Formulation And Evaluation of Valsartan Loaded Nanosponges for Oral Drug Delivery

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Abstract

Valsartan, a commonly prescribed hypertension drug, has limited therapeutic efficacy due to its low water solubility, slow absorption, and low bioavailability. These Nanosponges are well-known for their ability to increase the solubility of weakly water-soluble drugs, protect unstable drug molecules, and facilitate target drug delivery. The current study aimed to enhance valsartan's solubility by building inclusion complexes with β-cyclodextrin (β-CD) nanosponges. Crosslinkers are utilized in different molar ratios (1:2, 1:4, 1:6, and 1:8). The nanosponges were subsequently analyzed using Fourier transform infrared spectroscopy, scanning electron microscopy, a zeta sizer, and dissolution testing to determine drug release and flow properties, and all assessment tests met USP requirements. In vitro dissolution studies were carried out in 6.8 pH phosphate buffer. The optimal formulation was NM3, which released 99.67 percent after 180 minutes.

Keywords: *valsartan, β-cyclodextrin, diphenyl carbonate, ethyl cellulose, dichloromethane, polyvinyl alcohol, water, and ethanol.*

Introduction

Nanomedicines and nanotechnology are a branch of research that provide solutions to a variety of unresolved medication delivery therapeutic difficulties. Nanosponges are three-dimensional networks of spherical porous particles with colloidal diameters smaller than 1 μm and restricted size distribution, forming opalescent suspensions when distributed in water. Nanosponges are regarded as one of the most promising nanoscale delivery systems due to their high stability, carrier capacity, and ability to incorporate both hydrophilic and hydrophobic molecules. Furthermore, nanosponges can increase the solubility, chemical stability, and thus bioavailability of lipophilic medicines. Nanosponges have been used to distribute medications, biocatalysts, and gasses, as well as for harmful substance adsorption.[1] Hypertension is a major health issue in both industrialized and developing countries, resulting from elevated blood pressure and associated with cardiovascular problems such as heart failure, coronary heart disease, and stroke [2]. According to World Health Organization (WHO) data, cardiovascular illnesses are the leading cause of death worldwide, accounting for 17.9 million

deaths annually. Valsartan is classified as Class II in the biopharmaceutical categorization system (BCS), indicating strong permeability and poor solubility, resulting in dissolution-limited bioavailability during in vivo absorption [3]. As a result, increasing valsartan solubility could greatly improve its therapeutic efficacy.

Materials and Methodology

β-Cyclodextrin, Diphenyl carbonate, Dichloromethane, Ethyl cellulose, poly vinal alcohol. Nanosponges are prepared by using two different methods.

Nanosponges prepared using melt method

Diphenyl carbonate was employed as a cross-linking agent to make β-cyclodextrin nanosponges. The procedure involved mixing β-cyclodextrin with diphenyl carbonate in four molar ratios and heating at 90°C for two hours. The medication was then added to the molten mixture and swirled magnetically on a hot plate for an additional two hours. After cooling, the mixture was coarsely mashed with a mortar. To remove any unreacted β-cyclodextrin, thoroughly rinse the solid with deionized water, followed by acetone. The residual by-products and unreacted elements were removed using ethanol. The pure nanosponges were ultimately dried and stored at room temperature (25 °C) until needed.

Nanosponges prepared using Solvent diffusion method

Drug-loaded nanosponges were created utilizing the solvent diffusion method and a suitable polymer. To prepare the dispersion phase, a specific amount of medication and polymer was dissolved in 20 mL of organic solvent. Separately, the continuous phase was prepared by dissolving a suitable copolymer in 100 mL water. The organic dispersion was then progressively added to the aqueous phase, stirring continuously at 1000 rpm for around two hours with a magnetic stirrer. The resulting nanosponges were separated by filtration and then dried in a hot air oven at 40 degrees Celsius for approximately 24 hours before usage.

Table 1. Formulation for melt method

Ingredients	NM (1:2)	NM (1:4)	NM (1:6)	NM (1:8)
Drug (mg)	40	40	40	40
β - CD (mg)	200	200	200	200
Diphenyl carbonate (mg)	400	800	1200	1600

Table 2. Formulation for solvent diffusion method

Ingredients	NS (1:2)	NS (1:4)	NS (1:6)	NS (1:8)
Drug (mg)	200	200	200	200
Ethyl cellulose (mg) (Polymer)	400	800	1200	1600
Dichloromethane (ml) (solvent)	20	20	20	20
PVA (mg) (stabilizer)	300	300	300	300
Water (ml)	50	50	50	50

Evaluation tests

Solubility Studies

The solubility of Valsartan in methanol was examined. The solubility experiments were carried out by dissolving 10mg of medicine in a beaker containing solvent. The mixtures were mixed with a rotary shaker. Following completion, the samples were filtered with filter paper. UV spectrophotometry was used to evaluate the filtrated solutions.

Melting point

To assess the purity of the refined sample, it is melted in a borosilicate glass capillary tube.

Determination of λ max in methanol and pH 6.8 phosphate buffer:

10 µg/ml drug solution was prepared with methanol and pH 6.8 buffer scanned for absorbance using a UV-VIS spectrophotometer in the range of 200- 400nm.

Standard graph in methanol and pH 6.8 phosphate buffer:

V

arious concentrations of valsartan using pH 6.8 phosphate buffer and methanol. The absorbance was measured using UV-VIS Spectrophotometer at the wave length of 206nm and 212nm.

Percentage Yield

The percent yield of the formed valsartan nanosponges was evaluated as

$$\text{Percentage Yield} = \left(\frac{\text{Actual Yield}}{\text{Theoretical Yield}}\right) \times 100$$

Determination of Drug Loading

20 mg of valsartan nanosponges were properly weighed and mixed with 10 mg of methanol. After 45 minutes of mixing at 100 rpm at 25 ◦C, the solution was sonicated for another 10 minutes. After filtering through a 45µm membrane filter, the medicine was quantified spectrophotometrically at λmax 212 nm. The drug content of the generated nanosponges was calculated using the equation below.

$$Loading\ efficiency = \frac{Actual\ drug\ content\ in\ NS}{Theortical\ drug\ content} \times 100$$

FTIR

The FTIR study was performed using an FTIR Instrument. The spectra were captured across the frequency range of 4000-650 cm-1, and the major peaks were identified.

SEM analysis

A scanning electron microscope is used to examine the nanosponges' form and general morphology. To do this, the material was lyophilized and deposited on aluminum stubs, followed by sputter coating with gold particles.

Zeta Potential

A particle's zeta potential represents its entire charge as well as the stability of the formulation. The determination was made using a Malvern Instruments Zeta sizer.

***In vitro* drug release**

The release of drugs *in vitro* formulation is evaluated in 3 hours using a dissolution medium with a USP Type-11 apparatus. The nanosponge formulation was perforated and placed inside the basket containing 900 mL of dissolution medium. At specified time point 5 millilitre samples were removed and replaced with fresh medium to maintain a consistent volume. A UV-visible spectrophotometer was used to quantify the medication content in each sample by measuring absorbance at 206 nm.

Evaluation of Precompression Parameters:

Angle of repose: It is the maximum angle between the surface of a powder and the horizontal plane. ($\theta = \tan^{-1}(rh)$)

Bulk density: Bulk density is the ratio of the mass of powder to the bulk volume it occupies; it is often given in units such as g/cm³ or kg/m³ (bulk density=M/Vb)

Tapped density: The cylinders were placed on the bulk density instrument and hit 100 times. (Tapped density = M/Vt)

Car's index: It is utilized to assess the flowability of a powdered material

(CI= (TD−BT) / TDx100)

Hauser's Ratio: The Hauser ratio is an indicator of powder flowability.

Hauser's Ratio = Tapped density/bulk density

Post Compression Tests for Tablets

Weight variation test: It refers to the allowed weight difference between individual tablets in a batch.

Hardness: It measures the mechanical strength of a tablet. The values are in kg/cm².

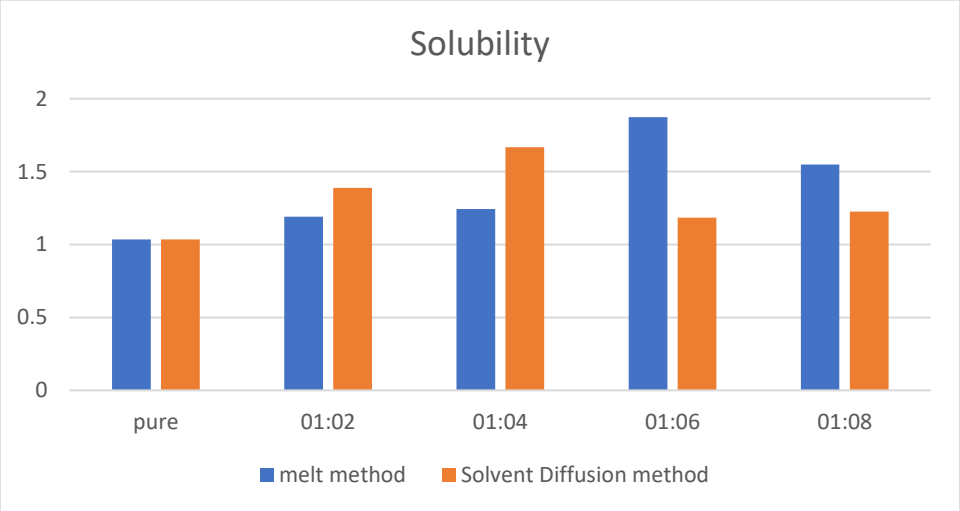
Friability test: Friability measures the tendency of tablets to crumble or break when subjected to mechanical shock during handling or transport.

Disintegration Test: It measures the time required for a tablet to break down into small particles under specific conditions.

Results and Discussion

Solubility Studies

Figure:1 Solubility



Melting Point for Valsartan

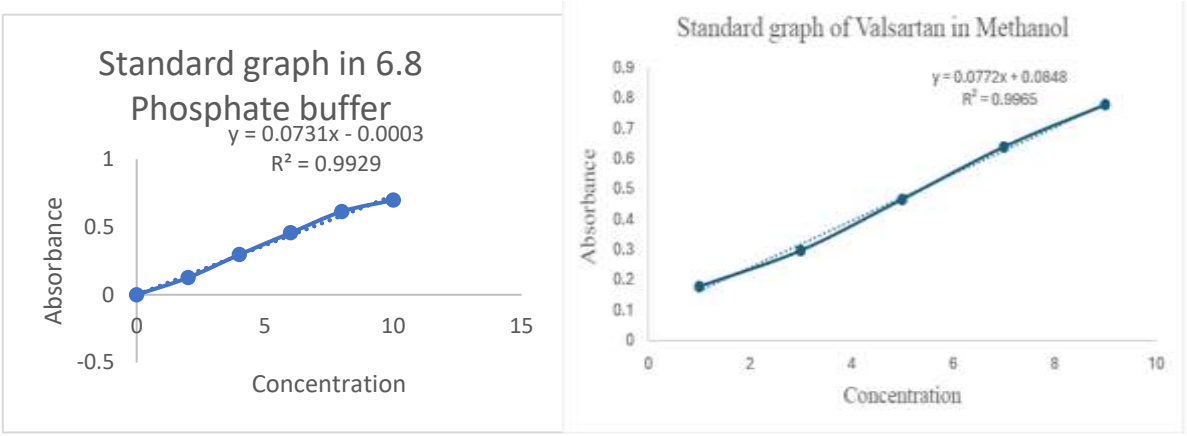
The melting point was found to be 110°C.

Absorption Maxima in Methanol And pH 6.8 Phosphate Buffer:

The wavelength of maximum absorbance (λ max) of valsartan was determined using pH 6.8 phosphate buffer. It was found to be 206nm.The wavelength of maximum absorbance (λ max) of valsartan was determined using methanol. It was found to be 212nm.

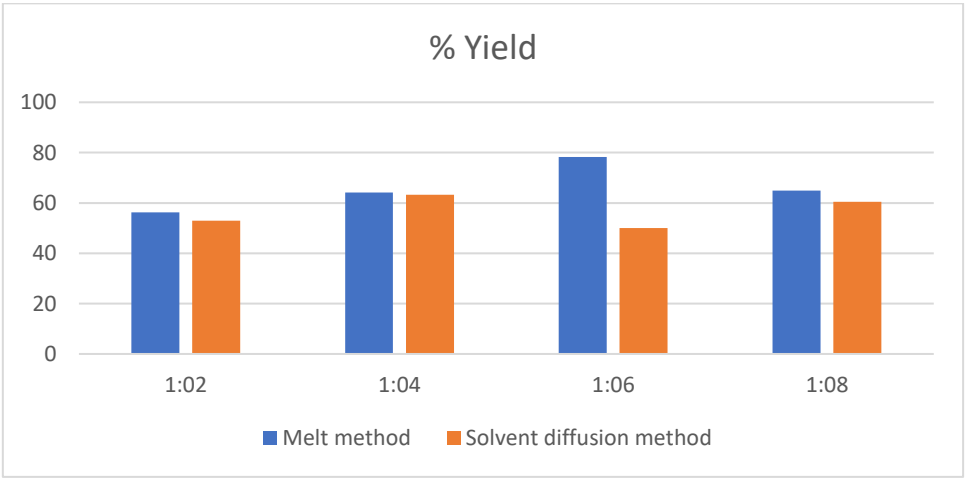
Standard Graph in pH 6.8 Phosphate Buffer and Methanol

Figure 2 and 3: Standard Graph



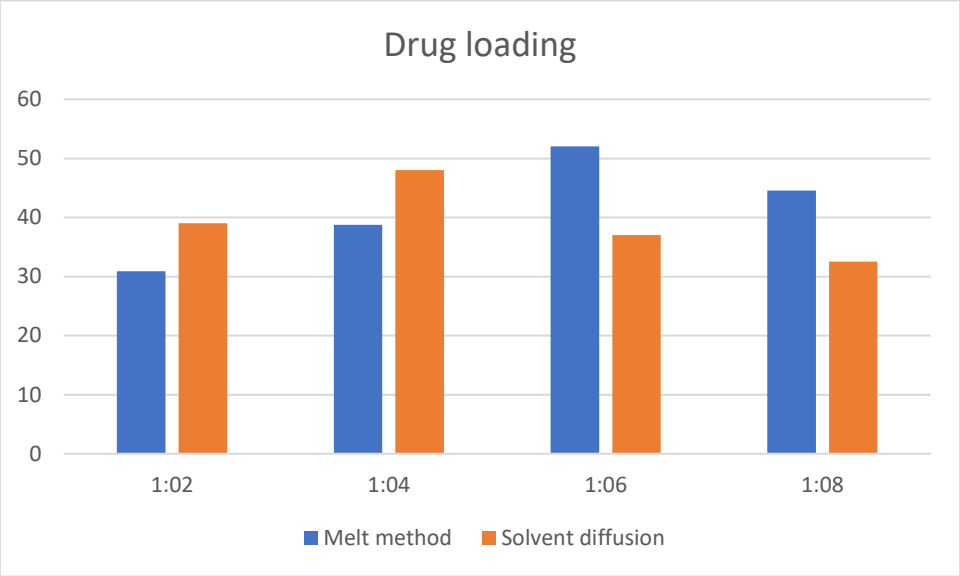
Percentage Yield

Figure 4: % yield



Drug Loading

Figure 5: Drug loading



Surface Morphology

A ZEISS scanning electron microscope was used to examine the surface properties of produced crystals. Imaging was performed with an electron beam at 3.00 kV, and the micrographs were recorded in secondary electron mode. The image was found to be 100nm and 200nm.

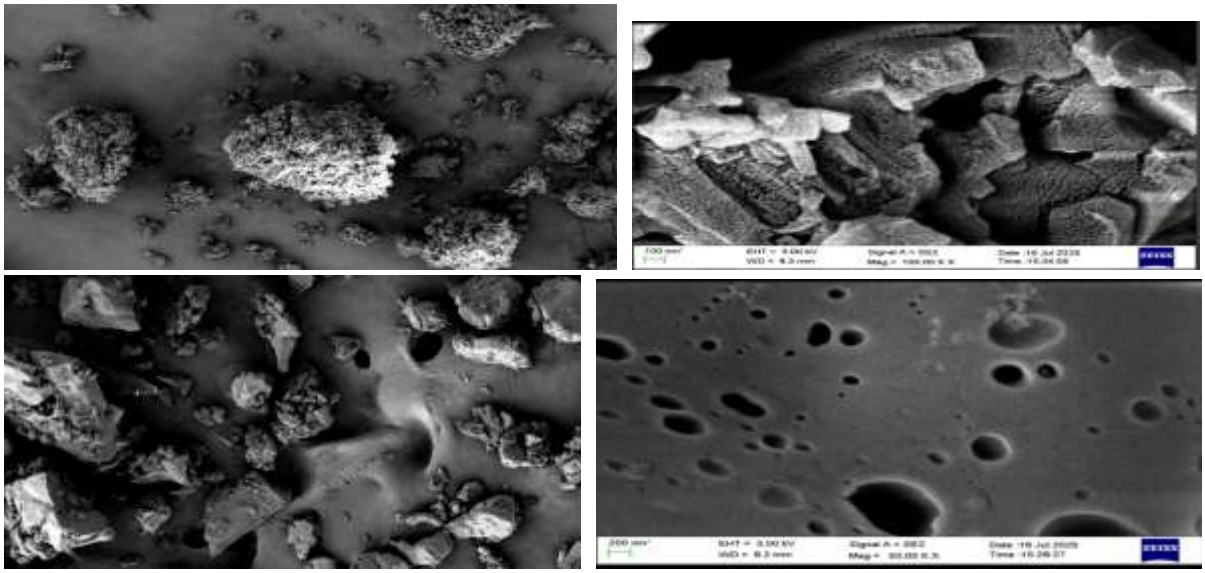


Figure: 6,7,8,9: 6 and 7 for melt method, 8 and 9 for solvent diffusion method

FTIR:

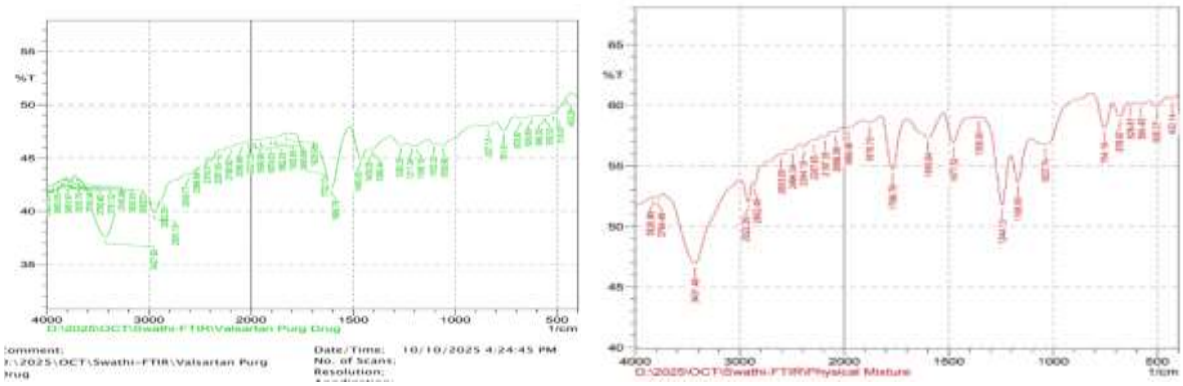


Figure: 10 and 11- Pure drug and Nanosponge formulation

Particle Size and PDI:

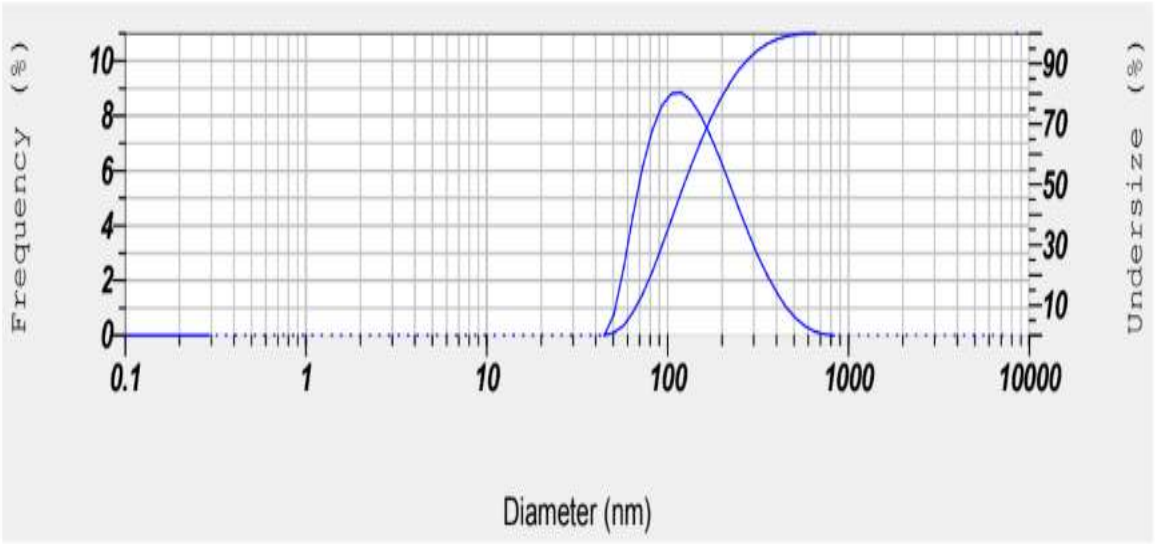


Figure 12: Size and PDI

The characterization of the prepared nanosponge formulation. The particle size was found to be 294 nm, confirming that the formulation is in the nanometer range. The polydispersity index (PDI) value of 0.400 indicates a uniform particle size distribution with good homogeneity.

Zeta Potential

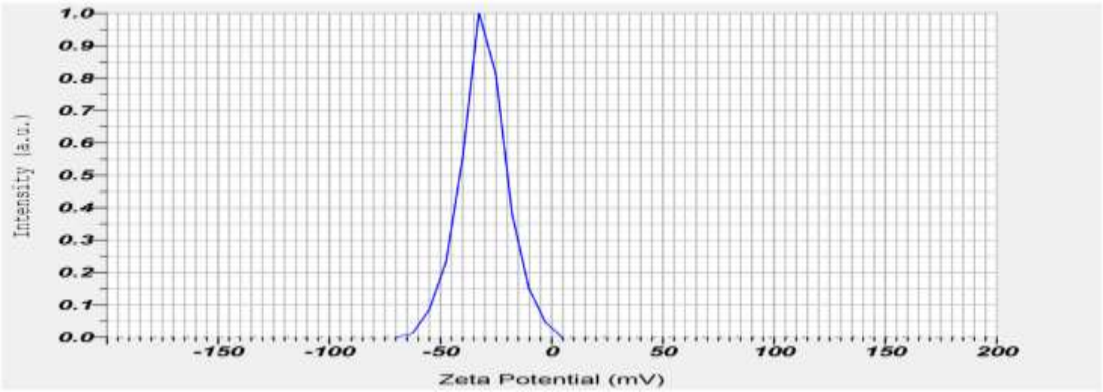


Figure 13: Zeta Potential

The characterization of the prepared nanosponge formulation. The zeta potential value of –30.6 mV shows that the nanosponges possess good electrostatic stability, preventing aggregation of particles.

Invitro Drug Release Studies

Figure 14: Melt Method Formulations

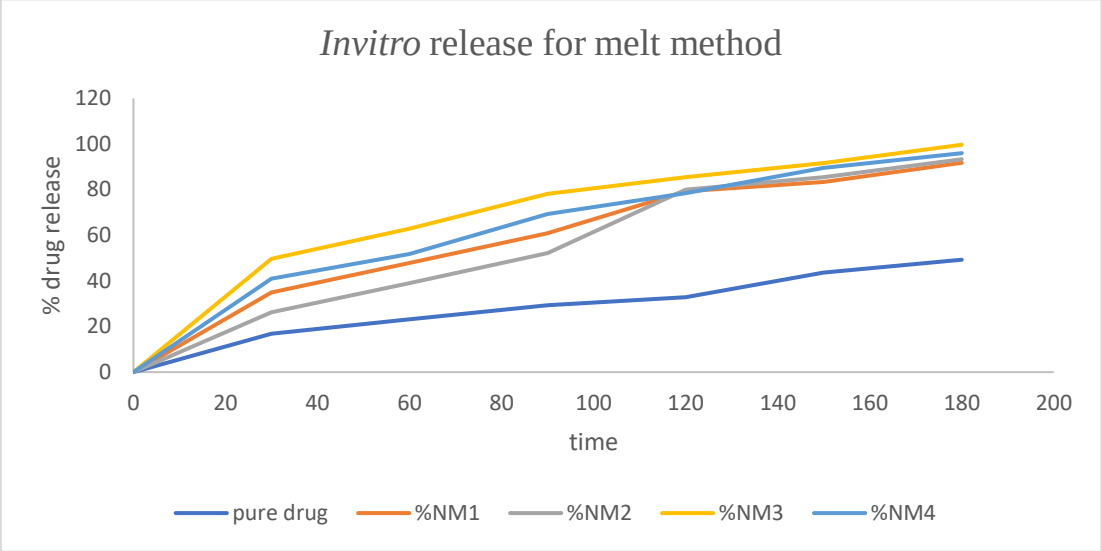
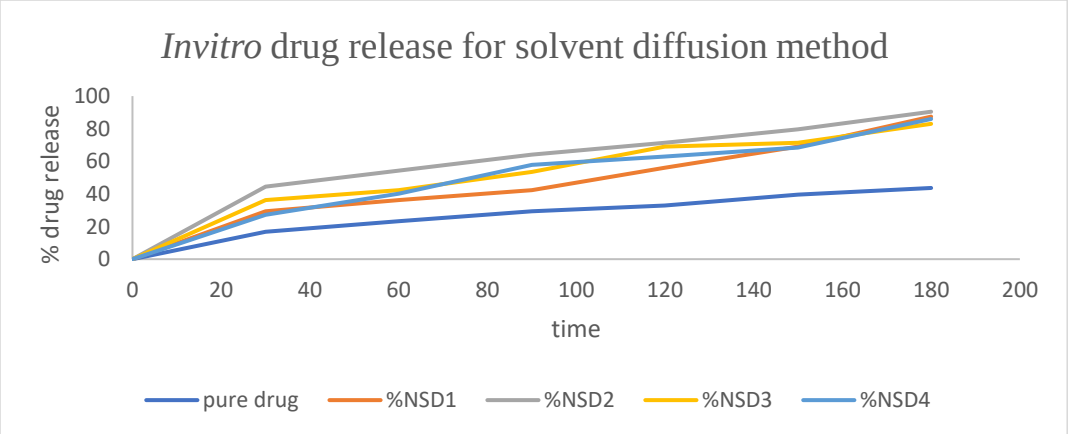


Figure 15: *Invitro* release for solvent diffusion method



Preparation of Nanosponge tablet for NM3

To prepare nanosponges tablets, first weigh all the required ingredients as per the formulation. Then transfer them into a clean mortar and mix well to get a uniform blend. Next, pass the mixture through a sieve to ensure even particle size. Finally, compress the blended powder into tablets using a tablet compression machine with suitable punches.

Table 3: Formulation table for tablet

Ingredients	**Quantity (mg)**
Nanosponge	Equivalent to 40mg of Valsartan
Micro crystalline cellulose	135
Talc	14
Magnesium stearate	7
Croscarmellose sodium	22
Total weight	750

EVALUATION OF PRECOMPRESSION BLEND

Table 4: Precompression parameters

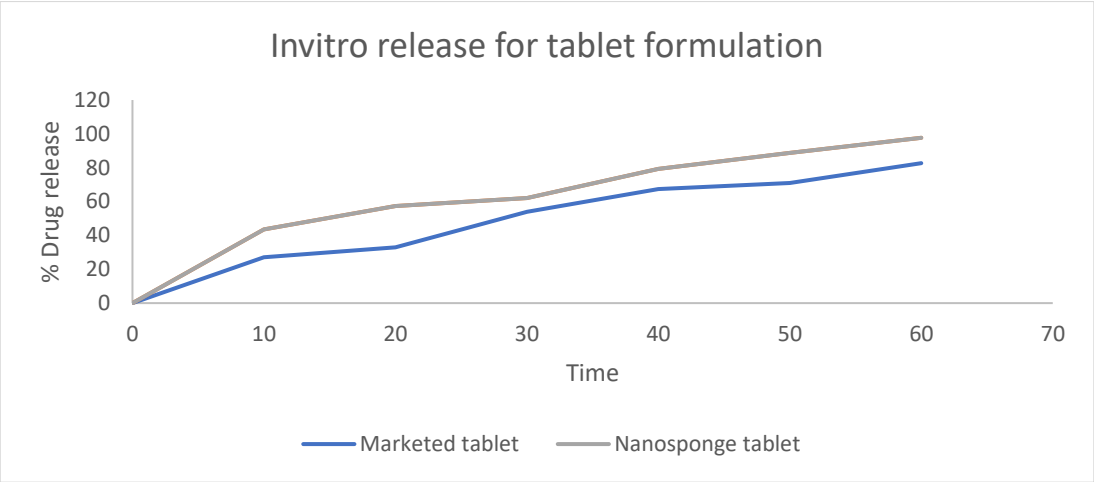
S.NO	**Precompression studies**	**Result**
1	Angle of repose	12.51°
2	Bulk density	350 (g/ml)
3	Tapped density	466 (g/ml)
4	Carrs Index	24.99%
5	Hausners ratio	1.33

EVALUATION TEST OF POST COMPRESSION BLEND

Table 5: Post compression parameters

Post evaluation studies	**Ranges**
Weight variation	748 ± 0.005 mg
Hardness	8 Kg/cm^2
Friability	0.9%
Disintegration time	28 Sec

Figure 16: *In Vitro* Drug Release Studies for Valsartan Nanosponge Tablet and Marketed Tablet



SUMMARY AND CONCLUSION:

The study concluded that valsartan-loaded nanosponges effectively enhanced the drug's solubility and dissolution rate. The optimized NM3 formulation showed the best performance with 97.67% release in 60 minutes. FTIR and SEM confirmed no drug–polymer interaction and uniform particle morphology. The melt method produced stable particles with ideal size and zeta potential. Overall, nanosponges proved to be a promising approach for improving valsartan's bioavailability**.**

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