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Research Article

Preparation and Evaluation of Solid Dispersion-Based Bilastine Effervescent Granules

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Abstract

Background: Bilastine (BLA) is a second-generation H1 antihistamine used to treat allergic rhinoconjunctivitis. Because of its limited solubility, it falls under class II of the Biopharmaceutics Classification System (BSC). The solid dispersion (SD) approach significantly improves the solubility and dissolution rate of insoluble medicines. ***Objective***: To improve BLA solubility and dissolution rate by formulating a solid dispersion in the form of effervescent granules. ***Methods***: To create BLA SDs, polyvinylpyrrolidone (PVP K30) and poloxamer 188 (PLX188) were mixed in various ratios (1:5, 1:10, and 1:15) using the kneading technique. All formulations were evaluated based on percent yield, drug content, and saturation solubility. The formulae with the greatest solubility enhancement were subjected to in vitro dissolution studies, Fourier transform infrared, and thermal analysis to study drug crystallinity and drug-polymer interactions. The best SD formula was made as effervescent granules using wet granulation and tested further. ***Results***: The SD3 formula, which contained PVP K30 in a 1:15 ratio, had the highest solubility and release. In phosphate buffer (pH 6.8), over 88.43% of the BLA was released within the first 15 minutes. The optimum formula's effervescent granules demonstrated excellent flow qualities, a disintegration time of 87 seconds, an acceptable pH of 5.9, and 9.7 mg of BLA dissolved in the first 5 minutes. ***Conclusions***: BLA dissolution can be improved via solid dispersion technique allowing for successful effervescent granules formulation.

Keywords: Bilastine, Effervescent granules solid dispersion, Kneading technique, PVP K30, PLX188.

تحضيير وتقييم حبيبات فوارة تحتوي على المتشتت الصلب للبيلاستين

الخلاصة

الخلفية: البيلاستين دواء من الجيل الثاني من مضادات الهستامين لعلاج الالتهاب التحسسي للملتحمة الانفية، ويصنف لقلة ذوبانيته في الماء كدواء من الصنف الثاني. اثبتت تقنية المتشتت الصلب فعاليتها في تحسين ذوبان وسرعة تحرر العديد من الادوية غير الذائبة. **الهدف:** تحسين ذوبانية وتحرر البيلاستين عن طريقه تحضيره بصيغة المتشتت الصلب لغرض تحويله الى حبيبات فوارة. **الطرق:** تم استخدام طريقة العجن لتحضير المتشتت الصلب للبيلاستين باستخدام البولوكزامر188 و فينيل بيرلوريدون ك 30 وبالنسب 1:5و1:10و1:15 من الدواء والحامل المائي. تم تقييم جميع الصيغ من ناحية النسبة الانتاجية ومحتوى الدواء وقابلية الذوبان المائية. ثم خضعت الصيغ ذات التحسن العالي للذوبانية لاختبار سرعة مدى تحرر الدواء. تم تحليل الصيغة المثالية للمتشتت الصلب حراريا بوساطة المسح التفاضلي الكالوري، حيود الاشعة السينية، و باستخدام التحليل الطيفي للاشعة تحت الحمراء تم دراسة التفاعل بين الدواء والناقل المائي. حضرت صيغة المتشتت الصلب المثالية كحبيبات فوارة باستخدام التحبيب الرطب وخضعت للتقييم ايضا. **النتائج:** اظهرت صيغة المتشتت الصلب للبيلاستين المحضرة باستخدام البولي فينيل بيرلوريدون ك 30 بنسبة 1:15 من الدواء والحامل المائي اعلى تحسين للذوبانية المائية واسرع تحرر للدواء، حيث حررت اكثر من 88.43% من الدواء في اول 15 دقيقة في الوسط الفوسفاتي ذو الرقم الهيدروجيني 6.8. كما أظهرت الحبيبات الفوارة المحضرة من صيغة المتشتت الصلب المثالية خصائص تدفق ممتازة، ووقت تفكك قدره 87 ثانية، ودرجة حموضة مقبولة تبلغ 5.9 و9.7 ملجم من الدواء المذاب في أول 5 دقائق. **الاستنتاج:** تم تحسين ذوبانية دواء البيلاستين بواسطة تقنية التشتت الصلب مما ساعد في تحضيره كحبيبات فوارة.

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INTRODUCTION

The limited aqueous solubility of many newly discovered drugs is a major barrier to their therapeutic effectiveness. Statistical studies reveal that about 40% of today's unique chemical entities have inadequate water solubility, leading to an insufficient dissolution rate [1]. As a result, finding novel approaches to overcome solubility restrictions is becoming more important in order to achieve the potential therapeutic benefits of these active molecules. One of these approaches is a solid dispersion system. Solid dispersion is a drug delivery technique that involves distributing the drug molecule within a physiologically inert matrix, typically to improve oral bioavailability [2]. Different methods such as melting (fusion), solvent evaporation, the melting-solvent method, and the kneading technique can prepare solid dispersions [3]. The kneading technique is one of the most frequently employed approaches in solid dispersion formulation to improve the solubility and dissolution rate of poorly water-soluble drugs. The technique involves triturating the drug to a submicron size. By dispersing the drug in a water-soluble carrier with the help of a few water drops, we can further reduce the drug particle size to the molecular level. Furthermore, the kneading method is suitable for thermolabile drugs because it doesn't require the use of heat [5]. Bilastine is an H1-antihistamine that doesn't make you sleepy [6]. It dissolves in water at a rate of 500 µg/ml, which puts it in class II according to the biopharmaceutical classification system [7]. The kneading technique was previously used in the preparation of solid dispersions of poorly water-soluble drugs like meloxicam [8], mesalamine [9] and valdecoxib [10]. This study aims to improve BLA apparent solubility and dissolution rate by formulating the drug as a solid dispersion using the kneading technique prior to effervescent granule formulation. Two different carrier polymers at three different ratios of drug to polymer were employed.

METHODS

Materials

Bilastine (BLA) was purchased from (Wuhan HSN Pharma Research Co., Ltd.), polyvinylpyrrolidone (PVP K30) from (Glentham Life Science, UK) and poloxamer188 (PLX188) from (Eastman Chemical Company, USA). All of other ingredients and solvents that were used in this study were of analytical grade.

Preparation of BLA SD formulas via kneading technique

BLA and the carrier polymer PVP K30 or PLX188 were combined in accurately weighted amounts in a glass mortar at the proportions of 1:5, 1:10, and 1:15. A structural paste was then obtained by gradually moistening the mixture with water that was added drop by drop, and the mixture was triturated for 30 minutes. After that, the paste was dried for 24 hours at 40 °C in an oven. Using a mortar and pestle, the dry mass was crushed, ground, and then passed through sieve number 60. The produced SDs were stored in glass-umber containers and preserved in a desiccator until further use [8]. The amount of BLA was fixed at 500 mg in all formulations. Table 1 provides a full description of the SD formulas prepared in this study. We determined the percent yield of the SD formulas using equation 1.

Table 1: Composition of BLA-SDs formulas prepared in this study

Formula code	Carrier Polymer	BLA:carrier (w/w)
SD1	PVP K30	1:5
SD2		1:10
SD3		1:15
SD4	PLX188	1:5
SD5		1:10
SD6		1:15

The actual weight of SD represents the weight of the formula retrieved after sieving [11]. The theoretical weight is the sum of the solid component weights.

$$\textbf{Yield (\%)} = \frac{SD\ actual\ wieght}{SD\ theorital\ wiegh} * 100 \ldots \textbf{Eq.1}$$

BLA solid dispersion equivalent to 10 mg of the drug was dissolved in 50 mL of methanol. The resulting solution was filtrated using 0.45 µm filter paper. The obtained filtrate was appropriately diluted with methanol and then examined using a UV-spectrophotometer at 275.4 nm. We calculated the content of BLA in SD using equation 2.

$$\textbf{Drug content\% w/w=} \frac{(Actual\ BLA\ content)}{(Theoretical\ BLA\ content)} * 100 \ldots \textbf{Eq.2}$$

Saturated solubility of pure drug and SD formulas

We examined the solubility of the BLA drug and the resulting BLA-solid dispersion by using screw-capped tubes containing 10 mL of deionized water with additional drug and BLA SD formula. After 48 hours at 25 °C in a water bath shaker, the tubes were filtered through a 0.45 µm filter paper [12]. Samples were properly diluted with deionized water and measured at 273 nm using a UV spectrophotometer. All samples were run in triplicate.

In vitro dissolution

BLA SDs with the highest apparent solubility were further assessed for improvement in dissolution rate. The USP XXII rotating paddle device (apparatus II) was used to examine the in-vitro release characteristics of pure BLA and BLA-SDs. Nine hundred mL of phosphate buffer pH 6.8 were used to dissolve a precisely weighted amount of BLA-SD, which is equivalent to 10 mg of pure BLA. The paddle was operated at a rotation speed of 50 rpm at 37 °C. At 5, 10, 15, 20, 25, 30, 40, 50, and 60 minutes, five milliliter samples were taken. Every sample was quickly replaced with an equal volume of fresh dissolution media in order

to maintain a constant volume of the release media for the duration of the investigation [13]. Samples were passed through a 0.45µm filter syringe prior to analysis using a UV spectrophotometer at 274 nm. The experiment was done in triplicate.

Evaluation of the optimum formula

The thermal properties of the pure BLA, the optimum formula, the associated physical mixture (PM), and the carrier polymer were assessed by differential scanning calorimetry (DSC) using automatic thermal analyzer equipment (Shimadzu, DSC-60, and Japan). Five milligrams of each sample were put in a non-hermetically sealed aluminum pan, which was heated at a rate of 10 °C per minute for a temperature range of 0 °C to 300 °C. We conducted the thermal analysis under atmospheric flow conditions [14]. Fourier transform infrared (FTIR) spectra were acquired with the use of the FTIR Shimadzu 8300 Japan. Potassium bromide was used to compress samples of pure BLA, PVP K30, PM and the optimum formula. The resulting spectrum range was between 4000-400 cm^{-1} wavenumbers [15]. Powder X-ray Diffraction (PXRD) analyses were performed on the optimum formula, associated PM, PVP K30, and pure BLA to determine their crystallinity. The test was conducted with the use of an X-ray diffractometer (DX2700BH, China). A speed rate of 5°/min was used to scan samples over a 2θ range of 3–80°C [16].

Preparation of BLA solid dispersion as effervescent granules

The effervescent granules of the optimum solid dispersion formula were further formulated by the wet granulation method. The BLA solid dispersion equivalent to 10 mg BLA was first weighted and mixed with the effervescence base (citric acid, tartaric acid, and sodium bicarbonate at ratios of 1:2:3.4, respectively). Aspartame was added as a sweetener and orange flavor was added as a flavoring agent to help improve the taste of the final product. Mannitol was then added to the final mixture as a diluent. The quantity of each component is shown in Table 2.

Table 2: Composition of the prepared effervescent granules

Ingredients	F1	F2
BLA-solid dispersion (SD3)	-----	160 mg
Pure BLA	10 mg	-----
Citric acid anhydrous	170 mg	170 mg
Tartaric acid	340 mg	340 mg
Sodium bicarbonate	578 mg	578 mg
PVP 2%(w/v)	0.5 ml	0.5 ml
Aspartame	30 mg	30 mg
Orange flavor	10 mg	10 mg
Mannitol	852 mg	702 mg
Total weight	2 g	2 g

The dough mass was then obtained by moistening the mixture with 0.5 ml of an ethanolic solution of 2% PVP. The mass was then wet sieved through sieve no. 20 and kept in an oven for 30 minutes at 40 °C. Finally, dry granules were sieved through sieve no. 18 to get uniform-sized granules. The product was stored in aluminum foil in a sealed container with desiccant for further evaluation [17]. Effervescent granules of pure BLA were prepared in parallel using the same method. A full presentation of the amounts used for each component is presented in Table 2.

Evaluation of the effervescent granules

In accordance with the European Pharmacopoeia, we determined the angle of repose to assess the flow properties of the prepared effervescent granules. The angle of repose was determined by allowing the prepared granules to pass through the funnel until the top of the conical pile became close to the tip of the funnel. The resulting conical pile's radius and height were recorded. The angle of repose of the prepared granules was determined by using the following equation [18].

$$\text{Tan } \Theta = h/r \quad \text{..... Eq.3}$$

where the Θ: angle of repose, h: height of the pile, and r: radius of the pile.

Bulk density can be determined by dividing the weight of the granules by their volume. It is expressed in g/ml. We determined the bulk volume (Vb) and the weight of the granules (M) by carefully placing the produced granules into a graduated cylinder [19]. The bulk density (ρ_b) was calculated using the following equation:

$$\rho_b = M / V_b \quad \text{..... Eq. 4}$$

The proportion of the granules' weight to their tapped volume is known as tapped density. An accurately weighed amount of the granules was placed in a graduated cylinder that was manually tapped until the volume was constant [20]. The tapped volume (V_t) and the weight of the granules (M) were determined. The tapped density was then calculated using equation 5.

$$\text{Tapped density } (\rho_t) = M / V_t \quad \text{..... Eq. 5}$$

where ρ_t = tapped density, M = weight of granules, and V_t = tapped volume of granules.

Carr's Index is based on the bulk density to tapped density values. It is considered as an indication for the powder's flow properties [21]. Equation 6 was used for calculating Carr's Index is as follows:

$$CI = \frac{p\ tapped - p\ bulk}{p\ tapped} * 100 \quad \text{..... Eq. 6}$$

where ρ_t = Tapped density, and ρ_b = Bulk density.

Hausner's ratio is an indicator of powder flow ease. The following equation is used to calculate it.

$$HR = \frac{p\ tapped}{p\ bulk} \quad \text{..... Eq. 7}$$

Where, ρt = Tapped density and ρb = Bulk density.

The angle of repose, Carr's index, and Hausner's ratio standard values are listed in Table 3 [22, 23].

Table 3: The flow properties classification of the granules according to Angle of repose, Carr's Index and Hausner's ratio [22,23]

Flow character	Angle of repose	Carr's Index	Hausner's ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Extremely poor	>65	>38	>1.60

A dose of 2 grams of effervescent granules equivalent to 10 mg of BLA was put into 200 ml of distilled water, and the time for a complete effervescence indicated by the complete settlement of bubbles in a clear solution was recorded [24]. After the granules completely dissolved, we measured the pH of the solution using a pH meter [25]. To measure the amount of drug dissolved in the prepared granules**,** two grams of effervescent granules equivalent to 10 mg of BLA were accurately weighted and added to 200 ml of distilled water. The solution was allowed to sit for five minutes, after which it was filtered using a 0.45µm filter membrane. The filtrate was appropriately diluted with distilled water, and using a UV-spectrophotometer, the absorbance was measured at 273 nm [26].

Statistical analysis

One-way ANOVA and a Tukey *post hoc* test or *t*-test were used to analyze data as samples allowed. When the *p*-value was less than 0.05, the differences were considered to be significant. GraphPad Prism 8 was used for statistical analysis.

RESULTS

All prepared SD formulas had a percentage yield of 95% or higher and a BLA content of 96% or higher, as shown in Table 4.

Table 4: The percent yield and drug content of the prepared SD formulas by kneading method [a]

Formula code	Yield (%)	Drug content (%w/w)
SD1	97.5	96.4±0.004
SD2	95.4	97.18±0.002
SD3	100	98.59±0.007
SD4	97.5	99.3±0.008
SD5	95.4	98.9±0.002
SD6	98.0	97.6±0.001

[a]: data are presented as mean ± standard deviation, n=3

Pure BLA has an aqueous solubility of 0.3 mg/ml which is considered very slightly soluble. The solubility of BLA was improved by the SD technique, as shown in Figure 1. In our study, we have assessed the effect of using two different polymers and different drug-polymer ratios on the apparent solubility. We discovered that all SD formulations made with the two polymers made it much easier for pure drugs to dissolve (p<0.05), and this was true for all drug-polymer ratios.

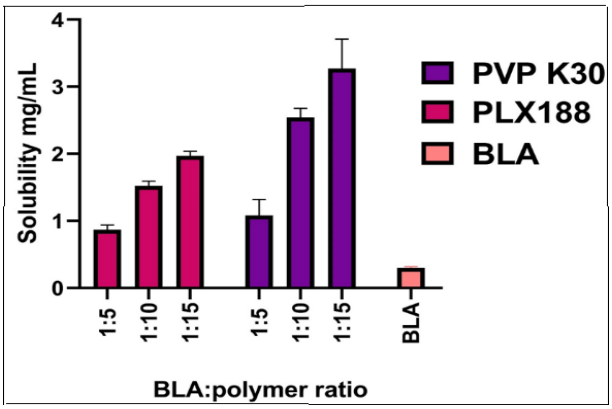

Figure 1: The saturation solubility of the BLA-SD formulas prepared by kneading method. Samples are presented as mean ± standard deviation, n=3. Studies were conducted at 25 °C.

The type and ratio of the polymers had a significant impact on the extent of solubility enhancement. In terms of the polymer ratio, we found that the solubility improvement was directly proportional to the polymer carrier content, meaning that as the polymer ratio increases, the solubility is improving. At a 1:5 ratio, both polymers showed significant solubility enhancement compared to the pure drug (p=0.0492 for PVP K30 and p=0.0065 for PLX188). A further increase in the drug polymer ratio to 1:10 (w/w) for PVP K30 and PLX188 resulted in an 8.3 and 5.03-fold improvement in apparent solubility, respectively, as shown in Figure 1. Further improvement was noted as the polymer ratio of 1:15 was used for PVP K30, with a successful enhancement of the solubility by 10.7 folds. For all drug-polymer ratios tested, PLX188 demonstrated a lower level of apparent solubility improvement than PVP K30. This difference in the level of solubility improvement was more profound as the carrier polymer content increased. As a result, PVP K30 was determined to be the best polymeric carrier for enhancing the solubility of BLA. This study aims to demonstrate the effect of polymer type and ratio on BLA drug release. We conducted a dissolution study on the PLX188 and PVP K30 SD formulas at a 1:15 ratio, focusing on the role of specific carrier polymers. The results showed that the SD formulas released 81.36% and 88.43% of the drug in the first 15 minutes, respectively, compared to a dissolution of 21.19% of the pure drug (Figure 2a). These results affirm the effectiveness of the SD technique in improving the dissolution rate of the BLA for both polymers. Similarly, the higher release noted for the PVP K30 formula further supports its superiority over PLX188. On the other hand, the SD formulas for the PVP K30 polymer at ratios of 1:10 and 1:15 showed a release of 75.36% and 88.43%, respectively, in the first 15 minutes, as shown in Figure 2b. We assessed and compared the release profiles of both to illustrate the value of employing the hydrophilic polymer in a solid dispersion formulation over a direct physical mixture. Results showed that the PM indeed improved BLA release over pure BLA, where BLA release was 54.83% compared to 21.19% for pure BLA in the first 15

minutes. However, this improvement is drastically lower than the improvement achieved by the SD formulation (Figure 2C).

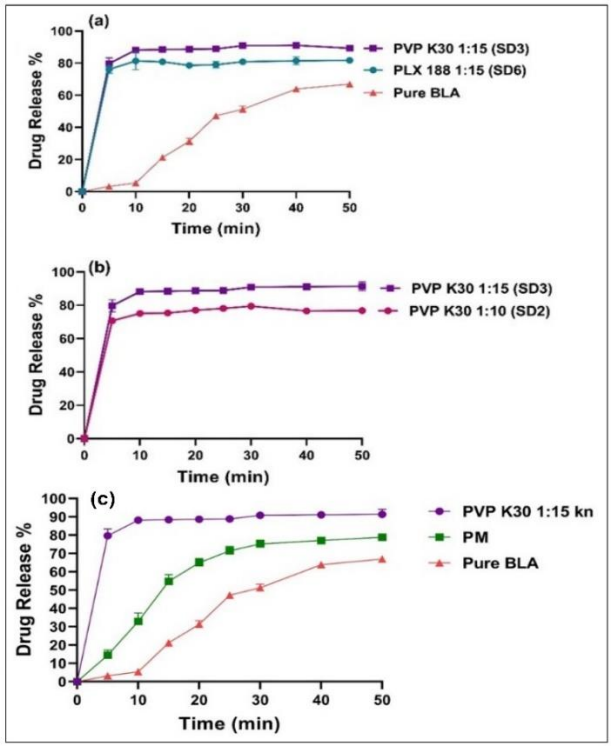

Figure 2: Effect of (**a**) polymer type (**b**) polymer ratio on the in vitro dissolution of BLA, and (**c**) dissolution of the optimum formula, related PM and pure drug. Samples are presented as mean±standard deviation, n=3. Studies were conducted in 0.05 M phosphate buffer (pH 6.8) at 37 °C.

These results collectively indicate that the PVP K30 at a 1:15 ratio (referred to as SD3 below) gives the highest solubility enhancement and faster drug release. Therefore, this formula was selected as the optimum formula and it was subject to further DSC, FTIR, and PXRD evaluation. The DSC thermogram of pure BLA is shown in Figure 3. The DSC pattern of pure bilastine has a single endothermic peak at 209 °C, which is the same temperature as what has been written about BLA's melting point [27]. This sharp endothermic peak was not present in the SD thermogram. Instead, only a single broad endothermic peak ranging from 80 to 117 °C was observed (Figure 3). On the other hand, the PM DSC pattern showed that the drug was crystallized because it had a sharp endothermic peak with a slight shift to a lower temperature (Figure 3). Figure 4A displays the FTIR spectra of pure BLA and PVPK 30. The BLA spectrum showed the typical BLA peaks reported elsewhere [28]. A strong peak was observed at 1670.0 cm^{-1}, potentially attributed to the C=O stretching band of the carboxylic acid. The C=C aromatic stretching vibrations were cleared by peaks at 1508 cm^{-1} to 1458 cm^{-1}. The C-O-C of ether contributed to the peak at 1253 cm^{-1}. Peaks at 1122 cm^{-1} were due to the C-N stretching vibration. Peaks at 3466 cm^{-1} are due to the O-H stretching vibration. Peaks at 3051 cm^{-1} and 2966 cm^{-1} are related to the C-H stretching of the aromatic ring.

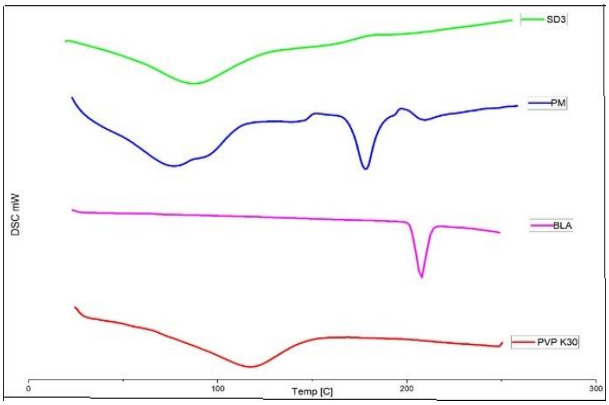

Figure 3: The DSC thermogram of PVP K30, pure drug, PM and the optimum formula (SD3).

Lastly, peaks at 2927 and 2858 cm^{-1} are related to the C-H stretching of aliphatic hydrocarbons (CH2 and CH3). In the PVP K30 spectra, the stretching vibration of the carbonyl group, which appears at 1674 cm^{-1}, was the most clearly characteristic peak. Additionally, the O-H stretching vibrations of the absorbed water caused a large peak to appear in the PVP k30 FTIR spectra at nearly 3000–3700 cm^{-1}, consistent with the literature-reported findings [29]. The FTIR spectrum of the selected solid dispersion formula (SD3) was also obtained, and it was compared with the FTIR spectra of BLA and PVP K30. The spectra for both showed mostly the distinctive peaks of PVP K30, possibly due to the high polymer ratio used (1:15 BLA: PVP K30). Additionally, a distinctive broad peak was observed at a range of 3545 cm^{-1} as a result of the formation of a hydrogen bond between the amide's nitrogen in PVPK 30 and the COOH functional group of BLA. Lastly, the solid dispersion was evaluated using XRD to learn more about the physical state of the drug in the solid dispersion formulation. Figure 4B displays the XRD diffractogram of pure BLA, PVP K30, and the chosen SD3 formula.

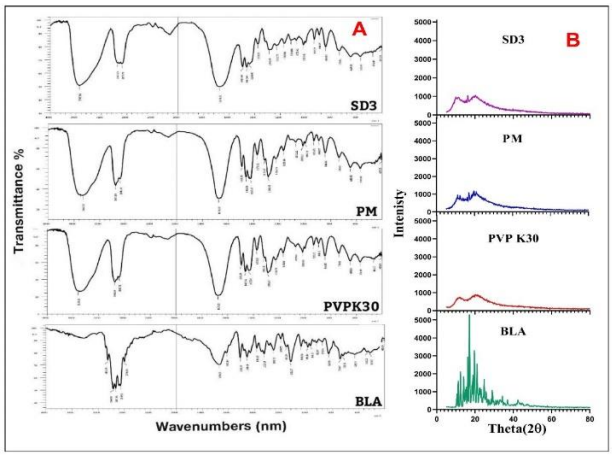

Figure 4: **A**) The FTIR pattern of pure drug, PVP K30, PM and the optimum formula (SD3); **B**) The PXRD pattern of Pure drug, PVP K30, PM and the optimum formula (SD3).

Pure BLA's XRD pattern revealed an intense peak at 2 (17.102) and further peaks at 2Ø (9.606, 11.184, 12.424, 13.997, 16.175, 19.757, 21.062, 22.640, 24.883, and 29.019) with lower intensities. While in the PVP K30 PXRD pattern, the molecules in the crystal lattice structure were arranged randomly, which resulted in a broad and dispersed pattern [30]. The physical mixture analog to the optimum SD formula's XRD pattern displayed the characteristic peaks of BLA at lower intensities. In contrast, the XRD pattern of SD3 demonstrated the disappearance of the major BLA characteristic peaks [31]. We prepared and evaluated effervescent granules (F2) in comparison with pure BLA-based effervescent granules (F1) to better illustrate the utility of the formulated solid dispersion in a pharmaceutical dosage form, without compromising the improved dissolution outcomes. The granule flow properties of both formulas are listed in Table 5.

Table 5: Flow properties of the BLA and SD3 effervescent granules

Flow parameter	F1	F2
Angle of repose (degree)	15.77±0.651	12.92±0.874
Bulk density	0.476±0.042	0.369±0.035
Tapped density	0.526±0.03	0.381±0.034
Carr's index (%)	9.5±0.045	3.14±0.364
Hausner ratio	1.10	1.03± 0.028

All the flow properties of the prepared granules (F1–F2) were excellent. Both granule formulations had comparable effervescent time and pH (Table 6). However, the amount released was significantly higher for the SD3-based effervescent granules than the pure BLA granules (p<0.001), see Table 6. SD3-based granules resulted in the dissolution of 97.3% of the BLA dose, compared to 49.8% for the pure BLA granules.

Table 6: The physical properties of the BLA and SD3 effervescent granules

Physical parameter	F1	F2
In vitro effervescent time (sec)	82±0.021	87±0.035
pH of solution	5.6±0.01	5.9±0.0
Amount of drug dissolved (mg)	4.98±0.046	9.73±0.127

The data represented an average mean of sample n=3

DISCUSSION

Limited drug molecule solubility remains one of the biggest challenges in the pharmaceutical industry. Sizable research is dedicated to addressing this problem with varying technologies and outcomes. Bilastine is one case of a limited-solubility drug that has only been addressed in a few studies. In this study, we sought to employ the solid dispersion technique to improve bilastine solubility, specifically the kneading method. The SDs formulas' good percentage yield and drug content determine the utility and accountability of the kneading method for the preparation of solid dispersions with minimal loss [32]. In the presence of both hydrophilic carriers, the apparent solubility of BLA was significantly improved. This improved solubility is mediated by the hydrophilic nature of the carrier polymer, which may have increased BLA wettability [33]. Our results showed PVP K30 to be superior to PLX188 in solubility enhancement. This polymer effect was also evident, though less profound, in the dissolution studies. Additionally, the polymer ratio had a positive impact on the dissolution rate, consistent with previous studies [34,35]. The resulting solubility enhancement is driven by the hydrophilic nature of the PVP K30 and possibly its role in keeping the drug in the supersaturation solid state, preventing the drug from returning to the less soluble crystalline form and its effect in stabilizing amorphous solid dispersions [36]. PVP K30 has a high glass transition temperature (Tg) of about 154 °C, which may help explain how it can keep drugs stable in their amorphous state for longer by stopping them from moving around and recrystallizing after being stored for a long time. In comparison, PLX188 has a low melting point (56–57 °C), which makes it appropriate for the preparation of solid dispersion systems using the melting method [37]. The selection of SD3 as the optimum formula was driven by its highest apparent solubility enhancement and faster dissolution rate profile. The DSC analysis revealed BLA's crystalline nature, as evidenced by the sharp endothermic peak. In the SD3 formula, a broad endothermic peak associated with the PVP K30 polymer was clearly visible [38]. These results suggest the conversion of the BLA drug from a crystalline to an amorphous state, which is an important factor in the solubility and dissolution rate enhancement. While the shift in melting point of BLA to a lower temperature can possibly be due to the dilution factor of the polymer [39], these results are corroborated by the XRD results of pure BLA, which clearly indicate its crystalline nature [40]. Similarly, the SD3 pattern indicates the conversion of BLA from a crystalline to an amorphous state within the PVP K30 carrier [31] and in PM, the lower intensities of the BLA peak can be attributed to the dilution factor. Collectively, the thermal analysis results support the conclusion that the increase in the drug solubility and dissolution rate is caused by this crucial conversion of the BLA in the SD formula [41]. This conversion was not associated with any chemical interaction, as confirmed by FTIR. Notably, the high ratio of PVP K30 in the FTIR spectra of the SD3 and its PM may have overshadowed the BLA peaks, but the absence of any additional peaks in their spectrum indicated that there was no chemical interaction between the drug and polymer carrier. Additionally, the hydrogen bonding demonstrated in the SD spectrum is attributed to the great stability of BLA when synthesized as a solid dispersion [42]. To demonstrate the significance of pre-formulating BLA as SD, the formulated SD was further prepared as an effervescent granule dosage form. This specific dosage form is palatable and allows for easy intake by pediatric and elderly patients [43]. Effervescent granules prepared using pure BLA and SD3 had comparable effervescent time and pH, both of which were within acceptable ranges [18, 44]. This was expected, as these two parameters are not affected by drug solubility. However, formulating BLA as a solid

dispersion favored a significantly higher release of the drug. Moreover, the prepared SD granules (F2) dissolve slightly more drug than the solid dispersion formula (SD3), suggesting that the presence of effervescent components further enhances drug solubility [26].

Conclusion

The kneading method for preparing bilastine as a solid dispersion has been found to be an efficient tool for increasing the apparent solubility of poorly water-soluble medicines. Solid dispersions containing PVP K30 improved bilastine aqueous solubility and dissolution rate more than PLX188, and both polymers had significantly better dissolution than the pure drug. The results of BLA SD-based effervescent granules provide a successful and promising alternative to traditional solid dose forms for increasing medication bioavailability and patient compliance.

Conflict of interests

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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