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Formulation and Characterization of Bilastine – Ternary Cyclodextrin Inclusion Complex

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Abstract

Bilastine (BLA) is a modern second-generation antihistamine employed to manage symptoms associated with allergic rhinoconjuctivitis and urticaria. However, it is very slightly soluble in water with low oral bioavailability, which affects its therapeutic action. The main objective of this research was to enhance the solubility and dissolution rate of BLA by complexation technique using beta cyclodextrin (β-CD) and its derivatives; hydroxypropyl beta cyclodextrin (HP-β-CD), methyl beta cyclodextrin(M-β-CD), and sulfobutyl ether beta cyclodextrin (SBE-β- CD). Binary and ternary complexes using different hydrophilic polymers such as (polyvinyl pyrrolidone (PVP), poloxamer, soluplus®, and hydroxyl propyl methyl cellulose (HPMC)) were prepared using kneading, solvent evaporation, co-grinding, and microwave methods. The resulting complexes were characterized for their percentage yield, drug content, solubility, and dissolution. The best complex was further characterized by XRD and FT-IR. The obtained results revealed that the ternary complex consisting of BLA, M-β CD, and soluplus ® (1mole /1mole / 5% w/w) prepared by solvent evaporation method, exhibited the highest solubility (about 11 times more than the pure BLA in distilled water and in buffer of pH 6.8) and the fastest release rate, where 90 % of BLA was released within the first 15 minutes at pH 6.8 with percentage yield of 89.3 % and 100 % drug content. Furthermore, the FTIR analysis confirmed the inclusion of BLA within the cavity of M-β CD. Additionally, the XRD diffractograms indicated the amorphous nature of the resulting complex. Therefore, it can be concluded that improving the solubility and dissolution of BLA was achieved with the utilization of a ternary inclusion complex formation.

Keywords: Bilastine, inclusion complex, cyclodextrins, methyl beta cyclodextrin , soluplus

Introduction

The concept of solubility is characterized quantitatively by the drug concentration within the saturated solution at a specific temperature [(1)]. Enhancing the solubility of poorly water soluble drugs, and improving their oral bioavailability remains one of the most challenging aspects of the drug development process especially, for oral drug delivery system. There are numerous techniques to enhance the solubility of poorly water soluble drugs, such as complexation, pH adjustment, micronization, solid dispersion, hydrotropy, micellar solubilization, and salt formation [(2,3,4)]. The selection of a technique depends on various factors, including the properties of the drug, the characteristics of the chosen excipients, and the intended dosage form [(5)]. According to the biopharmaceutical Classification System(BCS), the rate limiting step for drugs belonging to class II and class IV is their release from the dosage which depends on their solubility in gastrointestinal fluid. Improving the solubility of these drugs enhances their bioavailability [(6)].

Bilastine (BLA) is 2-[4-[2-[1-(2-ethoxyethyl) benzimidazole-2-yl] piperidine-1-yl] ethyl] phenyl]-2- methylpropane acid, has the chemical formula $C_{28}H_{37}N_3O_3$ (Figure 1), It is a highly selective H1-receptor antagonist, is a modern second-generation antihistamine employed to manage symptoms of allergy. It belongs to BCS class II drug with an absolute oral bioavailability of 60.67 % [(7)] due to low solubility [(8)]. A previous trial was made to improve the solubility of BLA through the use of solid dispersion using Hydroxy Propyl Cellulose as a hydrophilic polymer by solvent evaporation method [(9)].

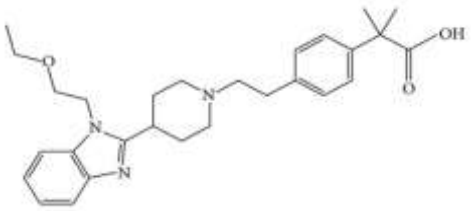

Figure 1 . Chemical structure of BLA [(8)]

Complexation with cyclodextrin is a technique that increases the apparent aqueous solubility of BCS class II and class IV drugs without decreasing their lipophilicity, so it can enhance their absorption through biological membranes [10]. Cyclodextrin (CD) can form an inclusion complex in which a drug molecule is included in a lipophilic cavity [10]. The three naturally occurring cyclodextrins are α-, β-, and γ-cyclodextrin consisting of six, seven , and eight glucopyranose units, respectively with different sizes of their cavity [11]. β-CD has been widely used in the early stages of pharmaceutical applications because of its availability and cavity size suitable for the widest range of drugs, but due to its low solubility, several higher solubility derivatives were synthesized including methyl beta cyclodextrin (M-β-CD), hydroxyl propyl beta cyclodextrin (HP-β-CD), and sulfobutyl ether beta cyclodextrin (SBE-β-CD) [12]. Cyclodextrin can fully or partially complex with large organic molecules by non-covalent interaction forces (hydrogen bond, Vander waals forces). Consequently, the physical and chemical properties of the included molecules may be modified, and the physical stability and the aqueous solubility can be improved [13]. It was reported that the solubility of norfloxacin was enhanced by employing inclusion complexation with HP-β-CD as a binary complex [14]. Moreover, it was observed that the solubilization efficacy of efavirenz can be enhanced by complexation with M-β-CD in the presence of PVP due to the formation of ternary complex [15].

The aims of this research are to improve the solubility and dissolution rate of BLA by cyclodextrin inclusion complex technique, using β-CD along with its derivatives such as HP-β-CD, M-β-CD, and SBE-β-CD. These derivatives were employed both individually and in combination with hydrophilic polymers to form binary and ternary complexes respectively. Diverse techniques were employed in the formation of these complexes.

Materials and Methods

Materials

Bilastine (BLA) was supplied by Hubei KDG Web Science & technology Co, Ltd, China. Beta cyclodextrin (β-CD) and cyclodextrin derivatives M-β-CD, HP-β-CD, and SBE-β-CD were purchased from Jinan research institute, Nankai University, China. Soluplus (Basf SE , Germany), poloxamer, PVP, HPMC E5 (Eastman chemical company,USA) All other analytical reagents were of analytical grade.

Method

Determination of BLA saturation solubility

An excess quantity of BLA was introduced into separated stoppered tubes, each containing 10 ml of DW, phosphate buffer pH 6.8, and 0.1 N HCl. Subsequently, these tubes were placed in a shaking water bath and incubated for 48 hours at 25 °C (DW) and 37 °C (phosphate buffer and HCl), then the samples were filtered using a filter syringe with 0.45µm pore size. The resulting filtrate after appropriate dilution, was analyzed for BLA using a UV visible spectrophotometer at λ max of BLA at 274 nm for DW and phosphate buffer and 278 nm for HCl. The study was done in triplicate [9].

Phase solubility study

Binary complex

The Higuchi and Connor method was employed to conduct a phase solubility analysis for a binary complex [16]. An excess quantity of BLA was introduced to 10 ml of water that already contained 2-10 mM of β-CD, HPβ-CD, Mβ-CD, or SBE-β-CD, separately. The tubes were placed in a water bath shaker with a controlled temperature of 25°C for 48 hours. The resulting mixtures were then filtered using a 0.45 µm filter syringe, and the filtrates were analyzed for the solubilized drug spectrophotometrically at λ max of 274 nm using suitable blanks with the same concentration of CDs. The molar ratio of the complex and its stability constant was determined by the following equation.

$$kc = \frac{slope}{S^{\circ}\,(1 - slope)}$$

Where S° is the intrinsic solubility of the drug, which refers to its solubility in an aqueous environment without the presence of CD, the Kc value is the stability constant of the complex, while the drug: CD molar ratio can be determined from the slope of the straight line obtained by plotting the molar concentration of BLA against the molar concentration of CD. A slope of less than one indicates the formation 1:1 molar ratio, while if the slope exceeds 1 indicates the formation of higher order complexes [17].

Ternary complex

To assess the impact of incorporating hydrophilic polymer on the formation of inclusion complexes, an additional phase solubility diagram was constructed by introducing an excess amount of BLA to 10 ml of aqueous solutions with increasing concentrations of the chosen cyclodextrin (2-10 mM) in presence of (0.25% w/v) of either soluplus®, HPMC E5, PVP k90, or poloxamer 407 [18].

Preparation of inclusion complex (IC)

The inclusion complex was prepared using different methods as shown in Table (1)

Kneading method

The IC was prepared by mixing one mole of BLA with one mole of the chosen CD with varying concentrations of selected polymer (0, 5, 10, 15% w/w from the total weight of complex) for five minutes, then water: ethanol mixture (1:1 v/v), was added drop by drop until the mixture transformed into a thick consistency that was kneaded for approximately 30 minutes. The resulting paste was dried in an oven at 50 °C for 24 hours. The dried

mass was pulverized and passed through a sieve with a mesh size no .60 and stored in airtight containers till further use [19].

Solvent evaporation method

A mixture containing one mole of the selected CD along with varying concentrations of the selected hydrophilic polymer (0,5,10,15 % w/w from the total weight of the complex) was prepared in water and added to ethanolic solution containing one mole of BLA with continuous stirring using a magnetic stirrer for one hour. The resulting suspension was dried in an oven at 40 °C for 24 hours. The dried mass was pulverized and sieved through sieve no.60 and stored for future investigation [18].

Microwave irradiation method (MWI)

In this method, one mole of BLA with one mole of the selected CD, and selected polymer in a concentration (0,5,10,15 % w/w from the total weight of the complex) were mixed. This mixture was then suspended in a solution of water and ethanol in a 1:1 volume ratio. The suspension was then subjected to MWI in a domestic microwave oven, operating at 450W power, for 120 seconds. The resulting product was cleansed by rinsing with a solvent mixture of water and ethanol to eliminate any remaining components. The product was then allowed to air dry, pulverized sieved by sieve no .60 and stored for further study [20].

Co- Grinding

One mole of selected CD and one mole of BLA along with varying concentrations of the selected polymer (0,5, 10, 15 % w/w from the total weight of the complex) were mixed for 45 minutes using mortar and pestle to achieve uniform blending, the resulting blend was passed through sieve no. 60. Then the product was stored for further study [21].

Physical mixture

A homogenous mixture was prepared by blending the drug with the selected CD and the selected polymer in a porcelain mortar for a few minutes. Subsequently, the mixture was sieved through a no. 60 sieve and suitably stored for further study [22].

Tables 1. Composition and preparation methods of BLA- ICs

Formula code	Method of preparation	Composition
K0	Kneading	BLA + selected CD
K5		BLA + selected CD + 5% w/w selected polymer
K10		BLA + selected CD + 10% w/w selected polymer
K15		BLA + selected CD + 15% w/w selected polymer
SE 0	Solvent evaporation	BLA + selected CD
SE 5		BLA + selected CD + 5% w/w selected polymer
SE 10		BLA + selected CD + 10% w/w selected polymer
SE15		BLA + selected CD + 15% w/w selected polymer
G0	Co-grinding	BLA + selected CD
G 5		BLA + selected CD + 5% w/w selected polymer
G 10		BLA + selected CD + 10% w/w selected polymer
G 15		BLA + selected CD + 15%w/w selected polymer
MWI 0	Microwave irradiation	BLA + selected CD
MWI 5		BLA + selected CD + 5% w/w selected polymer
MWI 10		BLA + selected CD + 10% w/w selected polymer
MWI 15		BLA + selected CD + 15% w/w selected polymer

Evaluation of inclusion complex

Determination of percentage yield (PY %)

The percentage yield was determined by dividing the actual weight of the obtained product by the theoretical weight of the initial components (drug, CD, and polymer) introduced into the system. The calculation of the percentage yield was performed using the equation below [23].

$$\%Yield = \frac{Actual\ weight\ of\ IC\ gained}{Theoretical\ weight\ of\ ICs\ components} \times 100$$

Determination of drug content

Accurately weighing complex equivalent to 10 mg of BLA was added to 50 ml of ethanol with stirring for 30 minutes by a magnetic stirrer. Then, 1 ml of the resulting solution was taken and suitably diluted with ethanol. The drug content was then spectrophotometrically assessed at the λ max 276 nm [9].

Determination of saturation solubility

The saturation solubility was determined by adding an excess amount of the prepared ICs separately into 10 ml of phosphate buffer pH 6.8 and 10 ml of DW [9]. The same procedure was continued as that mentioned for the determination of the saturated solubility of pure BLA.

In-vitro dissolution studies

A dissolution study was conducted using the USP type II dissolution test apparatus, in which an IC equivalent to 10 mg of the drug was utilized. The experiment was carried out at a temperature of 37 ± 0.5° C in 900 ml phosphate buffer (pH of 6.8) at 50 rpm. Samples (5ml) were withdrawn and replaced with fresh buffer periodically, filtered by a filter syringe with a pore size of 0.45µm. The concentration of the dissolved drug was measured using UV spectrophotometer at λ max 274[9]. To assess the dissolution profiles, a comparison was made between the resulting profiles of the inclusion complexes and that of the pure drug using the similarity factor *f*2 as in the following equation:

$$f2 = 50 \cdot \log\left\{100 \cdot \left[1 + \frac{1}{n}\sum_{t=1}^{n}(Rt - Tt)^2\right]^{-0.5}\right\}$$

Where (n) is the number of dissolution time points . (Rt) and (Tt) is the reference and test dissolution values at time t.

The two dissolution profiles cosidir similar when *f*2 values are higher than 50, otherwise, the profiles are not similar [24] .

Selection of the best complex

The complex of selected CD with high drug content, highest solubility, and fastest dissolution rate was selected for further study .

Characterization of the best complex

Fourier transform infrared (FTIR)

FTIR (FTIR- 8300 Shimadzu, Japan) was used to confirm the formation of the complex. The analyzed samples were pure BLA, selected CD, selected polymer, selected complex and its PM. The samples were compressed with potassium bromide and pressed it into a thin film disc. Spectral scanning was conducted in the range of 400-4000 cm^{-1} [25].

X-ray powder diffraction (XRD)

An X- ray diffractometer (XRD-2700 Haoyuan / China) was employed to assess the crystallinity of pure BLA, selected CD, selected polymer, selected complex, and its PM. The assessment was conducted using powder X-ray diffraction with a continuous scanning range at 2θ of 5-80 °, the operating voltage and current were 40-60 KV high tension voltage and 20-40 mA electrical current [26].

Statistical analysis

The results were analyzed by SPSS version 25 using one –way variance analysis (ANOVA) and t- test, with a significance level set at a P-value of 0.05.

A p -value > 0.05 was considered to be non – significant, whereas those with p- value < 0.05 was regarded as significant.

Results and Discussion

Saturation solubility of BLA

The saturated solubility of BLA was found to be 0.329 mg / ml in DW and 0.518 mg/ ml in phosphate buffer pH 6.8, indicating that the drug is very slightly soluble in both media. However, its solubility in 0.1 N HCl was 60.5 mg / ml indicating that the drug is soluble. These results agreed with previously documented values [8]. Therefore, the study was directed to enhance the solubility of BLA in DW and phosphate buffer pH 6.8 as a preliminary study for preparing the drug as a buccal dosage form.

Phase solubility study

Binary complex

The solubility of BLA exhibits a linear increase as the molar concentration of CD increases (Figure 2). This suggests a good correlation between the solubility and CD concentration (high R^2 value), with a slope of less than 1 for all CD types indicating the formation of a 1:1 molar ratio of drug: CD complex.

The stability constants for the complexes formed between BLA and various cyclodextrins, namely β-CD, HP-β- CD, M-β-CD, and SBE-β-CD, were determined to be 229, 72, 212, and 126 M^{-1}, respectively. Notably, all these stability constants fall within the range of 50 to 5000, which are considered suitable for the formation of stable and soluble complexes [27]. These results were in line with a previous study, where fenofibrate forms a stable complex with HP-β-CD with a stability constant of 630.0006 M^{-1} with enhanced dissolution [28].

Although both β-CD and M-β-CD showed convergent and highest stability constants values than others, however, M-β-CD was selected as the host molecule due to its greater solubility in aqueous solutions at room temperature (500 mg /ml) in comparison with β-CD (18.5mg/ml) so it is more suitable and applicable to be used in the formulation process [29].

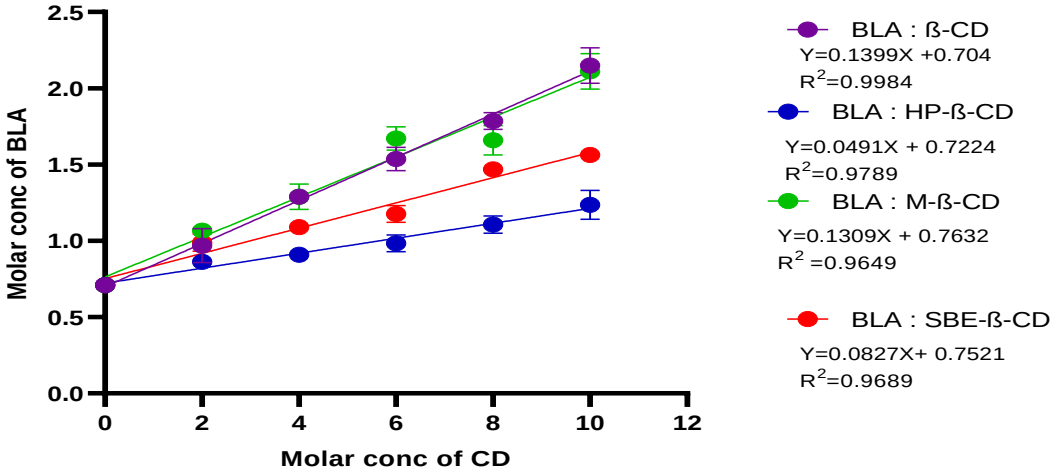

Figure 2. Phase solubility diagram of the binary complex of BLA with different types of CD at 25 °C in water

Ternary complex

The incorporation of water - soluble polymers (HPMC E 5, PVP K90, poloxamer 407, and soluplus ®) into the aqueous complexation solution affects the solubility of BLA (Figure 3). HPMC E 5, and PVP K 90 decreased the solubility of BLA, poloxamer 407 did not show a notable effect, whereas soluplus® had an enhancing effect. These findings were consistent with those obtained by Lula *etal* who found that various polymers had varying effects on the solubility of daidzein/cyclodextrin. These effects might be attributed to the conformational structure, degree of polymerization, and type of functional groups of the hydrophilic polymers [30, 31]. Utilization of soluplus® in conjunction with BLA and M-β-CD led to a notable enhancement in solubility compared with binary system with increased the stability constant from 212 to 433 M^{-1}, which ensured the formation of a more stable complex. The rationale for this could be related to cyclodextrin complexes, which can form aggregates that can solubilize hydrophobic drugs. Polymers can stabilize various types of aggregates, leading to a reduction in CD mobility and an enhancement in the solubility of these complexes. This is achieved by modifying the hydration properties of the CD molecules [30]. A Previous study reported that the solubility of atorvastatine calcium trihydrate was significantly increased by complexation with SBE-β-CD in the presence of soluplus® [22]. Therefore, soluplus® was the selected polymer for the preparation of the ICs.

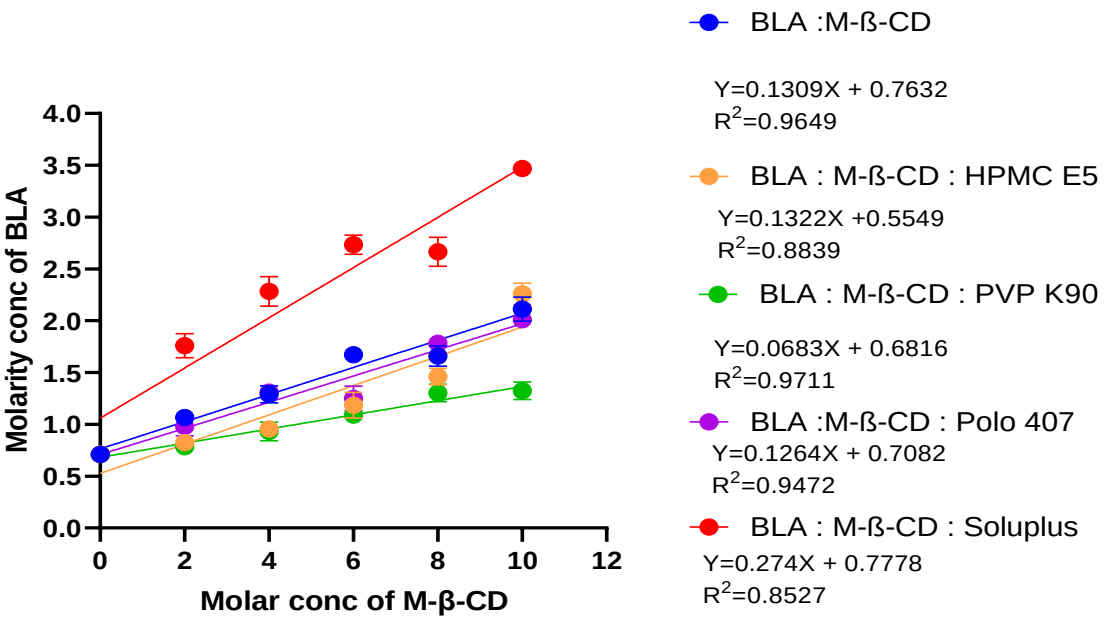

Figure 3. Phase solubility diagram of the ternary complex of BLA with different types of polymer at 25 °C

Evaluation of inclusion complex

Determination of percent practical yield

Table (2) displays the percentage yield of the complexes. High percentage yields were obtained using various methods. The yields values were ranging from 87 to 96 % depending on the preparation method. These high values indicate the efficiency of all these methods.

Determination of drug content

Table (2) shows, the drug content of the complexes ranged from 94.9 – 110 %, which aligns with the (USP) standards of an acceptable range (90 – 110 %), indicating that the drug was distributed uniformly and there was negligible loss of drug during the preparation.

Determination of saturation solubility

As shown in Table (2). All ICs had significantly ($P < 0.05$) enhanced the saturated solubility of the drug. In the binary system, the solubility of BLA was significantly ($P< 0.05$) increased, irrespective of the preparation method, mainly due to the formation of inclusion complex with M-β-CD [14].

In the ternary system, the presence of hydrophilic polymer significantly ($P<0.05$) improved the solubility of BLA compared to the binary system. This improvement can be attributed to soluplus®, which reduces the mobility of CD and enhances the solubility of these complexes in addition to its hydrophilic nature which improves the wettability [30].

All the preparation methods could increase the solubility of BLA but to different extent. Solvent evaporation and kneading methods produce the highest solubility.

IC prepared with 5%w/w soluplus® via solvent evaporation and kneading methods exhibit significantly ($P< 0.05$) higher solubility than ICs prepared with 10% w/w and 15 % w/w soluplus®, indicating that the solubility was not enhanced by the high polymer content. This result was in agreement with a previous study, that found no further enhancement in the solubility of dexibuprofen was obtained even when polymer concentration increased [32].

Table 2. Saturation solubility, percentage yield, and drug content of ICs

Formula	Method of preparation	Percentage Yield	Drug content (w/w) (%) Mean± SD (n=3)	Saturation Solubility mg/ ml in buffer 6.8 Mean ± SD (n=3) at 37°C	Saturation Solubility mg/ ml in DW Mean ±SD (n=3) at 25°C
Pure BLA	----------	----------	----------	0.518 ± 0.006	0.329 ± 0.024
K 0	Kneading	91.15	99.55 ± 0.022	2.333$^{*\bar{\alpha}}$ ± 0.017	1.274 $^{*\bar{\alpha}}$±0.053
K 5		91.7	99.7 ± 0.024	5.37 $^{\bar{\alpha}}$± 0.021	3.174 $^{\bar{\alpha}}$ ± 0.0989
K 10		87.7	110 ± 0.088	3.56 $^{\bar{\alpha}}$ ± 0.095	2.775± 0.0147
K 15		96.3	98.6 ± 0.02	3.258 $^{\bar{\alpha}}$ ± 0.649	2.8 ± 0.0703
SE 0	Solvent evaporation	95	97.7± 0.004	2.311$^{*\bar{\alpha}}$ ± 0.433	1.352 $^{*\bar{\alpha}}$ ± 0.0288
SE 5		89.3	100.3 ± 0.017	5.672 $^{\bar{\alpha}}$ ± 0.272	3.682 $^{\bar{\alpha}}$ ± 0.0105
SE 10		91.5	105.5 ± 0.013	3.570 $^{\bar{\alpha}}$ ± 0.167	2.630 $^{\bar{\alpha}}$ ± 0.0926
SE 15		91.6	94.98 ± 0.007	3.49 $^{\bar{\alpha}}$ ± 0.056	2.987 $^{\bar{\alpha}}$ ± 0.0535
G 0	Co-grinding	92.8	103 ± 0.002	1.32 $^{*\bar{\alpha}}$ ± 0.017	1.209 $^{*\bar{\alpha}}$ ± 0.0228
G 5		95	101.5 ± 0.019	2.85 $^{\bar{\alpha}}$ ± 0.085	2.329 $^{\bar{\alpha}}$± 0.085
G 10		92.7	97.2 ± 0.01	2.82 $^{\bar{\alpha}}$ ± 0.076	2.280 $^{\bar{\alpha}}$ ±0.009
G 15		89.6	99.4 ± 0.004	2.583 $^{\bar{\alpha}}$ ±0.008	2.274 $^{\bar{\alpha}}$ ± 0.826
MWI 0	Microwave	92.3	99.5 ± 0.005	1.16 $^{*\bar{\alpha}}$ ± 0.034	1.033 $^{*\bar{\alpha}}$ ± 0.019
MWI 5		90.14	101.7 ± 0.004	2.81$^{\bar{\alpha}}$ ± 0.038	2.247$^{\bar{\alpha}}$ ± 0.0034
MWI 10		93.8	100.4 ± 0.007	2.618 $^{\bar{\alpha}}$ ± 0.181	2.233 $^{\bar{\alpha}}$ ± 0.004
MWI 15		90.3	99.1 ± 0.003	2.43 $^{\bar{\alpha}}$ ± 0.027	2.156 $^{\bar{\alpha}}$ ± 2.156

Note: *= significant differences with pure drug, and $\bar{\alpha}$ = significant differences between binary and ternary system.

In – vitro dissolution study

This study aimed to investigate the impact of complex formation, soluplus® concentration, and preparation method on drug release. Complexes prepared by solvent evaporation and kneading methods only were subjected to this study as they have the highest solubility compared to the others.

The dissolution rate of pure BLA was below 40% in the first 15 min because of its low aqueous solubility, while more than 75 % drug release was observed in a binary system, the result revealed that the formation of inclusion complex significantly improved BLA dissolution [14]. As illustrated in Figures (4 and 5) and $f2$ values in Table (3). On the

other hand, the dissolution profiles of the ICs containing 5%, 10 %, and 15 % w/w of soluplus® prepared by either kneading or solvent evaporation methods were similar to each other with high release rate of more than 90% in the first 15 min. These are expected results according to the Noyes- Whitney equation, as this complex in presence of soluplus® enhanced the solubility of a drug [33]. A Similar finding was obtained by Mane P, wherein the docetaxel-ternary cyclodextrin complex improved the solubility and dissolution of docetaxel in comparison to the binary complex [34]. From the above results, 5% w/w soluplus® was the selected concentration, due to its highest solubility enhancing effect. In addition, the release profiles of K5 and SE5 are considered similar as they release more than 85% within 15 minutes [24]. Furthermore, these two methods can be considered efficient methods for preparing the ICs as they enhance the dissolution of the BLA in comparison with the PM of the complex components as shown in Figure (6).

Table 3. The similarity (*f*2 value) among the ICs formula

Formula	*f2*	Method
Pure drug + K0	13.3	Kneading
Pure drug + K5	14.1	
Pure drug + K10	16.9	
Pure drug + K15	15.2	
K5 + k10	58.2	
K5 + k15	70.8	
K5 + k0	42.8	
K5 + PM	22.3	
Pure drug + SE 0	20.6	Solvent evaporation
Pure drug + SE5	15.3	
Pure drug + SE10	18.1	
Pure drug + SE15	15	
SE5+ SE 10	59.2	
SE 5 + SE 15	68.4	
SE 5 + SE 0	47.2	
SE 5 + PM	25.9	

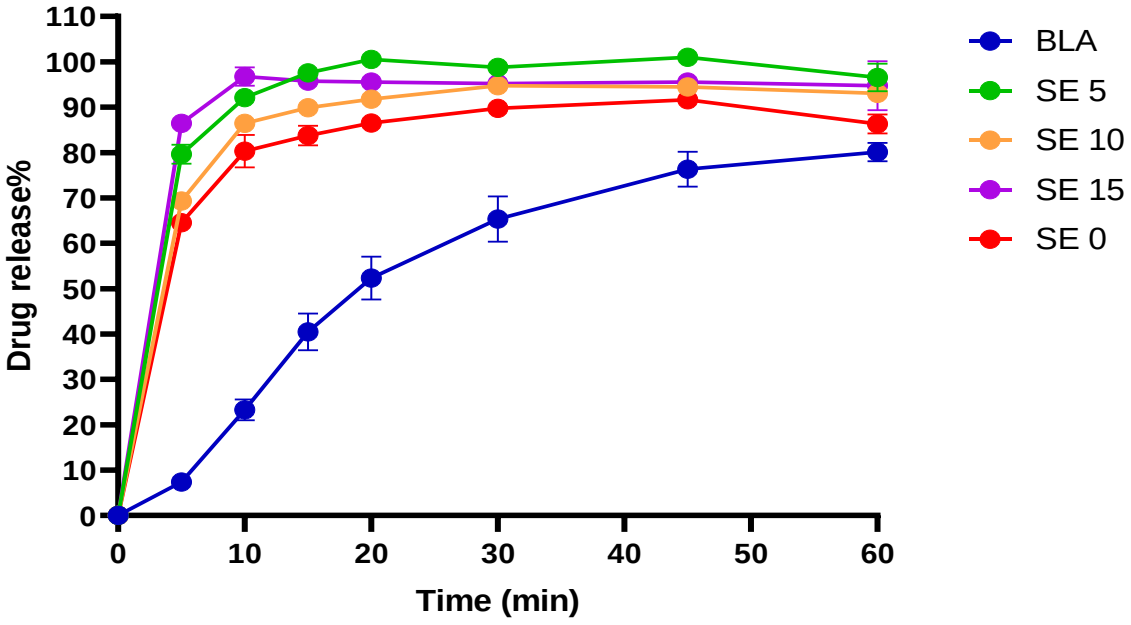

Figure 4. Dissolution profile of BLA ternary complex prepared by solvent evaporation method with different concentrations of soluplus® in phosphate buffer pH 6.8 at 37 °C

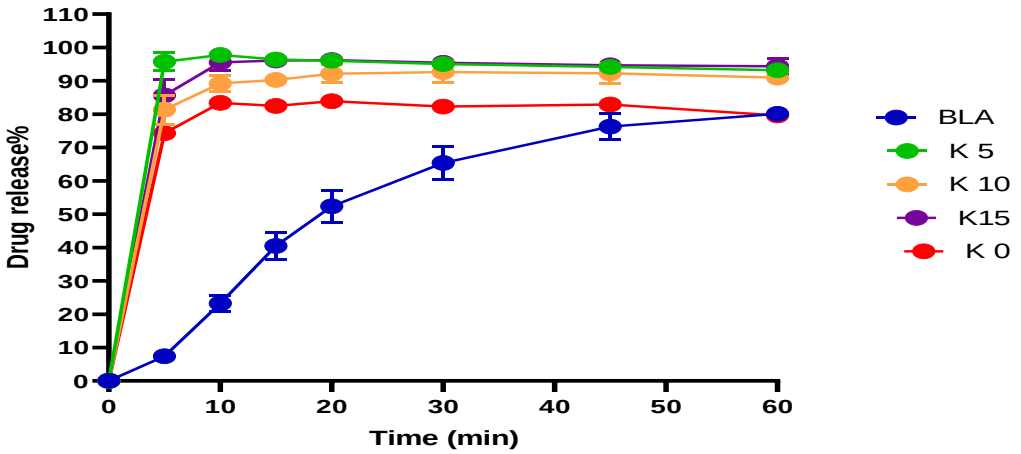

Figure 5. Dissolution profile of BLA-complex prepared by kneading method with different concentrations of soluplus® in phosphate buffer pH 6.8 at 37°C

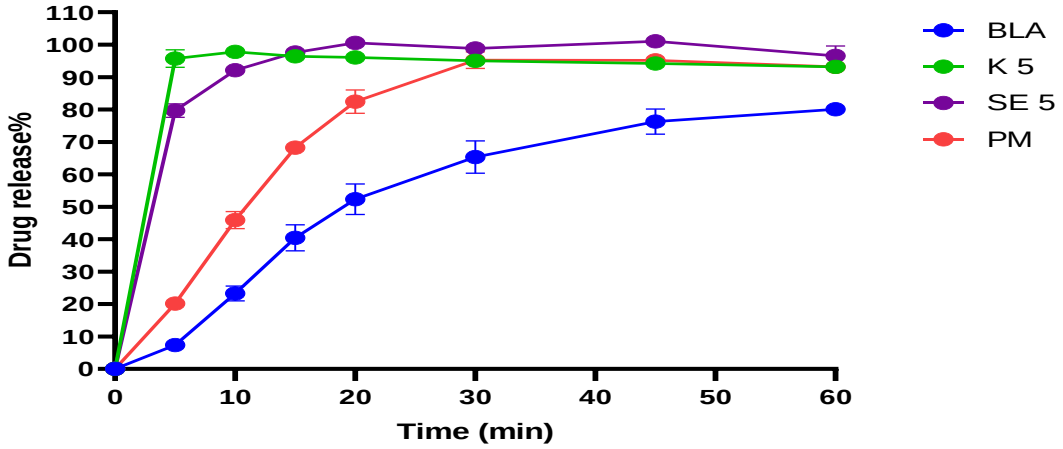

Figure 6. Effect of preparation method on the dissolution profile of BLA-Mβ-CD-5%w/w of soluplus® in phosphate buffer pH 6.8 at 37°C

Selection of the best complex

The SE 5 complex was selected as the best complex due to its high percentage yield, highest solubility, and fastest in vitro dissolution so it was subjected to further studies.

Fourier transform infrared (FTIR)

The FTIR absorption spectra for BLA, M-β-CD, soluplus®, SE 5, and its PM are presented in Figure (7). Bilastine showed its typical broad peak for free hydroxyl O-H stretching at 3416 cm^{-1}, C-H stretching for aliphatic and unstrained cyclic ring at 2928 and 2855 cm^{-1}, intense C=O stretching peak at 1665 cm^{-1}, aromatic amines display strong C-N stretching at 1326 cm^{-1} C-O stretching strong bands at about 1119 cm^{-1}, C=C in aromatic ring stretching at 1508 cm^{-1}. These results were in agreement with previous studies [8].

The FTIR spectrum of M-β-CD shows O-H stretching at 3389 cm^{-1}, C-H asymmetric and symmetric stretching at 2926 cm^{-1}, aliphatic ether (C-O-C ether bond) strong bond at 1156 cm^{-1}. These results were in accordance with previous documented results [35].

In addition, the FTIR spectrum for soluplus® displays the characteristic peak of a hydroxyl group at 3457 cm^{-1}, a symmetric and symmetric C-H stretching around 2924 and 2858 cm^{-1}, the intense C=O stretching of ester carbonyl at higher frequencies at 1732 cm^{-1}, C-O-C stretching of ester, consist of two a symmetrical coupled vibration, these bands occur at 1234 and 1103 cm^{-1} which agreed with previous studies [36].

The FTIR spectrum of the PM demonstrates the absence of the drug's O-H stretching band, possibly concealed by the O-H stretching of M-β-CD. Several BLA bands, including the C=C stretching peak at 1508 cm^{-1} and the C=O stretch at 1665 cm^{-1}, have shifted to lower wavelengths (1456 cm^{-1} and 1647 cm^{-1} respectively). These shifts suggest the presence of interaction even within the PM.

Furthermore, certain BLA peaks exhibit reduced intensity, likely due to dilution resulting from the mixing process.

On the other hand, the FTIR spectrum of the SE 5, demonstrates absence of the most characteristic peaks (3416, 2928, 2855 cm^{-1}) of the drug which may be due to the complete inclusion of BLA into the M-β-CD cavity.

The absorption bands of soluplus® do not appear in both PM and SE 5 spectra, possibly due to its extremely low concentration.

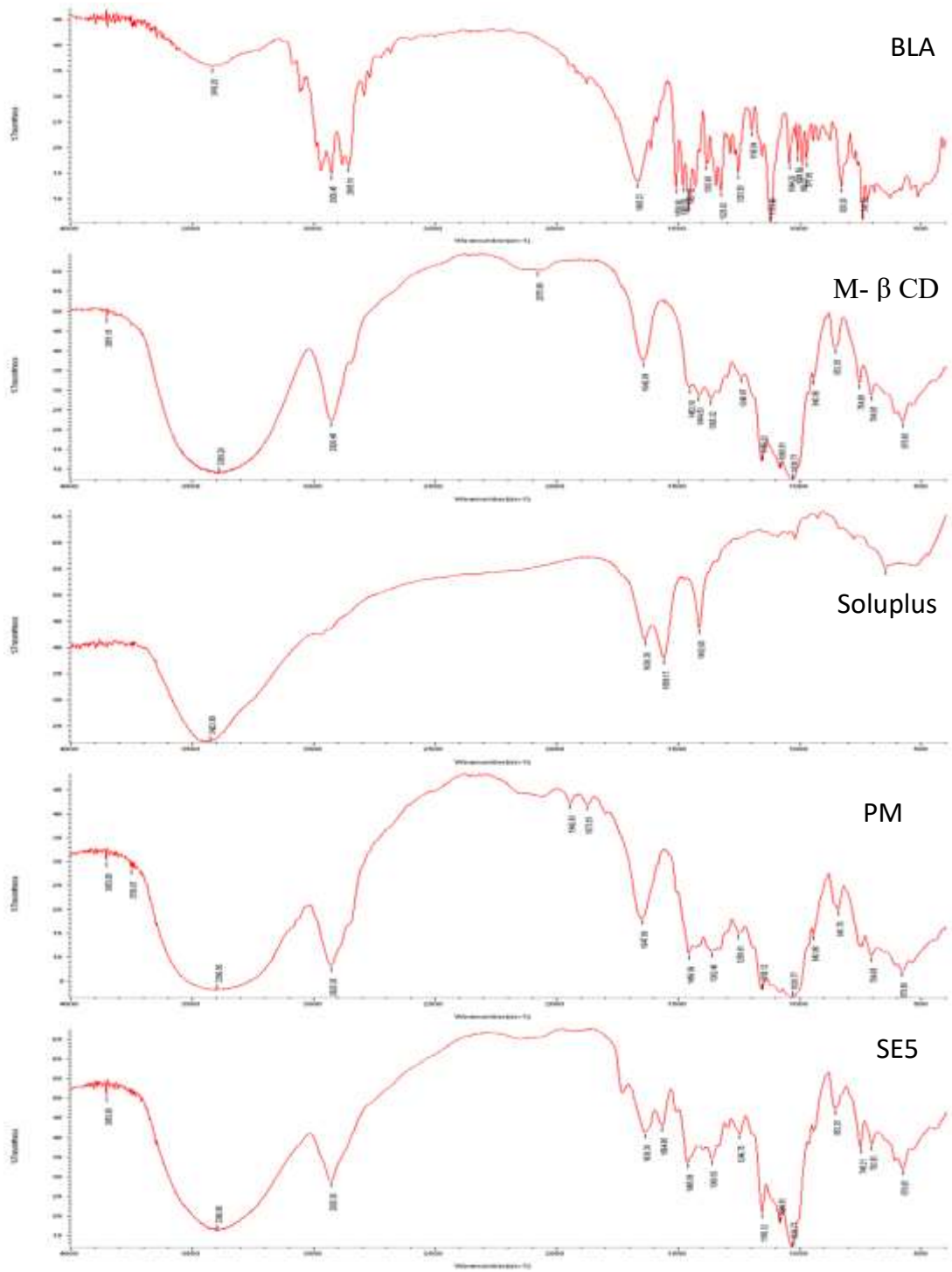

Figure7. FTIR spectrum of BLA, M-β-CD, soluplus ®, PM and SE 5

X-ray powder diffraction (XRD)

The X-ray diffractograms of pure BLA, soluplus, M-β-CD, PM, and SE 5 are shown in Figure (8).

The X-ray diffraction pattern of pure BLA powder indicated its crystalline nature, as evidenced by the presence of distinct peaks, at (2θ) 11.184°, 12.424°, 13.997°, 16.175°, 17.102°, 19.757°, 21.062°, 22.640, 24.883°, 29.019° resembling the documented values [8]. The X-ray diffraction pattern of both M-β-CD [37] and soluplus® exhibit broad, hollow peaks, confirming their amorphous forms. The diffraction patterns of PM exhibited typical BLA peaks with reduced intensity, primarily attributed to the dilution effect. On the other hand, the diffraction pattern of SE 5 demonstrated a more significant decrease in crystallinity compared to pure BLA and PM, as indicated by the complete disappearance of the intense BLA peaks with the possibility of formation of an amorphous inclusion complex.

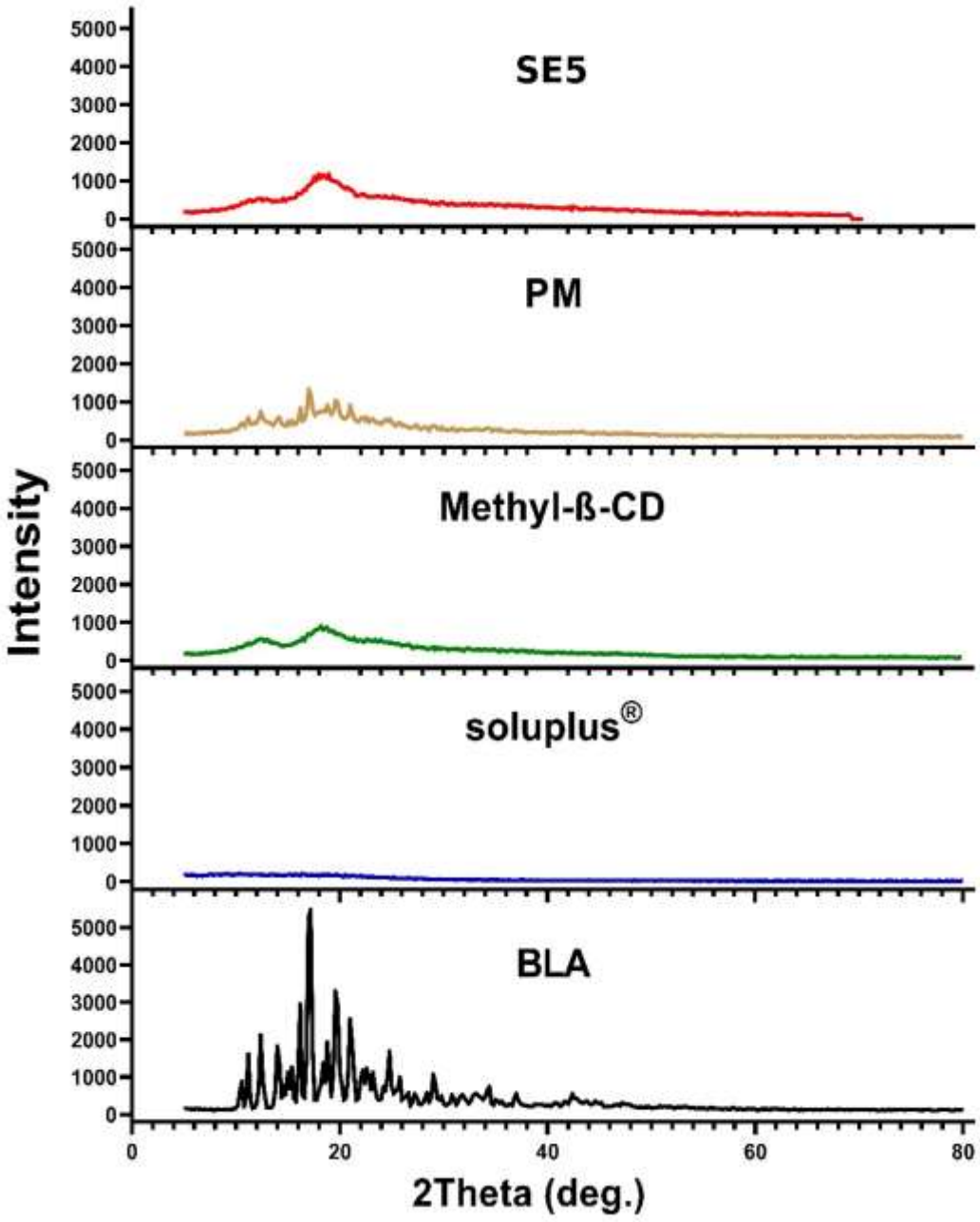

Figure 8. XRD diffractograms of BLA , Soluplus ® , M- β -CD , PM , and SE 5

Conclusion

The results suggested that the solubility and dissolution of BLA can be enhanced by preparing a complex with M-β-CD at 1:1 molar ratio which was further improved by the addition of 5%w/w of soluplus® as hydrophilic polymer using solvent evaporation method.

Characterization studies suggested a complete inclusion of BLA in the M-β-CD cavity with decreased crystallinity.

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Conflicts of Interest

None

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Ethics Statements

The research is an in vitro study so it does not require ethical approval from an ethics committee

Author Contribution

The authors confirm their contribution to the paper as follows: study conception and design: Eman B. H. Al-khedairy, data collection: Sura Salam Hatam. Both authors participate in writing, reviewing and approved the final version of the manuscript.

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تصييغ وتقيم بيلاستين- سايكلودكسترين كمعقد ضمني ثلاثي

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الخلاصة

البيلاستين هو دواء من الجيل الثاني لمضادات التحسس يستخدم لعلاج الاعراض المرتبطة بالتحسس .لكنه ضئيل الذوبان في الماء ذو توافر حيوي ضعيف ، مما يؤثر على فعاليته العلاجية. كان الهدف الأساسي من هذه الدراسة هو تعزيز قابلية الذوبان وسرعة التحرر للبيلاستين عن طريق تكوين معقد ذائب بأستخدام بيتا سايكلودكسترين ومشتقاتها مثل هيدروكسي بروبيل بيتا سايكلودكسترين ، ميثيل بيتا سايكلودكسترين ، وسلفوبيوتيل ايثر بيتا سايكلودكسترين كمعقد ثنائي وثلاثي مع أنواع مختلفة من المواد المحبة للماء مثل بولي فاينيل بيرليدون ، هيدروكسي بروبيل ميثيل سلولوز ، بولوكزامير ، و سوليوبلص ، تم تحضير هذه المعقدات بأستخدام طرق العجن والطحن ، تبخير المذيب ، طريقة الطحن المشترك وطريقة التشعيع بالميكروويف . وقد تم توصيف المعقد المحضر من حيث نسبة الإنتاج ومحتوى الدواء وقابلية الذوبان وسرعه تحرر الدواء، اما المعقد المختار فقد تم توصيفه بواسطة حيود الاشعة السينية والتحليل الطيفي بالاشعة تحت الحمراء.أظهرت النتائج ان المعقد الثلاثي المتكون من ١ مول بيلاستين / ١ مول ميثيل بيتا سايكلو دكسترين / ٥٪ وزن : وزن سولبلص المحضر بطريقه تبخير المذيب ، زيادة بالذوبانية حوالي احد عشر مره في الماء و في محلول بفر ذو اس هيدروجيني ٦,٨ ومعدل اطلاق سريع اكثر من ٩٠٪ في اول ١٥ دقيقة ونسبة إنتاجية عالية (٨٩,٣٪) و محتوى دواء(١٠٠٪) . كما أظهرت نتائج التحليل بالاشعة تحت الحمراء ان البيلاستين قد تم تضمينه في تجويف المثيل بيتا سايكلودكسترين ، اما حيود الاشعة السينية فقد اظهر الطبيعة الغير المتبلوره للمعقد الناتج . لذلك يمكن الاستنتاج ان تحسين ذوبانية وتحرر البيلاستين ممكن ان تتحقق بأستخدام المعقد الضمني الثلاثي .

الكلمات المفتاحية : بيلاستين ،المعقد الضمني، سايكلودكسترينات ، ميثيل بيتا سايكلودكسترين ، سولبلص