, metrology, energy, security, robotics, healthcare, information technology, biomimetics, pharmaceuticals, manufacturing, agriculture, construction, transport and food processing andstorage. Nanotechnology is interdisciplinary and it reverses the trend of specialization in specific disciplines. It integrates all disciplines like biomedicine, engineering and technology[7-9].

Nanotechnology in drug delivery:

The use of nanostructures such as polymeric Nanoparticles is a non invasive approach of penetrating the blood brain barrier for management of neurodegenerative disorders, cerebro-vascular and inflammatory diseases. New drug delivery methods enable pharmaceutical companies to reformulate the existing drugs in the market. Nanotechnology is strategic in developing drug delivery systems which can expand drug markets.

Polymeric Nanoparticles:

Polymeric Nanoparticles are colloidal solid particles with a size range of 10 to 1000nm and they can be spherical, branched or shell structures. The first fabrication of Nanoparticles was about 35 years ago as carriers for vaccines and cancer chemotherapeutics (23). They are developed from non biodegradable and biodegradable polymers. Their small sizes enable them to penetrate capillaries and to be taken up by cells, thereby increasing the accumulation of drugs at target sites.

Liposomes:

Liposomes were first developed about 40 years ago. They are small artificial vesicles (50–100nm) developed from phospholipids such as phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine and phosphatidylserine, which have been used in biology, biochemistry, medicine, food and cosmetics. The characteristics of liposomes are determined by the choice of lipid, their composition and method of preparation, size and surface charge. Liposomes have been applied as drug carriers due to their ability to prevent degradation of drugs, reduce side effects and target drugs to site of action.

Nanotubes:

Nanotubes are self-assembling sheets of atoms arranged in tubes. They may be organic or inorganic in composition and can be produced as single or multi-walled structures. A popular version of a nanotube involves the use of soluble fullerene derivatives, such as C60. Nanotubes have large internal volumes and the external surface can be easily functionalized[10].

Dendrimers:

Dendrimers are polymer based macromolecules formed from monomeric or oligomeric units, such that each layer of branching units doubles or triples the number of peripheral groups.

Gold Nanoparticles:

The preparation of gold Nanoparticles commonly involves the chemical reduction of gold salts in aqueous, organic or mixed solvent systems. However, the gold surface is extremely reactive and under these conditions aggregation occurs. To circumvent this issue, gold Nanoparticles are regularly reduced in the presence of a stabilizer, which binds to the surface and precludes aggregation via favorable cross-linking and charge properties[11].

Carbon Nanotubes:

Carbon nanotubes were initially discovered in 1991 in cathode deposits following the evaporation of graphite. Shortly after this report, carbon nanotubes were isolated after pyrolysis of hydrocarbons such as ethylene or acetylene over Nanoparticles of iron, cobalt or other dispersedmetals.

Quantum Dots: Quantum dots are luminescent Nanoparticles typically used for imaging in biological systems.

Nanowires: Nanowires are glowing silica wires in nanoscale, wrapped around single strand of human hairs.

Para-magnetic Nanoparticles:

Para-magnetic Nanoparticles are being used for both diagnostic and therapeutic purposes. Diagnostically para-magnetic iron oxide Nanoparticles are used as contrast agents in magnetic resonance imaging. They have a greater magnetic susceptibility than conventional contrast agents. Targeting of these Nanoparticles enables identification of specific organs and tissues.

Nanoporous Membranes:

Artificial nanoporous membranes are of current interest largely because of applications involving molecular sorting, sensing and separation. For any emerging membrane technology, transition to commercial success

requires both precise control over device performance and scalability of the membrane synthesis process[12].

Nano suspension:

A pharmaceutical Nanosuspension is defined as very finely dispersed solid drug particles in an aqueous vehicle for either oral and topical use or parenteral and pulmonary administration, with reduced particle size, leading to an increased dissolution rate and therefore improved bioavailability[13-17].

2. Methodology

Calibration curve of Valsartan in 1.2pH HCl buffer, 6.8pH phosphate buffer:

100mg of Valsartan drug was taken and added to methanol in a 100ml volumetric flask and volume was made up to 100ml, resulting in a standard stock solution of 1mg/ml. From the above standard stock solution 10ml was taken and added to 1.2pH buffer, 4.5pH sodium acetate buffer, 6.8 pH phosphate buffer media in a 100ml volumetric flask and volume was made up to 100ml to obtain 100µg/ml solution. From this working stock dilutions were prepared using corresponding buffer media. From the working stock solution 1, 2, 3, 4, 5, 6, 7, 8, 9ml of sample was taken and diluted up to 50ml using respective buffer media in a 50ml volumetric flask resulting in concentrations of 2,4,6, 8,10,12,14,16&18µg/ml solutions. These were analyzed at 248nm.

Preformulations studies:

Preformulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance with the goal of designing optimum drug delivery system. Preformulation yields basic knowledge necessary to develop suitable formulation. It gives information needed to define the nature of the drug substance and provide frame work for drug combination with pharmaceutical excipients in the dosage form. Hence, the following preformulation studies are carriedout[18-19].

- Organoleptic evaluation Flow Properties
- Particle size distribution Solubility
- Saturation Solubility
- Drug excipient Compatibility studies

Organoleptic evaluation:

The color, odor and taste of the drug were evaluated and recorded using descriptive terminology.

Flow Properties:

Bulk density:

Bulk density was determined by measuring the volume of a known mass of powder sample that has been passed through an appropriate screen into a graduated cylinder (Method I). Approximately 10gms of test sample, M was introduced into 25 mL dry measuring cylinder without compacting. The powder was leveled carefully and unsettled apparent volume V0, read to the nearest graduated unit. Bulk density was calculated, in g per mL, by the formula,(M)/ (V_O). Generally replicate determinations are desirable for the determination of this property.

Tapped density:

Tapped density was achieved by mechanically tapping a measuring cylinder containing a powder sample. After measuring the initial weight and volume, the cylinder was mechanically tapped and volume readings were taken until little further volume change is observed.

Measures of powder compressibility:

The compressibility index and Hausner ratio are measures of the property of a powder to be compressed. As such, they are measures of the relative importance of interparticulate interactions. In a free flowing powder, such interactions are generally less significant and the bulk and tapped densities will be closer in value. For poorer flowing materials,there are frequently greater interparticle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility index and the Hausner's ratio.

Particle size distribution:

The particle size distribution of both the drugs were measured by Malvern Master sizer 2000S. The system uses laser diffraction analysis consists of an optical instrument, the sample dispersion units Hydro S, Hydro P and Scirocco.

Saturation solubility: The solubility of drug is an important physicochemical property because it affects the bioavailability of the drug, the rate of drug release into dissolution medium and consequently, the therapeutic efficiency of the pharmaceutical product.

Drug Excipients compatibility:

Physical observation:

Physical mixtures of Drug and excipients were prepared by grinding specific ratios for drug and excipients in a mortar. Sample of 3-4grams was taken and loaded in a glass vial, covered with rubber stopper, sealed with aluminum cap and labeled properly. Samples were observed and the physical description was recorded for initial evaluation and loaded into stability chamber of 40^0C and 75% RH for 4 week to study compatibility of the drug with the selected excipients. At the end of 4^{th} week samples were removed, again observations were recorded to have a comparison with the Initial recorded observation[20].

Preparation of Valsartan Nanosuspension:

Valsartan Nanosuspension was prepared by simple beaker method using zirconium beads as milling media. The initial predispersion of Valsartan and polymer was passed through colloidal mill to ensure particle homogeneity. Various process parameters like volume of beads, stirring time and stirring speed were carefully monitored and optimized parameters were maintained for the formulation of Valsartan Nanosuspension. Valsartan micro suspension was also prepared with the same procedure.

Manufacturing procedure for the preparation of Valsartan Nanosuspension: The poloxamer was dissolved in required quantity of water and stirred to get clear solution. Then Valsartan was added to the poloxamer solution and stirring was continued for 30mins. This initial

predispersion of Valsartan was passed through colloidal mill for 15mins to get the homogenous smooth dispersion. The resultant dispersion was Nanonised with the help of beaker method and zirconium beads as milling media for 24hrs. The compositions of various trials are given in table 10.

Media milling:

Freshly prepared dispersion of the drug was placed in nanomill container. The milling chamber was charged with milling media (Zirconium Oxide Beads) (79) then rotated at a very high shear rate under controlled temperatures for several hours. The high energy shear forces are generated as a result of the impaction of the milling media with the dispersed drug resulting into breaking of micro particulate drug into Nanoparticulate drug. Periodically samples were collected for physical characterization and evaluation. Various process parameters like volume of beads, stirring time and stirring speed were carefully monitored and optimized parameters maintained for the formulation of Valsartan Nanosuspension[21-25].

Particle size analysis:

The particle size distribution of the Nanosuspensions were determined by photon correlation spectroscopy (80), using a Zeta seizer nanoseries instrument (Malvern Instruments, Worcestershire, UK). This technique yields the mean particle diameter and the range of the particle size distribution and polydispersity index (PDI). All the data presented are the mean values of the results on three independent samples produced under identical conditions. Particle charge (zeta potential): The determination of the zeta potential of a Nanosuspension is essential as it gives an idea about the physical stability of the Nanosuspension.

X-ray powder diffraction analysis:

The physical states of API in the different samples were evaluated by X-ray powder diffraction (XRPD). Diffraction patterns were analyzed with a Miniflex II X-ray diffractometer, where the tube anode was Cu with K = 15,405 A. The pattern was collected with a tube voltage of 30 kV and a tube current of 15mA of in step scan mode (4◦/min).

Differential scanning calorimetry:

Thermal properties of drug, polymer and Nanosuspension were investigated using a METTLER differential scanning calorimeter thermal analysis controller with an intracooler-2 cooling. About 3 to 5 mg of product was placed in perforated aluminum sealed 50µl pans and the heat runs for each sample was set from 40°C to 150°C at 10°C/min, under an inert environment using nitrogen.

Saturation solubility studies:

Solubility studies were done by shake flask method. An excess amount of dried Nanosuspension of drug Valsartan was taken along with the desired solvent as mentioned in table 5.23. The volumetric flasks were then fixed onto a water bath shaker and shaken for 24 hours at 37˚C ± 1ºC. Samples were removed after the specified time and filtered through 0.45µ m nylon 66 syringe driven membrane filter unit. The filtrates were then analyzed by UV spectrophotometer at 248nm respectively to evaluate the amount of Valsartan dissolved.

Fourier Transform Infrared Spectroscopy (FTIR):

The FTIR spectra were recorded for pure drug Valsartan, polymer (poloxamer) and optimized dried Nanosuspension formulation using KBr pellet technique. The pellets were prepared using KBr hydraulic press under hydraulic pressure of 150kg/cm^2. The spectrums were scanned over 3600-400 cm-1 at ambient temperature with a resolution of 4cm^{-1}, using FTIR 2500 apparatus and spectra were recorded.

Flow Properties

Sedimentation volume:

The rate of separation of the suspensions were determined by keeping 50ml portion of each suspensions in stoppered measuring cylinder and stored undisturbed at room temperature. The separation of clear liquid was noted at an interval of 2W and 4W. The sedimentation volume, F (%), was then calculated using the following equation[26-28].

Pourability:

This test is carried out on optimized suspension, after mixing thoroughly to ensure that the final preparation is pourable and will not cause any problem during filling and during handling of the dosage form.

Redispersion:

Fixed volume of each suspension (50 ml) was kept in calibrated tubes which were stored at room temperature for various time intervals (2W, 4W). At regular interval of 2W, one tube was removed and shaken vigorously to redistribute the sediment and the presence of deposit if any was recorded.

In-vitro dissolution of Nanosuspension:

The release rate of Valsartan from Nanosuspension was determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 ml 0.1 N HCl/6.8pH phosphate buffer, at 37 ± 0.5˚C and 50 rpm/min.

3. Results and Discussion

Table 1: Calibration data for the estimation of Valsartan (N=3) in 0.1N HCl

S.No	Concentration (µg/ml)	Absorbance ± SD
1	2	0.061 ±0.006
2	4	0.122 ± 0.01
3	6	0.180 ± 0.015
4	8	0.238 ± 0.016
5	10	0.298 ± 0.018
6	12	0.355 ± 0.021
7	14	0.41 ± 0.018
8	16	0.472 ± 0.014
9	18	0.535 ± 0.023

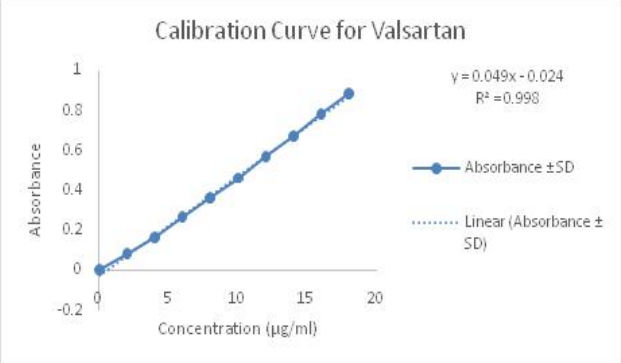

Figure 1: Calibration plot for the estimation of Valsartan in 0.1N HCl

Table 2: Calibration data for estimation of Valsartan (N=3) in 6.8pH phosphate buffer

S.No	Concentration (µg/ml)	Absorbance ± SD
1	2	0.08 ± 0.009
2	4	0.165 ± 0.013
3	6	0.266 ± 0.016
4	8	0.362 ± 0.021
5	10	0.461 ± 0.024
6	12	0.569 ± 0.018
7	14	0.67 ± 0.022
8	16	0.783 ± 0.026
9	18	0.887 ± 0.028

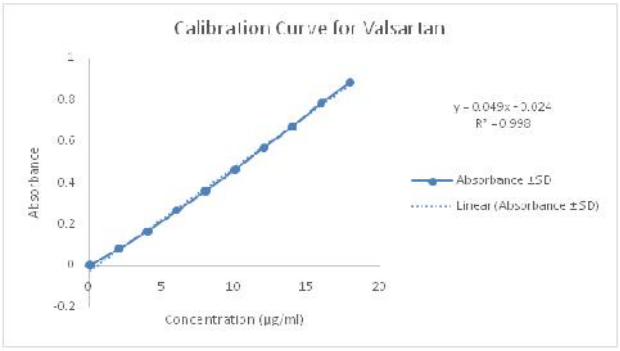

Figure 2: Calibration plot for the estimation of Valsartan in 6.8pH phosphate buffer

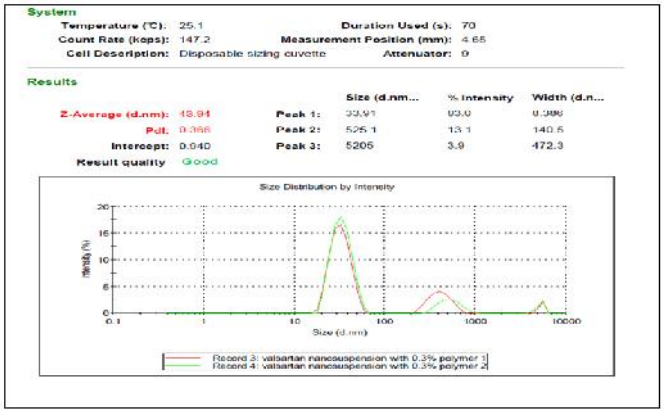

Figure 3: Particle size distribution of Valsartan Nanosuspension F3

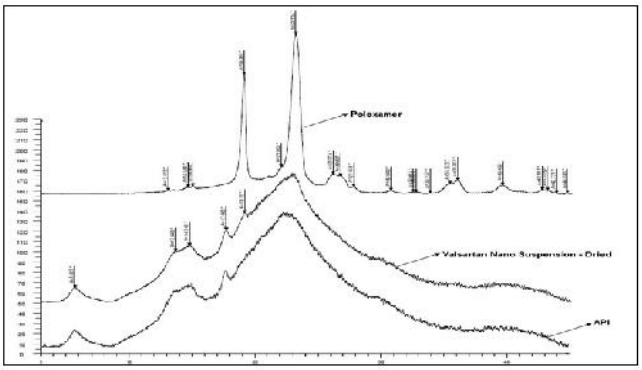

Figure 4: XRD data of Valsartan and Valsartan Nanosuspension

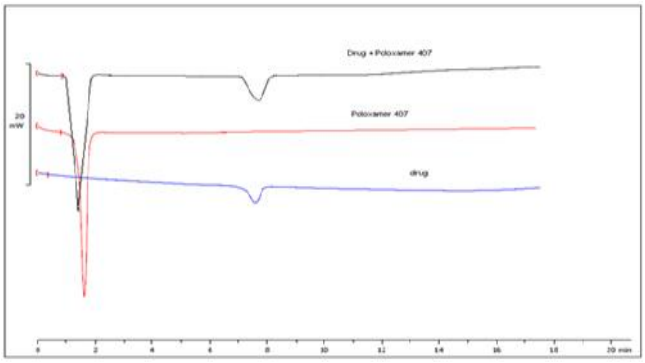

Figure 5: DSC graph of Valsartan API and Valsartan Nanosuspension

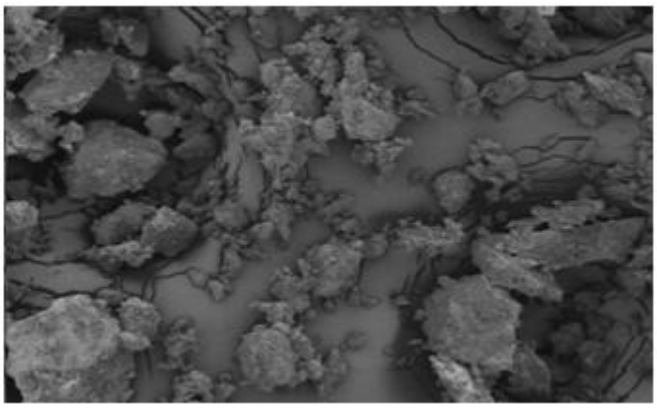

Figure 6: SEM image of Valsartan Nanosuspension

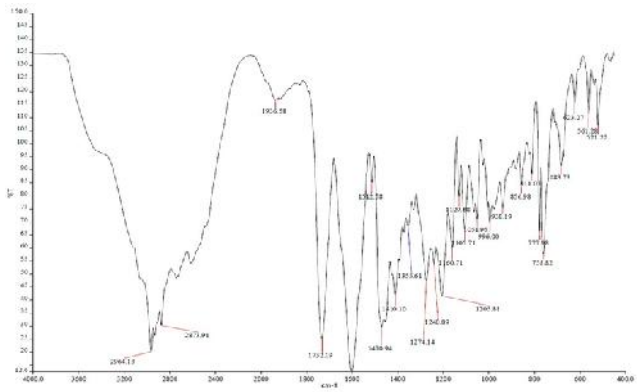

Figure 7: FTIR spectra of Valsartan

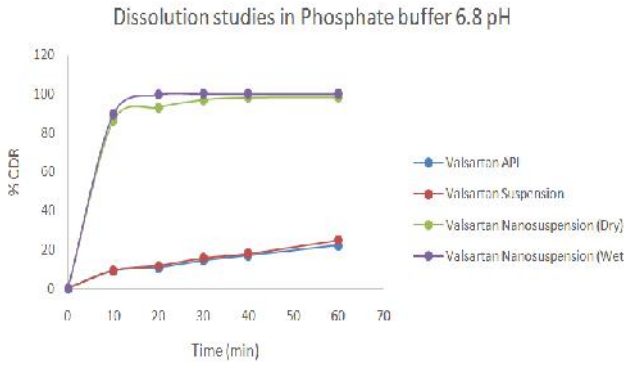

Figure 8: In vitro dissolution profile plot of Valsartan drug, Valsartan suspension and Valsartan Nanosuspension in 6.8pH phosphate buffer

4. Conclusion

Saturated solubility studies performed on Valsartan API in micronized form. The study found to exhibit highest solubility in 6.8pH phosphate buffer for Valsartan. The results of drug excipients compatibility studies suggest that there was no significant change in the physical appearance of premixture blends, when stored at 40^0C/75% RH for a period of 4 weeks when compared to initial sample[33-35]. Valsartan Nano suspension thus produced did not show any stability related problems when stored for 1 month at 40^0C/75%RH. The average particle size of the Valsartan optimized Nanosuspension thus produced was found to be 43nm with PDI of 0.366 indicating good physical stability of Nano suspension. The zeta potential of -19.5mV for optimized Valsartan Nanosuspension indicates the good physical stability of Nano suspension produced. The drug content of Valsartan in optimized Nanosuspensions were found to be in the range of 98.6 to 99.2. The FTIR study also indicating that there is no interaction between Valsartan drug substance and poloxamer due to Nanonisation process. Based on this *in-vitro* dissolution study it is evident that the Valsartan Nanosuspension exhibit high dissolution rate and extent probablydue to increase in surface area because of Nanonisation. Valsartan optimized Nanosuspension formulation found to follow first order model kinetics as R2 values were found to be 0.853.

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