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Development and Characterisation of Valsartan Immediate Release Dosage Form Using Solubility Enhancement Technique

Original Paper

Saripilli R.[1]✉, Teella P.[2], Nataraj Kalakonda S.[3]

[1]Centurion University of Technology and Management, IDCO Land, ODISHA INDIA
[2]M. Pharm, Aditya College of Pharmacy
[3]Shri Vishnu College of Pharmacy

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Abstract

Objective: The objective of the present investigation is to improve the solubility of valsartan and prepare immediate release tablets.

Materials and methods: To increase the solubility and bioavailability of valsartan, a low-soluble antihypertensive drug, immediate release dosage forms were formulated by a direct compression method using a solid dispersion technique with three different carriers (β-cyclodextrin, polyvinyl pyrrolidone K30 and poloxamer 188) at three different ratios (1:3, 1:4 and 1:5). Nine physical mixtures (PM1–PM9) were prepared and various physical parameters were characterised in *in vitro* release studies.

Results: Out of the prepared physical mixtures, PM8 showed the best results, with 94.2% of the drug dissolving within 30 min. Formulation PM8 solid dispersion further used for the preparation of valsartan immediate release tablets by using sodium starch glycolate superdisintegrant, at different concentrations (3%, 4% and 5%; i.e., IF1, IF2 and IF3 formulations, respectively). The optimised formulation showed friability and disintegration values of 0.456±0.9 and 6.2±0.4 min. Among the three immediate release formulations, IF2, which contains 4% sodium starch glycolate, demonstrated an 84.46% drug release in 30 min and a 99.69% drug release in 1 hr, indicating increased drug solubility. When compared with a valsartan pure drug, the solubility of the solid dispersion increased by 135.06-fold.

Discussion and conclusion: The results show that the optimised IF2 formulation demonstrated enhanced drug solubility by 135.06-fold, using a solid dispersion technique with poloxamer 188. This can be explained by the conversion of crystalline to an amorphous form of drug, leading to a reduction in the contact angle between the drug and the gastric medium. It can be concluded that poloxamer 188 is a suitable carrier and that use of a physical mixture technique is an applicable method to improve the solubility of valsartan.

Keywords *Immediate release tablets – valsartan – β-cyclodextrin – poly vinyl pyrrolidone K30 – Poloxamer 188 – Physical mixture*

INTRODUCTION

Compared to all other dosage forms, oral drug delivery is one of the best and preferred methods in terms of unit dose, patient compliance, high precision dosing, and so on. fast-disintegrating tablets and immediate release (IR) tablets have immediate onset of action, when compared with conventional dosage forms and other solid dosage forms, which can show immediate effects. The IR dosage form is one of the popular oral dosage forms as it eliminates the drawbacks of a conventional tablet and has a rapid onset of action. This novel drug delivery system improves the therapeutic activity of active pharmaceutical ingredients by delivering IR, fast-dissolving or fast-disintegrating dosages of the drug to the targeted site. Providing a better therapeutic amount of drug to the targeted or specific site and maintaining the required drug concentrations throughout the treatment period are the primary aims of this novel drug delivery system. Due to the advantages and benefits of using an oral drug form, there is a continuous growing interest in the development of IR dosage forms in the pharmaceutical industry.[1]

Hypertension is a condition where chronic elevation in systemic arterial pressure more than a certain threshold occurs. Cardiovascular risk is associated with a blood pressure elevation above 115/75 mmHg. Systolic blood pressure is the maximum pressure in the arteries when the heart contracts, while diastolic blood pressure is the minimum pressure in the arteries between heart contractions. Hypertension is a condition where symptoms do not generally show until the condition has become serious, hence known as the silent killer.[2–4] It is a condition that continues for a prolonged period, characterised by persistent increase in blood pressure higher than the normal range.[5] Due to its properties

* *E-mail: drsaripillirajeswari@gmail.com*

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and characteristics, valsartan (VAL) is a drug of choice for treatment of hypertension. VAL is an angiotensin II receptor blocker (ARB), a group of drugs that also include olmesartan, candesartan, telmisartan, irbesartan and losartan.[6]

VAL is a specific angiotensin II antagonist which acts on the angiotensin receptor 1 (AT1). It helps by blocking a angiotensin II substance in the body which causes thickening of blood vessels and thereby relaxes the blood vessels and decreases blood pressure. The lower blood pressure increases the blood supply and thereby oxygen supply to the heart. VAL binds to angiotensin I and works as an antagonist, which shows difference from other Angiotensin-converting enzyme inhibitor drugs mechanism of action is preventing the transfer of angiotensin I to II. VAL generally belongs to the biopharmaceutics classification system class II drugs, which have low solubility and high permeability. VAL is not fully lipophilic but it exhibits solubility on pH-dependent bases. It is available in unionised form at lower pH in the stomach, which facilitates better permeation; however, a rate-limiting factor is the drug's solubility.[7] A few examples of hydrophilic drugs include buspirone and betahistine dihydrochloride, while examples of lipophilic drugs include simvastatin, VAL and triamcinolone acetonide.[8] Most ARBs selectively bind to AT1, which prevents protein angiotensin II binding and leads to initiation of hypertensive effects, as well as stimulation, vasoconstriction and synthesis of aldosterone and anti-diuretic hormone and renal reabsorption of sodium. Generally, the physiological effects of VAL include reduced cardiac activity, reduced aldosterone levels, increased sodium excretion and reduced blood pressure. VAL also has low and variable oral bioavailability (BA) due to its poor aqueous solubility.[9]

The present investigation describes an approach to enhance the solubility and dissolution rate of VAL for better BA and pharmacokinetics for treatment of hypertension. The aim of the present work is to design and conduct an *in vitro* evaluation of VAL IR tablets using three different carriers at three different ratios. This work also aims to reduce disintegration time by using a superdisintegrant, sodium starch glycolate (SSG), in the formulation.

MATERIALS AND METHODS

Materials

VAL, poloxamer 188, β-cyclodextrin, polyvinyl pyrrolidone K30 (PVP K30), SSG and lactose were obtained from Yarrow Chem Products (Mumbai India), and microcrystalline cellulose, talc and magnesium stearate were obtained from Biochemical Reagents, Otto Chemica Biochemica Reagents.

Methods

Identification of drugs: The absorbance values of VAL at various concentrations (2, 4, 6, 8, 10 and 12 µg/mL) were determined using ultraviolet (UV)-visible spectrophotometer.

Table 1. Formulation of solid dispersions of valsartan using different carriers.

Formulation code	Carriers	Drug to polymer ratio
PM1	β-cyclodextrin	1:3
PM2	β-cyclodextrin	1:4
PM3	β-cyclodextrin	1:5
PM4	PVP K30	1:3
PM5	PVP K30	1:4
PM6	PVP K30	1:5
PM7	Poloxamer 188	1:3
PM8	Poloxamer 188	1:4
PM9	Poloxamer 188	1:5

PM, physical mixtures; PVP K30, polyvinyl pyrrolidone K30.

Solubility enhancement of VAL by preparing solid dispersions: Solid dispersion (SD) mixtures of VAL were formulated using different carriers (β-cyclodextrin, poloxamer 188 and PVP K30) at three different ratios (1:3, 1:4 and 1:5) and employing a physical mixing (PM) technique. In this technique, the drug and the carrier were placed in a mortar and pestle and were mixed gently until a homogenous mixture was obtained. The prepared homogenous mixture was passed through a sieve (no. 44) and then packed and stored in desiccators for further use. A formulation table for solubility enhancement of VAL is shown in Table 1.

Preparation of VAL IR tablets: Based on physicochemical characterisation and drug release studies, the PM8 formulation, which contains the drug and poloxamer 188 in a 1:4 ratio, was selected to formulate IR tablets with 3%, 4% and 5% SSG as superdisintegrant.[2] VAL PM, SSG, magnesium stearate and talc were added in a mortar and pestle and gently mixed for a few minutes. The prepared formulations (IF1–IF3) were evaluated in terms of precompression parameters, and by direct compression technique compressed into IR tablets using an 8-mm punch. The formulation for the IR tablet ingredients is given in Table 2.

EVALUATIONS

Compatibility Studies

Compatibility studies to determine drug–polymer compatibility were performed using differential scanning calorimetric studies (DSC), scanning electron microscope (SEM), Fourier transform infrared spectroscopy (FTIR) and X-ray diffraction studies (XRD).

Fourier transform infrared spectroscopy: An FTIR spectrometer from Agilent Technologies (Cary 630 FTIR, Germany) was used to obtain FTIR spectra. VAL, PM and IR formulation samples were directly placed on the sample holder and subjected to scanning from 400 to 4000 cm^{-1}.

Differential scanning calorimetry: DSC study was performed using DSC-6100 with a thermal analyser to confirm the drug's

Table 2. Formulation of valsartan immediate release tablets (IF1–IF3).[a]

Formulation code	VAL physical mixture	SSG (mg)	Lactose (mg)	Magnesium stearate (mg)	Total (mg)
IF1	200	6.9	20.8	2.3	230
IF2	200	9.2	18.5	2.3	230
IF3	200	11.5	16.2	2.3	230

[a]*Each batch contains 60 tablets.*
IF, immediate release formulation; SSG, sodium starch glycolate; VAL, valsartan.

physical state in PM and IR formulation and to ensure its compatibility with the excipients. DSC thermograms were analysed by taking 1 mg of accurately weighed samples in covered aluminium pans under nitrogen flow (20 mL/min) at a rate of 10°C min^{-1}. Scanning was done with the oven heated from 25°C to 350°C.

X-ray diffraction: The PW1710 X-ray diffractometer was used for XRD analysis at ambient temperature with an anode material Cu and graphite monochromatic, operated at 20 mA and 35 kV current. The Bragg's law ($n\lambda=2d \sin\theta$) is satisfied when the sample forms constructive interference with the incident rays. These diffracted X-rays were then detected, processed and counted. At 2θ range the sample scanning through, due to the orientation of the powdered material at random in maximum possible diffraction directions of the lattice.[10]

Evaluation of Precompressed Parameters

The following precompression parameters were used to analyse the flow properties of the prepared formulation: angle of repose, bulk density, tap density, Carr's compressibility index and Hausner's ratio.[11,12]

Angle of repose: The angle of repose was measured by funnel method. The maximum possible angle between the granules or powder surface of a pile and the horizontal plane explains the frictional forces of the loose powder. With a definite height fix the funnel to a stand and the powder was allowed to flow through the funnel. The heap radius (*r*) and height (*h*) of the granules or powder were measured, and the angle of repose (θ) was calculated using Eq. 1.

$$\theta = tan^{-1}\left[\frac{h}{r}\right] \quad (1)$$

Bulk density: Bulk density was measured by taking the mixture into a graduated cylinder from density apparatus. The weight of the powder (M) and the bulk volume (V_0) were determined, and the bulk density (ρ_o) was calculated using Eq. 2.

$$\text{Bulk density } (\rho_o) = \frac{M}{V_o} \quad (2)$$

Tapped density: At a fixed time, the apparatus was allowed to tap. The weight of the mixture (M) and the tapped volume in the cylinder (V_t) were determined. The tapped density (ρ_t) of the sample can be calculated using Eq. 3.

$$\text{Tapped density } (\rho_t) = \frac{M}{V_t} \quad (3)$$

Compressibility index: The rate at which it packed down and the powder sample's ability to flow can be determined by comparing the tapped density with the bulk density of the mixture. Carr's compressibility index can be calculated using Eq. 4.

$$\text{Carr's compressibility index} = \left[\frac{\rho_t - \rho_o}{\rho_t}\right] \times 100 \quad (4)$$

Hausner's ratio: Hausner's ratio is an indirect measure of the powder's flow index and can be calculated using Eq. 5.

$$\text{Hausner's ratio} = \frac{\rho_t}{\rho_o} \quad (5)$$

Evaluation of Postcompression Parameters

Postcompression parameters such as weight variation, thickness, hardness, friability, content uniformity, disintegration test and *in vitro* dissolution were determined.[13]

Weight variation: From each batch, 20 tablets were randomly taken, and using digital weighing balance their weights were individually determined. The collective weights of all the tablets gave an average weight.

Thickness: From each batch, 10 tablets were randomly taken, and using vernier callipers their thickness was measured. The readings were obtained and recorded in millimetres.

Hardness: From each batch, three tablets were randomly picked and the mean values were calculated. A Monsanto hardness tester was used to determine the hardness, expressed in kg/cm^2.

Friability: A sample of tablets equivalent to 6.5 g was weighed and the initial weight (W_o) was recorded. The sample was then placed in a Roche friabilator, with the rotation speed adjusted to 25 rpm for 100 revolutions. All the tablets

were then removed from the friabilator, and the fines were dedusted and the sample weighed. The final weight (W_f) was recorded. Eq. 6 was used to calculate %friability.

$$\%\text{Friability} = \left[\frac{W_o - W_f}{W_o}\right] \times 100 \quad (6)$$

Disintegration test: A United States Pharmacopeia disintegration test apparatus was used to determine the disintegration time in a gastric fluid medium with a pH of 1.2 at a 37±0.5°C temperature. The apparatus contains six tubes, with one tablet taken in each tube and a disc placed in each tube. The time required to disintegrate the tablets into fragments and passed through the mesh of the tube was recorded as the disintegration time.

Content uniformity: To determine drug content, 10 tablets were randomly taken and grounded to powder. From the grounded powder, accurately weigh powder equivalent to 40 mg of VLR and dissolved in gastric fluid (100 mL) with a pH of 1.2. Stirring was continued for 15 min, make the volume up to with buffer and filtered if necessary. Absorbance was measured using a Cary 60 UV-visible spectrophotometer (Agilent Technologies) at 205 nm.[9]

Wetting time and water absorption ratio: The time taken for a tablet to disintegrate or break when kept stable in a Petri dish containing 6 mL of gastric fluid with a pH of 1.2 as buffer on the tissue paper is described as the wetting time. Wetting time was measured as the time required to completely wet the tissue paper. The weight of the tablet before wetting was obtained (W_b), and again after wetting the tablet (W_a). For each batch, three trials were performed and the standard deviation was determined. The water absorption ratio (*R*) was determined using Eq. 7.

$$R = 100 \times \left[\frac{W_a - W_b}{W_a}\right] \quad (7)$$

***In vitro* release studies:** Dissolution studies of VAL, PMs and IR formulations were performed with 900 mL of gastric fluid with a pH of 1.2 as the dissolution medium. A USP type II dissolution apparatus at 50 rpm paddle rotation speed at 37±0.5ºC temperature was used. Using syringe, around 5 mL of the sample was withdrawn at a time interval of 5, 10, 15, 30, 45 and 60 min, and fresh dissolution medium maintained at 37 was replaced to keep the volume constant throughout the test. The samples were then filtered using 0.45 µm filter and then analysed for VAL content using a Cary 60 UV-visible spectrophotometer (Agilent Technologies, Germany) at 205 nm. The dissolution tests were carried out in triplicates in all formulations.[9]

Stability studies: Long-term and accelerated stability studies were performed as per the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.

Table 3. Concentration versus absorbance values of valsartan in 0.1 N Hydrochloric acid.

S. No.	Valsartan	
	Concentration (µg/mL)	Absorbance (205 nm)
1	2	0.223±0.29
2	4	0.402±0.24
3	6	0.543±0.20
4	8	0.707±0.16
5	10	0.862±0.11
6	12	1.029±0.09

Note: All values are expressed in mean±SD (n=3).

RESULTS

The present work describes the formulation of SDs of VAL (PM1–PM8) prepared using different carriers (β-cyclodextrin, poloxamer 188 and PVP K30) at three different ratios (1:3, 1:4 and 1:5). From the optimised PM8 SD formulation, IR tablets of VAL (IF1–IF3) were prepared using a synthetic superdisintegrant (SSG) at 3%, 4% and 5% concentrations by a direct compression method. Standard calibration curve of the drug was initially established and the results are shown in Table 3. A graph is plotted showing the concentration versus absorbance values, known as the calibration curve. A linear equation was obtained from the calibration plot.[5] The procedure was repeated three times. From all these three trails straight line equation whose intercept (c) values nearer to zero and coefficient of determination (r) values nearer to 1 was selected. The plotted graph and the scan are shown in Figure 1.

Compatibility Studies

FTIR spectroscopy: The FTIR peak of VAL, optimised PM8 SD formulation and optimised IF2 formulation is shown in Figure 2. The FTIR spectrum of VAL shows two carbonyl absorption bands at 1600 and 1710 cm^{-1}, assigned to the amide carbonyl and carboxyl carbonyl stretching, respectively.[13] The FTIR spectrum of poloxamer 188 is characterised by absorption peaks of the C-H aliphatic stretch at 2800 cm^{-1}, O-H stretch at 1320 cm^{-1} and C-O stretch at 1100 cm^{-1}, indicating the nature of poloxamer 188.[14] The SSG spectrum shows a broad band at 3260 cm^{-1}, which indicates O-H stretching compound . At 1000–1590 cm^{-1}, overlapping bands reflect symmetric and asymmetrical stretching of the C-O-C group.[15]

DSC studies: DSC analyses of VAL and the excipients were performed to evaluate any possible drug to polymer interaction. DSC thermograms were analysed to confirm the physical state of the drug in SDs and to determine its compatibility with the excipients. The thermograms of VAL,

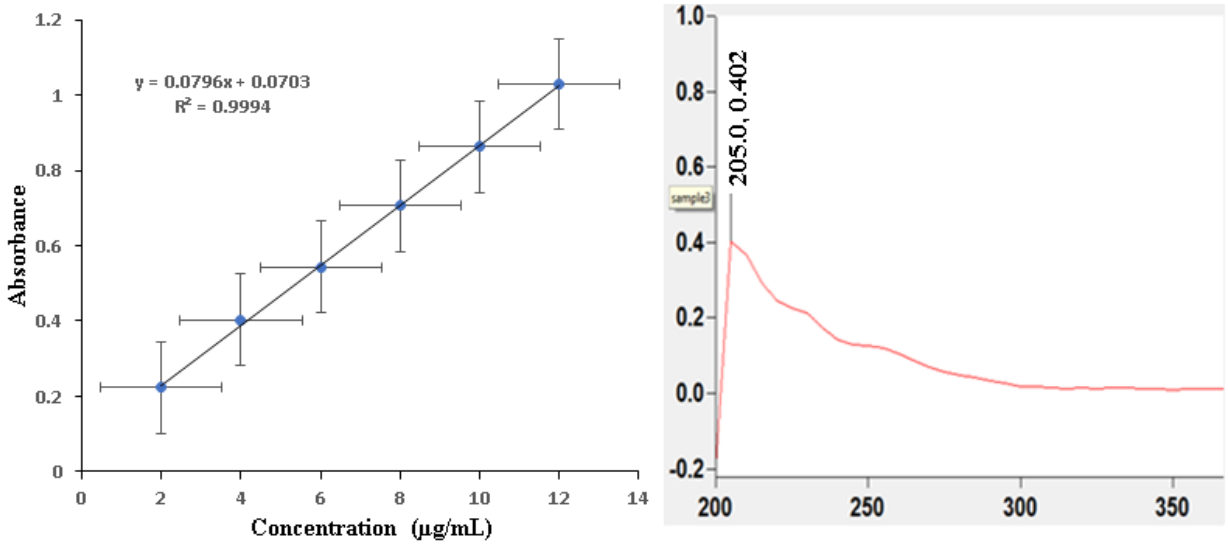

Figure 1. (a) Calibration curve of valsartan in a pH 1.2 buffer and (b) The wavelength scan or ultraviolet spectrum of valsartan.

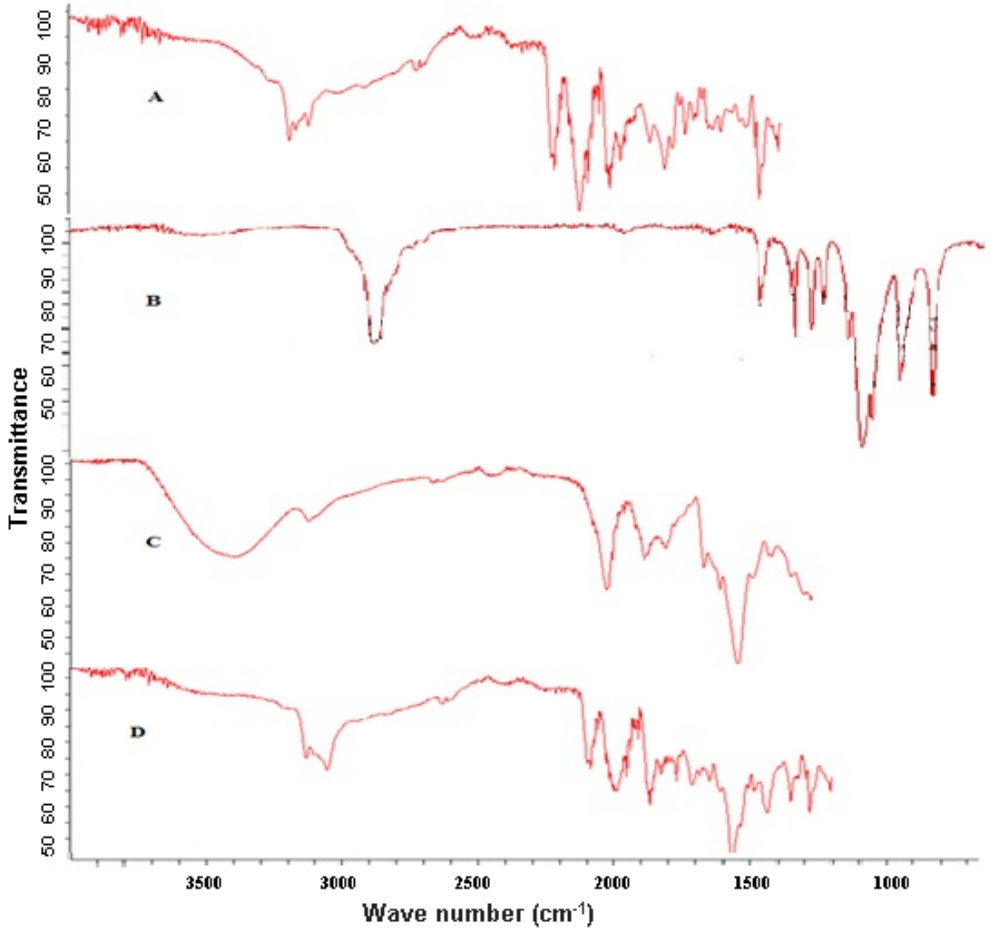

Figure 2. Fourier transform infrared spectroscopy of (a) Valsartan, (b) Poloxamer 188, (c) Sodium starch glycolate and (d) IF2 optimised formulation. IF, immediate release formulation.

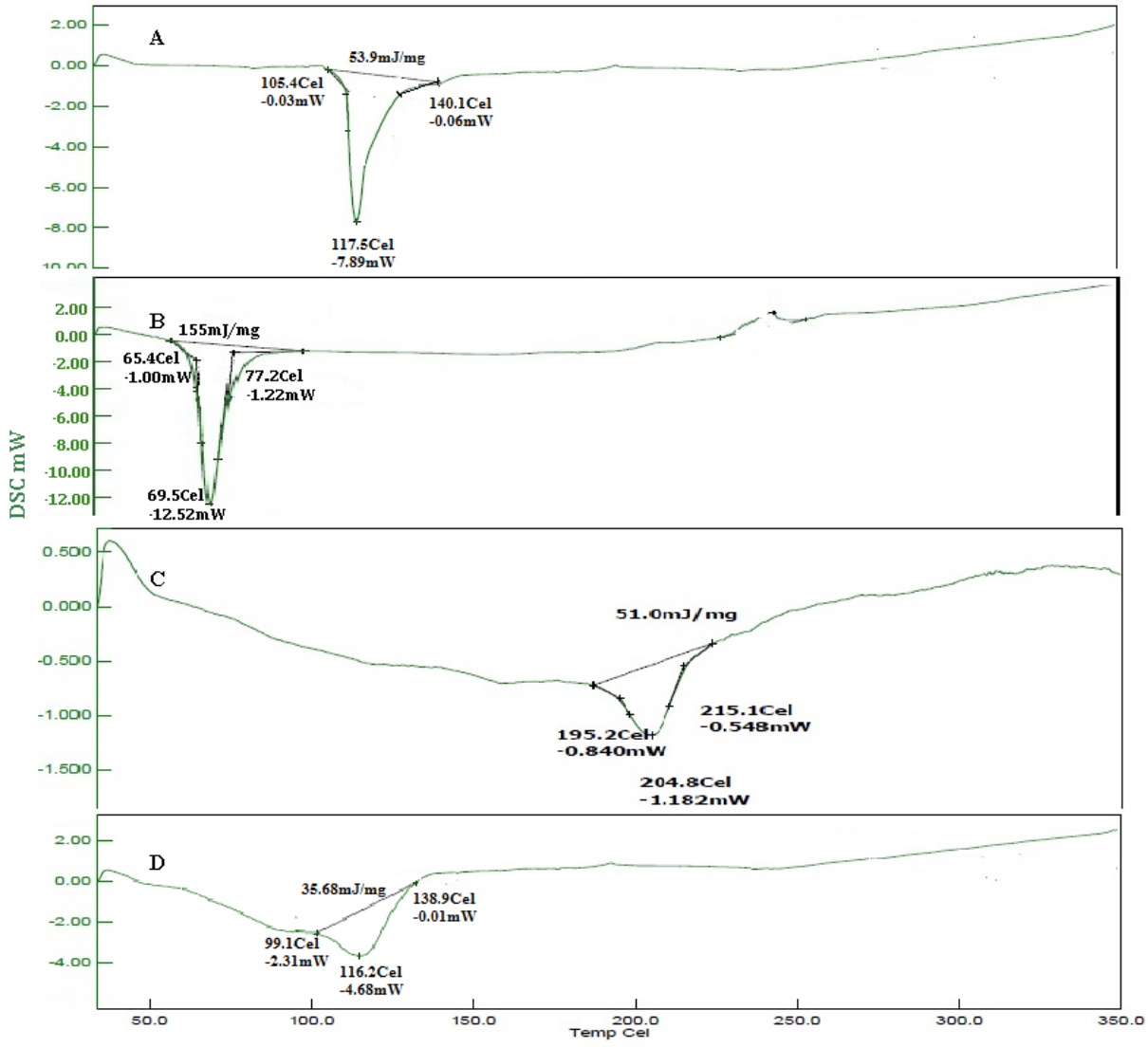

Figure 3. Differential scanning calorimetry thermogram of (a) Valsartan, (b) Poloxamer 188, (c) Sodium starch glycolate and (d) IF2 optimised formulation. IF, immediate release formulation.

poloxamer 188, SSG and optimised IF2 formulation are shown in Figure 3. The VAL showed a melting endotherm at 117.5°C,[15] whereas at 60.80°C a melting endotherm was shown by poloxamer 188.[16] SSG reached its peak at 204.8°C.[16] The optimised IF2 formulation showed a melting endotherm at 116.3°C.

XRD analysis: XRD results for VAL, poloxamer 188, SSG and the optimised IF2 formulation are shown in Figure 4. The XRD spectrum of VAL showed the crystalline form of the drug, demonstrated by distinct values of 19.24º, 23.78º and 38.50º at 2θ. The crystalline form of poloxamer 188 was achieved by two characteristic peaks at 19º and 23º broader peak.[15] SSG reached its peak at 19.68º and 23.92º.

Scanning electron microscopy: The SEM of VAL, SSG and the optimised IF2 formulation is shown in Figure 5. VAL appeared to be made of irregular crystalline structures.[15,17] SSG appeared globular to irregular in shape of varying sizes. In the optimised IF2 formulation, the structure of the VAL mixture crystals was completely different, which indicates the formation of a new structure in the optimised IF2 formulation containing poloxamer 188 and SSG. These findings indicate that the drug changed from crystalline to amorphous form.

***In vitro* dissolution analysis of SDs:** *In vitro* dissolution tests were carried out using a pH of 1.2 as buffer medium with 900-mL volume, at a temperature of 37±0.5℃ and speed of 50 rotations per minute using a USP type II dissolution apparatus. The studies revealed a significant variation between the release profile of VAL and VAL with carriers. All formulations showed a higher amount of drug released when compared with pure drug. Of all the carriers, poloxamer 188 at 1:4% showed a drastic change in its dissolution profile. The data are given in Table 4.

Table 4. In vitro drug release data of valsartan solid dispersions (PM1–PM9) using different carriers.

Time (min)	PM1	PM2	PM3	PM4	PM5	PM6	PM7	PM8	PM9
5	6.12±0.2	7.42±1.3	10.2±2.4	14.8±0.2	12.9±1.1	12.7±2.1	11.7±1.0	26.4±0.3	34.4±0.2
10	10.3±0.5	11.8±1.4	14.7±2.1	20.0±0.4	25.8±1.3	19.4±1.2	37.3±1.2	51.9±0.5	60.1±2.0
15	12.1±0.7	16.5±1.6	22.1±2.6	25.6±0.2	36±1.4	60.3±1.1	57.3±1.3	70.5±0.6	74.5±2.2
30	22.4±0.9	31.7±1.9	27.0±2.7	43.5±0.1	72.2±1.1	72.9±0.2	68.3±1.5	94.2±0.8	96.8±2.0
45	27.7±1.2	41.8±2.6	46.3±2.8	49.4±0.2	98.7±1.1	79.8±0.2	85.9±1.0	96.9±0.9	99.6±1.0
60	39.8±1.5	44.8±2.1	58.3±2.1	75.7±0.9	100.2±1.6	99. 6±0.1	91.4±0.1	99.9±1.0	99.6±1.1

Note: All values are expressed in mean±SD (n=3).
PM, physical mixture.

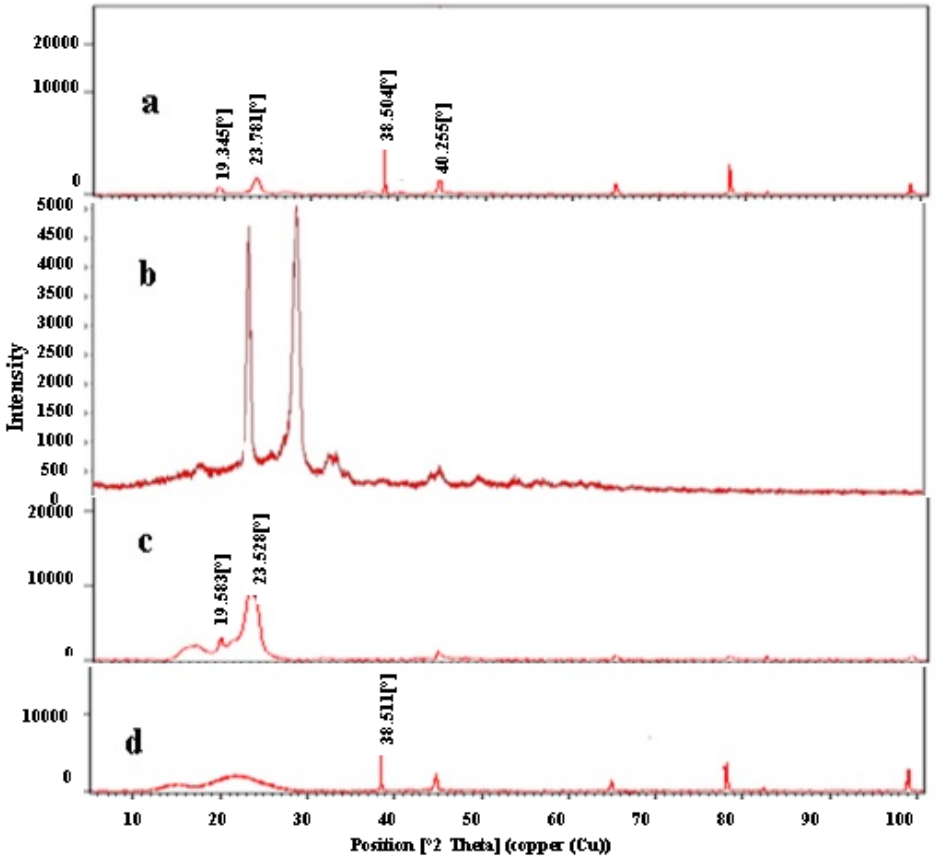

Figure 4. X-ray diffraction pattern of (a) Valsartan, (b) Poloxamer 188, (c) Sodium starch glycolate and (d) IF2 optimised formulation.
IF, immediate release formulation.

Precompression Properties

The flow properties of the prepared VAL IR formulation (IF1–IF3) were analysed to determine their suitability for direct compression.[18] The values are given in Table 5. The angle of repose was found lowest for IF2, with a value of 22.92°, and highest for IF3, with a value of 28.88°. A value less than 40° indicates the granules have good to moderate flow property. The compressibility index values for all the formulations varied between 1.42 and 6.66. An observed value less than 15% indicates the granules have good flow nature. Hausner's ratios values were observed to be between in the range of 1.06 and 1.12, which were below 1.18, indicating all the values were as per standard range, thus suggesting good flow properties.

Postcompression Properties

For all the prepared batches of tablets, the hardness was found to be in the range of 4–6 kg/cm^2. The friability of all the formulations ranged from 0.227% to 0.456%, which were less than 1%, while the drug content values ranged from 92.66%

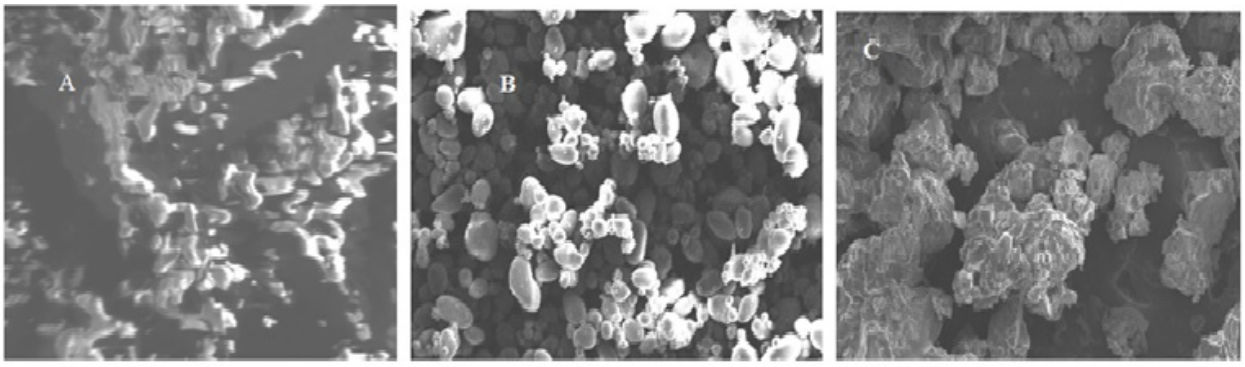

Figure 5. Scanning electron microscope images of (a) Valsartan, (b) Sodium starch glycolate and (c) IF2 optimised formulation. IF, immediate release formulation.

Table 5. Flow properties of valsartan immediate release formulations (IF1–IF3).

Formulation code	Angle of repose (°)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)	Hausner's ratio
VAL	42.54±0.2	542±0.2	522±1.1	27.38±1.1	1.37±2.0
IF1	28.36±0.3	600±0.6	666.6±1.2	9.99±1.2	1.11±1.3
IF2	22.92±0.6	500±0.5	600±1.5	6.66±2.0	1.12±0.6
IF3	28.88±0.5	461.5±30.9	491.8±2.0	6.15±2.5	1.06±3.2

Note: All values are expressed in mean±SD (n=3).
IF, immediate release formulation; VAL, valsartan.

Table 6. Postcompression parameters of valsartan immediate release formulations (IF1–IF3).

Formulation code	Weight variation[a] (mg)	Hardness[b] (Kg)	Thickness[c] (mm)	Friability[d] (%)	Drug content[e] (%)	Disintegration[b] (min)
IF1	215.3±2.5	4.75±0.3	2.03±0.5	0.228±0.3	92.66±3.5	5.3±0.2
IF2	212.3±2.5	4.56±0.3	2.12±0.1	0.456±0.9	97.15±1.4	6.2±0.4
IF3	218.3±1.5	4.75±0.3	2.09±0.4	0.227±2.1	100.3±0.8	4.5±2.1

Note: All values are expressed in mean±SD.
[a]n=20.
[b]n=3.
[c]n=30.
[d]n=10.
[e]n=6.
IF, immediate release formulation.

to 100.3%. The disintegration time of the IR formulations (IF1–IF3) was between 4.5 and 6.2 min. The values are depicted in Table 6.

In Vitro Drug Release of the VAL IR Tablets

In vitro drug release studies of the IF1–IF3 tablets indicated that drug release was based on the concentration of the superdisintegrant in the formulation. Formulations prepared with 4%, 5% and 6% SSG showed 88.63%–99.69% drug release in 60 min, as shown in Figure 6a. IF2, containing 4% SSG, demonstrated better drug release at 84.46% within 30 min; IF1, containing 3% SSG, demonstrated 72.17% drug release within 30 min; and IF3, containing 5% SSG, demonstrated 96.83% drug release.

Comparison of Dissolution Profile of the Optimised IF2 Formulated Tablet with VAL and VAL Marketed Tablet

The drug release profiles of the optimised IF2 formulation containing 1:4 ratio of drug and poloxamer 188 with 4% w/w SSG was compared with a marketed tablet (Figure 6b).

Stability Studies

Stability data of the long-term and accelerated studies are depicted in Table 7. The results of all the evaluated parameters were within the range and no other significant changes were observed throughout the study period.

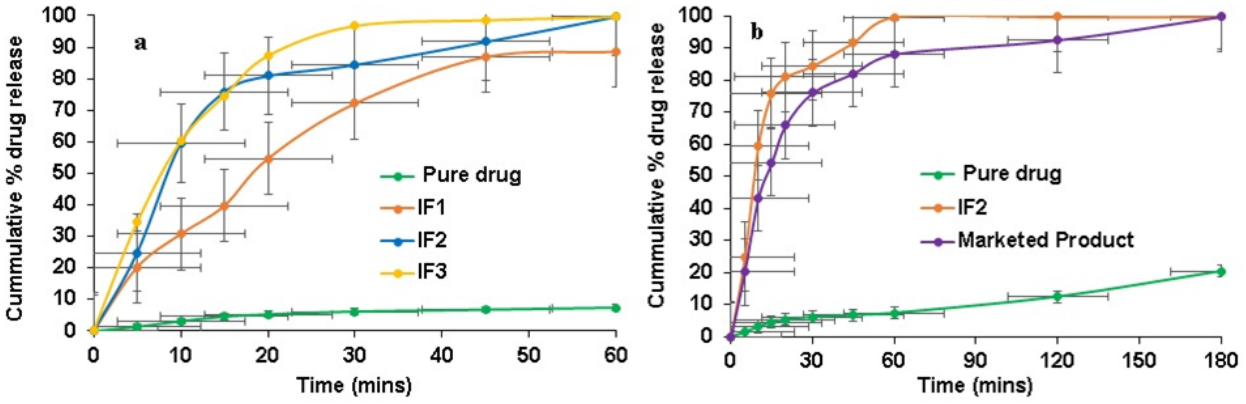

Figure 6. In vitro drug release profile of (a) Valsartan Pure drug with immediate release tablets (IF1–IF3) and (b) Valsartan IF2 optimised formulation with marketed product.

Table 7. Stability studies of valsartan immediate release formulation (IF2).

Storage condition	Duration (months)	Drug content[a] (%)	Disintegration (min)[b]	Drug release at 1 hr
Initial	0	97.15±1.4	6.2±0.4	99.69±0.01
Accelerated (40±2°C at 75±5% RH)	6	96.99±1.1	6.1±0.2	99.64±0.02
Long term (25±2°C at 60±5% RH)	12	97.11±0.9	6.1±0.5	99.59±0.03

Note: All values are expressed in mean±SD, (Where: a - n=6, b - n=3).
IF, immediate release formulation, RH - Relative Humidity

DISCUSSION

The standard calibration curve of the drug was initially established, and the graph demonstrates a linear straight line showing a linear equation: y=0.079x+0.07. The correlation coefficient value was 0.999, which indicates the standard curve follows the Beer-Lambert's law. The application of superdisintegrants in the IR tablet formulation is commercially feasible and highly effective. Superdisintegrants will help accelerate the disintegration of tablets due to their water absorption ability once the dosage form is exposed to an aqueous or gastric environment. The high water absorption property favours the breakdown of tablets, leading to faster disintegration. The disintegration has been reported to have an effect on drug dissolution.

The FTIR spectra of the VAL IR formulation showed the same characteristics, with carboxyl carbonyl and amide carbonyl stretching at 1700 and 1598 cm^{-1}. This shows that there was no major shift in the peak values of IR formulation mixtures when compared with the pure drug. The characteristic peaks corresponding to the bands of the VAL should be preserved in the spectra of the PM8 and IF2 to indicate that no chemical changes took place during the formulation. The optimised IF2 formulation showed endotherm at 116.3°C, indicating that formulation containing VAL, poloxamer 188, SSG derived peak shows reduces intensity suggests decreased crystallinity and the drug might have got converted into amorphous form when compared with VAL. The values were within the standard melting point range, indicating the absence of drug–polymer interactions. DSC enables the quantitative detection of all processes in which energy is required or produced. DSC studies can be used to investigate and predict any physicochemical interactions between the components of a formulation and therefore used in the selection of chemically suitable and compatible excipients. The XRD of the optimised IF2 formulation containing poloxamer 188 and SSG showed at 38.51° that few peaks of VAL, SSG, poloxamer 188 were absent and reduced peak intensity was observed. Therefore, the results obtained indicate that the drug in the optimised IF2 formulation was converted to an amorphous form. The SEM analysis of VAL and the optimised IF2 formulation describes a change in the crystalline form of the drug in the optimised IF2 formulation, improving the solubility of VAL in the IR formulation. The *in vitro* release studies of the optimised PM8 SD formulation containing poloxamer at a 1:4 ratio showed 94.24% drug release within 30 min. The poloxamer 188 present in the formulation reduced the contact angle between the dissolution medium and the drug, increasing the drug's wettability, which in turn led to the enhanced solubility of the drug. Hence, the formulation containing 5% SSG was considered optimum as per the goal. For the optimised IF2 formulation with 5% SSG, full drug release, that is 99.69% of the drug, was achieved at 60 min, with further increase in the concentration of SSG showing the same drug release, which may be due to the increased viscosity of SSG. Hence, 5% w/w SSG was considered the optimum concentration, which was proven by comparing the optimised IF2 formulation with a marketed product.

CONCLUSION

The present investigation describes the successful formulation and evaluation of the VAL IR tablet, an antihypertensive drug. VAL has poor water solubility and shows low and variable oral BA. For this purpose, solubility enhancement techniques were employed to increase the drug's solubility and BA. After conducting preformulation studies, the optimum formulation was selected from all formulations. First, the solubility of VAL was enhanced using various carriers (β-cyclodextrin, PVP K30 and poloxamer 188) at various ratios (1:3, 1:4 and 1:5). Among all the formulations, poloxamer 188 showed better release. Hence, poloxamer 188 was selected as the polymer to use to prepare IR tablets, with SSG used as the superdisintegrant at various concentrations (3%, 4% and 5%, at three formulations, i.e., IF1, IF2 and IF3) by a direct compression technique using an 8-mm punch. Among the three formulations, IF2, which contains 4% SSG, demonstrated 84.46% drug release in 30 min and 99.69% drug release in 1 hr. FTIR compatibility studies revealed that there was no interaction between the drug and the excipients. Pre- and postcompression studies revealed that all the results were within the official standard limits. *In vitro* dissolution studies revealed that the VAL optimised IF2 formulation showed a 135.06-fold increase in solubility when compared with pure drug. *In vitro* release studies comparing the formulated drug with a marketed product showed that the objective of the present work was fulfilled. VAL IR tablets can be a better alternative to conventional dosage forms.

AUTHOR CONTRIBUTIONS

Concept: R.S., P.T. Design: R.S., P.T. Data collection: R.S., P.T., N.K.S. Interpretation: R.S., P.T. Literature search: P.T., N.K.S. Writing: R.S., P.T.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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