ISSN: 2455-8109

International Journal of Farmacia (IJF)

IJF |Vol.11 | Issue 2 | Apr - Jun -2025

www.ijfjournal.com

DOI : https://doi.org/10.61096/ijf.v11.iss2.2025.77-86

Research

Formulation And Evaluation Of Valsartan Orally Disintegrating Films

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Published on: 08 May 2025

Published by:
DrSriram Publications

Abstract

The medication's efficacy and safety profile may be enhanced, dosage may be decreased, and the onset of action may be accelerated with oral disintegrating films. Compared to other conventional dose forms, it dissolves more quickly, is more stable, and has a longer half-life. Valsartan (VST) was selected for the sublingual route in order to produce fast-dissolving films that dissolves in saliva quickly and without the need for water. The influence on the dissolution profile is measured using VST. The solvent casting method was used to create the oral disintegrating films (ODF), which contained PEG 400 as plasticiser along with a natural polymer locust been gum; SSG and CCS used as a superdisintegrants in different concentrations.The results showed that the medicine vanished quickly. Data showed the VF3 and VF7 dissolved quickly, releases drug in 20 min. VF3 disintegrates in 46 seconds, and VF7 in 62 seconds. No particles were discovered after disintegration. Based on disintegration time and dissolving trials, it was concluded that VF3 and VF7 were the best formulation.

Keywords: Orally disintegrating films, Valsartan, Gellan gum, Sodium starch glycolate, Croscarmellose sodium, Hypertension, Solvent casting technique.

INTRODUCTION

Orally disintegrating tablets and Oro dissolving films are two of the fast-dissolving medication delivery technologies that have been developed as alternatives to traditional dose forms in order to help these individuals. Because oral medicine delivery has the highest compliance rate, especially among pediatric and geriatric patients, it is considered the most practical, affordable, and safest drug delivery method. Any medication delivery system's ultimate purpose is to successfully deliver the drug to the body. Among the different dosage forms, the oral disintegrating dosage form is the most popular commercial product[1]. The film decreases the risk of choking and the fear of choking, is simple to make, easy to handle and administer, and has handy packaging. It also lessens the taste that is unpleasant. These thin polymer films are also known as melt-in-mouth dosage forms (MDF), mouth

dissolving films (ODF), quick dissolving films (QDF), rapidly dissolving films (RDF), and oral dissolving films (ODF)[2].

Some formulations were developed earlier that are atorvastatin[3], zolmitriptan[4], levocetrizine dihydrocloride[5], amlodipine besylate[6], ondansetron[7], promethazine hydrochloride[8], risperidone[9].

Valsartan treats mild to moderate essential hypertension, is a crystalline white to off-white powder. VST soluble in methanol and ethanol[10]. One of the main risk factor for heart failure, peripheral vascular disease, coronary artery disease, stroke, blindness, and chronic renal disease is hypertension. In order to treat moderate to severe hypertension, the current study set out to develop an oral disintegrating films containing the drug valsartan.

MATERIALS & METHODS

Chemicals

Dexlansoprazole was obtained as gift sample from UniChem laboratories Ltd., Hyderabad. Gellan gum was purchased from Shilex Chemicals Pvt. Ltd., Delhi. Sod. Starch glycolate, croscarmellose sodium, polyethylene glycol 400 and citric acid were purchased from SD Fine-Chem. Ltd, Mumbai. Sodium saccharine was purchased from HI media Lab Pvt. Ltd., Mumbai. Orange flavour was purchased from Pentagon trading company, Mumbai. All the chemicals and excipients used were of analytical grade.

Calibration of VST

To a 100 millilitre volumetric flask, 100 milligrammes of carefully weighed VST are introduced. The volume was raised to 100 ml using a stock solution of 1 mg/ml of 6.8 pH phosphate buffer. In order to create solutions with concentrations of 5, 10, 15, 20, 25, and 30 µg/ml, the stock solution was further diluted using 6.8 pH phosphate buffer (0.5, 1, 1.5, 2, 2.5, and 3 ml are taken from stock solution and diluted with 100 ml buffer). A UV-VIS spectrophotometer (EI 1372, Electronics India, Pune, India) with a blank of 6.8 pH phosphate buffer was used to draw a standard graph and quantify the absorbance of these solutions at wavelength 250 nm.

Fourier Transform Infrared (FT-IR) Spectroscopy

Using a FTIR spectrophotometer (Bruker Alpha II FTIR Spectrometer, Mumbai, India) the drug's FT-IR spectra were recorded. When using the diffuse reflectance technique, the mid-IR 4000-400 cm-1 spectral region was covered. The sample is first dispersed in KBr (100 mg) using a motor, and the materials are subsequently triturated into a fine powder bed inside the container using a compression gauge. Five tonnes of pressure was applied for five minutes. Following the light route, the pellet was placed, the spectrum was recorded twice, and the characteristic peaks associated with the functional groups were determined.

Formulation Design[11]

A natural polymer known as gellan gum and super disintegrant such as sodium starch glycolate and croscarmellose sodium were used to create VST ODFs using the solvent casting method.
The formulae of different formulations are as follows:

Table 1: Formulation of Valsartan ODF

Ingredients (mg)	VF1	VF2	VF3	VF4	VF5	VF6	VF7	VF8	VF9
Valsartan	40	40	40	40	40	40	40	40	40
Gellan gum	80	80	80	80	80	80	80	80	80
Sod. Starch Glycolate (SSG)	--	1.6	3.2	4.8	6.4	--	--	--	--
Croscarmellose sodium (CCS)	--	--	--	--	--	0.8	1.6	2.4	3.2
PEG 400	8	8	8	8	8	8	8	8	8
Citric acid	2	2	2	2	2	2	2	2	2
Sod. Saccharine	2	2	2	2	2	2	2	2	2
Orange Flavor	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
Water (mL)	4	4	4	4	4	4	4	4	4

*The above formulation was calculated for single film of 2x2 cm size.

Preparation of ODF

We employed the solvent casting method to make valsartan ODF. The ODF of VST was produced using a natural polymer Gellan gum. Gellan gum was dissolve in 3 ml of water and left for five to six hours to allow the

polymer to swell. Then valsartan was dissolved in 1 mL of solvent. The drug solution had been added to the previously described polymeric solution after VST had been dissolved in a predetermined volume of solvent. Next was the addition of plasticisers, like PEG 400 and a saliva stimulating agent, citric acid. Sweetener and flavour were also added. The superdisintegrant such as sodium starch glycollate and croscarmellose sodium also added to polymeric solution. Mixing in a cyclo mixer about 15 to 20 minutes will homogenise the drug content. To release all trapped air bubbles, the solution is agitated for two hours in a magnetic stirrer and then left aside. In order to create a film, the solution is finally cast a square glass plate (10 cm x 10 cm x 1.7 cm, Othmro, Amazon, India) and let to air dry for overnight. After drying the film was meticulously taken out of the mold, it was inspected for flaws and trimmed to the proper size so that each strip would have the appropriate dosage (2×2 cm^2). Film samples that had cuts, air bubbles, or other flaws were not included in the investigation.

Evaluation of orally disintegrating films:

Thickness measurement[12]:

The film's thickness was measured five times using a micrometer screw gauge, and an average of three readings was determined.

Weight variation[13]

Using an analytical balance, the average weight of the mouths dissolving the oral films was calculated for each film.

Folding endurance[14]

The value of folding endurance is determined by the number of times the film could be folded in the same way without breaking.

Drug content uniformity

By evaluating the API content in each individual strip, content consistency is ascertained. 85–115% is the maximum content homogeneity[15].

Surface pH

The film that was going to be tested was put in a Petri dish, wet with 0.5 milliliters of distilled water, and left for thirty seconds. After allowing one minute for equilibration and contacting the formulation's surface with the pH meter's electrode, the pH was recorded. For every formulation, an average of three determinations was made[16].

Assay of the Films

The drug content of the prepared orally disintegrating films was tested. One film, chosen at random from the five, was weighed, then added to 100 milliliters of 6.8 pH buffer in a volumetric flask. For thirty minutes, a volumetric flask was submerged in a sonicator. The finished solution's absorbance was measured at 250 nm utilizing a UV Visible spectrophotometer against a 6.8 pH buffer blank. Concentrations and formulation amount were calculated using a standard graph.

Tensile strength[17]

The greatest stress applied to the point at which the strip specimen breaks is known as its tensile strength.

***In vivo* disintegration studies**

Disintegration test equipment was used. Disintegration time indicates film disintegration and decomposition. In a stainless steel wire mesh with 25 ml of pH 6.8 simulated salivary fluids, place the desired film size (2x2 cm2). The time it takes the film to dissolve is called disintegration time.

***In vitro* Dissolution test**[18]

An in-vitro dissolving analysis of the created ODF formulations was conducted using EI -1916, Electronics India, Pune, India; USP type I dissolution test instrument (basket). Drug concentration was determined using the standard graph and reported as a percentage of the drug that was released or dissolved. The release studies were conducted in six duplicates, and mean values were noted.

Release Kinetics[19]

The findings from the invitro diffusion investigation were used to investigate the order and mechanism of drug release kinetics of VST films. The kinetic models that were plotted included the zero order, first order, and Higuchi equations; the release was calculated using the Korsmeyer-Peppas equations.

Stability studies

The optimised formulations were tagged and placed in strip packing within aluminium foil. After that, they were kept at 40°C/75% RH. Maintained for three months and assessed, in accordance with ICH Guidelines, for their appearance, drug content, and drug release at predetermined intervals[20].

RESULTS & DISCUSSION

Calibration of VST

Prepare the stock solution by combining 50 mg of VST with 100 ml of water. Ten millilitres of this stock solution were extracted and diluted with water to achieve a total volume of one hundred millilitres. A calibration curve was established utilising diverse concentrations (2–10 µg/ml) and the appropriate dilution of the stock solution. The absorbance was measured at 250 nm. The figure illustrates the VST standard curve. The VST was calibrated using a pH 6.8 phosphate buffer; linearity was found with 0.9979 R^2 value.

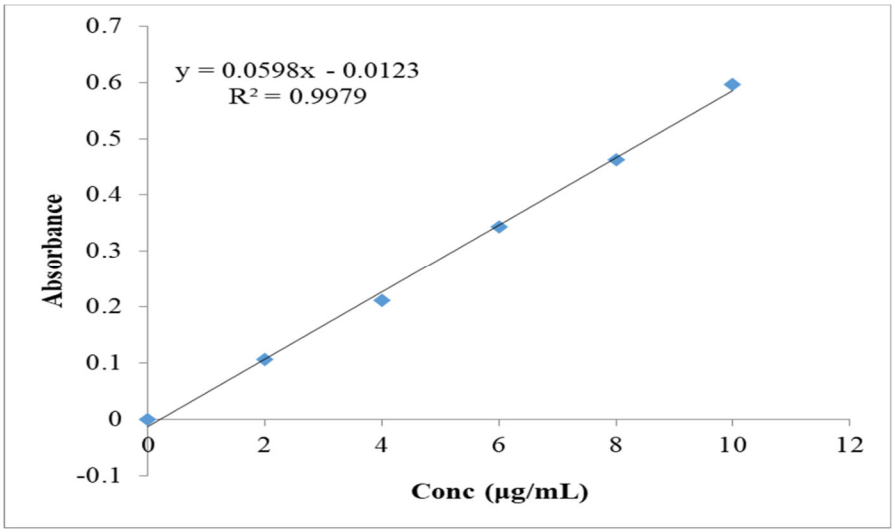

Fig 1: Standard Calibration Curve of VST in 6.8 pH phosphate buffer

Drug – excipient Compatibility Studies

FTIR spectrometer (Shimadzu FTIR-8400S, Japan) was used to determine the drug excipient compatibility, and the graphs from the figure were displayed. To find out if there was any interaction between the excipients and VST, the physical mixture was put through FTIR analysis. The lack of a drug-carrier chemical interaction is confirmed by the absence of any drug-characteristic peak appearance or disappearance. VST, gellan gum, sodium starch glycolate, croscarmellose sodium, and PEG 400 physical mixtures examined for chemical interactions. Pure VST and optimised sample underwent FTIR analysis to determine the presence of the pure API in the mixtures and to describe it.

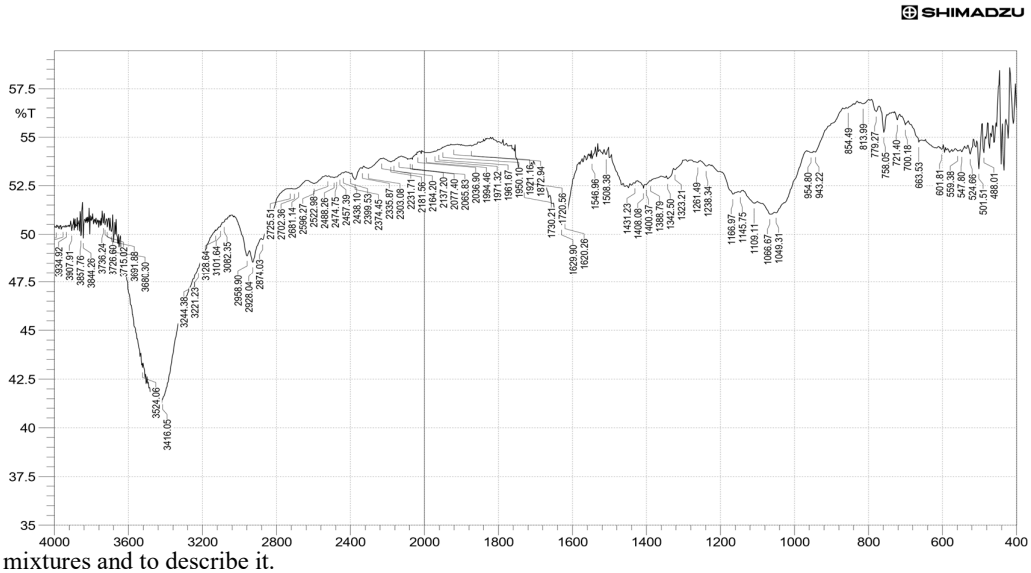

Fig 2: Pure VST FTIR Spectral Analysis

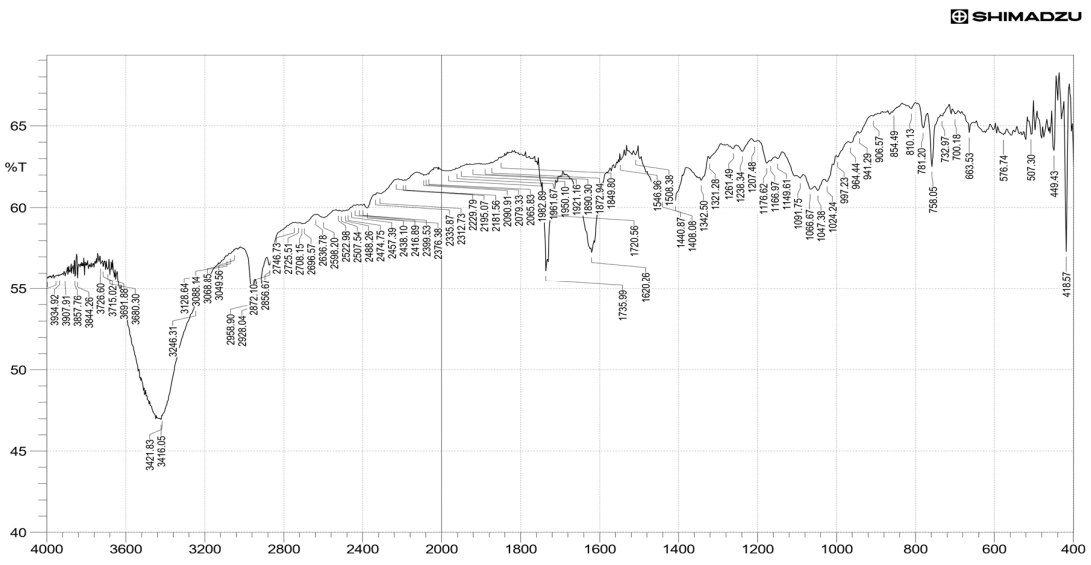

Fig 3: FTIR Spectral analysis of optimized formulation.

The obtained FTIR spectra are superimposed in the figure 2&3. The spectrum clearly shows the primary characteristic bands associated with pure VST, and the observations are in line with the scholarly literature. The principal peaks for N-H stretching were found at 2958.90 cm−3, C=O stretching at 1735.99 cm−3, C=C stretching at 1546.96 cm−3, and CN stretching at 1620.26 cm−3. There was no interaction, based on the observed absorption peaks of the drug and excipients.

Evaluation of ODF

Findings of all VST formulations showed in Table 2. VF1–VF9 were determined to be 90.56±0.57–126.67±0.76 µm thick. Based on the results of the aforementioned formulations, all of them demonstrated film thicknesses between 5 and 200 µm, which meets with the prior value's limit. It was discovered that the folding endurance value of VF1–VF9 was 124±3-156±5. For each formulation, the mean of the three findings was determined, and the standard deviation was also computed. The surface pH of each film was found to be within 6-7. The disintegration time for VF1–VF9 was 108±6-46±4 sec.

Table 2: Determination of Thickness, folding endurance and Surface pH of all formulations

F. Code	Thickness (µm)± SD	Folding endurance (folds)	Surface pH	In-vitro disintegration Time (sec)
VF 1	90.56±0.57	124±3	6.11±0.09	108±6
VF 2	92.41±0.68	138±7	6.14±0.11	73±5
VF 3	103.72±0.48	145±5	6.18±0.06	46±4
VF 4	117.16±0.35	151±4	6.23±0.12	54±5
VF 5	125.25±0.41	156±5	6.26±0.09	65±3
VF 6	100.36±0.72	128±6	6.09±0.11	81±5
VF 7	119.63±1.08	137±4	6.13±0.08	62±3
VF 8	121.42±1.02	142±7	6.19±0.12	66±5
VF 9	126.67±0.76	148±8	6.23±0.21	72±4

Table 3 displays the determination of Weight variation, Drug Content Uniformity and Assay the weight variance of all formulation's varies between 60.28±0.46-67.24±0.32. The findings of the calculation of the percentage of medication content for various formulations are ranging in between 91.68±0.26-107.62±0.29. The assay findings for each formulation are ranging in between 95.26±4.13-99.89±2.11.

Table 3: Determination of Weight variation, Drug Content Uniformity and Assay

F. Code	Weight variation	Drug Content Uniformity	Assay
VF 1	61.39±0.26	91.68±0.26	95.26±4.13
VF 2	60.28±0.46	92.24±0.33	96.51±3.25
VF 3	63.14±0.31	100.37±0.21	99.89±2.11
VF 4	61.26±0.18	101.49±0.18	98.12±3.82
VF 5	62.46±0.29	107.62±0.29	97.48±2.67
VF 6	63.61±0.34	99.42±0.31	97.39±4.12
VF 7	64.53±0.42	101.36±0.28	98.96±2.04
VF 8	66.38±0.18	100.38±0.19	97.46±3.32
VF 9	67.24±0.32	96.72±0.31	96.31±4.55

In-vitro dissolution

For VF1-VF9, the percentage cumulative drug release is shown in Figure 5 . Utilizing a Type I USP basket apparatus, the in vitro dissolution investigations were conducted in phosphate buffer with a 6.8 pH. In 20 minutes, VF3 with SSG released 99.98% of the drug and VF7 with CCS released 98.94%. As a result, it has been determined to be the best formulation.

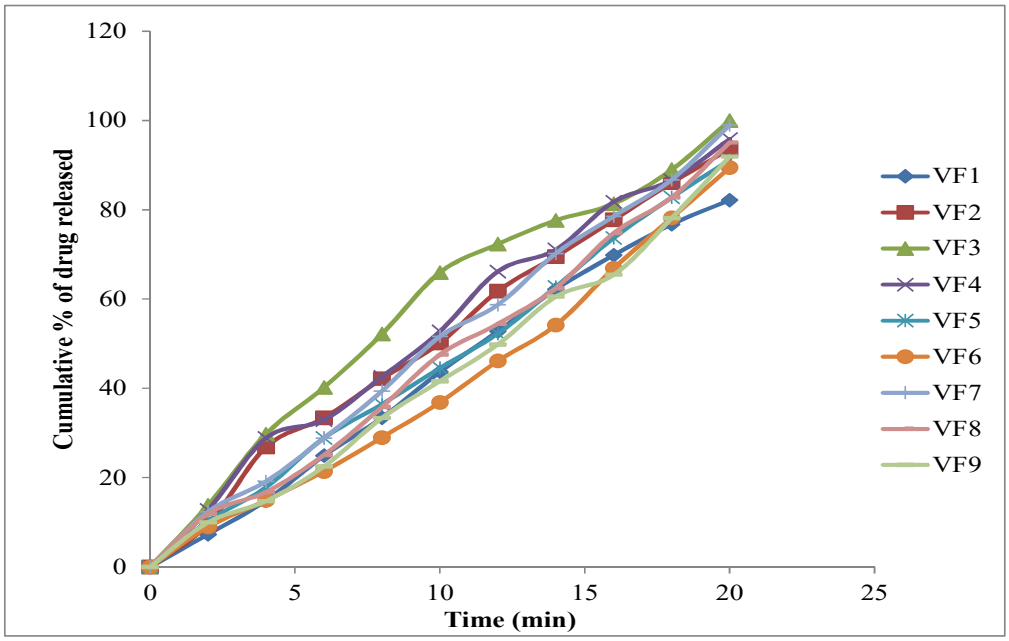

Fig 4: In vitro dissolution studies of formulations (VF1-VF9)

Release Rate Kinetics Application to Dissolution Data

A variety of models were used to study drug release kinetics. A number of release models, including first-order, zero-order, Higuchi, and Korsmeyer-Peppas, were fitted to the acquired data in order to investigate the mechanism of the dosage form's drug release rate kinetics.

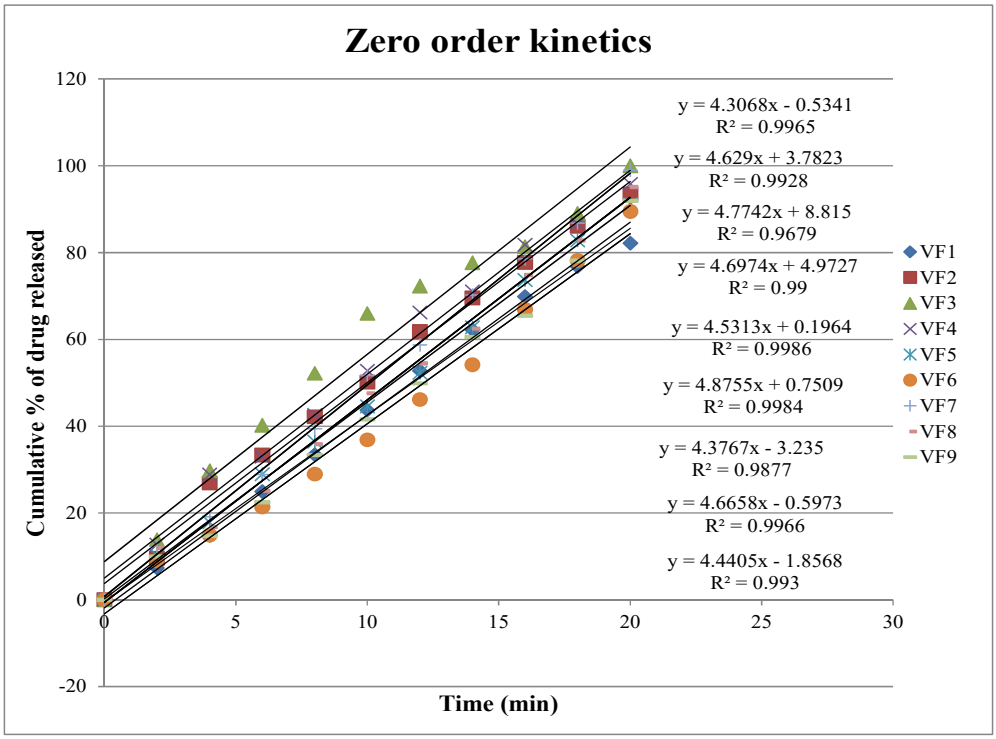

Fig 6: Zero order release kinetics graph of VST formulations (VF1-VF9)

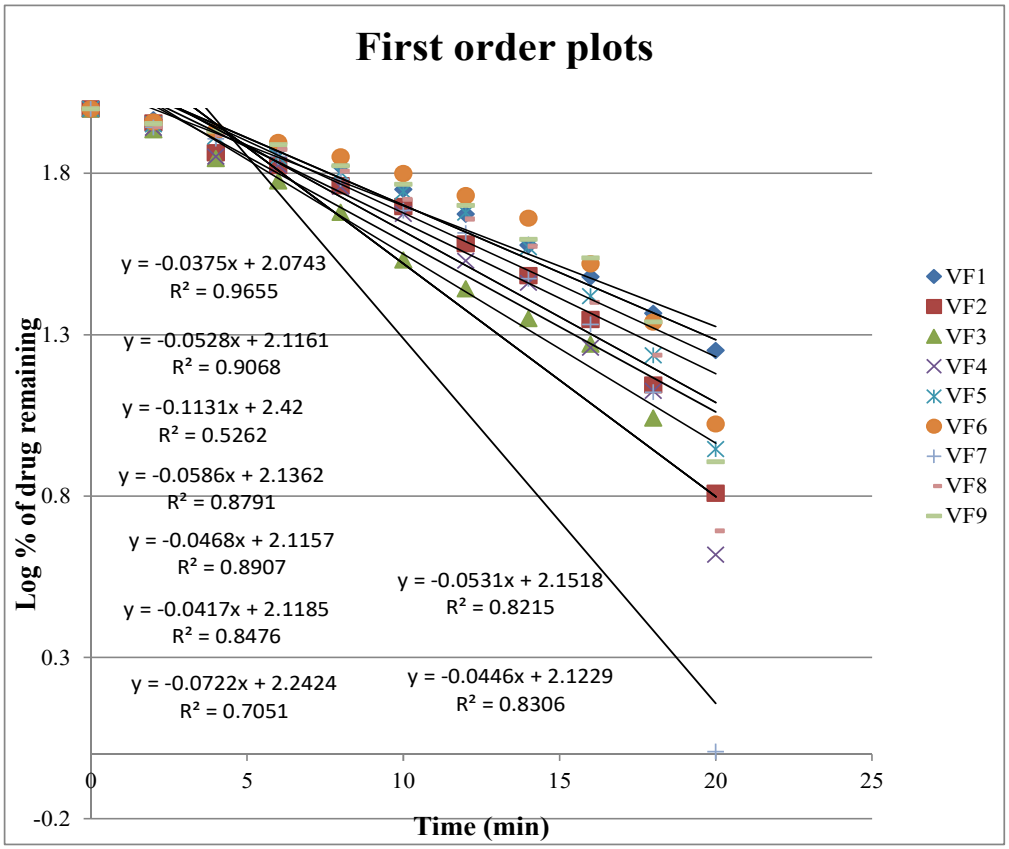

Fig 7: First order release kinetics graph of VST formulations (VF1-VF9)

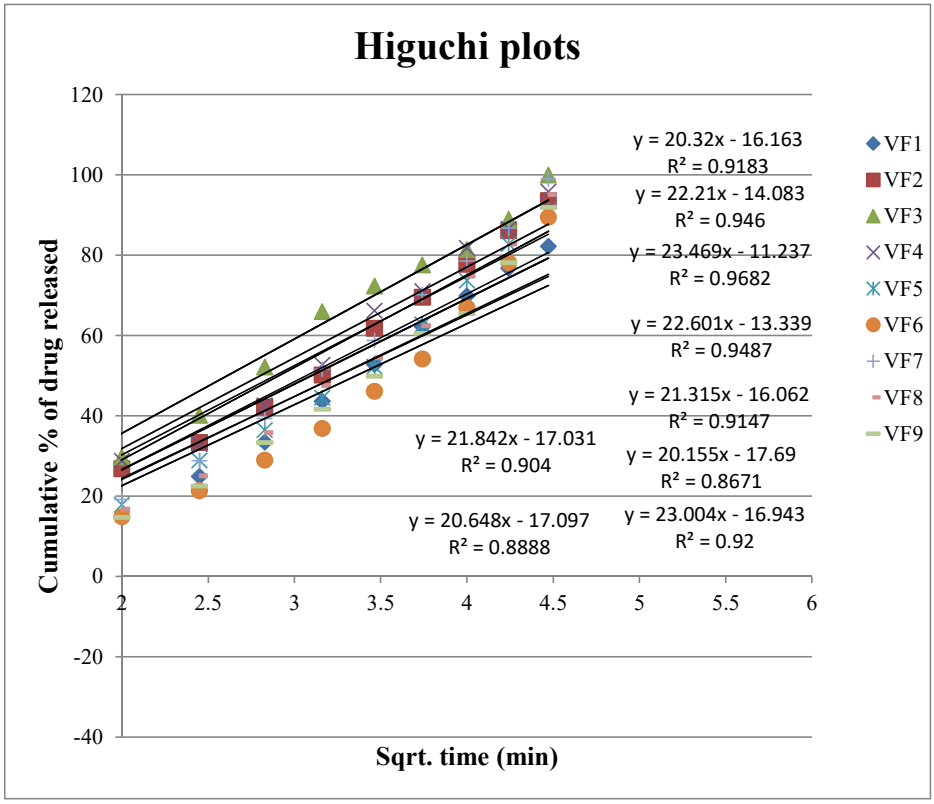

Fig 8: Higuchi release kinetics graph of VST formulations (VF1-VF9)

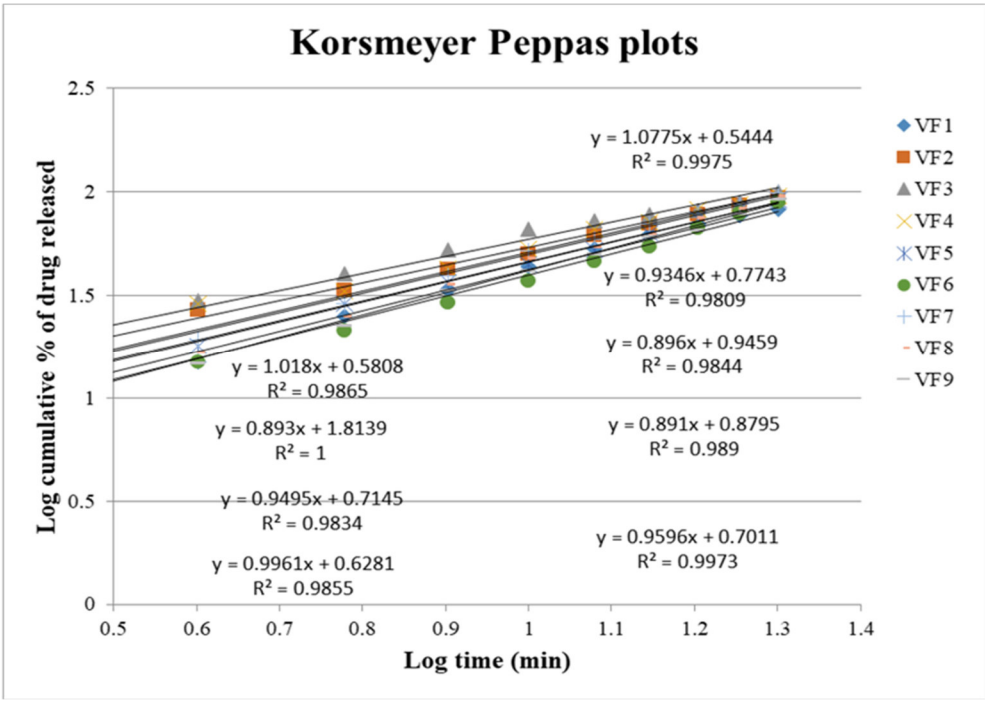

Fig 9: Korsmeyer-Peppas graph of VST formulations (VF1-VF9)

The drug release kinetics are summarized in Fig. 6 to 9 and indicated that VST followed zero order release from all the formulations. It is further noted that all the formulations followed diffusion mechanism of drug release (R^2

>0.6705) respectively. Koresmeyer peppas equation determines the drug transport mechanism based on the values of coefficient 'n'. If n=0.5 it is Fickian, if n=0.45 to 0.89 then non-Fickian transport, if n=0.89 it is Case II transport, and if >0.89 it is Super case transport. The 'n' values obtained for VF3, and VF7 were 0.896, and 0.893 respectively, which indicate that the drug transport mechanism from the VST was super case transport.[21]

Stability Studies

According to ICH recommendations, stability studies were carried out to assess the drug formulation's stability. The optimised VF3 and VF7 formulation was packaged in aluminium with a polyethylene laminate. The samples were kept at 40°C and 75% relative humidity for three months. Changes in the formulation's color, drug content, physical appearance, and drug release properties were investigated at the conclusion of the study period. In accordance with ICH requirements, stability experiments were conducted for the optimal formulation of VF3 and VF7 at room temperature, 40^0C/75%RH. The drug content percentage was examined at 0, 30, 60, and 90 days, all of which fall within the 95–105% acceptability range. It follows that the formulation is stable. Table displayed the stability study findings.

CONCLUSION

The solvent casting method was found to be successful in creating the VST films that dissolve quickly. Orally disintegrating films (ODF) have proven to be a successful treatment for patients who are psychotic, bedridden, or travelling in places without water. VST films were subjected to quality control testing, which included in-vitro diffusion, kinetic and stability investigations, disintegration time, surface pH, folding endurance, thickness, and weight fluctuation. Stability was observed for the optimised formulations VF3 and VF7 at accelerated stability conditions. As a result of prepared films' enhanced dissolving rate and rapid onset of action, patient compliance improved, therapy was successful, and their popularity grew in the near future.

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