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Original Article

Preparation and evaluation of valsartan orodispersible tablets using PVP-K30 and HPMC E3 solid dispersions by the solvent evaporation method

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Abstract

Background and purpose: Valsartan (Val), administered for hypertension, exhibits poor water solubility, resulting in low oral bioavailability. This study aimed to enhance the dissolution of Val by preparing orodispersible tablets (ODT) using solid dispersion (SD) technology with PVP and HPMC as hydrophilic carriers.
Experimental approach: After preparation of the SDs and physical mixtures of Val: PVP and Val: HPMC at various ratios, the physicochemical characteristics of these mixtures were analyzed. Then, the ODTs were prepared using the best SD sample and evaluated through USP tests.
Findings/Results: The saturation solubility of Val: PVP 1:1 and 1:2 at pH 6.8 was notably higher than that of pure Val. The SDs exhibited a superior dissolution rate compared to pure Val and its physical mixtures. Increasing the drug/carrier ratio resulted in a decrease in the percentage of drug in SD, with Val: PVP 1:1 SD showing significantly higher drug loading percentage compared to other formulations. All formulations exhibited entrapment efficiencies above 80%. Also, the flow of the SDs was good based on the Hausner ratio.
Conclusion and implications: The SDs exhibited more favorable attributes compared to pure Val and its physical mixtures. The research suggests that PVP and HPMC are effective carriers for improving the solubility and dissolution rate of Val. Additionally, mannitol was identified as a beneficial excipient for achieving the desired properties of ODTs. The findings can be applied to other drugs with similar solubility issues, paving the way to improve therapeutic outcomes for patients.

Keywords: HPMC; PVP; Solid dispersion; Valsartan.

INTRODUCTION

Valsartan (Val) is a generic name for (S)-N-valeryl-N-{[2′ -(1H-tertrazol-5-yl)biphenyl-4-yl]-metyl}-valine with a molecular weight of 435.519 g/mol (1). This compound serves as an orally active selective blocker of angiotensin II type 1 receptors, commonly prescribed for the treatment of mild to moderate hypertension, congestive heart failure, and post-myocardial infarction. In recent years, Val has been approved by the Food and Drug Administration (FDA) for the treatment of hypertension in children aged six years and older (2). It has been confirmed to be effective and well-tolerated in the treatment of the pediatric population. Additionally, it exerts inhibitory action on the renin-angiotensin-aldosterone system, making it a preferred choice for hypertensive pediatric patients with renal impairment (3).

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Val is categorized as class II of the biopharmaceutical classification system, characterized by high permeability but low water solubility. Due to the low solubility and dissolution rate of poorly water-soluble drugs such as valsartan, low bioavailability and limited clinical response are expected (1,4,5). Despite its rapid absorption, the oral bioavailability of valsartan is only about 23%, primarily due to its low solubility (6).

Numerous attempts have been performed to overcome the problems of low solubility and bioavailability of the drugs such as self-microemulsifying system, nanosuspension, formation of mucoadhesive pellets, and inclusion complexes with β-cyclodextrin, micronization, amorphous drug, surface adsorption, and solid dispersions (SDs) with hydrophilic carriers, micellar drug solubilization, dendrimers for drug solubilization, prodrug approach, and salt synthesis (5,7,8). Among these methods, SDs have attracted significant attention due to their great success in improving the bioavailability of poorly soluble drugs, and progress has been made in the development of reproducible and scalable manufacturing techniques (6).

SDs are dispersions of active pharmaceutical ingredients within inert carriers or matrices in a solid state. The particle size of the drug is reduced to nearly a molecular level during the solid dispersion process. The insoluble drug is exposed to the dissolution medium as very fine particles for rapid dissolution, while the soluble carrier dissolves. Polyvinylpyrrolidone (PVP) and hydroxypropyl methylcellulose (HPMC) are among the most commonly used hydrophilic polymeric carriers in SDs (9). This technique has been utilized to enhance water solubility and oral bioavailability of various drugs such as efavirenz (10), quercetin (11), nisoldipine (12), and so on.

Various studies revealed that SD of Val improved solubility, dissolution, and bioavailability (13-15). This has been shown in previous studies; SD of Val-mannitol has been successful in improving oral bioavailability and solubility (14). In addition, the solubility and dissolution rate of Val can be improved by the use of Val SDs with cyclodextrins (β-CD, HP β-CD) and PVP (PVP K-30) (16). Orally disintegrating tablets (ODTs) are designed for rapid onset of action and are more appropriate than conventional forms in acute conditions, such as patients who have water intake limitations. In addition, ODTs are well-suited for patients who cannot ingest conventional tablets, such as pediatric or geriatric patients, or those suffering from esophageal stricture (17). According to the previous studies, ODTs enhance patient compliance, low dosing, rapid onset of action, increased bioavailability, low side effects, and good stability (18). This study was undertaken to develop and characterize an SD system of Val. The objective was to enhance the drug's solubility through the solvent evaporation method using PVP K30 or HPMC E3 as carriers in various ratios. This study introduces a novel oral drug delivery formulation that combines SD systems with ODT systems. The formulation of the drug-loaded SD was optimized by investigating the effects of the PVP or HPMC ratio on the aqueous solubility of Val and the dissolution profiles of SDs. The optimized SD was used to develop and characterize ODTs containing Val for the management of pediatric or geriatric hypertension.

MATERIALS AND METHODS

Materials

Valsartan (Amin Pharmaceutical Company, Iran), PVP-K30 and HPMC E3 (Sigma-Aldrich, Germany), Kollidon® (BASF, Germany), and isomalt (PLANTINIT, Germany) were purchased. All other solvents and chemicals were of analytical grade and were obtained from Merck.

Preparation of physical mixtures and SDs by the solvent method

The SDs of Val:PVP and Val:HPMC were prepared at drug:carrier ratios of 1:1, 1:2, and 1:4 by the solvent evaporation method. In this method, Val and carriers were dissolved in the minimum amount of ethanol 96% create a clear, viscous, yellowish solution. After complete dissolution, the solvent was removed at 40 °C in an oven for 48 h. The resulting SDs were then pulverized using a mortar and pestle, passed through a 60-mesh sieve (250 μm), and stored

in a desiccator for further studies. The physical mixtures (PMs) of Val:PVP and Val:HPMC were also simply prepared by mixing the sieved fractions (less than 250 µm) of drug and carrier at the same ratios as the SDs using a mortar and pestle (19).

Characterization of the PM *and SD of Val*

Saturation solubility

For the measurement of saturation solubility, an excess amount of pure Val, PMs, and SD samples was added to 20 mL of double-distilled water and stirred at 100 rpm in an air bath at 25 °C for 48 h in triplicate. Then, the suspensions were centrifuged at a speed of 10,000 rpm for 5 min and filtered through a 0.45-µm filter. The filtered solutions were diluted, and the concentration of Val was determined at 250.5 nm on a UV spectrophotometer. The mean value and standard deviations were reported (20,21).

Drug content determination

For the determination of the percentage of drug in SD and drug content, SD samples were triturated in a mortar, and an equivalent of 40 mg of Val was weighed and dissolved in 10 mL of ethanol. Then, the solution was vortexed for 5 min and diluted and analyzed for Val at 250.5 nm using a UV spectrophotometer based on the calibration curve. The measurements were performed in triplicate, and the drug content (%) and percentage of drug in SD were calculated using the equations below (22):

$$\text{Drug content (\%)} = \frac{(\text{Entrapped drug})}{(\text{Total drug})} \times 100 \quad (1)$$

$$\text{Drug in SD (\%)} = \frac{\text{Entrapped drug}}{\text{Amount of polymer + drug}} \times 100 \quad (2)$$

In vitro drug release

An *in vitro* dissolution rate study was determined using United States Pharmacopeia (USP) dissolution testing apparatus 2 (paddle method) in triplicate at a temperature of 37 ± 0.5 °C and 50 rpm. The dissolution medium was 900 mL of aqueous phosphate buffer solution (pH 6.8). A certain weight of samples equivalent to 40 mg Val was added directly to the vessels. Five mL of the solution was withdrawn at different time intervals (5, 10, 15, 20, 30, 40, 50, and 60 min), and the samples were replaced with fresh dissolution medium. Then, the samples were filtered through a 0.45-µm membrane filter, diluted to a suitable concentration, and analyzed by a UV spectrophotometer (Shimadzu UV-1700, Japan) at λ_{max} of 250.5 nm. For cumulative drug release, first, the concentration of the drug in the medium was calculated according to the calibration curve. Then, the concentration was multiplied by the volume of dissolution medium to obtain the amount of drug released. After that, the result was divided by the amount of the drug used at the initial time point to achieve the drug release percentage. It is noteworthy that the amounts of the drug discarded at each time point were added to the amount of drug released for our calculation (23).

Bulk density, tapped density, and Carr's index

A certain mass of pure Val and each formula was measured and poured into a graduated cylinder. First, the initial volume of the sample was recorded as V_b, and the bulk density was determined according to equation 3. After that, the cylinder containing the sample was tapped until the change of powder volume remained constant. The new volume was recorded as V_t, and the tapped density was measured using equation 4. At the end, the flowability of the powders was determined by the Hausner ratio and Carr's index, which were calculated according to equations 5 and 6 (24).

$$\text{Bulk density} = \frac{\text{Mass}}{\text{Vb}} \quad (3)$$

$$\text{Tapped density} = \frac{\text{Mass}}{\text{Vt}} \quad (4)$$

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad (5)$$

$$\text{Carr's index} = \frac{(\text{Tapped density} - \text{bulk density})}{\text{Tapped density}} \times 100 \quad (6)$$

Powder X-ray diffraction

Powder X-ray diffraction (PXRD) patterns were recorded using a D8 Advance diffractometer (Bruker, Germany) to analyze the crystal state of the formulations. Samples of pure Val, PVP, and Val: PVP SD were exposed to Cu-Kα radiation source at 40 kV and 12 mA. The diffraction patterns were obtained in a 2θ scanning range of 1-40° (21).

Thermal analysis

The thermal analysis was performed with TGA and DTA techniques using the STA BÄHR 503 |apparatus. Samples of pure Val, PVP-K30, and Val:PVP SD were weighed at 1-2 mg in aluminum pans. The heating was set from 20 to 200 °C at a heating rate of 10 °C/min under a nitrogen atmosphere with a flow rate of 80 mL/min (25).

Preparation of tablets

In this study, crospovidone (Kollidon®), isomalt, and mannitol were examined as disintegrating agents to formulate the tablets to find the most suitable one for the formulation. A certain weight of 1:1 and 1:2 Val: PVP SDs equivalent to 40 mg Val, and other ingredients as shown in Table 1, were added to a mortar and mixed. Then, SLS was added and mixed. The mixed blend of drug-excipient was compressed using a single punch tablet machine (Cadmach, Ahmedabad, India) to produce tablets with a total weight of 150-250 mg and suitable hardness (26). Different formulations were tabulated in Table 1.

Evaluation of ODTs

Hardness

Hardness was determined by taking six tablets from each formulation, using a Monsanto Hardness Tester (27).

Friability

According to the USP 42 method, the friability of samples for 26 tablets (6.5 g) was measured using a Roche Friabilator. Twenty-six pre-weighed tablets were rotated at 25 rpm for 4 min. The tablets were then reweighed after removal of fines using a 60-mesh screen, and the percentage of weight loss was calculated.

$$\text{Friability (\%)} = \frac{\text{Loss in weight}}{\text{Initial weight}} \times 100 \qquad (7)$$

Disintegration time

Disintegration time was measured in 900 mL (pH 5.8) according to the USP 24 method at 37 ± 0.5 °C. The disintegration time of 6 individual tablets was recorded, and the average was reported (27).

Uniformity of the dosage unit

First, 10 tablets were selected randomly. Second, each tablet was weighed accurately on an analytical balance (M1, M2, ...), and the average weight of the tablets was calculated (W). A is the content of the drug substance (in percentage) obtained using UV spectroscopy. Then, using the results of a 3-time assay of each formulation, the amount of active ingredient in each tablet was calculated as a percentage (X1, X2, …) using the following equation:

$$Xi = Wi \times A/W \qquad (8)$$

Then, the mean amount of active ingredients in tablets (X) and standard deviations (SD) for X1, X2, ..., were calculated. Finally, the acceptance value was obtained using the USP formulas (detailed procedure is ascribed in the USP 42 (27).

Table 1. Composition and properties of various Val:PVP SD ODT tablets.

Ingredients (mg/tablet)	Formulation code										
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**
Val	40	40	40	40	40	40	40	40	40	40	40
PVP	80	80	80	80	80	80	80	40	40	40	40
Kollidon	7.5	15	18	20	22.5	36	36	15	15	15	15
Aspartam	1.5	1.5	0	0	0	0	0	0	0	0	0
SLS	0.075	0.750	0.900	1.000	0.075	0.075	0.075	0.075	0.075	0.500	0.500
Isomalt	20.92	12.75	21.30	3700	5.925	0	0	53.42	53.42	0	0
Sodium saccharin	0	0	1.8	2	1.5	1.5	1.925	1.5	1.5	1.5	1.5
Starch1500	0	0	18	20	0	27	34	0	50	0	0
Mannitol	0	0	0	0	0	15.42	8	0	0	103	153
Total weight	150	150	180	200	150	200	200	150	200	200	250

ODT, Orally disintegrated tablet; PVP, polyvinylpyrrolidone; SD, solid dispersion; Val, valsartan; SLS, sodium lauryl sulfate.

Statistical analysis

Statistical analysis was performed by one-way analysis of variance (ANOVA) followed by Tukey post hoc test using IBM SPSS Statistics 22. For all of the tests, the differences were considered statistically significant where $P < 0.05$. The final percentage of drug release after 60 min and the dissolution efficiencies of the formulations were analyzed by a one-way ANOVA test.

RESULTS

Characterization of SD

Saturation solubility

As seen in Table 2 saturation solubility of Val was 39.80 ± 4.89 µg/mL, indicating that Val is categorized as a poorly water-soluble drug as reported in the literature (5,14). However, the solubility of the drug significantly increased in the presence of PVP-K30 or HPMC E3 in PMs and SD samples.

Drug content

Table 2 depicts the SD drug content and the percentage of drug in SD for different formulations. As seen, with increasing the drug/carrier ratio, drug loading decreased. The percentage of drug for Val:PVP 1:1 SD was considerably higher than the others. SD drug content of all the formulations was greater than 80%. Also, using PVP as a carrier to prepare SD led to a significant enhancement of SD drug content toward HPMC.

Flowability test

The results of the flowability test of prepared Val SDs and PM with PVP and HPMC at various ratios (1:1, 1:2, and 1:4) are presented in Fig. 1. Our studies described that all the SDs, either PVP-based or HPMC-based, had good flowability and showed a significant difference in comparison to the PMs and pure drug. The compressibility index of all SDs was below 25% (Fig. 1A), and the Hausner ratios did not exceed 1.27 (Fig. 1B).

In vitro drug release

In order to evaluate the dissolution rate of Val from SDs, dissolution studies were performed. Dissolution profiles of pure Val, PM, and SD of Val with PVP K30 and HPMC E3 throughout 1 h are shown in Fig. 2. The dissolution rate of Val from all the SD formulations was higher than pure Val powder ($P < 0.05$). It was observed that in PVP-based SD, the drug release was more than 90% after 10 min (Fig. 2A), but in HPMC-based SD, it was about 80% (Fig. 2B).

Table 2. Physical properties of nanoparticles. Values are expressed as mean ± SD; n = 3. *$P < 0.05$ shows significant differences compared to Val.

Drug: carrier	Water solubility (µg/mL)	Drug content (%)	Drug in SDs (%)
Val	39.80 ± 4.89	-	-
Val: PVP 1:1 PM	109.46 ± 13.33*	-	-
Val: PVP 1:1 SD	110.10 ± 7.71*	102.73 ± 4.43	41.48 ± 3.06
Val: PVP 1:2 PM	110.20 ± 8.79*	-	-
Val: PVP 1:2 SD	111.38 ± 5.63*	98.61 ± 0.66	26.87 ± 0.59
Val: PVP 1:4 PM	115.65 ± 11.04*	-	-
Val: PVP 1:4 SD	103.47 ± 3.86*	100.09 ± 2.38	17.47 ± 0.49
Val: HPMC 1:1 PM	109.24± 4.56*	-	-
Val: HPMC 1:1 SD	93.22± 5.64*	87.36 ± 2.48	49.30 ± 0.33
Val: HPMC 1:2 PM	94.93 ± 9.99*	-	-
Val: HPMC 1:2 SD	98.56 ± 8.53*	80.60 ± 1.78	33.36 ± 0.79
Val: HPMC 1:4 PM	109.78 ± 9.93*	-	-
Val: HPMC 1:4 SD	100.59 ± 18.23*	82.98 ± 6.13	20.55 ± 0.88

PVP, Polyvinylpyrrolidone; SD, solid dispersion; PM, physical mixture; Val, valsartan; HPMC, hydroxypropyl methylcellulose.

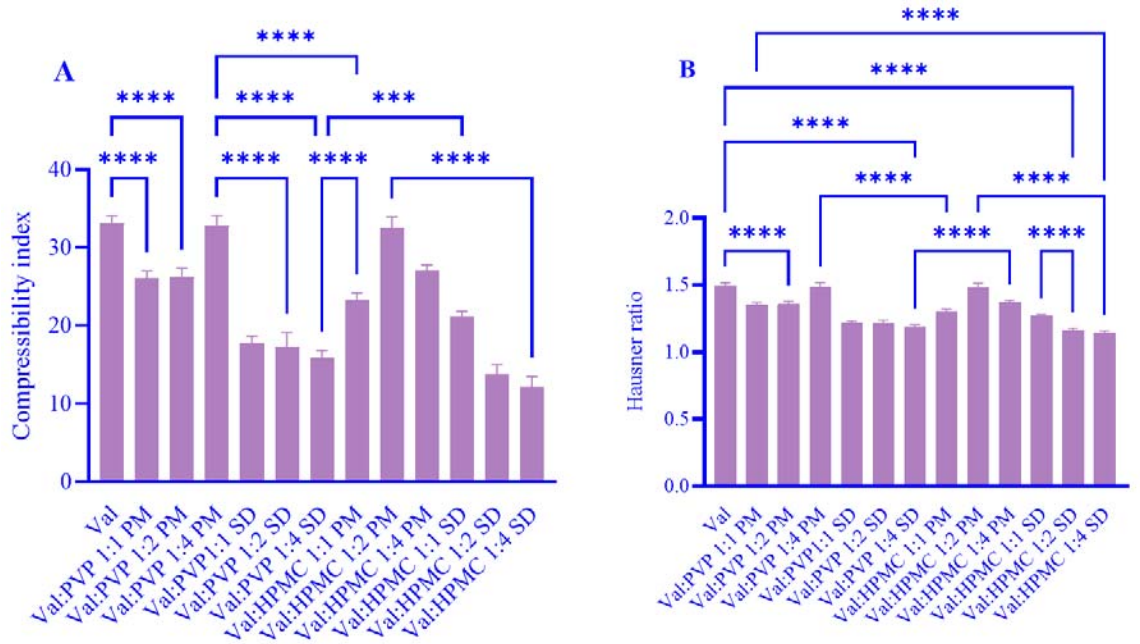

Fig. 1. Flowability results of different formulations of Val with PVP K30 and HPMC E3 in SD or PM. (A) Compressibility index, and (B) Hausner ratio. ***$P < 0.001$; **** $P < 0.0001$ indicate significant differences among the respective groups. Val, Valsartan; PVP, polyvinylpyrrolidone; HPMC, hydroxypropyl methylcellulose; SD, solid dispersion; PM, physical mixture.

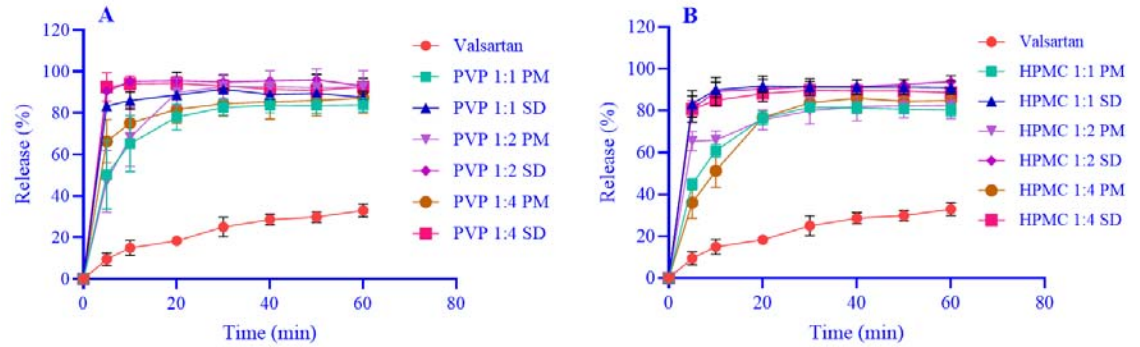

Fig. 2. Valsartan release profiles from (A) SDs or PMs of PVP K30 in different ratios (1:1, 1:2, 1:4), and (B) SDs or PMs of HPMC E3 in different ratios (1:1, 1:2, 1:4), (n = 3). PVP, Polyvinylpyrrolidone; HPMC, hydroxypropyl methylcellulose; SD, solid dispersion; PM, physical mixture

Table 3 summarizes the results of drug release percent, dissolution efficiency in 60 min (DE_{60}%), and mean dissolution time (MDT) of Val with PVP-K30 or HPMC E3 in PMs and SD samples. Comparing the PMs and SDs, Val release from the SD was much more rapid than from its corresponding PMs. The values of drug release%, DE_{60}%, and MDT confirmed that.

As seen in Fig. 2, there was a significant enhancement of drug release% in SD formulations in comparison to the pure drug ($P < 0.05$). Val:PVP 1:1 SD showed better dissolution rate than others, and there was a significant increase in the rate of dissolution of SD compared to the PM in the same ratio ($P < 0.05$).

All the formulations showed a noticeable increase in the DE_{60}% of the drug in comparison to the pure Val. Meanwhile, DE_{60}% of the SDs of Val were significantly higher than the PM in the same ratio (Table 3).

Experiments also revealed a significant difference among MDTs for free Val and SD or PMs, in which the MDT value for Val was the highest (10.12 ± 3.83), but for the others decreased. This value also decreased drastically for the SDs compared to the PMs (Table 3).

PXRD

To investigate the solid-state properties of active pharmaceutical ingredients in nanoparticles, XRD analysis is frequently used (28). The representative XRD patterns of Val. PVP and Val:PVP 1:1 SD are shown in Fig. 3. The diffractogram showed that the pure Val was in a crystalline state, whilst the SD represented an amorphous state. XRD pattern of Val showed characteristic diffraction peaks at 2θ values of 7.5°. Also, the diffractogram of Val showed intrinsic peaks at the diffraction angles, revealing a broad crystalline pattern (Fig. 3A). PVP K-30 did not show any fusion peak or phase transition means that a complete absence of any diffraction peak occurred and it is characteristic of amorphous compounds (Fig. 3B), which is in accordance with previous research (10,29). The pattern of SD did not show peaks corresponding to Val, demonstrating that Val was in amorphous form (Fig. 3C).

Table 3. Drug release percent, DE_{60}, and MDT of Val, Val:PVP, and Val:HPMC samples. *$P < 0.05$ shows significant differences compared to Val.

Drug: Carrier	Drug release ± SD (%)	DE_{60} ± SD (%)	MDT ± SD(min)
Val	32.99 ± 3.14	11.20 ± 1.15	10.12 ± 3.83
Val: PVP 1:1 PM	83.97 ± 3.45*	37.01 ± 2.45	6.59 ± 3.00
Val: PVP 1:1 SD	96.26 ± 2.35*	46.09 ± 0.29*	2.99 ± 0.55
Val: PVP 1:2 PM	92.65± 7.66*	40.73 ± 3.13*	7.19 ± 2.35
Val: PVP 1:2 SD	93.06 ± 3.57*	45.42 ± 1.07*	2.92 ± 0.18
Val: PVP 1:4 PM	87.22 ± 7.20*	39.24 ± 2.97	4.52 ± 1.03
Val: PVP 1:4 SD	95.92 ± 2.35*	44.42 ± 1.16*	2.16 ± 0.83
Val: HPMC 1:1 PM	80.23 ± 3.01*	35.71 ± 0.56	6.32 ± 0.22
Val: HPMC 1:1 SD	91.19 ± 3.24*	43.40 ± 1.80*	2.99 ± 0.14
Val: HPMC 1:2 PM	82.61 ± 6.52*	36.96 ± 2.45	5.25 ± 1.46
Val: HPMC 1:2 SD	92.61 ± 2.63*	43.37 ± 0.98*	3.20 ± 0.28
Val: HPMC 1:4 PM	84.82 ± 3.39*	37.05 ± 0.84	9.00 ± 2.07
Val: HPMC 1:4 SD	88.71 ± 2.35*	42.54 ± 0.25*	2.45 ± 1.28

Val, Valsartan; PVP, polyvinylpyrrolidone; SD, solid dispersion; PM, physical mixture; HPMC, hydroxypropyl methylcellulose; DE_{60}, dissolution efficiency in 60 min; MDT, mean dissolution time.

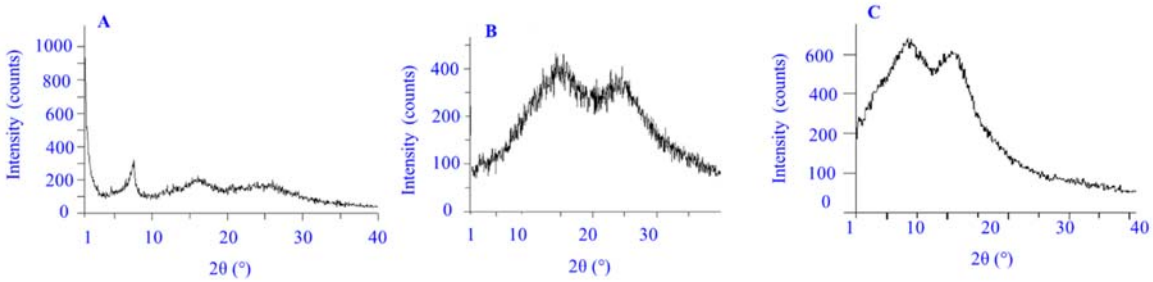

Fig. 3. The XRD pattern for the (A) pure Val, (B) PVP K-30, and (C) Val:PVP 1:1 SD. Val, Valsartan; PVP, polyvinylpyrrolidone; HPMC, hydroxypropyl methylcellulose; SD, solid dispersion.

Thermoanalysis of SD

The thermoanalytical curves of Val, PVP, and Val:PVP 1:1 SD are presented in Fig. 4. For Val, the DTA of pure Val was closely similar to that reported before (17). The TG profile showed a mass loss region starting at 80.413 °C and ending at 120.17 °C, which might be assigned to the dehydration process (Fig. 4A). The second decomposition step occurred at 142.99 °C, corresponding to the loss of C_5H_8O from the amide side chain of Val. For Val, the DTA of pure Val was closely similar to that previously reported (30). DTA thermogram of Val showed a sharp peak at 106.46 °C, which is attributed to the melting point of the drug (Fig. 4B). For PVP, TG thermogram represented that the polymer underwent weight loss at temperature ranges of 80-180 °C, which was complied with the DTA thermogram in which the TG was observed at 103.53 °C (Fig. 4A). The weight loss observed in PVP might be attributed to the loss of residual solvent and low molecular weight oligomers (31). The melting peak of VAL in the SD sample has been broadened, suggesting that the drug was incorporated well in SD in the amorphous state, which is consistent with the XRD pattern.

ODT characteristics

The composition and properties of various ODT tablets are shown in Table 4. Each formulation (F1 to F11) varies in the amounts of key ingredients, which significantly influence the tablets' properties, including hardness, disintegration time, friability, and weight variation. In this research, Kollidon was used as a super disintegrant, starch 1500 as a disintegrating agent, aspartame and sodium saccharin as sweetening agents, sodium lauryl sulfate or SLS as a lubricant, isomalt and mannitol as fillers or diluents, and disintegrating agents.

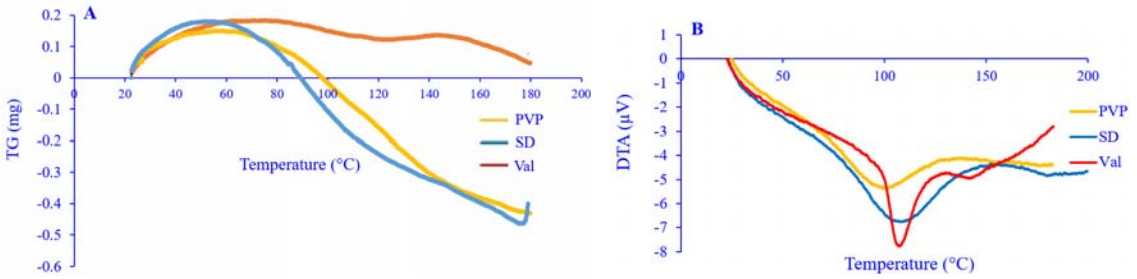

Fig. 4. (A) TG and (B) DTA of PVP, SD, and Val. TG, Thermogravimetric analysis; DTA, Differential thermal analysis; Val, Valsartan; PVP, polyvinylpyrrolidone; SD, solid dispersion.

Table 4. The results of the evaluation of different tablet formulations. *P < 0.05 shows significant differences compared F10 formulation.

Formulations	Hardness (N)	Friability (%)	Disintegration time (s)
F1	22.61 ± 1.23	2.29 ± 0.31*	187.66 ± 4.51*
F2	31.63 ± 1.73	1.74 ± 0.30*	143.33 ± 15.50*
F3	35.42 ± 0.97	0.21 ± 0.05	135.66 ± 11.24*
F4	35.79 ± 2.10	0.26 ± 0.02	128.33 ± 12.34*
F5	28.36 ± 0.91	2.07 ± 0.16*	125.66 ± 7.57*
F6	30.86 ± 0.94	1.85 ± 0.26*	105.66 ± 5.68*
F7	31.80 ± 0.32	0.93 ± 0.11	113 ± 13.45*
F8	30.24 ± 0.68	2.15 ± 0.24*	89.66 ± 7.02*
F9	30.59 ± 1.16	1.77 ± 0.22*	78.33 ± 6.11*
F10	31.91 ± 0.23	0.61 ± 0.17	30.66 ± 6.80
F11	32.33 ± 0.73	0.33 ± 0.03	18.33 ± 3.05

ODTs need to dissolve quickly once placed in the mouth, making disintegration time a key attribute of these formulations. Additionally, ODTs must possess adequate hardness and friability to endure handling without significant damage or wear. Ideally, ODTs should disintegrate in 60 s or less and have a hardness of 30-40 N. F1 was unsatisfactory because of low hardness (< 30 N) and undesirable disintegration time (~3 min). Also, tablet capping happened. Furthermore, the tablets were too narrow. So, to overcome this matter, the amounts of Kollidon and SLS were increased, and sodium saccharin was replaced by aspartame. Despite the proper hardness of tablets of F2 (~31 N), the disintegration time was unsatisfactory again (~2 min). Thus, we decided to add starch 1500 as a disintegrating agent at 10% (w/w) in the tablet (F3 formulation), but still disintegration time was a problem (~2 min). To get better properties for tablet hardness and disintegration, the total weight of tablets was increased to 200 mg (F4), but the disintegration time was kept at about 2 min. Formulations F5 to F7 did not show desirable disintegration times as well (~2 min). Both F8 and F9 showed moderate improvements but still did not achieve optimal disintegration times, remaining above the desired threshold for rapid release (~1.5 min). The percentage of mannitol was increased for F10 and F11, so the tablets disintegrated below 60 s (30 s and 18 s, respectively). Besides, the hardness of F11 was better than F10 due to the increase in mannitol amount.

Other tests were carried out on F11. The average diameter of ODTs ranged from 4.37 to 4.47 mm. Tablet friability did not exceed 1% of the weight of the tested tablet (0.33%). The *in vitro* disintegration time of the ODTs was 18 s, and the hardness was around 32.33 N. Acceptance value for the weight variation test was < 15. The results for the evaluation of different tablet formulations are shown inTable 4.

DISCUSSION

SDs are known as a product that consists of a hydrophobic drug dispersed in a hydrophilic carrier, resulting in the enhancement of the surface area and wettability. So, the water solubility of the drug and the dissolution rate are increased. Besides, agglomeration and release in a super saturation state could be decreased by interacting the poorly soluble drug molecule with hydrophilic carriers, which is probably due to the formation of soluble complexes between water-soluble polymeric carriers and the drug. Consequently, absorption and bioavailability are improved. Thus, preparing the SD is considered a promising method to overcome the poor aqueous solubility of the drugs (32). In our study, the water solubility of Val in SD samples was increased about 3-fold in comparison to the free drug (Table 2). Moreover, PVP and HPMC are the polymers that are commonly employed in amorphous SDs by preventing the recrystallization mechanism (33). PVP-based formulations in this experiment revealed better water solubility than HPMC-based, indicating that PVP is more efficient in improving Val aqueous solubility. Our study proved the successful preparation of amorphous SD of Val:PVP using the solvent evaporation method, which is confirmed by XRD and thermal analysis (Figs. 3 and 4). It should be noted that one of the useful impacts of SD is the transformation from the crystalline phase into the amorphous phase, which has a number of advantages, including increasing the dissolution rate of drugs or the possibility of enhancing the drug release (34,35). In this study, Val:PVP 1:1 SD was chosen as the optimum formulation, in which it showed the highest water solubility, SD drug content, drug release, and dissolution efficiency. PVP K30 was able to entrap and cover Val in the form of an SD. Thus, the crystallinity degree of SD decreased and turned into the amorphous state. As can be estimated, the conversion of crystalline habit to amorphous can increase the solubility of the drug by hindering molecular orientation. Also, by developing stronger drug-polymer interactions, the stability of an amorphous SD increases with the use of PVP K30 (29,36). This might elucidate the enhancement of the water solubility of Val in SD form studied in this experiment. Sethia *et al.* prepared an SD of carbamazepine with PVP K30 by supercritical fluid process. The result revealed a 12-fold increment of water solubility

of carbamazepine in SD compared to the pure drug (37). So, because of high hydrophilicity and the ability to form stable SD, PVP K30 is known as one of the best alternative carriers in preparing solid dispersions (38). The mechanism underlying these enhancements can be attributed to several factors associated with the transformation from crystalline to amorphous states. The amorphous form of Val within the SD increases the dissolution rate by reducing lattice energy barriers and increasing effective surface area for dissolution. This transformation is supported by XRD and thermal analysis, which confirm the conversion of Val into an amorphous state, thereby hindering molecular orientation and enhancing drug-polymer interactions. Such interactions not only stabilize the amorphous form but also contribute to improved solubility (29).

As indicated in Table 2, the percentage of drug content in PVP-based formulations was significantly higher than that in HPMC-based formulations, suggesting that the composition of the SD formulations has a substantial impact on drug content. Given the data presented by Fig. 3, the characteristic crystalline peaks of the drug were barely detectable in the PVP-based SDs, suggesting that the drug's crystalline structure may have been converted into an amorphous state. The presence of characteristic peaks indicates that Val exists as a crystalline material; however, the disappearance or weakening of these distinguishing peaks in the SDs signifies that a high concentration of the drug is dissolved in the solid state. This implies that the drug is either dispersed at a molecular level within the polymer matrix or exists in an amorphous state (39,40). As shown in Fig. 1, Carr's index (or compressibility index) and Hausner's ratio for the SDs indicated a significant decrease in the SD formulations compared to Val and the PM. A compressibility index greater than 25% suggests that the flow is rarely acceptable, while an index below 15% indicates satisfactory manufacturing of the formulation. The compressibility indices for all SD formulations were below 25%. Generally, a lower Hausner's ratio indicates better flowability of the powders; a Hausner ratio greater than 1.35 signifies poor flowability. In this study, the Hausner ratios of the SD formulations ranged from 1.14 to 1.27. One of the aims of this study was to increase the dissolution rate of Val by preparing its SDs. The results showed a significant enhancement in both the dissolution rate and dissolution efficiency of Val in SD form, which is consistent with the existing literature. In a study conducted by Ren *et al*., an SD of bicalutamide with PVP-K30 was prepared, demonstrating that approximately 98% of the drug was released during the initial 10 min (41).

Another example is done by Kim *et al*., which showed that the dissolution rate of mosapride citrate with PVP in SD could be increased (42). The same declaration for atorvastatin existed as the solubility and dissolution rate increased, and SDs could effectively reduce the serum lipid levels (43). The first statistical parameter for the cumulative dissolution process, which is responsible for an accurate drug release rate and reflects the time for the drug to dissolve, is MDT. The higher the MDT value, the greater drug-retarding ability. The MDT value observed in the case of SDs in our results was also much lower than that for the raw drug, and the calculated MDTs support the former findings. In this study, the results of dissolution rate and DE_{60}% for PVP-based SD were better than HPMC-based SDs (Table 3). This difference may be attributed to the swelling capacity of HPMC; due to its higher swelling properties during the dissolution test, the drug was released more slowly from the SDs (4). In other words, perhaps the presence of HPMC may not be sufficient to disperse the Val molecularly among carrier molecules at the analyzed proportions. Consequently, a glass suspension-type SD system may form, causing the drug molecules to aggregate due to their lipophilicity and create amorphous clusters. This results in a viscous gel layer around the drug clusters when this system encounters the dissolution medium. Therefore, it is expected that the viscous gel slows down the diffusion of the dissolution medium through it, leading to a diminished dissolution rate (44,45). In SD samples with PVP, a glassy solution-type of SD system was formed, and then Val could be dispersed molecularly among the polymer chains. Consequently, Val could dissolve rapidly after contact with the dissolution

medium (21). Therefore, it is verified that the type of carrier has a direct influence on dissolution. It is worth mentioning that the dissolution rates of SDs were noticeably greater than pure drug, which might be affected by the hydrophilic carriers such as PVP-K30 or HPMC E3 (Fig. 2). Indeed, results from dissolution data in this study support the view that the reduction of interfacial tension to medium dissolution caused by the hydrophilic effect of the carrier is responsible for a contribution to drug wettability, through the formation of a microenvironment, which facilitates solubilization around the particles and this is responsible for the improved drug dissolution rate (10). Another probability is that, based on the Noyes-Whitney equation, a higher surface area of solid dispersions displayed enhancement of dissolution (11). On the other hand, generally, the amorphous solids are more soluble and dissolve more quickly than the crystalline forms. Since the transformation of a crystalline drug to the amorphous state happened during the preparation of the solid dispersion, no lattice structures have to be broken down for dissolution to occur, and the dissolution rate increases. To conclude, many parameters might be involved to explicate the overall results, including decreased crystallinity or change into an amorphous phase, increased wettability, enhancement of surface area, etc. (11).

Given the former results, Val-PVP 1:1 SD was selected as the best formulation to continue the studies for producing ODT tablets.

ODTs should rapidly disintegrate in the buccal cavity to cause enhanced dissolution of the drug. Therefore, to formulate ODTs, disintegration time is the most important factor that should be considered. It can be concluded that the tablets containing mannitol display a rapid disintegration time, which is present in F10 and F11. Lura *et al.* demonstrated the suitability of both mannitol and isomalt in ODTs (46). However, our results indicated that mannitol-based tablets exhibit superior disintegration times compared to those formulated with isomalt or starch. From the results, it could be seen that formulations with mannitol fulfil the requirements for ODTs according to the USP (F10 and F11). It can therefore be suggested that mannitol, during the process of obtaining ODT, could act as a good disintegrant with the aid of Kollidon. Employing different combinations of disintegrants demonstrably reduced the disintegration time. It is in line with a previous study, which reported that the disintegration time of levocetirizine orodispersible tablets decreases along with the use of different disintegrants (47). The mechanism of Kollidon as a disintegrant is mediated *via* the swelling and capillary action of the super disintegrant, which causes the quick disintegration of tablets (48). Mannitol is a common excipient used for ODTs because of its sweet taste, mouth-feel, and negative heat of dissolution (49). Also in our study, it was shown that mannitol could act as a diluent and a disintegrant with the use of Kollidon. The probable explanation is that, as mannitol is a water-soluble polyol and consists of highly porous particles with a relatively large surface area, it could improve the attraction of water molecules into the dosage form, causing better water wettability and disintegration (3). Furthermore, our results showed that the hardness of tablets increases with the amount of mannitol. In a study that characterized the effect of mannitol on ODTs, it was proven that the hardness of ODT formulations increased with the increment of mannitol concentration, while disintegration time decreased (50). This is in agreement with our results, in which F11 showed better hardness and lower disintegration time in comparison with F10.

The common lubricants that should be used in tablet manufacturing include magnesium stearate, stearic acid, sodium stearyl fumarate, and sodium lauryl sulfate. These lubricants are essential to prevent sticking to the punch surfaces. Since magnesium stearate, stearic acid, and sodium stearyl fumarate reduce the solubility and disintegration rate, sodium lauryl sulfate was used in this study.

Since F11 showed the least disintegration time (18 s) compared to F1-F10, the other tests were done just on F11. In this research, weight variation, hardness, and friability were measured for F11. This formulation passed all the tests described in the pharmacopeia, and the results were found to be within prescribed limits and satisfied the criteria of ODTs.

Hardness for F11 was shown around 32.33 N, indicating that the tablets can withstand physical and mechanical stress conditions due to their good mechanical strength. Tablet friability was less than 1% of the weight of the tested tablet (0.33%), representing a good mechanical resistance of tablets. The weight variation test showed that the acceptance value was below 15 for ODTs and fulfilled the requirement of standard content uniformity, which confirmed the proper mixing of the excipients and the active pharmaceutical ingredient. The *in vitro* disintegration time of formulation F11 was determined to be 18 s. This rapid disintegration suggests that the formulation is well-suited for oral administration, facilitating disintegration and dissolution in the mouth.

CONCLUSION

In conclusion, this study demonstrated that both PVP-K30 and HPMC E3 are effective carriers for enhancing the dissolution profile of Val, a class II drug in the biopharmaceutical classification system. The SDs significantly increased Val's water solubility by transforming it into an amorphous phase at the molecular level. PVP-K30 emerged as the more suitable carrier, showing a greater impact on dissolution rate and efficiency at lower concentrations.

Furthermore, ODTs have gained popularity for their ease of administration, particularly among geriatric and pediatric populations. In this study, the Val:PVP 1:1 formulation exhibited superior characteristics compared to the Val:PVP 1:2 formulation. Mannitol proved to be an effective excipient, contributing to the desired properties of ODTs.

The F11 formulation was identified as optimal due to its hardness of approximately 32.33 N, rapid disintegration time of just 18 s, and friability below 1%, ensuring durability during handling. Additionally, its weight variation acceptance value was less than 15, indicating consistent weight across tablets. These attributes collectively suggest that F11 is well-suited for its intended purpose as an ODT, effectively combining therapeutic delivery with user-friendly characteristics. However, it is recommended that future research focus on several key areas to enhance the formulation and efficacy of Val SDs. First, exploring alternative hydrophilic polymers may provide improved performance or stability compared to PVP K30. Additionally, investigating combination therapies could uncover synergistic effects when Val is paired with other therapeutic agents in SDs. Finally, further *in vivo* studies are needed to confirm the efficacy and safety of this optimized formulation in humans.

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Conflict of interest statement

The authors declared no conflict of interest for this study.

Authors' contributions

A. Homayouni contributed to conceptualization, design, and coordination of the study; A. Homayouni and L. Dayani compiled and validated the data; M. Zaghian, L. Dayani, and Z. Keshavarz investigated and interpreted the data; M. Zaghian, Z. Keshavarz, Z. Fakhari, and F.S. Osooli contributed to the methodology; M. Zaghian contributed to project administration, collection and assembly of data; A. Homayouni supervised the project; M. Zaghian and L. Dayani wrote the original draft, reviewed, and revised the article. All authors have read and approved the finalized article.

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