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Universitas Hasanuddin

Andi Dian Permana <andi.dian.permana@farmasi.unhas.ac.id>

A manuscript number has been assigned

1 message

European Journal of Pharmaceutical Sciences <em@editorialmanager.com> Sat, Jul 17, 2021 at 11:54 AM
Reply-To: European Journal of Pharmaceutical Sciences <ejps@sdu.dk>
To: Andi Permana <andi.dian.permana@farmasi.unhas.ac.id>

Dear Dr. Andi Permana,

Your submission entitled "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" has been been assigned the following manuscript number: PHASCI-D-21-00937.

You will be able to check on the progress of your paper by logging on to Editorial Managers as an author.
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Thank you for submitting your work to this journal.

Kind regards,

Martin Brandl, Dr. rer. nat. habil
Editor In Chief
European Journal of Pharmaceutical Sciences

BUKTI REVIEW DARI REVIEWERS

Universitas Hasanuddin

Andi Dian Permana <andi.dian.permana@farmasi.unhas.ac.id>

Your Submission

1 message

European Journal of Pharmaceutical Sciences <em@editorialmanager.com> Sun, Oct 24, 2021 at 10:10 PM
Reply-To: European Journal of Pharmaceutical Sciences <ejps@sdu.dk>
To: Andi Permana <andi.dian.permana@farmasi.unhas.ac.id>

CC: christoph.saal@merckgroup.com

Ref.: Ms. No. PHASCI-D-21-00937R1
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
European Journal of Pharmaceutical Sciences

Dear Dr. Permana,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.
Also, if you are resubmitting the manuscript please specify the page of the PDF where the changes have been made

The revision should be submitted by 23/12/2021. If you cannot meet the above deadline, please contact me and explain why more time is needed. Extra time to revise manuscripts is granted on a case-by-case basis.

Note: While submitting the revised manuscript, please double check the author names provided in the submission so that authorship related changes are made in the revision stage. If your manuscript is accepted, any authorship change will involve approval from co-authors and respective editor handling the submission and this may cause a significant delay in publishing your manuscript.

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Yours sincerely

Christoph Saal, Dr. habil.
Section Editor
European Journal of Pharmaceutical Sciences

Reviewers' comments:

Reviewer #1: Title - 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

In the revised manuscript author has addressed all of my previous comments w/ either modification or justification. One minor comment regarding novelty still needs to be addressed., mentioned below. My recommendation is "Minor Revision" and manuscript can be accepted for publication after addressing following comment.

Comments-
1. Novelty: Provided justification is not entirely correct because the impact of different physiological conditions such as pH, buffer capacity, and ionic strength for Valsartan is reported. But may be use of VAL-SD-Modified release performance in biorelevant media could be additional information to the existing knowledge (https://doi.org/10.1080/10837450.2018.1536996)

Reviewer #2: The authors have met the referees' points and provided sufficient clarifications, therefore I recommend acceptance for publication.

Reviewer #3: The revised version of the manuscript shows some problems yet, and it should be revised:
- Table 1 - Are the units for the content of each component "%, v/w" or "%, w/v"?
- Line 285 - How much was the significance of the regression? It is necessary to show the value of p (compare fcalc with ftab).
- Line 604 - "50 ºC".

Data in Brief (optional):

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Universitas Hasanuddin

Andi Dian Permana <andi.dian.permana@farmasi.unhas.ac.id>

Submission Confirmation for PHASCI-D-21-00937R1

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European Journal of Pharmaceutical Sciences <em@editorialmanager.com> Tue, Oct 12, 2021 at 1:23 AM
Reply-To: European Journal of Pharmaceutical Sciences <ejps@sdu.dk>
To: Andi Permana <andi.dian.permana@farmasi.unhas.ac.id>

Ref.: Ms. No. PHASCI-D-21-00937R1
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

Dear Dr. Andi Permana,

European Journal of Pharmaceutical Sciences has received your revised submission.

You may check the status of your manuscript by logging onto Editorial Managers at https://www.editorialmanager.com/phasci/.

Kind regards,

European Journal of Pharmaceutical Sciences

International Journal of Pharmaceutics

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

--Manuscript Draft--

Manuscript Number:	IJPHARM-D-21-01621
Article Type:	Research Paper
Section/Category:	
Keywords:	Valsartan; Solid dispersion; Floating gel in situ system; Controlled release
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	Andi Dian Permana, Ph.D
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 hours 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, in 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.
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The Editor
International Journal of Pharmaceutics

June 14, 2021

Dear Sir/Madam,

I would like to submit our original manuscript entitled "**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**" by Himawan et al. for publication in *International Journal of Pharmaceutics.*

In this study, we developed a novel combination delivery approach consisting of floating *in-situ* gel and solid dispersion containing valsartan to both improve the solubility and sustaine the release of valsartan. 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). 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 hours 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, in can be hypothesized that the food intake did not affect the VAL release after 2 h in an empty gastric environment. 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.

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We believe that this finding will be of interest to the scientists working on pharmaceutical technology, pharmaceutics, polymer technology and correlation *in vitro* and *in vivo* evaluations. This manuscript has not been previously published in any language anywhere and that it is not under simultaneous consideration by another journal.

We appreciate your attention. We hope you will now consider publishing our research in *International Journal of Pharmaceutics* and look forward to hearing from you in due course.

Yours Sincerely,

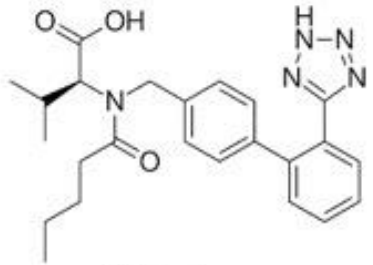
Andi Dian Permana (on behalf of all authors)
Faculty of Pharmacy
Hasanuddin University
Indonesia
Email: andi.dian.permana@farmasi.unhas.ac.id

Declaration of interests

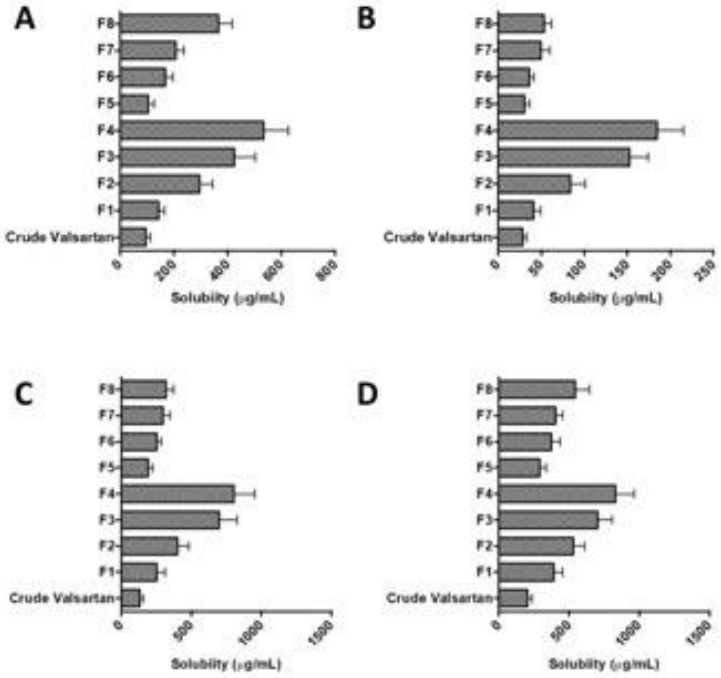
☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Graphical Abstract (for review)

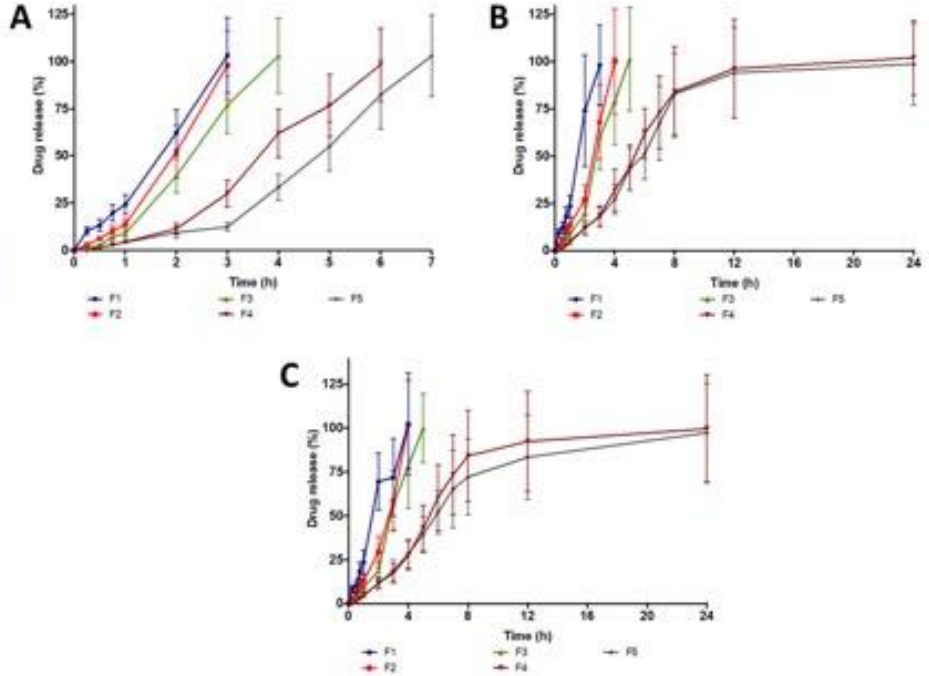


Valsartan



Improved solubility

Solid dispersion in floating *in-situ* gel



Sustained the release of valsartan in Fasted-State Simulated Gastric and FluidFed-State Simulated Gastric Fluid

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[1,2], Nana Juniarti Natsir Djide[1], Sandra Aulia Mardikasari[1], Rifka Nurul Utami[1], Andi Arjuna[1], Ryan. F. Donnelly[2], Andi Dian Permana[1*]

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Faculty of Pharmacy, Hasanuddin University, Makassar, Indonesia

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 hours 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, in 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.

Keywords: Valsartan, Solid dispersion, Floating gel in situ system, Controlled release

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). Its oral bioavailability is relatively low (23-39%) due to its poor water solubility and relatively short half-life (<6 hours). In the systemic circulation, VAL experiences extensive first-pass hepatic metabolism in the liver. It also possesses a high P-gp efflux and shows fluctuating oral bioavailability if taken in the presence of foods. These properties negatively affect its pharmacokinetics by decreasing the AUC by 40% and peak plasma concentration by 50% (Beg et al., 2012; Husseiny et al., 2018)

Several systems have been studied to improve the water solubility of drug substances, including solid dispersion (SD) (Yan et al., 2012). An SD is a drug dispersion in an amorphous polymer matrix, especially hydrophilic polymer such as PVP and PEG, where the drug is preferably in the molecularly dispersed state (dos Santos et al., 2018). The dispersed state has encompassed many forms, such as crystalline/glass solutions, eutectic mixtures, and amorphous/crystalline suspensions (Huang and Dai, 2014). A polymeric SD is considered an effective means to overcome API with low water solubility. Mechanisms contributing to the enhancement of API aqueous solubility and dissolution profile include inherently higher amorphous API apparent solubility, API dissolution in the carrier matrix, increasing particle porosity, reduced particle size , reduced agglomeration and aggregation (Krstić et al., 2020).

Synthetic hydrophilic polymers are often used in SD, due to their various advantages. 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 non-toxic, has extensive drug compatibility and high hydrophilicity. These characteristics make PEG 6000 a popular choice because it offers promising outcomes and flexibility in choosing a fabrication method (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., 2021a)

As mentioned previously, one of the reasons for biolow availability 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 drug formulations with specific therapeutic purposes have been designed based on the active ingredients' physiochemical, pharmacological, and pharmacokinetics properties (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). GRDDS may improve the bioavailability of drug molecules by maintaining continuous drug release in the gastrointestinal tract due to increased gastric residence time. Furthermore, using this system makes it possible to reduce the dosing frequency of

drugs and may help improve patient compliance. GRDDS could be beneficial, especially for drugs with a short half-life (Mahmoud et al., 2019; Shakya et al., 2013).

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 Sivaneswari, 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 will 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 mitiglinide calcium, an antidiabetic drug with a very short half-life and prolonged it release for 24 hours period (Mahmoud et al., 2019). Similarly, pregabalin (half-life 3-6 hours), 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 hours period (Madan et al., 2015).

In the present work, we report for the first time, 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). 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

Materials used in this research were valsartan, poly(vinyl pyrrolidone) (PVP) K-30, poly(ethylene) (glycol) (PEG) 6000, sodium alginate, hydroxyproplylmethyl cellulose (HPMC) K-100, sodium bicarbonate, calcium chloride, hydrochloric acid, acetonitrile, sodium dihydrogen phosphate, and distilled water. 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. The ingredients were listed in Table 1. All components were dissolved in 25 ml methanol. The solution was then poured into an evaporation dish and let air-dried at room temperature for 48 hours. The dries mass was then recovered, ground into powders, and stored in airtight containers.

Table 1. Formulation chart of valsartan solid dispersion system

	Formula Composition		
	Valsartan (g)	PVP K30 (g)	PEG 6000 (g)
F1	1	1	-
F2	1	2	-
F3	1	3	-
F4	1	4	-
F5	1	-	1
F6	1	-	2
F7	1	-	3
F10	1	-	4

149 *2.2.2. Analytical Method*

150 Valsartan concentrations in all the samples were quantified using an isocratic HPLC
151 method. The HPLC analysis of valsartan was carried out using a reverse-phase system
152 with LC-20A quaternary gradient pump with SPD-20A UV-Vis detector (Shimadzu
153 Prominence, Shimadzu, Kyoto, Japan). A Zorbax Eclipse Plus C18 column (Agilent,
154 4.6 x 150 mm) with a particle size of 5 µm was used as the stationary phase, and a mixture
155 of acetonitrile and water adjusted to pH 2.5 with water (40:60 v/v) was used as the mobile
156 phase. The process was carried out at 25°C with a flow rate of 1.0 mL/min and an injection
157 volume of 50 µL. Samples were measured at 275 nm using a UV detector.

158 A series of VAL solutions in various concentrations were prepared and measured using
159 the HPLC system explained above. The calibration curve was then constructed by plotting
160 concentration and peak area obtained from the chromatogram, which was then further
161 analyzed using linear regression, establishing the regression equation, coefficient of
162 determination, and residual sum of squares (RSS). The calibration curves were
163 constructed for three consecutive days to determine the linearity of the method. Limit of
164 Detection (LoD) and Limit of Quantification (LoQ) were calculated based on the standard
165 deviation of the calibration curve as per International Conference on Harmonization
166 (ICH) guidelines. The equation for LoD and LoQ were as follow:

167 $$LoD = \frac{3.3\,\sigma}{S} \quad (1)$$
168
169 $$LoQ = \frac{10\sigma}{S} \quad (2)$$
170

171 where σ is the standard deviation of the response and S is the slope of the calibration
172 curve. Three different concentrations of VAL solutions were prepared to represent the
173 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. 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 50 ml of methanol until fully dissolved with the aid of a sonicator bath for 30 minutes. 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 hours. After 24 hours, the solution was filtered, and the amount of VAL in the solution was determined using the abovementioned HPLC method.

2.2.5. Thermal Analysis

The VAL-SD with the highest solubility was subjected to differential scanning calorimetry (DSC) measurement using DSC 2920 (TA Instruments). Pure VAL was chosen as a comparison and both samples were scanned from 0 to 300°C. This measurement was performed to confirm the formation of a SD system.

2.2.6. X-Ray Diffraction Study.

Solid-state analysis was performed using an X-Ray diffractometer. XRD Instrument by Rigaku Corporation is used, and both the best VAL-SD and VAL were scanned from 5-60° 2θ.

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°). After the homogenous alginate dispersion was formed and cooled, sodium bicarbonate, calcium chloride, HPMC K-100, and Val-SD powder were added (Table 2). The mixture was then homogenized and stored in airtight containers before evaluation. Only Val-SD with the highest solubility was used for this section forward.

Table 2. Formulation chart of VAL-SD floating in-situ gel system

	Val-SD (Equal to Valsartan)	HPMC K100	Sodium Alginate	$NaHCO_3$	$CaCO_3$	Distilled Water
F1	1	0	2	1	1	up to 100 mL
F2	1	0,25	2	1	1	
F3	1	0,5	2	1	1	
F4	1	0,75	2	1	1	
F5	1	1	2	1	1	

2.2.8. In Vitro Gelation Study.

An *in vitro* gelation study of each of the formulation was carried out. 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 degree of gelling was scored visually (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.

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 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 hours, and 3 hours 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 hours, and samples were collected promptly. New dissolution media was added to the test vessel after each sampling with an equal volume of fluid taken. The amount of released drug was determined using the validated HPLC method.

2.2.12. Drug Release Profile Comparison and Kinetics

The difference (f_1) and similarity factor (f_2) calculations based on in vitro dissolution data were carried out using the following equations:

$$f_1 = \left\{\frac{\sum_{t=1}^{n}(R_t - T_t)}{\sum_{t=1}^{n} R_t}\right\} \times 100 \quad (3)$$

$$f_2 = 50 \times \log\left\{\frac{1}{\sqrt{1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2}} \times 100\right\} \quad (4)$$

In those equations, n is the sampling time, R_t is the reference dissolution percentage at time t, and T_t is the test dissolution percentage at time t. The difference factor (f_1) is the difference percentage between two dissolution rates at the overall sampling points. The similarity factor (f_2) is the logarithmic square-root transformation of the difference between the two formulations. The comparison will be concluded as similar if the value of f1 is lower than 15 and f2 is greater than 50 (Aliyah et al., 2021).

The dissolution kinetics of the formulations were determined using the best-fitted regression method based on the coefficient of correlation of the equations. Five different mathematical models were used to predict the dissolution profile of the formulation across all tested media. The equations were as follow:

$$Zero\ Order\ Kinetics: C_t = C_0 + k_0 t \quad (5)$$

$$First\ Order\ Kinetics: \ln C_t = \ln C_0 + k_1 t \quad (6)$$

$$Higuchi\ Model: C_t = k_H \sqrt{t} \quad (7)$$

$$Korsmeyer - Peppas\ Model: C_t = k_{KP} t^n \quad (8)$$

$$Hixson - Crowell\ Model: C_t^{1/3} = C_0^{1/3} k_{HC} t \quad (9)$$

C_t is the concentration of dissolved drug at time t, C_0 is the initial concentration of the drug in test media (at t=0), k_0 is zero-order kinetics constant, k_1 is first-order kinetics constant, k_H is Higuchi model constant, k_{KP} is Korsmeyer-Peppas model constant, and k_{HC} is Hixson-Crowell model constant. All calculations were performed using DD-solver software (Aliyah et al., 2021).

3. Results and Discussions

VAL is an antihypertensive drug whose effect arises from its antagonist action on angiotensin-II receptors. VAL is given orally with the dosage ranging from 20 mg up to 320 mg daily, depends on the underlying patient's condition. VAL bioavailability is low, ranging from 23% to 39% in humans, due to its low water solubility at a low pH value. VAL is a weak acid with pH-dependent aqueous solubility where its solubility increases as the pH rise. With two pKa values (3.9 and 4.73), VAL molecules will be unionized at pH values below 3.9 and ionized at pH values above 4.73 (Xu et al., 2016). These properties serve as a challenge for drug formulation containing VAL. In order to be absorbed faster through the oral route, the absorption process should occur in the gastric juice, as it is independent on the gastric emptying time. In this study, we propose a novel formulation combining two approaches: solubility improvement in acidic media by incorporating VAL into the SD system while simultaneously retaining its release in the stomach *via in situ* floating gel formation.

SD provides definite advantages in the solubility improvement of a poorly soluble drug. It is a relatively simple approach that takes advantage of the interaction of hydrophobic drugs with hydrophilic carriers. SD that exploits amorphous polymeric material as the carrier matrix is considered a second-generation SD and still widely studied until recent time. PEG and PVP are among the most used polymeric materials in an SD system. The properties and advantages of these polymers have been described and demonstrated in various studies (Afifi, 2015; Bley et al., 2010; Febriyenti et al., 2019; Lima et al., 2011; Zhai et al., 2017). An SD-containing polymeric matrix can be formed *via* multiple techniques such as melting, kneading, solvent evaporation, spray-drying, and lyophilization. The method selected depends on the properties of the drug and polymer used. The advantages and disadvantages of each of the processes also need to be considered.

PEG is a polymer of ethylene oxide with a wide-range molecular weight (200 to 300.000). Solid PEG is an interesting material used in SD formulations. It possesses unique characteristics, including its capability to form solid drug solutions, low melting point, fast solidification rate, nontoxic, and relatively cheap price (Eloy and Marchetti, 2014). PVP is an amorphous polymer (unlike PEG, which is semi-crystalline) with good biocompatibility and water solubility. It is used extensively in SD preparation as it offers many advantages, and one of the most prominent ones is the ability to stabilize amorphized drug crystals (Wang et al., 2017). 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. Eight different types of SDs with varying drug to polymer ratio and polymer composition

(composition according to Table 1.) were prepared in this study to compare the performance of PVP K-30 and PEG 6000 as a single polymeric carrier.

3.1. Analytical Method Validation

A HPLC method was developed and optimized for the quantification of VAL in testing media. The validation of the analytical method was completed per ICH guidelines. The LOD and LOQ values of the validated method were 1.06 µg/mL and 3.23 µg/mL in FaSSGF media. In FeSSGF media, the LOD and LOQ were 0.53 µg/mL and 1.62 µg/mL respectively. We found these values satisfactory for *in vitro* test used in this research. This method has a linearity range between 0.5 µg/mL and 50.0 µg/mL with R-squared >0.9995 both for FaSSGF and FeSSGF. 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., 2021b, 2019)

3.2. Saturation Solubility

We assessed the performance of the SD using the solubility test on four different media with different pH values, as shown in Figure 1. We 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 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 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).

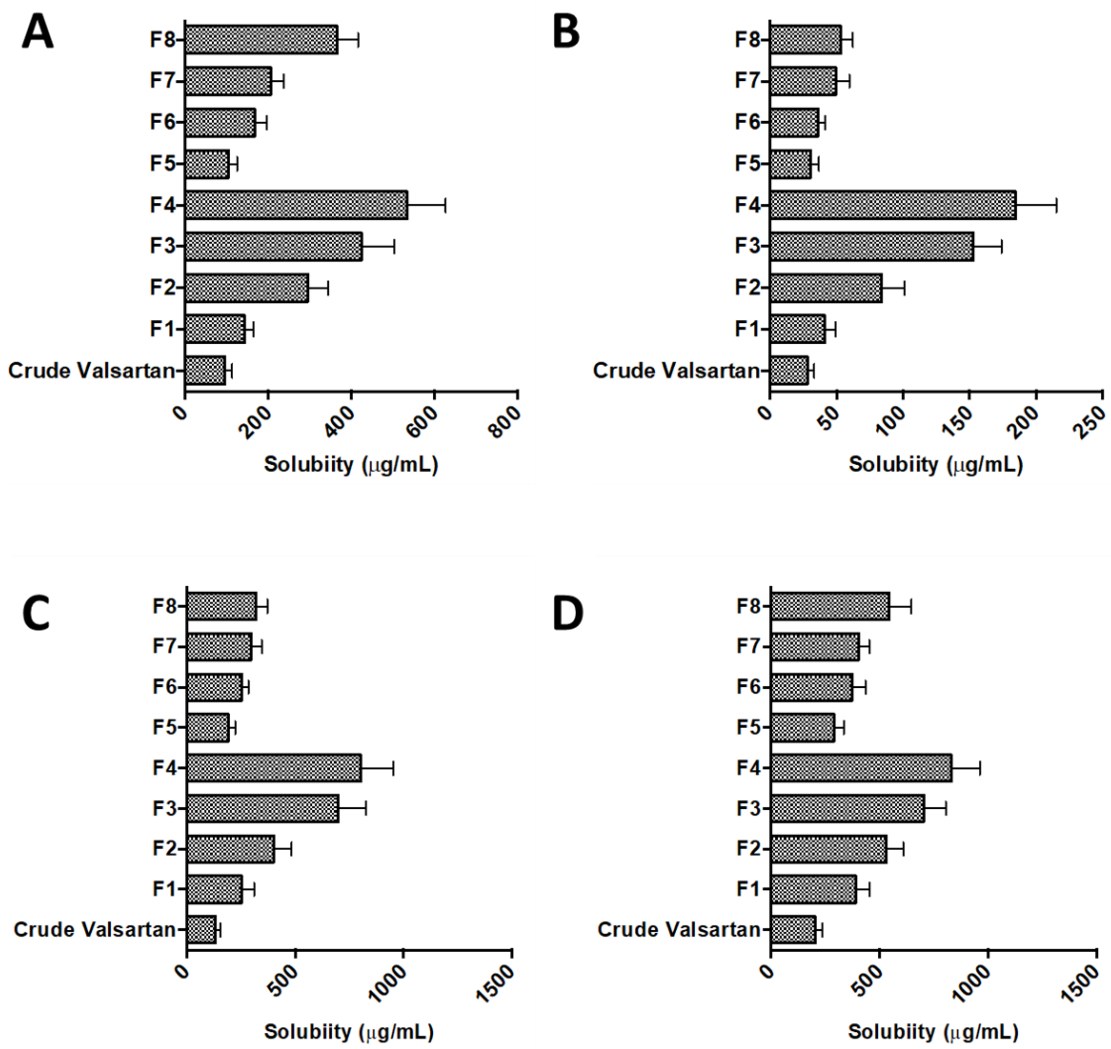

Figure 1. Saturation solubility study results of the SD formulation in (A) water, (B) HCl 0.1 M pH 1.2, (C) phosphate buffer pH 6.8 and (D) phosphate buffer pH 7.4 (means ± SD, *n* = 3)

3.3. Thermal Analysis

To further confirm the formation of the VAL-SD, we investigated the final mixture (F3) using DSC techniques. Valsartan has a corresponding melting point at 116.7°C, as shown in figure 2 (left) (A) by a sharp endothermic peak in that value. Compared to VAL-

SD (B), no sharp melting peak was observed in the thermogram. 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.

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 amorphize 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).

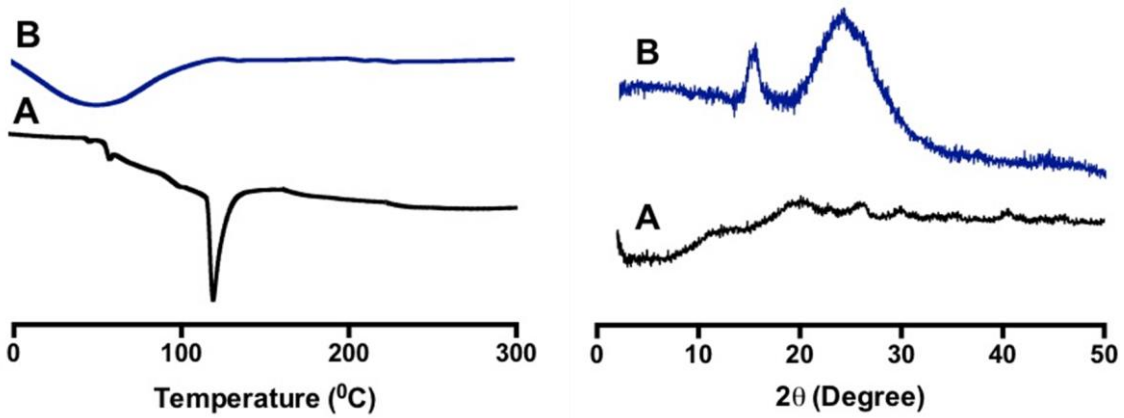

Figure 2. Thermogram (left picture) and Diffractogram (right picture) of (A) Valsartan and (B) VAL-SD

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 Figure 2 (right), VAL (A) showed a broad peak around 12° and 22°, indicating that the plain VAL was a crystalline powder. In contrast, the flat diffractogram of VAL-SD indicated that the system was indeed an amorphous solid with no trace of crystallinity. 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. This diffractogram agrees with the DSC results in confirming the amorphous nature of the VAL-SD.

3.5. Viscosity, In Vitro Gelation Time, Floating Time, and Gel Strength Measurement

Ion crosslinking-based *in-situ* gel delivery system for a gastroretentive 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 homogenously 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 CO_2 source. Maintaining the amount of $CaCO_3$ 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 Figure 3.A. We found that the viscosity of the formulations was between 219 ± 16 cps to 1103 ± 75 cps, with significant differences between 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.

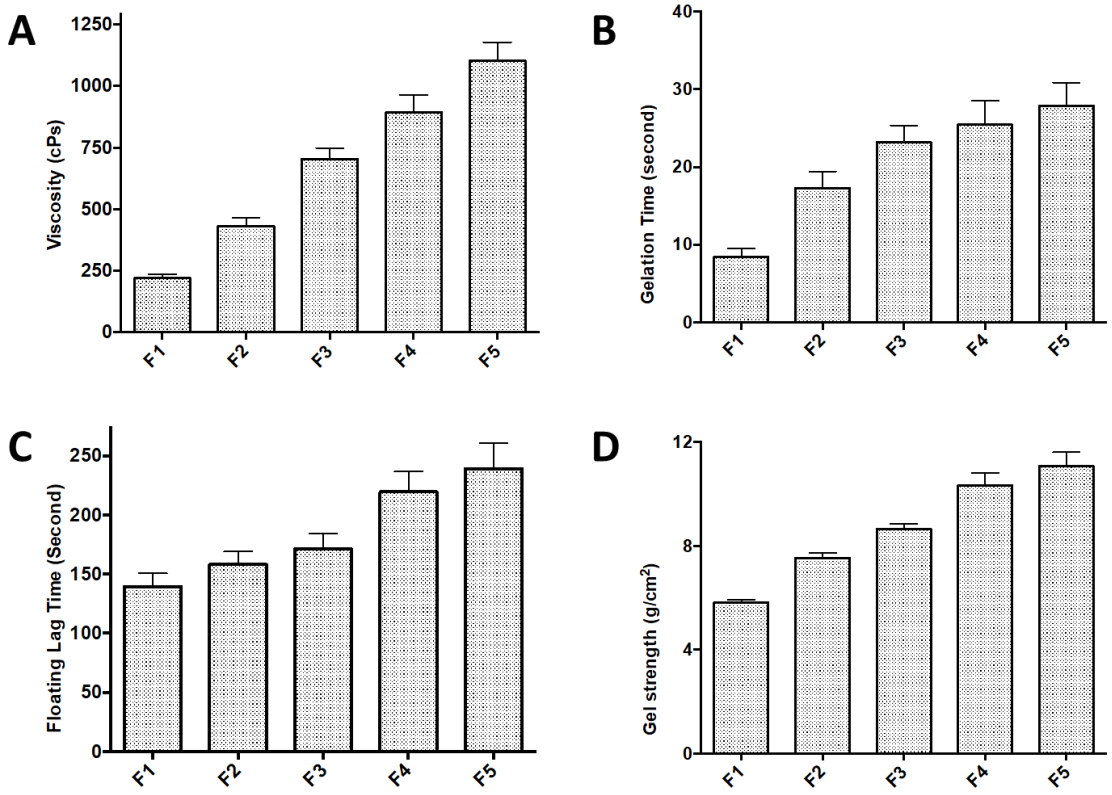

Figure 3. Comparison of (A) viscosity, (B) gel strengths, (C) gelation time and (D) floating lag time of all *in-situ* gel VAL-SD formulation (means ± SD, n = 3)

All studied formulations showed that they were capable of forming a gelled body upon contact with acidic media with gelation time below 30 seconds (Figure 3.B). 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 (Ca^{2+}) ion to form a crosslinked "egg-box" structure (Dodero et al., 2019). The calcium carbonate in this formulation was the source of the Ca^{2+} 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 Ca^{2+} 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 (CO_2) bubbles inside the gel network (Karemore and Avari, 2019). The CO_2 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, 2019). Availability of Ca^{2+} and CO_3^{2-} is vital during this phase as the CO_2 entrapment is greatly affected by the integrity of the outer gel barrier. Lower Ca^{2+} 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 CO_2 were used in this study, which were calcium carbonate and sodium bicarbonate, to improve the buoyancy of the preparation. The CO_2 gas from sodium bicarbonate helps the floating systems to gain more buoyancy without

adding extra Ca^{2+} 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 (Figure 3.C) and stayed buoyant even after 24 hours. The results showed that, as the HPMC concentration in the formulation 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).

Figure 3.D 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, 2019). If the gel failed to maintain its integrity and broke down when agitated in the gastric environment, it would be diffucult to achieve a consistent drug release profile. All formulations maintained structural integrity, and the gel strength of the gelled body can be seen in Figure 4.

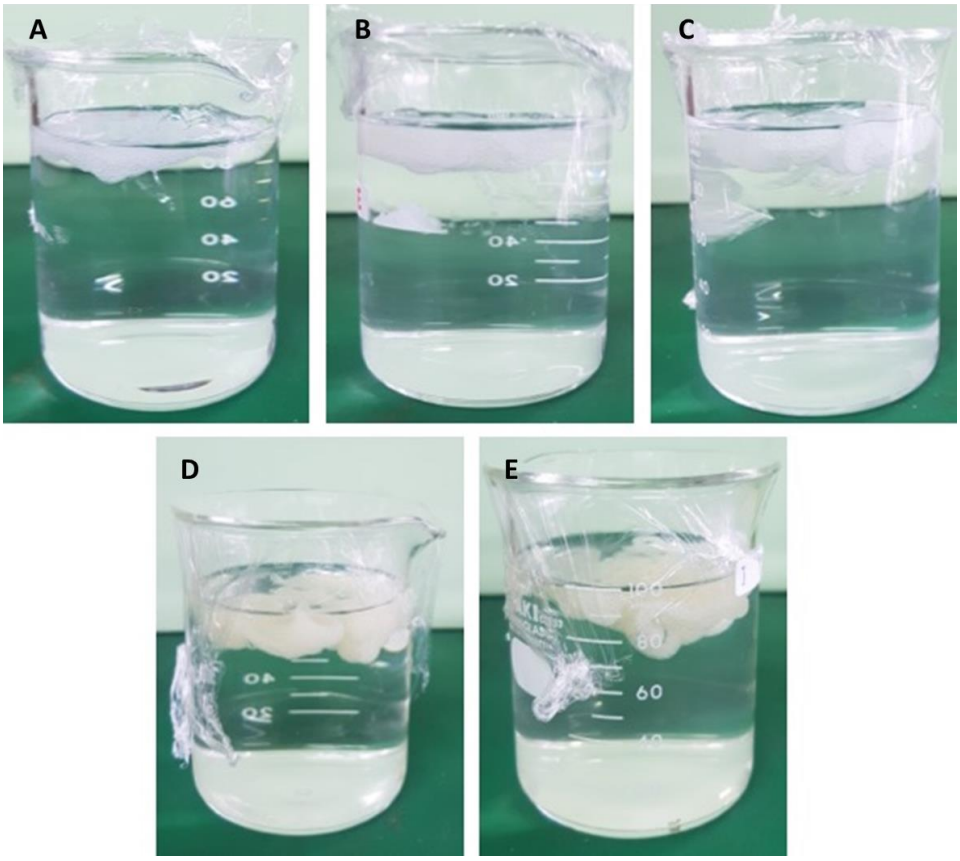

Figure 4. *In vitro* floating test of F1 (A), F2 (B), F3, (C), F4 (D) and F5 (E)

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. 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 released vs time of all formulation can be seen in Figure 5 and Figure 6.

The graph in Figure 5 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 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).

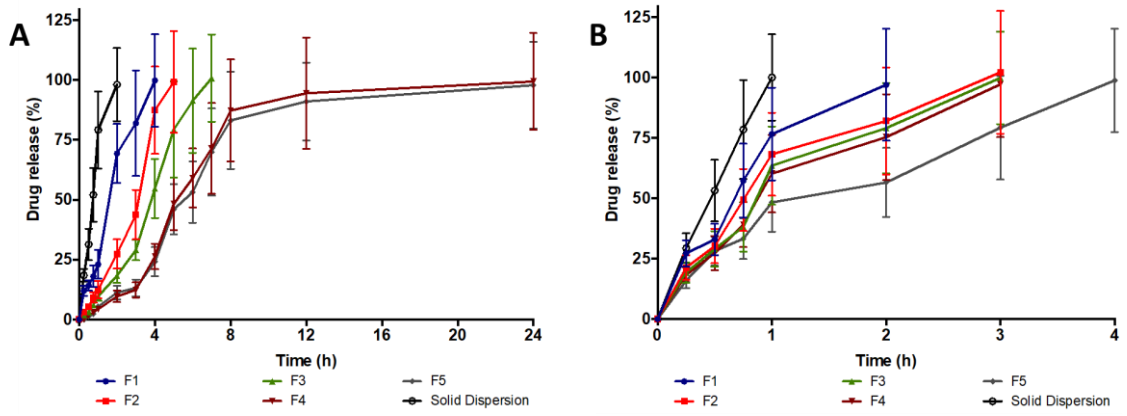

Figure 5. *In vitro* dissolution study of in-situ gel formulation in (A) FaSSGF and (B) FeSSGF (means ± SD, n = 3)

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 hours and 8 hours, while F4 and F5 can retain the drug up to 24 hours 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. 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.

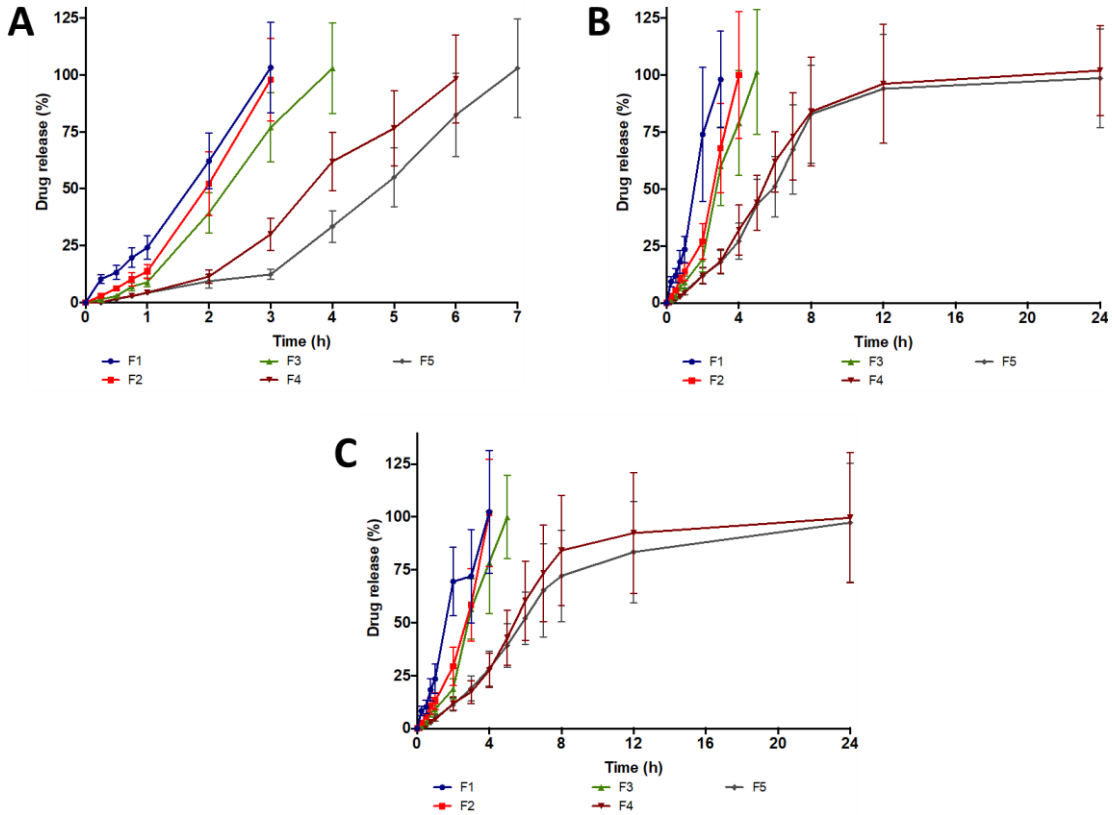

Figure 6. *In vitro* dissolution study of in-situ gel formulation in FeSSGF after (A) 1 hour in FaSSGF/condition C, (B) 2 hours in FaSSGF/condition D, and (C) 3 hours in FaSSGF/condition E (means ± SD, n = 3)

In this research, a comparison of the dissolution profile of the formulation in FeSSGF after it spent 1 hour, 2 hours and 3 hours 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 juice. 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 Figure 6. The difference between conditions can be seen from the graph, most notably when the floating *in-situ* gel spent 1 (condition C) hour and 2+ hours (condition D and 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 hours while in condition D and E, F4 and F5 were able to retain the drug and release it slowly in 24 hours.

The release profile difference in different media between formulations and the release profile of formulations between dissolution conditions were established using the similarity factor formula. Ten comparisons for each formula and 15 comparisons for each condition were made and calculated. The similarity factor results are shown in Table 3 and Table 4. When comparing conditions A and B (FaSSGF and FeSSGF media only), the results confirmed that all formulation exhibited different profiles that became more prominent as HPMC concentration increases. All formulations performed similarly in conditions A, D, and E, which proved that the formulation only partially possessed a pH-dependent release profile during the first two hours of gel-forming reaction. This property was further confirmed by the similarity results of F1 in comparison between different media. Some calculations showed "borderline" results, where only one criterion (usually f1) was fulfilled while the other one was not fulfilled with a slight deviation from the requirements. F3 showed this borderline behavior, while F4 and F5 showed drastic differences in performance in different test media. The comparison between formulae disclosed an exciting result, as it further confirmed the similarity between F4 and F5, which exhibited similar performances almost at every testing condition, except condition C. The outcome also verified that adding HPMC to the formulation gave a significant difference to the dissolution profile of the floating in-situ gel preparation. Interestingly, in FeSSGF, almost all formulations possessed similarities compared to each other, except when compared to F5 or sole VAL-SD.

Table 3. Comparison between five different dissolution condition of all formulation (F1-F5) and VAL-SD (The comparisons that were concluded as "different" were highlighted)

Curve 1	Curve 2	F1		F2		F3		F4		F5		VAL-SD	
		f1	f2	f1	f2	f1	f2	f1	f2	f1	f2	f1	f2
A	B	20.64	33.31	36.13	25.58	48.59	22.66	93.63	17.24	90.94	19.41	9.11	46.64
A	C	6.28	58.34	12.84	38.68	23.43	33.78	31.90	35.88	24.35	42.15	-	-
A	D	4.20	64.99	5.71	55.78	13.43	44.52	5.89	74.58	4.22	81.10	-	-
A	E	3.92	71.10	6.30	60.74	12.57	46.29	4.36	78.82	8.55	65.42	-	-
B	C	23.03	32.75	25.33	32.61	30.69	31.53	63.39	22.95	74.77	22.04	-	-
B	D	15.25	34.00	22.45	28.28	25.25	27.27	47.62	17.99	47.14	19.65	-	-
B	E	20.97	32.02	21.99	27.66	24.82	26.90	48.58	17.55	49.92	19.17	-	-
C	D	5.43	63.56	6.62	47.94	6.85	50.06	15.68	37.06	13.37	40.99	-	-
C	E	4.86	52.20	8.58	44.26	8.23	48.32	16.62	35.85	16.18	37.72	-	-
D	E	6.67	54.67	3.03	74.60	1.66	87.87	2.34	83.47	5.41	67.24	-	-

Notes: Condition A= FaSSGF, Condition B= FeSSGF, Condition C= 1 hour in FaSSGF then continued to FeSSGF, Condition D= 2 hours in FaSSGF then continued to FeSSGF, Condition C= 3 hours in FaSSGF then continued to FeSSGF

Table 4. Comparison between release profile of all formulation (F1-F5) and VAL-SD in five different dissolution condition (The comparisons that were concluded as "different" were highlighted)

Curve 1	Curve 2	Condition A		Condition B		Condition C		Condition D		Condition E	
		f1	f2	f1	f2	f1	f2	f1	f2	f1	f2
F1	F2	14.49	38.56	7.58	57.99	9.02	57.78	13.05	39.66	9.26	45.19
F1	F3	24.90	29.63	7.94	52.70	10.29	46.47	18.93	34.64	15.72	38.18
F1	F4	43.57	20.33	6.79	50.94	28.81	26.42	43.07	20.09	43.57	20.74

F1	F5	45.58	19.79	13.07	39.20	35.85	20.53	45.45	19.07	48.00	19.50
F1	SD	18.62	33.83	8.80	48.43	-	-	-	-	-	-
F2	F3	12.74	46.02	3.77	69.53	8.49	54.83	6.30	57.78	6.46	56.15
F2	F4	34.06	27.51	6.55	61.88	22.04	29.97	36.21	24.92	37.81	24.09
F2	F5	36.36	26.37	10.74	45.62	34.04	22.94	39.16	23.29	42.69	22.46
F2	SD	37.41	23.25	11.87	41.58	-	-	-	-	-	-
F3	F4	25.73	37.00	3.07	78.15	20.36	34.28	30.96	27.79	30.70	27.77
F3	F5	28.38	34.92	7.24	50.71	28.11	25.27	34.26	25.82	35.58	25.66
F3	DP	55.78	19.56	12.97	37.56	-	-	-	-	-	-
F4	F5	4.91	78.31	6.92	54.12	12.23	45.63	3.83	70.06	6.14	62.96
F4	DP	106.04	14.44	16.34	36.27	-	-	-	-	-	-
F5	DP	113.12	14.20	21.79	30.46	-	-	-	-	-	-

Notes: Condition A= FaSSGF, Condition B= FeSSGF, Condition C= 1 hour in FaSSGF then continued to FeSSGF, Condition D= 2 hours in FaSSGF then continued to FeSSGF, Condition C= 3 hours in FaSSGF then continued to FeSSGF

The dissolution data were fitted into five mathematical models to determine the release kinetic of the drug from the formulation. The VAL-SD alone exhibits a Hixson-Crowell (HC) release model in simulated fed media and Korsmeyer-Peppas (KP) model in the simulated fed media. In a more acidic fasted simulated media, the dissolution of the drugs occured in planes parallel to the solid surface while the SD particles diminish slowly. The geometrical form of the particles stayed constant during the dissolution process. This kinetic model is usually observed in solid preparation like tablets. VAL-SD dissolution kinetics most likely followed a non-Fickian diffusion (anomalous transport) in fed state simulated media. KP model is usually observed in a polymeric drug delivery system. Because the VAL-SD carrier is a polymeric material, swelling-relaxation of the polymer and the Fickian diffusion may be involved to a certain degree simultaneously (Costa and Sousa Lobo, 2001; Liu et al., 2010).

The dissolution kinetics of all formulations were evaluated, and the results were given in Tables 5 and 6. F1, F2, and F3 generally followed KP models except in FeSSGF, where they followed HC kinetic model. These outcomes were expected as floating *in-situ* gels fall into the polymeric delivery system category. The majority of the formulation showed n values greater than one, which means they follow super class-II transport of non-Fickian diffusion. In this case, the drugs' release was ruled by the macromolecular relaxation of the polymeric chain.

Interestingly, F4 and F5 behave in a HC kinetic manner most of the time, except in condition C of the dissolution test. F5 also had a similar release model in condition B. A more complex mechanism may rule the general release of the drug. We propose three central mechanisms that govern the dissolution process significantly. First, the polymeric structure that degraded over time should be considered, especially in the less acidic

environment. The second, which also may be related to the first one, was the pH of the test media, as it could affect the rigidity and integrity of the gel network. Lastly, the VAL-SD was incorporated into the preparation as an insoluble solid due to the minimum amount of water available for solubilization inside the formulation. This situation means that the VAL-SD needed to be dissolved first inside the gelled structure then the molecule will diffuse through the network into the media. The VAL-SD particle could also be released from the gel matrix when degraded/eroded during the dissolution process and dissolved in test media.

Table 5. Release kinetics fitted into different models based on *in vitro* release data for all formulation and VAL-SD alone in FaSSGF and FeSSGF (The models that were considered to be most fitted with the data for each formulation were highlighted)

	Formulation	R-squared value fitted into different models				
		ZO	FO	HG	KP	HC
FaSSGF	F1	0.9573	0.9114	0.8245	**0.9647**	0.9476
	F2	0.9481	0.8317	0.7067	**0.9790**	0.8705
	F3	0.9662	0.8589	0.7520	**0.9842**	0.8969
	F4	0.6719	**0.9685**	0.8000	0.8322	0.9233
	F5	0.6926	0.9085	0.8097	0.8453	**0.9304**
	SD	0.8027	0.9062	0.8462	0.9165	**0.9451**
FeSSGF	F1	0.6887	0.9323	0.9002	0.9318	**0.9593**
	F2	0.6415	0.9628	0.9412	0.9516	**0.9673**
	F3	0.7655	0.957	0.9286	0.9595	**0.9681**
	F4	0.7765	0.9675	0.9346	0.9668	**0.9717**
	F5	0.8042	0.9491	0.9557	**0.9794**	0.9407
	DP	0.9908	0.8696	0.8418	**0.9994**	0.934

Table 6. Release kinetics fitted into different models based on *in vitro* release data for all formulation and VAL-SD alone in FeSSGF after undergoing dissolution for 1 hour, 2 hours, and 3 hours in FaSSGF

	Formulation	R-squared value fitted into different models				
		ZO	FO	HG	KP	HC
1 hour in FaSSGF	**F1**	0.9785	0.8377	0.7167	**0.9942**	0.8855
	F2	0.9145	0.7747	0.6032	**0.9984**	0.8184
	F3	0.9403	0.8076	0.6601	**0.9901**	0.8511
	F4	0.9236	0.8123	0.665	**0.9873**	0.8483
	F5	0.8720	0.7522	0.611	**0.9928**	0.788
2 hours in FaSSGF	**F1**	0.9682	0.8475	0.7191	**0.9765**	0.8943
	F2	0.9311	0.8040	0.6565	**0.9895**	0.8442
	F3	0.9436	0.8257	0.6898	**0.9823**	0.8652
	F4	0.6840	0.9207	0.8288	0.8587	**0.9452**
	F5	0.7051	0.9206	0.8256	0.8613	**0.9434**
3 hours in FaSSGF	**F1**	0.9567	0.8996	0.8023	**0.9590**	0.9335
	F2	0.9232	0.7964	0.6467	**0.9925**	0.8355
	F3	0.9432	0.8267	0.6871	**0.9853**	0.8655
	F4	0.6792	0.9145	0.8181	0.8487	**0.9374**
	F5	0.7437	0.9498	0.8562	0.8957	**0.9650**

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 FeSGGF from 2-h release in FaSGGF. 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 release behavior 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 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

690 could be prolonged in less acidic media, such as in fed-state simulated gastric fluid
691 (FeSSGF), by letting it sit in more acidic media (fasted-state simulated gastric
692 fluid/FaSSGF) for at least two hours. Finally, to prove the efficacy of this approach,
693 extensive *in vivo* experiments will now be conducted.

694 **References**

695 Abou Youssef, N.A.H., Kassem, A.A., El-Massik, M.A.E., Boraie, N.A., 2015.
696 Development of gastroretentive metronidazole floating raft system for targeting
697 Helicobacter pylori. Int. J. Pharm. 486, 297–305.
698 https://doi.org/10.1016/j.ijpharm.2015.04.004

699 Afifi, S., 2015. Solid dispersion approach improving dissolution rate of Stiripentol: A
700 novel antiepileptic drug. Iran. J. Pharm. Res. 14, 1001–1014.
701 https://doi.org/10.22037/ijpr.2015.1725

702 Aliyah, A., Utomo, E., Permana, A.D., Ernawati, 2021. Development of liquisolid
703 formulation for improved sustained release of propranolol hydrochloride. Int. J.
704 Appl. Pharm. 13, 210–216. https://doi.org/10.22159/ijap.2021v13i2.40354

705 Alves, L.D.S., De La Roca Soares, M.F., De Albuquerque, C.T., Da Silva, É.R., Vieira,
706 A.C.C., Fontes, D.A.F., Figueirêdo, C.B.M., Soares Sobrinho, J.L., Rolim Neto, P.J.,
707 2014. Solid dispersion of efavirenz in PVP K-30 by conventional solvent and
708 kneading methods. Carbohydr. Polym. 104, 166–174.
709 https://doi.org/10.1016/j.carbpol.2014.01.027

710 Baird, J.A., Taylor, L.S., 2012. Evaluation of amorphous solid dispersion properties using
711 thermal analysis techniques. Adv. Drug Deliv. Rev.
712 https://doi.org/10.1016/j.addr.2011.07.009

713 Baxevanis, F., Zarmpi, P., Kuiper, J., Fotaki, N., 2020. Investigation of drug partition
714 kinetics to fat in simulated fed state gastric conditions based on drug properties. Eur.
715 J. Pharm. Sci. 146, 105263. https://doi.org/10.1016/j.ejps.2020.105263

716 Beg, S., Swain, S., Singh, H.P., Patra, C.N., Rao, M.B., 2012. Development, optimization,
717 and characterization of solid self-nanoemulsifying drug delivery systems of
718 valsartan using porous carriers. AAPS PharmSciTech 13, 1416–1427.
719 https://doi.org/10.1208/s12249-012-9865-5

720 Bley, H., Fussnegger, B., Bodmeier, R., 2010. Characterization and stability of solid

721 dispersions based on PEG/polymer blends. Int. J. Pharm. 390, 165–173.
722 https://doi.org/10.1016/j.ijpharm.2010.01.039
723 Costa, P., Sousa Lobo, J.M., 2001. Modeling and comparison of dissolution profiles. Eur.
724 J. Pharm. Sci. https://doi.org/10.1016/S0928-0987(01)00095-1
725 Daihom, B.A., Bendas, E.R., Mohamed, M.I., Badawi, A.A., 2020. Domperidone resinate
726 complex as new formulation for gastroretentive drug delivery. J. Drug Deliv. Sci.
727 Technol. 58, 101868. https://doi.org/10.1016/j.jddst.2020.101868
728 Desai, N., Purohit, R., 2017. Development of novel high density gastroretentive
729 multiparticulate pulsatile tablet of clopidogrel bisulfate using quality by design
730 approach. AAPS PharmSciTech 18, 3208–3218. https://doi.org/10.1208/s12249-
731 017-0805-2
732 Dodero, A., Pianella, L., Vicini, S., Alloisio, M., Ottonelli, M., Castellano, M., 2019.
733 Alginate-based hydrogels prepared via ionic gelation: An experimental design
734 approach to predict the crosslinking degree. Eur. Polym. J. 118, 586–594.
735 https://doi.org/10.1016/j.eurpolymj.2019.06.028
736 dos Santos, K.M., Barbosa, R. de M., Vargas, F.G.A., de Azevedo, E.P., Lins, A.C. da S.,
737 Camara, C.A., Aragão, C.F.S., Moura, T.F. de L. e., Raffin, F.N., 2018.
738 Development of solid dispersions of β-lapachone in PEG and PVP by solvent
739 evaporation method. Drug Dev. Ind. Pharm. 44, 750–756.
740 https://doi.org/10.1080/03639045.2017.1411942
741 Eloy, J.O., Marchetti, J.M., 2014. Solid dispersions containing ursolic acid in Poloxamer
742 407 and PEG 6000: A comparative study of fusion and solvent methods. Powder
743 Technol. 253, 98–106. https://doi.org/10.1016/j.powtec.2013.11.017
744 Febriyenti, F., Rahmi, S., Halim, A., 2019. Study of gliclazide solid dispersion systems
745 using PVP K-30 and PEG 6000 by solvent method. J. Pharm. Bioallied Sci. 11, 262–
746 267. https://doi.org/10.4103/jpbs.JPBS_87_18
747 Huang, Y., Dai, W.-G., 2014. Fundamental aspects of solid dispersion technology for
748 poorly soluble drugs. Acta Pharm. Sin. B 4, 18–25.
749 https://doi.org/10.1016/j.apsb.2013.11.001
750 Huang, Y., Zhang, Q., Wang, J.R., Lin, K.L., Mei, X., 2017. Amino acids as co-
751 amorphous excipients for tackling the poor aqueous solubility of valsartan. Pharm.
752 Dev. Technol. 22, 69–76. https://doi.org/10.3109/10837450.2016.1163390

753 Husseiny, R.A., Abu Lila, A.S., Abdallah, M.H., El-ghamry, H.A., 2018. Fast
754 disintegrating tablet of Valsartan for the treatment of pediatric hypertension: In vitro
755 and in vivo evaluation. J. Drug Deliv. Sci. Technol. 43, 194–200.
756 https://doi.org/10.1016/j.jddst.2017.10.014
757 Hwang, Kyu Mok, Nguyen, T.T., Seok, S.H., Jo, H. Il, Cho, C.H., Hwang, Kyu Min,
758 Kim, J.Y., Park, C.W., Rhee, Y.S., Park, E.S., 2019. Swellable and porous bilayer
759 tablet for gastroretentive drug delivery: Preparation and in vitro-in vivo evaluation.
760 Int. J. Pharm. 572, 118783. https://doi.org/10.1016/j.ijpharm.2019.118783
761 ICH, 2005. Validation of analytical procedures: text and methodology Q2 (R1). ICH
762 harmonised tripartite guideline.
763 Jafar, M., Salahuddin, M., Bolla, S.R., 2018. Gastric floating in-situ gel as a strategy for
764 improving anti-inflammatory activity of meloxicam. J. Appl. Pharm. Sci.
765 https://doi.org/10.7324/JAPS.2018.81114
766 Jahangiri, A., Barzegar-Jalali, M., Garjani, A., Javadzadeh, Y., Hamishehkar, H.,
767 Rameshrad, M., Adibkia, K., 2015. Physicochemical characterization and
768 pharmacological evaluation of ezetimibe-PVP K30 solid dispersions in
769 hyperlipidemic rats. Colloids Surfaces B Biointerfaces 134, 423–430.
770 https://doi.org/10.1016/j.colsurfb.2015.07.025
771 Jung, H.J., Ahn, H.I., Park, J.Y., Ho, M.J., Lee, D.R., Cho, H.R., Park, J.S., Choi, Y.S.,
772 Kang, M.J., 2016. Improved oral absorption of tacrolimus by a solid dispersion with
773 hypromellose and sodium lauryl sulfate. Int. J. Biol. Macromol. 83, 282–287.
774 https://doi.org/10.1016/j.ijbiomac.2015.11.063
775 Karemore, M.N., Avari, J.G., 2019. In-situ gel of nifedipine for preeclampsia:
776 Optimization, in-vitro and in-vivo evaluation. J. Drug Deliv. Sci. Technol. 50, 78–
777 89. https://doi.org/10.1016/j.jddst.2019.01.025
778 Kathpalia, H., Salunkhe, S., Juvekar, S., 2019. Formulation of gastroretentive sustained
779 release floating in situ gelling drug delivery system of solubility enhanced curcumin-
780 soy lecithin complex. J. Drug Deliv. Sci. Technol.
781 https://doi.org/10.1016/j.jddst.2019.101205
782 Kim, J.Y., Seo, J.W., Rhee, Y.S., Park, C.W., Park, E.S., 2014. Freeze-dried highly
783 porous matrix as a new gastroretentive dosage form for ecabet sodium: In vitro and
784 in vivo characterizations. J. Pharm. Sci. 103, 262–273.

785 https://doi.org/10.1002/jps.23798
786 Krstić, M., Manić, L., Martić, N., Vasiljević, D., Mračević, S.Đ., Vukmirović, S.,
787 Rašković, A., 2020. Binary polymeric amorphous carvedilol solid dispersions: In
788 vitro and in vivo characterization. Eur. J. Pharm. Sci. 150.
789 https://doi.org/10.1016/j.ejps.2020.105343
790 Lee, K.Y., Mooney, D.J., 2012. Alginate: Properties and biomedical applications. Prog.
791 Polym. Sci. https://doi.org/10.1016/j.progpolymsci.2011.06.003
792 Lima, Á.A.N., Soares-Sobrinho, J.L., Silva, J.L., Corrêa-Júnior, R.A.C., Lyra, M.A.M.,
793 Santos, F.L.A., Oliveira, B.G., Hernandes, M.Z., Rolim, L.A., Rolim-Neto, P.J.,
794 2011. The use of solid dispersion systems in hydrophilic carriers to increase
795 benznidazole solubility. J. Pharm. Sci. 100, 2443–2451.
796 https://doi.org/10.1002/jps.22436
797 Liu, F., Deng, D., Chen, X., Qian, Z., Achilefu, S., Gu, Y., 2010. Folate-Polyethylene
798 Glycol Conjugated Near-Infrared Fluorescence Probe with High Targeting Affinity
799 and Sensitivity for In Vivo Early Tumor Diagnosis. Mol. Imaging Biol. 12, 595–
800 607. https://doi.org/10.1007/s11307-010-0305-1
801 Madan, J., Adokar, B., Dua, K., 2015. Development and evaluation of in situ gel of
802 pregabalin. Int. J. Pharm. Investig. 5, 226. https://doi.org/10.4103/2230-
803 973x.167686
804 Mahmoud, D.B., Shukr, M.H., ElMeshad, A.N., 2019. Gastroretentive cosolvent-based
805 in situ gel as a promising approach for simultaneous extended delivery and enhanced
806 bioavailability of mitiglinide calcium. J. Pharm. Sci. 108, 897–906.
807 https://doi.org/10.1016/j.xphs.2018.09.020
808 Mahmoud, D.B.E.D., Marzok, S., 2020. In situ supersaturable polyhydrogels: A feasible
809 modification of the conventional hydrogels for the enhanced delivery of stomach
810 specific hydrophobic drugs. J. Drug Deliv. Sci. Technol. 58, 101744.
811 https://doi.org/10.1016/j.jddst.2020.101744
812 Nappinnai, M., Sivaneswari, S., 2013. Formulation optimization and characterization of
813 gastroretentive cefpodoxime proxetil mucoadhesive microspheres using 32 factorial
814 design. J. Pharm. Res. 7, 304–309. https://doi.org/10.1016/j.jopr.2013.04.014
815 Naveen, N.R., Gopinath, C., Rao, D.S., 2017. Design expert supported mathematical
816 optimization of repaglinide gastroretentive floating tablets: In vitro and in vivo

817 evaluation. Futur. J. Pharm. Sci. 3, 140–147.
818 https://doi.org/10.1016/j.fjps.2017.05.003
819 Ng, C.L., Lee, S.E., Lee, J.K., Kim, T.H., Jang, W.S., Choi, J.S., Kim, Y.H., Kim, J.K.,
820 Park, J.S., 2016. Solubilization and formulation of chrysosplenol C in solid
821 dispersion with hydrophilic carriers. Int. J. Pharm. 512, 314–321.
822 https://doi.org/10.1016/j.ijpharm.2016.08.062
823 Oh, T.O., Kim, J.Y., Ha, J.M., Chi, S.C., Rhee, Y.S., Park, C.W., Park, E.S., 2013.
824 Preparation of highly porous gastroretentive metformin tablets using a sublimation
825 method. Eur. J. Pharm. Biopharm. 83, 460–467.
826 https://doi.org/10.1016/j.ejpb.2012.11.009
827 Park, J.H., Choi, H.K., 2015. Enhancement of solubility and dissolution of cilostazol by
828 solid dispersion technique. Arch. Pharm. Res. 38, 1336–1344.
829 https://doi.org/10.1007/s12272-014-0547-6
830 Park, Y.J., Lee, H.K., Im, Y. Bin, Lee, W., Han, H.K., 2010. Improved pH-independent
831 dissolution and oral absorption of valsartan via the preparation of solid dispersion.
832 Arch. Pharm. Res. 33, 1235–1240. https://doi.org/10.1007/s12272-010-0814-0
833 Permana, A.D., Tekko, I.A., McCarthy, H.O., Donnelly, R.F., 2019. New HPLC–MS
834 method for rapid and simultaneous quantification of doxycycline,
835 diethylcarbamazine and albendazole metabolites in rat plasma and organs after
836 concomitant oral administration. J. Pharm. Biomed. Anal. 170, 243–253.
837 Permana, A.D., Utami, R.N., Courtenay, A.J., Manggau, M.A., Donnelly, R.F., Rahman,
838 L., 2020. Phytosomal nanocarriers as platforms for improved delivery of natural
839 antioxidant and photoprotective compounds in propolis: An approach for enhanced
840 both dissolution behaviour in biorelevant media and skin retention profiles. J.
841 Photochem. Photobiol. B Biol. https://doi.org/10.1016/j.jphotobiol.2020.111846
842 Permana, A.D., Utomo, E., Pratama, M.R., Amir, M.N., Anjani, Q.K., Mardikasari, S.A.,
843 Sumarheni, S., Himawan, A., Arjuna, A., Usmanengsi, U., Donnelly, R.F., 2021a.
844 Bioadhesive-Thermosensitive in Situ Vaginal Gel of the Gel Flake-Solid Dispersion
845 of Itraconazole for Enhanced Antifungal Activity in the Treatment of Vaginal
846 Candidiasis. ACS Appl. Mater. Interfaces 13, 18128–18141.
847 https://doi.org/10.1021/acsami.1c03422
848 Permana, A.D., Wahyudin, E., Ismail, Amir, M.N., Raihan, M., Anjani, Q.K., Utomo, E.,

Layadi, P., Donnelly, R.F., 2021b. New and sensitive HPLC-UV method for concomitant quantification of a combination of antifilariasis drugs in rat plasma and organs after simultaneous oral administration. Anal. Methods 13, 933–945. https://doi.org/10.1039/d0ay02258f

Pradhan, R., Kim, S.Y., Yong, C.S., Kim, J.O., 2016. Preparation and characterization of spray-dried valsartan-loaded Eudragit® E PO solid dispersion microparticles. Asian J. Pharm. Sci. 11, 744–750. https://doi.org/10.1016/j.ajps.2016.05.002

R Jivani, R., N Patel, C., M Patel, D., P Jivani, N., 2010. Development of a novel floating in-situ gelling system for stomach specific drug delivery of the narrow absorption window drug baclofen. Iran. J. Pharm. Res. IJPR 9, 359–68.

Rahamathulla, M., Saisivam, S., Gangadharappa, H. V., 2019. Development of valsartan floating matrix tablets using low density polypropylene foam powder: In vitro and in vivo evaluation. AAPS PharmSciTech 20, 1–10. https://doi.org/10.1208/s12249-018-1265-z

Rajinikanth, P.S., Mishra, B., 2008. Floating In Situ Gelling System of Acetohydroxamic Acid for Clearance of *H. pylori*. Drug Dev. Ind. Pharm. 34, 577–587. https://doi.org/10.1080/03639040701831819

Shakya, R., Thapa, P., Saha, R.N., 2013. In vitro and in vivo evaluation of gastroretentive floating drug delivery system of ofloxacin. Asian J. Pharm. Sci. 8, 191–198. https://doi.org/10.1016/j.ajps.2013.07.025

Sharma, A., Goyal, A.K., Rath, G., 2018. Development and characterization of gastroretentive high-density pellets lodged with zero valent iron nanoparticles. J. Pharm. Sci. 107, 2663–2673. https://doi.org/10.1016/j.xphs.2018.06.014

Sharma, A., Sharma, J., Kaur, R., Saini, V., 2014. Development and characterization of in situ oral gel of spiramycin. Biomed Res. Int. 2014. https://doi.org/10.1155/2014/876182

Sharma, S., Sarkar, G., Srestha, B., Chattopadhyay, D., Bhowmik, M., 2019. In-situ fast gelling formulation for oral sustained drug delivery of paracetamol to dysphagic patients. Int. J. Biol. Macromol. 134, 864–868. https://doi.org/10.1016/j.ijbiomac.2019.05.092

Singhavi, D.J., Pundkar, R.S., Khan, S., 2017. Famotidine microspheres reconstituted with floating in situ gel for stomach-specific delivery: Preparation and

881 characterization. J. Drug Deliv. Sci. Technol. 41, 251–259.
882 https://doi.org/10.1016/j.jddst.2017.07.017
883 Truong, D.H., Tran, T.H., Ramasamy, T., Choi, J.Y., Choi, H.G., Yong, C.S., Kim, J.O.,
884 2015. Preparation and characterization of solid dispersion using a novel amphiphilic
885 copolymer to enhance dissolution and oral bioavailability of sorafenib. Powder
886 Technol. 283, 260–265. https://doi.org/10.1016/j.powtec.2015.04.044
887 Umamaheshwari, R.B., Jain, S., Jain, N.K., 2008. A new approach in gastroretentive drug
888 delivery system using cholestyramine. Drug Deliv. 10, 151–160.
889 https://doi.org/10.1080/713840399
890 Vashisth, P., Raghuwanshi, N., Srivastava, A.K., Singh, H., Nagar, H., Pruthi, V., 2017.
891 Ofloxacin loaded gellan/PVA nanofibers - Synthesis, characterization and
892 evaluation of their gastroretentive/mucoadhesive drug delivery potential. Mater. Sci.
893 Eng. C 71, 611–619. https://doi.org/10.1016/j.msec.2016.10.051
894 Wang, B., Wang, D., Zhao, S., Huang, X., Zhang, J., Lv, Y., Liu, X., Lv, G., Ma, X.,
895 2017. Evaluate the ability of PVP to inhibit crystallization of amorphous solid
896 dispersions by density functional theory and experimental verify. Eur. J. Pharm. Sci.
897 96, 45–52. https://doi.org/10.1016/j.ejps.2016.08.046
898 Xu, W.J., Xie, H.J., Cao, Q.R., Shi, L.L., Cao, Y., Zhu, X.Y., Cui, J.H., 2016. Enhanced
899 dissolution and oral bioavailability of valsartan solid dispersions prepared by a
900 freeze-drying technique using hydrophilic polymers. Drug Deliv. 23, 41–48.
901 https://doi.org/10.3109/10717544.2014.903012
902 Yan, Y.D., Sung, J.H., Kim, K.K., Kim, D.W., Kim, J.O., Lee, B.J., Yong, C.S., Choi,
903 H.G., 2012. Novel valsartan-loaded solid dispersion with enhanced bioavailability
904 and no crystalline changes. Int. J. Pharm. 422, 202–210.
905 https://doi.org/10.1016/j.ijpharm.2011.10.053
906 Yousaf, A.M., Malik, U.R., Shahzad, Y., Mahmood, T., Hussain, T., 2019. Silymarin-
907 laden PVP-PEG polymeric composite for enhanced aqueous solubility and
908 dissolution rate: Preparation and in vitro characterization. J. Pharm. Anal. 9, 34–39.
909 https://doi.org/10.1016/j.jpha.2018.09.003
910 Zhai, X., Li, C., Lenon, G.B., Xue, C.C.L., Li, W., 2017. Preparation and characterisation
911 of solid dispersions of tanshinone IIA, cryptotanshinone and total tanshinones. Asian
912 J. Pharm. Sci. 12, 85–97. https://doi.org/10.1016/j.ajps.2016.08.004

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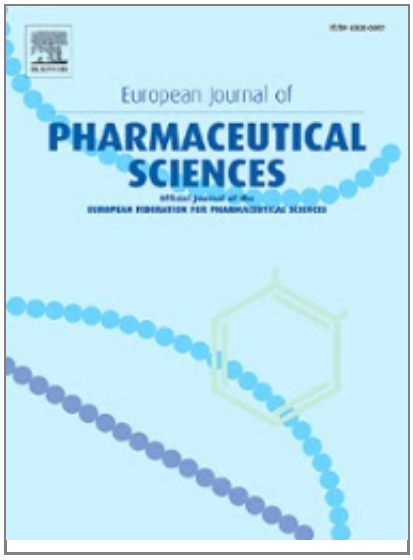

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