

Design and Optimization of Tezacaftor Liquisolid Tablet by Using Box-Behnken Design for Enhanced Dissolution Profile

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ABSTRACT

Introduction: Tezacaftor a drug falling under BCS class II due to its low solubility, the bioavailability is found around 20%. The novel liquisolid technique is used in this study to enhance the dissolution and thereby improve the solubility.

Objectives: The main objective of the study was to increase solubility of the drug, particularly at minimal doses.

Materials and Methods: 25 mg of liquisolid tezacaftor tablet was prepared using multi-level processing. Drug saturation was initially assessed in various non-volatile solvents and finalized transcutool shows better solubility for tezacaftor (i.e. 82.1 mg/mL). The angle of Repose was determined by using neusilin US2 as the carrier. Syloid FP 244 was used as the coating agent. These materials were chosen for their surface area (300 m²/g), which is high facilitating both absorption and adsorption. The Liquid Loading (LLF), excipient Ratio (R), disintegrating agent plays a crucial role in determining the effectiveness of drug dissolution and bioavailability enhancement in this technique. The prepared formulation evaluated by FTIR, XRD, DSC, Raman Mapping, and advanced powder flow testing methods.

Results: Employing a Design of Experiment (DOE) approach, including box-Behnken model the optimized batch was designed to achieve potential dissolution and bioavailability, thus increasing therapeutic efficiency.

Conclusion: The results proved the best dissolution percentage for the tezacaftor liquisolid tablet compared to the lactose-based conventional tablet, indicating maximal drug release.

Keywords: Design of Experiment, Dissolution, tezacaftor, Liquisolid Technique, Solubility.

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INTRODUCTION

CFTR gene mutation is the main cause for Cystic fibrosis which is a genetic disease resulting in dysfunctional CFTR protein, leading to accumulation of mucous in the respiratory and digestive systems [1]. It is found in 1 infant out of 3500 new-born [2]

Tezacaftor is mainly used in treatment of cystic fibrosis disease. Approved by USFDA in 2012, for patients with the G551D mutation, Tezacaftor, a Quinolinone-3-

carboxamide derivative, is a novel drug & act as a potentiator in the cystic fibrosis disease [3,4]

Tezacaftor can be used in conjunction with two more medications, such as lumacaftor, elexacaftor and ivacaftor, as a first-line therapy for cystic fibrosis [5]. Tezacaftor remains the sole potentiator in cystic fibrosis treatment. Belonging to BCS II class, it exhibits poor water solubility. Tezacaftor has bioavailability is less than 20% and due to its highly lipophilic nature, it has side

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effects such as headache and nasal congestion [7] The improvement in bioavailability and solubility of tezacaftor is essential and is attempted by using several methods by researchers for its better therapeutic effect.

Guntaka and Lankalapalli developed solid dispersions of ivacaftor using various polymers, including Soluplus, hypromellose (5 cps), and copovidone. These formulations achieved 95% drug release within 30 minutes, compared with only 9% release from the pure active pharmaceutical ingredient (API) [8].

Sowmya *et al.* prepared ivacaftor solid dispersions using the solvent evaporation method with carriers such as mannitol, crospovidone, and sodium starch glycolate. The formulation containing ivacaftor and crospovidone at a ratio of 1:3 exhibited the highest drug release, reaching 99.5% within 60 minutes [9].

Nakhla *et al.* developed ivacaftor-loaded poly(lactic-co-glycolic acid) (PLGA) microparticles using a single-emulsion solvent evaporation technique. Designed for subcutaneous administration, these microparticles provided sustained drug release, potentially reducing the need for frequent oral dosing and improving patient convenience [10].

Balaji Kalpana G. *et al.* prepared the gastro retentive alginate beads of ivacaftor. It gave maximum entrapment efficiency and high drug release for extended period of 12 hr [11] the dry powder aerosol preparation of ivacaftor was carried out by the researcher Guan J. *et al.*, [12] Nano emulsion of ivacaftor was prepared by Parihar A. *et al.* and successfully enhanced the solubility of ivacaftor [13].

Compared to above methods, Liquisolid technique is easy to prepare, novel, inexpensive, and yield stable formulation with industrial scalability. Literature survey reveals that liquisolid technique is not yet tried for solubility enhancement of tezacaftor.

Liquisolid technique requires the drug to be dissolved in non-volatile solvent and then suitable amount of carrier and coating agent is to be added to it, so that the mixture is freely flowable and non-adherent. The drug liquid blend (drug + non-volatile solvent) was suspended in the internal matrix of carrier agent and any extra liquid present on the carrier agent was then made coating agent the layer around it. Now the mixture is freely flowable, non-adherent and easy for compression to form the tablet [14,15].

This research paper includes the box Behnken design with DOE software for successful utilization of optimization of the process of liquisolid tablet of tezacaftor. The optimized batch contains suitable and proper quantity of excipients, so that it gives formulation with excellent quality attributes.

MATERIALS AND METHODS

Materials

Tezacaftor API was received from Alleviare Pvt. Ltd., New Delhi. Transcutol was purchased from Mahaveer Enterprises, Vijayawada. Gift samples of sodium starch

glycolate, neusilin US2, and syloid FP244 were received from Lupin Pharma Hyderabad. All chemicals and reagents used were of analytical grade.

Pre formulation Analysis

Tezacaftor was observed for its melting point, method development by UV spectroscopy for determination of λ_{max} (in Phosphate buffer pH 6.8 & methanol with 0.4% SLS) and for its organoleptic characteristics such as color and odour.

Saturation Solubility of Tezacaftor

Excess amount of Tezacaftor was added into the various suitable solvents like water, 0.1M HCl, Phosphate buffer 6.8, and Phosphate buffer pH 6.8 with 0.4% SLS (Dissolution Media) and non-volatile solvents.

To determine maximum solubility in each solvent, mixture was prepared using method as follows:

Excess amount of Tezacaftor is added to the 2 mL of each solvent in separate glass vials. Weigh and add excess quantity of Tezacaftor into the 2 mL of each solvent till the supersaturated solution is obtained. keep in a shaker orbital incubator at 25°C for 36 hr to achieve equilibrium. The resulting samples were filtered using 0.50 μm syringe filter. The filtrates were suitably diluted with methanol and analyzed for the drug content by using UV-spectrophotometer (Shimadzu UV 1800) at 254 nm.

Angle of Slide

Flowability test was performed by using polished metal plate with D cone [15,16]. 10 g of carrier was placed on one side of metal plate and add 0.1 mL of non-volatile solvent to it and mix thoroughly. The metal plate was then tilted, and angle was measured using the D-Cone. This procedure was repeated, by adding 0.1 mL of non-volatile solvent every time, till the powder particles start adhering to each other. The point at which powder freely flows is its optimum angle of slide. The optimum angle of the slide was 33° [16]. The quantity of non-volatile solvent required to obtain the optimal angle slide is recorded and is represented in Figure 2. A similar procedure was conducted for the coating agent [22]

Liquid Loading Factor (Lf)

Liquid loading factor was performed as per the method demonstrated in literature [15].

Evaluation of powder blend:

The R Excipient Ratio is calculated by dividing the amount of carrier by the amount of coating agent as shown below formula:

$$R = Q/q$$

Liquid load factor, on the other hand, is determined by dividing the drug liquid blend amount by the carrier amount as shown below formula:

$$Lf = W/Q \text{ (2)}$$

Research studies typically suggest an R value ranging from 5 to 50 However, they also indicates that, as the R

value increases, the quantity of coating agent reduces. Relationship between the Lf and R Excipient ratio is shown below formula:

$$Lf = \Phi + (\varphi / R) = 0.671 + (0.8 / R)^3$$

Where, R=5 to 50.

The Lf values are 0.831, 0.751, 0.711, 0.697, 0.691, and 0.681, corresponding to R values ranging from 5, 10, 20, 30, 40 and 50 respectively. Optimum value of R value is 20 according to spires [14,17].

Fraction of molecularly dispersed or dissolved drug in liquid medication (FM) as shown below formula:

$$FM = CL / CD$$

Where,

CL=Saturation solubility of Tezacaftor in Transcutol (%w/w).
CD=Drug concentration in non-volatile solvent Transcutol (%).

FM=1 and according to Spires FM value does not exceed unity as shown in below formula:

$$FM = 8.21\% \text{ w/w} / 9.1\% = 0.902$$

FM is directly proportional to the drug dissolution rate.

The quantity of carrier agents was calculated using following formula:

$$Q = W / Lf$$

Characterization of powder blend

The powder blend was reported for flow characteristic prior compression to tablet.

The flow characteristics are Bulk density, Tapped density, Angle of repose, Carr's index (%) and Hausner's ratio.

Formulation of Tezacaftor Liquisolid Tablet

25 mg of Tezacaftor was added to the 250 mg of transcutol in a 10 mL glass vial and heated on a water bath at 40°C for 5 min. The solution was thoroughly stirred with neusilin US2 and syloid FP244 followed by SSG as super disintegrant. The obtained Liquisolid complex is punched into tablets using 10 station multi-tooling machine (CADMACH), loaded with 13 mm punches. **Preliminary Screening of Liquisolid Tezacaftor Tablets:**

Tablets with different R values (ranging from 5 to 50) were prepared, as represented in Table 1.

Optimization of Tezacaftor Liquisolid Tablet using DOE Software

Box Behnken design with design expert software was used for optimization of this formulation. Tezacaftor drug is not soluble in less than 250 mg of Transcutol. As the process needs mere solubilization of drug, the second factor R value in range of 20-40 is chosen. The third factor is selected in range of 5-7% as we need Fast release dosage form. Formulation batches as per Box Behnken design in drug design software version 13, are tabulated in Table 2.

Post fitting in mathematical model on the desirability

function, design expert software was used to select the optimized batch. The desirable value in desirability function is always one. The minimum constrains values and maximum constrains value were obtained according to goal of responses. Checkpoint batch as per Box Behnken design were obtained. They contain the LS1 blend mixture with R value as 38.1, drug concentration in non-volatile solvent is 8.44% w/w, and liquid loading factor is 0.681. According to that Tezacaftor pure drug 25 mg solubilized in 268.45 mg transcutol with carrier (414.2 mg) and coating agent (10.9 mg) addition, followed by addition of sodium starch glycolate (31.5 mg). so that, unit tablet weight is 750mg is obtained.

Pre-compression evaluation of liquisolid powder compact

Evaluation of liquisolid powder compact includes tests such as FTIR, XRD, DSC, SEM and Raman mapping.

Advanced Powder Flow test

Advanced powder flow analysis was performed using Brookfield powder flow tester. Following parameters were evaluated:

Flow Function: Easy flowing to cohesive (FF range: 3 to 6),

Bulk Density: 0.2 g/cm³ to 1.0 g/cm³,

Wall Friction Angle: 20° to 40°,

Internal Friction Angle: 30° to 45°,

Compressibility: 10% to 30%

These parameters assess the friction between the powder and the surfaces at its contact. This evaluation is important for knowing how powders will behave in hoppers and during transport and evaluates how the volume of the powder changes under pressure, important for tablet formation and ensuring uniformity. This provides rapid and accurate measurements, saving time in the development and production processes.

Post-compression parameter of Tezacaftor Liquisolid Tablet

Dissolution Test

Phosphate buffer pH 6.8 with 0.4% SLS was used as a dissolution medium. Volume of dissolution media was taken as 900 mL and used with the USP type II Apparatus (paddle). Each formulation contains 25 mg of drug. Samples were withdrawn at intervals of 5, 10, 20, 30, 45, and 60 min, and filtered through a 0.8-micron syringe filter paper. Appropriate dilution was carried out. Absorbance was recorded using UV spectroscopy at a 248 nm wavelength.

Disintegration Test

Disintegration test was carried out in 0.1N HCl solution.

Drug content

The availability of drug in Tezacaftor Liquisolid tablet was calculated by dissolving the formulation in a suitable quantity of methanol using ultra sonicator. The drug content was determined at 254 nm using a

spectrophotometer (Shimadzu)

RESULTS AND DISCUSSION

Evaluation of Pre formulation Studies

Tezacafter was evaluated for preliminary identification characteristics. It is a white, odorless, and bitter-tasting powder. The melting point of Tezacafter was found to be 321.5°C. Drug analysis was done by UV Spectrophotometric method at 254 nm for methanol and 248 nm for Phosphate buffer pH 6.8 with 0.4% SLS, as shown in calibration curve (Figure 1).

Saturation Solubility of Tezacafter in Non-Volatile

Table 1: Screening of batches where R= 5, 10, 20, 30, 40 and 50.

Excipient ratio R	Drug liquid blend (W) mg	Neusilin US2 (Q) mg	Syloid FP244 (q) mg	Lf	Disintegrating agent (mg)	Weight of Compact(m g)
5	275	329.9	66.1	0.831	33.6	703.6
10	275	336.1	35.6	0.751	33.8	709.5
20	275	386.7	19.3	0.711	33.05	714.05
30	275	393.5	13.1	0.697	34.13	714.73
40	275	397.9	8.9	0.691	34.14	714.94
50	275	400.3	8.0	0.687	33.16	716.46

Determination of Angle of Slide

Optimum angle of slide was found to be 34°, which is acceptable flow range [18,19]

For the coating agent Φ value is 0.8, and for the Φ value of carrier is 0.671, as shown below

Φ = Maximum amount of non-volatile solvent (g)/ Weight of carrier (g) or weight of coating (g)

For carrier agent = $6.7/10 = 0.671$ and for coating agent = $8/10 = 0.8$.

The 0.671 g of non-volatile solvent comfortably absorbed of 1 g of carrier with good flowability. Similarly, the 0.8 g of non-volatile solvent comfortably adsorbed of 1 g of coating agent with good flowability as shown in Figure 2 [22]

Determination of drug liquid blend (W)

25 mg dose of Tezacafter was completely solubilized in 0.2675 mL of transcitol. Then the total drug liquid blend was 292.5 mg.

Determination of the weight of carrier agent (Q)

The carrier neusilin US2 concentration is determined. Putting the value of W=292.5mg and Lf=0.691, which depends on the excipient ratio (R) value. (Lf=0.691 when R=39.1) The required and calculated concentration of neusilin US2 is 423.3mg for the optimized batch.

Determination of the weight of coating agent (q)

The coating agent Syloid FP 244 concentration is determined. The required and calculated concentration of Syloid FP 244 is 10.8 mg for the optimized batch.

Optimization of Liquisolid Tezacafter Tablet

The DOE software statistical analysis plays an important role in finalizing optimized batch.

Solvents

Saturation solubility of Tezacafter in several solvents was carried out. Highest solubility was observed in transcitol that is 82.1 mg/ml. Hence it was selected for the development of liquisolid drug delivery system [18,19]

Selection of carrier and coating agent

Literature reveals that high surface area admits the use of neusilin US2 and syloid FP 244 as excellent carriers as coating agents [20,21] On this basis, the neusilin US2 and syloid FP 244 were selected as carrier and coating agent, respectively.

ANOVA for the Quadratic model

P-values not more than 0.0500 indicates model terms are viable in all the responses. The most factors in Analysis of Variance (ANOVA) are A (R), B (DT), and C (Non-volatile liquid). ANOVA is used for statistical modeling and experimental design for evaluation of the significance of different factors and their interactions in influencing a response variable.

Degrees of Freedom (d_f) mean number of independent values that contribute to the calculation, Sum of Squares (SS) represents the variation contributed by each factor, Mean Square (MS) obtained by dividing the sum of squares by the Degrees of Freedom (SS/d_f) and F-value is the ratio of mean square to residual mean square ($MS/MS_{residual}$). Higher the F-value indicates more significant effect.

Response 1 Disintegration time

This model of ANOVA include Sum of Squares (SS), which is 392.36, Degrees of freedom (d_f) is 9, Mean Square (MS) is 43.60, F-value is 55.44, and p-value is < 0.0001 . The lack of fit p-value is 0.1400, which is not significant, means that the model fits the data well. Lack of Fit is not significant means the residual error is low. B-Disintegration time has a very significant effect. The disintegration time always has a non-linear relation with the response so 1. A (R), AC, A^2 , and C^2 are not significant, means they do not have a strong effect on the response 1. Factor C is not significant, means they do not contribute much.

Response 2 Dissolution at 30 min time interval

In this model the Sum of Squares (SS) which is 7507.80, Degrees of Freedom (d_f) is 9, and Mean Square (MS) is 834.10, the F-value is 13.10, and p-value is 0.0016. This model is statistically significant. Lack of fit is 0.8936,

indicates its insignificance, indicating that the model fits the data well. Factor B (DT) has the strong effect, and factor A (R) also has a remarkable effect. High Quadratic

term B^2 , indicates a strong non-linear effect of B. The interaction between A and C is also significant.

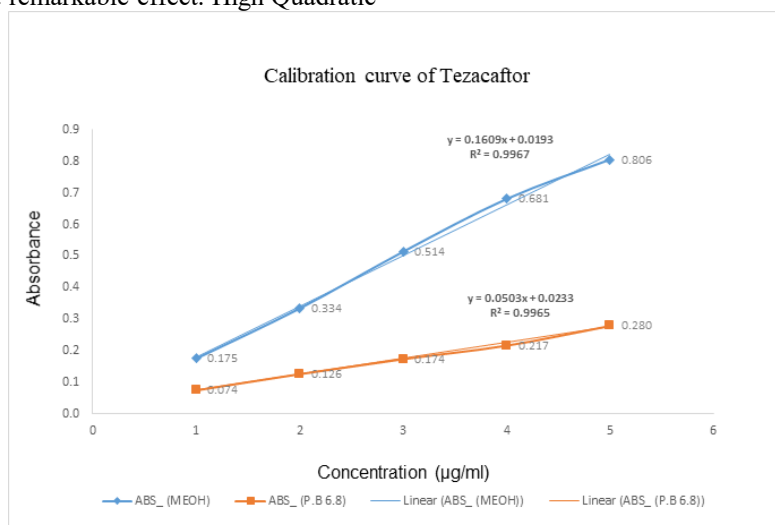


Figure 1: Calibration curve of Drug in methanol and phosphate buffer of pH 6.8 with 0.4% SLS.

Response 3: Dissolution at 60 minutes Time Interval

This model of ANOVA includes the Sum of Squares (SS), which is 1565.32, the Degrees of Freedom (df) are 9, and Mean Square (MS) is 173.80, the F-value is 22.90, and the p -value is 0.0002. This model is merely significant. Lack of fit is 0.0514, which is insignificant, indicating that the model fits the data in acceptable range. Factor A (R) has negotiable effect on the response. Factor B (DT) has a high influence on the response. Factor C (non-volatile liquid) has null significance on effect on the response.

Indirect proportionality of the R value to the coating agent concentration is countable. Coating agent generally retards the dissolution rate and thus, dissolution at 60 min increases as the R value increases, as shown in Figure 3. So as the disintegrating agent concentration increases, the dissolution and disintegrating time also increases.

Equation for Disintegration Time

Disintegration time = $+2.52 - 0.3625A - 5.23B - 0.5625C + 1.00AB + 0.1250AC + 1.15BC + 0.1275A^2 + 6.15B^2 + 0.0775C^2$

Equation for Dissolution at 30 min

Dissolution at 30 min = $+84.24 - 9.45A + 17.33B - 6.53C + 0.900AB - 15.30AC - 7.65BC + 3.11A^2 - 24.34B^2 - 8.15C^2$

Equation for Dissolution at 60 min

Dissolution at 60 min = $+102.96 + 0.2500A + 9.13B + 0.0750C + 1.60AB + 0.3000AC + 2.25BC - 1.36A^2 - 14.11B^2 + 2.50C^2$

The quadratic polynomial equations comprised of plus sign showed synergistic effects and negative sign was antagonistic effects. The factors A, B, C were excipient ratio (R),

disintegrating agent concentration, and non-volatile solvent concentration respectively.

In the data provided the disintegration time, excipient Ratio (R), disintegrating agent concentration, and non-volatile solvent concentration indicated have antagonistic effects. The results revealed at 30 min, excipient Ratio (R) and non-volatile solvent concentration claimed antagonistic effects and synergistic effects with concentration of disintegrating agent. The output of dissolution at 60 min, excipient Ratio (R), disintegrating agent concentration, and non-volatile solvent concentration claimed synergistic effects. The concentration of non-volatile solvent in the drug liquid blend is indirectly proportional to disintegrating rate. The overlay plot concludes that all the three responses meet their respective criteria and optimum range responses were recorded as represented in Figure 3.

Pre-compression parameters of Tezacaftor liquisolid compact

The bulk density, tapped density, hausner's ratio, Carr's index and angle of repose are crucial factors for determination the flow properties of the compact. The responses obtained were present within acceptable limits as indicated in Table 3.

FTIR Spectroscopy

The spectral observations reveal that there is no identifiable interaction between the excipients (Transcutol, Neusilin US2, Syloid FP 244, and Sodium starch glycolate excipient) and tezacaftor pure drug, as indicated in Figure 4.

X-ray Diffraction (XRD)

Pure form of Tezacaftor was tested for Crystallinity Studies and found to be 99.6%. LS1 mixture, indicates that pure drug tezacaftor is completely soluble in transcutol. No peak is observed in the LS1 mixture, as shown in Figure 4.

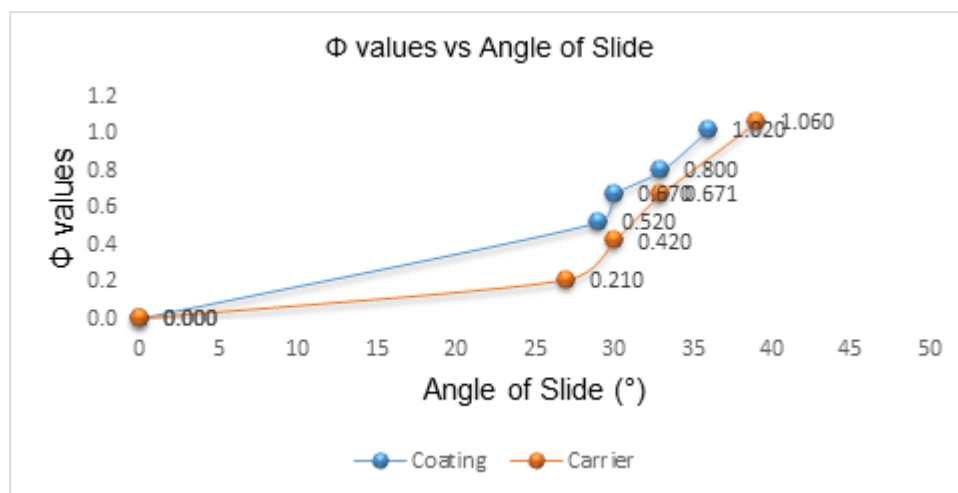


Figure 2: Angle of Slide of carrier and coating agent.

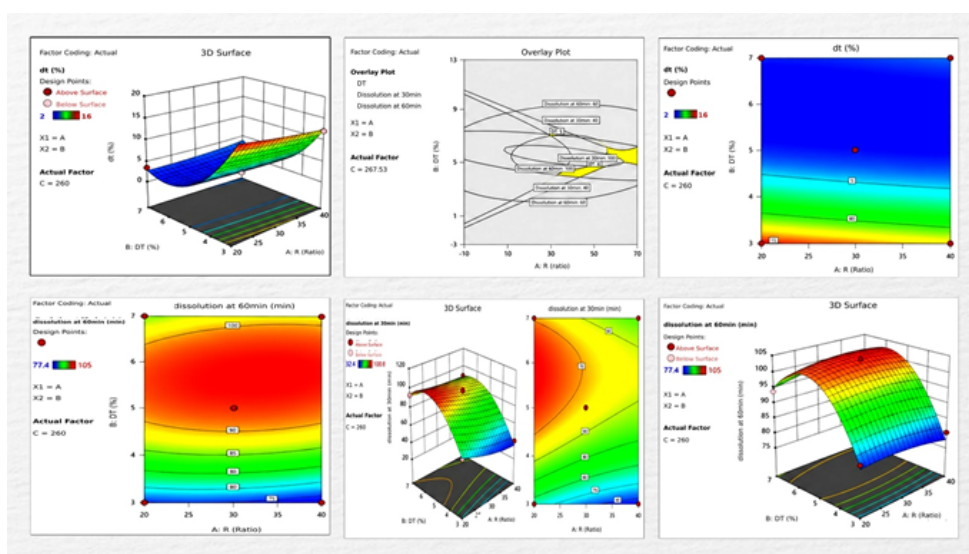


Figure 3: DOE profiling graphs of Tezacafter Liquisolid tablet.

Differential Scanning Calorimetry Study (DSC)

The DSC graph indicates that the conversion of solid form of tezacafter to amorphous form. The pure drug tezacafter shows the melting point at 319.51°C with a sharp endothermic peak while in the LS1 blend mixture, no peak is observed. The observations were indicated in Figure 4.

Scanning Electron Microscopy (SEM) Study

Pure tezacafter exhibits an elongated, nanowire-like crystalline morphology, whereas the LS1 mixture shows reduced particle size and crystallinity. The observations were indicated in Figure 4.

Raman Mapping

LS1 mixture as compared to the pure tezacafter drug in cartes low intensity as shown in Figure 4, This indicates conversion of drug to its Amorphous form. Raman mapping can also be used to find traces of crystalline medicine in formulations, even when the concentration of drug is below the XRD detection limit. Subsequently, it is an advantage to use Raman mapping in investigations to assess the crystallinity state and spatial distribution in

tezacafter liquid-solid compacts.

Advanced Powder Flow Test (PFT)

Stress (σ_c) and bulk density (ρ_b) are directly proportional to each other so if one parameter increases the other increases automatically, indicating compression of the material. The bulk density (333.1 kg/m³) corresponds to the applied stress (4.829 kPa). The fill density (242.7 kg/m³) compared to the maximum density (333.1 kg/m³) shows how much the powder is compacted under stress. The bulk density of the compact (250.6 kg/m³) helps in designing hoppers / feeders, ensuring that powders do not clog.

The relationship between Unconfined Failure Strength (kPa) and Major Principal Consolidating Stress (kPa) for a powder LS1 sample was indicated by Flow Function Graph. The red line indicates the experimental data of the powder's not confined failure strength (σ_c) at different consolidation stresses (σ_1). The better flow of the compact was represented by flatter curve in the red line FF curve. The black/gray line indicates a standard threshold for flowability classification. Light blue line indicates the arching criteria, the stress at which the material

is prone to form stable arches in hoppers. The higher flow index reports better flowability, including σ_1 (kPa), major principal consolidating stress has a value of 7.852, indicating the good flow of powder.

The effective angle of internal friction (δU) versus major principal consolidating stress (σ_1) for the LS1 Sample was indicated. σ_1 Critical is 0.095 kPa, representing the major principal stress at which the material starts to flow. δU Arching is 35.0° , which represents the angle at which usually arching occurs.

This graph shows the diameter of the rat-hole that forms in the powder in meters versus the depth of the powder column in meters. It provides various diameters with corresponding hopper angles.

The graph shows the normal stress versus resistance to flow. Tightly packed, smaller curves indicate less cohesive, freer-flowing materials. The shape and spread of these curves indicate cohesiveness, flowability, and yield strength of the material, as shown in Figure 5.

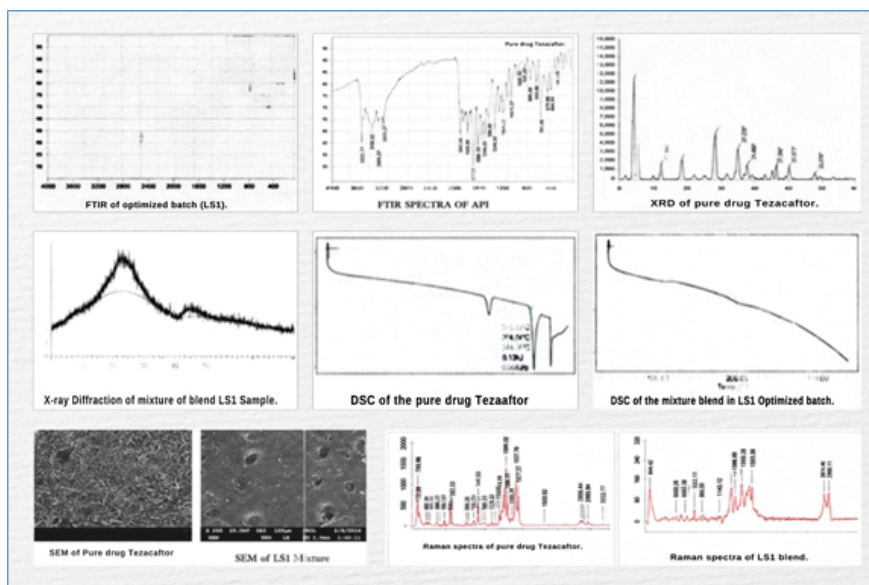


Figure 4: Characterization of tezacaftor liquisolid tablet & its LS1 (Blend) mixture.

Table 3: Properties of compacts before compression into tablet.

Batch	Bulk Density	Tapped density	Hausners index	Carrs index	Angle of Repose
F1	0.74±0.02	0.810±0.01	1.06±0.01	7.7±0.05	30°±0.6
F2	0.73±0.03	0.798±0.03	1.06±0.02	8.0±0.43	32°±0.6
F3	0.73±0.03	0.802±0.03	1.07±0.01	8.4±0.69	33°±1.2
F4	0.72±0.01	0.778±0.01	1.05±0.01	6.9±0.64	31°±0.6
F5	0.81±0.01	0.845±0.01	1.01±0.01	3.7±0.08	30°±0.6
F6	0.71±0.04	0.786±0.04	1.06±0.01	8.3±0.78	33°±1.2
F7	0.81±0.01	0.842±0.07	1.01±0.01	3.67±0.08	28°±1.0
F8	0.73±0.03	0.802±0.03	1.07±0.01	8.5±0.69	33°±0.6
F9	0.76±0.01	0.828±0.01	1.06±0.01	7.7±0.18	31°±0.6
F10	0.73±0.03	0.802±0.03	1.07±0.01	8.6±0.69	32°±0.6
F11	0.71±0.02	0.78±0.02	1.07±0.01	8.5±0.39	32°±0.6
F12	0.74±0.02	0.814±0.01	1.06±0.01	8.5±0.82	28°±0.6
F13	0.73±0.02	0.795±0.01	1.08±0.01	8.4±0.39	31°±0.6
F14	0.81±0.01	0.842±0.01	1.02±0.01	3.9±0.08	33°±1.0
F15	0.79±0.02	0.822±0.02	1.02±0.01	2.9±0.71	30°±0.6
F16	0.74±0.02	0.819±0.01	1.05±0.01	8.4±0.79	30°±1.2
F17	0.71±0.02	0.795±0.03	1.05±0.01	8.2±0.39	31°±0.6

(SD is standard deviation for $n=3$ observation).

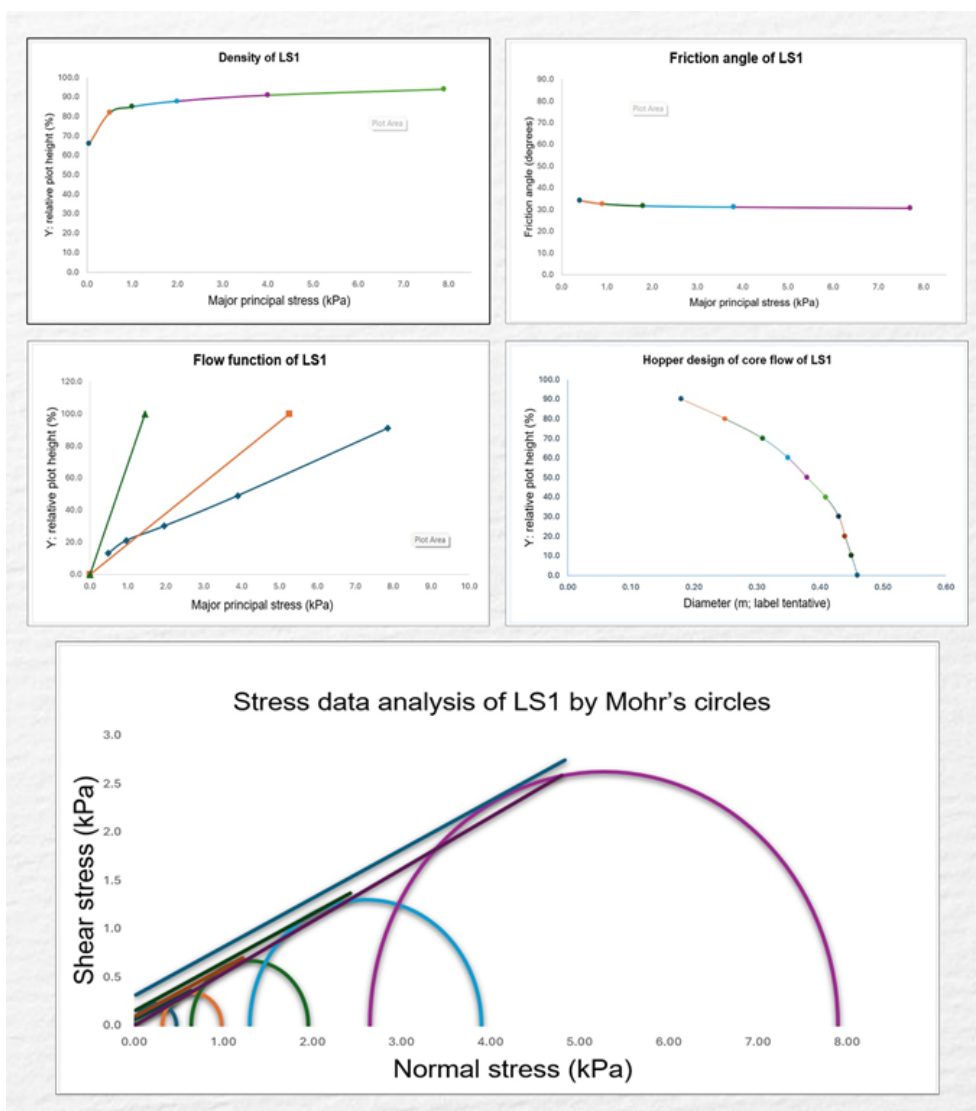


Figure 5: PFT Graph of LS1 (blend mixture).

Post-Compression Parameter

Optimized batch of tezacaftor liquisolid tablet reports 0.6% friability, 3.4 kg/cm^2 hardness, and size is found to be 4.95 mm in thickness and 1.2 cm in diameter.

Profiling by DOE of all the seventeen batches was indicated in Table 4. The concentration of disintegrating agent is 3% in formulation F6, F8, F11, and F16 affect the dissolution rate. It is proved that the decrease in concentration of disintegrating agent, reduces the dissolution rate. In all other formulations, concentration of disintegrating agent is 5% and 7% hence the dissolution rate and disintegrating time increases.

Drug content

The drug content of the liquisolid tezacaftor tablet was 101.5% w/w.

In vitro dissolution studies

Dissolution profile of tezacaftor liquisolid tablet with different ranges of (R values) excipient ratio were performed and found that the increase in R value increases the dissolution rate. The coating agent concentration in formulation was reduced by the increased R value. Coating agent minimizes the dissolution rate.

Table 4: Evaluation parameter of Tezacaftor Liquisolid Formulations.

Formulation	Dissolution at 30 min (%)	Dissolution at 60 min (%)	Disintegration time (min)
F1	53	102.4	3.7
F2	78.2	103.4	2.5
F3	87.2	99.8	2.2
F4	99.8	104	2.2
F5	87.2	101.6	3.3

F6	36.8	82	11
F7	87.2	101.6	2.6
F8	54.8	85	17
F9	89	106.4	4
F10	71	98.2	3.8
F11	33.2	86.8	18
F12	85.4	99.8	3.5
F13	86.2	103.6	2.6
F14	76.6	105.4	3.8
F15	45.6	104.4	2.8
F16	30.4	78.4	16
F17	85.4	93.8	3.9

With the data from Table 4, Optimized LS1 batch (tablet) is obtained. This batch shows the % drug release like the marketed preparation of tezacaftor. The drug release percentage of lactose-based tablet shows the 55.7%. The 50 mg granules of marketed preparation of tezacaftor shows the 95.02% drug release. The optimized liquisolid Tezacaftor tablet shows the 96.2% drug release.

DISCUSSION

The present study focused on enhancement of the dissolution of tezacaftor, by using box behnken design and through formulation of liquisolid tablet. The liquisolid technique was selected for improving the dissolution rates of poorly soluble drugs by increasing the surface area of drug by converting them into their amorphous forms. The optimized study using the box behnken design state denotes the significant influence of the 3 independent variables on the key responses. The quadratic model was identified to be best fit, as evidenced by statically significant *p*-value and high R^2 value, indicating good correlation between the illustrative and experimental data. In conclusion, the developed liquisolid tablet of tezacaftor offers the convincing platform for improving the solubility and dissolution of poorly soluble drugs. However, the optimized formulation (LS1) shows a similar drug release that is 97% as that of marketed preparation of tezacaftor named 50 mg symkevi granules. DSC, XRD, Raman mapping, FTIR, and SEM analysis also proved that the tezacaftor API can be converted to amorphous form. Advanced flow properties study indicated that the optimized formulation has excellent flow properties suitable for its industrial manufacturing.

SUMMARY

Liquisolid technique using transcitol as non-volatile solvent and neusilin US2 as carrier showed excellent result in enhancement of dissolution of tezacaftor. The optimized formulation resulted in high dissolution.

CONCLUSION

The present study aimed on the design and optimization of tezacaftor liquisolid tablet showing a higher dissolution rate as compared to the lactose-based tablet. The formulation with a drug concentration of 8.44% (w/w) and an excipient Ratio (R) of 38.1 was the optimal formulation. Tablet characterization i.e. Weight, hardness, friability, and

disintegration time meet good quality attributes. Optimized batch shows quick dissolution rate, good flowability, and acceptable tablet characteristics. A remarkable reduction in crystallinity and improved amorphous nature of drug particles was clearly observed in the SEM, XRD, and Raman spectra.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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