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(RESEARCH ARTICLE)

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Formulation and evaluation of valsartan solid dispersion for improvement of dissolution profile

Prapti Desai [1,*], Nitin Deshmukh [2], Apeksha Rajguru [1], Rohini Khedkar [1] and Rahul Jadhav [1]

[1] *Lecturer, Department of pharmacy, Elixir Institute of Pharmacy, Purandar- 412301, Pune, Maharashtra, India.*
[2] *Principal, Department of pharmacy, Elixir Institute of Pharmacy, Purandar-412301, Pune, Maharashtra, India.*

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Abstract

In terms of physicochemical factors, solubility is the most crucial to medication absorption and therapeutic efficacy. Bioavailability is low because the medicine is poorly soluble in water and is absorbed poorly in aqueous GIT fluid. In this research, a solid dispersion version of the hypertension drug valsartan was developed to improve its bioavailability and blood pressure-lowering effects. The solubility of Valsartan is improved by using the solid dispersion (kneading method) technique using Soluplus as a carrier (also act as taste masking agent). They were distinguished from one another based on studies examining solubility, in vitro dissolution, dissolving efficiency, and stability. X-ray diffraction, FT-IR spectroscopy, and differential scanning Calorimetry were used to investigate the solid state properties of dispersions (XRD). A 1:1 medication-to-polymer solid dispersion showed 97.77% drug release after 30 minutes. FTIR, DSC, and XRD analyses of solid dispersions all corroborated their formation. A DSC study shown that under accelerated climate settings, kneaded solid dispersion remained stable for 30 days longer than other solid dispersions.

Keywords: Valsartan; Soluplus; Solid dispersion; Kneading; Dissolution

1 Introduction

The most common and straightforward method of administering medication is orally. As compared to alternative oral dosage forms, solid oral dosage forms offer numerous benefits, including being stable, taking up less space, providing the appropriate quantity, and being simple to produce. This means that most newly developed chemical entities (CE) are intended for oral administration as solid dosage forms that reliably provide an adequate plasma concentration in living organisms. Taking a medicine orally may reduce its efficacy since most CEs don't dissolve well in water and are poorly absorbed by the body. Most possible CEs are only absorbed in the upper small intestine, despite their considerable permeability there. Absorption slows drastically beyond the ileum, indicating a narrow window of opportunity for absorption (1-4).

Since it's simple, painless, flexible, and the patient is more likely to comply with oral administration, it's widely used. Since they don't have to be produced in a sterile setting, solid oral delivery devices are less expensive to manufacture. Many novel methods for oral medication administration have emerged in recent years, with the goals of bettering patient compliance and taking into consideration the medicines' physicochemical and pharmacokinetic features. Computer-aided 3D printing (3DP), tablet manufacture using 3DP, and electrostatic drug deposition and coating are all examples of cutting-edge methods for creating and distributing medicines. The most convenient product would be one that can be eaten. The standard dose is represented by a single tablet or capsule.

*Corresponding author: Prapti Desai

Syrup, emulsions, suspensions, solutions, and elixirs are all examples of liquid oral dosage forms that are designed to carry a single dose of medication in volumes ranging from 5 mL to 30 mL. When it comes to orally administered medications, the tablet has clear advantages over the capsule (5, 6).

The difficulty of a medication to dissolve in water might be a greater barrier to absorption than the gut mucosa. Many medications that are absorbed rapidly in the small intestine have a delayed onset of action due to the time it takes for the drug to breakdown and the dosage form to release its contents. Drugs with a slow rate of dissolution are less bioavailable because it takes longer for the drug to dissolve than for it to leave its absorption sites. When it comes to how fast a pharmaceutical dissolves in water, "poorly soluble" medicines often have a water solubility rating of less than 100 mg/ml. examining the drug's solubility in water is another method for identifying "poorly soluble" medications. How much gastrointestinal (GI) fluids are required to dissolve a given dosage is the dose: solubility ratio. When this quantity is more than the volume of fluids that may be utilised, the bioavailability of a solid oral dose form can be estimated. Subpar drug absorption is associated with medications that don't dissolve well in water. This indicates that the medications are not functioning optimally or regularly. Drugs are classified into Classes II and IV by the Biopharmaceutics classification system (BCS) depending on how efficiently they are absorbed by and eliminated from the body. Medicines in the Class II BCS are very soluble in air but not water. Certain medicinal medicines' solubility improvement is connected to their bioavailability improvement (7-9).

2 Material and methods

2.1 Materials

2.1.1 Chemicals

Table 1 List of Chemicals

Sr. No.	Name of the ingredient,	Name of the Supplier
1	Valsartan	Aurobindo Pharma Ltd
2	Soluplus	BASF chemicals, Mumbai
3	Mannitol	Research lab, Islampur
4	Sodium saccharin	Loba Chemie, Mumbai, India
5	PVP K30	Research lab, Islampur
6	PEG 4000_	Research lab, Islampur
7	Cross carmellose sodium	Research lab, Islampur
8	Methanol	Research lab, Islampur
9	Microcrystalline cellulose	Research lab, Islampur
10	Magnesium stearate	Research lab, Islampur
11	Talc	Research lab, Islampur

2.1.2 Equipments

Table 2 List of equipments

Sr. No.	Name of the equipment
1	Analytical balance (LCGC, LCT-203)
2	Water bath Shaker
3	Hot air oven (BIO-TECHNICS, INDIA)
4	USP Dissolution apparatus II (ELECTROLAB, TDT-064)
5	UV visible spectrophotometer (SHIMADZU, UV 1800)

6	IR spectrophotometer
7	Stability chamber (LABHOSP)
8	Grinder
9	pH meter (CHEMLINE)
10	Tablet compression machine
11	Homogenizer
12	Melting point apparatus (NAVYUG INDIA)
13	Bulk density apparatus (ALMICRO)

2.2 Experimental work

2.2.1 Preformulation Studies (10-13)

Determination of Solubility of Valsartan

By utilizing the shake flask method, we determined that valsartan was soluble in 0.1 N HCL, methanol, and a phosphate buffer at pH 6.8.

Determination of Melting point of drug

The melting point of Valsartan was determined using melting point testing equipment.

Determination of λmax of Valsartan

The optimal dosage (λ max) of valsartan was determined by employing a solution consisting of methanol, water, and phosphatebuffer (pH 6.8).

IR Spectrum of Valsartan

Valsartan's infrared spectra were collected using a Fourier transform infrared spectrophotometer. Just after collecting a sample, it was transferred to the IR platform. The spectral wavelength was then swept between 4000 and 400 cm^{-1}.

IR Spectrum of carrier

The infrared spectra of the carrier was evaluated using a Fourier Transform Infrared spectrophotometer. Just after collecting a sample, it was transferred to the IR platform. The spectral wavelength was then swept between 4000 and 400 cm^{-1}.

Interaction between Valsartan and carrier

The Valsartan and carrier mixture's physical infrared spectrum was obtained using a Fourier Transform infrared spectrophotometer (Alpha E Bruker). A little sample was taken and placed straight onto the IR apparatus. Afterwards, the spectrum was scanned from a wavelength of 4,000 to 400 cm^{-1}.

Calibration curve of Valsartan

The optimal dosage (λ max) of valsartan was determined by employing a solution consisting of methanol, water, and phosphatebuffer (pH 6.8).

2.2.2 Phase solubility studies

Solubility was measured using the protocol described by Higuchi and Connors. The phase solubility experiment included a wide variety of hydrophilic carriers, including PEG 6000, PVP K30, and Soluplus. When the carrier concentration in the aqueous solutions increased (from 0.2 to 0.4 to 0.6 to 0.8 to 1.0 to 1.5 to 2% w/v), additional Valsartan was added. The resulting mixes were shaken for 48 hours at 37°C. The supernatant was filtered through a membrane with a pore size of 0.45 microns. The filtrate was analyzed using spectrophotometry after appropriate dilution (shimadzu, Pharmspec UV 1700, Japan) (15).

2.2.3 Selection of appropriate ratio of drug and carrier

Preliminary studies were conducted to determine the optimum drug carrier ratio to maximize drug solubility enhancement. Several drug-carrier mixes (0.5:1, 1:1, 1:1.5, and 1:2) were tested for solubility and dissolution.

Preparation Methods (16-18)

Physical mixtures (PM)

Valsartan PMs were prepared by combining the drug with a suitable carrier at ratios of 1:0.5, 1:1, 1:1.5, and 1:2 using a mortar and pestle. After that, we put the physical mixtures in a desiccator until we were ready to utilise them.

Preparation of Solid dispersions

Using Soluplus, the procedures of solvent evaporation, kneading, and melting were used to generate solid dispersions of Valsartan.

Solvent evaporation method (SE)

Valsartan and the carrier were dissolved in methanol at specific weights to create solid dispersions. After dissolving all of the material, the solvent was evaporated at ambient temperature and reduced pressure. The solid mass was subsequently crushed, and the ready-to-use solids were stored in desiccators.

Kneading method (KM)

After combining valsartan and carrier (1:0.5, 1:1, 1:1.5, or 1:2 w/w) with methanol, the mixture was kneaded for 30 minutes in a glass mortar. For 24 hours, the mixture was dried in a vacuum. The powder was sieved through a No. 60# mesh before being stored in a desiccator for further testing.

Melting method (MM)

The medication was dissolved in a hot carrier solution (at concentrations of 0.5%, 1.5%, 1.5%, and 2% by weight) and then chilled in an ice bath. After being dried in a desiccator, the resultant solid mass was crushed and sieved through a No. 60.

2.2.4 Characterization of Valsartan, Carrier and Solid dispersion (19, 20)

Drug content estimation

Carefully measuring out 50 mg of medication required adding the solid dispersion complex to a 100 ml volumetric flask. It was dosed with 100 mL of methanol. To ensure that all of the medication was extracted, the resulting liquid was swirled for an hour. After proper filtering and methanol dilution, the solution is ready for use. Using methanol as a blank, UV spectrophotometer measurements determined the concentration of the medication.

Saturation solubility studies

Saturation solubility studies were performed in distilled water, 0.1N HCl, and pH 6.8 phosphate buffer using the Higuchi and Connors technique. In summary, an excess of the pure medication was added to 25 ml of distilled water, 0.1N HCl, and a phosphate buffer with a pH of 6.8. During 24 hours at 37°C, the vials were shaken in a shaker. The supernatant solutions were collected after equilibration and filtered through a 0.45 m membrane. Using a UV-visible spectrophotometer, the valsartan concentration in the purified solution was calculated.

IR spectral analysis

Using a Fourier transform infrared spectrometer, we were able to get the infrared spectra of pure Valsartan, carrier, Valsartan: carrier (physical mixing), and solid dispersion (Alpha E Bruker). The spectrum scanned was from 400 cm-1 to 4000 cm^{-1}.

Differential Scanning Calorimetry (DSC)

Thermogram of Valsartan, Valsartan Soluplus, and Valsartan alone: Solid dispersion complex and Soluplus (physical mixture) thermogram were produced using a Mettler-Toledo DSC 821e equipment with an intra-cooler (Mettler-

Toledo, Switzerland). The samples were heated in a nitrogen environment at a rate of 10°C/min from 30 to 300 degrees Celsius.

X-ray Diffractiometry (XRD)

X-ray diffractiometry (PW 1729, Philips, The Netherlands) was used to record the X-ray diffraction patterns of pure Valsartan, carrier, Valsartan: carrier (physical mixing), and solid dispersion. A copper target, 30 kV of voltage, and 30 mA of current were used.

SEM analysis (SEM)

Pure Valsartan, carrier, drug: carrier (physical combination), and solid dispersion complex were analyzed using the JSM 5600 LV scanning electron microscope. Joel, Japan, Swivel Eyepiece Refractor.

Dissolution study of Valsartan and its solid dispersion complex in Phosphate buffer pH 6.8

The solid dispersion and Valsartan were put into 900 cc of phosphate buffer pH 6.8 and stirred at 50 rpm to see if they would dissolve. For the dissolving test, a sample of medicine powder equal to 40 mg was used. At regular times, a 5 ml aliquot was taken out and replaced with the same amount of dissolving solution. Spectrophotometric analysis was done on the samples that had been filtered. Three different tests were done.

3 Results

3.1 Preformulation Studies

3.1.1 Determination of Solubility of Valsartan

Valsartan was shown to be easily soluble in acetone and methanol, and just weakly soluble in water and 0.1 N HCL.

3.1.2 Determination of melting point of drug

Valsartan's melting point was discovered to be between 116 and 117 degrees Celsius.

3.1.3 Determination of ⅄ max of Valsartan

In methanol

Valsartan's ⅄ max in methanol was discovered to be 250 nm.

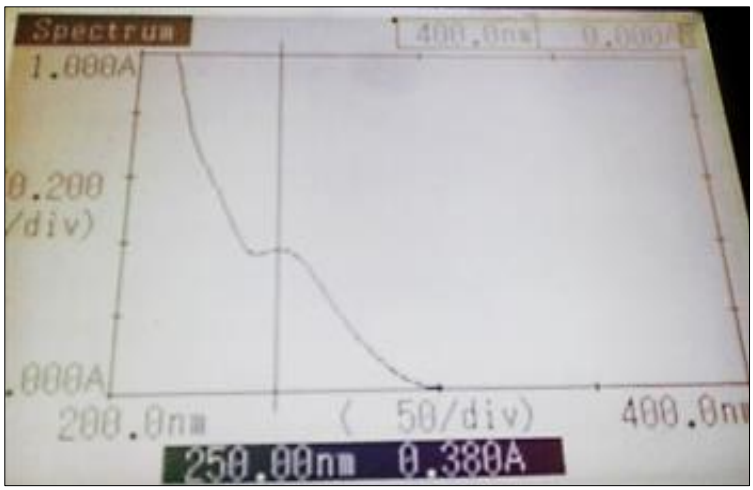

Figure 1 UV absorption spectra of Valsartan in Methanol

In distilled water

Valsartan's maximum concentration was discovered to be 250 nm in distilled water.

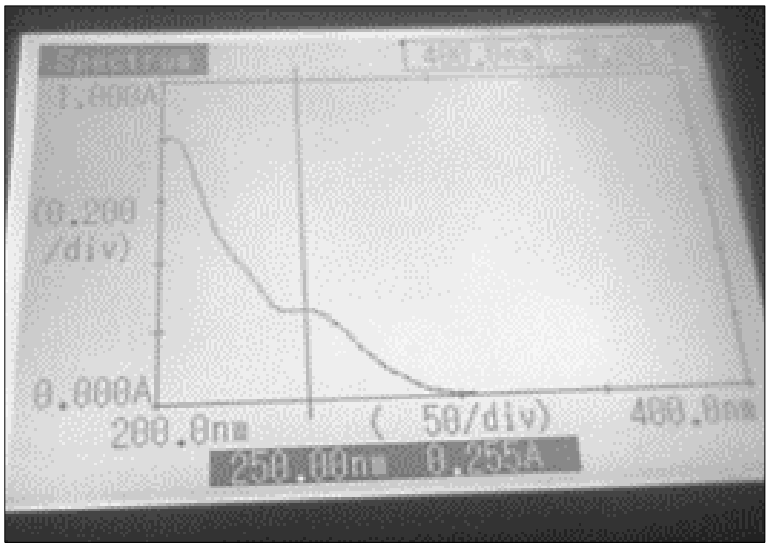

Figure 2 UV absorption spectra of Valsartan in distilled water

In pH 6.8

Valsartan's maximum wavelength was determined to be 250 nm at pH 6.8.

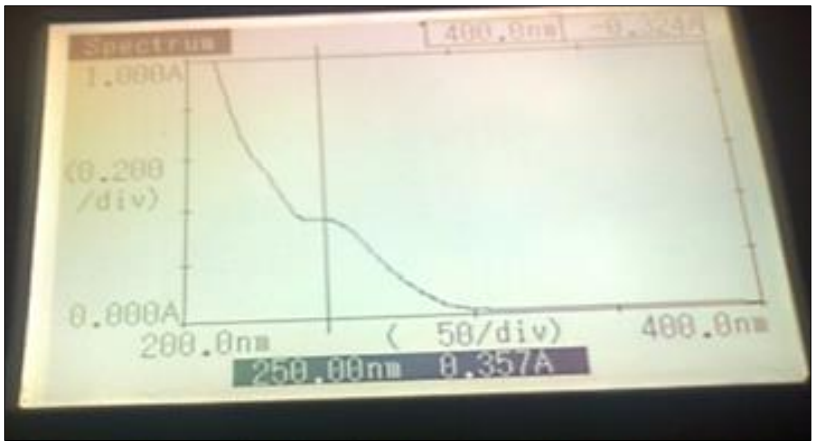

Figure 3 UV absorption spectra of Valsartan in pH 6.8

Table 3 Max of in different solvent system

Sr. No.	Solvent	Max
1	Methanol	250 nm
2	Distilled water	250 nm
3	PBS 6.8	250 nm

3.1.4 IR spectrum of Valsartan

The calculated IR spectra of pure Valsartan is shown in fig. 3.4.

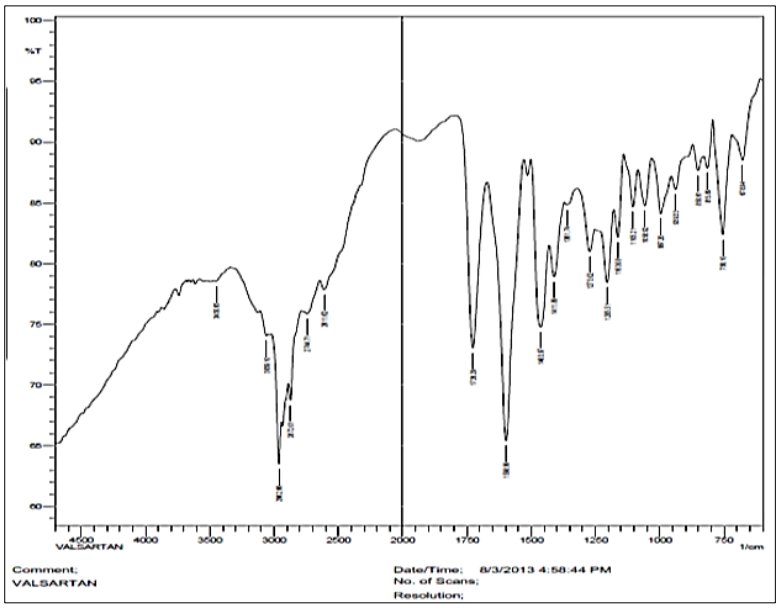

Figure 4 IR spectrum of Valsartan

Table 4 IR data of Valsartan

Sr. no	Type of Peak	Observed peak (cm-1)
1	C-H alkane	2963.76
2	C=O ketone	1732.73
3	C-N Tertiary amine	1205.33
4	N-H secondary amine	1602

3.1.5 IR spectrum of Soluplus

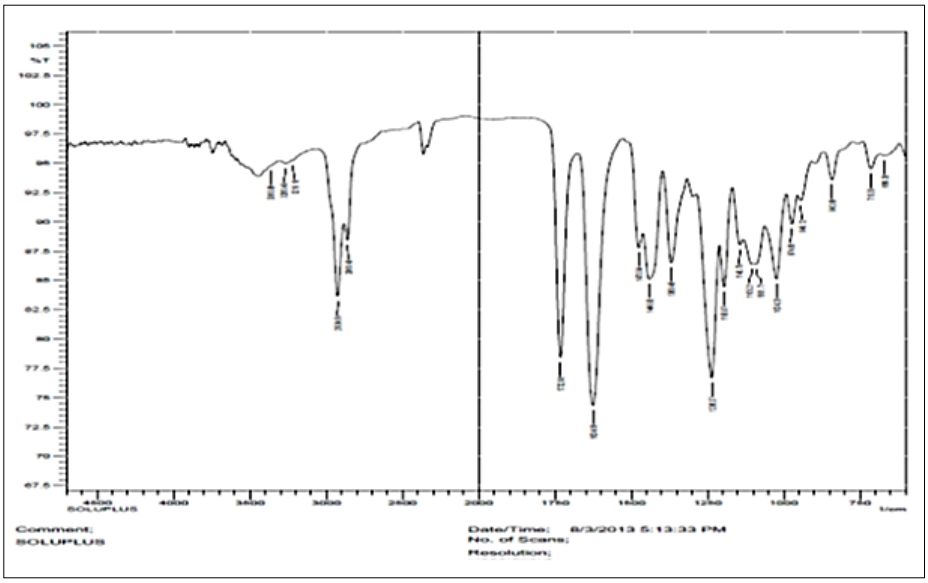

Figure 5 IR spectrum of Soluplus

Table 5 IR data of Soluplus

Sr.no	Type of Peak	Observed peak (cm-1)
1	C-H alkane	2963.76
2	C=O ketone	1732.73
3	C-N Tertiary amine	1205.33
4	N-H secondary amine	1602

3.1.6 Interaction between Valsartan and Soluplus (PM)

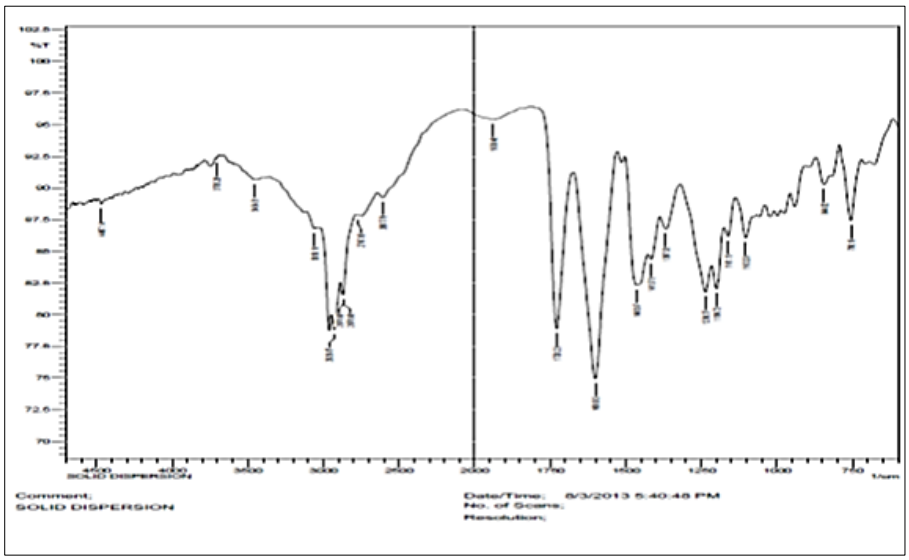

Figure 6 IR spectrum of Valsartan and Soluplus (PM)

Table 6 IR data of Physical mixture

Sr. no	Type of Peak	Observed peak (cm-1)
1	C-H alkane	2963.76
2	C=O ketone	1732.73
3	C-N Tertiary amine	1205.33
4	N-H secondary amine	1602

Figure 4 shows the IR spectra of both Valsartan and Soluplus when they are mixed together. Even though Soluplus barely changed Valsartan's absorption peak, the results show that the two drugs don't interact with each other.

3.1.7 Calibration curve of Valsartan

Calibration curve of Valsartan in methanol

At a concentration range of 5–30 µg/ml, a linear calibration curve for valsartan in methanol was obtained (r2 = 0.999).

Table 7 Readings for Calibration curve of Valsartan

Sr.No.	Conc.(µg /ml)	Absorbance
1	5	0.172
2	10	0.359
3	15	0.551
4	20	0.662
5	25	0.824
6	30	0.973

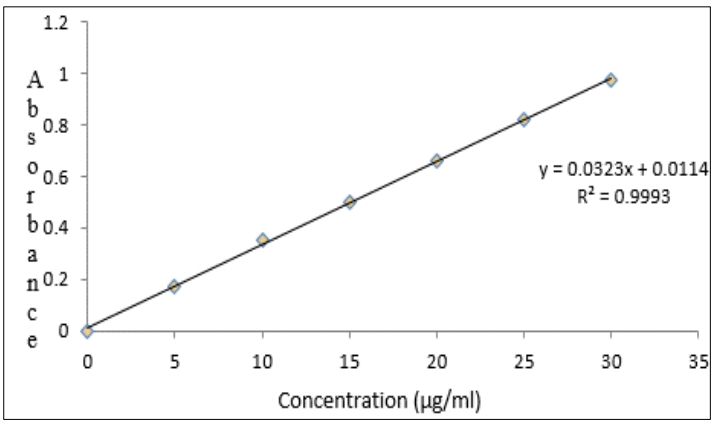

Figure 7 Calibration curve of Valsartan in methanol

Calibration Curve of Valsartan in distilled water

The linearity of the valsartan in water calibration curve was determined to be 0.997% between the 5 and 30 µg/m1 concentration range.

Table 8 Readings for Calibration curve of Valsartan

Sr. No.	Conc. (µg /ml)	Absorbance
1	5	0.152
2	10	0.27
3	15	0.443
4	20	0.621
5	25	0.761
6	30	0.94

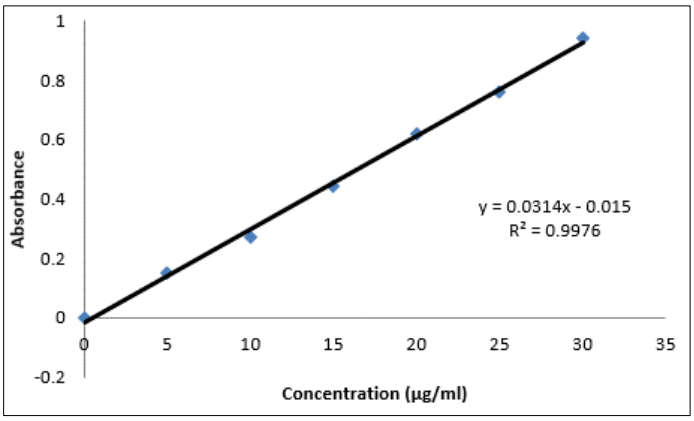

Figure 8 Calibration curve of Valsartan in water

Calibration Curve of Valsartan in PBS 6.8

Calibration curve of Valsartan in PBS 6.8 was found to be linear in the range of 5 to 30 µg/ml and Coefficient of correlation was found to be 0.997.

Table 9 Readings for Calibration Curve of Valsartan

Sr. No.	Conc. (µg/ml)	Absorbance
1	5	0.1733
2	10	0.3159
3	15	0.4761
4	20	0.7456
5	25	0.8761
6	30	1.0721

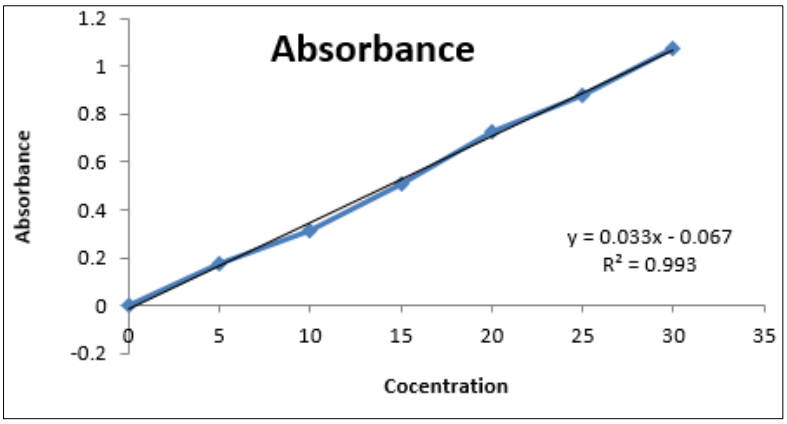

Figure 9 Calibration curve of Valsartan PBS 6.8

3.2 Phase solubility studies

Soluplus was chosen for the phase solubility study out of Soluplus, PVP K30, and PEG 6000. In Table 3.8, you can see how the phase solubility of valsartan affects how it works with hydrophilic carriers.

Table 10 Phase solubility data of Valsartan-hydrophilic carrier

Polymer	Conc. Of Polymer	Amount dissolved mg/ml
Soluplus	0	0.27
	0.2	0.716
	0.4	1.006
	0.6	1.17
	0.8	1.26
PVP K 30._	0	0.026
	0.2	0.376
	0.4	0.468
	0.6	0.504
	0.8	0.628
PEG 6000	0	0.027
	0.2	0.368
	0.4	0.408
	0.6	0.415
	0.8	0.450

From these data, we may infer that just one of the several hydrophilic carriers tested turned out to be successful. Soluplus showed that Valsartan was more soluble in water than it was previously believed to be.

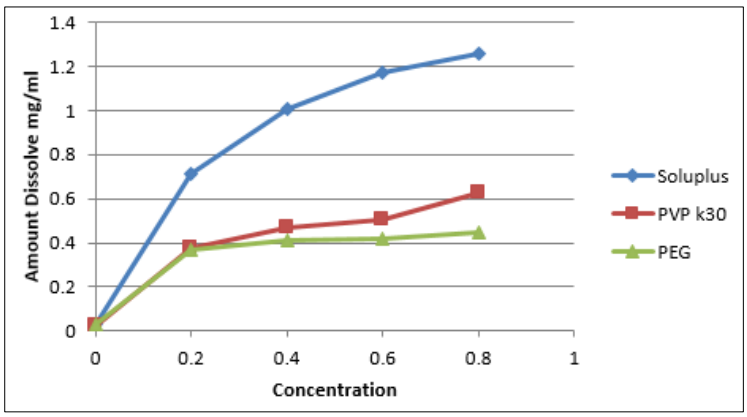

Figure 10 Phase solubility of Valsartan with Soluplus PVP K 30, PEG 6000

Soluplus solubility was improved because of Valsartan's phase solubility behaviour with a variety of hydrophilic carriers. Soluplus was used to create a solid dispersion of valsartan.

3.3 Characterization of Valsartan, Soluplus, physical mixture and solid dispersion complex

3.3.1 Drug Content

All solid dispersion formulations were evaluated for their medicine content, including those made by kneading, melting, and solvent evaporation. Kneading yielded SD with a drug content of 100.05 ±0.40, melting yielded SD with a drug content of 99.03 ±0.45, and solvent evaporation yielded SD with a drug content of 100.06 ± 0.15.

3.3.2 Saturation Solubility Studies

Valsartan's solubility in both pure water and phosphate buffer is shown in Table 3.9. (PH 6.8). Valsartan has a solubility in water of around 0.0271±0.009 mg/ml at 37 ± 2 degrees Celsius. Valsartan's solubility was drastically altered by the solution's pH. Water does not facilitate the dissolution of valsartan. The solubility of valsartan in phosphate buffer was determined to be 2.989±0.13 mg/ml (pH 6.8). Table 23 shows that the medication dissolves more easily in phosphate buffer (pH 6.8), thus that's what was used to make the solution.

Table 11 Saturation solubility studies

Sr. No.	Solvent	Solubility(mg/m1)*
1	Distilled Water	0.0271±0.009
2	PBS 6.8	2.989±0.13

3.3.3 IR Spectrum analysis

IR spectrum of solid dispersion (kneading Method 1:1)

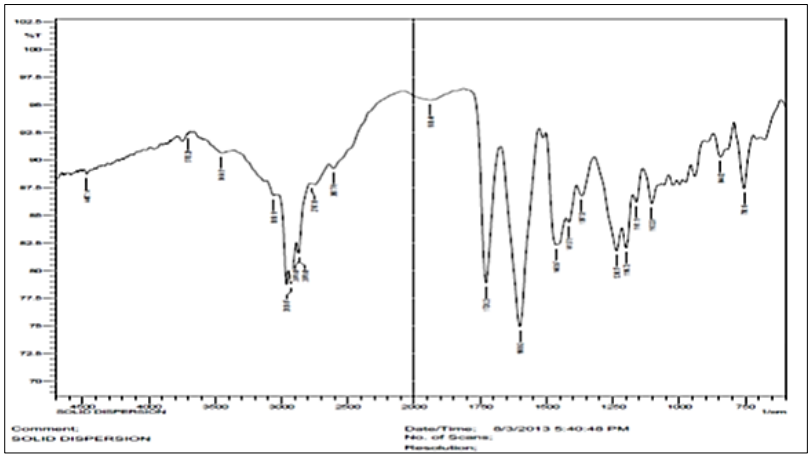

Figure 11 IR spectrum of optimized solid dispersion

3.3.4 Compatibility Study of Pure Drug, Soluplus, Physical mixture and Solid dispersion

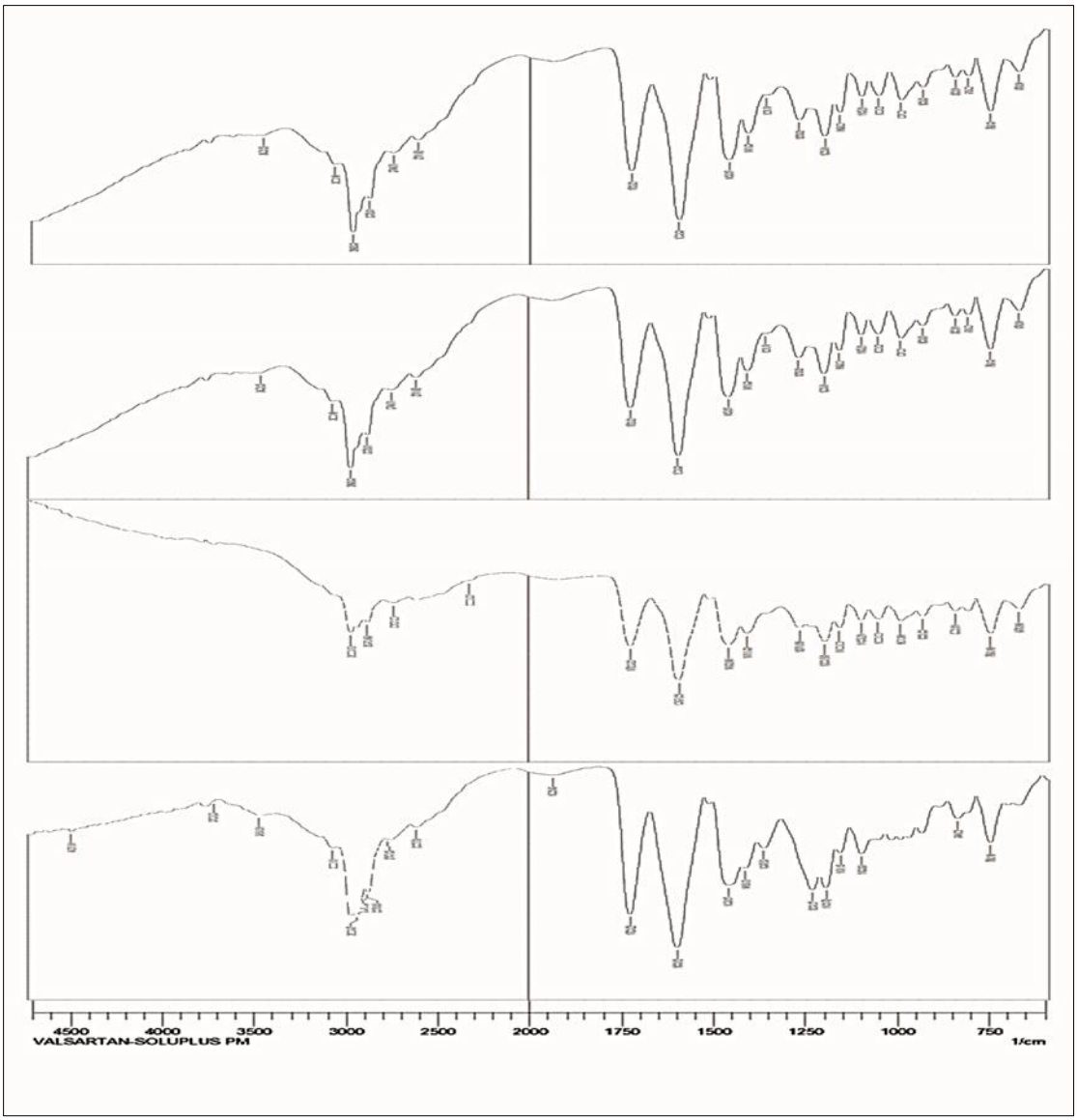

Figure 12 IR spectra of A-Pure drug, B- Soluplus, C-Physical Mixture, and D-Solid dispersion

3.3.5 Differential Scanning Calorimetry (DSC)

The DSC was used to examine the thermal stability of valsartan, Soluplus, PM, and a solid dispersion prepared through solvent evaporation. The DSC analysis of valsartan crystals revealed a single, distinct endothermic peak at 180.78°C. The drug's distinctive endothermic peak, as seen in a DSC thermogram of dispersed particles and solids, is losing its sharpness and intensity over time. Possible explanation: the medication has lost most of its crystalline form and become amorphous.

3.3.6 X ray diffraction analysis (XRD)

The XRD scan of pure Valsartan exhibits a significant crystallinity peak, whereas physical mixes and solid dispersions have fewer and weaker peaks. The mean and standard deviation for RDC were both 0.53. (PM). This finding suggests that treatment with Soluplus reduces the crystallinity of the drug, or causes it to become amorphous. It was found that the amorphene medication was reflected in a reduced peak intensity for the solid dispersion formulation compared to the PM.

3.3.7 Scanning electron microscopy (SEM)

The undiluted material has the appearance of a crystal with a slick, partially curled surface. Soluplus exists as spherical particles. Physical mixing of the drug and carrier at a weight ratio of 1:1 revealed that the drug was in crystalline form and was mixed with irregular Soluplus microparticles. Possible explanation: shrinking the physical mixture as part of the manufacturing process. The drug particles altered form, as seen by photomicrographs of the solid dispersion. They were discovered to be connected to the VAL crystal's surface and to have a more porous structure. The valsartan in the solid dispersion formulation was less crystalline, as seen by scanning electron microscopy (SEM) photomicrographs.

3.3.8 Drug release study

Effect of Soluplus on dissolution of Valsartan from its Physical mixture and solid Dispersion

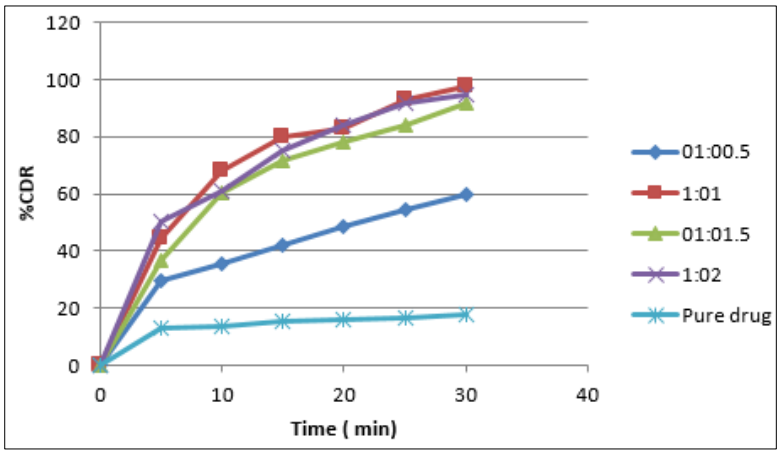

Figure 13 Drug release of physical mixture of Valsartan and Soluplus drug to polymer ration 1:05, 1:1, 1:1.5 and 1:2 PD: pure drug

Figure shows how physical mixtures of Valsartan and Soluplus in the ratios of 1:0.5, 1:1, 1:1.5, and 1:2, as well as the pure drug, dissolve in phosphate buffer pH 6.8. Table illustrate cumulative% drug release at 5 min (DP5), 10 min (DP10),15 min (DP15), 20 min (DP20), 25 min (DP25), 30 min , (DP 30)

Table 12 Drug release of Physical mixture

Formulation	**01:0.5**	**1:01**	**01:01.5**	**1:02**	**Pure drug**
Time (min)	**%CDR***	**%CDR***	**%CDR***	**%CDR***	**%CDR***
0	0	0	0	0	0
5	29.86 ± 0.69	44.41± 0.73	36.93± 1.79	50.25± 0.78	13.11 ± 0.14
10	35.47 ± 0.74	68.02± 0.85	60.15± 0.51	61.12± 0.14	13.57±0.10
15	42.04±0.92	80.04± 0.89	71.76± 0.32	75.47± 0.53	15.26 ± 0.12
20	4.35 ± 1.17	83.12± 1.39	78.28± 0.61	83.84± 1.07	15.98 ± 0.13
25	54.64 ± 0.82	93.12±0.73	84.12±0.75	91.69 ±0.29	16.67 ± 0.09
30	59.77± 1.8	97.77± 1.67	91.52± 1.24	94.49±0.60	17.59± 0.13

Drug release of solid dispersion prepared by kneading method

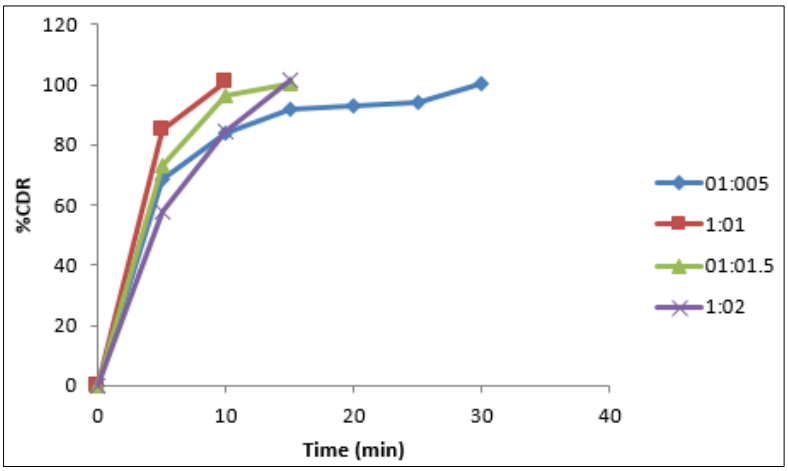

Figure 14 Drug release of solid dispersion prepared by kneading method

An SD with a drug-to-polymer ratio of 1:1 had already released 84.84% of the medicament by the time it was 5 mm long. As compared to other formulations created by kneading, those made with a drug-to-polymer ratio of 1:1 exhibited greater solubility. It is hypothesized that the addition of the hydrophilic surfactant contributes to a quicker dissolving rate of the Valsartan particles with surfactant because it makes the formulation wetter. While using the kneading technique, even drugs that didn't dissolve readily were able to do so since the medicine was evenly distributed throughout the hydrophilic carrier. Possible causes include Valsartan's amorphous state, reduced particle size, ease of wetting and dispensing, and lack of crystals. Dissolution slowed significantly as the drug-to-polymer ratio changed from 1:1:0.5 to 1:2. This is probably due to the fact that, at greater concentrations, Soluplus forms a gel. The findings suggest that a carrier level of 1:1 polymer to medication is optimal for increasing Valsartan solubility. Nevertheless, the medication was not rendered more soluble at Soluplus ratios of 1:1.5 or 1:2. Research demonstrated that modifying the polymer's rheological characteristics and thereby slowing the release of Valsartan by raising its concentration.

Table 13 Drug release of profile of solid dispersion prepared by kneading method

Formulations	**01:005**	**1:01**	**01:01.5**	**1:02**
Time (min)	**% CDR ***	**% CDR ***	**% CDR ***	**% CDR ***
0	**0**	**0**	**0**	**0**
5	68.34 ±10.37	84.84 ± 0.48	72.83 ± 0.67	58.02 ± 1.08
10	83.92± 1.04	100.60 ±0.39	96.49 ± 0.50	84.20 ± 0.67
15	91.76 ± 0.91		100.12 ± 0.84	101.37 ± 0.82
20	92.83 ± 0.28			
25	94.01 ± 0.72			
30	100.46 ± 0.66			

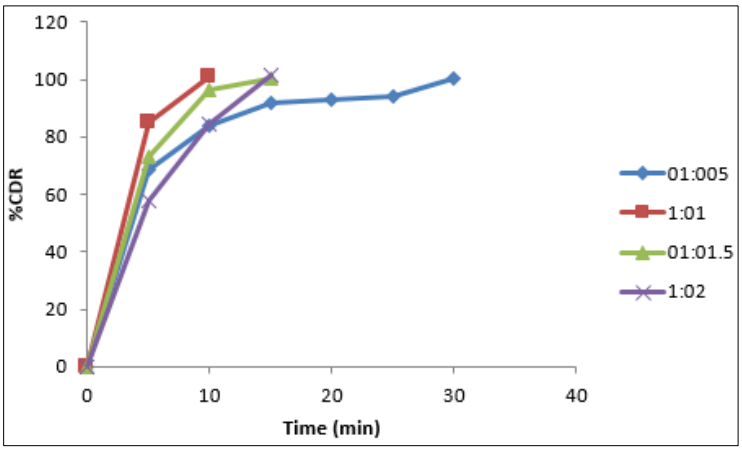

Figure 15 Drug release of profile of solid dispersion prepared by kneading method

4 Discussion

The solid dispersion of valsartan was shown to be more stable than that of other drugs when subjected to accelerated circumstances at room temperature for 30 days. Compared to the pure Valsartan medication, this solid dispersion was quicker and simpler to dissolve. The FTIR spectrum indicates that the medication and excipients in the formulation did not undergo any chemical reactions. Analysis scanning methods that vary the solvent evaporation solid dispersion formulation included amorphous valsartan, as determined by Calorimetry. Scanning electron microscopy research confirmed that Valsartan crystallized and then transformed into an amorphous state. The medication Soluplus significantly increased the solubility and dissolution rate of valsartan in solid dispersions.

5 Conclusion

In this research, the solubility rate of a solid dispersion of valsartan with Soluplus (PM) was significantly increased by co-grinding compared to that of valsartan in its natural form. The semi-crystalline phase may change to the amorphous phase during the co-grinding process.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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