**Ind. J. Pharm. Edu. Res., 2026; 60(4s):s1405-s1415.**
https://www.ijper.org

Original Article

# Formulation and Evaluation of Liquisolid Tablet with Enhanced Dissolution of Ivacaftor by Using Box-Behnken Design

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## ABSTRACT

**Introduction:** Ivacaftor a drug falling under BCS class II due to its low solubility, with a bioavailability of around 20%. In this study, the novel liquisolid technique is used to enhance the dissolution and ultimately improve the solubility. **Objectives:** The primary objective was to increase the efficiency of the drug, particularly in lower doses. **Materials and Methods:** The formulation containing 25 mg liquisolid ivacaftor tablet was prepared through a multi-step process. Initially, assessed the drug saturation solubility in various non-volatile solvents, whereas utilized transcutol shows higher solubility for Ivacaftor (i.e. 82.1 mg/mL). The angle of slide was determined by using neusilin US2 as the carrier and syloid FP 244 as the coating agent. The neusilin US2 and syloid FP244 materials were chosen for their high surface area (300 $m^2$/g), facilitating absorption and adsorption, respectively. The liquid loading factor, excipient Ratio (R), disintegrating agent in the liquisolid technique plays a crucial role in determining the effectiveness of drug dissolution and bioavailability enhancement. The liquisolid formulation evaluated by FTIR, XRD, DSC, Raman Mapping, and advanced powder flow testing. **Results:** Employing a Design of Experiment (DOE) approach, including box-Behnken model the optimized batch was formulated to achieve enhanced dissolution and bioavailability, thus maximizing the therapeutic efficiency. **Conclusion:** The results demonstrated a 100% dissolution for the Ivacaftor liquisolid tablet compared to the lactose-based conventional tablet, indicating superior drug release.

**Keywords:** Design of Experiment, Dissolution, Ivacaftor, Liquisolid Technique, Solubility.

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**Received:** 08-04-2026;
**Revised:** 22-06-2026;
**Accepted:** 17-07-2026.

## INTRODUCTION

Cystic fibrosis is a genetic disease caused by CFTR gene mutations, results in dysfunctional CFTR protein, leading to mucus accumulation in the respiratory and digestive systems.[1] It is found in 1 infant out of 3500 new-born.[2]

Ivacaftor is used in treatment of cystic fibroses disease. It is approved by the USFDA in 2012, for patients with the G551D mutation.[3] Ivacaftor, a Quinolinone-3-carboxamide derivative, is a novel drug and act as a potentiator in the cystic fibrosis disease.[4]

It is advised that ivacaftor be used in conjunction with two more medications, such as lumacaftor, elexacaftor and tezacaftor, as a first-line therapy for cystic fibrosis.[5] Ivacaftor remains the sole potentiator in cystic fibrosis treatment and other drugs such as Lumacaftor, Elexacaftor and Tezacaftor, act as corrector.[6] It belongs to BCS II class, exhibiting poor water solubility. Ivacaftor has bioavailability is less than 20% and due to their highly lipophilic nature, they have the side effect such as the headache, oro-pharyngeal infection, and nasal congestion.[7] The improvement in bioavailability and solubility of ivacaftor is essential and is attempted through using various methods by many researchers for its better therapeutic effect.

The Guntaka and Lankalapalli have prepared the solid dispersion of ivacaftor with different polymer such as soluplus, hypromellose 5 cps, and copovidone which shows 95% drug release rate in 30 min as compared to pure API (shows the 9% release).[8] Sowmya *et al.*, prepared the solid dispersion of ivacaftor by solvent evaporation method by using different carriers such as mannitol, crospovodine, and sodium Starch Glycolate. The Ivacaftor and carrier crospovodine (1:3) shows maximum drug release that is 99.5% in 60 min.[9] Nakhla *et al.*, formulate the Ivacaftor loaded PLGA microparticle by using a single emulsion solvent evaporation technique. The route of administration of prepared microparticle is subcutaneous injection with long-acting effect or sustained effect which eliminates the need of frequent daily administration of oral ivacaftor and hence it is suitable for patient

**DOI:** 10.5530/ijper.20262408

compliance.[10] Balaji Kalpana G. *et al*., prepared the gastroretentive 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 enhance the solubility of ivacaftor.[13]

As compared to above methods, Liquisolid technique is easy to carried out, novel, inexpensive, and provide stable formulation with industrial scalability. Literature survey reveals that, liquisolid technique is not yet tried for solubility enhancement of ivacaftor.

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

In this research paper, the box Behnken design with DOE software is successfully utilized to optimize the process of liquisolid tablet of Ivacaftor. The optimized batch contain suitable and proper amount of excipient, so that it gives liquisolid tablet which has excellent quality attributes.

## MATERIALS AND METHODS

### Materials

Ivacaftor API was received as a generous gift from MSN Laboratory Pvt. Ltd., Telangana. Transcutol was purchased from Doodle Enterprises, Aurangabad. Lupin Pharma Aurangabad provided gift samples of sodium starch glycolate, neusilin US2, and syloid FP244. All chemicals and regent used were of analytical grade.

### Preformulation Analysis

Ivacaftor was analyzed for melting point, method development by UV spectroscopy for determination of $\lambda_{max}$ (in methanol and Phosphate buffer pH 6.8 with 0.4% SLS dissolution media solvents) and for their organoleptic characteristics such as color and odor.

### Saturation Solubility of Ivacaftor

Excess amount of Ivacaftor was added into the various solvents including water, 0.1M hydrochloric acid, phosphate buffer 6.8, and Phosphate buffer pH 6.8 with 0.4% SLS (Dissolution Media). Also including non-volatile solvents. To determine maximum solubility in each solvent, mixture was prepared using method as follow:

Excess amount of ivacaftor is added to the 2 mL of each solvent (mentioned above) in separate glass vials. Weighing and adding excess quantity of ivacaftor into the 2 mL of each solvent is carried out till the supersaturated solution is obtained. These mixtures were kept in a shaker incubator at 25°C for 24 hr to achieve equilibrium. The resulting samples were filtered using 0.45 µm syringe filter. The filtrate of each mixture was suitably diluted with methanol and analyzed for the drug content by using UV-spectrophotometer (Shimadzu UV 1800) at 254 nm. This procedure was repeated for three times.

### Angle of Slide

Liquisolid flowability test was carried out by using polished metal plate with D cone.[15,16] It was carried 10 g of carrier was placed on the one side of metal plate, then added 0.1 mL of non-volatile solvent to it and thoroughly mixed. The metal plate was then tilted to allow it to shift to the other side, and the angle was measured using the D-Cone. This procedure was repeated, by incrementally adding 0.1 mL of non-volatile solvent each time, until the powder particles started adhering to each other.

The point at which powder was freely flowable is called optimum angle of the slide. The optimum angle of the slide was 33°.[16] The amount or quantity of non-volatile solvent required to obtain the optimum angle slide is noted is shown in Figure 2. A similar procedure was conducted for the coating agent.[22]

### Liquid Loading Factor (Lf)

Liquid loading factor was carried out as the method reported 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 (1):

$$R=Q/q \quad (1)$$

Liquid load factor, on the other hand, is determined by dividing the drug liquid blend amount by the carrier amount as shown below formula (2):

$$Lf=W/Q \quad (2)$$

Research studies typically suggest an R value ranging from 5 to 50.[14,17] However, it also indicates that, as the R value increases, the quantity of coating agent is reduced. Relationship between the Lf and R Excipient ratio as shown below formula (3):

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

Where, R=5 to 50.[18,19]

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 (4):

$$FM=CL / CD \quad (4)$$

Where,

CL=Saturation solubility of Ivacaftor in Transcutol (%w/w).

CD=Drug concentration in non-volatile solvent Transcutol (%).

FM=1 and according to Spires FM value not exceed unity as shown in below formula (5):

$$FM=8.21\%\ w/w / 9.1\%=0.902 \quad (5)$$

FM is directly proportional to the drug dissolution rate.

The amount of carrier agent was calculated from the following formula (6):

$$Q=W / Lf \quad (6)$$

## Evaluation of powder blend

The powder blend was estimated for their flow characteristic before compression into tablet.

The flow characteristic is bulk density, tapped density, angle of repose, Carr's index (%) and hausner's ratio.

## Formulating Liquisolid Ivacaftor Tablet

In the preparation of drug liquid blend, 25 mg of ivacaftor was added to the 250 mg of transcutol in a 10 mL glass vial, heated on a water bath at 40°C for 2 min. By heating, the resultant solution was thoroughly mixed with neusilin US2 as carrier and syloid FP244 as coating agent followed by sodium starch glycolate as superdisintegrant. The resulting Liquisolid compact is punched into tablets using 12 station multi-tooling machine (Rimek mini press-II, Karnavati Engineering, Ahmadabad), equipped with 13 mm punches. Preliminary Screening of Liquisolid ivacaftor Tablets: Tablets with different R values (ranging from 5 to 50) was prepared, as shown in Table 1.

## Optimization of Liquisolid Ivacaftor Tablet using DOE Software

Box Behnken design with design expert software was utilized for optimization of formulation.

The Ivacaftor drug could not dissolve in less than 250 mg of Transcutol, as the process needs complete solubilization of drug. The second factor R value in range of 20-40 is chosen because, as the R value is directly proportional to dissolution. The third factor disintegrating agent is selected in range of 5-7% because, we required immediate release dosage form. Formulation batches as per Box Behnken design in drug design software version 13, are shown in Table 2.

After fitting in mathematical model, based on the desirability function in design expert software was used to select the optimized batch. Most desirable value in desirability function is one. The minimum constrains values and maximum constrains value is obtained according to goal of responses.

Checkpoint batch as per Box Behnken design is obtained. It contains the LS1 blend mixture with R value is 39.1, drug concentration in non-volatile solvent is 8.54% w/w, and liquid loading factor is 0.691. According to that Ivacaftor pure drug 25 mg solubilized in 267.53 mg transcutol with carrier (423.2 mg) and coating agent (10.8 mg) addition, followed by addition of sodium starch glycolate (31.1 mg). so that, unit tablet weight is 757.6 mg is obtained.

## Pre-compression evaluation of liquisolid powder compact

Evaluation of liquisolid powder compact includes test 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 parameter were evaluated:

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

Bulk Density: 0.2 g/cm$^3$ to 1.0 g/cm$^3$,

Wall Friction Angle: 20° to 40°,

Internal Friction Angle: 30° to 45°,

Compressibility: 10% to 30% are some important parameters measured in a Powder-Flow tester instrument. This parameter assesses the friction between the powder and the surfaces it contacts, as it is important for understanding 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. It provides rapid and accurate measurements, saving time in the development and production processes is the great benefit of this test.

## Post-compression parameter of Liquisolid Ivacaftor Tablet

### *Dissolution Test*

Phosphate buffer pH 6.8 with 0.4% SLS acts as a dissolution medium. Volume of dissolution media was 900 mL and was used with the USP Apparatus II (paddle). Each formulation contains 25 mg of Ivacaftor. Samples were withdrawn at intervals of 5, 10, 20, 30, 45, and 60 min, and filtered through a 0.45-micron syringe filter paper. Appropriate dilution was carried out. Absorbance was recorded using UV spectroscopy at a 248 nm wavelength.

### Disintegration Test

Disintegration test carried out in 0.1N HCl solution.

### Drug content

The drug content of the Ivacaftor Liquisolid tablet was calculated by dissolving the formulation in a suitable quantity of methanol using of ultrasonicator. The drug content was determined at 254 nm using a spectrophotometer (Shimadzu).

## RESULTS AND DISCUSSION

### Evaluation of Preformulation Studies

Ivacaftor was evaluated for preliminary identification characteristics and observed as a white, odorless, and bitter-tasting powder. The melting point of ivacaftor was found to be 321.5°C, recorded on an optimelt melting point instrument.

Ivacaftor analysis was done by UV Spectrophometric 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 Ivacaftor in Non-Volatile Solvents

Saturation solubility of ivacaftor in various solvents such as tween 80, PEG 400, tween 20, oleic acid, glycerin, propylene glycol and transcutol is carried out. Highest solubility was observed in transcutol 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

In the various research papers found that due to high surface area, the neusilin US2 and syloid FP 244 act as excellent carriers as well

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

| R Excipient ratio | Drug liquid blend (W) mg | Neusilin US2 (Q) mg | Syloid FP244 (q) mg | Lf | Disintegrating agent (mg) | Weight of Compact (mg) |
|---|---|---|---|---|---|---|
| 5 | 275 | 330.9 | 66.1 | 0.831 | 33.6 | 705.6 |
| 10 | 275 | 336.1 | 36.6 | 0.751 | 33.8 | 711.5 |
| 20 | 275 | 386.7 | 19.3 | 0.711 | 34.05 | 715.05 |
| 30 | 275 | 394.5 | 13.1 | 0.697 | 34.13 | 716.73 |
| 40 | 275 | 397.9 | 9.9 | 0.691 | 34.14 | 716.94 |
| 50 | 275 | 400.3 | 8.0 | 0.687 | 34.16 | 717.46 |

**Table 2: Formulations of Ivacaftor Liquisolid Compact by using Box-Behnken design.**

| Formulation | R | Drug conc. In non-volatile solvent(%w/w) | Liquid load factor Lf | Ivacaftor drug mg | Non-Volatile Solvent mg | Carrier mg | Coating agent mg | Disintegrant mg | Unit Dose mg |
|---|---|---|---|---|---|---|---|---|---|
| F1 | 30 | 8.5 | 0.697 | 25 | 270 | 423.2 | 14.1 | 51.2 (7%) | 783.2 |
| F2 | 20 | 9.1 | 0.711 | 25 | 250 | 386.7 | 19.3 | 34.1 (5%) | 715.1 |
| F3 | 30 | 8.8 | 0.697 | 25 | 260 | 408.8 | 13.6 | 35.3 (5%) | 742.8 |
| F4 | 20 | 8.5 | 0.711 | 25 | 270 | 414.9 | 20.7 | 36.5 (5%) | 767.1 |
| F5 | 40 | 9.1 | 0.691 | 25 | 250 | 397.8 | 9.9 | 34.1 (5%) | 716.9 |
| F6 | 40 | 8.8 | 0.691 | 25 | 260 | 412.4 | 10.3 | 21.2 (3%) | 728.9 |
| F7 | 30 | 8.8 | 0.697 | 25 | 260 | 408.8 | 13.6 | 35.3 (5%) | 742.7 |
| F8 | 20 | 8.8 | 0.711 | 25 | 260 | 400.8 | 20.0 | 21.1 (3%) | 726.9 |
| F9 | 30 | 8.8 | 0.697 | 25 | 260 | 408.8 | 13.6 | 35.3 (5%) | 742.7 |
| F10 | 40 | 8.8 | 0.691 | 25 | 260 | 412.4 | 10.3 | 49.5 (7%) | 757.2 |
| F11 | 30 | 9.1 | 0.697 | 25 | 250 | 394.5 | 13.1 | 20.4 (3%) | 703.0 |
| F12 | 30 | 9.1 | 0.697 | 25 | 250 | 394.5 | 13.1 | 47.7 (7%) | 730.3 |
| F13 | 30 | 8.8 | 0.697 | 25 | 260 | 408.8 | 13.6 | 35.3 (5%) | 742.7 |
| F14 | 30 | 8.8 | 0.697 | 25 | 260 | 408.8 | 13.6 | 35.3 (5%) | 742.7 |
| F15 | 40 | 8.5 | 0.691 | 25 | 270 | 426.9 | 10.6 | 36.6 (5%) | 769.1 |
| F16 | 30 | 8.5 | 0.697 | 25 | 270 | 423.2 | 14.1 | 21.9 (3%) | 754.2 |
| F17 | 20 | 8.8 | 0.711 | 25 | 260 | 400.8 | 20.0 | 49.4 (7%) | 755.2 |

as coating agents.[20,21] On this basis, the neusilin US2 and syloid FP 244 are selected as carrier and coating agent, respectively.

## Angle of Slide for determination of flowability (Φ) value of carrier and coating agent

Optimum angle of slide was found to be 33°, 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 formula 7.

Φ=Maximum amount of non-volatile solvent (g)/
Weight of carrier (g) or weight of coating (g)--- (7)

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)

The 25 mg dose of ivacaftor was completely solubilized in 0.2675 mL of transcutol. So that the total drug liquid blend was 292.5 mg.

## Determination of the weight of carrier agent (Q)

The carrier neusilin US2 concentration is determined from formula (6). 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 optimised batch.

## Determination of the weight of coating agent (q)

The coating agent Syloid FP 244 concentration is determined from formula (1).

The required and calculated concentration of Syloid FP 244 is 10.8 mg for the optimised batch.

## Optimization of Liquisolid Ivacaftor Tablet

The statistical analysis in DOE software plays an essential role in obtaining optimized batch.

## ANOVA for the Quadratic model

*P*-values less than 0.0500 indicate model terms are significant in all the following responses. A (R), B (DT), and C (Non-volatile liquid) are factors in Analysis of Variance (ANOVA). The ANOVA is used in statistical modeling and experimental design to evaluate the significance of different factors and their interactions in influencing a response variable.

Sum of Squares (SS) represents the variation contributed by each factor, Degrees of Freedom ($d_f$) mean number of independent values that contribute to the calculation, 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). A higher F-value indicates a more significant effect.

## Response 1 Disintegration time

This model of ANOVA includes Sum of Squares (SS), which is 392.35, Degrees of freedom ($d_f$) is 9, Mean Square (MS) is 43.59, F-value is 55.43, and *p*-value is < 0.0001. The lack of fit *p*-value is 0.1401, which is not significant, indicating that the model fits the data well, meaning the unexplained variation is mostly random noise rather than systematic bias. Lack of Fit is not significant means the residual error is low.B-Disintegration Time has a very significant effect. As the disintegration time has a non-linear relation with the response 1. A (R), AC, $A^2$, and $C^2$ are not significant, meaning they do not have a strong effect on the response 1.Factor C is not significant, meaning they do not contribute much.

## Response 2 Dissolution at 30 min

In this model of ANOVA, the Sum of Squares (SS) which is 7507.78, Degrees of Freedom ($d_f$) is 9, and Mean Square (MS)

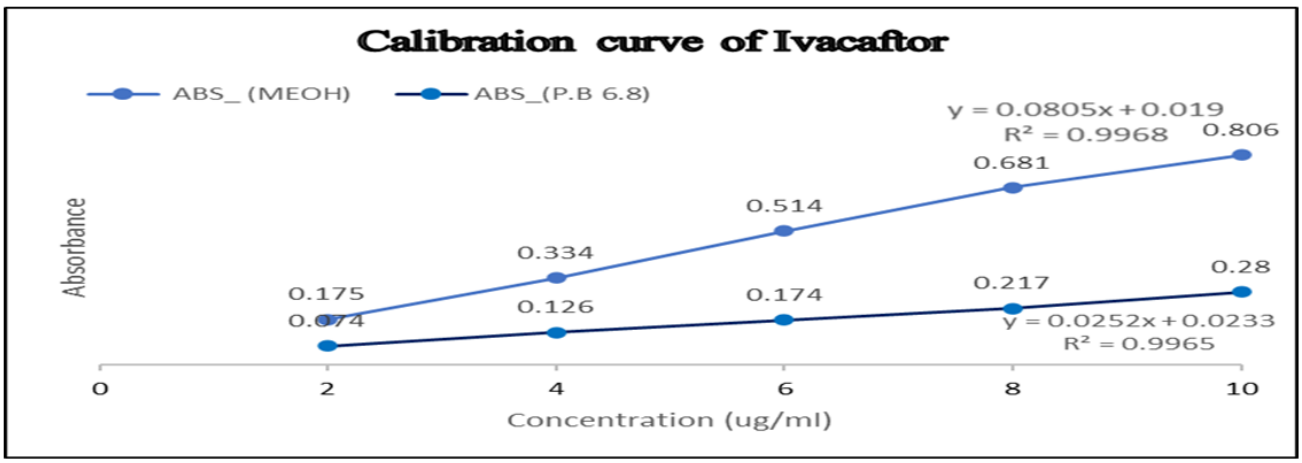



**Figure 1:** Calibration curve of Ivacaftor in methanol and phosphate buffer pH 6.8 with 0.4% SLS.

is 834.20, the F-value is 13.01 and *p*-value is 0.0014. The model is statistically significant. Lack of fit is 0.8942, which is not significant, indicating that the model fits the data well. Factor B (DT) has the strongest effect, and factor A (R) also has a significant effect. Quadratic term $B^2$ is highly significant**,** indicating a strong non-linear effect of B. The interaction of A and C is significant.

## Response 3 Dissolution at 60 min

In this model of ANOVA, include the Sum of Squares (SS), which is 1565.12, the Degrees of Freedom ($d_f$) are 9, and Mean Square (MS) is 173.90, the F-value is 22.89, and the *p*-value is 0.0002. The model is highly significant. Lack of fit is0.0514, which is not significant, indicating that the model fits the data acceptable range. Factor A (R) has little to no effect on the response. Factor B (DT) has a very strong influence on the response. Factor C (non-volatile liquid) has no significant effect on the response 3.

The R value is indirectly proportional to the coating agent concentration. Coating agent retards the dissolution rate. Thus, dissolution at 60 min increases as the R value increases, as shown in Figure 3. As the disintegrating agent concentration is increases the dissolution and disintegrating time were increases.

## Equation for Disintegration Time

Disintegration time=+2.52-0.3625A-5.23B-0.5625C+1.00AB 0.1250AC+1.15BC+0.1275A2+6.15B2 +0.0775C2

## Equation for Dissolution at 30 min

Dissolution at 30 min=+84.24 -9.45A+17.33B-6.53C+0.900 0AB-15.30AC-7.65BC+3.11A2-24.34B2-8.15C2

## Equation for Dissolution at 60 min

Dissolution at 60 miWn=+102.96+0.2500A+9.13B+0.0750C+1. 60AB+0.3000AC+2.25BC-1.36A2-14.11B2+2.50C2

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.

For disintegration time, excipient Ratio (R), disintegrating agent concentration, and non-volatile solvent concentration showed have antagonistic effects. In case of dissolution at 30 min, excipient Ratio (R) and non-volatile solvent concentration indicated antagonistic effects and synergistic effects were observed with disintegrating agent concentration. In case of dissolution at 60 min, excipient Ratio (R), disintegrating agent concentration, and non-volatile solvent concentration indicated synergistic effects were observed. The concentration non-volatile solvent in drug liquid blend is indirectly proportional to disintegrating rate.

From the overlay plot concluded that the all three responses meet their respective criteria and in optimum ranges responses were obtained is seen in Figure 3.

## Pre-compression parameter of liquisolid ivacaftor compact

The bulk density, tapped density, hausner's ratio, Carr's index and angle of repose are crucial factor for determine the flowability of compacts. All responses are obtained within acceptable limit as shown in Table 3.

## FTIR Spectroscopy

The spectra obtained show that there is no interaction between the excipients (Transcutol, Neusilin US2, Syloid FP 244, and Sodium starch glycolate excipient) and ivacaftor pure drug, as shown in Figure 4.

## X-ray Diffraction (XRD)

The Crystallinity of pure Ivacaftor was found to be 99.8%. From the LS1 mixture, it is obtained that pure drug Ivacaftor is completely solubilized in the transcutol solvent. So it is also

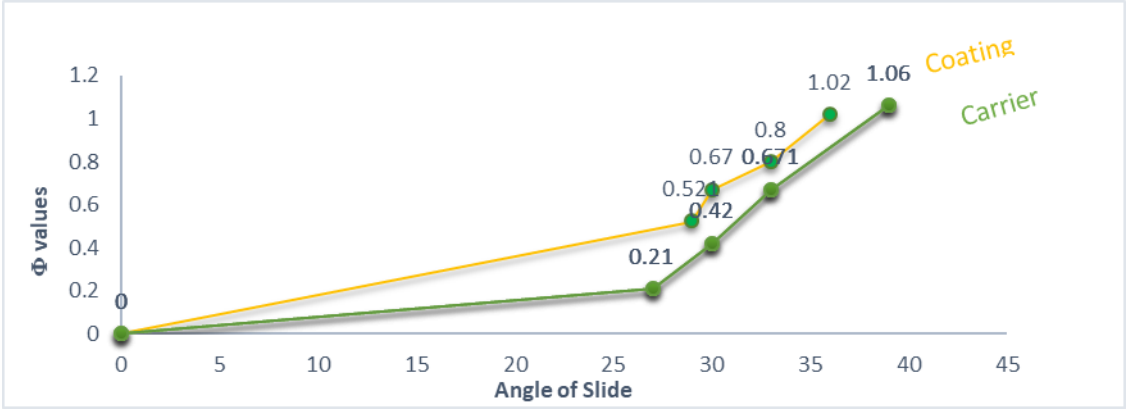



**Figure 2:** Angle of Slide of carrier and coating agent.

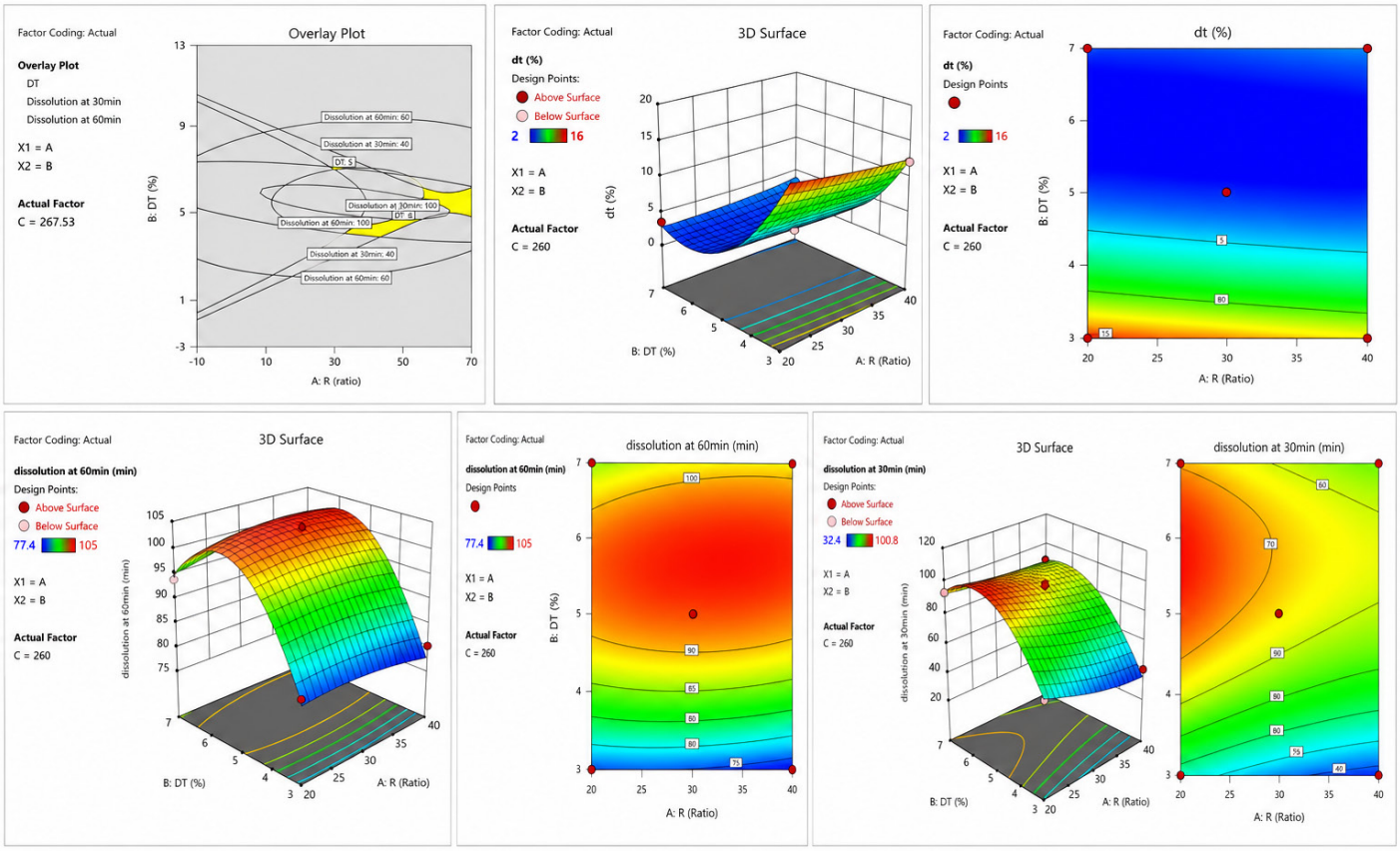



**Figure 3:** DOE Optimization graphs for Liquisolid Ivacaftor tablet.

observed that no peak is seen in the LS1 mixture, as shown in Figure 4.

## Differential Scanning Calorimetry (DSC)

From the DSC graph, it can be clearly concluded that the solid form of ivacaftor has been converted to the amorphous form. Because pure drug Ivacaftor shows the melting point at 321.51°C with a sharp endothermic peak. While in the LS1 blend mixture, no peak is observed in Figure 4.

## Scanning Electron Microscopy study (SEM)

Morphology of Pure drug Ivacaftor is long nanowire such as structure and crystalline compared to the LS1 mixture and reduction of particle size is observed, as shown in Figure 4.

## Raman Mapping

Reduced intensity was observed in the LS1 mixture as compared to the pure Ivacaftor drug as shown in Figure 4, it indicates that the drug is converted into amorphous form. Furthermore, it has been discovered that Raman mapping can be used to find traces of crystalline medicine in formulations, even when the drug's concentration is below the XRD detection limit. Consequently, it is advantageous to use Raman mapping in our investigations to assess the ivacaftor spatial distribution and crystallinity state in liquid-solid compacts.

## Advanced Powder Flow Test (PFT)

As the stress ($\sigma_e$) increases, the bulk density ($\rho_6$) also increases, indicating compression of the material. The highest recorded bulk density (334.1 kg/m$^3$) corresponds to the highest applied stress (4.830 kPa). The fill density (243.7 kg/m$^3$) compared to the maximum density (334.1 kg/m$^3$) shows how much the powder compacts under stress. The arching bulk density (250.6 kg/m$^3$) helps in designing hoppers or feeders, ensuring that powders do not clog or bridge.

Flow Function Graph shows the relationship between Unconfined Failure Strength (kPa) and Major Principal Consolidating Stress (kPa) for a powder LS1 sample. The red line flow function curve represents the experimental data of the powder's unconfined failure strength (σC) at different consolidation stresses (σ1). The flatter curve in the red line FF curve suggests better flowability. The black/gray line flowability threshold represents a standard threshold for flowability classification. Light blue line (Arching Flow Function - FF) represents the arching criteria, the stress at which the material is prone to forming stable arches in hoppers. A higher flow index suggests better flowability, including $\sigma_1$ (kPa), major principal consolidating stress has a value of 7.852, indicating the easy-flowing powder.

This graph shows the effective angle of internal friction (δU) versus major principal consolidating stress ($\sigma_1$) for the LS1

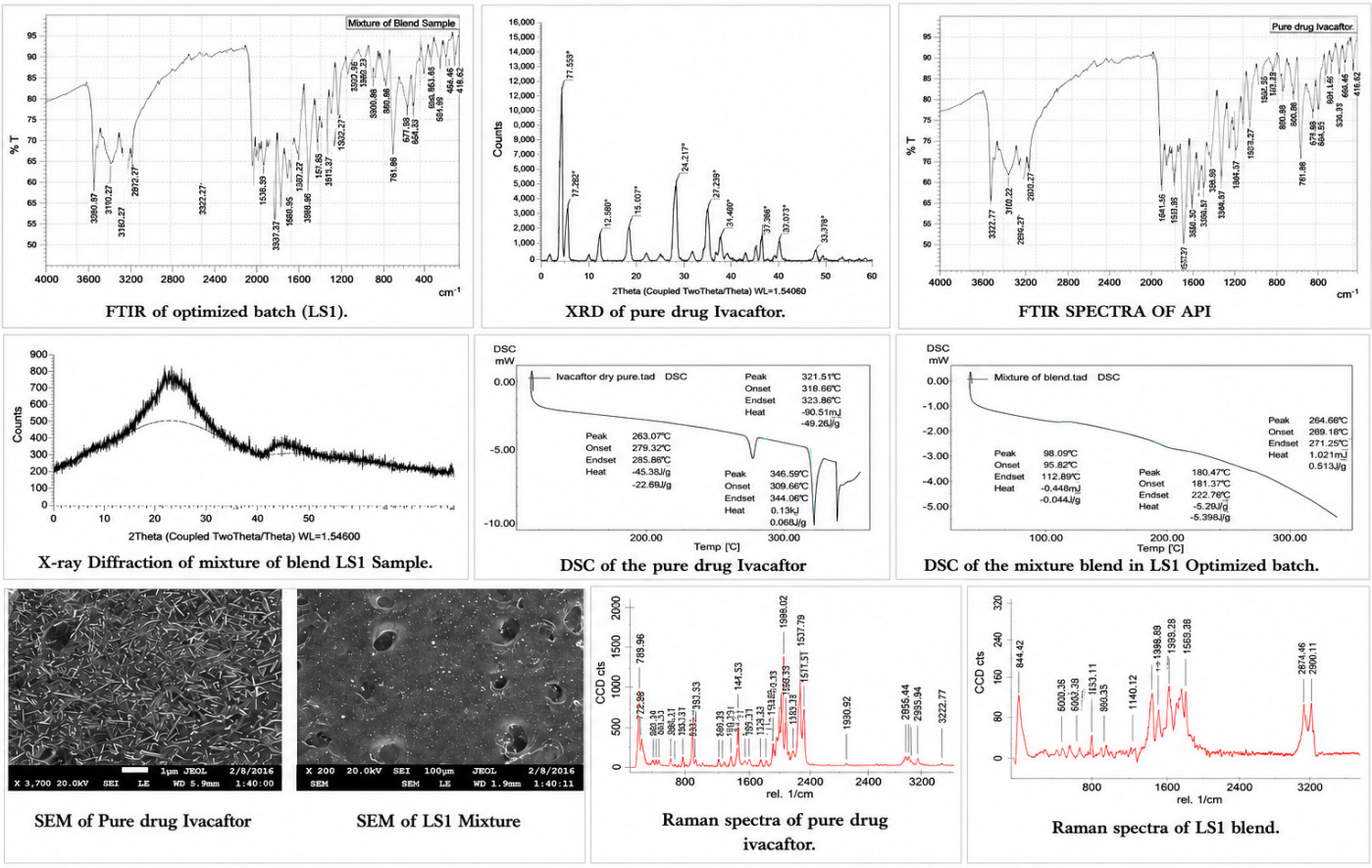
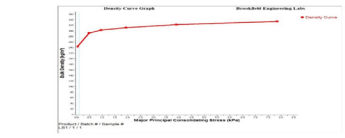



**Figure 4:** Characterization of Ivacaftor liquisolid tablet & its LS1 (Blend) mixture.

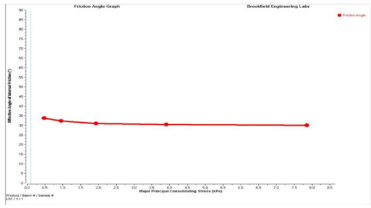
**Table 3: Properties of compacts before compression into tablet.**

| Batch | Bulk Density | Tapped density | Hausners index | Carrs index | Angle of Repose |
|---|---|---|---|---|---|
| F1 | 0.75±0.02 | 0.811±0.01 | 1.08±0.01 | 7.5±0.05 | 33°±0.6 |
| F2 | 0.74±0.03 | 0.799±0.03 | 1.08±0.02 | 7.8±0.43 | 31°±0.6 |
| F3 | 0.74±0.03 | 0.803±0.03 | 1.09±0.01 | 8.2±0.69 | 31°±1.2 |
| F4 | 0.73±0.01 | 0.779±0.01 | 1.07±0.01 | 6.7±0.64 | 32°±0.6 |
| F5 | 0.82±0.01 | 0.846±0.01 | 1.03±0.01 | 3.5±0.08 | 29°±0.6 |
| F6 | 0.72±0.04 | 0.787±0.04 | 1.08±0.01 | 8.1±0.78 | 31°±1.2 |
| F7 | 0.82±0.01 | 0.843±0.07 | 1.03±0.01 | 3.47±0.08 | 26°±1.0 |
| F8 | 0.74±0.03 | 0.803±0.03 | 1.09±0.01 | 8.3±0.69 | 33°±0.6 |
| F9 | 0.77±0.01 | 0.829±0.01 | 1.08±0.01 | 7.5±0.18 | 32°±0.6 |
| F10 | 0.74±0.03 | 0.803±0.03 | 1.09±0.01 | 8.3±0.69 | 30°±0.6 |
| F11 | 0.72±0.02 | 0.79±0.02 | 1.09±0.01 | 8.8±0.39 | 31°±0.6 |
| F12 | 0.75±0.02 | 0.815±0.01 | 1.08±0.01 | 8.0±0.82 | 29°±0.6 |
| F13 | 0.72±0.02 | 0.796±0.02 | 1.09±0.01 | 8.8±0.39 | 32°±0.6 |
| F14 | 0.82±0.01 | 0.843±0.01 | 1.03±0.01 | 3.5±0.08 | 32°±1.0 |
| F15 | 0.80±0.02 | 0.823±0.02 | 1.03±0.01 | 2.7±0.71 | 29°±0.6 |
| F16 | 0.75±0.02 | 0.820±0.01 | 1.09±0.01 | 8.5±0.79 | 31°±1.2 |
| F17 | 0.72±0.02 | 0.796±0.03 | 1.09±0.01 | 8.8±0.39 | 33°±0.6 |

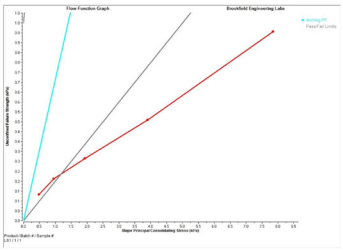
(SD is standard deviation for *n*=3 observation).



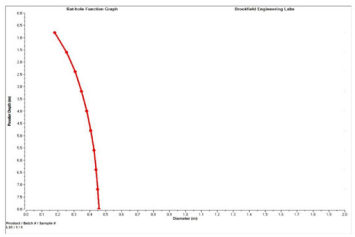
FF Density of LS1.



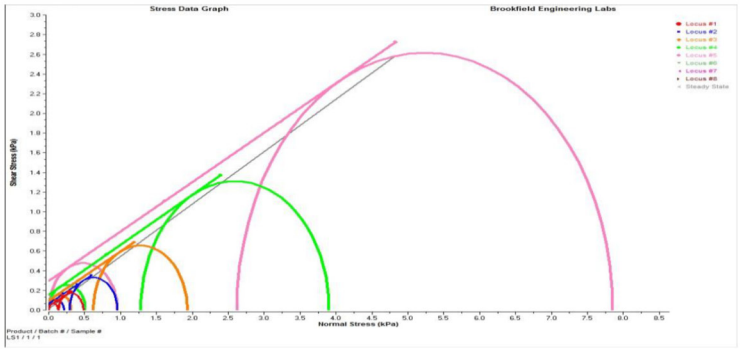
FF Friction angle of LS1.



FF Flow Function of LS1.



Hopper design of core flow of LS1.




Stress Data Analysis of LS1 by Mohr's Circle.

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

Sample. $\sigma_1$ 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 arching usually occurs.

The 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 the 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.

## Post-Compression Parameter

Optimized batch of liquisolid ivacaftor tablet shows the 0.7% friability, 3.5 kg/cm$^2$ hardness, and size is found to be 5 mm in thickness and 1.3 cm in diameter.

The DOE profile of all the seventeen batches was illustrated 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 as the decrease in disintegrating agent concentration, reduces the dissolution rate. In all other formulations, concentration of disintegrating agent is 5% and 7% hence the dissolution rate and disintegrating time increases.

In the optimized batch (LS1), observed responses are like the predicted responses.

## Drug content

The drug content of the liquisolid ivacaftor tablet was 102.0% w/w.

## *In vitro* dissolution studies

Dissolution profile of liquisolid ivacaftor tablet with different range of (R values) excipient ratio that is from 5 to 50, was performed and it is found that as the R value increases the dissolution rate is increases. The increases in R value reduces the coating agent concentration in formulation. Coating agent retards the dissolution rate.

**Table 4: Evaluation parameter of Liquisolid Formulations.**

| Formulation | Dissolution at 30 min (%) | Dissolution at 60 min (%) | Disintegration time (min) |
|---|---|---|---|
| F1 | 54 | 104.4 | 3.8 |
| F2 | 79.2 | 104.4 | 2.6 |
| F3 | 88.2 | 100.8 | 2.3 |
| F4 | 100.8 | 105 | 2.3 |
| F5 | 88.2 | 102.6 | 3.4 |
| F6 | 37.8 | 80 | 12 |
| F7 | 88.2 | 102.6 | 2.5 |
| F8 | 55.8 | 81 | 16 |
| F9 | 90 | 104.4 | 2 |
| F10 | 72 | 97.2 | 3.6 |
| F11 | 34.2 | 82.8 | 16 |
| F12 | 86.4 | 100.8 | 3.2 |
| F13 | 88.2 | 102.6 | 2.2 |
| F14 | 66.6 | 104.4 | 3.6 |
| F15 | 48.6 | 104.4 | 2.6 |
| F16 | 32.4 | 77.4 | 12 |
| F17 | 86.4 | 91.8 | 3.6 |

From the parameter from the Table 4, Optimized LS1 batch (tablet) is obtained. This batch shows the % drug release like the marketed preparation of ivacaftor (granules 25 mg). The percentage drug release of lactose-based tablet shows the 56.7%. The 50 mg granules of marketed preparation of ivacaftor shows the 97.02% drug release. The optimized liquisolid ivacaftor tablet shows the 97.2% drug release as shown in Figure 4.

## DISCUSSION

The present study aimed to enhance the dissolution of ivacaftor, by using box behnken design and through formulation of liquisolid tablet. The liquisolid technique was selected due to the efficacy in improving the dissolution rates of poorly soluble drugs by increasing the surface area of drugs and converting it into amorphous form. The optimized study using the box behnken design state the significant influence of the three independent variables such as excipient ratio, non-volatile solvent concentration, and concentration of disintegrating agent, on the key responses that is disintegrating time, dissolution at 30 min and dissolution at 60 min. The quadratic model was found to be best fit, as evidenced by statically significant *p*-value and high $R^2$ value, suggesting good correlation between the predicted and experimental data. In conclusion, the developed liquisolid tablet of ivacaftor offers the promising platform for enhancing the solubility and dissolution of poorly soluble drugs. Moreover, the optimized formulation (LS1) shows the similar drug release that is 97% as that of marketed preparation of ivacaftor named 50 mg ivacaftor granules. The various test such as DSC, XRD, Raman mapping, FTIR, and SEM analysis proved that the ivacaftor API is converted to amorphous form. Advanced flow properties study showed that the optimized formulation is having excellent flow properties suitable for its industrial manufacturing.

## CONCLUSION

In the present study, the ivacaftor liquisolid tablet shows a higher dissolution rate as compared to the lactose-based Ivacaftor tablet. The Ivacaftor Liquisolid formulation with a drug concentration of 8.54% (w/w) and an excipient Ratio (R) of 39.1 was the optimal formulation. Tablet characteristics such as weight, hardness, friability, and disintegration time meet good quality attributes. Optimized batch shows quick dissolution rate, good flowability, and acceptable tablet characteristics. The distinct reduction in crystallinity and enhanced amorphous nature of drug particles was clearly seen in the SEM, XRD, and Raman spectra.

## ACKNOWLEDGEMENT

The Authors are thankful to the Government of Maharashtra for providing the Mahatma Jyotiba Phule research scholarship for this project. The author expresses their gratefulness to the Y.B Chavan College of Pharmacy for providing facilities. The authors sincerely acknowledge MSN Laboratories Private Limited for providing the gift sample of Ivacaftor for analysis. We sincerely

express our gratitude to the R.C Patel Institute, Shirpur, for conducting the X-ray diffraction and powder flow testing. We also extend our thanks to MIT, chh. Sambhaji Nagar, for carrying out DSC. Furthermore, we acknowledge ICON Lab Mumbai for their support in SEM analysis. Also, we acknowledge the Sophisticated Analytical Instrument Facility (SAIF), Mahatma Gandhi (MG) University, Kottayam, for their support in Raman mapping analysis. Their valuable contributions significantly enhanced the quality of this research.

## ABBREVIATIONS

**DSC:** Differential scanning Calorimetry; **XRD:** X-ray Diffraction; **SEM:** Scanning electron microscopy; **BCS:** Biopharmaceutical classification system; **SLS:** Sodium lauryl sulphate; **FTIR:** Fourier transform infrared.

## CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

## FUNDING

The Government of Maharashtra, providing the research scholarship called Mahatma Jyotiba Phule research scholarship for this project.

## SUMMARY

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

## REFERENCES

1. Connett, G. Lumacaftor-Ivacaftor in the treatment of cystic fibrosis: design, development and place in therapy. Drug Design, Development and Therapy, 2019;13,2405-12. doi:10.2147/dddt.s153719.
2. Davies, J. C., Alton, E. W. F. W., and Bush, A. Cystic fibrosis. British Medical Journal, 2007;335(7632):1255-9. doi:10.1136/bmj.39391.713229.
3. Miao, Y., Zhao, S., Zuo, J., Sun, J., and Wang, J. Reduced the Food Effect and Enhanced the Oral Bioavailability of Ivacaftor by Self-Nanoemulsifying Drug Delivery System (SNEDDS) Using a New Oil Phase. Drug design, development and therapy, 2022;16:1531-46. https://doi.org/10.2147/DDDT.S356967.
4. Hadida, S., Van Goor, F., Zhou, J., Arumugam, V., McCartney, J., Hazlewood, A., *et al.* Discovery of N-(2, 4-Di-tert-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide(VX-770, Ivacaftor), a Potent and Orally Bioavailable CFTR Potentiator. Journal of Medicinal Chemistry,2014;57(23):9776-95. Doi: 10. 1021/jm5012808.
5. Middleton, P. G., and Taylor-Cousar, J. L. Development of elexacaftor - tezacaftor - ivacaftor: Highly effective CFTR modulation for the majority of people with Cystic Fibrosis. Expert Review of Respiratory Medicine, 2021;15(6):723-35. doi:10.1080/17476348.2021.1855980.
6. Pozniak, J., Ryšánek, P., Smrčka, D., Kozlík, P., Křížek, T., Šmardová, J., *et al.* Ivacaftor pharmacokinetics and lymphatic transport after enteral administration in rats. Frontiers in pharmacology, 2024;15(1331637):1-8. https://doi.org/10.3389/fphar.2024.1331637.
7. Kapoor, H. Ivacaftor: A Novel Mutation Modulating Drug. Journal of clinical and diagnostic research. 2014;8(11):1-6. doi:10.7860/jcdr/2014/6486.5158.
8. Guntaka, P. R., and Lankalapalli, S. Solubility and dissolution enhancement of Ivacaftot tablets by using solid dispersion technique of hot-melt extrusion- A design of experimental approach. Asian Journal of Pharmaceutical and Clinical Research, 2019;12(1):356-63. doi:10.22159/ajpcr.2019.v12i1.30369.
9. Sowmya M. Formulation and *in vitro* characterization of ivacaftor solid dispersion by solid solvent evaporation technique. World Journal of Pharmaceutical Sciences. 2024;12(01):45-55; https://doi.org/10.54037/WJPS.2022.100905.
10. Nakhla D. S., Mekkawy A.I., Naguib Y.W., Silva A.D., Gao D., Kim J.A., *et al.* Injectable long-acting ivacaftor-loaded poly (lactide-co-glycolide) microparticle formulations for the treatment of cystic fibrosis: *In vitro* characterization and *in vivo* pharmacokinetics in mice. International Journal of Pharmaceutics, 2024;650(123693):1-34. https://doi.org/10.1016/j.ijpharm.2023.123693.
11. Kalpana B.G., Bhaskar V.N, Ahmed Khan K.A., and, Prakash R.P. Formulation, optimization and evaluation of gastroretentive alginate beads of ivacaftor by using factorial design. Journal of Clinical and Pharmaceutical Research,2021;1(2):16-25.
12. Guan, J., Yuan, H., Yu, S., Mao, S., and Zhou, Q. T. Spray dried inhalable ivacaftor co-amorphous microparticle formulations with leucine achieved enhanced *in vitro* dissolution and superior aerosol performance. International journal of pharmaceutics, 2022;622:121859. doi: 10.1016/j.ijpharm.2022.121859.
13. Parihar, A., and Prajapati, B. G. Response Surface Methodology for an Improved Nanoemulsion of Ivacaftor and Its Optimisation for Solubility and Stability. Pharmacophore, 2023;14(5):1-8. https://doi.org/10.51847/lZAVr2gt5p.
14. Spireas, S., Liquisolid systems and methods of preparing same. US Patent,2002;09/568,475.May 10, 2000.
15. Argade, P., Patole, V. C., and Pandit, A. P. Liquisolid compact tablet of candesartan cilexetil with enhanced solubility using Neusilin US2, Aerosil 200 and Transcutol HP. Indian J Pharm Educ Res, 2019;53(3):457-67. DOI: 10.5530/ijper.53.3.78.
16. Hussain, Y., Cui, J., Dormocara, A., and Khan, H. The most recent advances in liquisolid technology: Perspectives in the pharmaceutical industry. Pharmaceutical Science Advances, 2024;2(100038):1-12. https://doi.org/10.1016/j.pscia.2024.100038.
17. Khames, A. Liquisolid technique: a promising alternative to conventional coating for improvement of drug photostability in solid dosage forms. Expert Opinion on Drug Delivery, 2013;10(10):1335-43. doi:10.1517/17425247.2013.798297.
18. Lu, M., Xing, H., Jiang, J., Chen, X., Yang, T., Wang, D., and Ding, P. Liquisolid technique and its applications in pharmaceutics. Asian Journal of Pharmaceutical Sciences, 2017;12(2):115-23. doi:10.1016/j.ajps.2016.09.007.
19. Burra, S.; Yamsani, M.; Vobalaboina, V. The Liquisolid Technique: An Overview. Braz. J. Pharm. Sci. 2011;47(3):475-82. https://doi.org/10.1590/S1984-82502011000300005.
20. Vasiljevic I., Turkovic E., Parojcic J., Data-driven insights into the properties of liquisolid systems based on machine learning algorithms. European Journal of Pharmaceutical Sciences. 2024;203(106927):1-12. https://doi.org/10.1016/j.ejps.2024.106927.
21. Kanugo A, Thanvi A., Neusilin US2 based liquisolid Compact technique for the enhancement of solubility and dissolution rate of olmesartan: Box-Behnken design approach. J Res Pharm.; 2023;27(1):52-66. http://dx.doi.org/10.29228/jrp.289.
22. Barbora Vranı´kova´, Jan Gajdziok, and David Vetchy Determination of flowable liquid retention potential of aluminometasilicate carrier for liquisolid systems preparation Pharm Dev Technol, 2015;20(7):839-44, DOI: 10.3109/10837450.2014.926921.

**Cite this article:** Chate MD, Lahoti SR. Formulation and Evaluation of Liquisolid Tablet with Enhanced Dissolution of Ivacaftor by Using Box-Behnken Design. Indian J of Pharmaceutical Education and Research. 2026;60(4s):s1405-s1415.