AI based Prediction of Stability and Dissolution Profiles of Ibrutinib Solid Dispersions

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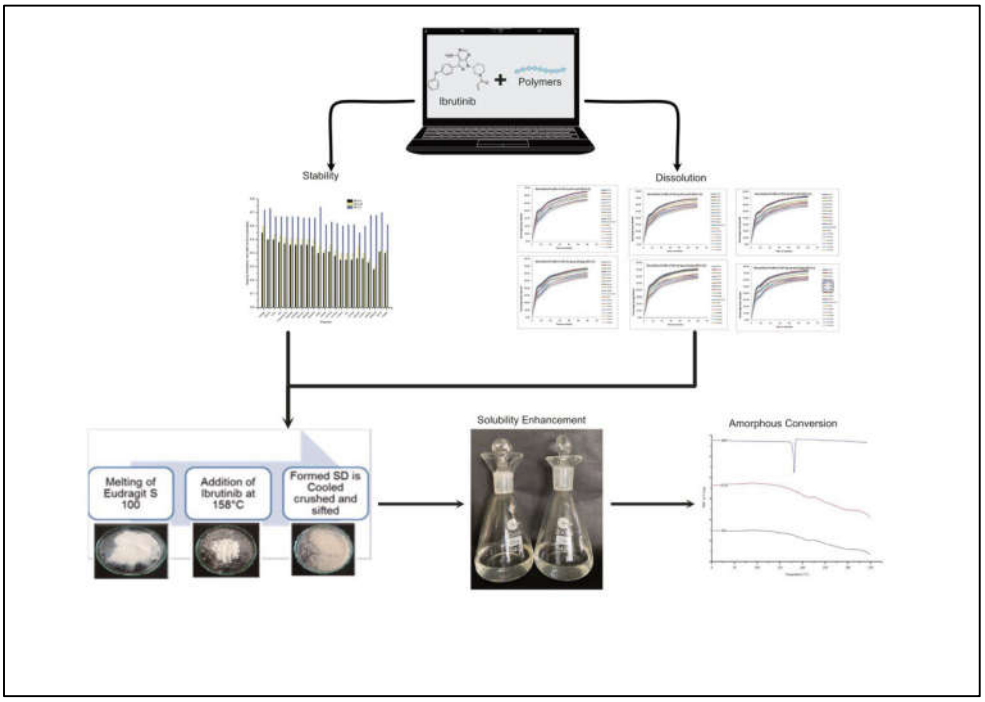
Abstract:
Solid dispersion is one of the most promising approaches for increasing solubility of poorly soluble drugs. Physical stability and drug dissolution are the two major challenges influenced by the type of polymer in formulation of poorly soluble drug as solid dispersion. Computational models can help in the design and optimization of formulation using mathematical prediction. In silico formulation of Ibrutinib solid dispersions was performed with different polymers using two different methods of hot melt and spray drying at three different drug ratios of 0.2, 0.33 and 0.5 for each method and their stability and dissolution were predicted using the PharmSD AI tool. Solid dispersion of ibrutinib eudragit was prepared by hot melt fusion method experimentally and evaluated for solubility, drug content , drug release and amorphous nature.Nature of the polymer, drug polymer ratio and preparation method were observed to affect the dissolution rate and stability of Ibrutinib. The dissolution rates were observed to increase when the drug polymer ratio was decreased from 0.5 to 0.2. Although the spray drying method improved the stability at 0.5 drug ratio, the hot melt method showed better stability at drug of 0.2. PVP grades that enhanced drug dissolution were found to exhibit lower stability. PEG grades which are highly stable, showed lower drug dissolution. Eudragit was observed to be one of the best performing polymers across hot melt and spray drying methods and at all three drug ratios, exhibiting comparatively higher stability with improved dissolution drug profile. Experimental solid dispersion preparation using Eudragit resulted in transformation of crystalline ibrutinib to amorphous form in the polymer matrix which results in 6 fold increase in solubility. R^2 of 0.98 was observed for the correlation of actual and predicted dissolution data. AI based prediction model aided to identify a best performing polymer for the solid dispersion of Ibrutinib with accuracy and supports its application in optimizing the formulation development.
Keywords: Prediction model, Solid dispersion, Ibrutinib, Eudragit, Dissolution, Stability.

Graphical Abstract:



1. INTRODUCTION

A drug with poor aqueous solubility exhibits dissolution rate limited absorption. Improving the solubility and dissolution rate of poorly water-soluble drugs will help to improve the oral bioavailability of pharmacologically active agents [1]. Solid dispersion formulation is one of the most promising approaches for increasing solubility. The basic principle involved in enhancing the poor solubility of the drug with solid dispersion includes complete removal of drug crystalline structure and its molecular dispersion in a hydrophilic polymeric carrier. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug is released as fine colloidal particles. This increases the surface area of dissolution rate and hence bioavailability of poorly water soluble drugs. The drug in the soluble hydrophilic carrier improves the dissolution rate by reducing particle size and increasing the particle porosity. Therefore by improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce the side effects [2].

Solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs [3]. Ibrutinib is selective and covalent inhibitor of the enzyme Bruton's tyrosine kinase, used for the treatment of B-cell malignancies [4]. It exhibits poor water solubility of 0.003mg/ml and highly lipophilic in nature with lop P value of 3.97 [5]. Ibrutinib is slightly soluble at pH 1.2, but practically insoluble at pH 3 to 8 due to its pKa of 6.58 (basic group)[6]. The bioavailability is approximately 2-8%. Attempts to improve the solubility of Ibrutinib through solid dispersion were reported earlier using different method like quench-cooling method, hot melt extrusion and by using polymer like copovidone and poloxomer. The results exhibited improved solubility and dissolution of Ibrutinib [6-9].

The major challenges with solid dispersions are stability and choosing the polymer. The Potential for recrystallization of the drug over time can result in reduced solubility and bioavailability. Traditional stability studies that require at least 3 to 6 months are time-consuming and delay predictions. The choice of the polymer is critical for solid dispersion. The polymer should be compatible over storage. The degree of solubility enhancement depends on factors such as the polymer's chemical structure, hydrophilicity, molecular weight, and the method used to prepare the solid dispersion. Each type of polymer offers unique advantages and limitations, making them suitable for specific preparation methods and applications[10,11].

Computational pharmaceutics integrates artificial intelligence and multi-scale modelling techniques into pharmaceutics, helping the optimization in formulation development by time savings and resource reduction [12,13]. The regulatory agencies like FDA promote applications of computational methods to pharmaceutics to improve the product quality, as this approach supports product design, conforming to the quality by design (QbD) strategy [14]. AI and machine learning algorithms are able to make data-driven predictions by an algorithm from large amounts of cumulated experimental data to build the quantitative formulation prediction model. Computational models can predict the behaviour of solid dispersions under various conditions, helping in the design and optimization of formulation reducing the time and cost of formulation. PharmSD is the AI driven formulation prediction platform. This tool helps to evaluate the properties related to solid dispersion based on the advanced machine learning algorithm. It helps to predict the physical stability of solid dispersion formulation by providing the stability predictions for the input drug against different kinds of polymers. It helps to predict the drug dissolution type and dissolution rate for the solid dispersion combination with different polymers.

In this study, we intended to have a systematic approach to select the polymer for the solid dispersion of Ibrutinib using well defined criteria of drug ratio, preparation method and examining its effect on drug dissolution behaviour and stability by predictive modelling using the AI tool, PharmSD .

2. METHODOLOGY

2.1 PREDICTION METHODS

The AI tool PharmSD version NC-SA 4.0 was used for this study. In silico formulation of solid dispersion of Ibrutinib with various polymers was performed and their stability and dissolution behaviour is studied using this prediction model.

2.1.1 Stability Prediction

The tab "SD Stability" is used for the insilico formulation of the solid dispersion of Ibrutinib with various polymers and its stability prediction. The input of drug molecule was done by inputting the SMILES of the drug Ibrutinib obtained from the pubchem website [15]. SMILES of Ibrutinib- Computed by OEChem 2.3.0 (PubChem release 2024.12.12*)* C=CC(=O)N1CCC[C@H](C1) N2C3=NC=NC(=C3C(=N2)C4=CC=C(C=C4) OC5=CC=CC=C5)N. After inputting the SMILES under the Input way, the parameters like storage temperature, relative humidity, preparation temperature, drug loading ratio and preparation technique are provided for in

silico preparation of solid dispersion. Storage temperatures of 40 ˚C /75% RH and 25˚C/60% RH were selected as per ICH guideline. Three different drug loading ratios of 0.2, 0.33, and 0.5 corresponding to the drug: polymer ratio of 1:4, 1:2 and 1:1 were selected for the preparation. Among the six techniques for preparation provided in the tool, namely Hot melt extrusion/Melting Method; Rotary evaporation; Spray drying; Spin Coated; High Speed Electrospinning; Grinding Method, two methods namely hot melt extrusion/Melting and Spray drying were selected for the preparation as they are the most commonly used and feasible methods. The preparation temperature of 158°C was set based on the melting temperature of the selected drug Ibrutinib. Trials at temperatures of 138°C, 148°C yielded low prediction scores, and trials at temperature 168°C and 178°C did not increase the result. Hence, the temperature was optimized to 158˚C.

The set parameters are submitted to generate the data. The AI model predicts the stability for 3/6 months for the processing and stability condition opted in step 2**.** It provides the molecular features and the predicted results for the solid dispersion of Ibrutinib with the various polymers. The stability data are processed further for evaluation. The values above 0.5 are considered stable and those below 0.5 are unstable.

2.1.2 Dissolution Prediction

The tab “SD Dissolution” is used for predicting the dissolution type and dissolution rate for the solid dispersion of Ibrutinib with various polymers. The Dissolution method database of FDA is used for the input of parameters. The dose is selected from the drugs database of FDA (highest dose in tablets)[16].

Predicting dissolution type

The input of drug molecule was done by inputting the SMILES of the drug Ibrutinib. After inputting the SMILES under the Input way, the parameters like preparation method (hot melt/spray drying), drug loading ratio (0.2/0.33/0.5), drug dose (420mg), medium (with surfactant), dissolution method (paddle type), medium type (pH 6.8 phosphate buffer saline), roation speed (75rpm) and medium volume (900mL) were selected. The set parameters are submitted to generate the data. The AI tool generates the predicted probability and the corresponding predicted SD type, precipitation or non-precipitation are obtained for all the polymers prepared as solid dispersion by two methods with three different drug polymer ratios. The data are processed for further evaluation and interpretation.

Predicting dissolution rate

Procedure under dissolution type prediction is repeated for predicting dissolution rate. The AI tool generates the predicted dissolution profile for the time points 5, 10, 15, 20, 30, 45 and 60 minutes for all the SD formulations prepared for three different polymer ratios by two methods of hot melt and spray drying. The results are exported for further evaluation.

2.1.3 Validation of Prediction

The application domain analysis was performed to validate the prediction model used for the solid dispersions of Ibrutinib. The application domain analyses are performed for three models, namely the Stability Model, SD Dissolution type Model and SD Dissolution Rate Model. Performance was assessed using two descriptors namely S-MACCS (Molecular ACCess System Keys) and S-ECFP4 (Extended Connectivity Fingerprints, Radius 2). The values are obtained as the mean and maximum scores for each descriptor and for metrics performance (T) and measures (Q). The radar charts are generated for visualization.

2.2. EXPERIMENTAL METHODS

2.2.1. Materials

Ibrutinib was obtained as a gift sample from Hetero Health care limited and Eudragit S100 was obtained from Evonik Laboratories. All the chemicals used were of analytical grade and glasswares of laboratory grade. Purified water (Milli-Q water purification system) was used in analytical studies.

2.2.2 Preparation of Solid dispersion

SDs of the drug Ibrutinib were prepared by hot melt fusion method. The solid dispersion of the drug Ibrutinib was prepared with polymer Eudragit S 100 in the ratio of 1:4(0.2g of drug with 0.8 of polymer). Eudragit was first melted at 180°C using a sand bath placed on a hot plate (HICON Laboratory Heating Plate). Ibrutinib was added to the molten polymer at 160°C, mixed well and cooled at room temperature to obtain the solid mass. The solidified mass was crushed, pulverized and passed through mesh #40. The resulting SDs were stored in dessicators.

2.2.3. Analysis

The UV-Visible Spectrophotometric method was used to analyze the prepared solid dispersion of Ibrutinib. The quantification of the drug was carried out by using a standard calibration curve based on beer-lambert law. The stock solution was prepared by dissolving 10 mg of Ibrutinib in 100 ml of ethanol to get 100µg/mL concentration. It was further diluted to 2, 4, 6, 8, 10, 12, 14, 16, 18 µg/mL standard solution by transferring 0.2 to1.8-mlf stock solution and made up to 10 mL. The absorbance of these samples were measured at 248 nm using UV-Visible Spectrophotometer (Systronics) against blank[17]. Calibration curve was plotted with different concentrations of Ibrutinib solution against their respective absorbance. This curve is used for the estimation of Ibrutinib in solubility and drug content studies.

2.2.4. Solubility

The solubility of Ibrutinib plain and prepared solid dispersion was determined in water by saturation solubility method. Excess quantity of the sample was added to 25 ml of water in conical flask. The bottles were capped tightly and kept at ambient temperature for 24 hours. The samples were filtered through membrane filter and analyzed by UV-Visible Spectrophotometer (Systronics) at 248nm for Ibrutinib. The experiment was carried out in triplicate.

2.2.5. Drug Content and release

A weighed quantity of the solid dispersion equivalent to 10 mg of Ibrutinib was taken and dissolved in ethanol, sonicated for 15 minutes and madeup to 100 ml. The resultant solution was filtered through a membrane filter, diluted suitably and analyzed using UV-Visible Spectrophotometer (Systronics) at 248nm for Ibrutinib content. The experiment was carried out in triplicate. The assay is calculated as follows:

$$Assay\ \%w/w = (Sample\ Absorbance)/(Standard\ Absorbance) \times Standard\ Concentration \times dilution\ factor \times 100$$

Plain Ibrutinib sample and Solid dispersion equivalent to 420 mg of Ibrutinib were studied for dissolution profile using 900 ml of 6% Polysorbate 20 in 50 mM Phosphate Buffer, pH 6.8, USP II apparatus, 75 RPM. Samples are withdrawn at time intervals, 10,20,30,45 and 60 minutes and analysed using UV-Visibile spectrophotometer at 248nm for Ibrutinib and the percentage drug released was calculated.

2.2.6. Characterization by Thermal Analysis

Thermal analysis was performed using a NETZSCH STA 449F3 analyzer by scanning the samples (Ibrutinib, Eudragit and Solid dispersion) between 30°C and 350°C at the heating rate of 20 °C/min under nitrogen.

3. RESULTS AND DISCUSSION

3.1. STABILITY

The results indicate that stability of the products tends to increase when drug polymer ratio is decreased from 0.5 to 0.2 for both methods across both storage conditions for all polymers under accelerated conditions (DR 0.2 > DR 0.33 > DR 0.5). This suggests that increasing the polymer content may contribute positively to the stability of the formulations.

Although Spray drying method was better at lower drug polymer ratios (0.5 and 0.33) no significant difference is observed in higher polymer content preparations of 0.2 DR. This could be due to the processing effect where uniform dispersion and drug protection is possible by spray drying than hot melt at higher drug concentration whereas the process had less impact when the preparation was done using higher polymer concentration i.e. lower drug ratio.

While almost the preparations of every polymer are stable in long term conditions, there is variability observed in accelerated storage conditions based on the nature of the polymer. (Figure 1,2, 3 and 4). PVP and PEG polymers which were stable in long term storage conditions, showed reduced stability in accelerated storage conditions especially in higher drug ratio preparations of DR 0.5 and DR 0.33. This indicates lack of compatibility of Ibrutinib with these polymers. PHEMA and Alginate exhibit variable stability across different ratios, particularly lower stability values with the drug polymer ratio of 0.5. This suggests these polymers are more sensitive to the drug load.

Among Gelucire, PAA and Eudragit which exhibited good stability in long term conditions, Gelucire and PAA was observed to have lower performance compared to Eudragit across different drug ratios and methods. The micellar behaviour and lower melting point of Gelucire would have contributed to this effect [18].

Eudragit was observed to be the best performing polymer across both hot melt and spray drying methods and all three drug ratios of 0.2.0.33 and 0.5 exhibiting the highest stability values comparatively: The stability data indicates that drug Ratio 0.2 tends to offer the best stability.

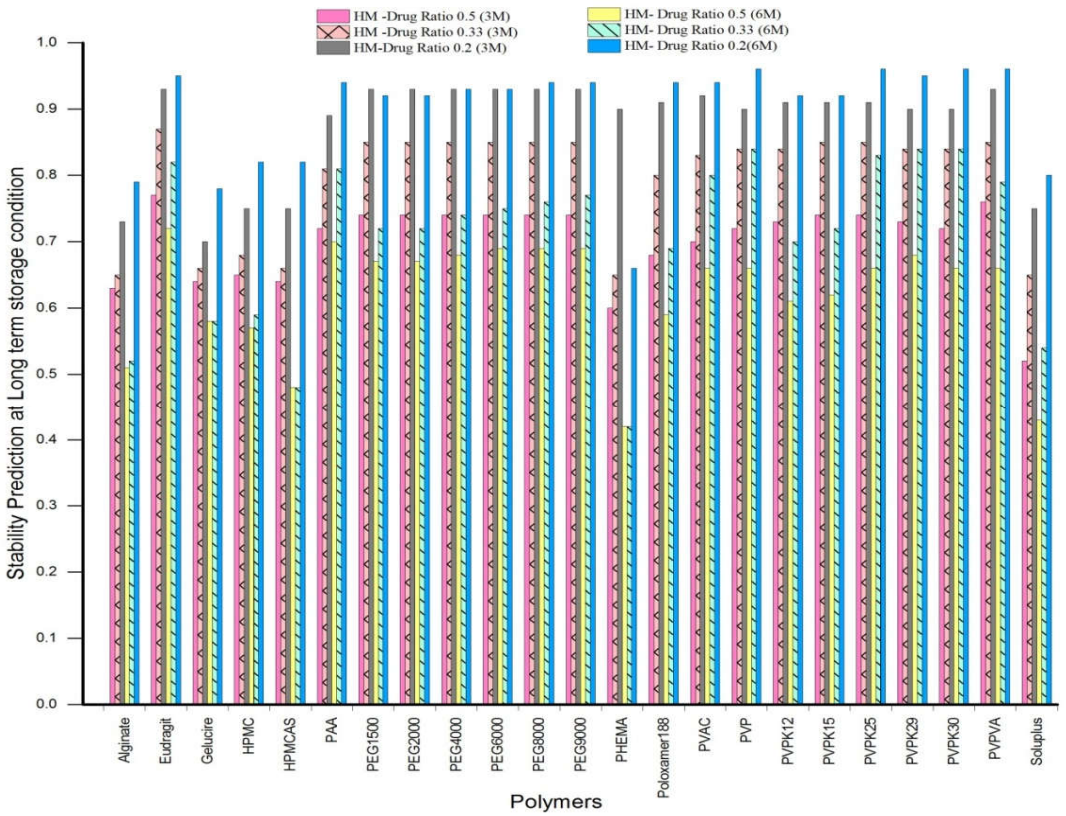


Figure 1: Comparison of Stability predictions for different Ibrutinib Solid dispersions prepared by Hot melt method at Long term storage condition (3 Months and 6 Months)

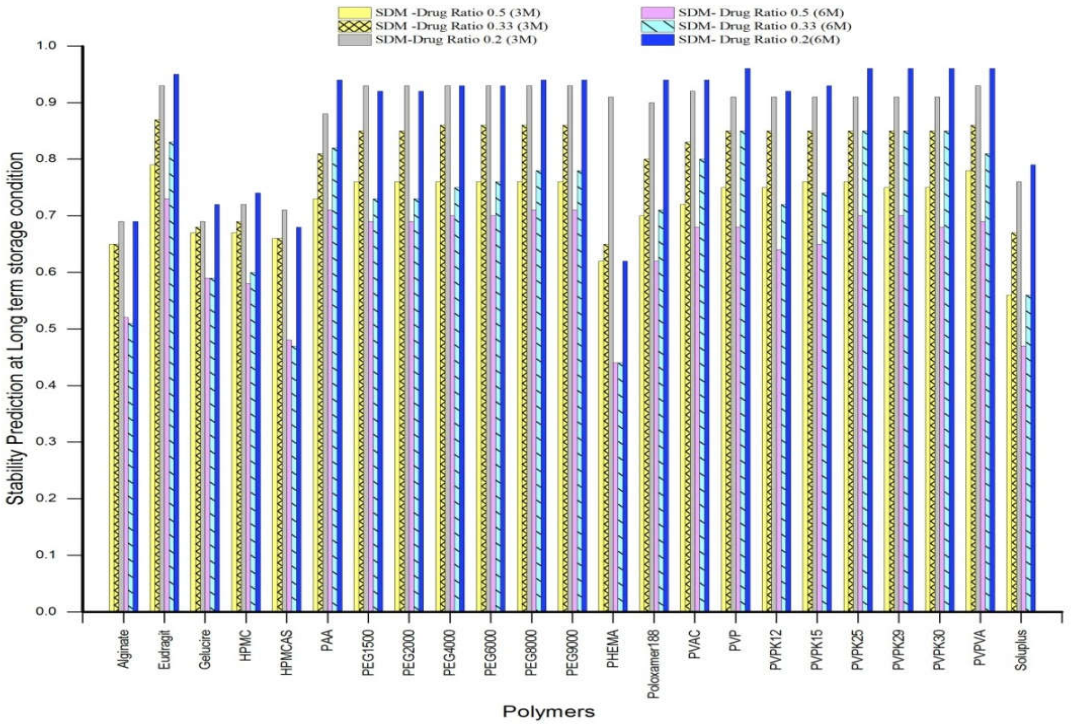


Figure 2: Comparison of Stability predictions for different Ibrutinib Solid dispersions prepared by Spray drying method at Long term storage condition (3 Months and 6 Months)

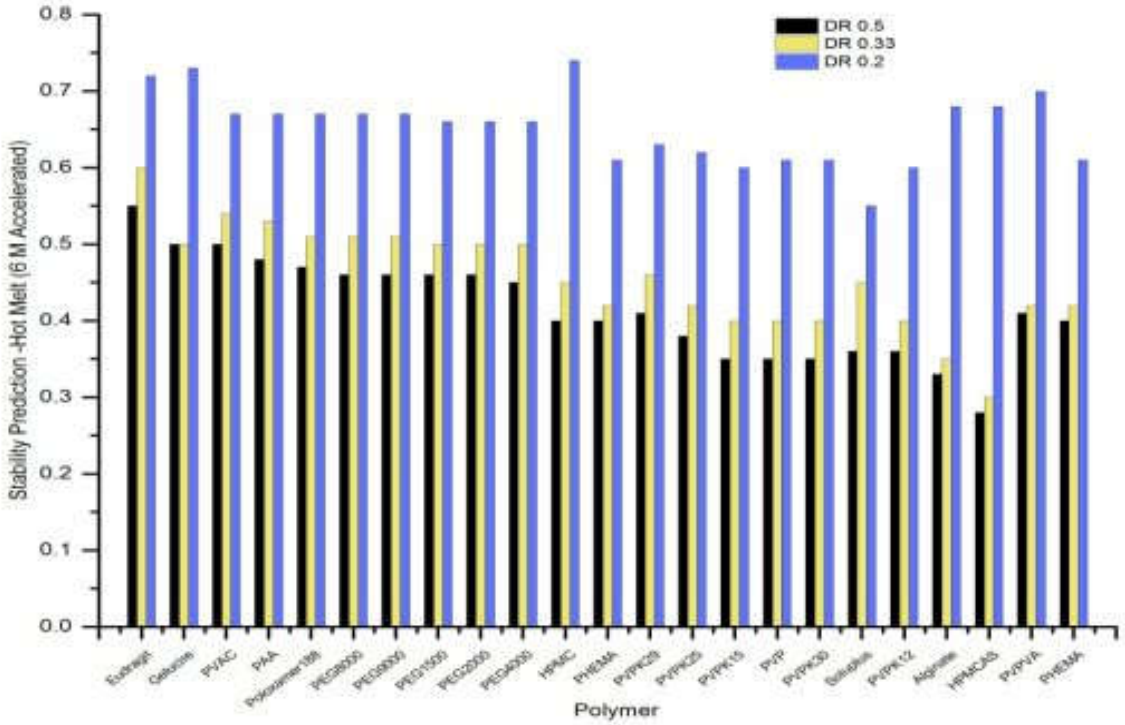


Figure 3: Comparison of Stability predictions for different Ibrutinib Solid dispersions prepared by Hot melt method at accelerated storage condition

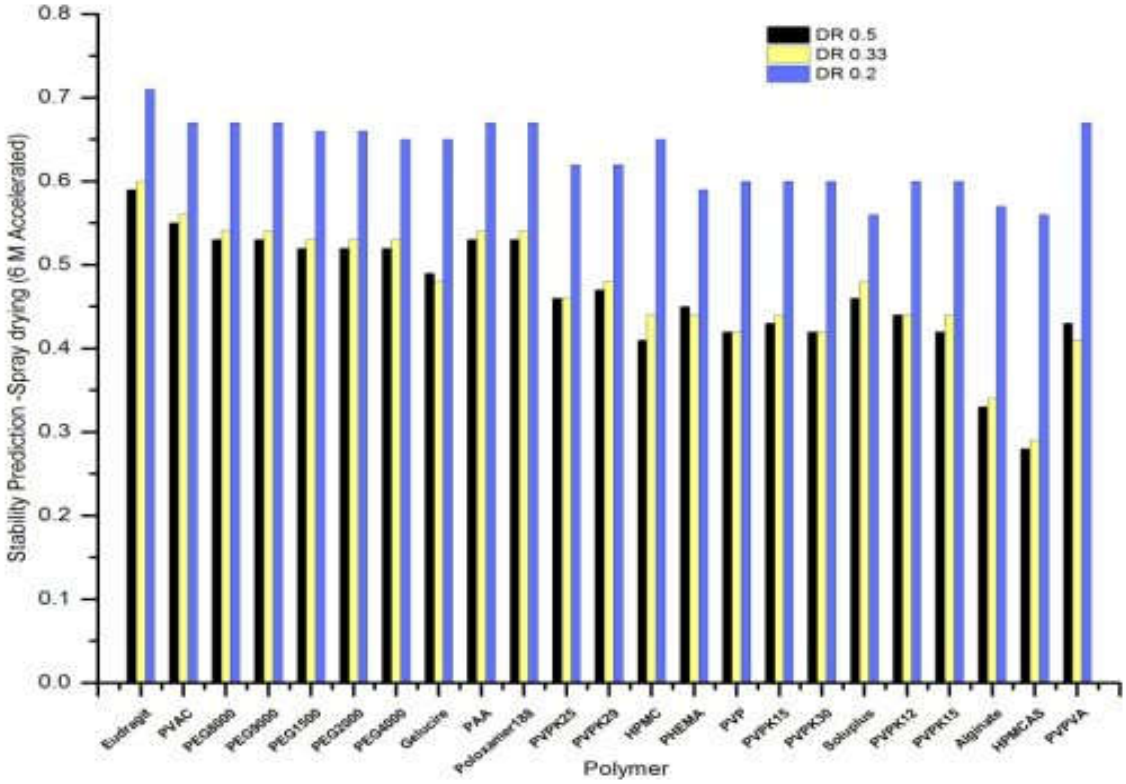


Figure 4: Comparison of Stability predictions for different Ibrutinib Solid dispersions prepared by Spray drying method at accelerated storage condition

3.2. DISSOLUTION

3.2.1. Dissolution Type

In solid dispersion systems, "non-precipitation type" refers to a type of formulation where the drug remains molecularly dispersed in the polymer matrix without precipitating out as a separate phase, such as crystals or amorphous particles. This “Parachute” like effect will result in an increased dissolution profile of the drug. In "precipitation type" solid dispersions, the drug may recrystallize or precipitate out of the polymer matrix, at the stage of super saturation potentially reducing its solubility of drug. This “Spring” like effect will decrease the dissolution rate of the drug [19,20].

The dissolution of Ibrutinib from the solid dispersion made using these different polymers are found to be non-precipitation which indicate that the drug does not form visible or detectable solid particles upon dissolution, maintaining its high solubility and bioavailability. This non precipitation is important for enhancing the solubility and improving the dissolution rate of poorly water-soluble drugs. By preventing precipitation, the drug stays in a more bioavailable form, improving absorption in the body [19].

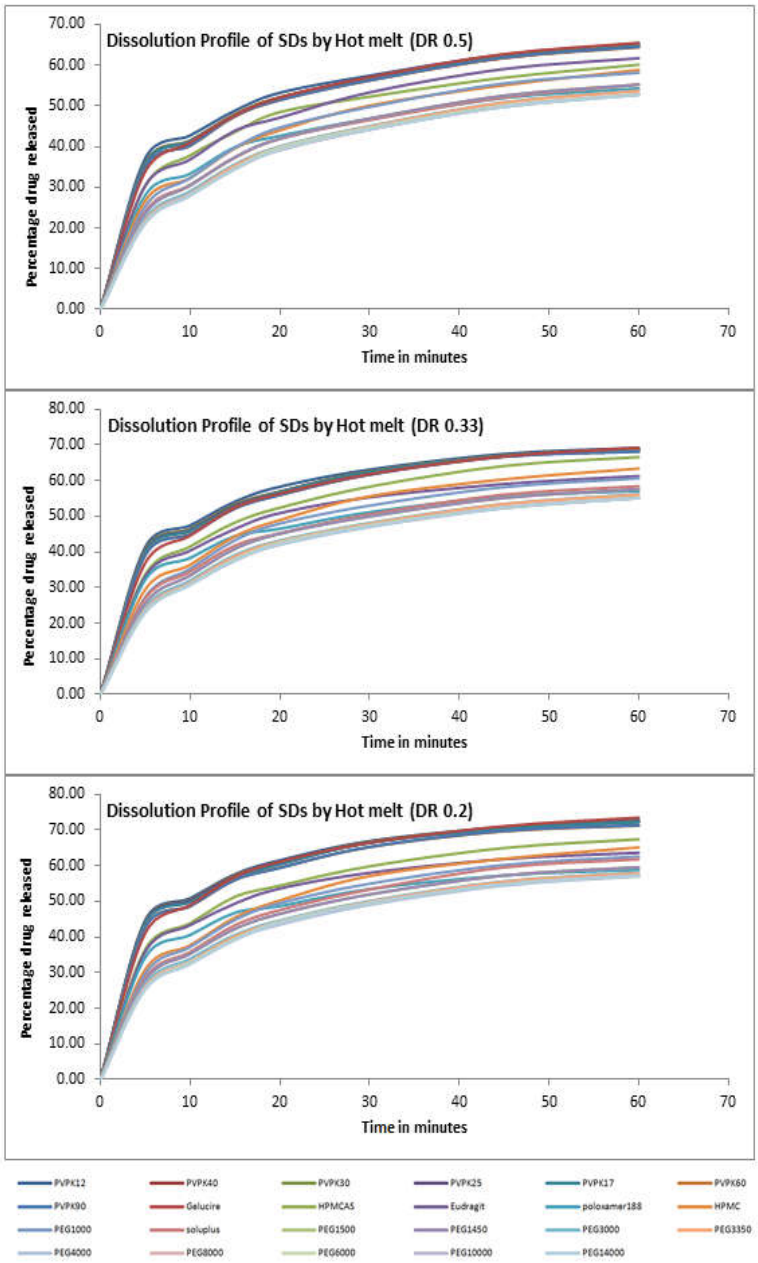


Figure 5: Dissolution profile of ibrutinib from solid dispersions prepared using Hot melt method having different drug polymer ratio.

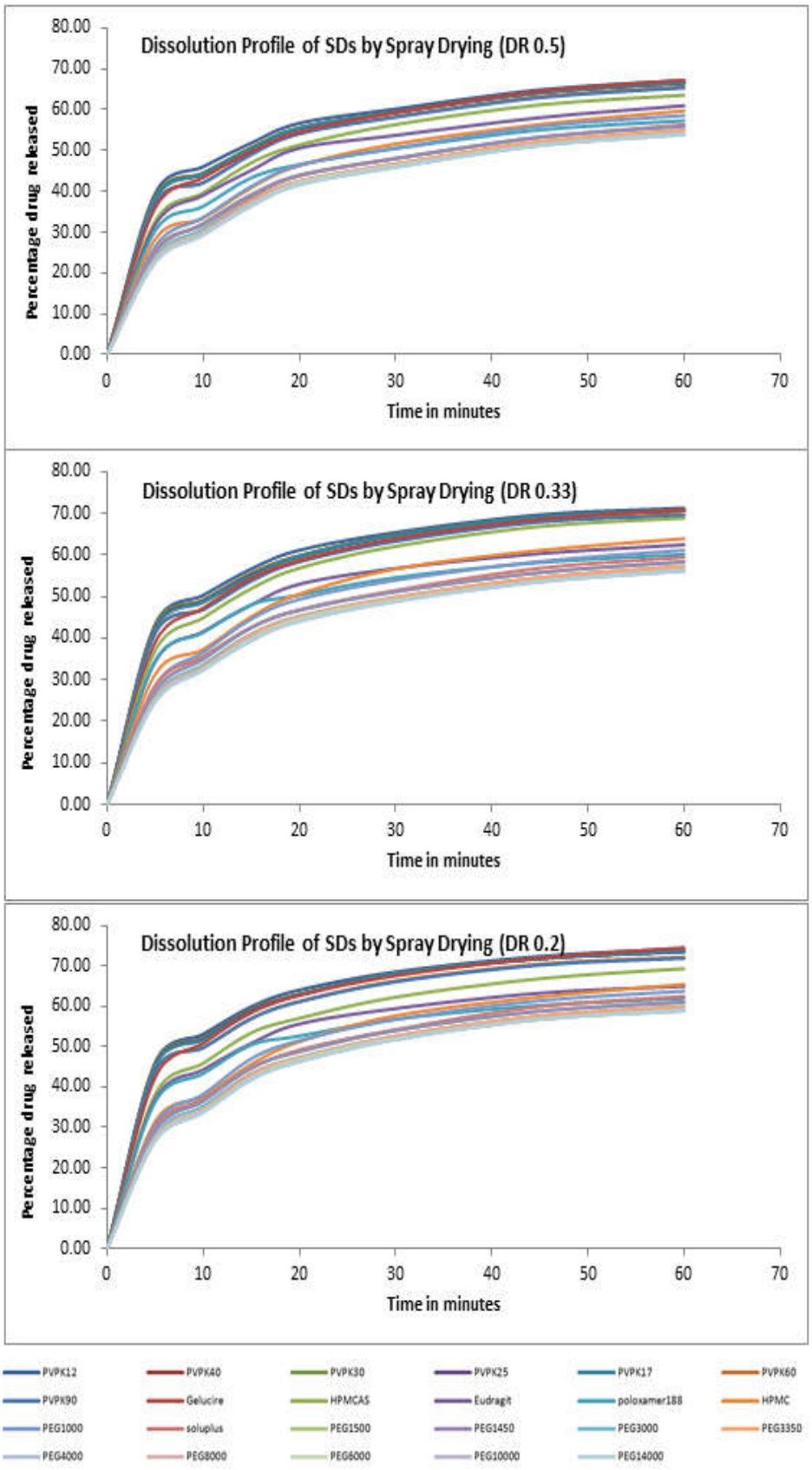


Figure 6: Dissolution profile of ibrutinib from solid dispersions prepared using Spray drying method having different drug polymer ratio.

3.2.2. Dissolution Rate

Figure 5 and 6 provide the dissolution profile of drug from solid dispersions prepared using Hot melt method and Spray drying method respectively, having different drug polymer ratio. Dissolution rates of solid dispersions of Ibrutinib prepared by hot melt method were almost similar to solid dispersion prepared by spray drying method with the difference being approximately 2% on average. The drug ratio (DR) was observed to have significant effect on dissolution. In both methods of preparation, as the drug ratio decreases from 0.5 to 0.2, the dissolution percentage was found to increase for many polymers (approximately 5-7%).This significant increase in dissolution suggests that higher polymer content can enhance the dissolution characteristics by enhancing the solubility [21].

Dissolution of Ibrutinib from PVP grade polymers was found to be higher than the PEG polymers comparatively (10-15%).More hydrophilic nature and ability to prevent crystallization of dissolved drug could be the reason for higher result for PVP polymers [21]. Formulations with similar chemical structures e.g various grades of PVP and various grades of PEG exhibit comparable dissolution rate within their category across both methods and all drug polymer ratios.

Gelucire (a mixture of saturated polyglycolized glycerides consisting of mono, di and tri glycerides and mono, di-fatty acids esters of polyethylene glycols) shows the highest dissolution percentages across all drug ratios in both the technique. Hydroxypropylmethylcellulose acetate succinate (HPMCAS) and Eudragit shows higher dissolution rates next to PVP and Gelucire.

Although a PVP polymer, HPMCAS and Gelucire shows better dissolution, their stability at accelerated storage conditions is comparatively less than Eudragit. The moisture absorbing nature of PVP [54] and lipid composition of Gelucire could have effect on reducing the stability at accelerated temperature and humid condition [22].

Hence considering the stability and dissolution rate predictions, Eudragit was selected as the suitable polymer for the preparation of solid dispersion of Ibrutinib. The drug ratio of 0.2 was selected based on the predictive results obtained for stability and dissolution (Figure 7). Eudragit S 100 is known to enhance the solubility of poorly soluble drugs and hence dissolution at pH values above 7.0. Eudragit S 100 forms strong intermolecular interactions that lead to enhanced physical stability in the solid-state as well as prolonged supersaturation[23].

Hot melt was selected for further experimental process among the two techniques used in the prediction study because it is a solvent-free process, reproducible, efficient and faster in production with reduced processing steps. Thus experimental batch of solid dispersion of Ibrunitib with eudragit at drug polymer ratio of 0.2 by hot melt method was prepared.

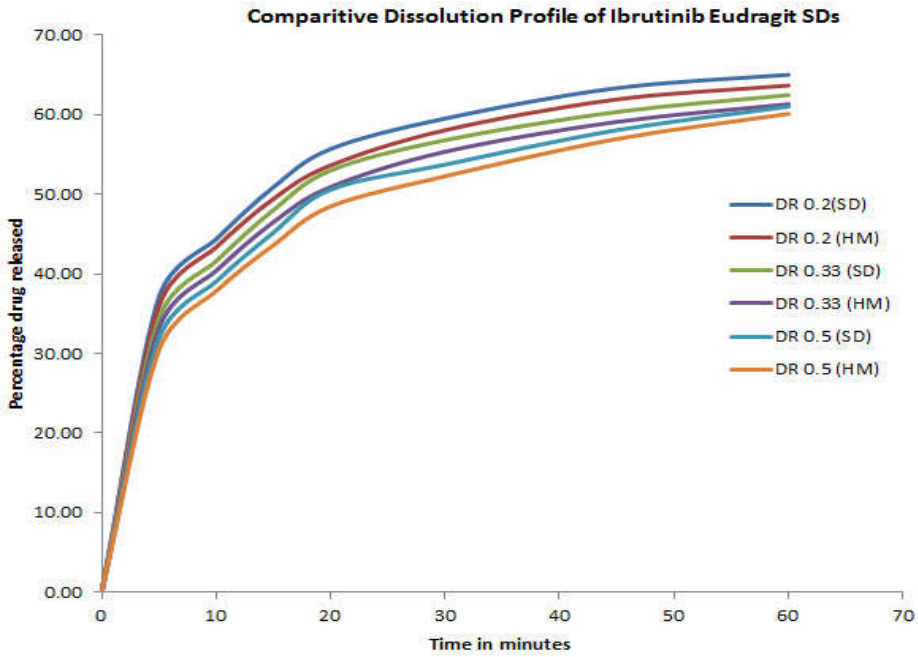


Figure 7: Comparative dissolution profile of Ibrutinib Eudragit SD having drug polymer ratio of DR 0.2, 0.33 and 0.5 by Hot melt (HM) and spray drying methods

3.3. VALIDATION

Figure 8 shows parameters and metrics of different predictive models for Stability, SD Type and SD Rate in Molecular ACCess System and Extended-Connectivity Fingerprints, Radius 4 system. S-MACCSis simple and fast, making it useful for smaller datasets against S-ECFP4, which is used for larger datasets and complex molecules like protein.

Table 1 shows the validation results for the predictions in S-MACCS. The Q mean values are significantly higher than T mean, indicating better predictive reliability and robustness. Thus the predictive modelling across all three application domains, demonstrates greater performance and reliability.

Table 1: Validation of results for Ibrutinib

Model	Descriptor	T Mean (±SD)	Q Mean
Stability Model	S-MACCS	0.340 ± 0.043	0.354
SD Type Model	S-MACCS	0.334 ± 0.041	0.351
SD Rate Model	S-MACCS	0.336 ± 0.042	0.353

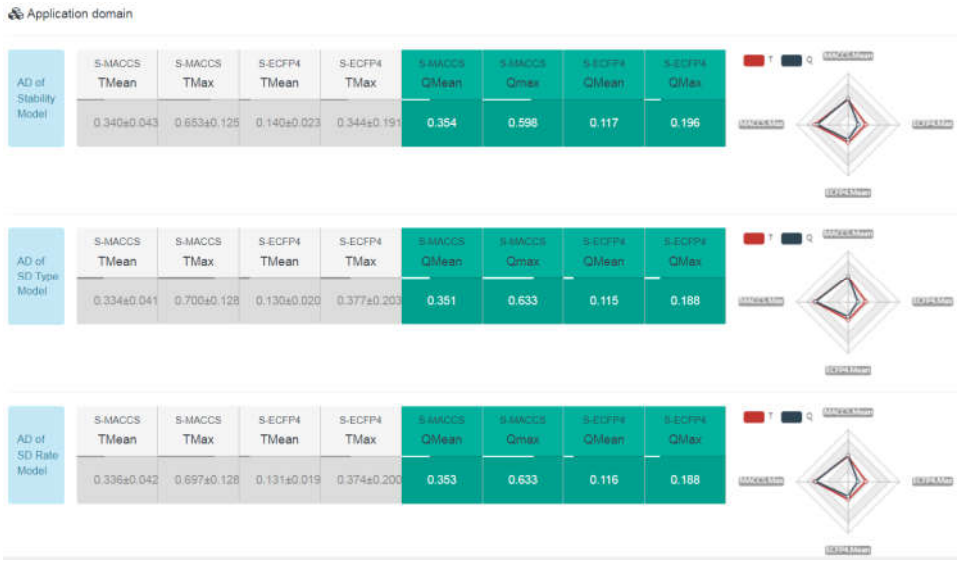


Figure 8: Application domain for Ibrutinib

3.4. SOLUBILITY

The saturated solubility of plain Ibrutinib was observed to be 0.992±0.268µg/mL and solubility of Ibrutinib from the solid dispersion was observed to be 6.248±0.540µg/mL. Approximately 6 fold increase in solubility was observed when the drug is formulated as solid dispersion (Table 2).

Table 2: Solubility of Ibrutinib Plain and Ibrutinib Solid dispersion

Sample	Appearance	Solubility (µg/mL)
Ibrutinib	White fluffy crystalline powder	0.992±0.268
Ibrutinib in solid dispersion	Off white free flowing powder	6.248±0.540

3.5. DRUG CONTENT AND DRUG RELEASE

Ibrutinib content was observed to be 19.82 ± 0.25mg per 100 mg of solid dispersion (Assay value of 99.91±1.28%w/w). The polymer did not interfere with the drug extraction and determination at the specified wavelength of 248 nm. Table 3 shows the predicted and experimental data of dissolution profile obtained for Ibrutinib Eudragit solid dispersion. Drug release is greater than 40% in 10 minutes against 5% for plain Ibrutinib, and more than 60% in 60 minutes as against 15% for plain Ibrutinib. The predicted and actual release data shows a strong positive correlation with r^2 value of 0.984, indicating the model accuracy and supports its application in optimizing the formulation.

Table 3: Dissolution profile of Ibrutinib Plain and Ibrutinib Eudragit solid dispersion (n=6)

Time (min)	Plain (% drug released)	SD Experimental (% drug released)	SD Predicted (% drug released)	Regression coefficient
10	5.21± 2.42	40.75± 2.10	43.33	
20	9.91± 1.50	54.91± 0.92	53.61	
30	14.82± 0.80	59.82± 1.32	58.03	r^2=0.984
45	15.05± 0.11	62.45± 0.90	61.88	
60	15.48± 0.08	64.08± 0.64	63.64	

3.6. THERMAL ANALYSIS

Figure 9 exhibit the DSC thermograms of plain Ibrutinib (IBR), Eudragit (EUR) and the solid dispersion sample of Ibrutinib in eudragit (SD). IBR thermogram shows a sharp crystalline peak around 158°C corresponding to melting point of Ibrutinib and EUR thermogram shows glass transition starting at around 175°C. SD sample shows absence of crystalline peak at 158°C indicating drug is dispersed in polymer in amorphous form when it is formulated as solid dispersion [24].The drug molecule transforms to amorphous form when dispersed in polymer matrix during the solid dispersion preparation process by hot melt fusion, resulting in significant increase in drug surface area. This increase in surface area in turn helps in enhanced solubility of drug which might results in enhanced and faster dissolution of drug in the medium[25].

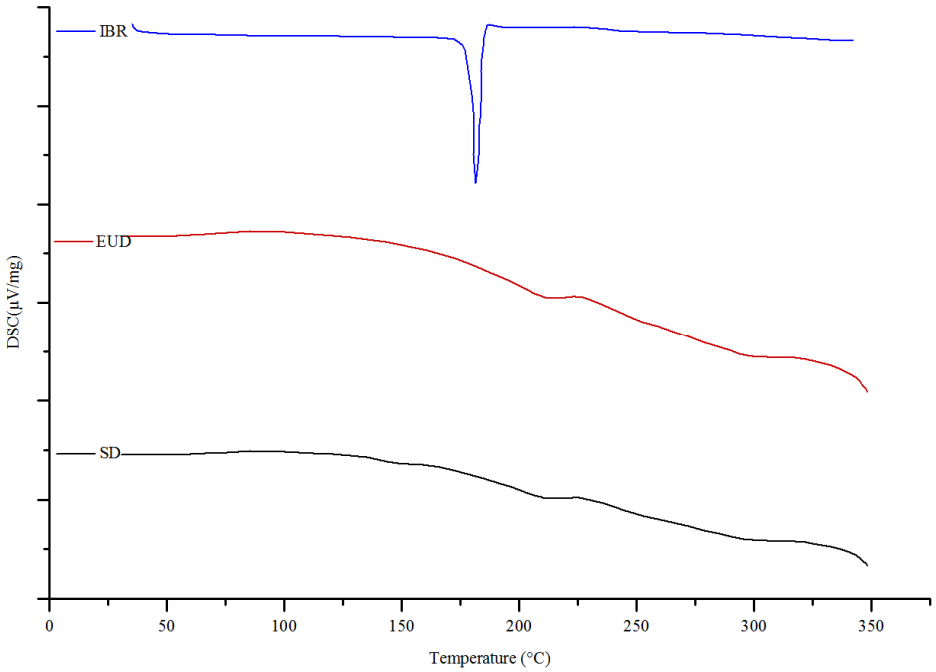


Figure 9: DSC thermograms of Ibrutinib (IBU), Eudragit (EUD) and Solid dispersion (SD) samples

4. CONCLUSION

In silico formulation of Ibrutinib solid dispersions was performed with different polymers using two different methods of hot melt and spray drying at three different drug ratios of 0.2, 0.33 and 0.5 for each method. The Dissolution type, rate of the solid dispersions and their stability at long term (25°C/60%RH) and accelerated (40˚C/75%RH) storage conditions were predicted using the PharmSD tool.The stability and dissolution rates were observed to increase when the drug polymer ratio was decreased from 0.5 to 0.2 for both preparation methods. Although the spray drying method exhibited improved stability at a higher drug polymer ratio (0.5), the hot melt method showed better stability at low drug polymer ratio of 0.2. PVP grades that enhanced drug dissolution were found to exhibit low stability. PEG grades which showed good stability showed lower dissolution than the other polymers.

Eudragit was observed to be one of the best performing polymer across both hot melt and spray drying methods and at all three drug ratios of 0.2, 0.33 and 0.5 exhibiting higher stability values than the other polymers. The dissolution type was found to be "non-precipitation" which prevents drug recrystallization of drug and enhances the dissolution rate. Eudragit exhibits an improved dissolution profile (greater than 40% in 10 minutes) when formulated as solid dispersion.

The solid dispersion of Ibrutinib when prepared experimentally using Eudragit by hot melt method at drug ratio of 0.2, increased the solubility of Ibrutinib to approximately 6 fold. The DSC thermogram confirmed the conversion of crystalline Ibrutinib into its amorphous form in the polymer matrix, thereby enhancing its solubility. R^2 of 0.98 was observed for the correlation of actual and predicted dissolution data.

The nature of the polymer, the ratio of drug to polymer, and the preparation method were observed to have significant effects on the dissolution and stability of Ibrutinib as indicated by this prediction model. Thus AI-based prediction model helped to select Eudragit as the suitable polymer for the solid dispersion of Ibrutinib with accuracy and supports its application in optimizing the formulation development

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