



A novel *in vitro* approach to investigate the effect of food intake on release profile of valsartan in solid dispersion-floating gel *in-situ* delivery system

Achmad Himawan^{a,b}, Nana Juniarti Natsir Djide^a, Sandra Aulia Mardikasari^a, Rifka Nurul Utami^a, Andi Arjuna^a, Ryan.F. Donnelly^b, Andi Dian Permana^{a,*}

^a Faculty of Pharmacy, Universitas Hasanuddin, Makassar, Indonesia

^b School of Pharmacy, Queen's University Belfast, Northern Ireland, United Kingdom

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ABSTRACT

Valsartan (VAL) is a BCS class II drug with low solubility and high permeability and, thus, its formulations often encounter low bioavailability problems. Its low bioavailability can be improved through enhanced formulation, such as incorporating it into a solid dispersion system (SD). The absorption can be further enhanced through gastroretentive systems. Herein, we developed a novel combination delivery approach consisting of floating *in-situ* gel and SD. VAL was incorporated with polymer carrier PVP and PEG 6000 and its solubility was then evaluated. The study found that VAL-SD containing PVP K-30 as the carrier with drug:PVP K-30 ratio of 1:3 shown highest solubility in different media. Moreover, DSC and XRD evaluations exhibited the change of VAL from crystal to amorphous following SD formulation. The SD was then formulated into floating *in-situ* gel preparations using sodium alginate as gel forming compound and HPMC as the controlled release matrix. The prepared VAL-SD floating *in-situ* gels were evaluated for their physical properties and drug release profile. The results showed that all physical evaluation of the floating *in-situ* gel formula possessed desirable physical properties and the use of HPMC in floating *in-situ* gel was able to sustain the *in vitro* release of VAL for 24 h in biorelevant media. Importantly, the effect of food intake on VAL release was also investigated, for the first time, showing that the VAL release could be controlled in FaSSGF (Fasted-State Simulated Gastric Fluid) in 2 h and FeSSGF (Fed-State Simulated Gastric Fluid) onwards. Thus, it can be hypothesized that the food intake did not affect the VAL release after 2 h in an empty gastric environment. Leading on from these results, *in vivo* studies in an animal model should be carried out to further assess the potency of this system.

1. Introduction

Valsartan (VAL) is an angiotensin II receptor-specific blocker with a high affinity to the angiotensin type I receptor and widely used to treat hypertension, post-myocardial infarction, and congestive heart failure (Beg et al., 2012; Huang et al., 2017; Park et al., 2010). VAL is given orally, usually in the form of tablets or capsules. This drug is acidic, has low aqueous solubility (<0.1 mg/mL) and high membrane permeability, indicated by its high log P value of 5.8. VAL belongs to Class II of the biopharmaceutical drug classification system (BCS) (Beg et al., 2012; Kumar et al., 2019; Trunov et al., 2021). Its oral bioavailability is relatively low (23–39%) due to its poor water solubility and relatively short half-life (<6 h). In the systemic circulation, VAL experiences extensive first-pass hepatic metabolism in the liver. These properties negatively affect its pharmacokinetics by decreasing the AUC by 40% and peak

plasma concentration by 50% (Beg et al., 2012; Hussein et al., 2018)

Several systems have been studied to improve the water solubility of drug substances, including solid dispersion (SD) (Yan et al., 2012). A polymeric SD is considered an effective means to overcome the active pharmaceutical ingredient (API) with low water solubility (Krstić et al., 2020). An SD is a drug dispersion in an amorphous polymer matrix, especially hydrophilic polymer, where the drug is preferably in the molecularly dispersed state (dos Santos et al., 2018). Synthetic hydrophilic polymers are often used in SD, due to their various advantages (Tekade and Yadav, 2020). Among all others, polyvinylpyrrolidone (PVP) K-30 is one of the superior choices. Its high-water solubility may aid the SD wettability and dissolution rate. PVP K-30 also can help stabilize the amorphized drug crystal (Jahangiri et al., 2015). Alongside PVP K-30, poly(ethylene glycol) (PEG) 6000 is also commonly used to prepare an SD system. It has a low melting point, is relatively nontoxic,

* Corresponding author at: Faculty of Pharmacy, Hasanuddin University, Makassar, Indonesia.

E-mail address: andi.dian.permana@farmasi.unhas.ac.id (A.D. Permana).

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has extensive drug compatibility and high hydrophilicity (Afifi, 2015; Zhai et al., 2017). Several studies have shown the effectiveness of PVP K-30 and PEG 6000 in improving the solubility of hydrophobic drugs, enhancing the bioavailabilities and, thus potentially improving the pharmacological activities of the drugs (Alves et al., 2014; Febriyenti et al., 2019; Permana et al., 2021b).

As mentioned previously, one of the reasons for low bioavailability of VAL is its short half-life. Therefore, to overcome this issue, one of the approaches that can be used is by controlling the release of VAL. Various controlled release system with different therapeutic purposes have been developed according to the physiochemical, pharmacological, and pharmacokinetics properties of the drugs (Sharma et al., 2014). Gastroretentive drug delivery system (GRDDS) has been proposed as an alternative to a conventional oral route delivery to overcome some of its many weaknesses. By formulating drugs substance into GRDDS, it is guaranteed that the whole dosage form remains within the stomach region for a longer duration (Kathpalia et al., 2019; Naveen et al., 2017; Rahamathulla et al., 2019). Importantly, several studies have reported the successful combination of GRDDS and solid dispersion systems, showing that this combination could enhance the solubility of poorly soluble drugs and further control the release behavior of the drugs (Alqurshi et al., 2017; Regulska et al., 2019).

Several mechanisms can be implemented to increase the gastric residence time of the drug of interest. Mechanisms such as floating systems (Kathpalia et al., 2019; Naveen et al., 2017; Shakya et al., 2013), mucoadhesive systems (Nappinnai and Sivanewari, 2013; Vashisth et al., 2017), resinate complexes (Daihom et al., 2020; Umamaheshwari et al., 2008), porous systems (Hwang et al., 2019; Kim et al., 2014; Oh et al., 2013), and density modified systems (Desai and Purohit, 2017; Sharma et al., 2018). The floating drug delivery system, especially the *in-situ* forming gel carrier, is particularly interesting. The system is meant for gastric retention and float on the gastric fluids' surface after contact, usually due to their low density, then produce a prolonged effect by slowing the release of the drug. These formulations remain in solution or suspension form before administration, but they undergo sol-to-gel transition once they reach the stomach. A study reported a successful formulation of a floating raft system of mitglinide calcium, an antidiabetic drug with a very short half-life and prolonged it release for 24 h period (Mahmoud et al., 2019). Similarly, pregabalin (half-life 3–6 h), an analog of gamma-aminobutyric acid, also had been successfully prepared into a floating gel *in situ* system. The formulation of pregabalin tailored its release to be sustained over 12 h period (Madan et al., 2015).

Previously, VAL has been developed into GRDDS (Cho et al., 2016; Prasanthi and Vidyavathi, 2017). However, the dosage forms were given in the fasted state only. The effect of food intake on the dissolution profiles of VAL have not been studied. Additionally, the effect of various physiological conditions, including pH, buffer capacity and ionic strength of the gastrointestinal fluid in fasted and fed conditions on the *in vitro* dissolution behavior of VAL has been reported (Hamed, 2018). However, the study was conducted for immediate release tablets, showing the low residence time of VAL in the gastric environment. As previously explained, due to the characteristics of VAL, it was important to enhance the solubility and to sustain the release of VAL. Therefore, in the present work, we report the combination approach of the SD and the floating gel *in-situ* formulation to improve the solubility and control the release of VAL. Initially, a suitable single polymer matrix system was assessed to develop the SD formulation based on its water saturation solubility. Afterwards, the VAL-SD was incorporated into a floating gel *in-situ* formulation. Finally, the *in-situ gel* formulations were evaluated for their physical properties and drug release profile. Importantly, for the first time, we further investigated the effect of food intake on the *in vitro* release profiles of VAL in biorelevant media using FaSSGF (Fasted-State Simulated gastric Fluid) and FeSSGF (Fed-State Simulated Gastric Fluid) from solid dispersion-floating gel *in-situ* dosage form. The outcomes of this study could be beneficial to be applied to investigate

the effect of food intake on *in vitro* release profiles of various drugs from other drug delivery systems.

2. Materials and method

2.1. Materials

Valsartan (purity > 98%) was obtained from Tokyo Chemical Industry Ltd. (Tokyo, Japan). Poly(vinyl pyrrolidone) (PVP) K-30, poly (ethylene) (glycol) (PEG) 6000, sodium alginate, sodium bicarbonate, calcium chloride and sodium dihydrogen phosphate were obtained from Sigma-Aldrich (Dorset, UK). Hydroxypropylmethyl cellulose (HPMC) K-100 M were obtained from (Colorcon, England). All materials and reagents were analytical grade and used without further purification.

2.2. Methods

2.2.1. Preparation of valsartan solid dispersion

Valsartan solid dispersion (VAL-SD) was prepared using the solvent evaporation method. Eight different formulations were prepared, containing 1 g of VAL in all formulations. Specifically, PVP K30 was used with the drug:polymer ratio of 1:1, 1:2 1:3 and 1:4 for F1, F2, F3 and F4, respectively. Additionally, SDs from PEG 6000 were also prepared with the drug:polymer ratio of 1:1, 1:2 1:3 and 1:4 for F5, F6, F7 and F8, respectively. All components were dissolved in 25 ml methanol. The solution was then poured into an evaporation dish and let air-dried at 25 °C, RH of 40% for 48 h. The dries mass was then recovered, ground into powders, and stored in airtight containers.

2.2.2. Analytical method

Valsartan concentrations in all the samples were quantified using an isocratic HPLC method. The HPLC analysis of valsartan was carried out using a reverse-phase system with LC-20A quaternary gradient pump with SPD-20A UV-Vis detector (Shimadzu Prominence, Shimadzu, Kyoto, Japan). A Zorbax Eclipse Plus C18 column (Agilent, 4.6 x 150 mm) with a particle size of 5 µm was used as the stationary phase, and a mixture of acetonitrile and water adjusted to pH 2.5 with trifluoroacetic acid (40:60 v/v) was used as the mobile phase. The process was carried out at 25 °C with a flow rate of 1.0 mL/min and an injection volume of 50 µL. Samples were measured at 275 nm using a UV detector.

A series of VAL solutions in various concentrations were prepared and measured using the HPLC system explained above. The calibration curve was then constructed by plotting concentration and peak area obtained from the chromatogram, which was then further analyzed using linear regression, establishing the regression equation, coefficient of determination, and residual sum of squares (RSS). The calibration curves were constructed for three consecutive days to determine the linearity of the method. F-tests were performed to evaluate the significance of the regression and the lack of fit values (de Souza et al., 2007). limit of detection (LoD) and limit of quantification (LoQ) were calculated based on the standard deviation of the calibration curve as per international conference on harmonization (ICH) guidelines (Permana et al., 2021a). Three different concentrations of VAL solutions were prepared to represent the low, mid, and high portion of the calibration curve. The measured results were used to calculate the precision and accuracy parameter of the method. The method was considered valid if the mean accuracy (%RE) and precision (%CV) fall between 15% of the actual value (Permana et al., 2021c, 2019). In comparison, the LOQ is acceptable if the results did not deviate more than 20% from the mean (ICH, 2005).

2.2.3. Determination of drug recovery

An amount of VAL-SD dried powder (F1-F8), equivalent to 50 mg VAL (calculated from the theoretical weight), was dispersed in 10 ml of methanol until fully dissolved with the aid of a sonicator bath for 10 min. The final solution was then filtered through a 0.45 µm membrane

filter and quantified using the validated HPLC method.

2.2.4. Determination of saturation solubility

Each Val-SD dried powder (F1-F8) was dispersed in an excessive amount of four different test media (purified water, hydrochloric acid 0.1 M pH 1.2, phosphate buffer saline (PBS) solution pH 6.8, and PBS solution pH 7.4) in a glass vial. The vial was then placed in a shaking incubator set at 37 °C for 24 h. After 24 h, the solution was filtered, and the amount of VAL in the solution was determined using the above-mentioned HPLC method.

2.2.5. Thermal analysis

The VAL-SD and VAL were subjected to conventional differential scanning calorimetry (DSC) measurement using DSC 2920 (TA Instruments). Samples (5 mg) were properly sealed in aluminum pan by employing pressure. Pure VAL was chosen as a comparison and both samples were scanned from 0 to 300 °C with 10 °C/min ramps. The analysis was under N₂ purge with flow rate of 40 mL/min. This measurement was performed to confirm the formation of a SD system.

Thermogravimetric analysis (TGA) was carried out using a thermogravimetric analyzer, model Q-50 (TA Instrument Waters, USA). The analysis was under N₂ purge with flow rate of 40 mL/min. Approximately 5 mg of sample were put into aluminum pan, and heated from 25 °C to 300 °C. The heating rate used was 10 °C/min

2.2.6. X-Ray diffraction study

Solid-state analysis was performed using an X-Ray diffractometer (Rigaku Corporation, England), connected with Cu K β radiation. VAL and all SD formulations were scanned within the angular range between 5° and 50° (2 θ). The analysis was performed using continuous mode with a step scan speed of 5° per minute and a sampling width of 0.02°

2.2.7. Formulation of solid dispersion loaded floating gel in-situ

Alginate-based floating in-situ gel formulations were prepared by dispersing sodium alginate in hot water (~80 °C). After the homogenous alginate dispersion was formed and cooled, sodium bicarbonate, calcium chloride, HPMC K-100 M, and Val-SD powder were added (Table 1) while being stirred at °C at 200 rpm. The mixture was kept stirred until the homogenous dispersion was obtained. The final formulation was stored in airtight containers before evaluation. Only Val-SD with the highest solubility was used for this section forward. In this study, F3 with the ratio of VAL:PVP of 1:3 was used. After the determination of drug recovery, 4.04% w/v of SD (equal to 1% w/v of VAL) was used. In our preliminary study, it was found that the ratio of 2:1:1 of sodium alginate:NaHCO₃:CaCO₃ resulted in optimum gelation and floating properties. The increase in this ratio did not produce better properties. Accordingly, we used this ratio in our study. A previous study has used HPMC in the floating in-situ gel system with the concentration between 0.5–0.7% w/v (Karemore and Avari, 2019a). In our study, we investigated different concentration of HPMC which were below and above of the reported study.

2.2.8. In vitro gelation study

An in vitro gelation study of each of the formulation was carried out.

Table 1
Formulation chart of VAL-SD floating in-situ gel system.

	Val-SD (%) w/v (Equal to Valsartan)	HPMC K100M (%w/v)	Sodium Alginate (%w/v)	NaHCO ₃ (%) w/v)	CaCO ₃ (%w/ v)	Distilled Water
F1	1	0	2	1	1	up to 100
F2	1	0,25	2	1	1	mL
F3	1	0,5	2	1	1	
F4	1	0,75	2	1	1	
F5	1	1	2	1	1	

An aliquot of 10 mL of the dispersions was measured and added into 500 ml 0.1 N hydrochloric acid solution (pH 1.2) in beaker glass with continuous stirring. The agitation was kept at a minimum to avoid disruption on the gel that was formed. The time required by the formulation to form a gel was denoted as gelation time (Singhavi et al., 2017).

2.2.9. In vitro floating study

The floating study was performed using USP Dissolution Apparatus II. An aliquot of 10 mL of the floating in-situ gel formulation was drawn up using a disposable syringe and placed in a 4.5 cm diameter Petri dish (without lid). The Petri dish was then placed in the dissolution vessel containing the 500 ml 0.1 N HCl (pH 1,2) without disturbing it. The time that was taken by the gel-forming liquid to rise to the surface of the medium and the time taken by the gel to float continuously on the surface of the medium were noted as the floating lag time and the duration of floating. The temperature of the medium was maintained at 37 ± 0.5 °C during the test (Singhavi et al., 2017).

2.2.10. Viscosity measurement and gel strength measurement

The viscosity was determined using Brookfield Viscometer DV III (Brookfield Engineering Laboratories, MA) at 50 rpm using spindle number 2. For gel strength measurement, a Rheometer (TA Instrument, USA) was used. All measurements were performed in triplicate at 25 °C.

2.2.11. In vitro drug dissolution study

The drug release profile was determined using USP Dissolution Apparatus II (paddle) at 50 rpm. For each floating gel in-situ formula, 10 ml dispersion (equal to 100 mg of VAL) was used and put in a dissolution vessel filled with 900 ml of test media. Five different test conditions were used in this study to simulate the performance of the formulation in the fasted gastric state, fed gastric state, fed gastric state after 1 hour, 2 h, and 3 h in fasted condition. FaSSGF (Fasted-State Simulated Gastric Fluid) was prepared by dissolving 1.999 g of NaCl in purified water, adjusted to pH 1.5 with HCl 1 M, and then the volume was made up to 1 L using purified water (Permana et al., 2020). For FeSSGF (Fed-State Simulated Gastric Fluid), skimmed milk and acetate buffer pH 5.0 were mixed at a 1:1 ratio. For each liter of the media, 500 mL of milk and 480 mL acetate buffer were mixed under constant stirring using a magnetic stirrer. The mixture was then adjusted to pH 5 with 1 M HCl, and the volume was made up to 1 L using acetate buffer (Baxevanis et al., 2020). The dissolution tests were carried out for 24 h, and samples were collected at predetermine times (0.25 h, 0.5 h, 0.75 h, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 12 h and 24 h). New dissolution media was added to the test vessel after each sampling with an equal volume of fluid taken. To extract VAL for the FeSSGF media, 5 mL was added into 1 mL of collected samples. The mixture was sonicated for 10 min in a bath sonicator. Afterward, the mixture was centrifuged at 10,000 rpm for 15 min. The amount of VAL in the supernatant was determined using the validated HPLC method.

2.2.12. Statistical analysis

GraphPad Prism® version 6 (GraphPad Software, San Diego, California, USA) was applied in order to perform statistical analysis. Data was denoted as statistically different when $p < 0.05$.

3. Results and discussions

In this study, an SD system containing VAL in PVP K-30 and PEG 6000 matrices was prepared using the solvent evaporation method with methanol as the solvent. This method was selected because it simplifies manufacturing techniques as it does not require a specialized machine to perform, especially in the laboratory scale. Eight different types of SDs with varying drug to polymer ratio and polymer composition were prepared in this study to compare the performance of PVP K-30 and PEG 6000 as a single polymeric carrier. It has been previously reported in

several studies that generally, the concentration of polymers used in the SD preparation was at least similar to the active ingredient concentrations (Borde et al., 2021; Wang et al., 2021). Therefore, in this study, the ratio values of 1:1, 1:2, 1:3 and 1:4 of drug:polymer were prepared. Specifically, it was important to note that the use of methanol which was less than 25 mL did not result in clear solution. Accordingly, 25 mL was used to dissolve all formulations. After the preparation of SDs, we did not find the residual content of methanol in the final products. Furthermore, the yield values of all formulations were reported to be $91.23 \pm 1.32\%$, $93.09 \pm 2.09\%$, $93.74 \pm 3.01\%$, $92.87 \pm 2.11\%$, $91.98 \pm 2.81\%$, $92.17 \pm 3.07\%$, $91.19 \pm 2.17\%$ and $92.73 \pm 2.38\%$ for F1, F2, F3, F4, F5, F6, F7 and F8.

3.1. Analytical method validation

A HPLC method was developed and optimized for the quantification of VAL in testing media. The representative chromatograms of VAL in FaSSGF and FeSSGF media are shown in Fig. 1A and 1B. UV spectrum of VAL in FaSSGF and FeSSGF media are shown in Fig. 1C and 1D. The validation of the analytical method was completed per ICH guidelines. The LOD and LOQ values of the validated method were $1.06 \mu\text{g/mL}$ and $3.23 \mu\text{g/mL}$ in FaSSGF media. In FeSSGF media, the LOD and LOQ were $0.53 \mu\text{g/mL}$ and $1.62 \mu\text{g/mL}$ respectively. We found these values satisfactory for in vitro test used in this research. This method has a linearity range between $0.5 \mu\text{g/mL}$ and $50.0 \mu\text{g/mL}$ with $R\text{-squared} > 0.9995$ both for FaSSGF and FeSSGF. Fig. 1E and 1F exhibit the calibration curves of VAL, showing its linearity. Importantly, $F\text{-tests}$ showed that the lack of fit was not significant ($p = 0.18$ for FaSSGF and 0.21 for FeSSGF). Additionally, F_{cal} values were found to be 1.89 and 2.02 for FaSSGF and FeSSGF, respectively. These values were smaller than F_{tab} (4.28), presenting the linearity of the calibration curve. Intra and inter-day measurement to establish the precision and accuracy of the method were also satisfactory as both $\%RSD$ and $\%RE$ were within the acceptance limit ($<15\%$) (Permana et al., 2021c, 2019).

3.2. Drug recovery and saturation solubility

In the drug recovery measurement, the recoveries of VAL in all formulations were $99.76 \pm 0.47\%$, $98.93 \pm 0.38\%$, $99.11 \pm 0.26\%$, $99.81 \pm 0.31\%$, $98.91 \pm 0.42\%$, $99.21 \pm 0.36\%$, $99.01 \pm 0.42\%$ and $99.19 \pm 0.17\%$ for F1, F2, F3, F4, F5, F6, F7 and F8, respectively. Furthermore, we assessed the performance of the SD using the solubility test on four different media with different pH values, as shown in Table 2. We

Table 2

Saturation solubility study results of the SD formulation in water, HCl 0.1 M pH 1.2, phosphate buffer pH 6.8 and phosphate buffer pH 7.4 (means $\pm$ SD, $n = 3$).

Samples	Solubility ($\mu\text{g/mL}$)			
	Water	pH 1.2	pH 6.8	pH 7.4
Crude	96.32 ± 16.43	28.19 ± 4.93	132.81 ± 23.32	203.39 ± 33.01
F1	143.14 ± 21.32	41.24 ± 8.12	254.01 ± 57.43	391.56 ± 63.21
F2	295.43 ± 49.11	84.11 ± 17.02	401.24 ± 82.35	531.38 ± 78.14
F3	423.91 ± 78.54	152.71 ± 21.23	698.43 ± 128.39	703.81 ± 102.03
F4	534.14 ± 92.91	184.32 ± 30.92	802.84 ± 150.21	829.53 ± 132.18
F5	103.59 ± 21.31	30.65 ± 6.04	192.19 ± 31.18	291.22 ± 44.28
F6	167.62 ± 29.44	36.19 ± 5.31	254.91 ± 29.71	373.62 ± 62.09
F7	205.65 ± 31.43	49.39 ± 10.32	297.04 ± 48.81	403.39 ± 49.74
F8	365.37 ± 51.04	53.04 ± 9.18	321.65 ± 51.22	543.71 ± 102.83

observed that the solubility trend of all SD formulations was similar in all testing media. This study confirmed that VAL and all VAL-SD formulations show higher solubility at a higher pH value which further proves that VAL retains its pH-dependent solubility profile even after transforming it into an SD system. This pH-dependent solubility was mainly due to its free carboxylic acid functional group (Park et al., 2010). This exciting finding suggests that it is possible to increase the solubility of a drug substance without altering the environment of the absorption site (e.g., adding pH modifier into a formulation). This system can enable flexibility in the formulation of a drug delivery system for such drugs where the pH of the absorption location greatly influences their solubility, especially when administered via the oral route.

In an SD system, the matrix can act as a solubilizer. Due to their hydrophilic nature of the carrier, they can improve the SD wettability, thus improving its solubility in an aqueous system. PVP and PEG are hydrophilic polymers often used in solid dosage forms as an excipient to enhance the dissolution and bioavailability of drugs (Ng et al., 2016). Comparing PVP K-30 and PEG 6000 formulation, the SD system using PVP K-30 as the carrier showed a very distinct superiority compared to the PEG 6000 counterpart. The solubility difference between the

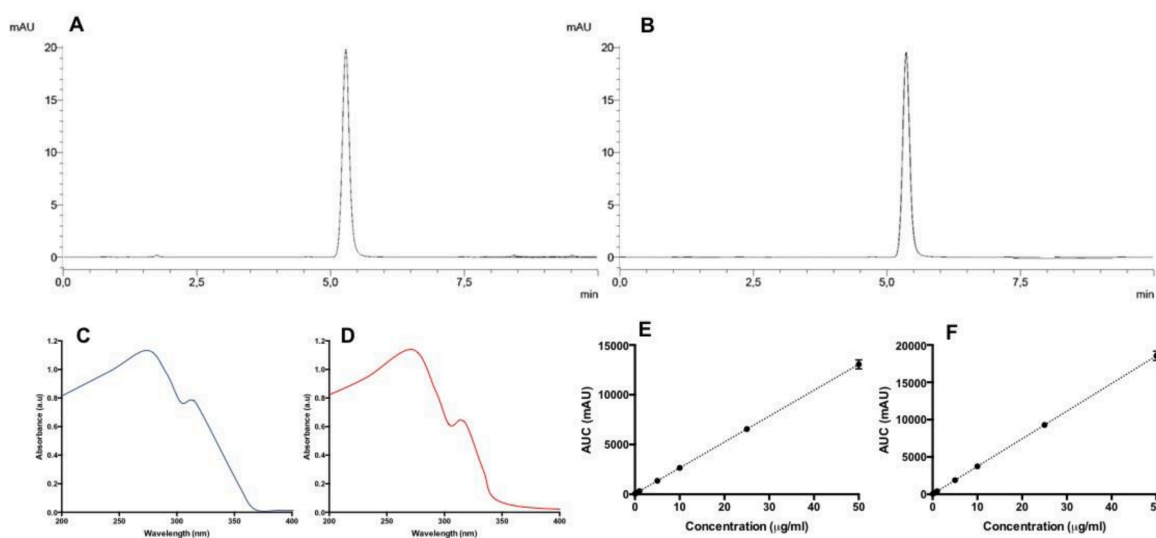


Fig. 1. Chromatogram of VAL in FaSSGF (A) and FeSSGF (B). UV spectrum of VAL in FaSSGF (C) and FeSSGF (D). Calibration curve of VAL in FaSSGF (E) and FeSSGF (F).

formulation (comparing PVP K-30 and PEG 6000 system with the same polymer to drug ratio) was found the around 1.3 to 2.0-fold and was more significant in acidic media when it reached more than a 3.0-fold difference. At its higher polymeric to drug ratio, PEG 6000 only raised the solubility of VAL to 2.0-fold in acidic media, while the PVP K-30 system increased VAL's solubility up to 6.0-fold. In addition to its superior performance, PVP K-30 is an excellent choice, since it can inhibit drug crystallization in solid and liquid states (Yousaf et al., 2019) and stabilize the SD system for a more extended period and extend its

shelf-life. VAL-SD F3 and F4 show no significant solubility difference in all media ($p > 0.05$) if compared to each other. For this study, Val-SD F3 was used for further tests because it shows better solubility with minimal polymer matrix than F4. Choosing an SD system with a lower drug to matrix ratio should always be preferred, since it may ensure more extensive drug loading and lower bulkiness of the final SD product. A study using Chrysosplenol C, a different drug model, also indicated that PVP showed greater importance in increasing the aqueous solubility of a hydrophobic drug as the SD solubility of the drug was superior when

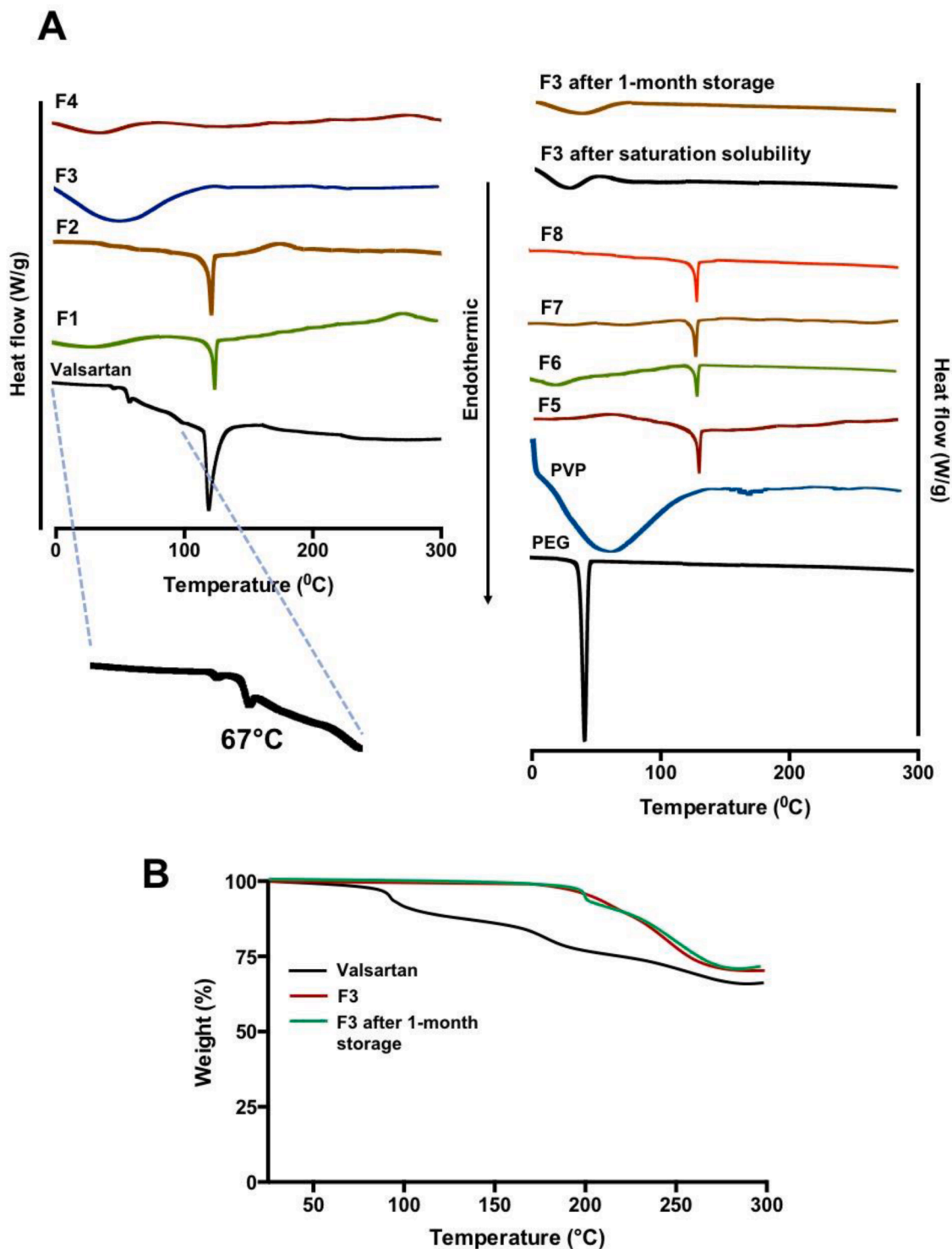


Fig. 2. DSC thermogram VAL, all formulations of VAL-SD, VAL-SD (F3) after saturation solubility and 1-month storage (A). TGA curves of VAL, as well as VAL-SD (F3) after saturation solubility and 1-month storage (B).

using PVP K-30 compared to PEG 6000. The finding in the said study was supported by the fact that the drug was more soluble in PVP K-30 aqueous dispersion than PEG 6000 solution (Ng et al., 2016). In our study, the saturation solubility values of all formulations after 24 h were also investigated. The results showed that there was no significant difference in the values ($p > 0.05$), suggesting that 24 h was sufficient time to determine the saturation solubility.

3.3. Thermal analysis

To further confirm the formation of the VAL-SD, we investigated the final mixture using DSC techniques. Thermogram of PVP showed a broad peak before 100 °C, due to the evaporation of water from hydrophilic polymer. In PEG thermogram, a sharp peak was observed at 58 °C, showing its melting point value. Valsartan has a corresponding melting point at 116.7 °C, as shown in Fig. 2A by a sharp endothermic peak in that value. Additionally, endothermic peak was also observed at 67 °C. This might be due to the water loss of the compound during the analysis. Similar result was observed by Santinon et al., showing that the water loss of VAL during DSC resulted in a peak detected between 60 °C and 70 °C (Santinon et al., 2021). In VAL-SD formulation, only F3 and 4 exhibited no sharp melting peak in the thermogram, indicating the successful transformation of amorphous state in the SD form. On the other hand, other formulations showed a peak at the melting point of VAL. These results were in a good agreement with the solubility evaluations, showing that VAL from F3 and F4 showed the highest solubility compared to other formulations. A successful study in formulating valsartan into SD using HPMC and Poloxamer 188 also shows a similar habit in thermogram, where no VAL melting peak was observed in the final product (Xu et al., 2016). This finding may indicate the amorphous behavior of the SD system. Amorphous solids do not exhibit distinct endothermic peaks upon melting. This characteristic is due to the irregular intermolecular bond arrangement inside the solid structure, unlike the more orderly bond in the crystalline counterpart. The thermogram also indicated the formation of one continuous phase of an amorphous SD system. Importantly, after the evaluation of the saturation solubility, the non-dissolved SD was collected and was dried. Afterwards, the DSC analysis was performed, showing that the formulation was still in the amorphous form, indicated by the absence of a peak at

the melting point of VAL. Additionally, as shown in Fig. 2A, after 1-month storage at 25 °C in an airtight container, SD-VAL was able to maintain its amorphous state, indicating the stability of SD formulation.

Amorphous one-phase SDs have significant drug-carrier interaction, which leads to complete miscibility of drug and carrier components. Such systems are homogenous at their molecular level. In the attempt to amorphized a crystalline drug, a high drug-to-matrix ratio may be needed to maintain the amorphous state of the mixture over time during storage. An order of 50% by weight or more is considered satisfactory in most cases (Baird and Taylor, 2012). In this study, the VAL-SD (F10) has a 75% matrix component and 25% drug substance (Yousaf et al., 2019).

In TGA analysis curve, it was observed that pure VAL showed a mass decrease around 100 °C (Fig. 2B). This is in an agreement with DSC analysis result, showing the water loss of VAL. On the other hand, in after the formulation into SD, F3 did not show any mass loss at the similar temperature where VAL showed a mass loss. This indicated that there was no residual solvent in the formulation. Importantly, 1-month storage did not change the TGA curve of VAL in SD formulation.

3.4. XRD analysis

In this research, we used XRD to assess the solid-state properties of the VAL-SD in comparison with plain VAL. As shown in Fig. 3, VAL showed a broad peak around 12° and 22°. The broad peak in XRD pattern of VAL was also observed in several studies (Park et al., 2018; Santinon et al., 2021), indicating the polymorphic form of VAL used in this study. In contrast, the flat diffractogram of F3 and F4 indicated that the system was indeed an amorphous solid with no trace of crystallinity. As shown in Fig. 3, other formulations showed two peaks around 12° and 22°, implying that VAL was not in an amorphous state. This result was in accordance with the results from DSC analysis. Similar findings had been reported by some studies using different drug and polymer mixture, where the authors observed amorphous solid as the form of the final SD system like Sorafenib in Soluplus SD (Truong et al., 2015), Cilostazol in Eudragit mixture (Park and Choi, 2015), and Tacrolimus in HPMC/SLS mixture (Jung et al., 2016). Crystalline material diffracts the X-ray beam at a certain angle because of the ordered and repeated crystalline structure, while amorphous solids do not. Similar to DSC analysis, after saturation solubility and 1-month storage in an airtight container, F3

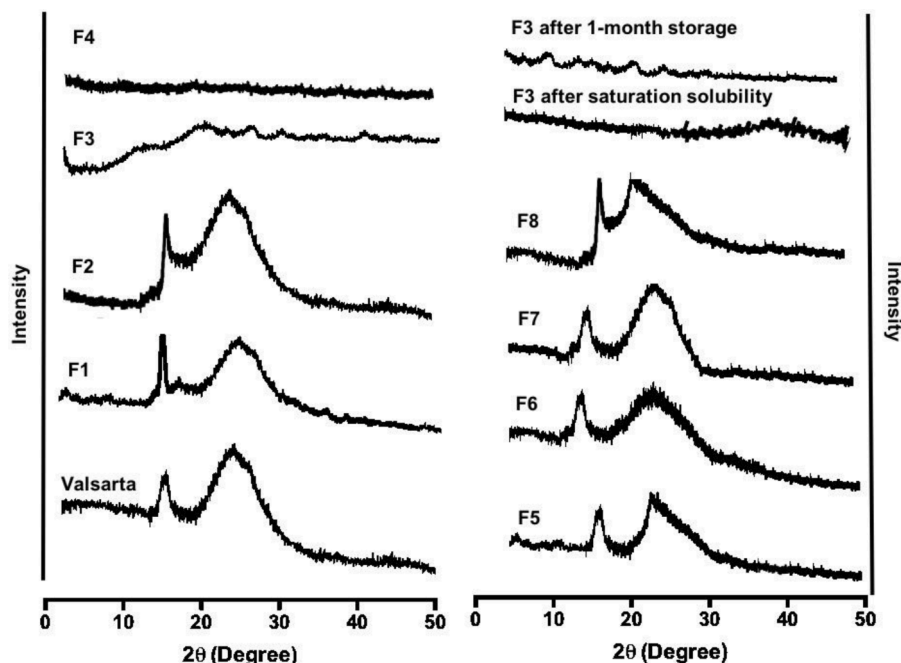


Fig. 3. Powder XRD diffractogram of VAL-SD, VAL-SD (F3) after saturation solubility and 1-month storage.

was able to maintain VAL in the amorphous state.

3.5. Viscosity, in vitro gelation time, floating time, and gel strength measurement

Ion crosslinking-based *in-situ* gel delivery system for a gastro-retentive purpose serves a unique strategy in delivering a controlled release formulation in the liquid dosage form. Because the floating *in-situ* gel formulation used in this study is a thermodynamically non-stable system, careful control of viscosity is crucial as it one of the quality attributes that can affect the stability of the dosage form. Enough viscosity is required to ensure that the non-soluble excipient in the formulation stays homogeneously dispersed upon standing, but low enough to retain its free-flowing properties and ease the swallowing process (Madan et al., 2015; R Jivani et al., 2010). Calcium carbonate is the non-soluble part of the formulation that acts as a calcium ion and secondary CO₂ source. Maintaining the amount of CaCO₃ to be consistent in each dosing is vital because it plays a significant role in gel-forming and the floating habit of the formula (Rajinikanth and Mishra, 2008). In many studies, it had proven to be some of the contributing factors in tailoring the desired release properties of this kind of formulation (Mahmoud et al., 2019; R Jivani et al., 2010). The pre-gelation viscosity of all *in situ* floating gel formulations is illustrated in Fig. 4A. We found that the viscosity of the formulations was between 219 ± 16 cps to 1103 ± 75 cps, with significant differences among formulations ($p < 0.05$). It is clearly shown that the viscosity of the formulation rises as the concentration of the HPMC rise. HPMC is a hydrophilic polymer used as a gelling agent and thickening agent in many pharmaceutical formulations. The concentration used in this formulation is lower than its concentration as a gelling agent to maintain the free-flowing character of the preparation.

All studied formulations showed that they were capable of forming a gelled body upon contact with acidic media with gelation time below 30 s (Fig. 4B). Gel formation in this formulation was triggered by the

complexation reaction between the carboxyl group from the guluronic moieties in the alginate polymeric network and calcium (Ca²⁺) ion to form a crosslinked "egg-box" structure (Doderio et al., 2019). The calcium carbonate in this formulation was the source of the Ca²⁺ ion. Still, since the carbonate form of the calcium salt is insoluble in water, the dispersion remained liquid during storage. When the liquid formulation meets acidic media (such as the gastric juice), the calcium carbonate reacts with the acid, forming soluble calcium salt and carbon dioxide gas. The newly liberated free Ca²⁺ ion triggers the crosslinking of the alginate polymer network, increasing its viscosity. If enough calcium ion is present, the system eventually forms a gel-like structure (Sharma et al., 2019).

It is essential to make the gelled system float and stays afloat in gastric juice to achieve the formulation's gastroretention characteristics. The buoyancy in this floating system comes from the entrapped carbon dioxide (CO₂) bubbles inside the gel network (Karemore and Avari, 2019b). The CO₂ bubbles were formed when the gas was liberated from carbonate and bicarbonate reaction with acid, while the system also thickened when the crosslink reaction takes place. With the entrapped gas, the gelled body became less dense than its surrounding liquid, turning it into a floating mass (Karemore and Avari, 2019b). Availability of Ca²⁺ and CO₃²⁻ is vital during this phase as the CO₂ entrapment is greatly affected by the integrity of the outer gel barrier. Lower Ca²⁺ concentration may compromise the structural integrity and results in a weaker gel structure, while a higher concentration of this ion may negatively affect the buoyancy property of the gel (Abou Youssef et al., 2015). Two sources of CO₂ were used in this study, which were calcium carbonate and sodium bicarbonate, to improve the buoyancy of the preparation. The CO₂ gas from sodium bicarbonate helps the floating systems to gain more buoyancy without adding extra Ca²⁺ ions, which impairs the gel structure. In our study, the *in vitro* buoyancy test showed that all formulations could float with floating lag time between two to almost four minutes (Fig. 4C) and stayed buoyant even after 24 h. The results showed that, as the HPMC concentration in the formulation

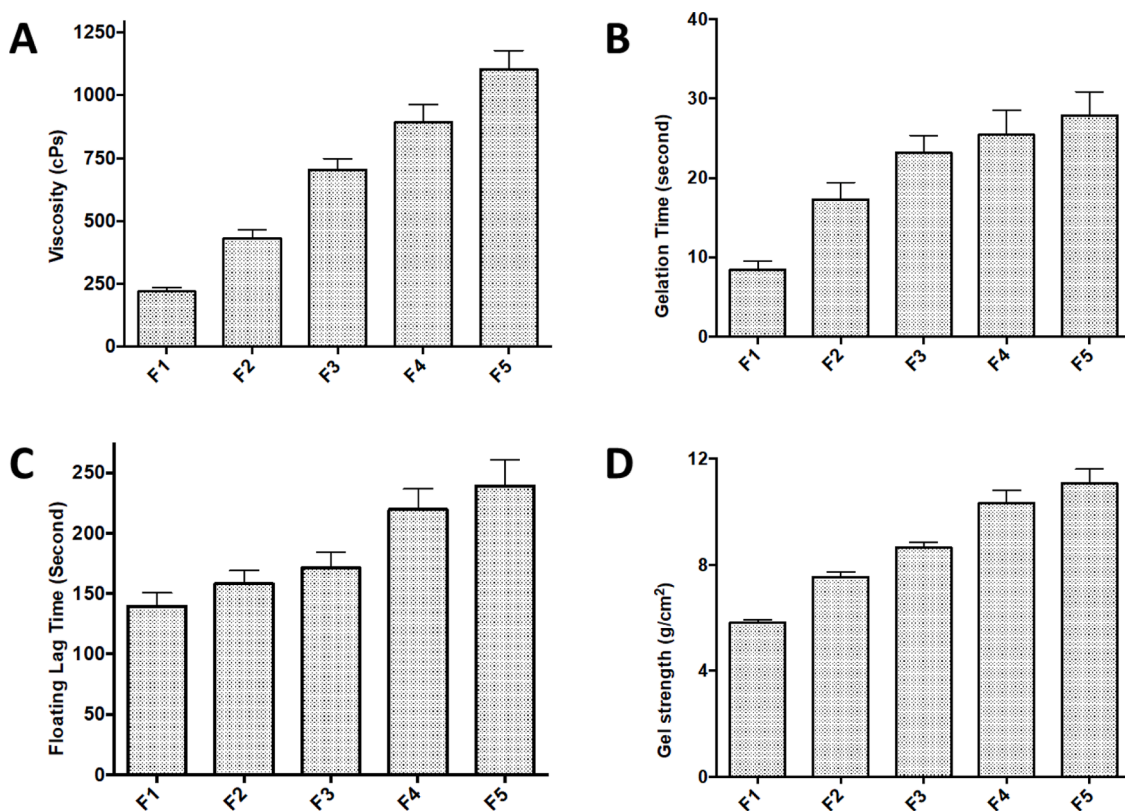


Fig. 4. Comparison of (A) viscosity, (B) gel strengths, (C) gelation time and (D) floating lag time of all *in-situ* gel VAL-SD formulation (means ± SD, $n = 3$).

increased, both gelation and floating time also increased. This phenomenon was most likely contributed by the fact that the post-gelation viscosity of the formula also increases (following a similar profile with the pre-gelation viscosity) as the HPMC concentration gets higher. The microenvironment of the viscous body hinders the penetration of the acidic solution into the gel and retards the reaction between the acid and the carbon dioxide source (Mahmoud and Marzok, 2020). Similar findings related to prolonged lag time due to increasing polymeric material in the system also reported in different drug model formulations (Mahmoud et al., 2019).

Fig. 4D shows the gel strength of the gelled formulations. Changing the concentration of HPMC by 0.25% up to 0.75% gives a significant increase ($p < 0.05$) in the gel strength properties of the formulation but increasing the concentration to 1% does not yield a substantial change of the gel strength ($p > 0.05$). The trend that was shown in this test is in agreement with the viscosity measurement results, which was mainly due to the gel-forming characteristics of HPMC polymer. Maintaining a rigid gel structure is essential in floating gel formulation. This type of delivery depends on the available gel surface that makes contact with the dissolution media where the diffusion occurs. Drug molecules trapped in a complex 3D structure of the gel network needs to travel across the system to enter gastric fluid (Karemore and Avari, 2019b). If the gel failed to maintain its integrity and broke down when agitated in the gastric environment, it would be difficult to achieve a consistent drug release profile. All formulations maintained structural integrity, and the gel strength of the gelled body can be seen in Fig. 5.

3.6. In vitro dissolution study

The formulated floating *in-situ* gel's performance containing VAL-SD was assessed based on the release profile of the preparation. The goal was to achieve a prolonged drug release over time and achieve 100% dissolved drug at the end. The burst effect was considered undesirable. This effect could potentially prevent the formulation to obtain controlled release manner (Hsu et al., 2015). Additionally, it has been reported that the burst release could elevate the drug concentration to near toxic concentration (Hsu et al., 2015). The dissolution characteristic of the formulation and VAL-SD in Fasted-State Simulated Gastric Fluid (FaSSGF) and Fed-State Simulated Gastric Fluid (FeSSGF) were studied. In addition, a comparison of the dissolution profile of all formulations was studied in the additional three dissolution conditions. The aim was to predict the formulations behaviors if they were ingested in fasted states, and then a meal was taken after that. These conditions were simulated by replacing the FaSSGF with FeSSGF after the formulation spent times in the previous media. The results in the form of a graph representing cumulative drug release (%) vs time of all formulation can be seen in Fig. 6 and Fig. 7.

The graph in Fig. 6 shows that the VAL-SD alone exhibits a good dissolution characteristic where a complete dissolution can be achieved before the fourth hour in fasted-state and before the first hour in fed-state. This difference was most likely due to the pH-dependent nature of VAL solubility and the different pH values of FaSSGF (pH 1.5) and FeSSGF (pH 5.0) media, so the drug exhibited a faster solubility rate in fed condition. VAL is considered an acidic drug, so its dissolution in

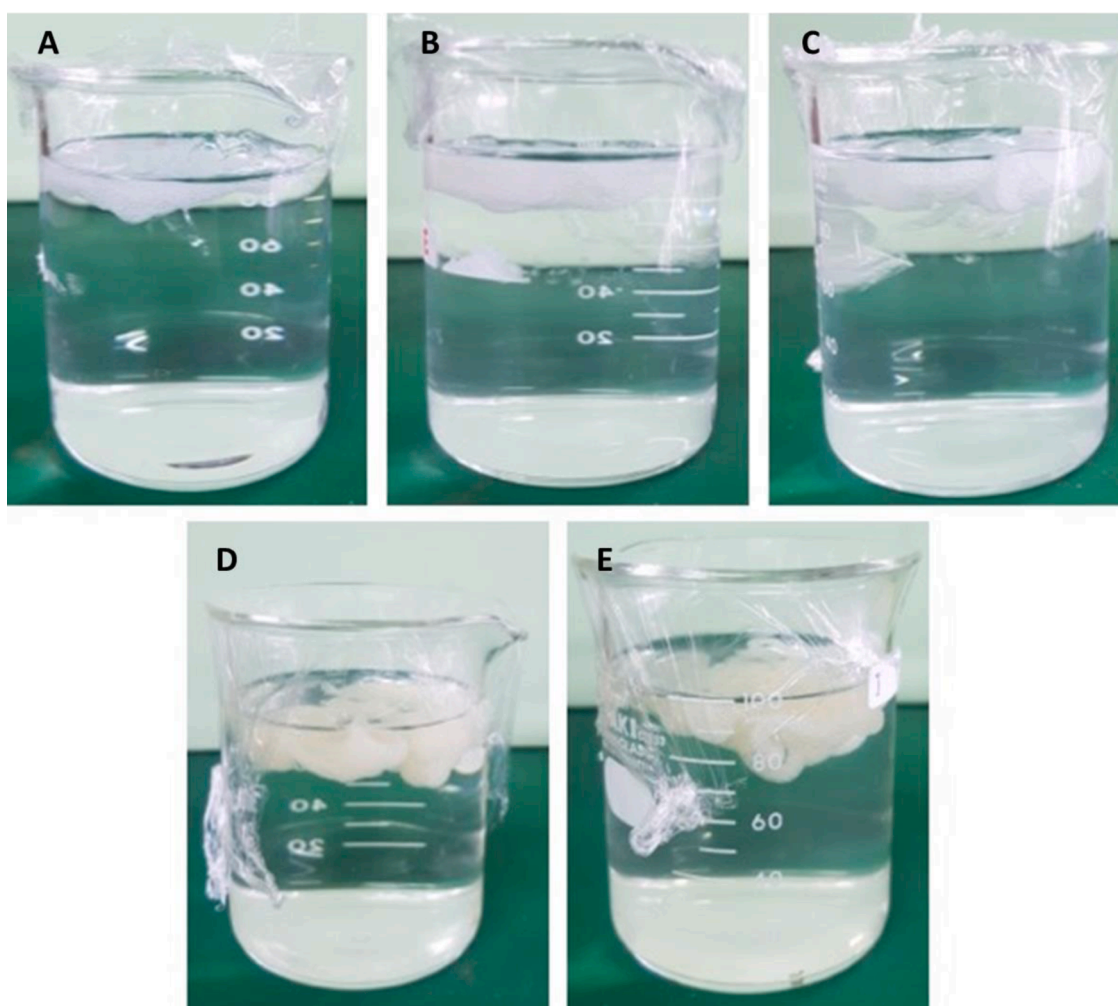


Fig. 5. In vitro floating test of F1 (A), F2 (B), F3 (C), F4 (D) and F5 (E).

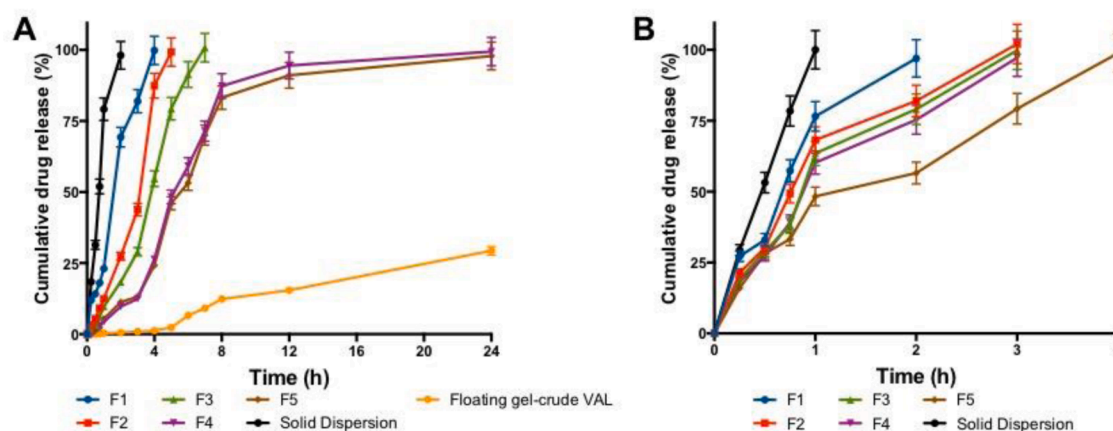


Fig. 6. In vitro dissolution study of in-situ gel formulation in (A) FaSSGF and (B) FeSSGF (means $\pm$ SD, $n = 3$).

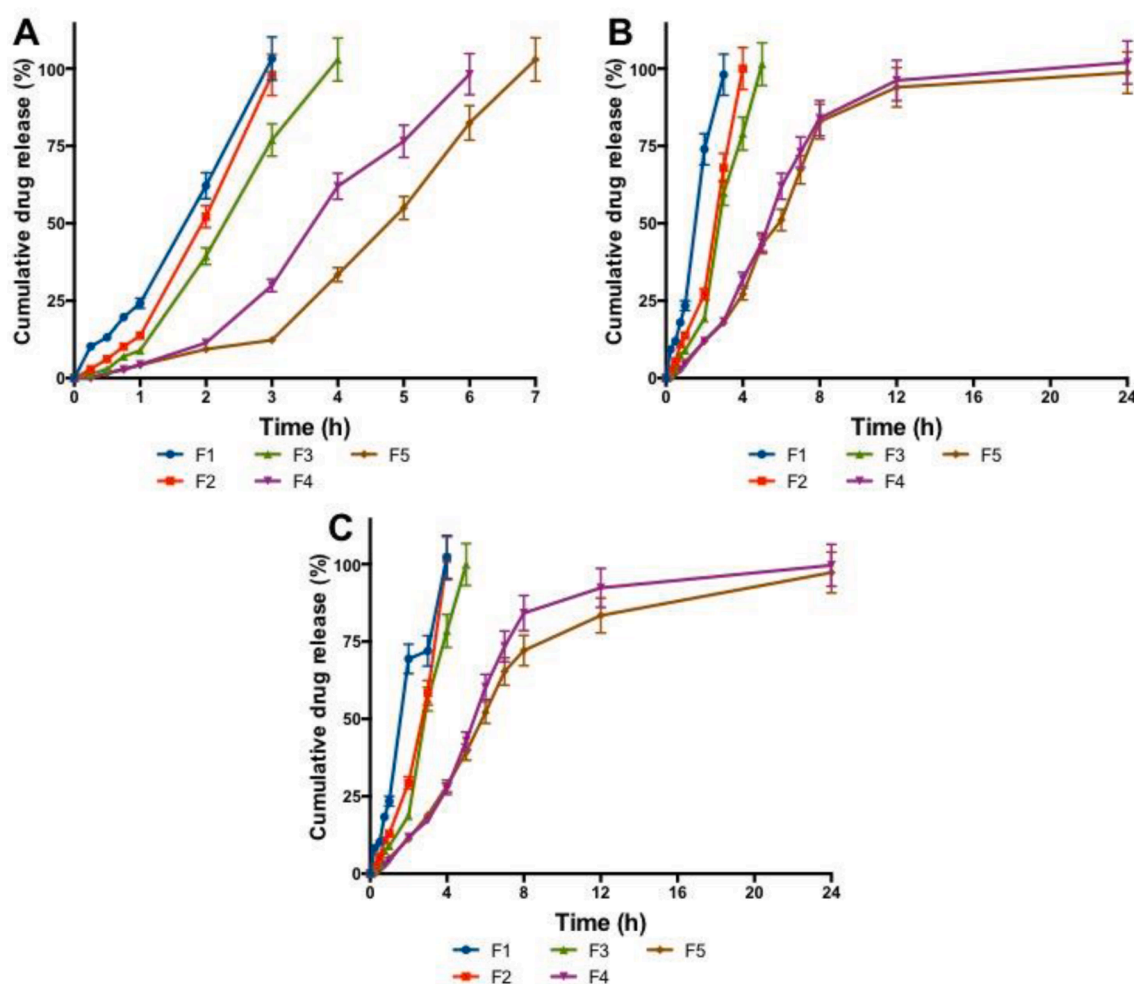


Fig. 7. In vitro dissolution study of in-situ gel formulation in FeSSGF after (A) 1 hour in FaSSGF/condition C, (B) 2 h in FaSSGF/condition D, and (C) 3 h in FaSSGF/condition E (means $\pm$ SD, $n = 3$).

acidic gastric solution was generally poor compared to more basic intestinal fluid. However, in this study, a 100% release in the simulated gastric fluid was successfully achieved, which was remarkable and suited the final goal of this research. When we aimed to formulate a drug into a gastroretentive system, assuring that complete dissolution can be accomplished in an acidic media should be the first problem to address. As an acidic drug, the VAL absorption window is in the gastric area

because all VAL molecules are in the unionized form (Pradhan et al., 2016). Some studies report as low as 2% of drugs released using a different SD polymer system (Yan et al., 2012). All formulations showed excellent cumulative dissolution properties due to the inclusion of SD in the formula. The improvement of drug release in the SD system was attributed to the hydrophilic effect of the matrix that can reduce the surface tension of the drug and the dissolution media, leading to better

wettability, solubility, and dissolution (Lima et al., 2011).

The study showed that VAL could achieve 100% dissolved drug when the VAL-SD was incorporated into floating *in-situ* gel formulation with prolonged-release at varying extent. F1, F2, and F3 had extended-release between 4 h and 8 h, while F4 and F5 can retain the drug up to 24 h before reaching complete dissolution. In this study, floating *in-situ* gel without HPMC (F1) was able to prolong the release of the drug up to two folds if compared with VAL-SD alone, both in fasted and fed state. This finding confirmed the ability of the floating Ca-alginate matrix to retard the drug release to a certain level, thus served as a suitable carrier. To further improve this sustained release property, HPMC was introduced to the formulation as a second polymeric material. It has been previously reported that the molecular weight of the polymer used could affect the *in vitro* dissolution profile of drugs (Akbari et al., 2011). Among various type of HPMC, HPMC K100M (MW of 1150 kDa) has been widely used as an optimum polymer for controlled and sustained release dosage forms (Kumar et al., 2007; Roy et al., 2012). The inclusion of HPMC made the release curve steeper both in fasted and fed state simulated media. The more HPMC was used, the more gradual the slope of the release profile. A higher concentration of HPMC in the formula could retard the release of the drug from the gelled matrix because the density of the gel network also became denser and rigid (Jafar et al., 2018; Madan et al., 2015). Based on the graph, this experiment demonstrated that changing the HPMC concentration from 0.5% to 0.75% drastically altered the release profile in a more acidic environment. In a less acidic test media, this effect was not observed. Also, F4 (HPMC 0.5%) and F5 (HPMC 1%) does not exhibit a significant difference in term of the dissolution profile in FaSSGF media, in contrast with the difference observed in FeSSGF. As the amount of Ca^{2+} ion is limited, some of the free carboxyl units in the polymeric alginate chain were unlikely to have the crosslinking reaction. These accessible carboxyl units can interact with the medium resulting in different gel habits. Sodium alginate generally has thicker viscosity in acidic media and can reach its maximum viscosity at pH 3–3.5. At lower pH, the free carboxyl moieties will become protonated and form hydrogen bonds with neighboring functional groups (Lee and Mooney, 2012). This phenomenon was expected to be responsible, at least partially, for the different release profiles of calcium alginate-based matrix in FaSSGF and FeSSGF. Additionally, the dissolution profile of VAL from floating gel *in situ* system without being formulated into SD system was also investigated. As shown in Fig. 6, after 24 h, less than 30% of VAL was released from the formulation. Accordingly, this implied that it was important to improve the solubility of VAL by SD system in order to further control the release using floating gel *in situ* system.

In this research, a comparison of the dissolution profile of the formulation in FeSSGF after it spent 1 hour, 2 h and 3 h in FaSSGF was made. As previously discussed, the drug release from floating *in situ* gel formulation is pH dependent. In order to form a gel, the formulation should contact low pH environment in empty gastric. However, it is important to bear in mind that it is impossible for the patient to keep their stomach empty to achieve sustained release for 24 h. Therefore, in this study, we aimed to simulate how food intake would affect the formulation's performance because food intake could alter the pH of gastric fluid. This property was essential to establish as an *in-situ* crosslinked calcium alginate-based delivery system that relies heavily on the low pH of the gastric environment. The findings were illustrated in Fig. 7. The difference among conditions can be seen from the graph, showing the significant difference ($p < 0.05$) among the cumulative release of VAL from floating *in-situ* gel after spending 1 hour (condition C), 2 h (condition D) and 3 h (condition E) in FaSSGF before transferring it FeSSGF. As the formulation spent 2+ hours more acidic media, the dissolution profile showed more retarded release than the formulation that spent only 1 hour in it. The formation of a gel-like structure after the formulation made contact with acidic dissolution medium is time-dependent. This was mostly due to the slow release of calcium ions from the calcium carbonate trapped inside the gel structure. When the preparation made

contacted with acids, the surface of the liquid was the first portion of the formulation that formed a gel, creating a skin-like surface that encloses the remaining liquid. The acid then slowly permeated the "skin" layer into the structure and react with the remaining calcium carbonate. A more rigid and crosslinked network was formed as the contact time increase, and it was reflected in the dissolution profile. In condition C, all formulation released all the drug content before 7 h while in condition D and E, F4 and F5 were able to retain the drug and release it slowly in 24 h. Afterwards, the "spring and parachute" effect of the formulation was also observed. It was noticed that in condition D and E, F4 and F5 exhibited immediate spring profile in 6 h. Following this, the supersaturation of VAL was maintained until 24 h. This phenomenon was also observed in several formulations containing solid dispersion (Chavan et al., 2020; Hanada et al., 2018; Wendelboe et al., 2017). It was important to note that several studies have reported the instability of VAL in acid conditions. However, the instability was reported when VAL was placed in acid condition after 24 h and in temperature above 50 °C (Alqurshi et al., 2017; Regulski et al., 2019), which was not the case in this study. In room temperature, the degradation of VAL in acid condition was not observed less than 24 h (Rao et al., 2010). Moreover, significant efforts have been made by several researchers to develop the gastroretentive systems for VAL, showing that these systems could successfully control the release of VAL in gastric environment without any instability issue (Biswas et al., 2013; Cho et al., 2016; Prasanthi and Vidyavathi, 2017).

Based on the findings discussed here, it is apparent that the combination approach of SD and floating gel *in-situ* was able to enhance the solubility and sustain the release of VAL over 24-h period. Importantly, for the first time, we proved that the release of VAL from this system was not affected after transferring the formulation to FeSSGF from 2-h release in FaSSGF. Therefore, from these *in vitro* studies, in order to maintain the sustained release profile of VAL, it can be anticipated that the oral administration of this system can be followed by food intake after 2 h. However, in future studies, the pharmacokinetic study in a suitable *in vivo* animal model should be performed. Moving forwards, the pharmacodynamic studies should also be carried out to evaluate the effectiveness of this combination approach.

4. Conclusion

In the present study, we found out that the inclusion of VAL into PVP K-30 or PEG 6000 matrices improved its solubility. PVP K-30 showed superior performance compared to the PEG 6000 counterpart. The drug-to-matrix ratio of 1:3 gave the most favorable results for this study. We proved that the inclusion of VAL-SD into a crosslinked-based floating *in-situ* gel carrier was able to sustain VAL release from the formulation. The concentration of HPMC as the second polymeric material played a significant role in determining the characteristics and the performance of the preparation. Approximately 100% drug release could be achieved over a wide range of time. Increasing HPMC concentration could prolong the drug release mainly due to the more complex gel network and higher viscosity/gel strength. Importantly, we developed a novel *in vitro* approach to investigate the effect of food intake of VAL release from SD-floating gel *in-situ* formulations. We observed the pH-dependent drug release from the dissolution study where it released the drug faster in less acidic media. Essentially, the release of the drug could be prolonged in less acidic media, such as in fed-state simulated gastric fluid (FeSSGF), by letting it sit in more acidic media (fasted-state simulated gastric fluid/FaSSGF) for at least two hours. Finally, to prove the efficacy of this approach, extensive *in vivo* experiments will now be conducted.

CRediT authorship contribution statement

Achmad Himawan: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Nana Juniarti Natsir Djide:** Methodology, Writing – original draft. **Sandra Aulia Mardikasari:**

Methodology, Writing – original draft. **Rifka Nurul Utami:** Methodology, Data curation. **Andi Arjuna:** Data curation, Writing – review & editing. **Ryan.F. Donnelly:** Writing – original draft, Writing – review & editing. **Andi Dian Permana:** Conceptualization, Writing – review & editing, Project administration, Funding acquisition, Validation, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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