

Original Research Article

Influence of excipient selection on carbamazepine solubility and stability in solid-state pharmaceuticals: Developing a predictive model for optimized drug formulations

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Abstract

Purpose: To determine the effect of excipient choice on solubility and stability of carbamazepine (CBZ), so as to develop a model for optimal drug formulation.

Methods: Four excipients, namely polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), polyethylene glycol (PEG) and lactose, were chosen. Carbamazepine was mixed with each of the excipients in a 1:1 (w/w) ratio to form a solid dispersion through solvent evaporation technique, in which a solution of both CBZ and the excipient is evaporated to dryness. Solubility was determined by dissolution profile and physical and chemical stability of the formulations was determined using differential scanning calorimetry (DSC), powder x-ray diffraction (PXRD) and Fourier Transform Infrared spectrophotometer (FTIR).

Results: The DSC analysis showed excipients bearing different melting point of 120, 125, 130 and 118 °C, for PVP, HPMC, PEG and lactose, respectively. Polyvinyl pyrrolidone, HPMC and lactose had 45, 47 and 46 % crystallinity, respectively. The degree of crystallinity was lowest in PEG at 42 %. The solubility-enhancing effect of PVP was significantly higher than that of HPMC and lactose ($p < 0.05$). In contrast to PEG, PVP was less efficient with a mean difference of 2.1 ($p = 0.001$). The significantly higher solubility enhancement ability indicates that PEG possesses a better solubility efficiency compared with other surfactants.

Conclusion: The finding has revealed that both PVP and PEG improve the solubility of CBZ, while HPMC, on the other hand, and improves the stability of the medicine.

Keywords: Excipient, Solubility, Stability, Solid-State Pharmaceuticals, Carbamazepine

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INTRODUCTION

Pharmaceutical formulations are prepared by combining active pharmaceutical ingredients (API) and non-reactive as well as functional materials, referred to as excipients, which play important roles in the stability, solubility and effectiveness of the drugs. Successful

formulation development is extremely significant in the pharmaceutical industry because APIs are in most cases, stabilized in different solid-state forms in order to improve their bioavailability and patient compliance [1]. Excipients play significant roles since they affect the physical and chemical characteristics of drug, such as solubility, stability and shelf-life. Incorporation of excipients with

APIs in the solid-state, i.e., powders, tablets and capsules, requires understanding of the molecular processes involved in possible interactions leading to degradation or crystallization or poor dissolution rates that may affect drug action [2]. Most drugs contain poorly soluble APIs which exhibit complex dissolution profiles. Assessment of dissolution mechanisms and estimation of API dissolution profiles from intrinsic dissolution, as well as actual tablets, are the primary focus in pharmaceutical development. In the last decades, several empirical, semi-empirical and mechanistic mathematical models have been proposed to describe API dissolution profiles from a variety of solid pharmaceutical dosage forms such as matrix systems, erodible tablets, microspheres, hydrogels, powders and other immediate release systems [3]. The creation of a theoretical model that will allow for a comprehensive analysis of the dissolution mechanism of poorly soluble APIs, along with satisfactory applicability and high predictive potential, remains a challenging task in pharmaceutical science and development [4,5]. Solubility determines how easily and how fast the API gets absorbed across the gastrointestinal track into the circulatory system. Low solubility could negate the optimum efficacy of the drug, especially in the case of amphiphiles or sparingly soluble moieties [6].

Stability, on the other hand, relates to the shelf life and vulnerability of the formulation to factors such as temperature, humidity and light. In solid-state pharmaceuticals, there are specific types of excipients that ensure APIs do not undergo phase changes or chemical degradation, thus increasing the shelf life of the product as well as its efficacy [7]. In the formulation process, excipients are commonly used and polymers such as polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP) were suitable for improving solubility of poorly soluble drugs. Also, sugars such as mannitol have been employed in formulation of pharmaceutical products [8]. However, to date, the specific role of these excipients on API solubility and dissolution, including how they influence these factors, is not well explained. Since the dissolution of various poorly soluble APIs appear to exhibit a number of dynamic features, it becomes quite challenging to provide an adequate description of their dissolution profiles and an appropriate assessment of their dissolution processes [9]. Furthermore, since the formation of the API dissolution profile depends on the characteristics of the excipients, the presence of the latter compromises the dissolution mechanism analysis and prediction of the specific API dissolution profile.

Excipients are generally regarded as inactive; however, they can interact randomly with APIs, causing toxicity or reduced efficacy. Therefore, comprehending the status of excipient - API interactions is critical for obtaining safe, effective, and stable formulations [10]. The objective of this study is to analyze the effect of selected excipients on solubility and stability of CBZ in solid-state and to establish a model for the best formulation.

EXPERIMENTAL

Materials

Polyvinylpyrrolidone, HPMC, PEG, Lactose and carbamazepine were gifts from Sama Alfayhaa Pharmaceutical Industries, Iraq.

Selection criteria for excipients and drugs

Four excipients were chosen based on some unique properties of each compound. Polyvinylpyrrolidone is a synthetic, water-soluble, non-ionic polymer obtained by the polymerization of the monomer (N-vinylpyrrolidone). It is used to improve solubility through modulation of hydrogen bonding interactions. HPMC offers stability by setting up a shield around the drug particles, while PEG enhances solubility through high hydrophilicity, molecular crowding, and by forming hydrogen bonds with molecules. In addition, the choice of lactose is based on its inert nature in the experiment. Carbamazepine is selected as a biopharmaceutics class II status since it is poorly soluble and highly permeable hence it exhibits a difficult behavior in solid-state stability and solubility patterns.

Preparation of solid dispersions

Carbamazepine was mixed with each excipient in a 1:1 (w/w) ratio to form a solid dispersion through solvent evaporation technique, in which an aqueous solution of both CBZ and the excipient is evaporated to dryness.

Characterization techniques

Differential scanning calorimetry (DSC)

DSC was performed using Shimadzu differential scanning calorimeter Mettler, in order to assess the thermotropic properties and thermal behavior of the excipients. About 5 mg of the sample were sealed in the aluminium pans and heated at the rate of 10 °C/min, covering a temperature range of 40 to 400 °C.

Powder X-ray Diffraction (PXRD)

Powder X-ray Diffraction (PXRD) was used to examine the crystallinity. Amorphization arising from the interaction between the excipients may help enhance solubility. Solid samples were characterized through PXRD to determine the crystalline structure of excipient. Determination was done with a Bruker D8 Advanced diffractometer (Bruker Corp., Billerica, MA, USA) fitted with a Cu K Alpha source at 40 kV and 40 mA. The data collection was done in a step-scan technique with a step size of 3° per minute through 2 θ of 5° to 60°.

Fourier-Transform Infrared Spectroscopy (FTIR)

Fourier-Transform Infrared Spectroscopy (FTIR) was utilized in identifying chemical interactions like hydrogen bonding by observing specific peaks corresponding to all the excipients. FT-IR (Shimadzu, Japan) was obtained after making potassium bromide discs in the range of 4000 to 500 cm⁻¹ to detect drug-excipients interaction.

Solubility test

Solubility tests on the CBZ-excipient blends entailed a dissolution test in simulated intestinal fluid of 900 ml at a pH of 6.8 (phosphate buffer) due to gastrointestinal effects. To determine the dissolution profile of the tablets, dissolution samples at 5, 15, 30, 60, 90, and 120 minutes were obtained.

Data analysis and model development

To analyze thermal (DSC), crystalline (PXRD) and chemical (FTIR) interaction data of each CBZ-excipient formulation, descriptive statistics option available in SPSS 28 was employed to obtain mean, standard deviation, variation coefficient and variance. A one-way ANOVA was used to analyze the data and determine whether there is a significant difference in solubility increase (fold increase) among the different excipients. Significant differences between excipients were determined using Tukey's HSD post-hoc and Bonferroni corrections were applied for multiple comparisons of crystallization or degradation at various time points.

RESULTS

CBZ-excipients interaction data

Differential scanning calorimetry (DSC) analysis established differences in thermal characteristics of the different excipients with PVP, HPMC, PEG

and lactose (Figure 1) bearing a different mean thermal melting point of 120, 125, 130 and 118 °C, respectively. The highest mean temperature was shown by PEG (130 °C), which could potentially offer better thermal stability than other excipients and thus better stability of CBZ at higher temperatures. As far as reliability is concerned, PVP and HPMC had comparatively lower standard deviations (3.5 and 2.8 °C, respectively) for their thermal behavior along with CBZ, while lactose exhibited comparatively higher deviation (4.0 °C), thus suggesting that its efficacy may vary when exposed to different storage temperatures (Table 1). Based on these results, it may be argued that PEG may improve the thermal stability of CBZ to a greater extent, even though HPMC manifested itself as another promising candidate for the applications demanding stable thermal characteristics. Table 1 presents the crystallinity percentage obtained from powder X-ray diffraction (PXRD) analysis. From the result (Figure 2), PVP had 45 % crystallinity, while for HPMC and lactose; it was slightly higher at 47 and 46 %, respectively. The degree of crystallinity was lowest in PEG at 42 %. Lower crystallinity, as demonstrated with PEG, is usually attributed to higher amorphous characteristics that are likely to enhance solubility and possibly also bioavailability. The results suggest that the increased amorphous character of PEG may make it beneficial for its use as a solubility-enhancing excipient, while HPMC and lactose, which showed a higher degree of crystallinity, may have their solubility and stability affected in a different manner. To determine the possibility of interaction between CBZ and each excipient, chemical interaction analysis entailing measurement of the heights of peaks by FTIR was performed (Figure 3). The highest peak intensity was obtained for PEG and then for PVP, HPMC and lactose, confirming different degrees of chemical interactions in the polymeric system (Table 1). This increased peak intensity observed with PEG is indicative of a higher interaction with CBZ through better hydrogen bonding or other simple chemical interactions, which, in turn, might improve the solubility by increasing the dispersion of CBZ in the excipient matrix. The differences in the peak intensity of the excipients, with standard deviation being 0.03 for PEG and 0.06 for lactose, also indicated that PEG and PVP might have a more favorable and stable interaction with CBZ, which may promote solubility and bioavailability. Lactose had the lowest mean peak intensity and the highest variability and may therefore interact least with CBZ, making it least protective and exerting the least effect on solubility or chemical stability.

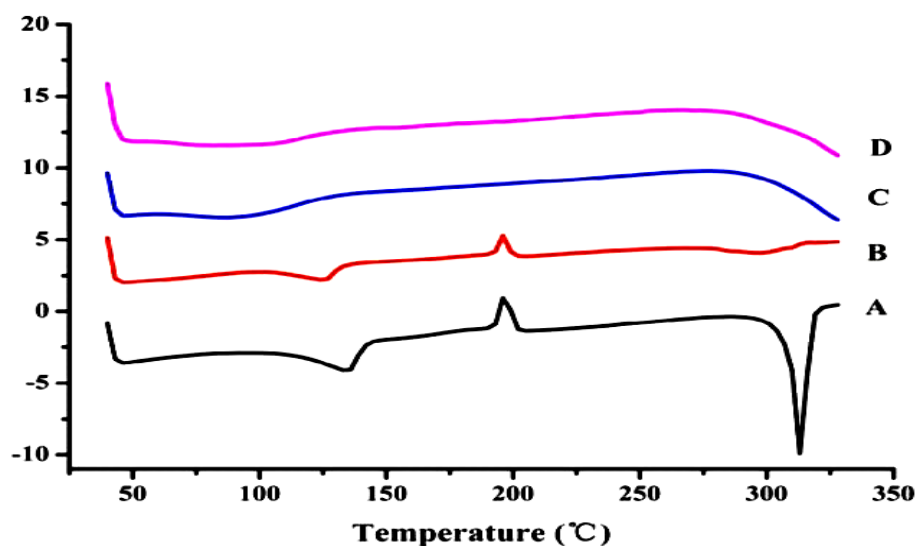


Figure 1: Thermal Properties of excipients (A =PVP, B=Lactose, C=HPMC, D=PEG)

Table 1: Descriptive statistics for CBZ-excipients interaction data

Parameter	Excipients	Mean $\pm$ SD	Variance
Thermal properties (DSC, °C)	PVP	120 $\pm$ 3.5	12.25
	HPMC	125 $\pm$ 2.8	7.84
	PEG	130 $\pm$ 3.2	10.24
	Lactose	118 $\pm$ 4	16
Crystallinity (PXRD, %)	PVP	45 $\pm$ 1.5	2.25
	HPMC	47 $\pm$ 1.3	1.69
	PEG	42 $\pm$ 1.8	3.24
	Lactose	46 $\pm$ 1.7	2.89
Chemical interaction (FTIR, Peak intensity)	PVP	0.85 $\pm$ 0.04	0.0016
	HPMC	0.82 $\pm$ 0.05	0.0025
	PEG	0.87 $\pm$ 0.03	0.0009
	Lactose	0.8 $\pm$ 0.06	0.0036

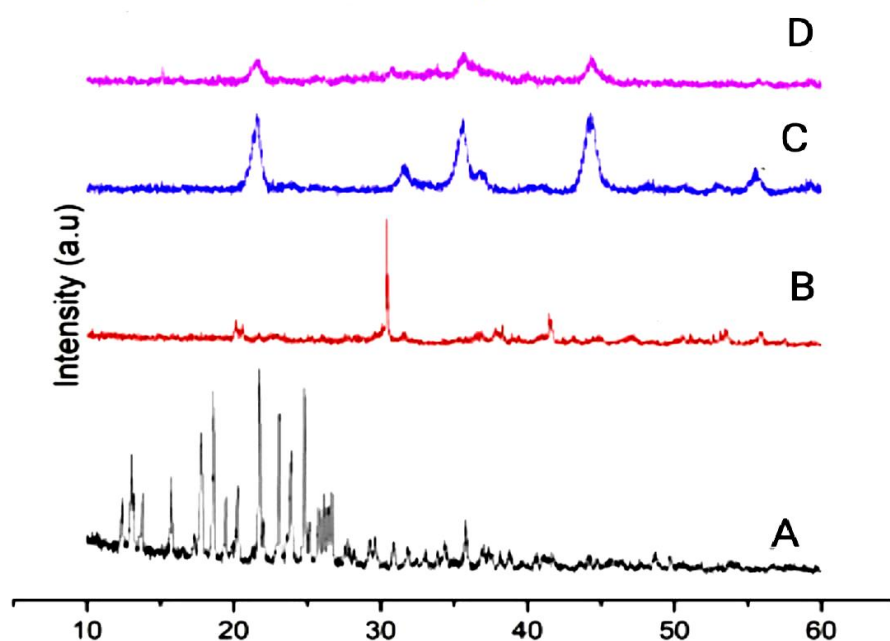


Figure 2: Crystallinity (PXRD, %) of excipients (A =Lactose, B=PVP, C=PEG, D=HPMC)

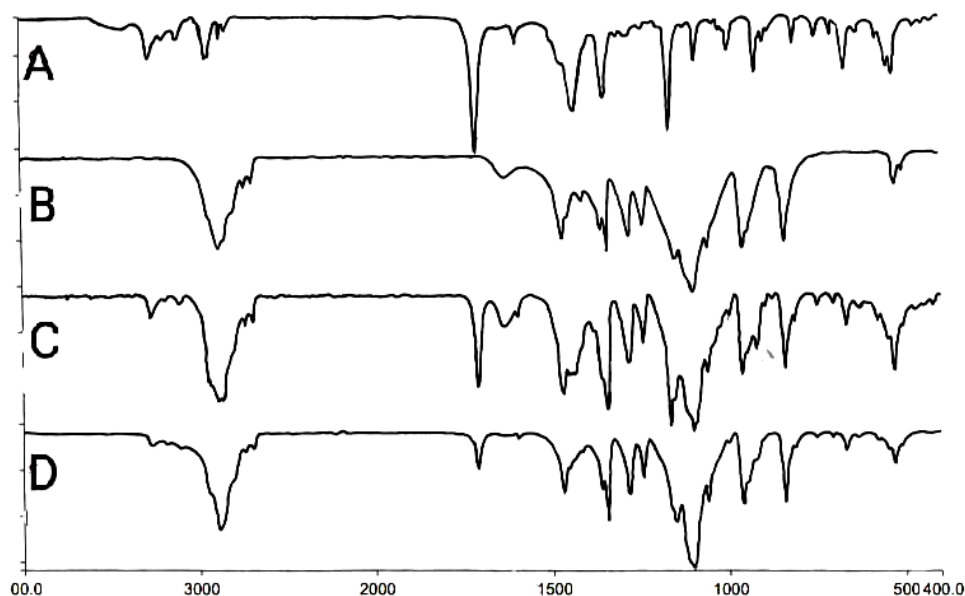


Figure 3: FTIR spectra of of excipients (A =PVP, B=Lactose, C=PEG, D=HPMC)

Table 2: One-Way ANOVA results for solubility increase

Source of Variation	Sum of Squares	df	Mean Square	F-value	P-value
Between excipients	55.67	3	18.56	12.43	0.002
Within excipients	45.21	20	2.26		
Total	100.88	23			

Solubility between excipients and CBZ

The one-way ANOVA was conducted to determine whether there are statistically significant differences in the change in solubility of carbamazepine (CBZ) when combined with different excipients. To evaluate this, the Sum of Squares was first computed between excipients. From the result in Table 2, a value of 55.67 was obtained as the sum of squares. Dividing this sum by its degrees of freedom ($df = 3$), a mean square value of 18.56 was obtained. The excipients Sum of Squares was also used in the analysis, which explains variance in solubility measurements with reference to a specific category of excipients, like PVP solubility in water. Within-group variation was found to be lower (sum of squares of 45.21), resulting in a mean square value of 2.26 (Table 2). Lower within-group variability revealed that solubility measures were homogeneous within each group of excipients and the differences between the groups were more focused and not masked by intra-group variability.

The F-value obtained from the ANOVA is 12.43. The between-group mean square is 18.56, and the within-group mean square is 2.26. This high F-value indicates that there are significantly large

differences in solubility improvement across the excipient types and that the variability attributed to the excipient type is much larger than the variability within each excipient type. In other words, a high F-value enhances confidence that differences in solubility witnessed across the groups (excipients).

This indicates that the results achieved are statistically significant, and this is underlined by the p -value of 0.002 ($p \leq 0.05$). As a practical implication, the low p -value enables one to reject the null hypothesis, which postulated that all the excipients would improve solubility in the same manner. However, the data suggest that it is true that one of the excipients that were used in this study had a different effect on the solubility enhancement of CBZ from the others. Therefore, the analysis of variance suggestively reveals that the choice of one or the other excipients influences the solubility of CBZ.

Tukey's post-hoc analysis

To determine which excipient had the most impact on the solubility of CBZ, a pairwise comparison of each excipient was executed (Table 3). Comparing PVP with other excipients, the result showed that the solubility-enhancing

effect of PVP was higher than that of HPMC, with a mean difference of 1.25 ($p = 0.003$). This low p -value suggests that it is highly likely that PVP provides enhanced solubility compared to the HPMC. In contrast to PEG, PVP was less efficient with a mean difference of 2.1 ($p = 0.001$). The significantly higher solubility enhancement ability indicates that PEG possesses a better solubility efficiency compared with other surfactants. When compared with lactose, PVP was also slightly superior with a mean difference of 0.75 and a p -value of 0.045 and thus statistically significant, which confirms PVP as a slightly better choice than lactose for improving solubility.

Furthermore, when comparing HPMC with PEG, a mean difference of 0.85 and a p -value of 0.032 were obtained. This statistically significant result shows that solubility is improved in PEG than in HPMC, although the effect is not as high as that shown by PVP with PEG. Conversely, a non-significant difference in solubility was observed between HPMC vs lactose (mean difference = 0.5; $p = 0.2$). This means that both HPMC and lactose are efficient in increasing the solubility of CBZ without one being more effective than the other. Lastly, pairwise comparison of PEG with lactose revealed that the mean difference was 1.6 with $p = 0.05$, suggesting a statistically significant comparison. Once again, the solubility of CBZ was found to increase with the addition of PEG as compared to lactose, which further indicates that the properties of PEG can play a more significant role in increasing solubility than lactose, which is only inert filler.

The impact of hydrogen bonding ability, molecular weight and excipient type on dissolution and stability of CBZ in solid-dosage forms was analyzed using the regression model (Table 4). Per the HBC, the coefficient (β) was 0.67, with a standard error of 0.15. As for this variable, the t -value is equal to 4.47, while the p -value equals 0.001 which means that such a result is statistically significant. This also shows that an excipient's ability to engage in hydrogen bonding was positively and significantly correlated with the solubility and stability of CBZ.

The obtained β of 0.67 indicates that derivatives with increased hydrogen bonding offer enhanced CBZ solubility and stability; improved hydrogen bonding might facilitate better molecular interactions as well as reduced crystallization of CBZ and better dispersion throughout the solid excipient matrix. Attribution of hydrogen bonding corresponds with the facts in pharmaceutical science where it has been identified to have major role in enhancing the solubility and stability of compounds such as CBZ.

For the coefficient for molecular weight, the coefficient is -0.32 for molecular weight with standard error of 0.11 using t -test value of -2.91 and P value of 0.008. This negative sign further means that the solubility and stability of CBZ decrease as molecular weight increases. Significantly low p -value implies that the excipients with lower molecular weight have higher potential to improve the solubility and stability of CBZ. Smaller molecules may dissolve more homogeneously with CBZ molecules, decreasing solubility without adding extra volume that may compromise stability through phase separation or crystallization. Consequently, selecting the excipients with small molecular masses can be beneficial with regard to stability in formulations.

Concerning the coefficient for excipient type, it is a categorical variable where the coefficient is equal to 1.25, with standard error of 0.18, t -statistic of 6.94, and p -value of 0.000; hence, it is highly significant. This high β value suggests that the type of excipient used (for instance, PEG, PVP, HPMC, or lactose) has a significant influence over the solubility and stability of CBZ. The large value of the coefficient and significance show that there is need to consider other excipient properties in addition to the ability to engage in hydrogen bonding and molecular size. The various manners in which one excipient influences the objective substance, like the hydrophilic characteristic of PEG or the stabilizing nature of PVP, indicate that solubility and stability determinants may differ considerably depending on the type of excipient chosen during the selection process.

Table 3: Tukey's HSD *Post-Hoc* test for pairwise comparisons in solubility enhancement

Comparison	Mean Difference	Std. Error	P-value
PVP vs. HPMC	1.25	0.32	0.003
PVP vs. PEG	2.1	0.35	0.001
PVP vs. Lactose	0.75	0.28	0.045
HPMC vs. PEG	0.85	0.3	0.032
HPMC vs. Lactose	0.5	0.31	0.2
PEG vs. Lactose	1.6	0.29	0.005

Table 4: Regression analysis of excipients' properties on solubility and stability

Independent variable	Coefficient (β)	Standard error	T-value	P-value	Adjusted R^2	MAE
Hydrogen bonding capacity	0.67	0.15	4.47	0.001	0.85	1.35
Molecular weight	-0.32	0.11	-2.91	0.008		
Excipient type (Categorical)	1.25	0.18	6.94	0		

From Fit and Accuracy, R^2 value is 0.85, which is adjusted R^2 , hence the quality of the regression model is 85 % since the solubility and stability of CBZ can be explained by the excipients' properties pitched in the model. This high value of adjusted R^2 means that the model fits well, indicating that hydrogen bonding capacity, molecular weight, and excipient type are important parameters that affect CBZ's behavior in formulations. The mean absolute error (MAE) of 1.35 also helps in proving that the model was a good predictor of solubility and stability of compounds, given these properties of the compounds.

The results of the multiple regression analysis prove that the solubility and stability of CBZ are significantly affected by properties of the excipients, which include the hydrogen bonding capacity, molecular weight, and type of the excipient. It has been found that the solubility and stability of CBZ are improved when the hydrogen bonding capacity of the excipients is higher and molecular weight of the excipients is low. This clearly indicates that these properties together offer a strong composite platform for assessing the outcome of CBZ in solid-state formulations, thereby helping to choose the right type of excipients for achieving the desired drug performance.

DISCUSSION

This study aimed to explore the influence of excipient choice on the dissolution and stability of CBZ in solid forms. Carbamazepine is an antiepileptic drug that is characterized by low solubility and polymorphism that complicates its bioavailability and stability [11]. The study sought to examine which of the chosen excipients (PVP, HPMC, PEG, or lactose) enhances the solubility and stability of CBZ. In this regard, a predictive model for the formulation of a drug was derived to solve the stability problems of CBZ by identifying the differences in the chemical reactions between the drug and the excipients. The work employed DSC, PXRD, FTIR, to make comparative analysis of various formulations of excipients and drugs based on solubility, polymorphism and other physical characteristics over time.

The study revealed that the solubility of CBZ was enhanced when the PVP and PEG were employed as the additives. Polyvinylchloride has the ability to form hydrogen bonds with CBZ, thus minimizing its crystallization and increasing its dissolution. Like polyvinyl alcohol (PVA), PEG also played the role of a plasticizer to increase the dissolution rate and wetting of the drug. While HPMC encased the drug particles in a protective layer to enhance the stability of the system the effectiveness of solubility enhancement was lower than PVP or PEG. Lactose, used as filler, had the least effect on CBZ solubility but contributed to the stability of the formulation without affecting its efficiency. The FTIR results supported the chemical interactions, especially those involving hydrogen bonding between CBZ and PVP or HPMC, which enhanced solubility and stability.

The results of the present study are in line with findings of other prior studies that investigated the impact of excipients in enhancing the solubility and stability of PPDs. Patel and co-workers demonstrated that as both PVP and PEG raised the solubility of the CBZ effectively [12]. Their work mainly concentrated on the improvement of the solubility of poorly soluble drugs by employing PVP and PEG. From their study, PVP was observed to enhance solubility through hydrogen bonding with the drug molecules and PEG increased the dissolution rate through its plasticization effect. In this study, DSC and PXRD results suggest that these excipients could affect the crystallinity of CBZ, thus enhancing its solubility. This study indicated that PVP and PEG can be used as potential excipients for improving the solubility of poorly soluble drugs.

Also, this present research supports the study done by LaFontaine and his group, especially on solubility benefit improvement throughout solid dispersions, with the help of HPMC and PVP [13]. Results from the research showed that stability of the prepared formulation was improved due to the ability of HPMC to provide a physical barrier to the drug particles. The FTIR spectra of this study presented a high level of hydrogen bonding between HPMC and CBZ, thus supporting its role in enhancing stability of the drug without a large effect on solubility.

Previously, Bolmal *et al* [14] examined the effect of PEG and lactose on solubility of CBZ in their study [14]. They identified that solubility was enhanced for PEG but not for lactose. This previous study is in concordance with this current research, wherein it was shown that PEG had a profound effect on the solubility of CBZ, while lactose affected CBZ solubility to a very small extent. A critical examination of the stability profiles of formulated drugs under the accelerated examination stress regime has been previously reported [15]. The researchers enunciated that the stability of the drug increases with the increase in the molecular weight and hydrophilic properties of the excipients. This research corroborates this previous finding by demonstrating that the hydrophilic and high molecular weight excipients, like PVP and HPMC, further improved the CBZ stability under far-from-equilibrium conditions of accelerated storage. The stability testing in this study demonstrated that formulations containing these excipients were more stable.

Recently, Tian's group investigated the polymorphic behavior of drugs in solid-state formulation, which posits that excipients hinder the polymorphic transformation and stabilize the drug [16]. From these results, PVP and HPMC arrested the polymorphic transformation, thus enhancing both solubility and stability of CBZ. Findings from this research have established that these excipients prevent the formation of less soluble polymorphs. Also, the influence of various excipient characteristics on improved solubility has been previously reported, and among excipients, PEG has been described due to its molecular structure [17]. With the findings from the multiple regression analysis in this study, excipients such as PEG have been shown to enhance the solubility of CBZ through molecular characteristics.

The regression model adopted in this research revealed that PEG had a direct relationship with solubility enhancement. Previously, solubilizing studies on the use of lactose as an excipient revealed that there was little influence on the solubility of poorly soluble API [18]. Similarly, no significant enhancement of CBZ solubility with lactose was seen in the current research. Subsequently, solubility studies carried out through PXRD and dissolution test also indicated that lactose had a negligible effect. Similar to results from a previous study, the present results discussed the stabilizing impact of PVP and PEG in drug formulations [19]. These excipients greatly improved the aggregation stability of the drugs, and have established that PVP and PEG not only improved the solubility of the CBZ but

also its stability under changeable conditions. Stability tests from this study also demonstrated that the formulations with PVP and PEG were more stable as compared to formulations without these excipients.

A Predictive Model for Optimized Drug Formulations is a statistical prediction model formulated with a view to predicting the effect of the chosen excipients on the solubility and stability of CBZ. Therefore, based on this study, the model applies the excipient properties such as hydrogen bonding capability, molecular weight and type (PVP/HPMC, PEG/Lactose) to determine how they will promote the solubility and long-term stability of CBZ. The findings showed that the properties of excipients impact the performance of CBZ, thereby providing a basis to forecast the best excipient blend for enhanced bioavailability and stability. This model can be useful for developing formulations with better bioavailability and stability of the active ingredient, along with the choice of the most suitable excipients.

CONCLUSION

The solubility and stability of drugs in their solid-state form are key factors that influence their bioavailability and overall therapeutic efficacy. The findings of this study show that the choice of excipients plays a crucial role in enhancing the solubility and stability of Carbamazepine (CBZ) in solid-state pharmaceuticals. Polyvinylpyrrolidone and polyethylene glycol are more efficient for the solubility enhancement of CBZ, mainly because of their hydrogen bonding properties and plasticizing effect, respectively. Although this is less effective for enhancing solubility, it plays a major role in the stability aspect of the formulation by acting as a shield around the particles of the drug and thus avoiding the polymorphic changes. Furthermore, the predictive model coined in this study presents potential as a tool for formulating the right drug based on the characteristics of the excipients.

DECLARATIONS

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Ethical approval

Not applicable.

Use of Artificial intelligence/Large language models

The authors confirm that AI-based tools were used solely for language editing and manuscript polishing purposes (e.g., grammar, phrasing, and clarity). No AI tools were used to generate content, interpret data, or influence study design, results, or conclusions. All intellectual contributions, study analyses, and interpretations reported in the manuscript are the original work of the authors.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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