Hindawi
International Journal of Chemical Engineering
Volume 2024, Article ID 8734695, 13 pages
https://doi.org/10.1155/2024/8734695

Research Article

A Retrospective Analysis of Polymer Selection Using Solvent Casting: Formulation and DoE Optimization of the Amorphous Solid Dispersion of Amoxicillin Trihydrate by a Spray Drying Method

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Received 30 January 2024; Revised 14 March 2024; Accepted 25 March 2024; Published 8 April 2024

Academic Editor: Michael Harris

Background. Amoxicillin trihydrate possesses poor solubility, compressibility, and flow behavior. Amorphous solid dispersion prepared by spray drying could solve all three problems at the same time. *Objective*. To prepare amorphous solid dispersion after screening of polymers by solvent casting method using a spray drying method. *Methods*. The solvent casting method was used to screen polymers, PVP/VA S-630, PVP K30, Soluplus, PEG 4000, HPMC AS, and HPMC HP55, in 1 : 1 and 2 : 3 ratios and followed by spray drying after polymer selection. *Results*. The dissolution performance of the formulation improved with time. The optimum feed rate and feed concentration were found to have an impact on the flow properties and particle size of spray-dried formulations, and they were selected as independent variables in a 3^2 full factorial statistical design. The ANOVA and regression analysis suggest that the developed regression model has a significant overall fit to the data and can explain a substantial proportion of the variability in the dissolution at 10 minutes. The optimized batch was selected based on the decisive factors of minimum and maximum values of response variables. Overall, the optimized batch demonstrated improved characteristics in terms of percentage yield (32.81%), dissolution at 10 min (49.70%), and angle of repose at 31.42°. *Conclusion*. This study provides valuable insights into optimizing formulation strategies for preserving the amorphous state of drugs and contributes to the development of stable pharmaceutical formulations.

1. Introduction

Amoxicillin trihydrate, which is chemically (2S,5R,6R)-6-[[(2R)-2-Amino-2-(4-hydroxyphenyl) acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptanes-2-carboxylic acid trihydrate, Figure 1, is an analog of ampicillin, semisynthetic, broad-spectrum, beta-lactam antibiotic with bacteriolytic and bactericidal activity against many Gram-positive and Gram-negative microorganisms. Amoxicillin trihydrate is widely used in the treatment of genitourinary tract infections; otitis media, nose, and throat infections; upper and lower respiratory tract infections; *helicobacter pylori* infections; and pharyngitis, tonsillitis, and urogenital tract infections [1]. It binds to the penicillin-binding protein (PBPs) and inhibits the final step of transpeptidation in peptidoglycan synthesis and the synthesis of the bacterial cell wall.

It is generally known that antibiotic compounds in powder form are not suitable for formulation purposes, as these powders generally perform poorly when it comes to flowability, which leads to difficulties in the production of final dosage forms such as tablets. Tablets comprise the most widely used dosage form due to their low cost of manufacturing as compared to other formulations, accurate

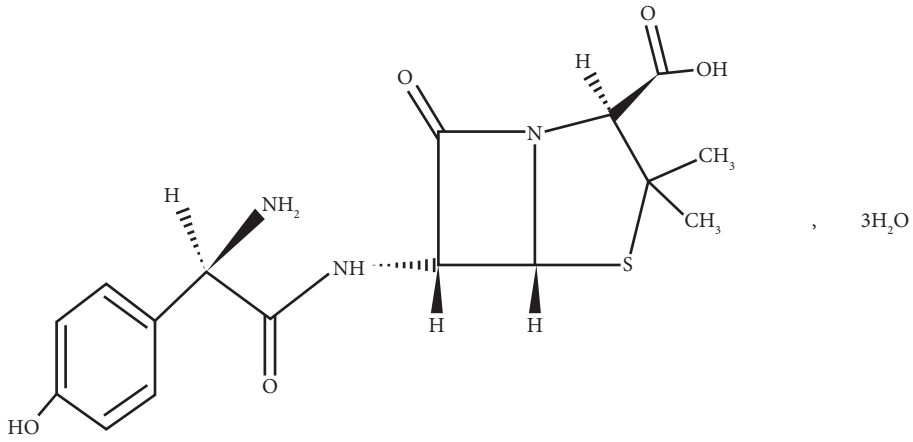

Figure 1: Molecular formula of amoxicillin trihydrate (AT).

dosing, and patient convenience. Direct compression and wet or dry granulation are two methods for making tablets [2, 3].

Direct compression is simple, improves productivity, and is a cost-effective method of tablet manufacturing as compared to wet or dry granulation. Direct compression eliminates many steps (like granulation, drying, etc.) of the dry granulation and wet granulation techniques [4, 5]. However, it requires excellent flowability and compressibility, but contrarily, amoxicillin trihydrate has poor flowability and compressibility, which leads to its characteristics and direct compression is very difficult and creates challenges in the production of final dosage forms such as tablets [6]. Consistent final product quality requires precise dosing, which is challenging to achieve in the case of poor flowability. To address these problems, it requires improvements in flowability and compressibility that facilitate tablet manufacturing by direct compression.

"Solid dispersions as a technique of increasing dissolution and oral bioavailability for weakly water-soluble medicines," Sekiguchi and Obi reported in 1961. All drugs are dispersed within a single solid carrier matrix in solid dispersion. Solid dispersion is classified based on the molecular arrangement of the drug and carrier [7]. Either the drug is a separate crystalline or amorphous particle suspended in the carrier, or the drug and carrier coexist as a single amorphous phase. Solid dispersion can be prepared using several different techniques, such as solvent evaporation, hot melt extrusion, rotary evaporation, and spray drying. [8].

In recent decades, spray drying has emerged as a prominent processing technology for developing amorphous solid dispersions of drugs. It is a one-step process that can convert suspension or solution into dry powder. In this process, the API and excipient are dissolved in a common volatile solvent and atomized into a stream of hot gas. As the solvent evaporates from the droplet, the solutes rapidly solidify, trapping the API in an amorphous state within the carrier matrix. Drugs are often in an amorphous state in solid dispersions prepared by spray drying; therefore, the solubility and the dissolution rate are significantly increased [9].

Spray drying is the most suitable technique for controlling the production and process variables of powder, such as particle size, shape, and density. It is the most important characteristic of flow property and compressibility [10]. Solid dispersion products prepared by spray drying are available commercially, such as Insweek® and Intullation®.

Based on this consideration, the objective of this research was to formulate an amorphous solid dispersion of amoxicillin trihydrate by a spray drying technique for dissolution enhancement in comparison with existing formulations and an improvement in compressibility and flow properties of amoxicillin trihydrate. This research is motivated by the pressing need to enhance the solubility and overall bioavailability of amoxicillin trihydrate. The novelty lies in the systematic exploration of various polymers, including PVP/VA S-630, PVP K30, Soluplus, PEG 4000, HPMC AS, and HPMC HP55, through solvent casting and subsequent optimization via a 3^2 full factorial statistical design. The formulation strategies presented herein aim to contribute to the development of stable pharmaceutical formulations with improved characteristics. While the findings contribute valuable insights into formulating strategies for preserving the amorphous state of drugs, it is crucial to acknowledge the limitations of the study. The study primarily focuses on the impact of feed rate and feed concentration on the characters like flow properties and dissolution rate of spray-dried formulations. While this investigation provides significant insights, other formulation parameters and external factors may influence the overall performance of the amorphous solid dispersion.

2. Materials and Methods

2.1. Materials. Amoxicillin trihydrate was provided as a gift sample by Bharat Parenterals Ltd. PVP/VA S-630 (Plasdone S-630) and HPMC AS were provided as gift samples by Ashland Global. Soluplus® and Poloxamer 407 were purchased from BASF. PVP k30, PEG 4000, DCM, acetone, and methanol were purchased from Molychem Chemicals. HPMC HP55 was purchased from Hipax Ester Pvt. Ltd., Maharashtra. Kyron T314 was purchased from Doshion Polymers Solution Pvt. Ltd. Microcrystalline cellulose (MCC) was purchased from RanQ Remedies Pvt. Ltd. Aerosil was purchased from Evonik. IPA was purchased from Lucemill Ltd.

2.2. Preparation of Amorphous Solid Dispersion by Spray Drying

2.2.1. Selection of Suitable Excipient for Spray Drying by Film Casting Method. The excipients are generally selected based on the requirement of a final solid dispersion with the required characteristics. Based on the required final characteristics of solid dispersion, a suitable range of primary excipients should be selected. The primary material selected and its physical properties significantly influence the characteristics of the solid dispersion. Polymers, such as PVP/VA S-630, Soluplus, Poloxamer-407, polyvinylpyrrolidone (PVP K-30), HPMC AS, PEG-4000, and HPMC HP55, were used in the current investigation.

2.2.2. Procedure for Selection of Carrier by a Film Casting Method. A schematic illustration of the film casting technique is shown in Figure 2. Binary mixtures of amoxicillin trihydrate with PVP/VA S-630, PVP K30, Soluplus, PEG 4000, HPMC AS, HPMC HP 55, and Poloxamer 407 in (1 : 1) and (2 : 3) ratios dissolve in methanol with the help of SLS. The solutions were poured onto $4 * 8\,cm^2$ glass plates and then cast into films using a K42—four-sided film applicator (Mumbai). A fixed gap of 200 μm in the film applicator was used, which resulted in uniform film application on the plates (Figure 2). Transparent to translucent films were produced when the plates were dried at room temperature to remove the organic solvent for 6 h. Dry film was scraped for the initial DSC sample, and after 1 month, the miscibility of the drug carrier in the stabilized amorphous form of the drug was analyzed [11].

2.2.3. Solvent Selection for Preparation of Feed Solution to be Spray-Dried. Solvent selection is a crucial stage in the manufacturing of solid dispersions, having significant implications for processability, stability, and performance. In general, solvents selected for the preparation of feed solutions provide a high process throughput, which is influenced by solution viscosity, solvent vapor pressure, the heat of vaporization, and API or excipient solubility in the spray solvent. Water is commonly used as a spray drying solvent because it is inexpensive, nontoxic, and does not produce solvent residue like organic solvents.

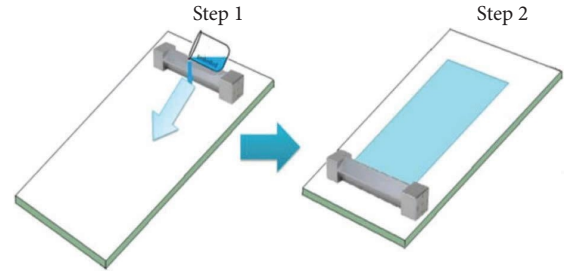

Figure 2: Schematic representation of film casting method.

Furthermore, solvent selection is based on the solubility and affinity of the drug and excipient toward the solvent. In the present research work, the solvent used is dichloromethane because drugs and excipients are formed into uniform suspensions in dichloromethane. The advantage of using dichloromethane as a solvent is that it has a lower boiling point (39.6°C) and evaporates quickly at lower temperatures [12].

2.3. Spray Drying. Spray drying is a one-step process that can be performed in continuous mode. Spray drying involves atomizing a solution or suspension containing one or more components of the desired product, converting it into droplets by spraying, and then quickly evaporating sprayed droplets into solid powder with hot air at the requisite temperature and pressure [13]. Spray drying is performed in a laboratory-scale spray dryer (LU-222 Advanced, Lab Ultima, Mumbai). The spray drying process is carried out in a co-current airflow spray dryer in which hot air and sprayed solution together move in the same direction, and the set spray drying orifice diameter is 0.7 mm. All parameters were set according to the requirements, and spray drying was carried out for all preliminary batches.

2.3.1. Preliminary Trials Carried Out by Spray Drying Technique. In this study, a lab-scale spray dryer was used. Various parameters influence the drying process. Parameters, such as feed rate, inlet temperature, pressure, and carrier/excipient amount, were optimized during the preliminary studies.

2.3.2. Selection of Experimental Protocol from Preliminary Trials. Based on the above preliminary studies, it was concluded that feed rate and feed concentration have a significant effect on product quality and quantity. A 3^2 full factorial design was employed for the optimization of feed rate and feed concentration. The use of three levels indicates the possibility of a nonlinear relationship between two factors and the response. The full regression equation contains linear terms, quadratic terms, and all interactions between the factors. Based on the preliminary study, PVP/VA S-630 was kept constant, and as the feed rate impacted the flow properties of the formulation, it was selected as a variable. Feed concentration is also a significant parameter, which needs to be optimized.

2.4. Experimental Design. A 3^2 full factorial design was employed to assess and quantify the impact of independent variables on dependent variables. A total of nine experimental trials were generated at each stage by Design Expert 12.0 Trial Version performed in all possible combinations. Based on the preliminary studies, feed rate (X_1) and feed concentration (X_2) were selected as independent variables (Table 1), while percentage yield (Y1), dissolution at 10 min (Y2), and an angle of repose (Y3) were selected as dependent variables.

2.5. Evaluation Parameters

2.5.1. Fourier Transform Spectrum Study. Identification of drugs and compatibility between drugs and excipients were carried out by FTIR analysis with the help of the potassium bromide (KBr) disk method [14]. In this sample, the correct ratio of KBr powder was used. The sample/KBr mixture is then placed into a die and compacted using a hydraulic press. A spectrophotometer (Shimadzu, Japan) was used to record FTIR spectra between 450 and 4000 cm^{-1} with a resolution of 4 cm and 45 scans.

2.5.2. Differential Scanning Calorimetry. The differential scanning calorimetry (DSC) investigation involving amoxicillin trihydrate and various polymers was carried out utilizing the Shimadzu DSC-60 model, coupled with the TA-60WS Thermal Analysis System software. Sample preparation comprised accurately weighing 2–5 mg of amoxicillin trihydrate and each polymer. Instrument calibration adhered to manufacturer guidelines to ensure accurate results. The DSC instrument parameters were set with a temperature range of 25°C to 300°C, a heating rate of 10°C/min, and a nitrogen purge rate of 50 mL/min. Aluminum pans and lids were employed for sample encapsulation. The analytical procedure encompassed a baseline scan with an empty pan to establish a reference, followed by the loading, sealing, and analysis of individual samples under preset parameters.

2.5.3. Angle of Repose. The angle of repose was calculated using the standard fixed funnel method [15]. It indicated the maximum angle created between the surface of the pile of powder and the horizontal plane. In this technique, a glass funnel was positioned at a specific height (h) above graph paper placed on a flat horizontal surface. The formulation was continuously poured through the funnel until the apex of the conical pile just touched the funnel's tip. The angle of repose (h) was then calculated using the following formula:

$$\theta = \tan^{-1}\left(\frac{h}{r}\right), \tag{1}$$

where θ = angle of repose, h = height of pile, and r = radius of the pile.

2.5.4. Tapped Density and Bulk Density. Bulk and tapped densities were measured according to the United States Pharmacopeia (USP) [16]. Bulk density is the quotient of weight to the volume of the sample. A 100-mL Class A graduated cylinder was modified to reduce the test sample size. Before being added to the cylinder, samples were sieved through a No. 18 mesh to break up any agglomerates. The starting volume of the powder ranged from 60 to 75 mL before tapping. The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. Tapped density is obtained by mechanically tapping a graduated measuring cylinder containing a powder sample 500 times from a height of 1.5 inches. The Carr index for each ASD was calculated using these densities.

2.5.5. Carr's Index. In recent years, the compressibility index and the closely related Hausner's ratio have become simple, fast, and popular methods of predicting powder flow characteristics. The percentage compressibility index, or Carr's index, was used to express the flowability of amorphous solid dispersion based on bulk density and tapped density [17]. The Hausner ratio was used to express the cohesiveness of amorphous solid dispersion based on bulk density and tapped density. The percentage compressibility index (Care Index) was determined as 100 times the proportion of the difference between tapped and bulk density for tapped density.

$$\begin{aligned} \text{Carr}'\text{s index} &= \left(\frac{\text{tapped desity} - \text{bulk density}}{\text{tapped density}}\right), \\ \text{Hausner}'\text{s ratio} &= \frac{\text{tapped density}}{\text{bulk density}}. \end{aligned} \tag{2}$$

2.5.6. Powder X-Ray Diffraction (PXRD). Powder X-ray diffraction is an indispensable tool for the characterization of amorphous solid dispersion. Powder X-ray diffractometers are used to understand the structural quality analysis of compounds [18]. The X-ray diffraction analysis of the pure drug and prepared amorphous solid dispersion was recorded by using a powder X-ray diffractometer equipped with Cu-Ka radiation (1.54060 Å) and Ni filters. The applied voltage and current used were 40 kV and 30 mA, respectively. The scanning range was between 5 and 80° (2θ) with a scanning speed of 1 min^{-1}.

2.5.7. In Vitro Dissolution Study. *In vitro* dissolution studies were carried out according to the USP 38 type-II paddle apparatus at 75 RPM using 900 mL of water as the dissolution medium, and the temperature was maintained at 37 ± 0.5°C [2]. Dissolution samples were collected at 0 min, 10 min, 20 min, 30 min, and 60 min in 5 mL aliquots each time using emerald plastic syringes and immediately replaced by a prewarmed fresh dissolution medium. The collected sample was passed through a 0.45-μm PVDF syringe filter and diluted further with dissolution media. All diluted samples were measured at 228 nm using the Shimadzu UV-1800 spectrophotometer.

Table 1: Design batches with coded and decoded values.

Batch no.	Independent variables			
	Coded value		Decoded value	
	Feed rate (ml/min) (X_1)	Feed concentration (gm/100 ml) (X_2)	Feed rate (ml/min)	Feed concentration (gm/100 ml)
F_1	−1	−1	3	3.75
F_2	0	−1	4	3.75
F_3	1	−1	5	3.75
F_4	−1	0	3	5.625
F_5	0	0	4	5.625
F_6	1	0	5	5.625
F_7	−1	1	3	7.5
F_8	0	1	4	7.5
F_9	1	1	5	7.5

3. Results and Discussion

3.1. Selection of Carrier by Film Casting Method. The selection of carriers was performed using the film casting method via the miscibility check and stability after one month. The selection of an appropriate carrier is a difficult task. Of the carriers available for solid dispersion, an ideal carrier should be stable and improve amorphicity and dissolution [11, 19]. The film casting method is used to check whether a drug can form stable amorphous dispersion or miscibility with a carrier or not. For the selection of the carrier, two, drug-to-carrier, ratios 2 : 3 and 1 : 1, were studied using materials like PVP k30, PVP/VA S-630, HPMC AS, HPMC HP55, PEG 4000, and Soluplus®. The DSC thermograms were studied on Day 1 and after one month to evaluate the amorphicity of the dried film.

In Figure 3, the results of a one-month stability study after casting a dried film on a glass plate are presented for different molecular ratios of PVP K30, PVP/VA S-630, and HPMC AS (1 : 1 and 2 : 3). Figure 3(a) clearly demonstrates that the 1 : 1 ratio of PVP K30 fails to effectively stabilize the drug in its amorphous form, leading to drug crystallization. Over the course of one month, an endothermic peak is observed, indicating changes in the amoxicillin trihydrate compound.

However, when PVP K30 is present in a ratio of 2 : 3, the drug shows remarkable stability in its amorphous state. This is evidenced in Figure 3(b), where the drug peak is absent both initially and after one month, as observed in the DSC thermogram. These findings align with the conclusions of Parikh et al., who also noted the absence of any endothermic or exothermic peaks in the DSC thermogram, indicating the drug's presence in its amorphous form [11].

The reason behind the improved stability of the drug in its amorphous state when PVP K30 is present in a 2 : 3 ratio can be attributed to the specific interactions and molecular arrangement facilitated by this particular ratio. The higher proportion of PVP K30 in the formulation likely enhances its ability to encapsulate and protect the drug molecules, preventing their crystallization and maintaining their amorphous structure. This provides valuable insights into optimizing the formulation composition for ensuring the desired stability of amorphous drugs.

The thermogram of PVP/VA S-630 (in a 1 : 1 ratio) indicates the presence of an endothermic peak, suggesting that the drug did not remain stable in its amorphous form after one month though mixture formed amorphous dried film at the end of a day, as demonstrated in the accompanying Figure 3(c). The DSC thermogram of the PVP/VA S-630 drug film (2 : 3), both initially and after one month, indicates the absence of any endothermic or exothermic peaks. This suggests that the drug has been successfully stabilized or mixed homogeneously with the carrier in its amorphous form, demonstrating stability over the course of one month. This information is supported by Figure 3(d).

The utilization of HPMC AS in a 1 : 1 and 2 : 3 proportion does not demonstrate sufficient efficacy in preserving the drug's amorphous state (as observed in Figures 3(e) and 3(f)). Over the course of one day and one month, the drug displays both endothermic and exothermic peaks, which indicate the occurrence of crystallization. The reason behind this outcome could be attributed to the inadequate compatibility between the drug and the chosen ratio of HPMC AS. The specific interaction between the drug and the excipient is crucial for maintaining the amorphous form. In this case, the combination of HPMC AS in the mentioned ratios fails to establish a stable environment for the drug, leading to the observed crystallization phenomenon. Furthermore, exploration of alternative excipients or modification of the ratio may be necessary to enhance the stabilization of the drug in its desired amorphous state.

The addition of HPMC HP55 in a 1 : 1 ratio successfully maintains the stability of amoxicillin trihydrate in its amorphous state, as evidenced by the DSC thermogram obtained after one month (Figure 4(a)). In contrast, using HPMC HP55 in a 2 : 3 ratio fails to stabilize the drug in its amorphous form, resulting in drug crystallization after one month, as depicted in Figure 4(b). The reason for this discrepancy could be attributed to the altered composition of HPMC HP55 in the 2 : 3 ratio. It is possible that the higher proportion of HPMC HP55 in relation to amoxicillin trihydrate disrupts the desired interactions between the molecules, preventing the formation of a stable amorphous structure. This imbalance in the formulation might lead to increased mobility and decreased molecular packing, facilitating the drug's transition into a crystalline state. Hence,

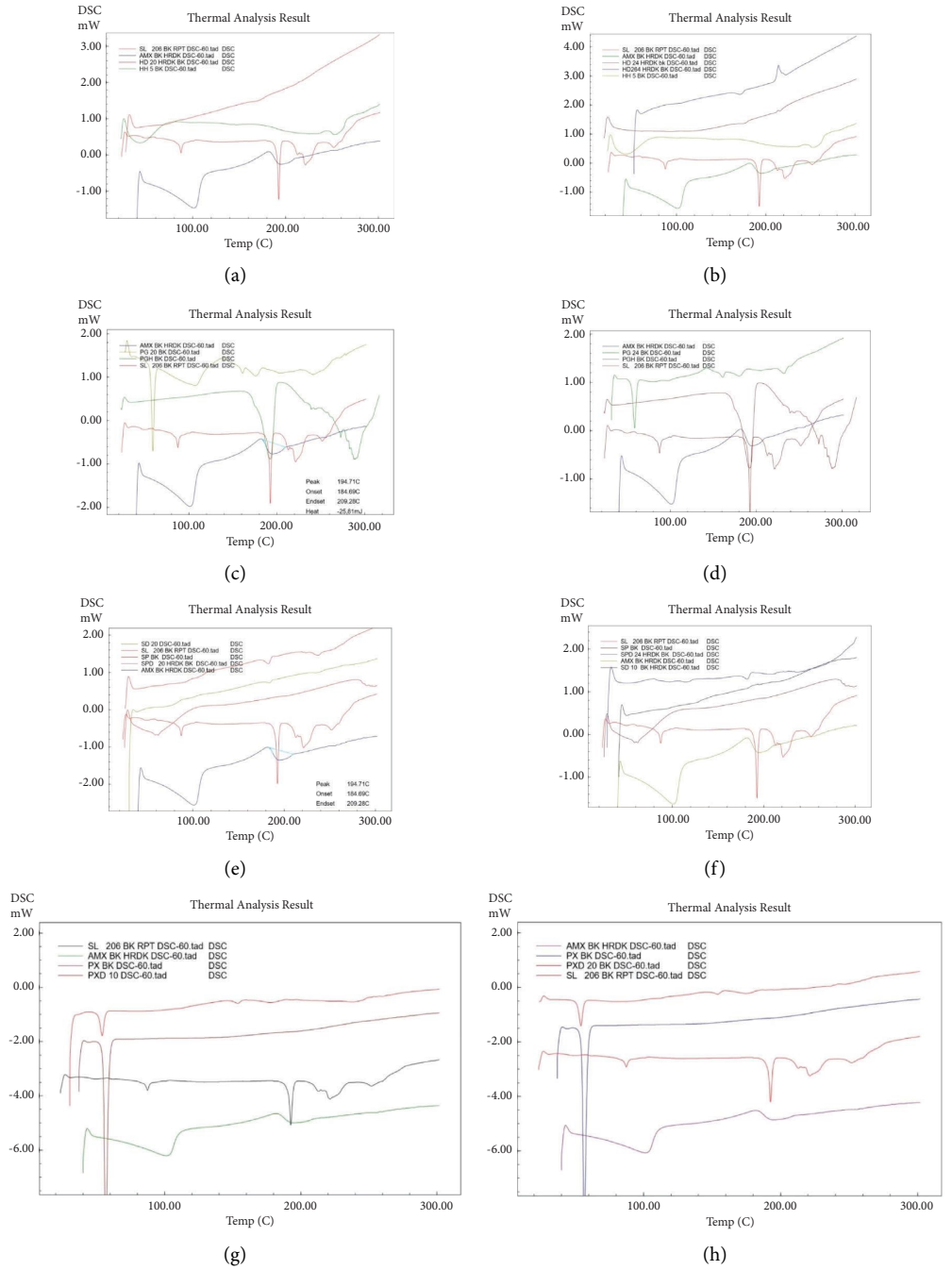

Figure 3: DSC thermogram after 1-day and 1-month stability (a) AT: PVPK30 (1 : 1), (b) AT: PVPK30 (2 : 3), (c) AT: PVP/VA S-630 (1 : 1), (d) AT: PVP/VA S-630 (2 : 3), (e) AT: HPMC AS (1 : 1), (f) AT: HPMC AS (2 : 3), (g) AT: POLOXAMER 407 (1 : 1), (h) AT: POLOXAMER 407 (2:3) (sample codes in thermogram: AMX—amoxicillin trihydrate, SL—SLS (sodium lauryl sulfate), PK—PVP k30, PVD10—film at initial time (drug + PVP k30 + SLS), PVP 24—film at 1 month (drug + PVP k30 + SLS), PVD20—film at initial time (drug + PVP k30 + SLS), PVP 20—film at 1 month (drug + PVP k30 + SLS), PV 630—PVP/VA S-630, PD10—film at initial time (drug + PVP/VA S-630 + SLS), VAD24—film at 1 month (drug + PVP/VA S-630 + SLS), PD10 BK—film at initial time (drug + PVP/VA S-630 + SLS), VAD20—film at 1 month (drug + PVP/VA S-630 + SLS), HAS—HPMC AS, HASD—film at initial time (drug + HPMC AS + SLS), HS24—film at 1 month (drug + HPMC AS + SLS), HAD 20 20—film at initial time (drug + HPMC AS + SLS), HS20—film at 1 month (drug + HPMC AS + SLS), PX—Poloxamer 407, PXD10—film at initial time (drug + Poloxamer 407 + SLS), PXD20—film at initial time (drug + Poloxamer 407 + SLS)).

the 1 : 1 ratio of HPMC HP55 appears crucial for achieving the desired stability of amoxicillin trihydrate in its amorphous form.

The DSC thermogram of 2 : 3 and 1 : 1 ratios of PEG 4000 with the drug indicates that the drug cannot be stabilized in its amorphous state (Figures 4(c) and 4(d)). The thermogram

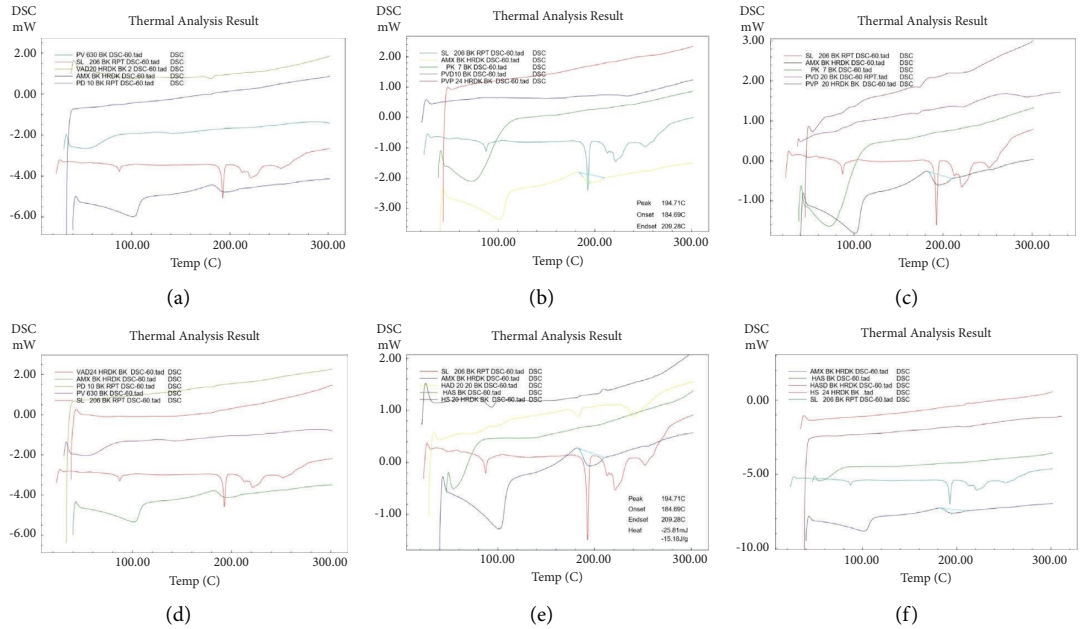

Figure 4: DSC thermogram after 1-day and 1-month stability (a) AT: HPMC HP55 (1 : 1), (b) AT: HPMC HP55 (2 : 3), (c) AT: PEG4000 (1 : 1), (d) AT: PEG4000 (2 : 3), (e) AT: SOLUPLUS (1 : 1), (f) AT: SOLUPLUS (2 : 3) (sample codes in thermogram: AMX—amoxicillin trihydrate, SL—SLS (sodium lauryl sulfate), HH 5—HPMC HP 55, HD24—film at initial time (drug + HPMC HP 55 + SLS), HD264—film at 1 month (drug + HPMC HP 55 + SLS), HH 5—HPMC HP 55, HD20—film at 1 month (drug + HPMC HP 55 + SLS), PGH—PEG 4000, PG24—film at initial time (drug + PEG 4000 + SLS), PG20—film at initial time (drug + PEG 4000 + SLS) SP—Soluplus, SD10—film at initial time (drug + Soluplus + SLS), SPD24—film at 1 month (drug + Soluplus + SLS), SD20—film at initial time (drug + Soluplus + SLS), SPD20—film at 1 month (drug + Soluplus + SLS)).

reveals that the endo- and exothermic peaks of the drug and drug carrier are not compatible and do not form a molecularly dispersed mixture. As a result, the drug's stability in the amorphous form is not achievable initially, as depicted in the accompanying figure. This is likely due to the lack of miscibility and molecular dispersion between the drug and carrier components.

Soluplus in ratios of 2 : 3 and 1 : 1 effectively stabilizes the drug in an amorphous state during the initial phase. However, over a period of one month, these ratios fail to consistently maintain the drug's amorphous state, resulting in drug crystallization. This phenomenon is evident in the DSC thermogram (Figures 4(e) and 4(f)), which displays both endothermic and exothermic peaks. The reason behind this instability could be attributed to several factors. One possible explanation is that the solubility of the drug in the Soluplus matrix decreases over time, leading to the formation of drug crystals. Additionally, environmental factors, such as moisture or temperature fluctuations, might contribute to the loss of amorphous stability. It is also possible that the chosen ratios of Soluplus are not ideal for long-term stabilization of the drug in an amorphous form, indicating the need for further optimization of the formulation.

The stability-preserving properties of Poloxamer 407 in both 2 : 3 and 1 : 1 ratios decline over the course of one month when it comes to maintaining the amorphous state of amoxicillin trihydrate (Figures 4(g) and 4(h)). This decrease in stability can be attributed to certain factors. One possible reason for the diminished stability is the limited solubility of amoxicillin trihydrate in the Poloxamer 407 formulations. Over time, the solubility of the drug may decrease, leading to the precipitation of amoxicillin trihydrate crystals. The formation of crystals disrupts the amorphous structure, reducing the stability of the drug. Another factor that contributes to the decreased stability is the propensity of Poloxamer 407 to undergo gelation. Poloxamer 407 is known for its gel-forming properties, which are beneficial for maintaining the amorphous state of drugs. However, over time, the gel network may degrade or weaken, causing the drug molecules to aggregate or crystallize, thus diminishing the stability of amoxicillin trihydrate.

Additionally, environmental factors such as temperature and humidity can also impact the stability of the drug in the Poloxamer 407 formulations. Changes in these conditions may promote the degradation or recrystallization of amoxicillin trihydrate, further reducing its stability in the amorphous form. To maintain the stability of amoxicillin trihydrate in its amorphous state for longer durations, alternative formulation strategies or excipients with enhanced solubility, anticrystallization, and gel-stabilizing properties may need to be explored.

In conclusion, the stability of amoxicillin trihydrate in its amorphous form is influenced by the molecular ratios of various excipients in the formulation. The presence of PVP K30 in a 2 : 3 ratio demonstrates remarkable stability, preventing drug crystallization over a one-month period. Same

was the case with PVP/VA S-630 when used in ratio 2 : 3. On the other hand, the 1 : 1 ratio of PVP K30 and PVP/VA S-630 fails to effectively stabilize the drug, leading to crystallization. Similarly, the utilization of HPMC AS in both 1 : 1 and 2 : 3 ratios does not provide sufficient efficacy in preserving the drug's amorphous state, resulting in crystallization. The addition of HPMC HP55 in a 1 : 1 ratio successfully maintains stability, while the 2 : 3 ratio leads to drug crystallization. The use of PEG 4000 in both ratios fails to stabilize the drug in its amorphous state. Soluplus in both ratios effectively stabilizes the drug initially, but fails to maintain long-term stability, leading to drug crystallization. Poloxamer 407 in both ratios also exhibits a decline in stability over time, attributed to limited solubility, gelation properties, and environmental factors.

These findings highlight the importance of selecting appropriate excipient ratios to achieve the desired stability of amorphous drugs. The specific interactions and molecular arrangements facilitated by the chosen ratios play a crucial role in preventing drug crystallization [20]. Furthermore, optimization of the formulation composition, including exploration of alternative excipients with enhanced properties, may be necessary to enhance the stabilization of amoxicillin trihydrate in its amorphous form. Additionally, environmental factors should be considered when designing formulations to ensure long-term stability [21].

Overall, this study provides valuable insights into optimizing formulation strategies for preserving the amorphous state of drugs and contributes to the development of stable pharmaceutical formulations. In next step, spray drying was used to develop a stable formulation using drug with PVP K30 and PVP/VA S-630 in a 2 : 3 ratio and with HPMC HP55 in a 1 : 1 ratio. Preliminary trials were carried out using different inlet and outlet temperatures, feed rate, aspiration speed, pressure, and solvent and solvent quantity. During preliminary trials HPMC HP55 and PVP K30, formulation did not give positive results on the parameters of amorphous state (DSC thermogram), percentage yield (>30%), flow property (angle of repose <40), and sphericity and compressibility index (<25). Hence, further trails were carried out using drug and PVP/VA S-630 (Plasdone) in 2 : 3 ratios. The samples were subjected to FTIR analysis, and AT was found to be noninteracting with the Plasdone (Figure 5).

These trial batches had narrow particle size distributions, and they were not influenced by the drying rate, energy input in the drying chamber. At the end of preliminary trails, inlet temperature was fixed at 70°C, outlet temperature at 40 ± 5°C, aspiration speed at $30 \pm 5\ \mathrm{Nm}^3$/hr, and pressure at 0.5 Bar. Feed rate and feed concentration were found to have impact on flow properties and particle size of spray-dried formulation and so were selected as independent variables in 3^2 full factorial statistical design.

3.2. Statistical Optimization of Design Batches. Table 2 presents data on various parameters for different samples labeled F_1 to F_9. The percentage of the desired product obtained after a chemical or manufacturing process. The values range from 18.20% to 37.63%. F_3 shows the highest yield, while F7 has the lowest. The bulk density is defined as the mass of the sample per unit volume, without any external forces applied. The bulk densities for all samples are 0.222 gm/ml or 0.250 gm/ml. The tap density is defined as the mass of the sample per unit volume after applying tapping or vibration which results in decrease of porosity due to rearrangement of particles. The tapped densities for all samples are similar, ranging from 0.250 gm/ml to 0.285 gm/ml. Carr's index ranges from 11.200% to 12.280%. Lower values indicate better flowability. F_1 and F_2 have the lowest Carr's index, suggesting good flowability. A parameter used to assess powder compressibility. All samples have a Houser's ratio around 1.126 to 1.140, indicating similar compressibility characteristics. The angle of repose is the maximum angle at which a pile of powder remains stable. It provides insight into the flowability and cohesiveness of the powder. Angle of repose values ranges from 29.74° to 41.009°. Higher values indicate lower flowability. F_9 has the highest angle of repose, suggesting poor flowability compared to the other samples. From the analysis, we observe variations in percentage yield, flowability (Carr's index and angle of repose), and angle of repose among the different samples. F_3 shows the highest yield, F_1 and F_2 exhibit good flowability, and F_9 has the poorest flowability. These variations could be attributed to differences in formulation, processing conditions, or other factors specific to each sample.

The provided data (Table 3) represent the results of a dissolution study conducted for the formulation development of an amorphous solid dispersion using the spray drying method. The table includes the time intervals (in minutes) and the corresponding values for various batches (F_1 to F_9). The dissolution performance of the developed formulation improved with time. The dissolution values at 60 minutes demonstrated the highest dissolution percentages (>90%), indicating that the formulation continued to dissolve and release the active ingredients as time progressed.

The sum of squares represents the variability explained by the regression model and the residual variability. In this case, the regression model explains 397.632 units of variability, while the residual (unexplained) variability is 2.074 units (Table 4). The significance F value determines the overall significance of the regression model. It is obtained by comparing the F value to a critical value from the F-distribution. The low p value of 0.001 indicates that the regression model is statistically significant. The R-squared value indicates the proportion of variability in the dependent variable Y1 that is explained by the independent variables in the regression model. In this case, the R-squared value is 0.994, which suggests that the model accounts for 99.4% of the variability in the percentage yield.

The coefficient values indicate the magnitude and direction of the effect. For example, a positive coefficient suggests a positive relationship with the percentage yield, while a negative coefficient suggests a negative relationship. The significance of each coefficient (indicated by the p values) determines if it is statistically significant in the model.

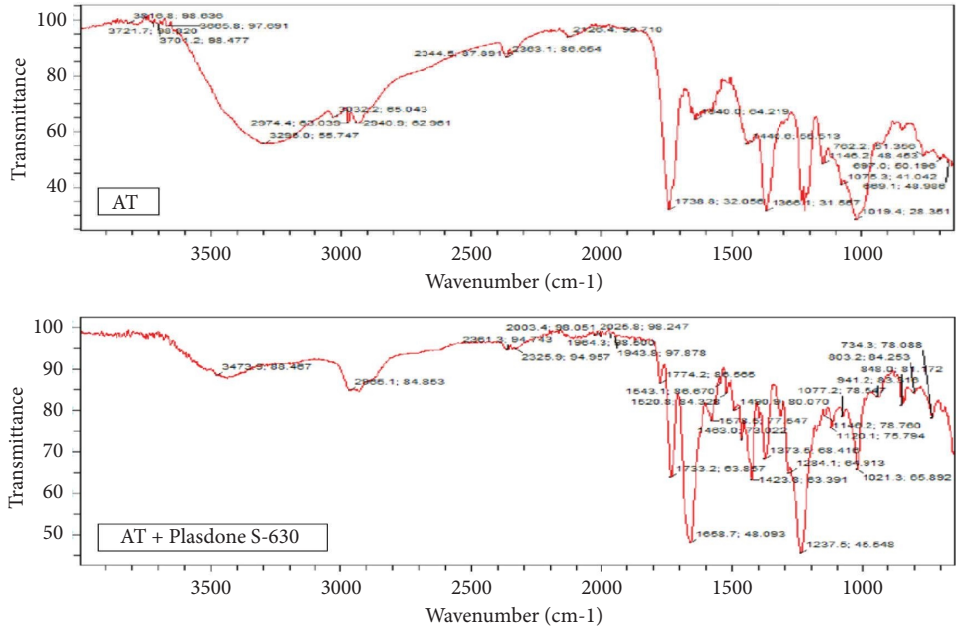

Figure 5: FTIR of AT and AT + Plasdone after 1 month.

Table 2: Evaluation of design batches.

Run	Percentage yield* (Y1) (%)	Dissolution at 10 min* (Y2) (%)	Angle of repose* (Y3) (°)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Houser's ratio	Inter particle porosity
F_1	33.33 ± 1.56	44.88 ± 1.23	29.74 ± 0.50	0.222	0.250	11.20	1.126	0.509
F_2	34.24 ± 2.34	51.82 ± 0.98	32.82 ± 0.34	0.222	0.250	11.20	1.126	0.509
F_3	37.63 ± 1.68	61.09 ± 2.56	34.59 ± 0.12	0.250	0.285	12.28	1.140	0.492
F_4	23.65 ± 1.34	52.52 ± 1.85	31.21 ± 0.22	0.250	0.285	12.28	1.140	0.492
F_5	26.72 ± 3.21	61.98 ± 1.97	34.59 ± 0.27	0.250	0.285	12.28	1.140	0.492
F_6	29.25 ± 2.57	65.00 ± 0.68	38.65 ± 0.24	0.250	0.285	12.28	1.140	0.492
F_7	18.20 ± 1.09	63.22 ± 2.85	33.69 ± 0.39	0.222	0.250	11.20	1.126	0.509
F_8	18.71 ± 2.10	73.82 ± 2.16	38.65 ± 0.28	0.250	0.285	12.28	1.140	0.492
F_9	21.37 ± 1.28	74.95 ± 1.66	41.01 ± 0.51	0.250	0.285	12.28	1.140	0.492

*$n = 3 \pm$ SD.

Table 3: Dissolution test of design batches.

Time (min)	Percentage drug release (%)								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
10	44.88 ± 1.23	51.82 ± 0.98	61.09 ± 2.56	52.52 ± 1.85	61.98 ± 1.97	65.00 ± 0.68	63.22 ± 2.85	73.82 ± 2.16	74.95 ± 1.66
20	59.94 ± 1.56	62.32 ± 2.71	74.01 ± 1.68	65.32 ± 1.45	76.06 ± 0.68	79.35 ± 1.06	75.49 ± 2.74	81.98 ± 0.86	83.71 ± 1.52
30	73.25 ± 2.14	79.82 ± 1.85	83.57 ± 1.35	79.34 ± 2.01	83.64 ± 1.32	82.98 ± 1.89	86.57 ± 1.73	90.24 ± 1.83	90.25 ± 2.11
60	91.46 ± 1.61	93.51 ± 2.54	90.84 ± 1.98	91.25 ± 0.98	95.99 ± 2.29	94.52 ± 2.16	98.67 ± 2.84	99.03 ± 2.61	101.77 ± 1.26

Table 4: ANOVA table of dependent variable Y1—percentage yield after DoE.

	Y1—percentage yield					
	β_0	β_1	β_2	β_{11}	B_{22}	B_{12}
Coefficient value	26.08	2.17	−7.82	0.68	0.70	−0.28
p value	2.9516	0.0076	0.0001	0.3301	0.3156	0.5455
	df	SS	MS	F	Significance F	R^2 value
Regression	5	397.632	79.526	115.025	0.001	0.994
Residual	3	2.074	0.691			
Total	8	399.706				

Table 5: ANOVA table of dependent variable Y2—dissolution 10 min time after DoE.

	Y2—dissolution 10 min time					
	β_0	β_1	β_2	β_{11}	B_{22}	B_{12}
Coefficient value	61.342	6.736	9.033	−2.263	1.796	−1.12
p value	$5.20 * 10^{-5}$	0.004	0.001	0.225	0.313	0.364
	df	SS	MS	F	Significance F	R^2 value
Regression	5	783.621	156.724	35.461	0.007	0.983
Residual	3	13.258	4.419			
Total	8	796.880				

Table 6: ANOVA table of dependent variable Y3—angle of repose after DoE.

	Y3—angle of repose					
	β_0	β_1	β_2	β_{11}	B_{22}	B_{12}
Coefficient value	35.183	3.268	2.699	−0.541	0.264	0.617
p value	$7.72 * 10^{-6}$	0.001	0.002	0.364	0.638	0.183
	df	SS	MS	F	Significance F	R^2 value
Regression	5	110.037	22.007	42.801	0.005	0.986
Residual	3	1.542	0.514			
Total	8	111.580				

Table 7: Constraints of optimization.

	Constraints		
Name	Goal	Lower limit	Upper limit
Feed rate (ml/min)	Maximize	−1	1
Feed concentration (gm/100 ml)	Maximize	−1	1
Percentage yield (%)	Maximize	30	33
Dissolution at 10 min (%)	Maximize	45	50
Angle of repose (°)	Minimize	30	35

The individual coefficients ($\beta_0, \beta_1, \beta_2, \beta_{11}, B_{22}, B_{12}$) and their respective p values provide information about the statistical significance of each independent variable. The variables $\beta_1, \beta_2, \beta_{11}$, and B_{22} have p values less than 0.05, suggesting they are significantly related to the percentage yield. The variables β_0 and B_{12} have p values greater than 0.05, indicating that they may not be statistically significant in this context.

The regression model (Table 5) shows a significant overall fit to the data, as indicated by a low p value (0.007) for the regression F test. This suggests that the regression model is able to explain a significant amount of the variability in the dissolution at 10 minutes.

The coefficient of determination (R^2) value is also provided, which tells us the proportion of the total variability in the response variable (Y2) that is explained by the regression model. In this case, $R^2 = 0.983$, indicating that approximately 98.3% of the variability in the dissolution at 10 minutes can be accounted for by the variables included in the model.

The constant term (β_0) is 61.342, indicating the baseline dissolution at 10 minutes when both X_1 and X_2 are zero. X_1 (β_1) has a coefficient of 6.736 and a p value of 0.004, suggesting it has a statistically significant effect on the dissolution at 10 minutes. X_2 (β_2) has a coefficient of 9.033 and a p value of 0.001, indicating that it also has a significant effect on the dissolution at 10 minutes. $X1^2$ ($\beta 11$), $X2^2$ ($\beta 22$), and $X1X2$ ($\beta 12$) have a relatively high p value of 0.225, suggesting that it might not have a significant impact on the dissolution at 10 minutes.

In summary, the ANOVA and regression analysis suggest that the developed regression model has a significant overall fit to the data and can explain a substantial proportion of the variability in the dissolution at 10 minutes. The variables X_1 and X_2 appear to have a significant impact on the dissolution, while the squared terms and the interaction term ($X1^2$, $X2^2$, and X1X2) might not be statistically significant in this model.

The data in Table 6 represent the results of a regression analysis conducted on the angle of repose (Y3) data in the context of solid dispersions. The p values associated with these coefficients indicate the statistical significance of each variable in the regression equation. The regression analysis also provides information about the goodness of fit of the model. The degrees of freedom (df) for regression, residual, and total are 5, 3, and 8, respectively. The sum of squares (SS) for regression and residual are 110.037 and 1.542, respectively. The mean squares (MS) for regression and residual are 22.007 and 0.514, respectively.

The F value and significance F indicate the overall significance of the regression model. A higher F value and a lower significance F indicate a stronger relationship

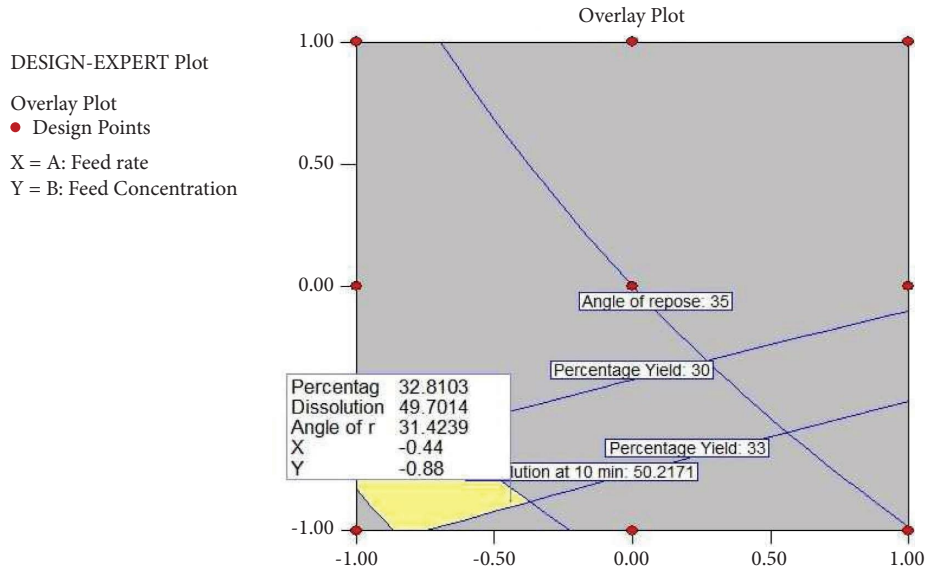

Figure 6: Overlay plot of response variables (optimum feed rate: −0.44 (3.56 mL/min), feed concentration: −0.88 (3.975 gm/100 mL)).

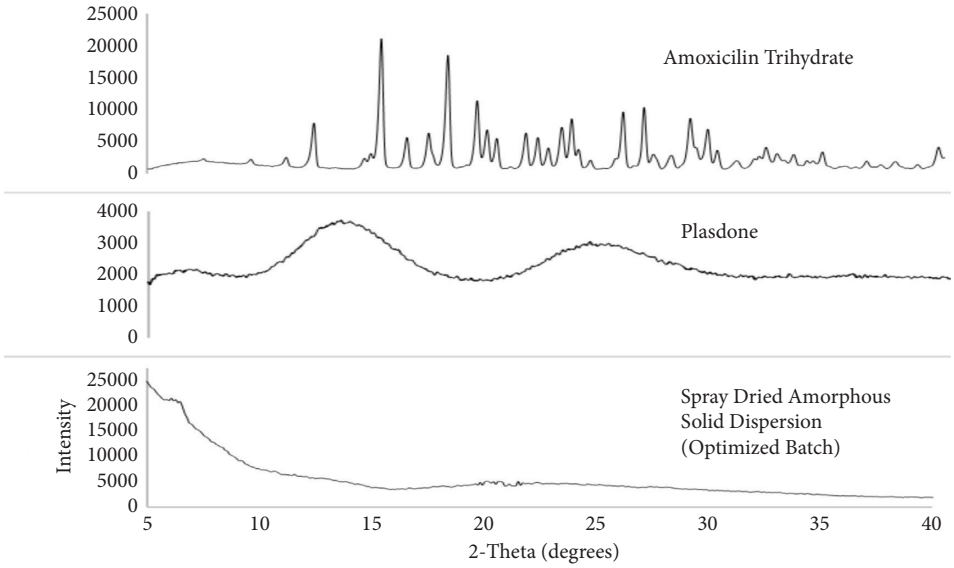

Figure 7: PXRD results showing no signs of crystallinity for spray-dried amorphous solid dispersion (optimized batch).

between the independent variables and the angle of repose. In this case, the obtained F value (42.801) with a very low significance F (0.005) suggests a highly significant relationship. Additionally, the R^2 value, representing the proportion of the total variation explained by the model, is 0.986. This indicates that the model explains approximately 98.6% of the variation in the angle of repose.

The objective was to maximize the feed rate and feed concentration, as well as the percentage yield and dissolution at 10 minutes, while minimizing the angle of repose. The optimization process generated several suggested solutions for the spray-dried dispersion of amoxicillin trihydrate, and the optimized batch was selected based on the decisive factors of minimum and maximum values of response variables, as shown in Table 7. Among the suggested solutions, the formulation with the highest desirability value of 0.916 was chosen as the optimized batch. The corresponding values of the variables and response variables for the optimized formulation are presented in Figure 6.

The combined optimization of the response variables led to the selection of the formulation with the highest desirability value. The desirability function takes into account the desired ranges for all investigated formulation variables, and the value ranges from 0 to 1, with higher values indicating a more desirable formulation. Overall, the optimized batch demonstrated favorable characteristics in terms of percentage yield, dissolution at 10 minutes, and angle of repose. These results suggest that the optimized solid

dispersion formulation of amoxicillin trihydrate could potentially exhibit improved dissolution behavior and enhanced pharmaceutical performance. In a study reported by Jiale et al. [22], they were able to improve the solubility and mask the taste of azithromycin using Eudragit®RLPO as polymer, amorphous solid dispersion by hot melt extrusion. Another study on amoxicillin reported solubility enhancement using spray drying to formulate solid dispersion and finally achieved sustain release up to 24 h using HPMC and fast release within 60 min using HP-β-CD [23].

3.3. PXRD Study. Amorphous solid dispersion formation was evidenced by PXRD analysis of the spray-dried mixture in optimized batch as shown in Figure 7. It was revealed that there was complete disappearance of the crystal peaks of AT in optimized batch, proving formation of amorphous solid dispersion, spray-dried. Mark et al. [24] also reported the similar findings, reporting fading of diffraction spots for crystalline compound.

4. Conclusion

The results and discussion section of the study focused on the selection of carriers for solid dispersion using the film casting method. The goal was to find carriers that would improve the amorphicity and dissolution of the drug while also providing stability. Various carriers, including PVP K30, PVP/VA S-630, HPMC AS, HPMC HP55, PEG 4000, and Soluplus, were studied at different drug-to-carrier ratios (2 : 3 and 1 : 1). The study emphasized the importance of selecting appropriate excipient ratios to achieve the desired stability of amorphous drugs. Furthermore, trials were carried out using the drug and PVP/VA S-630 in a 2 : 3 ratio. The specific interactions and molecular arrangements facilitated by the chosen ratios played a crucial role in preventing drug crystallization. The feed rate and feed concentration were identified as influential variables for the flow properties and particle size of the spray-dried formulation. The drug with PVP/VA S-630 showed promising outcomes. Overall, the study provides valuable insights into the selection of carriers and formulation strategies for preserving the amorphous state.

Data Availability

The data that support the findings of this study are made available from the corresponding author upon reasonable request.

Additional Points

Highlights. Enhanced Solubility: Amoxicillin dispersion overcame poor solubility through spray drying. Polymer Screening: PVP/VA S-630, PVP K30, Soluplus, PEG 4000, HPMC AS, and HPMC HP55 tested via solvent casting method. Optimization Factors: Full factorial design revealed feed rate and concentration impact on spray-dried formulations. Statistical Modeling: ANOVA and regression analysis validated a significant fit for dissolution data. Optimized Formulation: Improved yield, flowability, and particle characteristics in the selected batch.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

The authors acknowledge student start-up and innovation policy, Government of Gujarat, India (SSIP/PHASE-1/2019/13).

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