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Research Article

Development, Characterization and *In vitro* Evaluation of Solid Self-Emulsifying Drug Delivery Systems (S-SEDDS) Containing Valsartan

Mine Diril[1], Gülbeyaz Yıldız Türkyılmaz[1,2,3*], Eda Gülmezoğlu[1], Hatice Yeşim Karasulu[1]

[1]Department of Pharmaceutical Technology, Faculty of Pharmacy, Ege University, Izmir, Turkey;
[2]Center For Drug R&D and Pharmacokinetic Applications (Argefar), Ege University, İzmir, Turkey;
[3]Department of Biopharmaceutics and Pharmacokinetics, Faculty of Pharmacy, Ege University, Izmir, Turkey

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Abstract

Hypertension is main risk factor for cardiovascular disease. Valsartan is a widely used, effective and well-tolerated antihypertensive agent by specifically blocking the action of angiotensin II on the angiotensin Type 1 receptor. However, it is absorbed from upper part of the gastrointestinal tract and is poorly soluble in this region due to its acidic environment, and its oral bioavailability is only 25%. The aim of this study is to develop a new dosage form as an alternative to commercial formulation of Valsartan (VST). For this purpose, it is aimed to increase the solubility of the VST and to develop a solid self-emulsifying drug delivery system (S-SEDDS) with a pH-independent solubility. Solubility studies were carried out to determine the self-emulsifying drug delivery system (SEDDS) components where the VST showed the highest solubility. According to these studies; Isopropyl myristate (3.5 mg/mL) was used as oil phase, Capyrol 90 (19.8 mg/mL) and Tween 20 (32.5 mg/mL) as surfactants and Transcutol HP (168.9 mg/mL) as co-surfactant. Pseudo-ternary phase diagrams were plotted determined by the solubility studies. SEDDS formulations containing VST were adsorbed to Avicel pH101 and hydroxypropyl methyl cellulose (HPMC) separately by wet granulation technique and characterization studies were carried out. The developed VST-SEDDS, VST-SEDDS-Avicel, and VST-SEDDS-HPMC formulations increased VST release compared to the commercial product in pH 1.2 environment. In addition, it was observed that the VST-SEDDS-Avicel formulation was not affected by fed, fasting conditions and pH changes. Therefore, VST-SEDDS-Avicel formulation increases the pH-independent solubility and can be a potential formulation candidate for antihypertensive therapy.

Keywords: Valsartan, Solid Self-Emulsifying Drug Delivery Systems, SEDDS, Antihypertensive

*Corresponding Author: gulbeyaz.yildiz@ege.edu.tr
Mine Diril's ORCID number: 0000-0002-7154-8511
Gülbeyaz Yıldız Türkyılmaz's ORCID number: 0000-0002-8601-0263
Eda Gülmezoğlu's ORCID number: 0000-0002-1570-6140
Hatice Yeşim Karasulu's ORCID number: 0000-0002-1860-8255

Valsartan İçeren Katı Kendiliğinden Emülsifiye Olabilen İlaç Taşıyıcı Sistemlerin (S-SEDDS) Geliştirilmesi, Karakterizasyonu ve İn vitro Değerlendirilmesi

Öz

Hipertansiyon, kardiyovasküler hastalık için ana risk faktörüdür. Valsartan, anjiyotensin II'nin anjiyotensin Tip 1 reseptörü üzerindeki etkisini spesifik olarak bloke ederek yaygın olarak kullanılan, etkili ve iyi tolere edilen antihipertansif ajandır. Ancak gastrointestinal sistemin üst kısmından emilir ve buranın asidik ortamı nedeniyle bu bölgede az çözünür ve oral biyoyararlanımı sadece %25'tir. Bu çalışmanın amacı, Valsartan'ın (VST) ticari formülasyonuna alternatif olarak yeni bir dozaj formu geliştirmektir. Bu amaçla, VST'ın çözünürlüğünü artırmak ve pH'tan bağımsız bir çözünürlüğe sahip olan katı kendiliğinden emülsifiye olabilen ilaç taşıyıcı sistem (S-SEDDS) formülasyonu geliştirmek hedeflenmiştir. VST'ın en yüksek çözünürlük gösterdiği SEDDS bileşenlerini belirlemek için çözünürlük çalışmaları yapılmıştır. Çözünürlük çalışmalarına göre; yağ fazı olarak izopropil miristat (3.5 mg/mL), yüzey etkin maddeler olarak Capyrol 90 (19.8 mg/mL) ve Tween 20 (32.5 mg/mL), yardımcı yüzey etkin madde olarak ise Transcutol HP (168.9 mg/mL) kullanılmıştır. Çözünürlük çalışmaları ile belirlenen yardımcı maddeler ile üçgen faz diyagramları çizilmiştir. VST içeren SEDDS formülasyonları Avicel pH101 ve Hidroksipropil metil selüloz'a (HPMC) ayrı ayrı yaş granülasyon tekniği ile adsorbe edilmiş ve karakterizasyon çalışmaları yapılmıştır. Geliştirilen VST-SEDDS, VST-SEDDS-Avicel ve VST-SEDDS-HPMC formülasyonları pH 1.2 ortamında ticari ürüne göre VST salınımı arttırmıştır. Ayrıca VST-SEDDS-Avicel formülasyonunun açlık, tokluk durumlarından ve pH değişiminden etkilenmediği gözlenmiştir. Bu nedenle VST-SEDDS-Avicel formülasyonunun, pH'tan bağımsız çözünürlüğü arttırdığı ve antihipertansif tedavi için potansiyel bir formülasyon adayı olabileceği söylenebilmektedir.

Anahtar Kelimeler: Valsartan, Katılaştırılmış Kendiliğinden Emülsifiye Olabilen İlaç Taşıyıcı Sistemler, SEDDS, Antihipertansif

1. Introduction

Hypertension is one of the leading health problems in developing and developed countries. The World Health Organization states that hypertension, which has a high prevalence, ranks first among the preventable causes of death in the world. Valsartan (VST) , the subject of our study, is a potent, highly selective and orally active antihypertensive drug belonging to this group. VST exerts its effect by binding to the angiotensin II type I receptor. Thus, a decrease in blood pressure is achieved [1,2]. However, there are studies showing that the bioavailability of VST is around 25%. VST is water soluble at neutral pH. However, due to the two weakly acidic parts it contains (pKa 3.9 and 4.7), it shows solubility depending on pH. Increasing the pH from 4 to 6 increases the solubility of VST by 1000 times, but the nonionic form increases and lipophilicity decreases. Therefore, the rate of absorption of VST across the gastrointestinal tract is also affected by pH [3].

Lipid-based systems increase drug absorption from the gastrointestinal tract by accelerating the dissolution process, reducing the particle size to molecular levels, facilitating the formation of the dissolved phase, providing a solid state solution with the carrier, changing the drug uptake, changing the enterocyte-based transport, increasing the transport of the drug into the systemic circulation via the intestinal lymphatic system [4].

The preparation of lipid-based system formulations has a simpler process than the preparation of solid dosage forms such as tablets and capsules[5]. Excipients used in the composition of lipid-based formulations; lipids/oils (natural or synthetic origin), surfactants (hydrophilic or hydrophobic), hydrophilic solutions or co-surfactants. After preparation, they can be dispersed in solutions containing suitable fruit extracts or diet liquids, or they can be offered for use in soft gelatin capsules and hard gelatin capsules. In addition, solid pharmaceutical dosage forms can be prepared by adsorbing a liquid self-emulsifying system to an inert powder (Avisel, Aerosil, HPMC, etc.) [6-8].

In this study, VST, an active substance with low solubility, high permeability (class II) or low permeability, high solubility (class III) according to the Biopharmaceutical Classification System (BCS), was used to as active ingradient. S-SEDDS formulations were developed with self-emulsifying drug delivery systems (SEDDS) with Avicel pH 101 and Hydroxypropyl methylcellulose (HPMC) by wet granulation technique. In addition, the aim of this study is to perform *in vitro* characterization studies and comparatively evaluation *in vitro* release studies.

Developed SEDDS, S-SEDDS formulation, commercial tablet formulation and Powder VST were compare for *in vitro* release studies at pH 1.2 (simulate gastric fluid), pH 4.5, pH 6.8 (simulate intestinal fluid) . In addition, simulation of gastrointestinal conditions is essential to adequately predict the *in vivo* behavior of especially weakly acidic drugs[9, 10]. Therefore, in this study, *in vitro* release studies for VST-SEDDS, VSTS-SEDDS, commercial formulation and Powder VST using Fasted State Simulated Intestinal Fluid (FaSSIF), Fed State Simulating Intestinal Fluid (FeSSIF), Fasted State Simulated Gastric Fluid (FaSSGF) media in addition to pH 1.2, pH 4.5 and pH 6.8 were comparatively evaluated. Based on *in vitro* studies, the VST-S-SEDDS formulation is expected to increase oral bioavailability more than the commercial product.

2. Materials and Methods

2.1.Materials

VST was a generous gift from Bilim Pharmaceuticals (Beyoglu, Istanbul). Capyrol® 90 (Propylene glycol monocaprylate), Labrafil® M 1944 CS (polyoxyethylated oleic glycerides), Labrafil® M 2125 CS (Linoleoyl Polyoxyl glycerides) and Transcutol® HP (Diethylene glycol monoethyl ether) were kindly provided by Gatteffose (Saint-Priest, France). Oleic acid, Soybean oil, Isopropyl Myristate (IPM), Span®80 (sorbitan monooleate), Tween® 20 (Polyoxyethylene sorbitan monolaurate) were purchased from Sigma Aldrich (Darmstadt, Germany). Tween® 80 (polyoxyethylene sorbitan monooleate), Ethanol and Isopropyl alcohol were procured from Merck (Darmstadt, Germany). Fasted State Simulated Gastric Fluid (FaSSGF), Fasted State Simulated Intestinal Fluid (FaSSIF) and Fed State Simulated Intestinal Fluid (FeSSIF) media were acquired from Biorelevant (London, England).

2.2. Methods

2.2.1. Screening Tests

VST solubility in various oils, surfactants, co-surfactants was determined using the shake-flask method. Briefly, excess VST was added to 2 mL of each ingredient, stirred in a shaker (200 rpm, CAT S20, Germany) in the dark for 72 hours at room temperature. At the end of the 24th, 48th and 72nd hours, the mixture was centrifuged (Nüve 800R, Turkey) at 25°C at 3000 rpm (3045xg) for 15 min. The supernatant was removed, diluted and quantified by HPLC [11].

2.2.2.HPLC Analysis

VST quantification method in the SEDDS and S-SEDDS formulations were developed and validated using high-performance liquid chromatography (HPLC) with an Agilent (HP 1100, USA) Series instrument using different literature data. Analysis were performed with a Zorbax SB C18 (150 mm × 4.6 mm, 3.5 µm) column at 25°C. The mobile phase consisted of Acetonitrile: 0.1M phosphate buffer (55:45, v/v) and adjusted to pH 2.7 with trifluoroacetic acid at an isocratic flow rate (1.0 mL/min). VST was detected by monitoring the absorbance at 250 nm with an Ultraviolet-Visible detector [12,13].

2.2.3.Preparation of SEDDS

Pseudo ternary phase diagram is used to determine the optimum formulation for SEDDS [14] . Optimum formulations giving the largest area and calculated from the center of gravity in the computer program were prepared by mixing all components (oil, surfactant and co-surfactant) by using water titration method. After identification of SEDDS region by water titration, the oil, surfactant, cosurfactant combinations were selected according to the obtained micro-emulsion area results by the constructed phase diagrams [15].

Briefly, after performing phase diagrams studies, oil, surfactant and co-surfactant were prepared by mixing in a magnetic stirrer at 50 rpm and heating up to 37˚C to obtain a clear solution. VST(80 mg) was added to 0.5 mL of the oily mixture. VST was dissolved by mixing with a magnetic stirrer at 50 rpm to obtain a clear solution.

2.2.4. Characterisation of VST-SEDDS

VST-SEDDS formulation was analyzed for various physicochemical attributes. The physical appearance were evaluated. The pH, electrical conductivity and refractive index of VST-SEDDS formulation was measured using pH meter (Mettler Toledo, Switzerland), conductometer (Jenway 4071, England) and refractometer (Krüss DR301-95, Germany) respectively. The viscosity of formulation was measured at 37 ± 1 ºC by using Ula spindle in a viscosimeter (Brookfield DVII + Pro, USA).

The droplet size and zeta potential values of the VST-SEDDS formulation were determined by using zetasizer (Malvern Nano ZS, England) device at room temperature (25 ± 2 ºC) by diluted with the optimum amount of water in the ternary phase diagram. The VST content of SEDDS was determined by using HPLC with validated method. The developed formulations were added dropwise to 1000 mL of distilled water at 37±0.5˚C, which was mixed at 100 rpm using the USP (XXII) type II dissolution apparatus and emulsification time was assessed visually. For the thermodynamic stability of VST-SEDDS formulation, heating-cooling cycle, centrifugation test and freezing-thawing cycle studies were done [16].

2.2.5. Preparation of S-SEDDS

SEDDS formulations containing VST were adsorbed into inert carriers (Avicel pH101 and HPMC separately) and granulated by wet granulation technique. Dry mixture was obtained by drying in an oven at 45˚C for approximately 1 hour. Different amounts of formulation were loaded into inert carriers and the compositions were determined for optimal formulations.

2.2.6. Characterisation of VST-S-SEDDS

The physical appearance, bulk density, tapped density (Logan Tap 2S, USA), dimensional analysis with vibrating screen (Retsch, Germany), emulsification time, particle size were evaluated.

2.2.7. Chemical and Pyhsical Stability

The formulations prepared to examine the stability of S-SEDDS formulation were stored at 25±2˚C, 60±5% relative humidity and 40±2˚C, 75±5% relative humidity for 12 months. In the stability study, the samples were controlled for 12 months at t=0, that is, at the time of onset and at the 1st, 3rd, 6th, 9th and 12th months. S-SEDDS formulations containing VST in hard gelatin capsules (00) were taken into stability study and the stability of these systems were evaluated.

2.2.8. *In vitro* Release Studies

In vitro release studies of the VST-SEDDS, VST-S-SEDDS, commercial formulation and powder VST were performed using a rotary paddle method (pH 1.2, 4.6, 6.8, FaSSIF, FeSSIF, FaSSGF) at 37°C ± 1°C at 50 rpm. Three parallel release studies were performed for each formulation. Formulations were placed in hard gelatin capsules (number 00) with 80 mg/0.5 mL VST. Samples from the dissolution media were collected at 0, 5, 10, 20, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, 480 and 1440 min. The supernatant was filtered (0.45 μm pore size) and quantified by HPLC [17].

2.11. Statistical Evaluation

Obtained *in vitro* results were evaluated statistically. Differences or similarities between the results were interpreted. Student t test or ANOVA variance analysis for parametric tests and Krusger Wallis analysis for nonparametric tests were preferred. $P < 0.05$ was considered significant.

3. Results and Discussion

3.1.Screening Tests

Solubility studies were carried out in various oils, surfactants and co-surfactants. Based on this, it was decided to formulation trials were conducted as a oil phase isopropyl myristate (3.5 mg/mL), as sufactans Capyrol 90 (19.8 mg/mL) and Tween 20 (32.5 mg/mL), as a co-surfactant Transcutol HP (168.9 mg/mL) (Table 1).

Table 1. Solubility sudies of VST in oils, surfactants, co-surfactants and aqueous phase (n=3)

Oil, Surfactant, Co-surfactant and Aqueous Phase	The Amount of Dissolved VST(mg/mL) (±SD)
Oleic Acid	3.20±0.023
Soybean Oil	2.40±0.01
Isopropyl myristate	3.50±0.57
Capyrol 90	19.79±0.89
Labrafil M 1944 CS	17.50±0.6
Span 80	9.80±1.1
Tween 20	32.45±0.87
Tween 80	24.50±3.4
Cremophor EL	32.34±1.98
PEG 600	93.43±5.2
Transcutol HP	168.90±6.4
Water	0.09±0.001
pH 1.2	0.04±0.004
pH 6.8	3.87±0.056

3.2 HPLC analysis

HPLC method was developed and validated to determinate *in vitro* release studies of VST. Validation was evaluated according to the criteria recommended by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The data for the analytical curves constructed (n=3) suggest acceptable linearity method over a concentration range of 0.5–50 µg/mL for *in vitro* release. The linear regression equation was determined by the least squares method and thus the correlation coefficients were calculated, these results were shown at Table 2. Average recovery at 80, 100 and 120 µg ml^{-1} ranged from 98.00% to 102.00%. The value of average precisions relative standard deviations were all below 2%. All other validation parameters were within acceptable limits.

Table 2. Linearity, LOD and LOQ results

Media	Concentration range (µg/mL)	Equation	R^2	LOD (µg/mL)	LOQ (µg/mL)
pH 1.2	0.5-50	y = 17.400x+5.3110	0.9999	0.070	0.210
pH 4.5		y = 18.015x+2.1077	0.9991	0.027	0.081
pH 6.8		y = 17.692x+0.6017	0.9999	0.031	0.093
FaSSIF		y= 17.606x-1.2497	0.9999	0.035	0.105
FeSSIF		y=17.813x-7.6681	0.9994	0.029	0.087
FaSSGF		y=16.815x-6.3273	0.9991	0.060	0.180

3.3.Preparation and Characterisation of VST-SEDDS

Oil-in-water (o/w) emulsions often require higher hydrophilic lipophilic balance (HLB) value 10-14 [18]. Considering the HLB value of the o/w emulsion, there SEDDS formulations were prepared different surfactant/co-surfactant ratios (1: 0.5, 1: 1, 1: 1.5). 1:1 surfactant/co-surfactant ratios were given the extensive microemulsion area, it was showed at Figure 1.

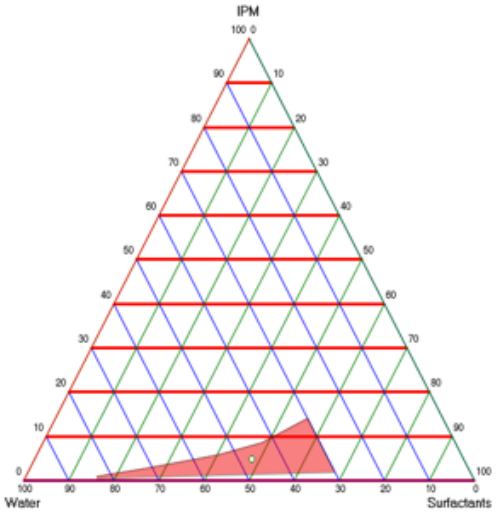

Figure 1. Pseudoternary-phase diagrams of SEDDS of 1:1 surfactant/ co-surfactant ratios

VST was dissolved in SEDDS formulation composition at 80 mg/0.5 mL ratio. The clear VST-SEDDS formulation was obtained without phase change. The physical appearance of the VST-SEDDS formulation was examined and the developed system was observed to be transparent, homogeneous and no phase separation.

The pH value of VST-SEDDS formulation was found to be 3.74. The electrical conductivity of formulation was measured 89 µS/cm. This result indicated that the type of the emulsion form was oil in water (o/w) [19] . Viscosity was measured as 47 cP (150 rpm, 98% torque) for VST-SEDDS formulation.The refractive index was found 1.45 and this result was used for droplet size analysis. The mean droplet size and zeta potential value were 105.2 ± 15 nm and 0.069 ±0.005, respectively. The polydispersity index (PDI) gives a measure of particle size distribution. A PDI <0.5 indicates a homogeneous system and a narrow particle size distribution [20, 21]. PDI result of 0.2 showed that the VST-SEDDS formulation is a homogeneous system. Quantification analysis was performed by validated HPLC method and the % content was found to be 100.2%. In self-emulsification, the time to emulsify gives information about the efficiency of the system [22]. In a similar study by Balakumar et al. [23], they stated that formulations with emulsification time less than one minute would be stable. VST-SEDDS was completely dispersed in 10 seconds in accordance with the literature. Thermodynamic stability studies were carried out with formulation [24]. No stabilization problems such as phase separation or precipitation were observed in the VST-SEDDS formulation.

3.5. Preparation and Characterisation of S-SEDDS

SEDDS formulations containing VST were adsorbed into Avicel pH101 and HPMC separately and granulated these formulations by wet granulation technique. S-SEDD systems were successfully obtained in the appearance of homogeneous, white pellets. Hausner ratio (=final/initial density) and Carr index (=%difference of final and initial density relative to final) value were calculated with bulk density (=weight/initial volume) and tapped density (=weight/tapped volume) results as indices of packing ability (Table 3). According to these findings, it was observed that the flow of our granules were weak. In the dimensional analysis, VST-SEDDS-Avicel was found to be 98.4% in the 2000-1400 μm mesh size range, while VST-SEDDS-HPMC was found to be 94%. These results show the successful development of granules with homogeneous dimensions. VST-SEDDS-Avicel was completely dispersed in 30 seconds, while VST-SEDDS-HPMC is 5 minutes. Particle sizes for VST-SEDDS-Avicel and VST-SEDDS-HPMC were found 186.3±1.362 nm and 129.1±5.36 respectively. It was observed that the granulation technique slightly increased the droplet size.

Table 3. Properties of experimental S-SEDDS

	Bulk density	**Tapped density**	**Hausner ratio**	**Carr index (%)**
VST-SEDDS-Avicel	0.288	0.4301	1.492	32.98
VST-SEDDS-HPMC	0.222	0.308	1.389	27.98

3.6. Chemical and Pyhsical Stability

Physical and chemical analyzsis of VST-SEDDS-Avicel and VST-SEDDS-HPMC formulations were performed at 25±2˚C, 60±5% relative humidity and 40±2˚C, 75±5% relative humidity for 12 months. At the end of 12 months, there was no significant change for physicochemical analyses and content of active substance at both stability conditions.

3.7. *In vitro* Release Studies

In vitro release assays are very important by reason of examining the *in vitro* success of the developed novel formulations and employed for predict drug release *in vivo* of drug [25]. For this purpose, *in vitro* release studies of powder VST, commercial formulation, VST-SEDDS and VST-S-SEDDS formulations in pH 1.2, pH 4.6 and pH 6.8 environments were performed. VST has an acidic structure and its bioavailability is 25%. Its solubility is low at low pH and it may be absorbed very low in the upper part of the gastrointestinal tract [3, 26]. Therefore, it is very important to increase its solubility at low pH (pH 1.2) with the developed drug delivery system.

Based on *in vitro* release experiments at pH 1.2 at the end of the 24th hour, the commercial formulation released 62.99% and VST powder 9.41%, while VST-SEDDS 90.73%, VST-SEDDS-Avicel 82.48%, VST-SEDDS-HPMC 77.25% (Fig. 2). This result shows that the developed SEDDS and S-SEDDS formulations were able to increase the release percentage of VST by increasing the solubility at pH 1.2. The results of *in vitro* release studies performed in pH 4.6 and pH 6.8 are given in Figure 2-B and Figure 2-C, respectively. The solubility of VST-SEDDS-HPMC formulations increased in pH 4.6 and pH 6.8 compared to powder VST, similar to the commercial product. However, VST-SEDDS and VST-SEDDS-Avicel formulations showed higher *in vitro* release in these media than the commercial formulation. VST-SEDDS-HPMC, one of the S-SEDDS formulations, showed a slower release profile at all pHs compared to the VST-SEDDS-Avicel formulation. The reason is that HPMC resulted in a decrease in release of drug from the matrices [27].

Physiological ambient pHs given in the guidelines for low solubility active substances cannot adequately reflect *in vivo* conditions. Therefore, biocompatible environments that mimic gastrointestinal conditions have been developed. The contents, osmolality, pH and buffer capacity of these media vary according to fed and fasting conditional [28]. Dissolution studies were performed with powder VST, commercial formulation, VST-SEDDS and VST-SEDDS-Avicel in fed and fasting conditional (Figure 2-D, Figure 2-E- Figure 2-F). Since HPMC shows slow release properties, it has not been studied. In the developed VST-SEDDS formulation, fed state increase the release (FaSSGF 44.57%, FaSSIF 79.82%, FeSSIF 99.55%). This is because other amphiphilic substances such as bile salts, phospholipids, monoglycerides and fatty acids in the intestinal contents have a great effect on the solubility, dissolution rate and absorption of some drugs in the fed state [29]. Developed VST-SEDDS-Avicel, on the other hand, is not affected by fed and fasting state (FaSSGF 37.57%, FaSSIF 100.16%, FeSSIF 98.39%).

As a result, solubility of each SEDDS formulation increased in all dissolution media, especially in acidic media as targeted. Only the VST-SEDDS-HPMC formulation showed a slower release rate by changing the release profile due to the polymer structure. VST-SEEDS and VST-SEDDS-Avicel showed similar release profile ($p>0.05$ at pH 1.2, pH 4.6, pH, 6.8, FaSSGF, FeSSIF). Among these two formulations, VST-SEDDS-Avicel provided a faster release profile than VST-SEDDS in FASSIF medium due to its pH-independent solubility ($p<0.05$).

In a previously published study, PK and PD studies of the SEDDS formulation were performed and it was observed that its bioavailability increased 423% compared to the commercial product [15]. In this study, it is predicted that a similar or even better PK response will be obtained due to the pH-independent solubility of the S-SEDD formulation, which exhibits similar release properties. For this purpose, *in vivo* studies are planned with the tablet dosage formulation to be prepared with the addition of excipients that will increase its compressibility.

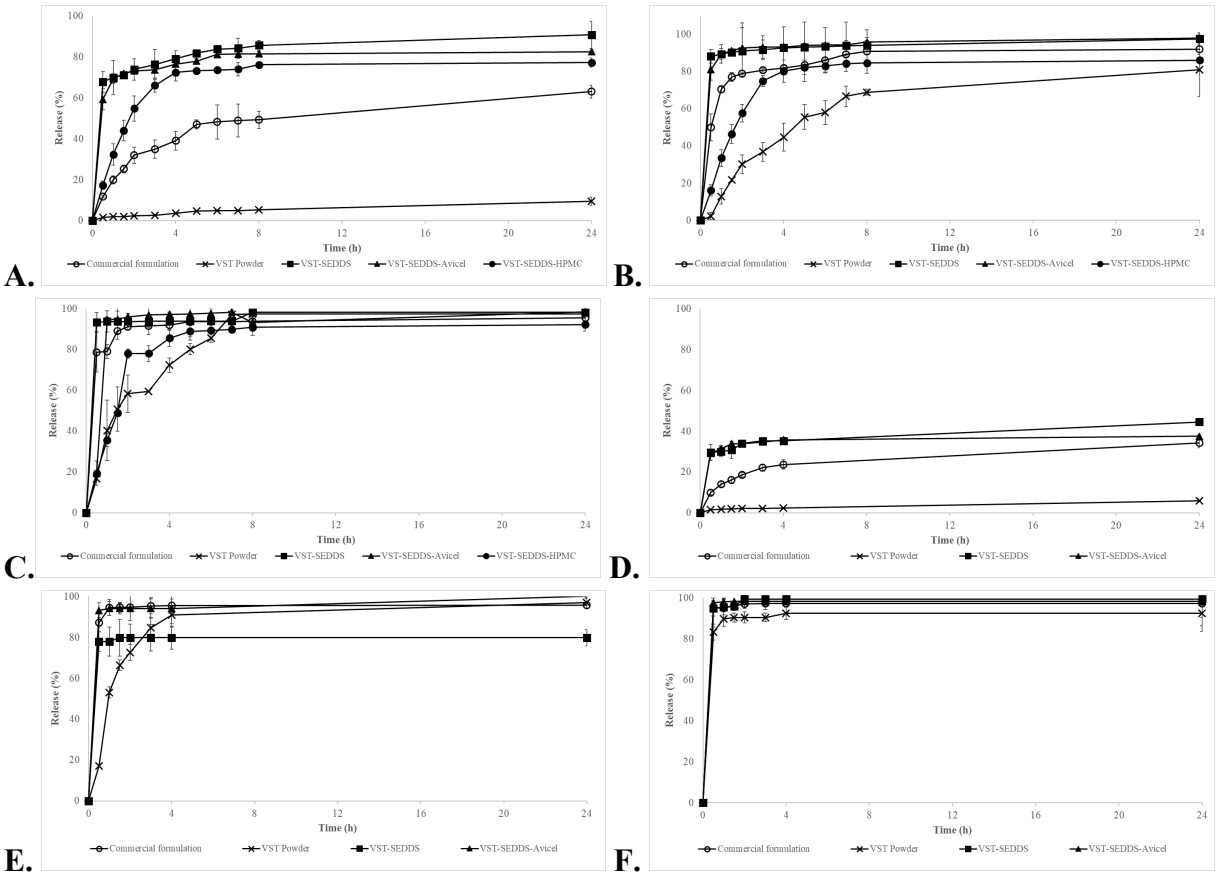

Figure 2. VST release profile from VST-SEDDS, VST-SEDDS-Avicel, VST-SEDDS-HPMC, VST powder and Commercial formulation A. in pH 1.2 medium; B. in pH 4.6 medium; C. in pH 6.8 medium; D. in FaSSGF; E. in FaSSIF; F: in FeSSIF

4. Conclusions

Self-microemulsifying drug delivery systems have been studied and proven in recent years to increase the solubility and bioavailability of especially low-solubility substances. Solid self-emulsifying drug delivery systems, which have been studied recently, are obtained from liquid SEDDS formulations with various solidification techniques for easier packaging, better stability, and lower production cost. In this study, SEDDS and S-SEDDS formulations containing VST were successfully developed and evaluated *in vitro* performance. Since VST shows low solubility at low pH, it is very important to develop a formulation with increased solubility at this pH. With the developed VST-SEDDS, VST-SEDDS-Avicel and VST-SEDDS-HPMC formulations, the release of VST was increased in the pH 1.2 environment compared to the commercial product. In addition, especially with the VST-SEDDS-Avicel formulation, it increased the release of VST compared to the commercial formulation with a release profile that is not affected by fed, fasting state and pH variation. As a result of *in vitro* release studies, VST-SEDDS and VST-S-SEDDS formulations may be novel dosage forms that can increase *in vivo* bioavailability and these formulations may be recommended as alternative antihypertensive drug delivery systems.

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Ethics in Publishing

There are no ethical issues regarding the publication of this study.

Author Contributions

Author contributions was not submitted by authors.

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