IJPSR (2023), Volume 14, Issue 6 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 06 October 2022; received in revised form, 22 November 2022; accepted 25 November 2022; published 01 June 2023

DESIGN AND DEVELOPMENT OF MODIFIED RELEASE TABLET BY MIXED SOLVENCY ASSISTED SOLID DISPERSION OF VALSARTAN

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Keywords:

Modified release, Mixed solvency, Solid dispersion, Valsartan, Poorly water soluble

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ABSTRACT: In the present investigation, newly developed solid dispersion technology that precludes the use of organic solvent and decreases the individual concentration of hydrotropic agents, simultaneously decreasing their toxic potential, was employed for preparing dispersions of valsartan. Valsartan is a pro-drug which has poor bioavailability because of poor solubility as it belongs to BCS class II. Study aims to enhance the solubility of valsartan by mixed solvency approach. Solution was made by using different co-solvents to enhance the solubility of valsartan. Camphor, thymol were used as solvents to increase the solubility of valsartan. A mixture of camphor: thymol (1:1) was selected for solubility enhancement of valsartan. FTIR study did not show any interaction between drug and excipients. Prepared solid dispersions were evaluated for flow properties, XRD, DSC, and SEM were also compressed to form tablets. Dissolution studies of prepared tablets were carried out using USP Type II Apparatus. The stability study for up to one month showed no significant changes by evaluation parameter. It was concluded that the concept of mixed solvency solid dispersion is novel, safe and cost-effective technique for enhancing the bioavailability of poorly water soluble drugs by dissolving drug in non-ionized form.

INTRODUCTION: Product development scientists often encounter significant difficulties in solving the problem of poor water solubility of drug candidates in the development of pharmaceutical dosage forms. Slow absorption rate results in an erratic and variable profile of drug level.

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DOI: 10.13040/IJPSR.0975-8232.14(6).2862-76

This article can be accessed online on www.ijpsr.com

DOI link: http://doi.org/10.13040/IJPSR.0975-8232.14(6).2862-76

A solid dispersion is a system in which the concentration of the drug is more than its saturation solubility at room temperature. The excess drug separates as a solid phase which is dispersed in the vehicle in crystalline or amorphous forms.

Together with the permeability, the solubility behavior of the drug is a key determinant of its oral bioavailability. There have always been drugs for which solubility has presented a challenge for developing a suitable formulation for oral administration. Solid dispersion technologies are particularly promising for improving BCS Class II drugs' oral absorption and bioavailability. More than one-third of the drugs listed in the U.S.

Pharmacopoeia fall into the poorly water-soluble or water-insoluble categories. A couple of decades ago, it was reported that more than 41% of the failures in new drug development had been attributed to poor biopharmaceutical properties, including water insolubility. Water insolubility can postpone or completely halt new drug development preventing the much-needed reformulation of the currently marketed products. As per the mixed solvency concept, every substance (whether liquid, gas or solid) has solubilizing power. Supercritical fluid technology is based on the solubilizing power of a gas, CO_2, in its liquid state. Melted PEG-4000, PEG-6000, PEG-8000 (melting point about 65-70°C) and melted urea (m.p. 132- 135°C) dissolve diclofenac sodium (m.p. 283°C).

This shows that melted PEGs and urea act as a solvent for diclofenac sodium. Melted ibuprofen (m.p. 78°C) dissolves diclofenac sodium (m.p. 283°C), salicylic acid (m.p. 159°C) and niacinamide (m.p. 132°C) which again show that melted ibuprofen acts as solvent for diclofenac sodium, salicylic acid and niacinamide. Mixed solvency is the increase in solubility of poorly soluble drugs by the addition of more than one solubilizing agent. Use of these agents in combination may enhance the solubility of poorly soluble drugs by miraculous synergistic effect in addition to the additive effect [1-4].

Newly developed hydrotropic solid dispersion technology precludes the use of organic solvents. Salient feature of the new method is that hydrotropic agent (carrier) is water-soluble, whereas the drug is insoluble in water. However, in the presence of a large amount of hydrotropic agent in water, the drug gets solubilized due to the phenomenon of hydrotropic solubilization. Then water is removed by suitable evaporation technique to get a solid mass (a solid dispersion). In the absence of hydrotropic agent, water is not a solvent for poorly water-soluble drugs; therefore, the proposed method is different from the common solvent method and is a novel application of the hydrotropic solubilization phenomenon. Similar to the above-mentioned hydrotropic solid dispersion, the present research work utilizes the mixed solvency concept for developing a solid dispersion, precluding the use of organic solvent, for making the sustained release tablets of valsartan. So, the objective of the present research work was to formulate the solid dispersion of valsartan and to develop its controlled-release tablet (to reduce the side effects). Tablet formulation comprises of solid dispersion of valsartan with solubility modifiers and release-controlling polymers, which would exhibit a similar release rate throughout the GI tract, irrespective of the pH of the environment [6-8].

MATERIALS AND METHODS:

Materials: Valsartan was obtained from IPCA Ltd. Mumbai. Polycarbophil was purchased from Lubrizol. Thymol, Camphor, Lactose, Microcrystalline Cellulose, HPMC K100, Xanthan Gum, Magnesium Sterate and Talc was purchased from Research Fine Lab Ltd.

Method:

Drug Characterization:

Melting Point: The melting point of valsartan was determined using the open capillary method. The drug powder sample was packed in a capillary and the melting point was determined in Thiel's tube.

Spectrophotometric Analysis of Valsartan: Ten mg of valsartan was weighed accurately and transferred to a 100 ml volumetric flask. To this 10 ml methanol was added to dissolve, and the volume was made upto 100 ml with de-mineralized (DM) water so as to obtain a stock solution of 100µg/ml. From this stock solution, a dilution of 20µg/ml was made with distilled water, and the sample was scanned between 200 nm to 400 nm on a double beam UV/Visible spectrophotometer (Shimadzu® 1600) [9].

Construction of Calibration Curve of Valsartan: The calibration curve of valsartan was constructed by preparing appropriate serial dilutions from the prepared stock solutions of 0.1N HCl, buffer pH 6.8, methanol. They further analyzed at the previously determined λmax using UV-visible spectrophotometer, and the recorded absorbance for each sample was plotted versus the concentration to obtain valsartan calibration curve.

FT-IR Study of Valsartan: The FTIR analysis of Valsartan was carried out for qualitative compound identification. The FTIR spectra for pure drug and with other excipients were obtained by placing the drug directly into the cavity and were determined

by FTIR spectrophotometer in the wave number region of 4000-400 cm^{-1}.

DSC Study of Valsartan Drug Sample: A Mettler Toledo DSC STARe SYSTEM was used for all the DSC studies performed on the drug and solid dispersion. The DSC uses Stare Software V8.10 for its operation. Samples ranging from 8 to 15 mg were used and the results were normalized using Stare software to compare the results. The samples were placed in a 100 µL pan. The pans are covered with a lid, and the lid is crimped into place.

A pinhole is made on the lid to vent out any gas which might result while heating. The pan is placed inside the furnace using an empty pan as a blank. The DSC was calibrated using indium (5-10 mg) with a melting onset temperature at 156 ± 0.2ºC and zinc with a melting onset temperature of 419.6±0.70C as the standards. The two processes show a heat flow of 28.45± 0.6J/g and 107.5±3.2 J/g for indium and zinc, respectively.

X-RD Study of Valsartan Drug Sample: PAN analytical X-Pert Pro V1.6 with X Pert Data Collector V2.1 software was used equipped with a $CuKa_2$ anode tube and diffractometer of radius 240 mm. The XRD scan was performed using BB004 flat stage.

The powdered sample was placed in an aluminum sample holder which had a one-inch square with a depth of 0.5 mm. Data were collected by scanning the sample at 45 kV and 40 mA. Samples were scanned from 5-50°2θ at a step size of 0.0170 and scan rate of 1.0º/min.

Scanning Electron Microscopy (SEM) of Valsartan: Scanning electron microscopy is a type of electron microscopy that images the sample surface by scanning it with a high-energy beam of electrons. The electrons interact with the atoms that make up the sample producing signals that contain information about the sample's surface topography, composition, and other properties, such as electrical conductivity. SEM was used to investigate the solid state physical structure of the prepared solid dispersions. SEM photographs of valsartan and its solid dispersion were obtained using a scanning electron microscopic model JEOL JSM 5600 with accelerating voltage from 0.5 to 30 KV.

Pre-formulation Study:

Construction of Calibration Curve of Valsartan in Different Solvents:

Preparation of Calibration Curve of Valsartan in Distilled Water: Ten mg of valsartan was accurately weighed and transferred to a 100 ml volumetric flask. To this 40 ml of distilled water was added to dissolve the drug, and the volume was made up to 100 ml with DW. Then, 10 ml of this solution was taken in another 100 ml volumetric flask, and the volume was made up to 100 ml with DW.

The concentration of this resulting solution (stock solution) was 50 µg/ ml. appropriate dilutions were made from stock solution with DM water in the 5-30 µg/ml concentration range. The absorbances of the resulting drug solutions were observed using a double-beam UV/Visible spectrophotometer (Shimadzu 1700) at 250 nm against the respective blanks.

Preparation of Calibration Curve of Valsartan in Ethanol: Ten mg of valsartan was accurately weighed and transferred to a 100 ml volumetric flask. To this 40 ml of ethanol was added to dissolve the drug, and the volume was made up to 100 ml with ethanol.

Then, 10 ml of this solution was taken in another 100 ml volumetric flask, and the volume was made up to 100 ml with ethanol. The concentration of this resulting solution (stock solution) was 50 µg/ ml. Appropriate dilutions were made from stock solution with ethanol in a concentration range of 6-60 µg/ml. the absorbances of the resulting drug solutions were observed using a double-beam UV/Visible spectrophotometer (Shimadzu 1700) at 250 nm against the respective blanks.

Preparation of Calibration Curve of Valsartan in Methanol: Ten mg of valsartan was accurately weighed and transferred to a 100 ml volumetric flask. To this 40 ml of methanol was added to dissolve the drug, and the volume was made upto 100 ml with methanol. Then, 10 ml of this solution was taken in another 100 ml volumetric flask, and the volume was made up to 100 ml with methanol. The concentration of this resulting solution (stock solution) was 50 µg/ ml.

Appropriate dilutions were made from stock solution with methanol in a concentration range of 2-20 µg/ml the absorbances of the resulting drug solutions were observed using a double beam UV/Visible spectrophotometer (Shimadzu 1700) at 250 nm against the respective blanks.

Solubility Study of Valsartan: Solubility study was performed by the Shake Flask Method. The excess drug along with different solvents was taken in 10ml stoppered volumetric flasks. Solubility of Valsartan was determined in distilled water, ethanol, methanol and pH across the GITin pH 6.8 and pH 7.2. The flasks were subjected to shaking in an orbital shaker for 24 Hours at 25ºC and 60 rpm speed and further equilibrated for next 24 Hours. Then the solutions were filtered through Whatmann filter paper (0.45µm). The absorbances were recorded on UV Spectrophotometer of these filtered solutions after appropriate dilutions to determine the solubility using the respective solvents as blank.

Drug-Excipient Physical Compatibility Studies: This study was performed to determine any physical change in the drug when used with various formulation excipients. The drug was mixed with excipients in the 1:1 ratio and was kept in glass vials properly capped and sealed with aluminum foil. Two vials of each sample were kept at room temperature for one month period. After every week for one month, the vials were withdrawn and any change in physical appearance and color of the contents was observed.

Formulation Development:

Formulation of Solid Dispersion by Mixed Solvency Concept: For the preparation of solid dispersion in 1:1 ratio, accurately weighed 1.5 gm of valsartan was dispersed in 20 ml of eutectic mixture (1:1 ratio of camphor- thymol) in a beaker and dissolve it.

When the clear solution is obtained, add 1.5 gm of polycarbophil powder and dissolve it completely. Remove all camphor and thymol with the help of boiling water bath by dipping the beaker in a water bath. This process may take about 30 minutes, forming a white sustained release solid dispersion of valsartan in polycarbophil.

On cooling, it should be powdered. After complete drying, solid dispersion was crushed using a glass pestle mortar and passed through sieve # 60. The same procedure was used to prepare solid dispersion in the ratio of 1:2, 1:3, 1:4, 1:5 and 1:6 using an appropriate eutectic mixture.

TABLE 1: COMPOSITION OF SOLID DISPERSION

S. no.	Batch Code	Drug : Polymer ratio	Quantity taken (gm)	
			Valsartan	Polycarbophil
1	SD1	1:1	1:5	1:5
2	SD2	1:2	1:5	3:0
3	SD3	1:3	1.5	4.5
4	SD4	1:4	1.5	6
5	SD5	1:5	1.5	7.5
6	SD6	1:6	1.5	9:0

Evaluation of Prepared Solid Dispersion:

Determination of Drug Content in Solid Dispersion: Initially, 100 mg of solid dispersion was taken respectively in 100 ml volumetric flask. About 60 ml of methanol was added, flask was shaken to dissolve the content completely, and the volume was made up to the mark with methanol. The solution obtained was analyzed spectrophotometrically at 250 nm against methanol. From this drug, content was determined.

Determination of Percent Yield: The percent yield of valsartan solid dispersions was determined according to the method described using the following expression.

% yield= (weight of prepared SD x 100) / (Wt. of drug + carrier)

Determination of Solubility of Solid Dispersion: Valsartan solid dispersion 10 mg was weighed and transferred to a flask containing 50 ml distilled water. The flasks were subjected to shaking in an orbital shaker for 24 h at 25ºC and 60 rpm speed and further equilibrated for the next 24 h. Then the solutions were filtered through Whatmann filter paper (0.45µm). The absorbances were recorded on

UV Spectrophotometer of these filtered solutions after appropriate dilutions to determine the solubility using the respective solvents as blank.

Micromeritic Properties of Solid Dispersions: Any method of measuring powder flow must be practical, useful, reproducible, and sensitive and yield meaningful results. Therefore, an appropriate strategy is using multiple standardized test methods to characterize the various aspects of powder flow as the pharmaceutical scientist needs.

The following micromeritic properties of the solid dispersions were studied:

- Bulk density
- Tapped density
- Hausner ratio
- Compressibility index
- Angle of repose

Bulk Density: Accurately weighed 10 gm of solid dispersion was filled in a 50 ml graduated cylinder and after 3 tappings on a wooden surface, its unsettled volume, Vo was noted. The following formula calculated the bulk density in gm/cm3 and recorded in **Table 1.**

$$\text{Bulk density (Do)} = M / Vo$$

Where, M = Mass of powder taken, Vo= Apparent volume of powder.

Tapped Density: Accurately weighed, 10 gm of powdered solid dispersions were filled in a 50 ml graduated cylinder. The tapping of the cylinder was done on a wooden surface for 500 times and the tapped volume V_i was noted. Tapping was continued further for additional 750 times and the tapped volume, Vf was noted. The difference between two tapping volumes was less than 2%, so Vf was considered a tapped volume. The tapped density was calculated in gm/cm3 by the following formula and recorded in **2.**

$$\text{Tapped density (Df)} = M/Vf$$

Where, M = weight of sample powder taken, Vf = final tapped volume

Hausner Ratio and Compressibility Index: The compressibility index (CI) and Hausner ratio are measures of the propensity of the powder to be compressed. As such they are the measures of inter-particulate interactions. In a freely flowing powder, such interactions are less significant, and bulk densities and tapped densities are closer in value. For a poorly flowing powder, there are frequently greater inter-particulate interactions and, therefore, a greater difference in the bulk density and tapped density.

Hausner Ratio: Tapped density and bulk density were measured, and the Hausner ratio was calculated using the following formula and recorded in table 5.14

$$\text{Hausner ratio} = Df / Do$$

Where, Do = Bulk density, Df = Tapped density

Compressibility Index (CI): It was calculated using the following formula, and recorded in table 5.14

$$C.I. = \{Vo - Vf)/Vo\} \times 100$$

Where, Vo = Initial volume of untapped powder, Vf = Tapped volume

Angle of Repose: The angle of repose is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. A glass funnel was held in place with a clamp on ring support over a plate. The funnel height through which the powdered solid dispersion was to pass was fixed relative to the base. Approximately 25 g of powdered solid dispersion was transferred through the funnel. The height of the pile (h) and the base (r) radius were measured with the ruler. The relationship between angle of repose and powder flow is mentioned in table 7.8. The angle of repose was calculated using the formula mentioned below and is reported in **Table 1.**

$$\text{Tan } \theta = h/r \text{ or } \theta = \tan^{-} h/r$$

Where, h = height of pile, r = radius of the base of the pile, θ = angle of repose

FTIR Study of Solid Dispersion: Sample of drug and polymer by ATR sampling technique, the spectrum was scanned over the frequency range between 4000 and 600cm^{-1} and at 4 cm resolution. Appearance, disappearance or broadening of absorption band(s) on the spectra of the solid

dispersions and the polymeric carriers in comparison with the spectrum of the drug were used to determine possible interactions between pure drugs and polymers

XRD Studies of Solid Dispersion: Powdered x-ray diffraction pattern for the solid dispersion using drug: polymer (1:6) is depicted. XRD studies were performed to check for any crystallinity in the formulation after it was made and after the stability studies were performed. Avoiding recrystallization of the drug in the formulation was one of the goals of this study.

DSC Study of Valsartan Solid Dispersion: A Mettler Toledo DSC STARe SYSTEM was used for all the DSC studies performed on the drug and solid dispersion. The DSC uses Stare Software V8.10 for its operation. Samples ranging from 8 to 15 mg were used, and the results were normalized using Stare software to compare the results. The samples were placed in a 100 μL pan. The pans are covered with a lid, and the lid is crimped into place. A pinhole is made on the lid to vent out any gas which might result while heating. The pan is placed inside the furnace using an empty pan as a blank. The DSC was calibrated using indium (5-10 mg) with a melting onset temperature at 156 ± 0.2ºC and zinc with a melting onset temperature of 419.6±0.70C as the standards. The two processes show a heat flow of 28.45± 0.6J/g and 107.5±3.2 J/g for indium and zinc, respectively.

SEM Study of Vvalsartan Solid Dispersion: Scanning electron microscopy is a type of electron microscopy that images the sample surface by scanning it with a high-energy beam of electrons. The electrons interact with the atoms that make up the sample producing signals that contain information about the sample's surface topography, composition and other properties such as electrical conductivity. SEM was used to investigate solid state physical structure of the prepared solid dispersions. S.E.M. photographs of piroxicam and its solid dispersion were obtained using a scanning electron microscopic model JEOL JSM 5600 with accelerating voltage from 0.5 to 30 KV.

Pharmacokinetic Study of Solid Dispersion: The plasma exposure of valsartan after an oral administration of valsartan in different formulations was examined in rabbits. Male rabbits (4–6months of age, 2.5–3.0 kg and male) were housed according to the guidelines and policies for animal experiments, housing, and care of the CPCSEA. The animal study adhered to the principles of the Institutional Animal Ethical Committee Guidebook. The Institutional Ethical Committee approved the study protocol for the Use of Animals in Research. Before oral drug administration, the rabbits were fasted overnight with free access to water. On study days, the rabbits were placed in a rabbit holder. Doses were administered orally, after which 3 mL of water was administered to facilitate swallowing. Valsartan solid dispersion and pure valsartan were selected for the *in-vivo* study. Blood samples (1 mL) were collected from the marginal ear vein 1, 2, 3, 6, 12 and 24 h after the drug was administered. Immediately after the blood was collected, the serum was separated by centrifugation at 3000 rpm for 10 minutes. The serum was then transferred to a fresh Eppendorf tube and stored at −4°C. Analysis was carried out using a high-performance liquid chromatography (HPLC) system. The catheters were removed and the rabbits returned to their cages after the final blood samples were collected 24 hours after dosing.

HPLC Assay: The validated HPLC method determined plasma concentrations of valsartan. In brief, the mobile phase comprised methanol: 0.1 % opa water at a ratio of 70:30. The elution was isocratic at ambient temperature with a flow rate of 1.0 ml/minute. The separation was achieved using a C18 column (4.6 mm × 250 mm). The calibration curves included all the drug concentrations measured in clinical practice with within and between-day accuracies, and the precisions were in accordance with Food and Drug Administration (FDA) guidelines. The calibration curves (n = 5) were found to be linear over the entire concentration range of valsartan with a correlation coefficient (R2) value of 0.999

Chromatographic Conditions: The following chromatographic conditions were established by trial and error and were kept constant throughout the experimentation

HPLC: AGILENT (1100)

METOPt ware: Chemstation

Column: id 4.6 x 250 mm length

Particle size packing: 5 µm

Stationary phase: C-18 (COSMOSIL)

Mobile Phase: Methanol: 0.1 % OPA Water 70: 30

Detection Wavelength: 248 nm

Flow rate: 1.0 ml/min

Temperature: Ambient

Sample size: 20 µl

Formulation of Modified Release Tablet of Valsartan: Valsartan modified release tablets were prepared by direct compression method. The corresponding amount of drug and excipients were accurately weighed and mixed properly and the matrix tablets were prepared by direct compression using punching machine. Each tablet contains 291 mg solid dispersion equivalent to 40 mg of drug valsartan. The composition of each tablet was shown in **Table 3**. All ingredients required for formulation were collected and weighed accurately and passed through sieve no 40. They were subjected to polybag mixing for 10–15min to obtain a uniform powder blend. Magnesium stearate was added to the powder blend and mixed again for 4–5min, Blend was subjected to compression by using tablet Minipress (10mm round punches).

Evaluation of Tablets:

Pre-compression Evaluation Parameters

Micromeritic Properties:

Bulk density
Tapped density
Angle of repose
Hausner ratio
Compressibility index

Post-Compression Evaluation Parameters: Tablets were subjected to various evaluation parameters including

Weight Variation
Tablet Hardness
Friability
Thickness
In-vitro Drug Release

***In-vitro* Dissolution Studies:** The *in-vitro* dissolution studies were performed using the USP-II (Paddle) dissolution apparatus at 50 rpm. Dissolution media was 0.1 N HCl for first 2 hrs and phosphate buffer pH 6.8 for remaining hrs and temperature was maintained at 37±0.5ºC. A 5ml was withdrawn at specific time intervals and same volume of fresh medium was replaced. The withdrawn samples were diluted with pH 6.8, filtered and analyzed on UV spectrophotometer at 250 nm using pH 6.8 as a blank. Percentage cumulative drug release was calculated.

Mathematical Modelling of Drug Release Profile: Investigation for the drug release from the Valsartan sustain release matrix tablets was done by studying the release data with zero order, first order kinetics and Higuchi equation. The release mechanism was understood by fitting the data to the Korsmeyer Peppas model.

Zero-order Kinetics: When the data is plotted as cumulative % drug release versus time, if the plot is linear then the data obeys zero-order release Kinetics, with a slope equal to K0. The following equation would predict zero-order release:-

$$At = A0 - K0t$$

Where, At= Drug release at time t‟. A0= Initial drug concentration. K0 = Zero-order rate constant (hr-1).

First-order Kinetics: When the data is plotted as log cumulative % drug remaining versus time yields a straight line, indicating that the release follows first-order kinetics. The constant "K‟ can be obtained by multiplying 2.303 with the slope values. The following equation would predict first-order release:-

$$\text{Log } C = \log C0 - Kt / 2.303$$

Where, C = Amount of drug remained at time t‟. C0 = Initial concentration of drug.

K = First-order rate constant (hr-1).

Higuchi's Model: When the data is plotted as cumulative drug release versus square root of time,

yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to "K" (Higuchi's 1963).

Drug release from the formulation by diffusion has been described by following

Higuchi"s classical diffusion equation:

$$Q = [D\varepsilon / \varepsilon (2A - \varepsilon CS) CSt] 1/2$$

Where, Q = amount of drug released at time t". D = Diffusion co-efficient of the drug in the matrix. A = Total amount of drug in unit volume of matrix. CS = Solubility of the drug in the matrix. ε = Porosity of the matrix. t = Tortuosity.

Korsmeyer Equation/ Peppa's Model: When the data is plotted as log of drug released versus time, yields a straight line with a slope equal to „ n" and the „K" can be obtained from y- intercept. To study the mechanism of drug release, the release data were also fitted to the well-known exponential equation (Korsmeyer equation/ Peppa"s law equation), which is often used to describe the drug release behavior from polymeric systems.

$$Mt / Ma = Ktn$$

Where, Mt / Ma = the fraction of drug released at time t. K = Constant incorporating the structural and geometrical characteristics of the drug/polymer. n = Diffusion exponent related to the mechanism of the release. Above equation can be simplified by applying log on both sides,

$$Log\ Mt / Ma = Log\ K + n \log t$$

RESULTS:

Organoleptic Properties:

Appearance: White powder

Odor: Odorless

Drug Characterization: Characterization of the drug was carried out by using Melting point, UV spectroscopy, FT-IR spectroscopy and Differential scanning calorimeter (DSC).

Melting Point: The melting point of valsartan was determined using the capillary method. The melting point was found to be in range between 110°C and 116°C, which is identical to the reported melting point.

TABLE 2: MELTING POINT OF DRUG BY CAPILLARY METHOD

Sample	Melting point (Test)	Melting point (Reference)
Drug	116ºC	110-116˚

Spectrophotometric Analysis of Valsartan: The scanning of valsartan was performed in methanol at range 200-400 nm. The λmax was found to be at 250 nm. The UV spectrum of valsartan is shown in **Fig. 1.** Valsartan exhibited λmax at 250 nm. This λmax were the same as reported in the literature.

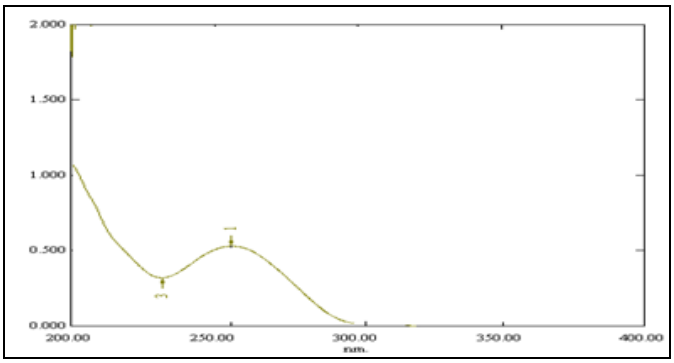


FIG. 4: UV SPECTRUM OF VALSARTAN IN METHANOL

FT-IR Spectroscopy of Valsartan: The FT-IR spectrum of valsartan was carried out to confirm the drug. The FTIR spectrum of valsartan depicts in **Fig. 2**. A spectrum of the pure drug (valsartan) shows a sharp exothermic. This indicates that valsartan is crystalline in nature. The spectrum obtained showed identical peaks as reported in the reference sample of valsartan.

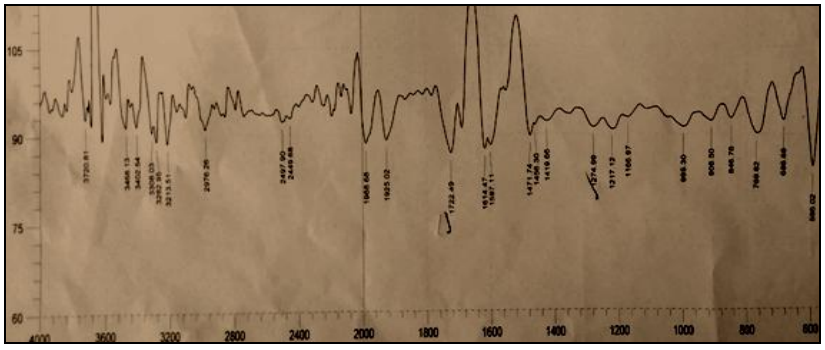


FIG. 2: FTIR SPECTRA OF VALSARTAN PURE DRUG

DSC Study of Valsartan Drug Sample: Differential scanning calorimetry of pure valsartan was carried out to confirm the drug. Valsartan drug sample had a sharp endothermic peak at 116°C that corresponded to the melting point of valsartan. The DSC spectrum of valsartan drug sample is shown in **Fig. 3.** The DSC spectrum of valsartan was same as reported in the literature.

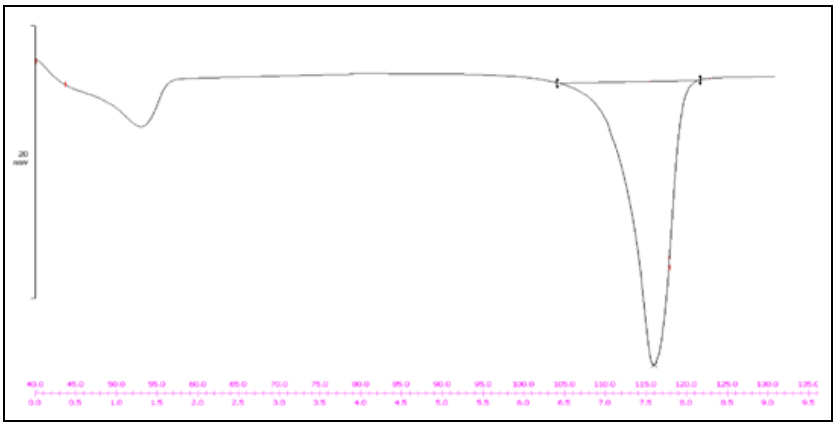


FIG. 3: DSC SPECTRUM OF VALSARTAN DRUG SAMPLE

X-RD Study of Valsartan Drug Sample: The diffractogram of semi-crystalline valsartan showed numerous distinct peaks in the in low intensity, indicates that valsartan is in semicrystalline state with characteristic peaks appearing at a diffraction angle of 2Θ. X-ray diffraction spectra of valsartan drug sample were the same as reported in the literature. The X-ray diffraction spectra of valsartan drug sample are shown in **Fig. 4.**

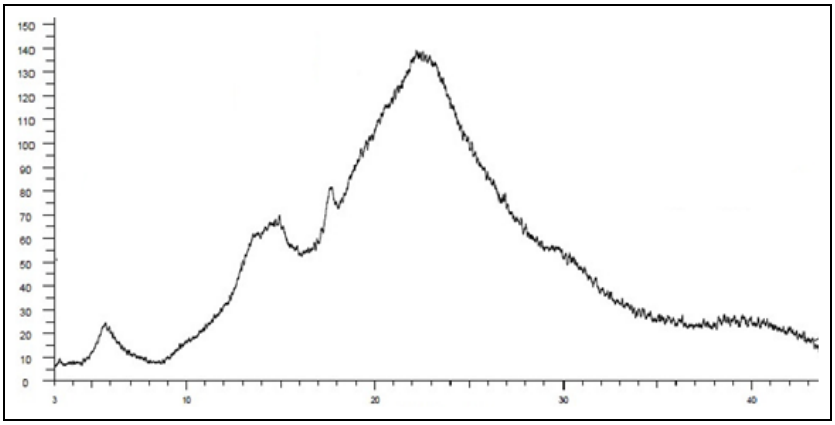


FIG. 4: X-RAY DIFFRACTOGRAM OF VALSARTAN DRUG SAMPLE

Drug-Excipient Physical Compatibility Studies: This study was performed to determine any physical change in the drug when used with various formulation excipients. In the one-month compatibility study, no change was observed in the drug's color and other physical characteristics. This showed that there was no incompatibility between the drug and the excipients used.

Solubility Study of Valsartan: The solubility of valsartan in various solvents is depicted in **Table 3**. The comparative statement of solubility of Valsartan in the different solvent is presented graphically in **Fig. 5**. The solid dispersions of ratio 1:1 to 1:3 does not form properly. Since they were no longer taken into consideration for further studies of solubility determination, drug content, and percentage yield.

Determination of Solubility of Solid Dispersion: The solubility of valsartan in solid dispersion prepared by mixed solvency method in different ratios. As compare to pure drug, the solid dispersion prepared by mixed solvency showed highest solubility in distilled water. This investigation suggested that, it might be possible due to preparation of solid dispersion using eutectic

mixture and increased wettability of valsartan, hence solubility.

Determination of Drug Content in Solid Dispersion: Valsartan drug content (%) with Solid dispersion with a different drug: polymer ratio is shown in **Table 3**. The entire percent drug shown in tables was found within general specifications. It is proved that the formulation that were prepared can be continue for further evaluation.

Determination of Percent Yield: The percent yield of valsartan solid dispersions is shown in table 16. Valsartan solid dispersion had a yield of 98.95%, 96.56% and 96.47% for the drug-polymer ratios of 1:4, 1:5 and 1:6 (SD4, SD5 and SD6), respectively.

Micrometric Properties of Solid Dispersions: The closeness of values of bulk density and tapped density indicates the free-flowing property of solid dispersions.

The values of compressibility index, Hausner ratio and angle of repose indicate that the flow character of solid dispersion is good, good, and excellent, respectively. The results of micrometric properties of solid dispersions are shown is **Table 3.**

TABLE 3: RESULTS OF MICROMETRIC PROPERTIES OF SOLID DISPERSIONS

S. no.	Parameter	Result	Inference
1	Bulk Density (gm/cm^3)	0.329	Free flow
2	Tapped Density (gm/cm^3)	0.379	Free flow
3	Compressibility Index	13.16	Good
4	Hausner Ratio	1.15	Good
5	Angle of repose	22º	Excellnt

XRD Studies of Solid Dispersion: The Powdered x-ray diffraction study of valsartan solid dispersion indicated a diffraction peak characterized by the complete absence of any diffraction peak characteristic of an amorphous compound. The enhancement in the dissolution rate of the drug from the solid dispersion is ascribed to the marked reduction in the crystallinity of the drug. From **Fig. 5** and **9**, it is observed that there is increase in intensities of the characteristic peak in case of solid dispersion. The XRD pattern of valsartan shows intense and sharp peaks that prove the crystalline nature of valsartan. Also, XRD patterns of solid dispersion gave sharp and intense peaks and are thus easily comparable with that of valsartan. This indicates that the dissolution rate in solid dispersion has decreased more, resulting in the sustained release action.

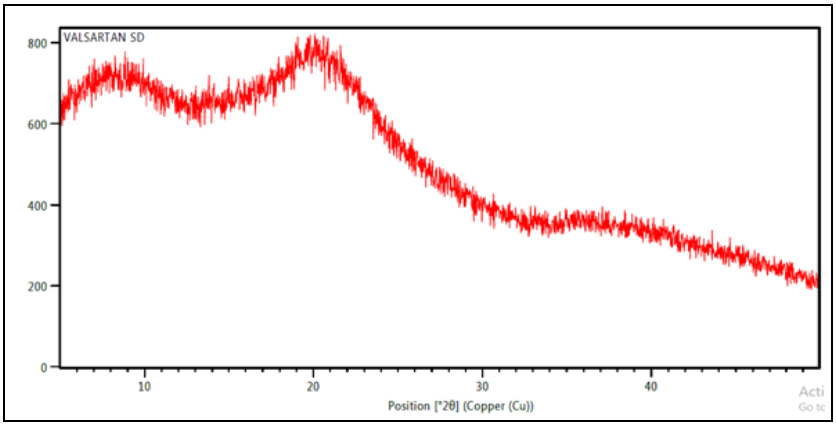


FIG. 5: XRD OF VALSARTAN SD (1:6)

DSC Study of Valsartan Solid Dispersion: The DSC thermogram of Valsartan pure drug was shown endothermic peak at 116°C, indicating that the drug is highly crystalline. The absence of drug peak in the solid dispersion formulation (1:6) indicating the drug was converted into an amorphous form. As the intensity of the endotherm was markedly decreased in the solid dispersion, the faster dissolution rate of the drug from the solid dispersion is attributed to the reduction in the crystallinity of the drug. Crystallization inhibition is attributed to the entrapment of the drug molecules in the polymer matrix during solvent evaporation. The DSC curve of the crystalline form

of pure drug (valsartan) exhibits a sharp endothermic peak at 116.82°C, attributed to melting. However, the solid dispersion resulted in complete suppression of the drug peak **Fig. 6**, suggesting homogeneous dissolution of the drug in polymer and also showing that there is no interaction between drug and polymer.

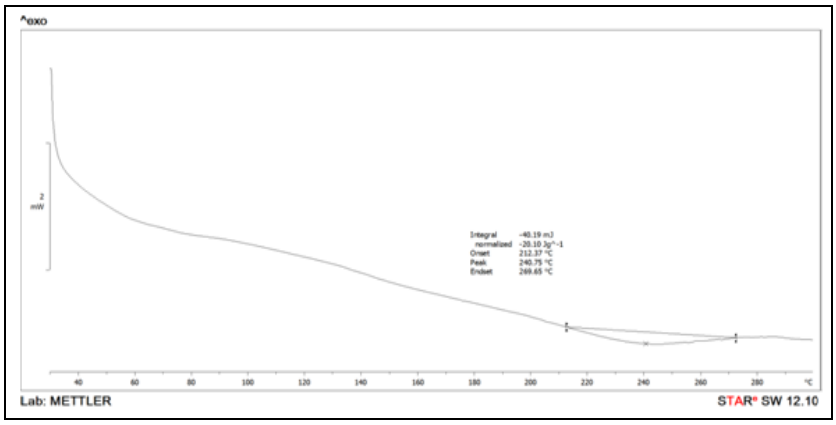


FIG. 6: DSC THERMOGRAM OF VALSARTAN SD (1:6)

SEM Study of Valsartan Solid Dispersion: SEM photographs for pure drug and optimized solid dispersion is shown in **Fig. 7** and **8,** respectively. The drug crystals seemed to be smooth-surfaced, irregular in shape and size. In case of Solid dispersions, it was difficult to distinguish the presence of drug crystals. The drug surface in solid dispersion seems to be more porous in nature. Solid dispersions appeared as uniform and homogeneously mixed mass with a wrinkled surface. Drug crystals appeared to be incorporated into the particles of the polymer. SEM photographs of pure valsartan **Fig. 7** shows irregularly shaped structures, indicating the crystallinity of valsartan. In the case of SDs, it was difficult to distinguish the presence of valsartan crystals. Valsartan crystals appeared to be incorporated into the polymer. The solid dispersion looked like a matrix particle.

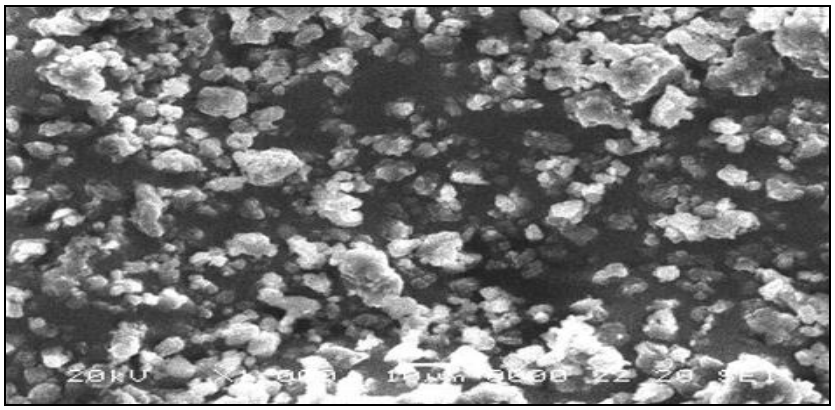
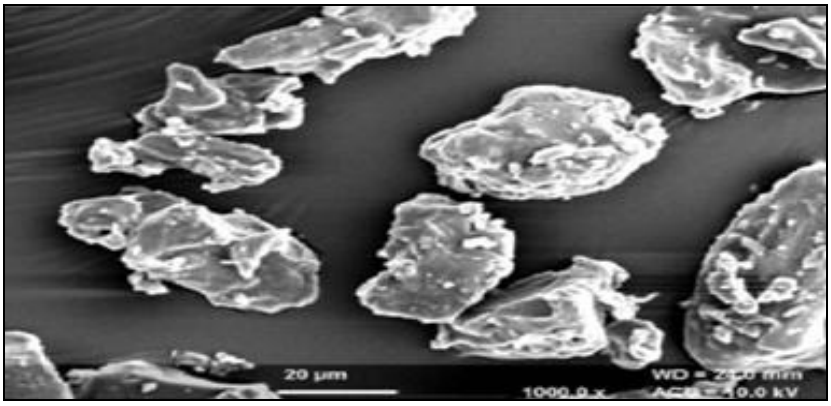


FIG. 7: SEM PHOTOGRAPH OF VALSARTAN



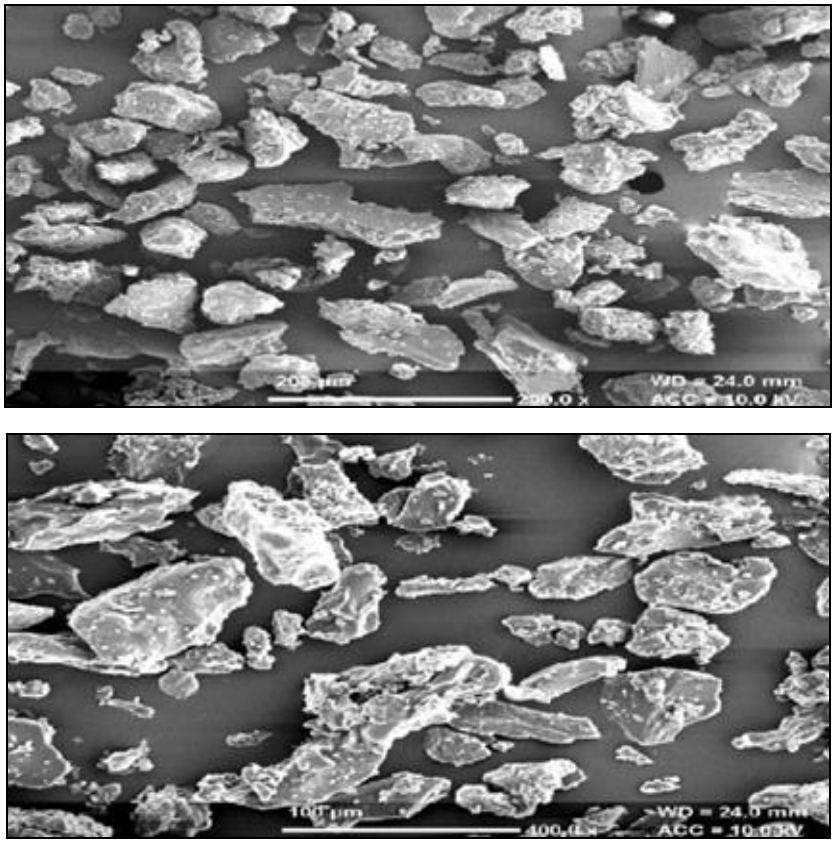


FIG. 8: SEM PHOTOGRAPHS OF VALSARTAN SOLID DISPERSION (1:6)

Evaluation of Tablets:

Pre-Compression Evaluation Parameters:

Micromeritic Properties: For each type of formulation, blends of Valsartan and other excipients were prepared and evaluated for various parameters such as bulk density, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose. Bulk density was found in the range of 0.355- 0.3850 g/cm3 and the tapped density between 0.4101- 0.4880g/cm3 indicating both parameters were found to be within limits. Using the above two density data, Carr's compressibility index were calculated. The compressibility index and Hausner's ratio was found in the range of 7.27-18.42 % and 1.053-1.24 respectively indicating that all powder blends showed excellent to acceptable flow properties. The flow property of all powder blends was better explained from angle of repose. The angle of repose was found in the range of 25.33-31.43°. The results of angle of repose showed all powder blends exhibited good to acceptable flow properties.

Post-Compression Evaluation Parameters:

Hardness: Hardness test was performed by "Monsanto hardness tester". All the formulations have an average hardness in between 4.5 to 5.07 kg/cm^2. This ensures good handling characteristics of all formulation batches.

Thickness: All the formulations were evaluated for their thickness using "Vernier callipers" as per procedure in methodology section 4 and the results are shown in **Table 3**. The average thickness for all the formulations was found in the range of 3.29-5.58 mm which is within the allowed limit of deviation *i.e.* 5% of the standard value.

Friability: Friability is determined to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. The friability of prepared tablets was determined by using "Roche friabilator". The entire controlled release matrix tablet formulations were evaluated for their percentage friability and the results are shown in table no.19. The average percentage friability for all the formulations was found in between 0.26% to 0.44%, which is found within the pharmacopoeial limit (i.e., less than 1%). So the maximum friability was 0.444% observed for F9 and the minimum friability 0.260% observed for F1.

Weight Variation: As the powder material was free-flowing, the tablets obtained were uniform in weight due to uniform die-fill with acceptable variation as per IP standards. The weight variation for all formulations was found in the range of 458.92 to 463.01 mg and results were dissipated in **Table 3** All the formulated tablets passed the weight variation test as the % weight variation was within the pharmacopoeial limits (<5%). The weights of all the tablets were found to be uniform with low standard deviation values.

***In-vitro* Dissolution Studies:** The *in-vitro* release study was performed in 0.1 N HCl for the first 2 hrs, then the medium was replaced by phosphate buffer pH 6.8), and the study continued for 24 hour. In this study HPMC K100 M was chosen as polymer and it was combined with Xanthan gum to explore their sustain release capability. The *in-vitro* release data for HPMC K100 M-Xanthan gum-based Valsartan sustain released tablets are represented in table 20 and illustrated in **Fig. 9** The *in-vitro* release of Valsartan, from prepared matrix tablets formulations, was mainly affected by dissolution medium, the concentration of polymers. The *in-vitro* release of Valsartan was higher in the first 8-12 hours in all formulations. The in-vitro release of Valsartan form prepared matrix tablets also depends on the swelling behavior of the tablets; the higher the tablet swells comparatively, the lesser amount of drug release. Formulation F1, F2, F3 showed almost all drug releases within 16 hrs, 18 hrs and 19 hrs, respectively.

Thus, these formulations were not considered good as the maximum amount of drug was released before the desired period, i.e., 24 hrs. Formulation F4 and F5, respectively, prolong Valsartan's release to 24 hrs. This might be because the self-assembled poly electrolyte complexes film was formed on the surface of cross-linking agent-polymer-based system. The swelling study also showed that a formulation that contains a higher concentration of cross-linking agent showed higher swelling capacity and prolonged the drug release to 24 h.

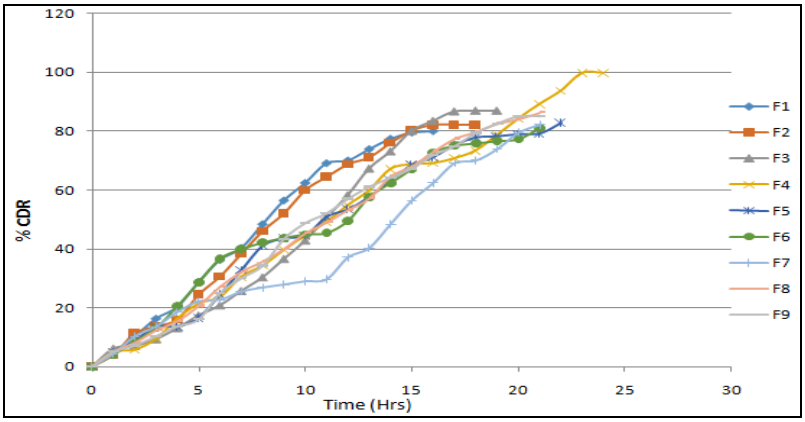


FIG. 9: COMPARATIVE DISSOLUTION PROFILE OF THE FORMULATIONS F1 TO F9

Release Kinetic Studies: All formulations' in-vitro drug release data were analyzed to determine the drug release's kinetics. The obtained data were fitted to zero order kinetics, first-order kinetics, Higuchi model and Korsmeyer-peppas model. The highest correlation coefficient (r^2) obtained from these method gives an idea about model best fitted to the release data. From the results of kinetic studies, the correlation coefficient "r" examination indicated that the drug release followed zero order kinetics, Higuchi model and Korsmeyer-peppas model release kinetics that means extend the release. The relative complexity of the prepared formulations may indicate that the combination of diffusion and erosion possibly controlled the drug release mechanism.

CONCLUSION: The pre-formulation studies like the angle of repose, bulk density, tapped density Haunser's ratio and Carr's index of all formulations were found to be within the standard limits. The powder mixtures were compressed into the tablet and evaluated for post-compression parameters like weight variation, thickness, hardness, friability, and drug content. All the formulation batches showed acceptable results. The *in-vitro* drug release was studied with USP Type-II dissolution apparatus in both simulated gastric and intestine fluid for 24

hours. Results showed that formulations F4 (99.78%) sustained drug release over 24 hours. The *in-vitro* drug release follows first order and indicates that non-Fickian could be the mechanism of drug release. Stability studies showed that the tablet formulations were stable throughout the stability period.

From all the above studies, it was concluded that the approach of mixed solvency is novel, safe, and user friendly. It also eliminates the problem of toxicity associated with the use of toxic organic solvents. So, it may be employed in the dosage form development of drugs where sustained release is desired. The dissolution pattern may be improved by studying suitable drug: polymer ratio.

ACKNOWLEDGMENT: The authors are thankful to the Principal and Management of Sanjivani College of Pharmaceutical Education and Research, Kopargaon, for providing the necessary facilities to carry out this research work and for their constant encouragement during the project.

CONFLICTS OF INTEREST: The author(s) declared that they have no competing interest.

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How to cite this article:
Landge VV, Kothawade SN, Kuskar SD, Albhar SN, Netane SS and Pande VV: Design and development of modified release tablet by mixed solvency assisted solid dispersion of valsartan. Int J Pharm Sci & Res 2023; 14(6): 2862-76. doi: 10.13040/IJPSR.0975-8232.14(6).2862-76.