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Original Article

Formulation and Evaluation of Valsartan Tablets Using Starch Succinate as Novel Super Disintegrant by Using 3^2 Factorial Design

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ABSTRACT

Aim: The current study focuses on enhancing the dissolution pace of Valsartan, as BCS Class II. The objective is to develop fast-dissolving tablets of Valsartan by forming complexes with β-Cyclodextrin (β-CD). **Materials and Methods:** To achieve this, Valsartan-βCD (1:1 M) complexes were prepared and used to formulate tablets with the help of primojel and starch succinate, following a 3^2 design approach. **Results:** The tablet powder blends demonstrated excellent flow properties, making them suitable for direct compression. All the prepared tablets met the disintegration time specifications outlined in the Indian Pharmacopoeia for uncoated tablets. The design of the Valsartan fast-dissolving tablet formulation was based on 3 levels of factor X1 (Primojel) at concentrations of 5%, 6.25% and 7.5%, and 3 levels of factor X2 (starch succinate) at concentrations of 5%, 6.25%, and 7.5%, with respect to the mean weight of the tablet (250 mg).The study further established equations for Disintegration Time (DT) and the Portion of Drug dissolved in 10 min (PD10) to evaluate the performance of the formulated fast-dissolving Valsartan tablets. Based on the obtained results, it is evident that intensifying the amount of the super disintegrants in the formulation ensued in a decrease in the disintegration time of the dosage form. **Conclusion:** The optimized tablet (C1) demonstrated promising attributes with a disintegration time of only 15 sec and an impressive 85.69% dissolution within 10 min. Consequently, the successful formulation of fast-dissolving tablets of Valsartan was achieved through the use of primojel and starch succinate, a novel super disintegrant.

Keywords: Valsartan, Starch Succinate, Fast Dissolving Tablets, Primojel, Optimization.

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INTRODUCTION

The oral route of drug delivery is widely considered the most reliable drug delivery system due to its ease of consumption and convenience. Solid drug dosage forms, in particular, offer enhanced stability and robustness. They are easy to handle and are a popular choice among patients for taking medicines. This results in better subject compliance and improved drug treatment compared to other routes of administration.

Valsartan is a specific angiotensin II type 1 antagonist used to treat hypertension either alone or in combination with different antihypertensive agents. Unlike other angiotensin receptor antagonists, Valsartan does not possess uricosuric effects and lacks an active metabolite. By blocking the angiotensin II receptor, Valsartan hinders the negative regulatory response on renin secretion. Although this leads to elevated plasma renin action and circulating angiotensin II levels, it does not overwhelm the antihypertensive effect of Valsartan on blood pressure. For even better results, Valsartan can be used in combination with thiazide diuretics or Calcium Channel Blockers (CCBs) to potentiate its anti-hypertensive actions.[1]

Based on its permeability characteristics, Valsartan falls under Class II of the biopharmaceutical classification system, characterized by low dissolution rate due to its limited aqueous solubility but high permeability through membranes. However, despite its high permeability, Valsartan faces challenges in terms of poor solubility in the Gastrointestinal (GI) medium and significant metabolism, resulting in a low oral bioavailability of only 12%. This limited bioavailability is attributed to its reduced extent and rate of absorption.

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To achieve the desired therapeutic action, it is essential to enhance the rate of dissolution and bioavailability of Valsartan. Currently, the standard doses available for Valsartan are 40 mg and 80 mg. Numerous methods are been explored to improve the dissolution rate and aqueous solubility of poorly soluble drugs like Valsartan. These methods include strong electrolyte salt formation, micronization, nanosuspensions, polymorphs, complexation, Solid Dispersion (SD), prodrugs and the addition of solvents or surfactants as buffers.[2]

The primary target of the current investigation is to formulate and assess Valsartan fast-dissolving tablets using primojel and starch succinate through a 3^2 factorial design. Starch succinate, a novel modified starch obtained by the modification of Tapioca starch with succinic anhydride, is also investigated for its potential application as a super disintegrant in this research. The work focus to estimate the influence of these components on the dissolution rate and bioavailability of Valsartan to enhance its therapeutic effectiveness.

MATERIALS AND METHODS

Preparation of Tapioca Starch Succinate

To begin the process, take a beaker and place it on a weighing machine. Use the tare button to set the weight to zero. Add 10 g of starch powder to the beaker and then carefully add water until the total weight reaches 90 g. Stir the mixture to ensure proper mixing, resulting in a 10% w/w starch solution. Next, adjust the pH of the starch solution to the range of 8.5-9 by slowly adding NaOH. In a separate beaker, weigh 20 g of acid anhydrides and add 10 ml of ethanol to it. Stir the mixture using a magnetic stirrer for 1 hr. Combine the solution of acid anhydrides and ethanol with the previously prepared starch solution, and carefully adjust the pH to 6.5 using dilute HCl. Allow the mixture to settle, and then separate the supernatant fluid from the collected suspension. Transfer the collected suspension to a silicon tray. Place the tray in a forced air oven and dry the contents at 50°C for 48 hr. Once the drying process is complete, grind the dried product and sieve it through #80 and #40 sizes.[3]

Preparation of Valsartan-β CD Inclusion Complexes

The solid insertion complexes of Valsartan with β-CD were set using the kneading method. In this process, Valsartan and β-CD were powdered together inside a mortar using a little quantity of solvent, which was a fuse of alcohol (ethanol) and H_2O in a 1:1 ratio. The resulting mixture formed thick slurry, which was kneaded for duration of 45 min. Subsequently, the kneaded mass was dried at 55°C until it reached a dry state. Once dried, the mass was powdered and then sieved through a mesh with a size of No. 80. This method facilitates the formation of stable solid inclusion complexes of Valsartan with β-CD, which can offer advantages in terms of improved solubility and dissolution characteristics for the drug.

Preparation of Rapid Disintegrating Tablets of Valsartan by Direct Compression Method

In the preparation process, inclusion complexes of Valsartan-βCD (1:1 M), equivalent to 40 mg of the drug, were first formed using the kneading method. These complexes were then assorted with super disintegrants, directly compressible diluent and further excipients in a plastic container. The resulting powder blend was subjected to direct compression using an 8mm, round-shaped leveled punch in a multi-station tablet compression apparatus (Cadmach, Ahmedabad, India). The compression process aimed to achieve a tablet hardness of 4-6 kg/cm^2 using 9 mm flat punches.[4]

This method facilitates the production of tablets containing Valsartan-βCD inclusion complexes along with other excipients, providing a convenient and efficient way to deliver the drug in a solid dosage form.

Fourier Transform Infrared Spectroscopy (FT-IR)

The samples of Valsartan tablets were set in the format of KBr pellets to facilitate Fourier-transform infrared (FT-IR) spectroscopy analysis. The KBr pellets containing the Valsartan tablets were then subjected to scanning in the spectral limits from 4000 cm^{-1} to 400 cm^{-1} using an FT-IR spectrophotometer.[5]

Characterization of Tablet

The formulated tablets were subjected to several evaluation parameters to assess their quality and performance. The key evaluations conducted were:[6]

Tablet Hardness

Tablet hardness refers to the ability of the tablet to withstand mechanical stress and breakage. It is an important characteristic to ensure the tablet's integrity during handling and transportation. The firmness of the tablets was measured employing a tablet hardness tester.

Tablet Friability

Tablet friability determines the tablet's resistance to abrasion and the likelihood of producing fines or fragments during handling and packaging. The friability study was executed employing a friability tester, and the portion of weight reduction was studied.

Tablet Disintegration Time

Tablet disintegration time is the interval utilized by the tablet to disintegrate down into little particles when exposed to a specified environment (e.g., simulated intestinal fluid or simulated gastric fluid). Disintegration time was measured using a disintegration test apparatus.

Tablet Drug Content

Tablet drug content analysis ensures that each tablet contains the intended amount of the Active Pharmaceutical Ingredient (API). Samples of the tablets were assayed to determine their drug content.

In vitro Dissolution

In vitro dissolution is a critical test that evaluates the rate at which the drug is released from the tablet under specified conditions (e.g., in simulated gastric or intestinal fluids). The dissolution profiles of the formulated tablets are studied employing a dissolution apparatus.

By conducting these evaluations, researchers can determine the tablets physical and chemical properties, their drug release behavior, and their overall quality. These results are crucial for ensuring that the formulated Valsartan tablets meet the required standards and are suitable for therapeutic use.

RESULTS AND DISCUSSION

The intention of the current work is to develop and assess Valsartan fast dissolving tablets using primojel and starch succinate through a 3^2 factorial design. Starch succinate, a novel modified starch derived from Tapioca starch through the use of succinic anhydride, is investigated for its application as a super disintegrant in this research.

The formulations of Valsartan tablet preparation and the post-compression parameters are presented in Table 1. The concentration of Valsartan was measured at an absorbance of 250 nm in 6.8 Phosphate buffer using a UV-visible spectrophotometer. To validate the analytical approach, a calibration curve was constructed, and its accuracy, linearity, interference and precision were verified. The calibration curve followed Beer's rule within the concentration limits of 2-10 µg/ml. The method demonstrated good reproducibility, with low Relative Standard Deviation

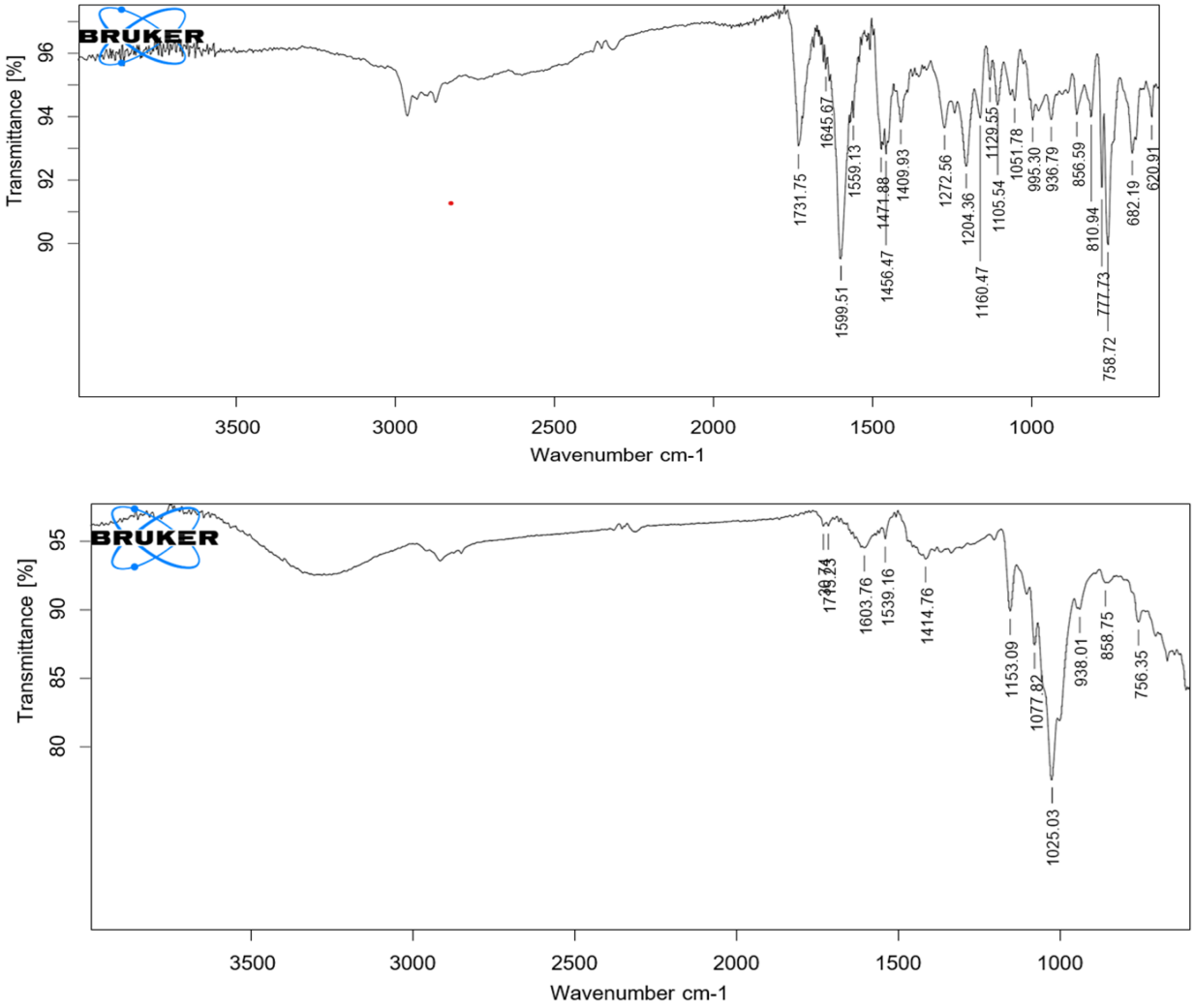

Figure 1: FT-IR spectra of Pure Valsartan and Pure Valsartan+βCD.

(RSD) values (<1.21%), ensuring the reliability of the analytical technique.

The affinity of the drug, Valsartan, with the excipients, specifically β-cyclodextrin, was assessed using FTIR studies. The FT-IR spectrum of the optimized solid dispersion was illustrated in Figure 1 showed the spectra of Valsartan alone. The FTIR peaks observed in both spectra were found to be identical, indicating that there were no interactions among Valsartan and the other excipients employed in this work, namely β-cyclodextrin.

The absence of any significant changes in the IR peaks suggested that Valsartan retained its molecular structure and integrity when formulated with β-cyclodextrin. This is crucial as it ensures that the drug remains stable and effective in the prepared solid dispersion, which is essential for achieving the desired therapeutic outcomes.[7]

The FTIR analysis provided valuable evidence of the compatibility between Valsartan and the excipients used, supporting the suitability of the formulation for potential pharmaceutical applications.

Formulation and Evaluation of Valsartan Tablets employing β-CD by Using 3^2 Factorial Study using Primojel and Starch Succinate

The study aimed to formulate and evaluate Valsartan tablets utilizing β-Cyclodextrin (β-CD) along with Primojel and Starch succinate through a 3^2 factorial design. Each tablet was designed to contain 40 mg of Valsartan and was prepared using the direct compression procedure based on the formulae provided in Table 1.

Prior to compression, the blends of tablet ingredients in each formulation were assessed for their flow characteristics. The compressibility index and angle of repose are calculated to evaluate the flow characteristics of the mixtures. The obtained outcomes, revealed that the angle of repose (θ) values ranged from 15° to 22° and the compressibility index (%) values varied between 10% to 12% for different formulations.[8]

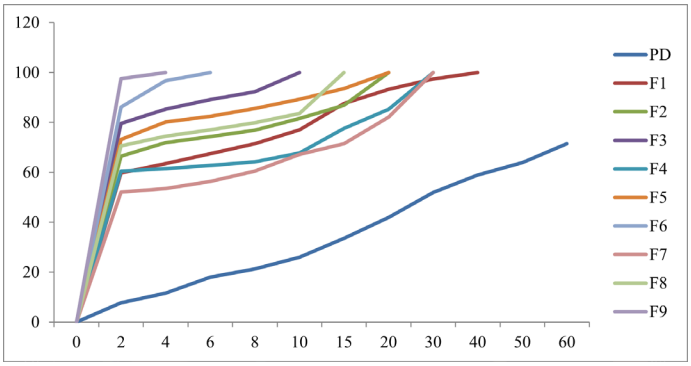

Figure 2: Dissolution Profile of Valsartan Tablets Prepared. PD*=Pure Drug.

The study continued by evaluating all the prepared tablets for various characteristics, including hardness, drug content, disintegration time, friability and dissolution rate.

The firmness of the tablets was set up to be in the limits of 4.0 to 6.0 kg/cm^2. This indicates that the tablets possess adequate mechanical strength, which is important for their handling and transportation without breakage or damage.

In the friability test, the weight loss observed was less than 1% for all the tablets, which suggests that they exhibit good resistance to abrasion and do not produce excessive fines during handling.

The Valsartan content of the tablets was found to be within the acceptable range of 100±3%, indicating that the tablets contain the specified amount of the active pharmaceutical ingredient (Valsartan).

The disintegration times of the tablets ranged from 15 to 30 sec. All tablets met the official disintegration time specification for uncoated tablets, ensuring that they disintegrate rapidly upon ingestion, which is crucial for fast dissolution and drug release.[9]

The study investigated the dissolution speed of different Valsartan tablets formulated in pH 6.8 phosphate buffers. The dissolution evidence was examined using zero and first-order kinetics for each tablet formulation.

The analysis revealed that the correlation coefficient (r) values are high for the first-order compared to the zero-order model. This suggests that the dissolution of Valsartan tablets prosecuted first-order kinetics, indicating that the speed of dissolution is proportional to the remaining amount of the drug in the tablet.

The correlation coefficient (r) values obtained from the first-order model ranged from 0.929 to 0.997. These high r-values indicate a strong correlation between the observed dissolution data and the predicted values based on the first-order kinetic model. The various Valsartan dissolution parameters, along with the corresponding data and results, are tabulated in Table 2. Additionally, Figure 2 graphically represents the dissolution

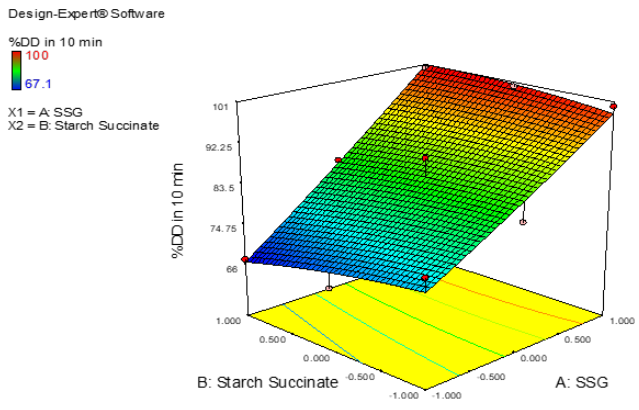

Figure 3: 3D Surface plot for % DD in 10 min.

profiles of the different Valsartan tablets, providing a visual representation of the drug release behavior over time.

In the formulation of Valsartan Fast Dissolving Tablets using a 3^2 factorial study, the percentage of independent variables 'Primojel' and Starch succinate are determined based on a chosen three-level, two-factor plan. The selected factors were varied at three levels, and their effects on the dependent variables, namely Disintegration Time (DT) and the percentage of drug disintegrated in 10 min, were assessed.

To determine the final equations for these dependent variables, the significance of the parameters was evaluated at a 95% confidence interval ($p<0.05$). The polynomial equations were then constructed to represent the relationships between the independent variables (Primojel and Starch succinate

Table 1: Formulae and Post Compression Parameters of Valsartan tablet formulations.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Valsartan*	40	40	40	40	40	40	40	40	40	40
Acacia	5	5	5	5	5	5	5	5	5	5
Sodium Starch Glycolate	12.5	15.63	18.75	12.5	15.63	18.75	12.5	15.63	18.75	15.69
Starch Succinate	12.5	12.5	12.5	15.63	15.63	15.63	18.75	18.75	18.75	16.80
MCC	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
TotalWeight	250	250	250	250	250	250	250	250	250	250
Post Compression Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Hardness (Kg/cm^2)	4.0± 0.11	4.50± 0.09	5.00± 0.08	5.25± 0.09	4.36± 0.07	4.96± 0.06	6.00± 1.36	5.75± 0.07	5.44± 0.06	5.43± 0.12
Percentage Drug Content (%)	100± 1.91	99.92± 1.94	99.68± 1.86	99.81± 1.75	99.72± 1.64	100± 1.97	98.6± 1.74	98.9± 1.52	100± 1.93	99.19± 1.48
Percentage Friability (%)	1.0	0.5	0.9	0.25	0.65	0.56	1.0	0.7	0.12	0.10
Disintegration time (Seconds (sec))	30 sec	19 sec	17 sec	26 sec	17 sec	15 sec	23 sec	16 sec	13 sec	12 sec

Table 2: Dissolution study parameters of solid dispersions.

Release Kinetics	R^2 Values First Order	R^2 Values Zero Order	K1 Values
PD	0.994	0.963	0.020
F1	0.989	0.747	0.116
F2	0.929	0.831	0.129
F3	0.967	0.920	0.332
F4	0.957	0.847	0.086
F5	0.944	0.779	0.175
F6	0.997	0.943	0.612
F7	0.958	0.877	0.077
F8	0.946	0.883	0.180
F9	0.997	0.987	0.783

PD: Pure Drug.

percentages) and the dependent variables (Disintegration Time and the percentage of drug dissolved in 10 min).

By employing this factorial study and analyzing the obtained data, the study aims to establish mathematical models that describe the influence of Primojel and Starch succinate percentages on the critical parameters of Valsartan Fast Dissolving Tablets, which are Disintegration Time and the rate of drug dissolution in the first 10 min. These equations will assist in optimizing the formulation to achieve desired disintegration and dissolution properties for the tablets.[10]

The formulation of Valsartan tablets utilized a factorial design with three levels of factor X1 (Primojel) and factor X2 (Starch Succinate). The concentrations of Primojel and Starch Succinate were selected at 5%, 6.25%, and 7.5%, calculated based on the total tablet weight, which was 250 mg.

The intention of this factorial work was to explore the impact of different combinations of X1 and X2 on achieving rapid dissolution of Valsartan formulations. Nine Valsartan fast-dissolving tablet formulations were obtained by implementing the factors (X1, X2) according to the 3^2 factorial study designs. These formulations were then analyzed to identify the optimal composition required to achieve the desired drug release profile. Additionally, the combined effects of X1 and X2 were assessed to understand their relevance in enhancing the dissolution rate of Valsartan.

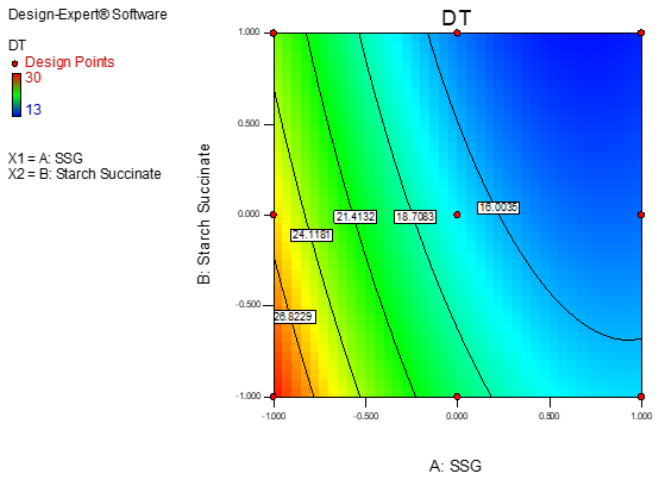

Figure 4: Counter Plot for DT of Valsartan tablet.

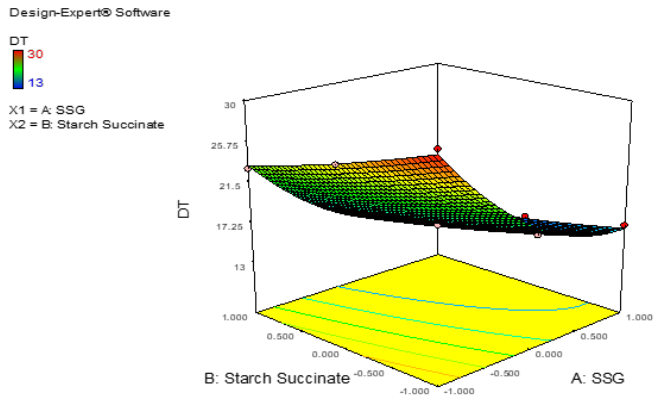

Figure 5: 3D SurfacePlot for DT of Valsartan tablet.

Each level of Primojel and Starch Succinate was coded as follows: -1 represented 5%, 0 represented 6.25%, and +1 represented 7.5%. This coding scheme helps in analyzing the effects of different concentrations and facilitates the comparison of the formulations.

Design Expert 7 software was used to derive Polynomial equations for Disintegration Time (DT), percentage drug dissolved in 10 min PD6 and percentage drug dissolved in 10 min (PD10).

The given Equation is a polynomial expression for 3^2 Factorial study

$$Y=b_0+b_1 X1+b_2 X2+b_{12} X1X2+b_{11} X1^2+b_{22} X2^2\ldots (1)$$

Where Y constitute dependent factor, b_0 represents the response of arithmetic mean across the F1-F9 batches, and b1 represents the predicted value for X1 factor.[11] The primary impacts (X1and X2) show the report that obtain when you gradually increase each factor from a low value to the high. The reaction alters when 2 factors are changes at once, as manifested by the interaction term (X1X2). To work non-linearity, the polynomial terms ($X1^2$ and $X2^2$) are inserted in equation. By creating one intermediate concentration as check point the validity of the resulting equations was confirmed. The expression for Disintegration time (DT), percentage drug dissolved in 10min (PD_{10}) developed as follows.

$$Y1=17.11–5.67X1-2.33X2+0.75\ X1X2+3.33X1^2+0.33\ X2^2(DT)$$

$$Y2=85.27+14.70X1-\ 1.30\ X2+\ 2.48\ X1X2\ +0.54X1^2-0.76\ X^2X^2(PD10)$$

Y1=Response of disintegration time (DT).

Y2=Response of percentage drug dissolved in 10 min (PD10).

The negative sign for factor X1 (Primojel) in the Y1 equation (Disintegration Time) indicates that as the concentration of Primojel decreases, the disintegration time increases. This means that higher levels of Primojel lead to faster disintegration of the tablets.

Similarly, the data from the experimental study shows that both X1 (Primojel) and X2 (Starch succinate) influence the disintegration interval of the tablets. The concentrations of both factors affect the length of time required for drug release, with higher concentrations of both Primojel and Starch succinate resulting in shorter disintegration times.

The study also compared the dissolution parameters observed from the experimental data with those predicted from the polynomial equations. The response surface plots depicted the response of X1 and X2 on Disintegration Time (DT) and Percent

Table 3: Predicted and Actual Values of Valsartan by Design Expert Software for Optimized Formulation.

Predicted Values		Actual Values	
DT (sec)	PD10 (%)	DT (sec)	PD10 (%)
13-18	85	15	84.65

of Drug Dissolved in 10 min (PD_{10}), These plots illustrate the relationship between the factors and the response variables, helping to identify the optimal formulations that yield the desired disintegration and drug dissolution characteristics.

Ultimately, the optimized formulations validate the derived expressions for the dependent variables, namely Disintegration Time (DT) and Percentage of Drug Dissolved in 10 min (PD_{10}). This confirms the accuracy and reliability of the polynomial equations in predicting the disintegration time and drug dissolution behavior of the Valsartan tablets. The study's findings and optimized formulations can be crucial in formulating tablets with desired release profiles and ensuring the efficacy and quality of the pharmaceutical product.

The optimized tablet (C1) demonstrated a disintegration time of 15 sec and achieved 85.69% drug dissolution within 10 min. This result determines the rationality of the derived equations for the dependent variables, as shown in Figures 3-5. Based on the outcomes, it can be negotiated that an elevation in the quantity of the super disintegrant (Primojel and Starch succinate) leads to a decrease in the disintegration time of the dosage form. This indicates that higher levels of the super disintegrant facilitate faster disintegration of the tablets, which is desirable for rapid drug release. Moreover, the drug release sequence can be altered by relevant selection of the X1 and X2 levels (Primojel and Starch succinate concentrations). This suggests that the dissolution speed of the drug can be controlled by adjusting the amounts of the super disintegrants, allowing for tailored drug release profiles. One particular formulation, F9, exhibited an impressive disintegration time of 13 sec and achieved 100% drug release within just 4 min. This formulation showcases the potential of the optimized tablet to rapidly release the drug, which may be particularly beneficial for certain medical conditions or patient populations. The dissolution specifications anticipated from the polynomial equations and the actual values noticed from the experimental outcomes are summarized in Table 3. The agreement between the anticipated and noticed values further validates the accuracy and reliability of the derived polynomial equations in describing the drug release behavior of the Valsartan tablets.[12] This suggests that starch succinate holds promise as an effective excipient for enhancing the dissolution and disintegration properties of Valsartan tablets, potentially leading to improved drug delivery and therapeutic outcomes

CONCLUSION

The study involved formulating tablets containing 40 mg of Valsartan using β-cyclodextrin (β-CD) along with primojel and starch succinate, prepared through the direct compression method. The outcomes demonstrated that the tablet powder mixes in every case exhibited magnificent flow properties, making them acceptable for direct compression. Furthermore, all the prepared tablets met the official disintegration time specifications for uncoated tablets, indicating that they disintegrated within the specified time frame upon ingestion. The analysis of dissolution kinetics revealed that the correlation coefficient (r) value was high for the first-order compared to the zero-order model. This suggests that the dissolution of Valsartan tablets followed first-order kinetics, where the drug's delivery rate is correlated to the remaining amount of the drug in the tablet. Additionally, the study observed that an increase in the amount of the super disintegrant (starch succinate) resulted in a decrease in the disintegration time of the tablets. This indicates that higher concentrations of starch succinate led to faster disintegration, facilitating rapid drug release. Based on these findings, it can be concluded that starch succinate can be used as a novel super disintegrant, alongside other commercial super disintegrants, for the formulation and optimization of fast dissolving tablets. This suggests that starch succinate holds promise as an effective excipient for enhancing the dissolution and disintegration properties of Valsartan tablets, potentially leading to improved drug delivery and therapeutic outcomes.

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CONFLICT OF INTEREST

The authors confirm that there are no conflicts of interest regarding the publication of this article.

ABBREVIATIONS

BCS: Biopharmaceutics Classification System; **β-CD:** β-cyclodextrin; **X1:**Primojel; **X2:** Starch succinate; **PD10:** Portion of drug dissolved in 10 min; **PD:** Pure drug; **DT:** Disintegration Time; **C1:** Optimized tablet; **CCBs:** Calcium Channel Blockers;

GI: Gastrointestinal; **SD:** Solid dispersion; **NaOH:** Sodium hydroxide; **HCl:** Hydrochloric acid; **FT-IR:** Fourier-transform infrared; **H_2O:** Water; **KBr:** Potassium bromide; **API:** Active pharmaceutical ingredient; **RSD:** Relative Standard Deviation; **UV:** Ultraviolet, **nm:** Nanometer; **cm:** Centimeter; **mm:** Millimeter; **kg:** Kilogram.

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