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Formulation and characterization of bilastine - cyclodextrin inclusion complex loaded as an oral fast dissolving film

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ABSTRACT: Oral fast dissolving films (OFDFs) are the most innovative oral solid pharmaceutical dosage form, especially for elderly and pediatric patients who may have dysphagia. Bilastine (BLA), is a second – generation antihistamine used to manage allergy symptoms; it is very slightly soluble in water. The main objective of this research was to enhance the solubility and dissolution rate of BLA by complexation technique. Ternary complex of BLA: methyl β- cyclodextrin (M-β-CD): soluplus® 5% w/w was prepared via solvent evaporation technique as a trial to enhance its solubility to be prepared as OFDF by incorporated into aqueous polymeric solution. Seven formulas of OFDFs were prepared using the solvent casting method using Polyvinyl alcohol, Hydroxy propyl methyl cellulose E5, and Pullulan as polymers that form film, PEG 400, and glycerin as plasticizers. The prepared films were estimated for their physical, and mechanical properties, drug content, and dissolution rate. The results showed that,the prepared complex enhanced the solubility of the BLA in water (11 times more than the pure BLA in distilled water) and it was easily utilized for the preparation of the OFDFs. The PVA-based formulation in the presence of glycerin as a plasticizer (F4), showed a homogenous clear film with accepted folding endurance (300), the shortest disintegration time (16.66 seconds), and complete release within five minutes. In conclusion, complexation of BLA with M-β CD was an efficient method for enhancing its solubility and dissolution rate to be easily prepared as OFDF with acceptable physical properties.

KEYWORDS: Bilastine; Cyclodextrin-complex; Methyl-β-cyclodextrin; oral fast- dissolving films; ternary complex.

1. INTRODUCTION

The oral solid dosage forms are known for their self- administration and accurate dosing. However, they sometimes demonstrate challenges, including little bioavailability, needing time to start their action, and dysphagia, especially among pediatric and geriatric patients. Among the various systems for delivering drugs, are orodispersible tablets and oral fast- dissolving films (OFDFs) have been demonstrated as popular options to solve these problems [1,2].

In addition, OFDFs provide the advantage of rapid disintegration and dissolution upon contact with the tongue without the need for chewing or additional liquids, except for normal saliva [3].

The OFDF is preferred over orodispersible tablets as it is flexible with larger surface area that gives greater dissolution. The preparation of the oral fast- dissolving film, required the drug to be soluble in aqueous solvents to get a clear homogenous film accepted by patient. Therefore, the solubility of the drug is one of the challenges that should be considered in the preparation of this dosage form [4].

Bilastine (BLA) is 2-[4-[2-[1-(2-ethoxyethyl) benzimidazole-2-yl]piperidine-1-yl]ethyl]phenyl]-2-methyl propane acid, has the chemical formula $C_{28}H_{37}N_3O_3$ (Figure 1). It is a modern-second-generation antihistamine employed to manage symptoms associated with allergic rhino conjunctivitis and urticaria. It belongs to Biopharmaceutical Classification System (BCS) class II with an absolute oral bioavailability of 60.67 % due to its low solubility [5,6].

Complexation with cyclodextrin is a technique that improves the apparent solubility of class II drugs in the aqueous environment without decreasing their lipophilicity, so it can enhance their absorption through biological membranes [7, 8].

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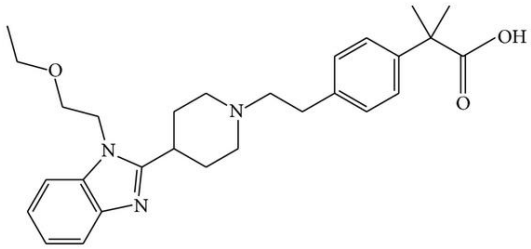


Figure 1 . Chemical structure of BLA [6]

Different derivatives of cyclodextrins were synthesized from the naturally occurring β cyclodextrin to improve its solubility, including methyl beta cyclodextrin (M-β-CD), hydroxyl propyl beta cyclodextrin (HP-β-CD), and sulfobutyl ether beta cyclodextrin (SBE-β-CD) with higher solubility [9].

This study aimed to prepare and characterize the BLA-cyclodextrin complex for the preparation of the oral fast-dissolving film.

2. RESULTS

2.1. Evaluation of BLA-cyclodextrin complex

The prepared complex, resulted in a high percentage yield of approximately 89.3%, suggesting the effectiveness of this method, and 100% drug content, indicating negligible loss of drug during the preparation. Notably, the ternary complex significantly ($P< 0.05$) enhances the solubility (3.682 mg / ml in DW) compared to the pure drug (0.329 mg/ ml). Moreover, it exhibits the complete release, reaching 100% within 5 minutes in comparison to 17.7 % obtained from the pure BLA. As illustrated in Figure (2).

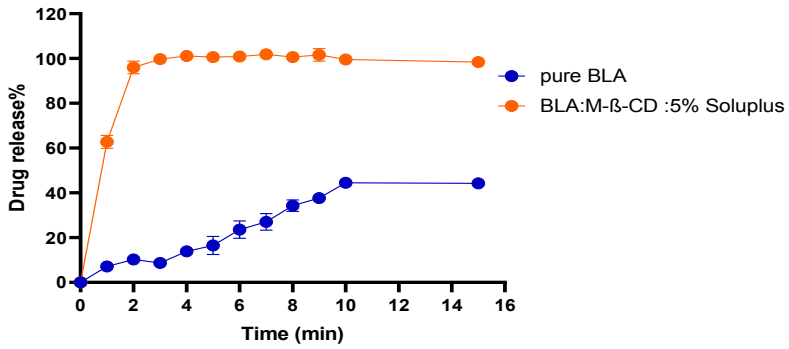


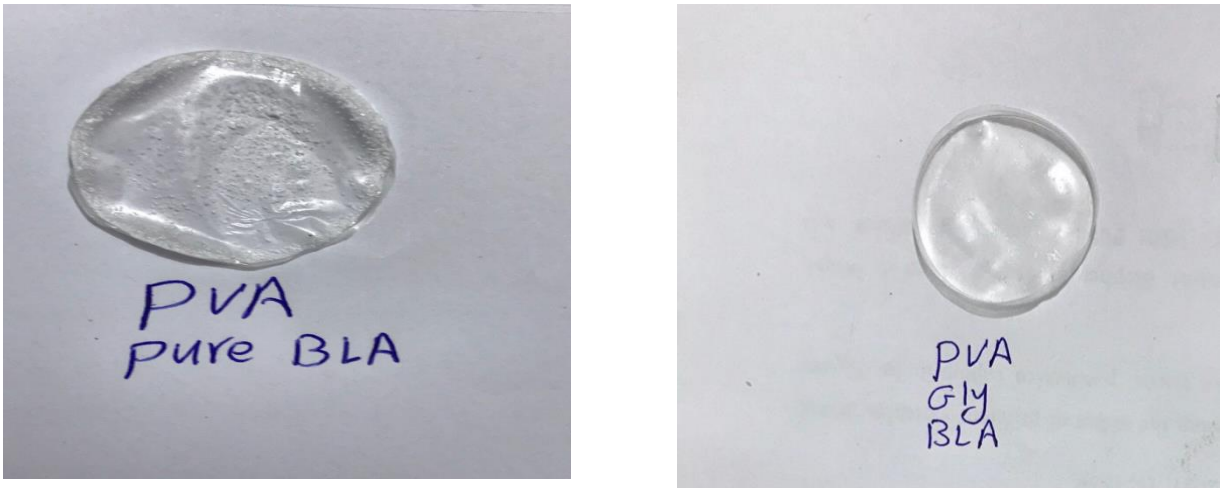
Figure 2: *In- vitro* dissolution profile of pure BLA and BLA: M-β-CD: 5% soluplus complex in phosphate buffer (pH 6.8) at 37°C

2.2. Evaluation of the OFDFS

2.2.1. Appearance and surface texture

The OFDF prepared with pullulan (F1) was observed to exhibit an unsatisfactory texture, as they immediately fractured when removed from the Petri dish. Similarly, films produced with Hydroxy propyl methyl cellulose E5 (HPMC E5) (F2) and a combination of HPMC E5 and Polyvinyl alcohol (PVA) (F3) appear unsuitable for use as they are sticky.

In contrast, formulations F4, F5, F6, and F7, which contained PVA, exhibited a smooth, uniform, transparent, colorless, and soft surface, while that containing pure drug was non-homogenous, as illustrated in Figure 3.



A B

Figure 3. Photograph of oral fast-dissolving film. (A) loaded with pure BLA and (B) loaded with BLA: M-β-CD: 5% Soluplus complex

2.2.2. Thickness

As indicated in Table (1), it can be observed that the average thickness of the prepared OFDFs is in a range of (0.023±0.015) to (0.076±0.0057) mm within the accepted limit.

2.2.3. Weight variation

The average weights of OFDFs are shown in Table 1. They were uniform, passed the weight variation test with small ± SD.

2.2.4. Drug content

The formulated films (F4, F5, F6, F7) exhibited practically and acceptable drug content (87-99 %).

Folding endurance

Folding endurance was found between 270 and 302 times.

2.2.5. Surface pH determination

Each of the formulated films exhibited an acceptable pH range (6.6-6.9), as indicated in Table (1).

2.2.6. In-vitro disintegration time

The time for disintegration of OFDFs, ranges from 13.33 to 28.66 seconds, as illustrated in Table 1.

Table 1. Some physicochemical properties of the prepared oral films of BLA

Formula code	Weight (mg) ± SD	Drug content± SD	Thickness (mm)	Folding endurance	Disintegration time (sec) ± SD	pH
F4	98.33 ± 4.04	9.9 ± 0.001	0.023 ± 0.015	300	16.66 ± 1.52	6.9
F5	96.66 ± 4.50	8.9 ± 0.007	0.066 ± 0.055	270	26.33 ± 2.51	6.7
F6	88 ± 5.0	9.3 ± 0.004	0.076 ± 0.0057	302	28.66 ± 1.52	6.7
F7	91.33 ±1.52	8.7 ± 0.008	0.023 ± 0.0057	288	13.33 ± 1.52	6.6

2.2.7. *In- vitro dissolution study*

Figure 4 demonstrates fast dissolution profiles of the various BLA-complex loaded OFDFs, F4, F5, F6, and F7 in comparison with that containing pure drug F8 indicated by $f2$ of 12.66, 17.8, 19.1, 24.3 respectively. Moreover, F8 showed enhanced dissolution (Figure 5) in comparison to BLA ($f2$ = 44.98). Accordingly, F4 was selected as the best formula, as it has accepted physical properties with fastest release among other formulas.

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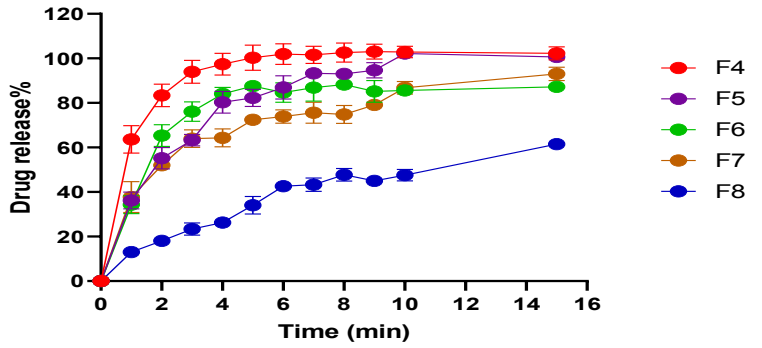

Figure 4. *In- vitro* dissolution of OFDFs in phosphate buffer (pH 6.8) at 37°C

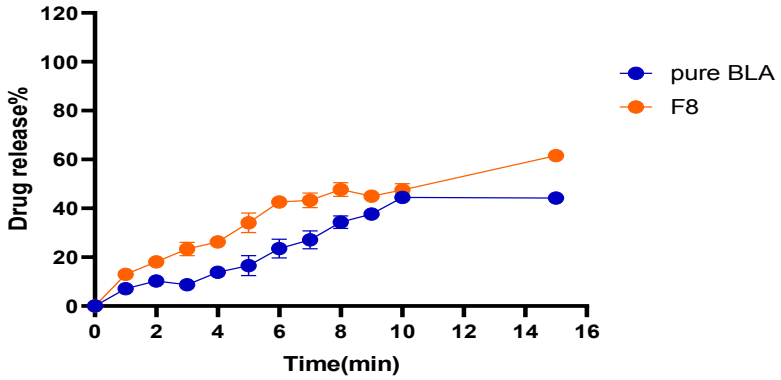

Figure 5. *In- vitro* dissolution of pure BLA and F8 in phosphate buffer (pH 6.8) at 37°C

3. DISCUSSION

The high solubility and dissolution of the prepared inclusion complex is mainly due to the solubility-enhancing effect of cyclodextrin as a complexing agent in the presence of soluplus® as hydrophilic polymer to form a ternary complex. This finding was consistent with earlier research that showed complexation of docetaxel with CD in the presence of hydrophilic polymer improved the solubility of the poorly soluble drug [10]. Therefore, this complex was utilized for the preparation of the OFDF. Some OFDFs formulations were excluded from further investigation; (F1) produced unsatisfactory texture that is broken when removed from the Petri dish, also F2 and F3 with sticky nature due to the highwater sorption property of HPMC E5**.** A similar finding was obtained by Sri *et al* who failed to peel off the OFDF of aripiprazole prepared with HPMC from the Petri dish [11]. The average thickness of the prepared OFDFs falls within an acceptable range, indicating the suitability of the solvent-casting technique for oral film formulation [1].

The results of drug content were aligned with the specified content range of 85% to 115 % [12]. The lower standard deviation in drug content suggests that the BLA-inclusion complex is evenly dispersed throughout the film matrix. This indicated that the methods and conditions for the formulation development were appropriate [13]. The folding endurance is within acceptable limits [14], indicating that the plasticizer amount was suitable [15]. The rapid disintegration results, indicating the ability of the media (phosphate buffer) to hydrate the PVA, therefore the disintegration occured quickly when the polymer was hydrated and swell. This result is in agreement with the previous study which found that OFDF of dicyclomine,

prepared with PVA disintegrated very fast due to the property of PVA that increases the surface wettability and swelling of the film [16].

The higher wettability of the film by the use of PVA as the film forming polymer and the better solubility and dissolution of BLA due to complex formation are the reasons for the fast dissolution characteristics of OFDFs. These results were in line with previous studies, where piroxicam-cyclodextrin complex loaded OFDF showed rapid disintegration and fast dissolution due to enhanced solubility of piroxicam through complex formation [17]. On the other hand, the concentration of the polymer had an impact on the release of the drug. F4 and F5, with about 50% PVA, showed faster release than F6 and F7, with about 45% PVA. This result was in agreement with that obtained by Mahaparale S and Wagh BS, who stated that, fast release is associated with an increase in polymer concentration when it is used within a range of 45-55%. As the polymer concentration increases up to 55%, there is a subsequent reduction in drug release, as the drug is retained within the polymer matrix [18].

In addition, the faster release was obtained by formulas containing glycerin as plasticizer (F4, and F6) in comparison to those containing PEG400 (F5 and F7), which may be attributed to the hygroscopic nature of glycerin, which enhances absorption of humidity by the film. This, in turn, enhances the film's hydrophilic properties and expands the internal spaces within the polymer's molecular structure by diminishing the internal hydrogen bonds and the polymer chains [19]. This result was in agreement with previously documented result where, the OFDF of metoclopramide hydrochloride prepared with glycerin as plasticizer showed highest dissolution rate of drug [20]. In addition, the enhanced dissolution of F8 in comparison to pure BLA indicates that the component of the film also had an effect in enhancing the dissolution of BLA.

4. CONCLUSION

This study showed that it is possible to formulate bilastine - cyclodextrin inclusion complex loaded as an oral fast dissolving film using PVA as a film forming polymer and glycerin as a plasticizer by solvent casting method. It was observed that the concentration of polymer and type of plasticizer affects the physical properties of the prepared OFDFs. F4 formulation was considered as the best according to the obtained results with disintegrating time of 16 sec and complete drug release in 5 min.

5. MATERIALS AND METHODS

5.1. Preparation and evaluation of bilastine- cyclodextrin complex

A mixture containing one mole of the M-β-CD along with 5% W/W soluplus® as hydrophilic polymer was prepared in water and added to an ethanolic solution containing one mole of BLA with continuous stirring for one hour by a magnetic stirrer. The obtained suspension was dried in an oven at 40 °C for 24 hrs. to ensure complete evaporation of ethanol. The dried product was subsequently grinded and sieved through a no .60 sieve [21]. The resultant product was evaluated for its production yield, drug content, saturated solubility study in distilled water, and its dissolution in phosphate buffer (pH 6.8) was also determined to be compared with that of the pure drug [8].

5.2. Preparation of BLA-cyclodextrin complex-loaded OFDFs

The solvent casting technique was employed to prepare fast-dissolving films of BLA inclusion complex [22]. Utilizing PVA, HPMC E5, and Pullulan as film-forming polymers. The required quantity of polymer for one film was dissolved in a suitable volume of hot distilled water at 50 °C with continuous stirring for one hour by a magnetic stirrer to get a homogenous solution. Subsequently, the solution was allowed to cool, and a plasticizer was added with stirring for about an hour. Mannitol, as a sweetening agent, was solved in 2 ml of hot distilled water and added to the polymer solution. An aqueous solution of BLA- M-β-CD (equivalent to 10 mg BLA) was prepared separately and added to the polymer solution with continuous stirring for another hour. The mixture was set aside to get rid of entrapped air bubbles. The final uniform solution was cast onto a 3.5cm-diameter Petri dish to dry overnight at room temperature. After drying, the film was carefully removed from the Petri dish and stored suitably for further evaluation [4, 23, 24]. Seven formulations of BLA- inclusion complex loaded OFDFs were prepared, as shown in Table 2.

Additional OFDF (F8) was prepared using pure drug, by same procedure mentioned previously, to compare the effect of the loaded complex on the release of the resulting film.

Table 2. Composition of OFDF containing BLA-inclusion complex

Components (mg)	F1	F2	F3	F4	F5	F6	F7	F8
BLA-inclusion complex equivalent to Pure BLA	10	10	10	10	10	10	10	10
PVA			25	50	50	45	45	50
HPMC E5		50	25					
Pullulan	50							
PEG					10		9	
Glycerin	10	10	10	10		9		10
Mannitol	6	6	6	6	6	6	6	6

5.3. Characterization of the OFDF

5.3.1. Physical appearance and surface texture

The visual assessment of OFDF formulation, such as uniformity, color, smoothness, clarity, homogeneity, and transparency, was considered [25].

5.3.2. Thickness

The film 's thickness was assessed at five distinct points using a vernier caliper micrometer. The data is presented as the average of three repeated measurements and should fall within the acceptable limit (5-200µm) [26, 27].

5.3.3. Weight variation

The study involved individually weighing of three films on digital balance to assess weight variation, and then calculating the average weight. For the film to be accepted, the weight of films should provide a small SD [28].

5.3.4. Drug content

One film was placed in 100 ml phosphate buffer solution (pH 6.8) with stirring using a magnetic stirrer for 30 minutes. The resulting solution was analyzed for BLA content by UV-spectrophotometer at 274 nm [29]. The test was repeated in triplicate.

5.3.5. Folding endurance

The experiment involved manual folding the film at the same site until a crack is observed. The film that withstands 250 times or more folding was considered to have acceptable flexibility [16].

5.3.6. Surface pH determination

Each film was carefully positioned in a Petri dish and moistened with 5 ml of distilled water at room temperature. The pH was assessed by contacting the pH meter with the surface of the formulation. The accepted value should be close to the pH of the oral cavity. A pH value, whether acidic or alkaline, could potentially lead to irritation of the oral mucosa [14].

5.3.7. In-vitro disintegration time

A clean and dry petri dish contained 5ml of phosphate buffer solution (pH 6.8) at 37°C was prepared. One circular film of 9cm ^{2} was then carefully positioned on the solution within the Petri dish, with gentle and continuous agitation. The second at which the film begins to break or disintegrate indicates the disintegration time. 30 seconds or less is considered the acceptable limit for rapid-dissolving films [26].

5.3.8. In- vitro dissolution study

The experiment was conducted using USP type II (paddle apparatus) in which one circular film 9cm ^{2} was placed in 900 ml of phosphate buffer (pH 6.8) at 37°C and rotated at 50 rpm. Samples of 5 ml were withdrawn at regular time intervals and replaced with same volume of fresh buffer, the samples were filtered using a 0.45 µm filter syringe and analyzed for the dissolved drug at λ max of 274 nm using a UV spectrophotometer. All measurements were performed in triplicate [29]. The resultant profiles were compared with that of the prepared complex to investigate the effect of film component on the release of the drug. To assess the dissolution profiles, a comparison was made between the resulting profiles of the OFDFs using the similarity factor $f2$ 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) represents the number of time points for dissolution. (Rt) and (Tt) denote the dissolution values at time t for the reference and test. If the $f2$ values are greater than 50, two dissolution profiles are considered similar. Otherwise, the profiles are not similar [30].

5.4. Statistical analysis

The results were analysed by SPSS version 25 using 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.

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