https://doi.org/10.31351/vol34iss1pp218-229

Solubility and Dissolution Rate Enhancement of Bilastine by Solid Dispersion Technique

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Received 20/10/2023, Accepted 21/1/2024, Published 29/3/2025

Abstract

Bilastine is non-sedating, new-brand H1 antihistamine, the drug has a problem of poor aqueous solubility and accordingly low dissolution rate, and low bioavailability. Solid dispersion is one of the most effective techniques for improving the solubility and the dissolution rate of poorly soluble drugs by the dispersion of drug within an inert hydrophilic carrier. The aim of this study is to increase the solubility and dissolution rate of the Bilastine using Solid dispersion technique. Twenty-nine Bilastine Solid dispersion formulas were prepared using different carrier polymers including Pluronic F127 (Poloxamer407), Poloxamer188, Urea, Polyethylene glycol 6000 (PEG6000) and Polyvinylpyrrolidone (PVP K30) and employing two different preparation methods (solvent evaporation and kneading method) at different drug: polymer ratios (1:1,1:3,1:5,1:10,1:15).The prepared Solid dispersion formulas were evaluated for their percent yield, drug content, aqueous solubility, dissolution rate. The crystallinity of pure drug and the selected formula was tested by the XRPD and DSC. In addition, the interaction between the blastine and the PVP K30 was assessed using FTIR. The Solid dispersion technique successfully improved the solubility and dissolution rate of Bilastine. The formulas prepared by the Solid dispersion technique have good percent yield and higher drug content. The characterization results of the selected formula reveal the conversion of the pure drug from crystal to the more soluble amorphous form which is confirmed by the XRPD and DSC analysis. The improvement was largely dependent on the polymer type and drug: polymer ratio. The solubility improvement using different polymers was in the following order: PVP K30> PLX188> PEG6000> Urea> PLX407. The solid dispersion formula that showed the best outcomes in terms of dissolution improvement was prepared using the solvent evaporation technique employing PVP K30 at ratio of drug: polymer of 1:15. The optimized formula showed 10 folds increment in the solubility compared to pure Bilastine. It can be concluded that the solid dispersion technique can successfully improve the solubility and dissolution rate by solvent evaporation method with careful selection of the carrier polymer and drug: polymer ratio.

Keywords: Bilastine, Solid dispersion technique, Aqueous solubility, Solvent evaporation, PVP K30.

Introduction

Bilastine (BLS) is H1 antihistamine of the second generation that has selective peripheral, non-sedating effects [(1)]. BLS was first approved in the European Union in 2010 indicated for the treatment of symptomatic allergic rhino conjunctivitis (seasonal and perennial) and urticaria, and is now available in around 100 countries worldwide [(2)] and is sold by FAES Farma under the brand name Bilaxten®. BLS has low aqueous solubility that was determined to be 500 ug/ml in the pH range of 5-8 which classify the drug as BSC class II [(3)]. Aqueous solubility is a key physicochemical property influencing the absorption of drugs and therapeutic efficacy [(4)]. Low drug solubility and low drug dissolution rate in water and aqueous G.I.T. fluid are common causes of inadequate bioavailability. One of the most challenging in drug research continues to be finding ways to improve new drug molecules solubility [(5)]. Several strategies have been proposed and evaluated for their capability of altering drug solubilities. Examples of such strategies are co-crystals, complexation, nanocrystals, emulsions, and self-micro (nano) emulsification [(6)]. Similarly, attempts have been made to enhance the aqueous solubility of Bilastine like formation of orotate salt of Bilastine [(3)] and the formation of inclusion complex of Bilastine [(7)] with varying outcomes. Another effective and promising techniques for solubility enhancement are solid dispersion (SD) formulation [(8)]. The SD concept, which was first introduced by Sekiguchi [(9)], is defined as the dispersion of one or more active materials in an inert carrier that can be produced by different methods such as fusion (melting), solvent evaporation, or kneading processes, such that the matrix is hydrophilic, whereas the drug is not [(10)]. SD technique have been successfully employed to improve the solubility of small drug molecules

including spironolactone [11], Silymarin [12], Nebivolol [13] with promising outcomes. However, scarce literature is available on the formulation of BLS SD. This study aims to use the solid dispersion technique to improve the solubility and dissolution of BLS. Two methods have been attempted employing different carrier polymers at varying drug: polymer ratio.

Materials and methods:

Materials

Bilastine (BLS) was purchased from (Wuhan HSN Pharmaresearch Co., Ltd.), Poloxamer 407 (PLX407) and Poloxamer 188 (PLX 188) were from (Eastman Chemical Company, USA), Urea from (Thomas Baker Pvt. Ltd., India), polyvinylpyrrolidone (PVP K30) from (Glentham Life Science, UK), and PEG 6000 from (BASF, Germany). All other reagents were of pharmaceutical grade.

Methods

Preparation of physical mixture (PM)

Accurately weighed amounts of the powders were geometrically mixed in a glass mortar to create the physical mixture for the selected SD formula. The mixture was then passed through sieve no. 60 and kept in the desiccator for future use.

Preparation of BLS-solid dispersion by solvent evaporation

An accurately weighed amount of BLS and the carrier polymer were dissolved separately in 10 mL and 20 mL of methanol, respectively. The two solutions were then mixed on a magnetic stirrer for 45 minutes [14]. The mixture was then poured into a petri dish and allowed to dry in the oven at 40 °C for 48 hours. The solidified mass was scraped, crushed, and ground using a mortar and pestle before being passed through sieve no. 60. The prepared SDs were kept in an amber glass containers and kept in a desiccator for further analysis [15]. The amount of BLS was fixed at 500 mg in all formulas. A complete list of all carrier polymers and drug: polymer ratios used is summarized in Table 1.

Table 1. Composition of BLS-SD Prepared by the Solvent Evaporation Method.

Formula	Carrier polymer	Drug: carrier ratios (by weight)
F1	PLX407	1:1
F2		1:3
F3		1:5
F4		1:10
F5	Urea	1:1
F6		1:3
F7		1:5
F8		1:10
F9	PVP K30	1:1
F10		1:3
F11		1:5
F12		1:10
F13		1:15
F14	PLX188	1:1
F15		1:3
F16		1:5
F17		1:10
F18		1:15
F19	PEG 6000	1:1
F20		1:3
F21		1:5
F22		1:10
F23		1:15

Preparation of BLS-solid dispersion by the Kneading Method

A precisely weighed amounts of BLS and the associated water-soluble carrier (Table 2) were mixed and triturated for 30 minutes. The mixture was then hydrated by dropwise addition of 1:1 water: methanol solution until a paste was obtained [16]. The paste was then dried in an oven at 40 °C for 24 hours. The dry mass was crushed and ground using a mortar and pestle and passed through sieve no. 60. The prepared SDs were kept in an glass umber containers and kept in a desiccator for further analysis [17].The BLS amount was fixed at 500 mg in all formulations.

A full description of carrier polymers and drug: polymer ratios used are presented in Table 2.

Table 2. Composition of BLS-SD Prepared by Kneading Method.

Formula	Carrier polymers	Drug: carrier ratios (by weight)
F24	PLX188	1:10
F25		1:15
F26	PVPK30	1:10
F27		1:15
F28	PEG 6000	1:10
F29		1:15

Characterization of BLS solid dispersions

Percent yield

The percent yield of the prepared solid dispersion was calculated using equation 1, where the actual weight of the solid dispersion represents the SD weight after sieving. The theoretical weight of the solid dispersion represents the mathematical sum of the dry component [18].

$$PY\% = \frac{(actual\ weight\ of\ the\ solid\ dispersion)}{(theroratical\ weight\ of\ the\ solid\ dispersion)} \times 100 \quad \textbf{Eq. 1}$$

Drug content

BLS solid dispersion equivalent to 10 mg BLS was dissolved in 50 mL of methanol, and the mixture was filtered using a 0.45µm filter paper. The filtrate of the drug was appropriately diluted with methanol, and the drug solution was examined using a UV-spectrophotometer at 275 nm. BLS content in the solid dispersion was calculated using equation 2 [19].

$$drug\ content\ \% = \frac{Actual\ BLS\ weight}{Theoretical\ BLS\ weight} \times 100 \quad \textbf{Eq. 2}$$

Saturated solubility of BLS and BLS-SD

The prepared BLS-solid dispersion's solubility was tested by adding excess amount of BLS SD formula to screw-capped tubes that contain 10 mL of deionized water. The tubes were left in water bath shaker for 48 hours at 25 °C and then filtered using 0.45µm filter paper [20]. Samples were appropriately diluted with deionized water and examined with a UV spectrophotometer at 273 nm.

In vitro dissolution:

The *in-vitro* dissolution profiles of pure BLS and BLS-SDs were determined using the USP XXII rotating paddle device (apparatus II). An accurately weighted amount of the BLS-SD equivalent to 10 mg of pure drug was dispersed in the dissolution media (900 mL of phosphate buffer pH 6.8) at 37.5 ± 0.5°C and a rotating speed of 50 rpm [21]. Five milliliter samples were withdrawn at predetermined time points of (5, 10, 15, 20, 30, 45, and 60) minutes. To maintain constant release media volume throughout the study, each sample was immediately replaced with an equivalent volume of fresh phosphate buffer pH 6.8. The samples were filtered through a 0.45µm filter syringe and examined with a UV spectrophotometer at a wavelength of 274 nm. The experiment was conducted in triplicate and included only the SD formulas that showed the highest solubility. The experiment was done in triplicate.

Differential scanning calorimetry (DSC)

The thermal properties of pure BLS, a chosen SD formula, PM, and the pure carrier polymer were examined using an automatic thermal analyzer equipment (Setram, Evo131, France). Each sample (5 mg) was placed in an aluminum pan that was not hermetically sealed and heated at a rate of 5°C per minute throughout a temperature range of 0°C to 300°C. The analysis was conducted under the conditions of atmospheric flow [22].

Fourier transform infrared (FTIR)

The Fourier transform infrared spectroscopy (FTIR) spectra were performed using the FTIR Shimadzu 8300 Japan. Small amounts of samples of pure BLS, BLS SD, PM, and the carrier polymer of the selected formula were compressed with KBr. The spectrum obtained was between the wavenumbers of 4000 - 400 cm^{-1} [23].

Powder X-ray diffraction (PXRD)

The PXRD was used to identify any changes in the crystalline nature of the drug, specifically changes to an amorphous form in the SD formulation. The X-ray diffractograms of the BLS drug, the best carrier polymer, their PM, and the optimized SD formula were obtained by using an X-ray diffractometer (DX2700BH, China) at a scanning speed of 5°/min over a 2θ range of 5 - 80 [24].

Statistical analysis

Solubility data were analyzed using one-way ANOVA followed by Tukey post-hoc test as required. Differences were determined to be significant at p-value < 0.05. Statistical analysis was conducted using GraphPad Prism 8.

Results and Discussion

Percent yield

The percent yield for all BLS-SD formulas prepared in this study are presented in Table 3. All prepared SDs had percent yield higher than 90%, reflecting the efficiency of the two methods applied. This high percent yield is one of the advantages of the solid dispersion technique which eliminates drug

and carrier polymer loss and maximizes technique productivity.

Drug content

The drug content of the prepared BLS-SD formulas was in the range of (93-102%), as shown in Table (3), which indicates negligible loss of the drug during preparation and homogenous dispersion of the BLS particles in all prepared BLS-SD formulas. The high drug content is another attribute of the solid dispersion technique that contributes to its applicability in pharmaceutical formulations.

Table 3. The Percent Yield and the Drug Content of BLS Solid Dispersion Using Different Methods [a]

Formula	Percentage yield (PY%)	Drug content % (w/w)	Formula	Percentage yield (PY%)	Drug content % (w/w)
F1	98.2%	102% ± 0.003	**F16**	97.25%	98.8% ±0.016
F2	97.4%	99.3% ± 0.004	**F17**	97.5%	100.1% ± 0.009
F3	97%	99.5% ± 0.004	**F18**	96.2%	97.8% ± m0.002
F4	97.05%	100.2% ± 0.008	**F19**	94.5%	95% ± 0.003
F5	95%	98.8% ± 0.003	**F20**	95%	99.98% ± 0.003
F6	98.5%	99.2% ± 0.009	**F21**	97%	102% ± 0.010
F7	96.6%	98.4% ± 0.003	**F22**	96.4%	99.92%±0.005
F8	93.3%	97.7 ± 0.000	**F23**	95.6%	101% ± 0.006
F9	97%	96.5% ± 0.006	**F24**	95.4%	98.9% ± 0.002
F10	92%	96.6% ± 0.003	**F25**	98%	97.6% ± 0.001
F11	93.3%	99.8% ± 0.002	**F26**	95.4%	97.18% ± 0.002
F12	100%	93% ± 0.002	**F27**	100%	98.59 ± 0.007
F13	96.8%	95.7% ± 0.007	**F28**	95.4%	100.1% ± 0.009
F14	95%	94.6% ± 0.007	**F29**	97%	99.47% ± 0.004
F15	97.08%	97.5% ± 0.024			

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

Saturation solubility of BLS and BLS-SD

Several factors can affect the extent of solubility improvement through solid dispersion. In the current study, we examined the effect of using different carrier polymers at different drug-to-polymer ratios prepared by two different methods. Generally, BLS-SD prepared by the two methods showed a higher aqueous saturation solubility in comparison to that of pure drug as shown in Figure 1. This could be due to the hydrophilic nature of these carriers, the decrease in particle size, and the increase in the surface area of contact between the drug particles and the solvent compared to the drug alone [(25)]. Additionally, improved wettability, high porosity [(26)] and the hydrogen bonding formation between BLS and carrier polymers which was confirmed by FTIR (see below) could be contributing to the enhancement in the solubility [(27)]. Concerning the effect of carrier polymer ratio, there is a relatively less enhancement in BLS solubility by using low BLS:polymer ratio, specifically 1:1 and 1:3 drug: polymer (w/w) ratios. These ratios resulted in only 2.1 and 2.4 folds increment in solubility respectively compared to pure BLS. Significant differences in solubility for all polymers used were noted starting at a 1:5 drug: polymer (w/w) ratio. Further improvement in solubility was detected as the drug:polymer ratio was increased to 1:10 for all polymers used except PLX 407, Figure 1A. The PLX 407 and Urea showed significant improvement in solubility ($P > 0.05$) compared to the pure drug. However, the SDs were shown to have relatively less solubility enhancement compared to the other carriers used. Therefore, they were eliminated from further investigation. For the other carriers that were selected for further investigations, the solubility enhancement can be ranked according to the polymer type in the following sequence: PVP K30 > PLX 188 > PEG 6000. A further increase in drug:polymer ratio to 1:15 resulted in an even higher increase in apparent solubility with the extent of improvement being polymer-dependent, Figure 1A. PEG 6000 showed the least improvement in solubility while PVP K30 showed the highest improvement in apparent solubility (10.8 folds), Figure 1A. The effect of polymer ratio can be attributed in part to improved wettability which is the first step in dissolution [(28)] . Additionally, higher polymer content contributes to increased system amorphism which was further confirmed by subsequent thermal analysis. BLS SDs using PEG 6000, PLX 188, and PVP K30 were also prepared by the kneading method. The solubility results showed nearly consistent outcomes to that obtained with the solvent evaporation method in terms of PVP K30 being the most effective carrier polymer in improving BLS apparent solubility. It was found that the solubility of BLS was not significantly improved ($p>0.05$) when the same ratio was used to prepare SDs formulations using different methods.

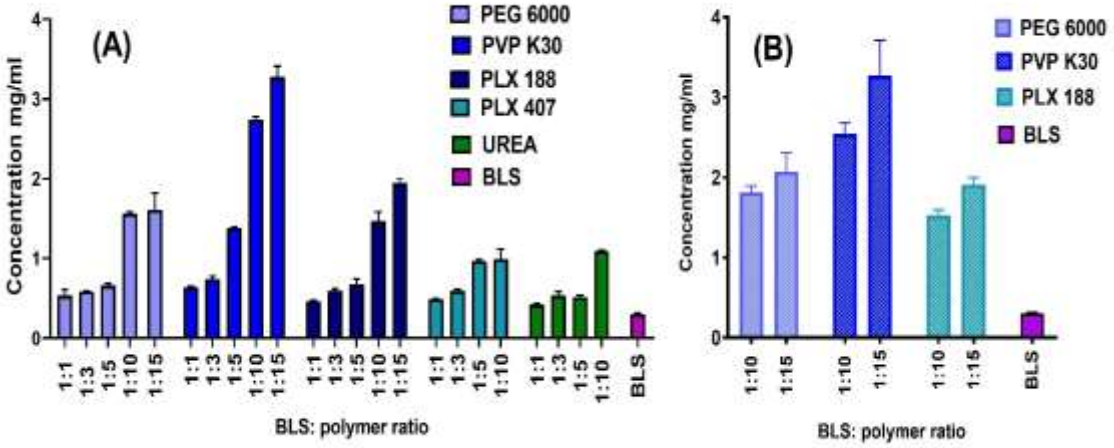

Figure 1. The saturation solubility of the BLS-SD formulas prepared by (A) solvent evaporation method and (B) kneading method. Samples are presented as mean ± standard deviation, n=3. Studies were conducted at 25 °C.

In vitro dissolution

Based on the apparent solubility studies, PVP K30 and PEG 6000 were selected to further evaluate the role of carrier polymer, drug:polymer ratio, and SD preparation method on BLS dissolution. Both PVP K30 and PEG 6000 carriers enhanced the dissolution rate of BLS, but faster release was obtained from the PVP K30 formula. The SD prepared with polymer to drug ratio of 1:15 by the solvent evaporation method demonstrated 89.2% of the BLS release in the dissolution medium after 10 minutes ($p<0.05$) which is higher than that of PEG6000 and pure BLS (76% and 5.11% respectively) as shown in Figure 2A. Therefore, the PEG 6000 formula (F23) was eliminated from further investigations. The varying effects of polymers in modifying the dissolution of a drug in a solid dispersion system has been previously reported [29]. Specifically, PVP K30 was reported to be superior to other polymers in improving the apparent saturated solubility and dissolution rate of poorly soluble drugs [30, 31]. PVP K is one of the most commonly used polymeric carriers to formulate solid dispersion. Among them, PVP K30 grade was utilized as polymeric carrier to get the preferred result between dissolution rate and polymer [32]. PVP K30 is employed as a solubilizing agent to increase the solubility, dissolution rate, and hence bioavailability of poorly soluble drugs in different techniques. PVP K30 forms water-soluble complexes with many drugs that have inadequate aqueous solubility because of its hydrophilic property. It was also suggested to prevent the back transformation of the dissolved drug to the crystalline state and keep it in amorphous state by maintaining the physical stability of the drug in solid state [33]. For PVP K30-based SDs prepared by the same method at varying drug:polymer ratio, different results were noted for the two methods used. To elaborate, SD formulas (F26 and F27) that were prepared by the kneading method showed significant increase in the dissolution rate by increasing the drug polymer ratio at 1:10 and 1:15 ratios that released (76% and 88.2%) of the drug after the first 10 minutes , which is consistent with the previous findings about positive proportionality of the effect of polymer ratio on the solubility and dissolution [28]. On the other hand, for SDs prepared by the solvent evaporation method (F12 and F13) increasing the polymer content had non-significant effect on the initial release at 10 minutes (81.12% and 89.2%). Thereafter, significant differences were noted in the amount released at later time points starting from the 15 minutes time point (86% and 92.3%). Nevertheless, the amount released from all SD formulations was significantly different than pure drug and PM [34]. Similarly, PVP K30 SDs prepared at the highest drug: polymer ratio using different methods (F13 and F27) showed no significant difference between their dissolution profiles at all time points. The SDs prepared by SE and KN methods at 1:15 ratio released 89.2% and 88.2% of the drug in aqueous media at time of 10 minutes and then to similar levels at the end of the study, as seen in Figure 3C. These results are in agreement with the solubility study results in confirming the superior effect of the polymer carrier over the effect of the preparation method.

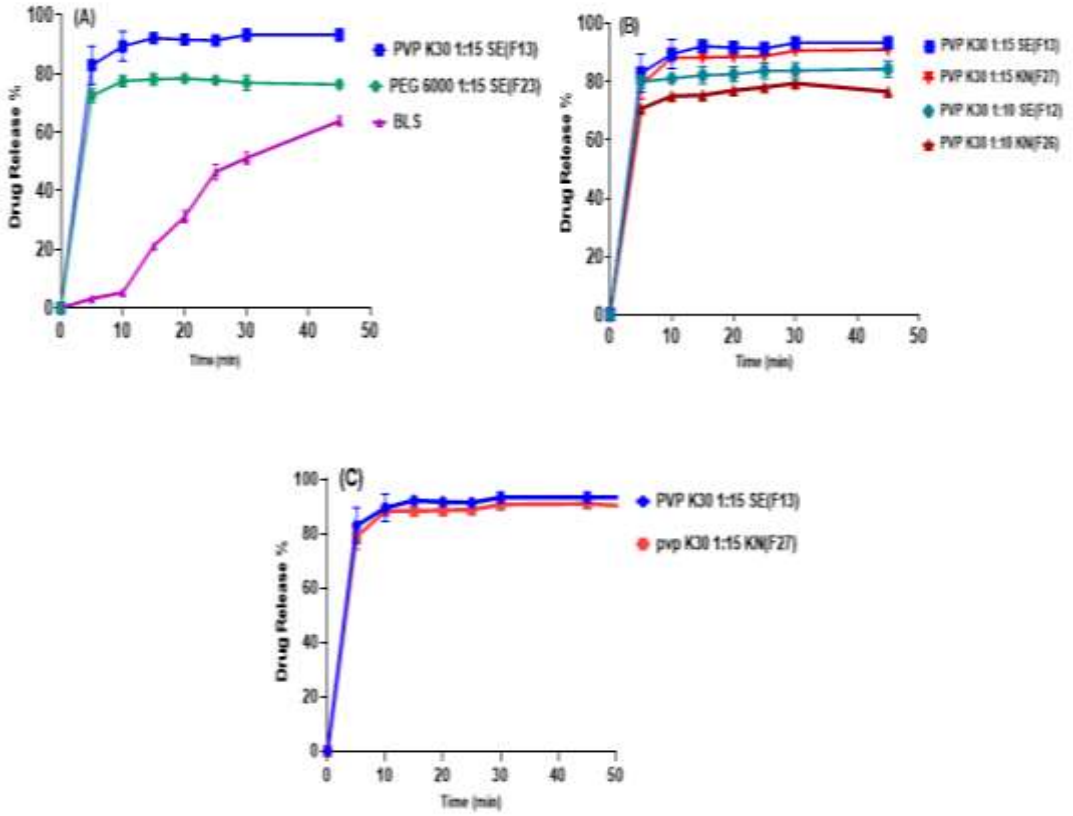

Figure 2. The in vitro release of BLS SDs prepared in this study (A) The effect of polymer type on the in vitro drug release by solvent evaporation method at 1:15 ratio, (B) The effect of BLS:PVP K30 ratio on the drug release profile from BLS-solid dispersion by solvent evaporation and kneading methods and (C) The effect of preparation methods of BLS:PVP K30 solid dispersion on BLS drug release profile at 1:15 ratio. Samples are presented as mean ± standard deviation, n=3. Studies were conducted in 0.05 M phosphate buffer (pH 6.8) at 37 °C.

To illustrate the role of solid dispersion technique in improving BLS dissolution, a physical mixture of PVP K30 and BLS was prepared and evaluated in parallel with the associated SD and pure BLS, Figure 3. The physical mixture demonstrated 30% BLS released compared to 5.11% of the pure drug release in the first 10 minutes. The improved dissolution in the physical mixture is expected and can be attributed to improved BLS wetting driven by the hydrophilic nature of PVP K30. When prepared as SD, there was a superior increase in the dissolution where more than 80% of BLS was released in the first 10 minutes compared to 30% in the PM, Figure 3. The superior dissolution of the SD dispersion is largely stemming from BLS amorphization in the SD which was confirmed by the PXRD (see below, Figure 5) in addition to improved wetting rate [35].

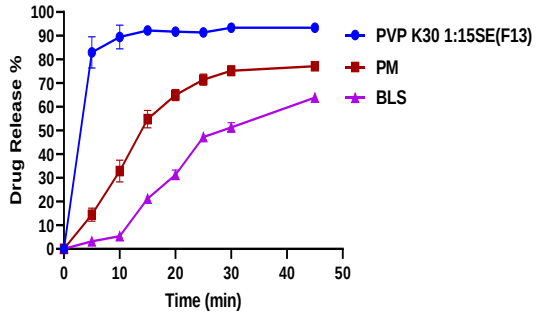

Figure 3. The *in vitro* release of the selected formula F13, associated PM and pure BLS. Samples are presented as mean ± standard deviation, n=3. Studies were conducted in 0.05 M phosphate buffer (pH 6.8) at 37 °C.

Selection and evaluation of the optimum formula

Although both F12 and F13 prepared by solvent evaporation method showed higher improvement of the BLS dissolution rate, Figure 2C, F13 showed higher apparent solubility than the F12 (10.8 versus 9 folds), Figure 1A. Consequently, F13 (prepared by solvent evaporation method using PVP K30 at drug:polymer ratio1:15) was selected as the optimum formula depending on the highest solubility of the drug and higher drug dissolution improvement and was further evaluated.

Differential scanning calorimetry (DSC)

The DSC thermograms of the PVP K30 and pure BLS are shown in figure 4. The BLS thermogram shows intense sharp peak at 209°C corresponding to drug melting point and indicating the crystalline nature of the drug which is continent with previous studies [36]. PVP K30 thermogram showed a broad endothermic peak from 80 to 124 °C due to the loss of residual moisture [37, 38]. The disappearance of the pure BLS endothermic peak in the selected SD formula thermogram was noted (figure 4) indicating the conversion of drug to amorphous state. In the physical mixture, BLS remains in the crystalline form with slightly reduction in the melting peak intensity of drug which is possibly due to dilution effect with the high polymer ratio of PVPK 30.

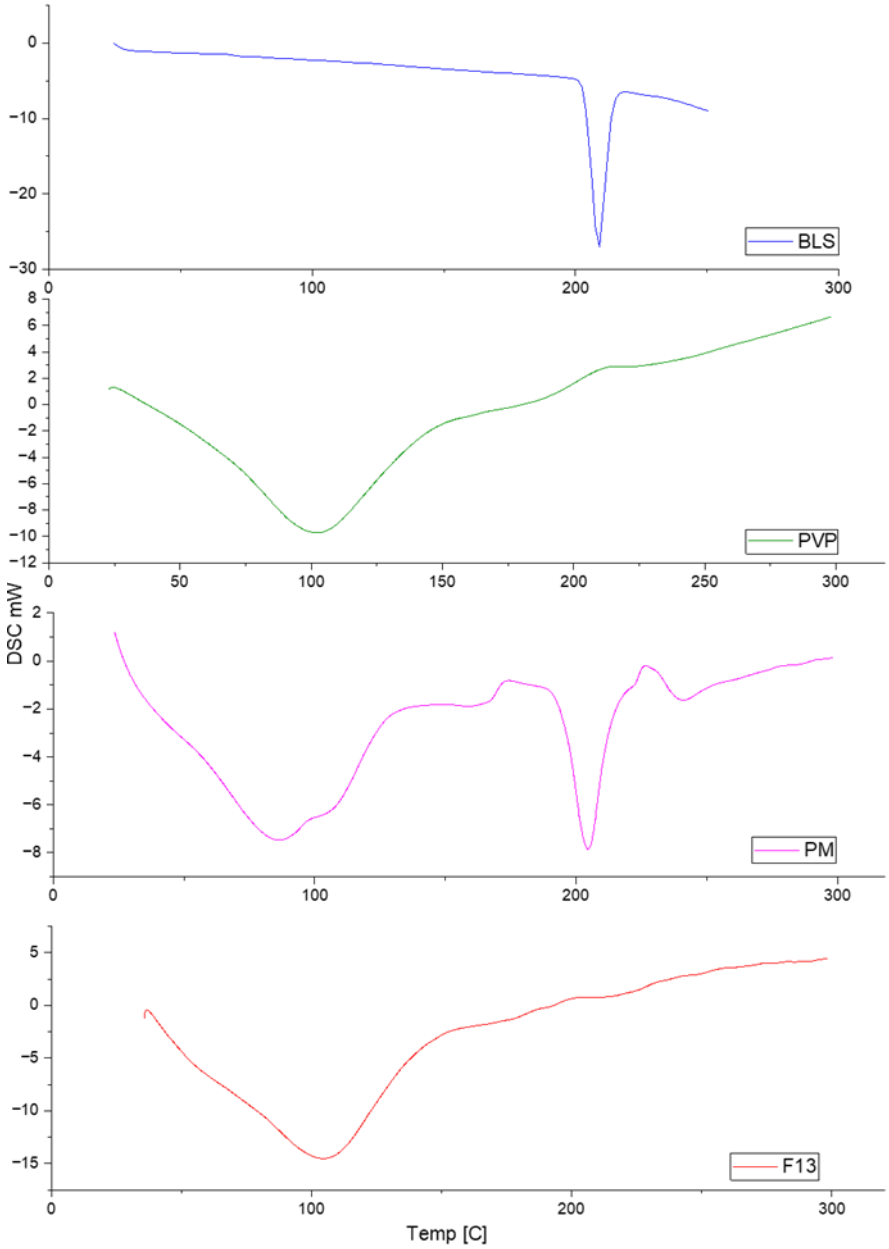

Figure 4. DSC thermogram of the BLS (Pure drug), PVPK30 (Polyvinylpyrrolidone), PM (Physical mixture), and F13 (Solid dispersion).

Fourier transform infrared (FTIR)

The FTIR spectrum of pure BLS and PVPK 30 are shown in Figure 4. The spectrum of BLS exhibited the characteristic peaks of BLS at 3466 cm^{-1} which are assigned to O-H stretching vibration [39]. The most evident peak in the spectrum of PVP K30 was the Stretching vibration of the carbonyl group that appear around 1674cm^{-1}. Also, the FTIR spectrum of PVP displayed a broad peak at about 3000–3700 cm^{-1} due to O-H stretching vibrations of absorbed water , these results supported the previous results [40]. The FTIR spectrum of the selected solid dispersion formula (F13) was performed and compared with that of BLS and PVP K30 FTIR spectrums separately. The FTIR spectrum of F13 and it is physical mixture show the presence of the mostly characteristic peaks of the PVP K30 that overwhelmed the peaks of BLS drug due to the use of high polymer ratio at 1:15 (BLS: PVP K30). The absence of new peaks in the SD spectrum confirmed the lack of chemical interaction between drug and the polymer carrier. A characteristic broad peak was noticed at range of 3545 cm-1 due to hydrogen bonding formation between the COOH of BLS and the nitrogen of amide in PVPK 30. The presence of the hydrogen bond indicated the high stability of BLS when formulated as solid dispersion [41].

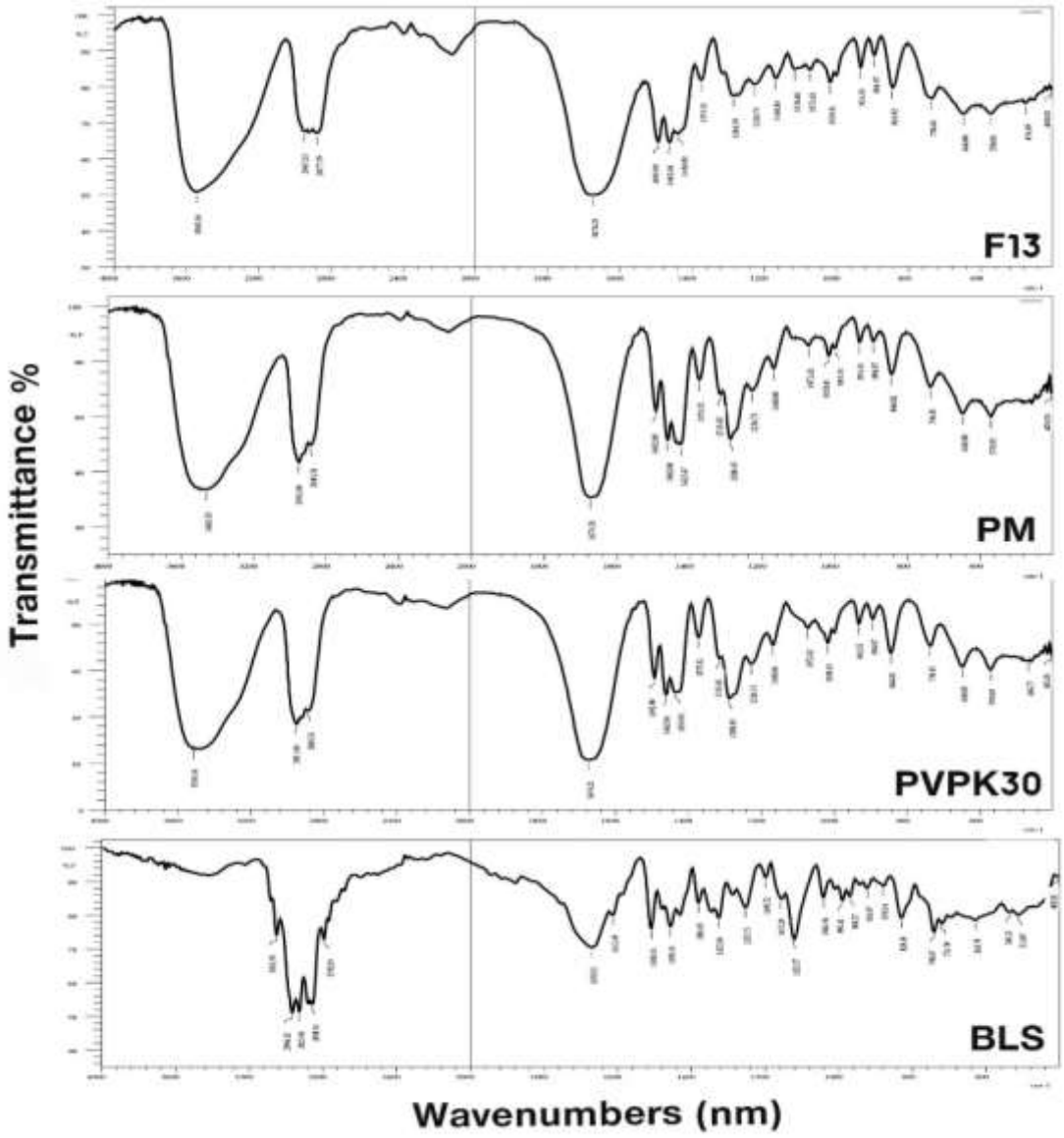

Figure 5. FTIR of the BLS (Pure drug), PVPK30 (Polyvinylpyrrolidone), PM (Physical mixture), and F13 (Solid dispersion).

Powder X-ray diffraction (PXRD)

The XRD studies were performed to get insights into the physical nature of the drug in the solid dispersion formulation [42]. The XRD diffractogram of pure BLS, PVP K30 and the selected F13 formula were shown in Figure 5.

The XRD pattern of pure BLS showed a highly intense peak (Braggs peak) at 2Ɵ (17.102) and other peaks with lower intensities at 2Ɵ (9.606, 11.184, 12.424, 13.997, 16.175, 19.757, 21.062, 22.640, 24.883, 29.019) which indicate the crystalline nature of pure BLS [43]. The XRD pattern of PVP K30 showed a broad and scattered pattern due to the random arrangement of the molecule in the crystal lattice structure [44]. The physical mixture XRD pattern of F13 showed the distinctive peaks of BLS at lower intensity possibly due to the diluting effect of PVP K30 carrier. In contrast, the XRD pattern of SD F13 showed a complete absence of the major BLS characteristic peaks and the presence of amorphous halo indicating the conversion of BLS from crystalline to amorphous state within the PVP K30 carrier [45]. This conversion of the drug in the SD formula was the essential element in increasing the drug solubility and dissolution rate [46].

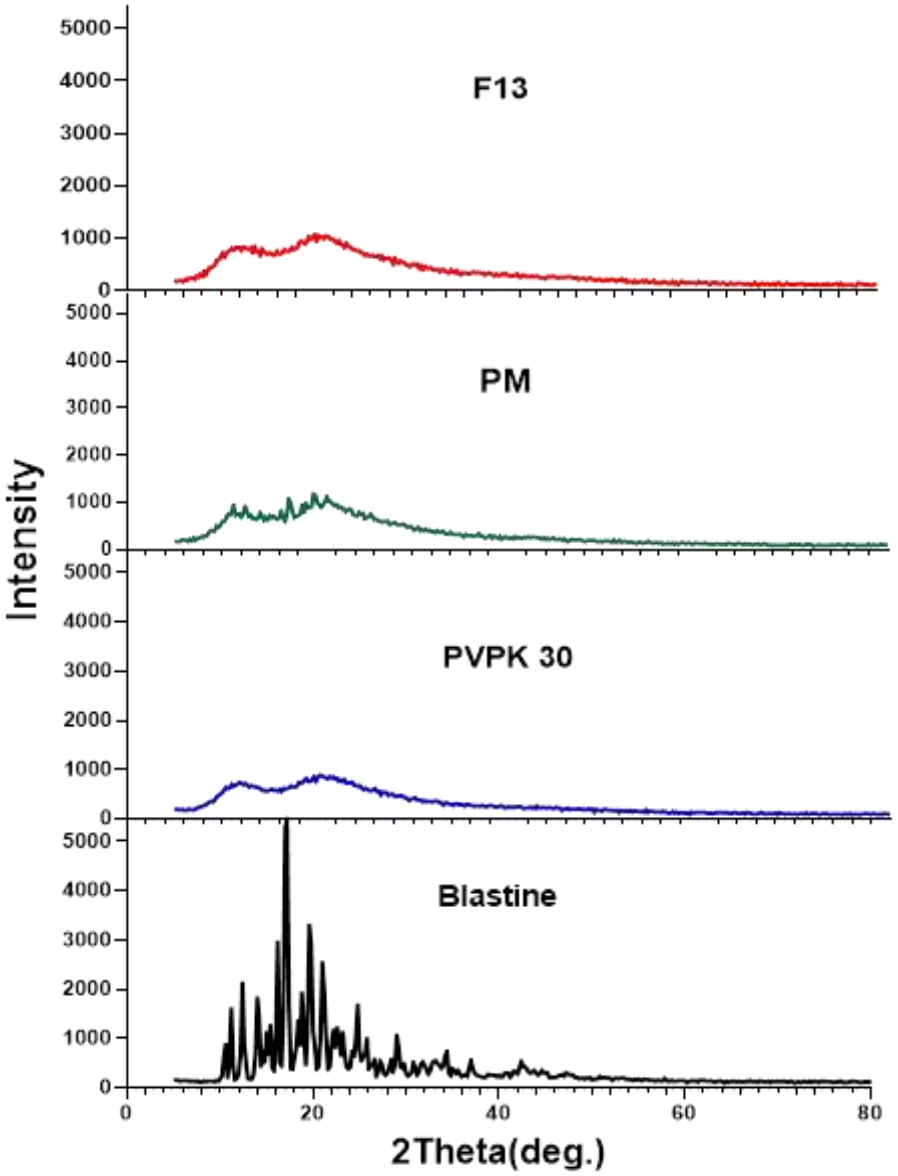

Figure 6. The PXRD pattern of BLS (Pure drug), PVP K30 (Polyvinylpyrrolidone), PM (Physical Mixture), and F13 (Solid dispersion).

Conclusion

According to the results obtained from the current study, the solubility and dissolution rate of BLS were efficiently improved using the solid dispersion technique. PVP K30 was the best carrier utilized. F13 that is prepared from 1:15 drug to polymer carrier and prepared by SE method shows solubility improvement by 10 folds and higher dissolution rate.

Acknowldegments

The authors would like to thank the faculty memebr at the department of pharamceutics, University of Baghdad, College of Pharmacy for their supprot and insigtful disscutions througout the study.

Conflicts of Interest

The authors declare that no conflicts of interest.

Funding

According to the authors, The research was not financially supported by any institution.

Ethics Statements

No ethical approvals are required for the study

Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: M. H. A. and K. K A.; data collection: M. H. A.; analysis and interpretation of results: M. H. A. and K. K A.; draft manuscript preparation: M. H. A. and K.K A. All authors reviewed the results and approved the final version of the manuscript.

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تحسين ذوبانية ومعدل تحرر دواء البلاستين باستخدام تقنية التشتت الصلب

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الخلاصة

البلاستين هو دواء جديد مضاد للهستامين غير مسبب للنعاس ، يعاني البلاستين من مشكلة انخفاض الذوبانية في الماء وانخفاض القدرة على التحرر السريع مما يؤدي اللى قلة التوافر الحيوي .تقنية التشتت الصلب هي احدى التقنيات شديدة الفعالية لتحسين ذوبانية وسرعة تحرر الادوية قليلة الذوبانية وذلك بتشتيت الدواء داخل حامل محب للماء.

الهدف من هذه الدراسة هو تحسين ذوبانية ودرجة التحرر لدواء البلاستين في الماء باستخدام تقنية التشتت الصلب. تضمنت الدراسة تحضير تسعة وعشرون صيغة من الصلب المنتشر باستخدام حاملات مائية مختلفة تتضمن البولكزامر٤٠٧،البولكزامر ١٨٨، اليوريا، بولي ايثيلين جلايكول والبولي فينيل بيرلوريدون ك ٣٠ بطريقتي تحضير مختلفتين همه تبخير المذيب وطريقة العجن وبنسب مختلفة من الدواء والحامل المائي (١:١و١:٣و١:٥و١:١٠و١:١٥). تم توصيف المنتشر الصلب من حيث النسبة الإنتاجية ومحتوى الدواء و قابلية الذوبان في الماء و سرعة تحرر الدواء بالمقارنة مع الدواء النقي. تم تحديد تبلور الدواء و الصيغة المختارة من الصلب المنتشر باستخدام حيود الأشعة السينية. كما تم ايضاً دراسة توافق البلاستين مع الناقل المستخدم في الصيغة المختارة عن طريق دراسة التحليل الطيفي بالأشعة تحت الحمراء.

أظهرت نتائج الدراسة نجاح تقنية الصلب المنتشر في تحسين ذوبانية وسرعة تحرر الدواء واعتمد هذا التحسن بشكل كبير على نوع ونسبة الحامل المائي المستخدم. حيث كانت كفاية الحامل على تحسين ذوباني البلاستين بالترتيب التالي: PVP K30> PLX188> PEG6000 > Urea> PLX407 . كما اظهرت النتائج افضلية صيغة الصلب المنتشر المحضر باستخدام طريقة التبخير بالمذيبات بوساطة الحامل المائي البولي فينيل بيرلوريدون PVP K30 و نسبة الدواء:للحامل المائي ١:١٥ مقارنة بباقي الصيغ التي تم اختبارها حيث أظهرت الصيغة المختارة زيادة بمقدار ١٠ أضعاف في ذوبان الدواء النقي . لذلك يمكن استنتاج أن تقنية التشتت الصلب قد نجحت في تحسين الذوبان ومعدل تحرر الدواء بطريقة التبخير بالمذيبات مع الحذر باختيار نوع الحامل المائي ونسبة الحامل المائي المستخدمة.

الكلمات المفتاحية: بلاستين، تقنية الصلب المنتشر، الذوبانية المائية،التبخير بالمذيبات،بولي فينيل بيرلوريدون.