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Research Article

Formulation and evaluation of medicated lozenges containing the solid dispersion of Clotrimazole /PEG 6000 for the treatment of oral candidiasis

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Abstract

The study aimed to formulate Clotrimazole (CLM) as solid dispersion medicated lozenges with enhanced dissolution for treating oropharyngeal candidiasis. They are suitable for many patients and easy to administer. The study used the solvent evaporation method to prepare solid dispersions of CLM using polyethylene glycol 6000 and polyvinyl pyrrolidone at different drug-to-carrier weight ratios. The study found that PEG 6000, when used at a 1:1 weight ratio, significantly improved the dissolution of CLM. The results of the FTIR studies showed that the drug was dispersed within PEG 6000, and there was no drug interaction with the excipients used in medicated lozenge formulations. A 3^2-factorial design was used to develop, optimize, and evaluate nine formulations of the solid dispersion of CLM/PEG 6000 medicated lozenges for improved therapeutic outcomes. We fabricated the lozenges using biocompatible polymeric gelling agents (chitosan, methyl cellulose, and sodium alginate) at three different levels (0.5, 1, and 1.5%). All the medicated lozenges were uniform in weight and drug content within USP limits, with complete drug release rates ranging from 10–20 minutes for chitosan and sodium alginate formulations, compared to 60 minutes for methyl cellulose. The results showed that the type of polymer and its concentration significantly impacted drug release. The optimized formulation, F-3, containing 1.5% CH, exhibited a drug release of 100.83% ±0.68 at the end of 10 minutes. It demonstrated significant antifungal activity against *Candida albicans* ($p < 0.05$), making it suitable for drug delivery in the oral cavity.

1. Introduction

Candida, a yeast genus, is present in healthy humans but increases susceptibility to candidiasis due to antibiotic treatment, diabetes, immunodeficiency, or AIDS. *Candida albicans* is the most frequently diagnosed opportunistic pathogen, with infections in immune-suppressed patients potentially spreading and being fatal [1, 2]. The antifungal agent used for treating candidiasis depends on the severity of the illness, with local therapy used for local infections and a combination of local and systemic medicines for systemic infections [3]. Local therapy is the primary treatment for oral and pharyngeal candidiasis, using antifungal agents like echinocandins and azoles, whose effectiveness depends on contact time and medication concentration [4].

Clotrimazole (CLM) is an imidazole antifungal drug that has a broad spectrum of antifungal activity in the treatment of *Candida albicans* and other fungal infections, in the treatment of metronidazole-resistant *trichomoniasis* symptoms, and activity against some gram-positive bacteria. The mode of action of CLM is based on the inhibition of ergosterol biosynthesis, which leads to lysing the fungal cell membrane, and the inhibition of peroxidase, which results in the accumulation of peroxide in the cell, leading to cell death. It has a poor aqueous solubility of 0.49 mg/L at 25 °C, which leads to poor and erratic bioavailability, with a maximum concentration (C_{max}) attained after 6 hours when administered orally. Soluble in polyethylene glycol 400, ethanol, and methanol [5, 6].

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Despite effective antifungal therapy, CLM has extensive hepatic inactivation and causes gastric disturbance, in addition to its poor solubility, which restricts its use for topical application [7]. It has been available in topical creams, lotions, powders, vaginal inserts, and pessaries. The troches, containing 10 mg of CLM, were used five times daily for 14 days to treat oropharyngeal candidiasis and three times daily to prevent it in immune-compromised individuals. CLM troches are not sold in the European Union but are widely available in the USA and other countries [8]. These dosage forms are administered in large doses to give a therapeutic effect with unwanted side effects. The solubility and permeability of a drug affect its absorption and bioavailability, which in turn determine its therapeutic effectiveness [9]. Several approaches have been used to address the poor solubility and dissolution issues of CLM. By using the inclusion complexation method [10], solid dispersions and inclusion complexes were subsequently formulated into suppositories [11]. For transdermal drug delivery, CLM was formulated into nanoemulsions, gels containing penetration enhancers, invasome gels, and ufosomes [5,12-14]. For oral administration, it was made into chewing gum, jelly, and in situ gel [15-17]. It was also made into vaginal films and nanofiber [18] for delivery into the vagina. In this research, the solid dispersion technique was employed to improve the apparent solubility and dissolution. Solid dispersions (SDs), formed through melting, solvent, or solvent-melting techniques, contain active ingredients in an inert carrier, with drug presence in molecular, amorphous, microcrystal, or colloidal states. In SDs, commonly used polymeric carriers like polyethylene glycols (PEGs), polyvinyl pyrrolidones (PVPs), hydroxyl propyl methyl cellulose (HPMC), and surfactant carriers have high water solubility [19]. PEGs and PVPs are two classes of extensively used excipients that are hydrophilic, stable, and basically non-irritating to the skin. They are utilized in both pharmaceutical and cosmetic formulations. They are typically thought of as non-irritating and non-toxic compounds [20].The most popular and straightforward method of medication administration is via the oral route, which has the highest active surface area of any drug delivery system. Solid dosage forms are widely used because they are simple to administer, precise in their amount, allow for self-medication, reduce pain, and most importantly, ensure patient compliance [21]. Pharmaceutical dosage forms for local delivery need to remain at the site of infection and be able to release the drug. Dosage forms like lozenges improve the onset of action, avoid hepatic metabolism, eliminate water consumption, and reduce dose frequency to minimize side effects.

The use of medicated lozenges is more effective than oral gels due to their ability to maintain precise doses and concentrations in the oral cavity. The medicated lozenges are sweetened and dissolved in the mouth, treat local irritation or infection, and allowing systemic drug absorption through the oral cavity. The lozenges are beneficial for patients who cannot swallow solid oral doses, as they maintain drug levels in the oral cavity, reduce gastric irritability, and prevent first-pass metabolism [22, 23]. Chitosan (CH) is a cationic polysaccharide with excellent mucoadhesive properties, used in transmucosal drug delivery formulations. It is safe, biocompatible, and biodegradable [24]. Chitosan also has healing properties for wounds and burns, promoting recovery from ulcers. It activates neutrophils and macrophages, promoting the migration of nuclear polymorph and mononuclear cells and accelerating tissue regeneration and angiogenesis [25]. Methyl cellulose (MC) is a widely used polymer in oral and topical pharmaceuticals, used as binding agents in tablet formulations. It can be added as a dry powder or solution or as a disintegrant. Methyl cellulose can also be used to produce sustained-release preparations. It is a thermosensitive material that can crosslink and turn into a hydrogel when heated up to 37 °C [26]. Sodium alginate (SA) is a nontoxic, water-soluble, and biodegradable anionic polymer with hydroxyl and carboxyl groups that binds to buccal mucosa mucin. It's used in the pharmaceutical and food industries as a binder and disintegrant in tablet formulations. SA's hygroscopic nature facilitates water absorption, causing faster film disintegration in the oral cavity [27].

The aim of this work was to formulate and evaluate the solid dispersion of clotrimazole medicated lozenges for improved dissolution and the treatment of orophayngeal candidiasis. This study employed the solvent evaporation method to prepare solid dispersions of CLM with polyvinyl pyrrolidone and polyethylene glycol, which are then formulated into highly effective medicated lozenges. The lozenges are made with sucrose and dextrose as bases and sweeteners, polymeric gelling agents for softness and adherence, and citric acid as an acidulant.

2. Materials and methods:

Clotrimazole (CLM) was obtained as a gift sample from Global pharmaceutics, Yemen, polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG 6000) (LobaChemie, India), Methanol (Sigma-Aldrich, Germany), sucrose (HPLC, India, dextrose, citric acid, disodium hydrogen orthophosphate, potassium dihydrogen orthophosphate, sodium chloride (Labtech chemicals, India)

Chitosan (CH), methyl cellulose (MC), sodium alginate (SA) (SD Fine Chemicals, India), soyabean casein digest medium (broth); ref M011, HIChrom candida differential agar; ref M1297A, D-(=)-glucose anhydrous, barium chloride dehydrate, Sabouraud dextrose agar, ref M063, Mueller Hinton agar, ref M173 (HIMEDIA, Laboratories, India) and methylene blue (BDH, England). The experiments utilized pharmaceutical-grade materials supplied by the manufacturer, and deionized water was used in all experiments. The antifungal studies utilized materials sources from the Supreme Board of Drugs and Medical Appliances in Aden, Yemen.

2.1. Preparation of the solid dispersions of CLM

The solvent evaporation was used to produce CLM solid dispersion with PEG 6000 (SD 1, SD 2 and SD 3) and PVP (SD 4, SD 5 and SD 6) [28, 29]. The chosen weight ratios (w/w) for CLM to carriers were 1:1, 1:2, and 1:5. A sufficient amount of methanol was added to dissolve the precisely weighed amount of polymer. Then, the weighed amount of CLM was added to the polymer solution and stirred continuously at room temperature until dry. After that, after completing the drying in an oven at 40 °C for 24 hours, the solid mass was crushed and sieved through sieve no. 80. All the prepared solid dispersions were kept in screw-capped glass vials in a desiccator until needed.

2.2. Characterization CLM solid dispersions

2.2.1. Production yield of CLM solid dispersions

The production yield of all prepared solid dispersions of CLM was calculated according to the following equation [30]:

$$Production\ yield\ (\%) = \frac{weight\ of\ the\ collected\ SD}{weight\ of\ CLM + polymer} \times 100$$

2.2.2. Drug content

An accurate amount of each solid dispersion formulation equivalent to 20 mg of CLM was placed into a 25-ml volumetric flask and dissolved by methanol to obtain a concentration of 0.8 mg/ml. Then 10 ml of this solution was diluted with phosphate buffer at pH 6.8 and methanol (60:40 v/v) and assayed for drug content by using a UV spectrophotometer at λ_{max} 262 nm (Advanced Microprocessor Single Beam Spectrophotometer Li-295, Lasany, India). The percentages of drug content were calculated using the following equation [28]:

$$Drug\ content\ (\%) = \frac{Actual\ drug\ content}{Theoretical\ drug\ content} \times 100$$

2.2.3. *In-vitro* dissolution studies

The USP dissolution apparatus type I was utilized to evaluate the *in-vitro* dissolution profile of colorless hard gelatine capsules containing 10 mg of CLM pure dug and its solid dispersions with PEG 6000 (SD-1, SD-2, and SD-3) or PVP 40000 (SD-4, SD-5, and SD-6) [30].

The capsules were dissolved in 900 ml of pH 6.8 phosphate buffer at 37°C and rotated at 100 rpm in the dissolution apparatus. Samples were withdrawn at time intervals of 5, 10, 15, 30, 60, 90, and 120 minutes, and the dissolution medium volume was adjusted to 900 ml by replacing it with fresh phosphate buffer at the same temperature. Samples were filtered and analyzed using a 262 nm spectrophotometer, and CLM concentration was determined using a standard calibration curve equation.

2.2.4. Dissolution data analysis

Similarity factor f2 and dissolution efficiency (% DE) over the time period of 2 h [31]. The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. The following equations were used to calculate the similarity factor f2:

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

Where (n) is the number of withdrawal points, (Rt) is the percentage of drug dissolve from pure CLM, and (Tt) is the percentage of drug dissolve from the CLM solid dispersions at time (t). The acceptable range of f2 is between 50 and 100, which means an average difference of ≤ 10% at each withdrawal time. The dissolution efficiency (%DE) was calculated using the following equation:

$$DE\ (\%) = \frac{\int_{t1}^{t2} y.dt}{y100.t} \times 100$$

Where y is the percentage of dissolved product. DE is the area under the area under the dissolution curve between time point's t1 and t2, expressed as a percentage of the curve at maximum dissolution, y100, over the same time period.

2.2.5. FTIR spectroscopic studies

The FTIR spectra of the pure CLM, PEG 6000, physical mixture, and solid dispersion of CLM with PEG 6000 at a 1:1 weight ratio were recorded using a FTIR spectrophotometer (PerkinElmer Spectrum, version 10.6.2) over the wavelength number range of 4000–450 cm^{-1}. In addition, the drug-excipient compatibility was evaluated by

determining the spectra of sucrose, CH, and the physical mixture of formulations F-3.

2.2.6. Design of experiment

A 3^2 factorial design was used to produce nine medicated lozenges containing solid dispersion of CLM/PEG 600 using Design Expert software version program 13. The study examined the effect of two independent factors, A: polymer type and B: polymer concentration, each with three levels (low: -1, medium: 0, and high: 1), on the dependent factor, the percentage of drug release (Y) (Table 1). The selected hydrophilic polymeric gelling agents, chitosan (CH), methylcellulose (MC), and sodium alginate (SA), were used as independent factors at concentrations of 0.5% (-1), 1% (0), and 1.5% (1).

2.2.7. Preparation e of the solid dispersion of CLM/PEG 6000 medicated lozenges

The medicated lozenges, each containing 10 mg of CLM solid dispersed in PEG 6000 (weight ratio 1:1), were prepared through heating and congealing [32,33]. The required amount of sucrose was dissolved using deionized water and continuous stirring on a magnetic stirrer on a hot plate at 150°C. Dextrose was added to sucrose syrup, stirring continuously, until a plastic mass was formed. The temperature was reduced, and the solid dispersed drug, along with citric acid and hydrophilic gelling agents like chitosan, methylcellulose, or sodium alginate, was added to the plastic mass. A flavoring with a coloring agent was added to the mixture, which was then poured into molds, air-dried for an hour, and wrapped in aluminum foil (Figure 1). Nine formulations of CLM lozenges, each 2 gm in weight, were prepared with varying amounts of hydrophilic gelling agents, as shown in Table 2.

2.3. Evaluation of the solid dispersion of CLM/PEG 6000 medicated lozenges organoleptic properties, weight uniformity, and drug content

The medicated lozenges were assessed for their acceptability through visual observation of their color, taste, odor, and surface texture. The weight uniformity was determined by taking ten medicated lozenges were chosen randomly and weighed. The weight of each should not deviate from the mean weight by more than 5%. The nine formulae were tested for drug content uniformity by dissolving one medicated lozenge in a pH 6.8 salivary simulated buffer solution using a 25-ml volumetric flask and centrifuging at 3000 rpm for 15 minutes. The drug absorbance was measured using a spectrophotometer at a maximum wavelength of 262 nm against a blank after diluting 5 ml of the supernatant with methanol [34].

Table 1: 3^2 factorial design of the solid dispersion of CLM/PEG 6000 medicated lozenges

Run	Formulation code	Independent factors	
		A: polymer type	B: polymer concentration %
1	F-1	1	-1
2	F-2	1	0
3	F-3	1	1
4	F-4	-1	-1
5	F-5	-1	0
6	F-6	-1	1
7	F-7	0	-1
8	F-8	0	0
9	F-9	0	1
(Y) Dependent factor (response)	Maximum and fast drug release rate (%)		

2.4. *In vitro* drug release studies

The USP rotating paddle dissolution test type II apparatus was used for dissolution studies of the drug from medicated lozenges [35]. The study used 250 ml simulated saliva phosphate buffer solution (pH 6.8), maintained at 37°C and 50°C, and withdrawn samples at predetermined intervals 5, 10, 15, 20, 25, 30, 45, and 60 minutes, replacing them with fresh medium kept at the same temperature.The samples were centrifuged at 3000 for 15 minutes and analyzed using a UV spectrophotometer at a wavelength of 262 nm. The drug concentration and dissolved amount were calculated using the standard calibration curve of CLM, y = 0.0019 × - 0.0014, slope: 0.0019, and the intercept: 0.0014 with correlation coefficient R2 = 0.9998, and drug dissolution profiles were created by plotting cumulative percentages over time.

2.5. Antifungal activity of the solid dispersion of CLM/PEG 6000 medicated lozenges

The study was conducted in the Supreme Board of Drugs and Medical Appliances' Aden microbiological laboratory. Almadeinah Center's laboratory provided a *Candida albicans* specimen. The specimen underwent routine identification and revitalization procedures, including activating and growing *Candida albicans* and testing its susceptibility to CLM-pure drug (St), solid dispersion CLM-medicated lozenges F-3 (T), and pH 6.8 saliva stimulating buffer (Ct).

HIChrom Candida Differential Agar was utilized to identify *Candida albicans* species, which were then identified through morphological features after 72 hours of incubation at 25°C. *Candida albicans* was revitalized using Soyabean Casein Digest broth. The solidified Sabouraud Dextrose agar was streaked by revitalized fungi using a sterile loop and incubated at 37°C for 24 hours.

The inoculum was prepared from 24-hour-cultured colonies grown on Sabouraud Dextrose Agar, picked using a sterile loop, and suspended in 5 ml of sterile water. The suspension was mixed thoroughly and adjusted for turbidity to yield 1x 10^6 - 5x 10^6 cells/ml, comparing it with a 0.5 McFarland Standard solution. The antifungal activity of the solid dispersion of CLM/PEG 6000 medicated lozenges was tested using the agar-well diffusion method, using Muller Hinton Agar and sterile Petri dishes. Three 6 mm-diameter wells were produced by using a Pasteur pipette on the culture medium with constant distances, and each well was filled with solutions of CLM pure drug, medicated lozenges of F-3 (10 µg/50 µl), and pH 6.8 saliva simulating buffer. The zone of inhibition, which is only characterized by the absence of fungal growth around the wells, was determined after 24 hours of incubation at 37 °C for comparison [1,18].

Statistical Analysis

The evaluation parameters were conducted in triplicate, with results expressed as mean values and standard deviations (±S.D). In the case of antifungal studies, six replicates were performed and an analysis of variance-single factor was used, and the difference was considered to be significant at a p-value of < 0.05.

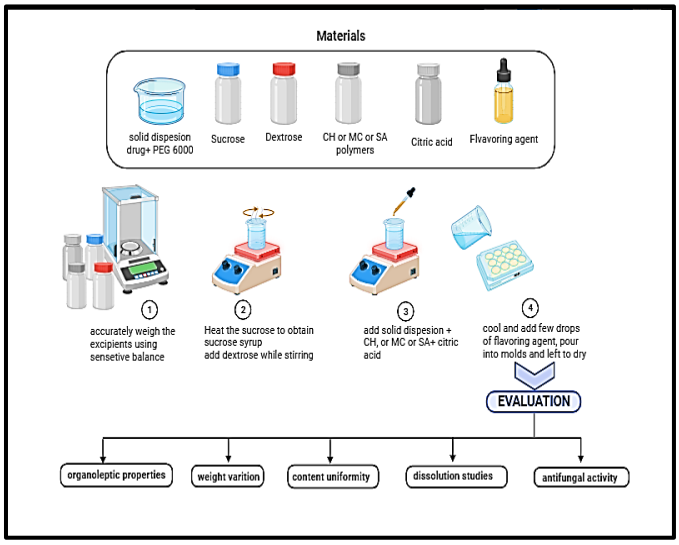

Figure 1: Scheme represents the experimental procedures of the solid dispersion of CLM/PEG 6000 medicated lozenges

3. Results and Discussions

Production yield of CLM solid dispersions

The production yield values of the six formulations of CLM solid dispersions ranged from 93.22 ±3.11% to 96.15 ±2.80%, as depicted in Table 3. These results were in agreement with Raj *et al. and* Thadanki *et al.*, who reported similar results of production yield percentage for nebivolol and for lercanidipine solid dispersion [36, 37].

Table 2: The composition of the solid dispersion of CLM/PEG 6000 medicated lozenges

Ingredients (mg)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Clotrimazole	10	10	10	10	10	10	10	10	10
***PEG 6000**	10	10	10	10	10	10	10	10	10
Sucrose	1460	1450	1440	1460	1450	1460	1450	1440	1460
Dextrose	500	500	500	500	500	500	500	500	500
CH	10	20	30	-	-	-	-	-	-
***MC**	-	-	-	10	20	30	-	-	-
***SA**	-	-	-	-	-	-	10	20	30
Citric acid	10	10	10	10	10	10	10	10	10
Flavoring & coloring agent	QS	QS	QS	QS	QS	QS	QS	QS	QS
Total (gm)	2	2	2	2	2	2	2	2	2

*PEG 6000: Polyethylene glycol 6000; MC: Methylcellulose; SA: Sodium alginate

Drug Content

The drug content of the prepared CLM solid dispersions was in the range of 96.79 ±1.34% to 102.94 ±1.55% (Table 3), indicating that the solvent evaporation technique was appropriate for the preparation of solid dispersions of CLM with PEG 6000 and PVP [38].

Table 3: The evaluation parameters of CLM and solid dispersions of CLM with PEG 6000 and PVP.

Parameter	CLM	CLM: PEG 6000			CLM: PVP		
		SD 1	SD 2	SD 3	SD 4	SD 5	SD 6
Production yield (%)	-	93.22 ±3.11	96.15 ±2.80	94.67 ±2.89	93.67 ±3.24	95.44 ±1.40	94.93 ±2.50
Drug content (%)	-	96.79 ±1.34	97.88 ±2.14	102.9 ±1.55	99.34 ±2.89	101.9 ±1.75	97.70 ±3.05
Q_{15}	23.3 ±2.3	76.61 ±2.60	62.12 ±2.83	32.15 ±0.42	65.72 ±2.12	60.94 ±3.18	27.66 ±0.78
Q_{30}	32.5 ±4.4	93.96 ±1.65	66.78 ±3.96	33.18 ±1.91	86.08 ±2.55	59.22 ±4.03	31.92 ±2.62
T_{50} (minutes)	> 120	10	15	> 120	15	15	> 120
Similarity factor (f_2)	-	15.13	23.95	54.27	17.95	27.22	52.69
DE (%)	28.9	85.52	65.89	35.69	79.54	60.03	33.58

Mean ± S.D, Q15 & Q30: amount dissolved at 15 & 30 minutes, respectively; T50: time required to dissolve 50% of CLM; DE: dissolution efficiency.

***In vitro* dissolution studies**

The dissolution studies were carried out for the pure CLM and its solid dispersions in phosphate buffer of pH 6.8. Figures 2 shows the dissolution profiles of pure CLM and its solid dispersions with PEG 6000 (SD1, SD2, and SD3) and PVP (SD4, SD5, and SD6) over a period of 2 h. Table 3 presents the cumulative amount dissolved (%) within 15 and 30 minutes and the time to dissolve 50% CLM for different formulae. From the results, it was observed that the dissolution rate of pure CLM was very low; 23.28 ±2.37% and 32.45 ±4.42% within 15 and 30 minutes, respectively and T50 was not reachable after 2 hours. On the other hand, the dissolution rate of the drug from its solid dispersions was enhanced at weight ratios of 1:1 (SD 1 and SD 2) and 1:2 (SD 3 and SD 4) with PEG 6000 and PVP. Solid dispersions of the hydrophobic drug with PEG 6000 and PVP enhanced the dissolution rates by decreasing the particle size of the drug, increasing drug wettability, preventing drug aggregation, and possibly affecting the crystallinity of the drug. As well as the use of the solvent evaporation method, produced a highly porous structure due to the rapid removal of the solvent [39]. Increasing the weight ratio to 1:5 of CLM: PEG 6000 and CLM: PVP resulted in a significant decrease in CLM dissolving rate to 33.18 ±1.91% (SD 5) and 31.92 ±2.62% (SD 6), respectively. This phenomenon may be related to the creation of a highly viscous boundary layer adjacent to the dissolving surface of the polymer-generated dispersion during the dissolution process, which limits the drug's diffusion rate and therefore dissolution [40].

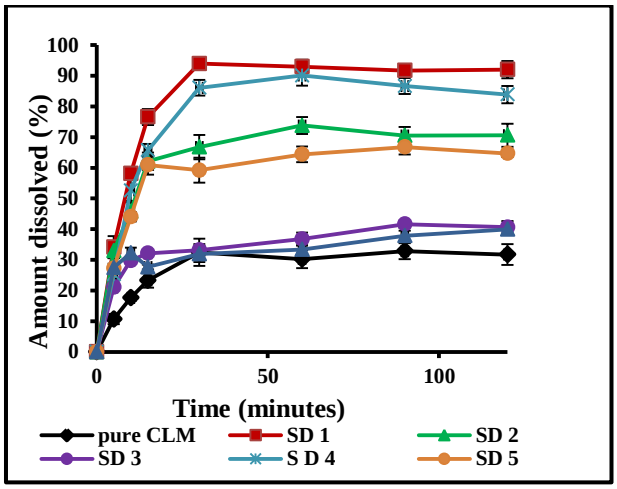

Figure 2: In vitro dissolution of pure CLM and from solid dispersions with PEG 6000 (SD 1: 1:1, SD 2: 1:2 & SD 3:1:5) and PVP (SD 4: 1:1, SD 5: 1:2 & SD 6: 1:5) in phosphate buffer pH 6.8.

FTIR Spectroscopic Studies

Characterization of CLM solid dispersion

Figure 3 (A, B, C, and D) shows the FTIR spectra of CLM and PEG 6000, a physical mixture, and the solid dispersion of weight ratio 1:1 between CLM and PEG 6000. The FTIR spectrum of CLM revealed distinct absorption peaks at 3064.06 cm^{-1} for aromatic C-H stretching, 1584.92 cm^{-1} for aromatic C=C stretching, 1566.25 cm-1 for C=N stretching, 1081.35 cm^{-1} and 1040.89 cm^{-1} for C-N stretching, and 764.76 cm^{-1} for aromatic C-H bending [41]. PEG 6000's FTIR spectra showed C-H stretching at 2881.56 cm^{-1} and C-O (ether) stretching at 1146.60 cm^{-1} [42,43]. It was observed that the CLM absorption peak appeared in the spectra of the physical mixture, with no difference noted. The CLM absorption peak appeared in the spectrum of the physical mixture, and there was no difference in the positions of the CLM and PEG 6000 peaks. However, in the solid dispersion, the absorption peak at 3064.06 cm^{-1} disappeared, and the heights of the peaks at 1584.92 cm^{-1} and 1566.25 cm^{-1} were slightly reduced, but the other peaks remained [37]. The inclusion of CLM in the solid dispersion is critical to increasing drug solubility in the medicated lozenges.

Drug-Excipient Compatibility Studies

The FTIR spectra of CLM, sucrose, CH, and the physical mixture of the formulations F-3 were obtained to explore the possible interaction between CLM and the excipients

Formulation code	Weight variation (mg), mean ±S.D	Drug content (%), mean ±S.D
F-1	2.043 ±0.071	101.10 ±0.25
F-2	2.057 ±0.062	100.95 ±0.17
F-3	2.044 ±0.040	101.78 ±0.33
F-4	2.041 ±0.035	100.83 ±0.34
F-5	2.035 ±0.037	100.87 ±0.24
F-6	2.050 ±0.027	102.29 ±0.69
F-7	2.029 ±0.032	101 ±0.26
F-8	2.028 ±0.032	100.98 ±0.25
F-9	2.031 ±0.025	101.01 ±0.33

Table 4: The evaluation parameters of the prepared solid dispersion of CLM/PEG 6000 medicated lozenges (F-1-F-9).

utilized in the formulation of medicated lozenges (Figure 3: A, E, F, and G).

CH had a broad absorption band at 3336.39 cm-1 due to the superposition of O-H and N-H stretching, a polysaccharide characteristic, at 2898.71 cm-1 due to aliphatic C-H stretching vibrations, at 1150.41 cm-1 due to asymmetric stretching of the C-O-C bridge of glycoside linkage, and at 1041.61 cm-1 due to C-O stretching [41]. As shown in Figure 3 (G), the spectrum of the physical mixture of the formula F-3 showed the sum of the characteristic peaks with the substantial presence of the drug in the solid dispersed state with PEG 6000.

Evaluation of the solid dispersion of CLM/PEG 6000 medicated lozenges organoleptic properties, weight uniformity, and Drug content

The organoleptic properties of the solid dispersion CLM-medicated lozenges were found to be satisfactory, with a smooth texture, pleasant odor, and attractive yellow color (Figure 4). The addition of PEG 6000 and other polymeric gelling agents CH, MC, and SA to the formulations contributed to the softness and smooth dissolution of the lozenges in the oral cavity, making it convenient for patient compliance during administration. It was observed that the weight was uniform within each prepared medicated lozenge formulation, as presented in Table 4. The weight uniformity of the medicated lozenges is crucial for ensuring accurate dosing and consistency in each dosage form. This characteristic is essential for maintaining product quality and efficacy. The drug content percentages (Table 4) ranged from 100.87±0.24 to 102.29±0.69, falling within the permitted limits for all manufactured medicated lozenges that contain no more than 110% nor less than 90% of the amount stated on the label [44].

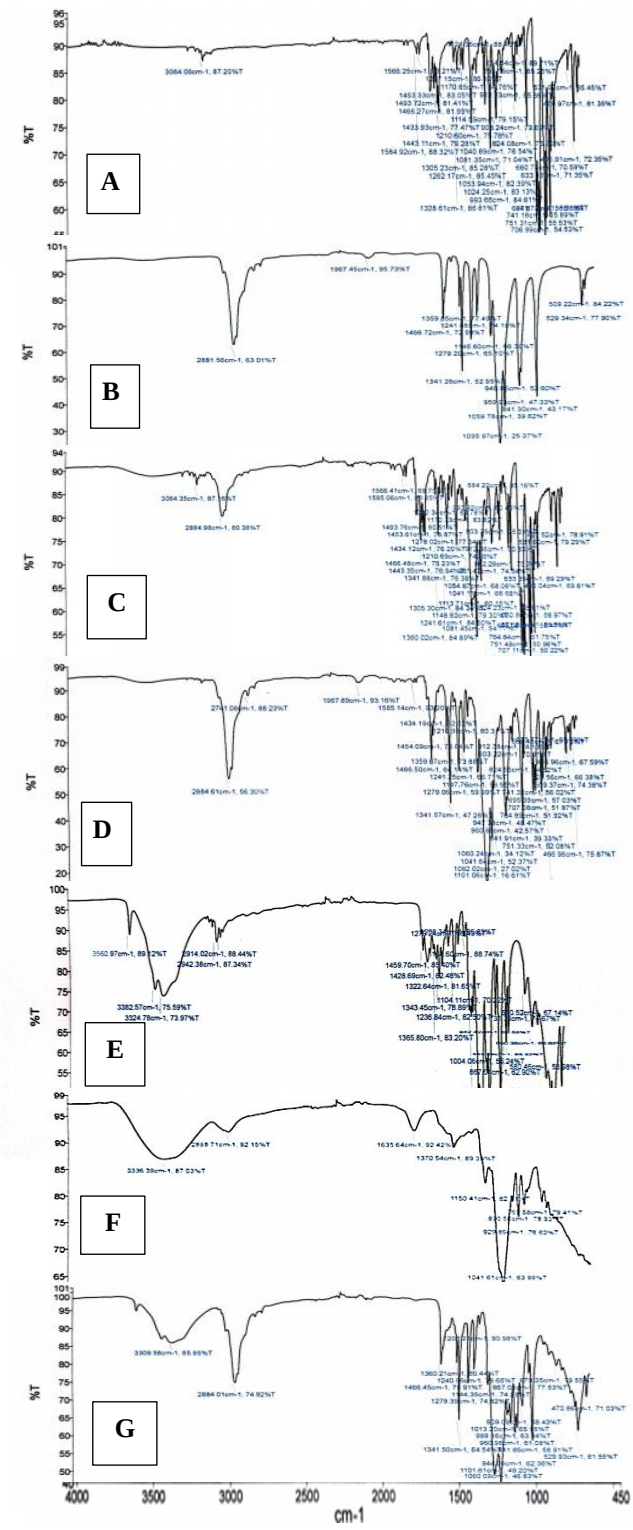

Figure 3: FTIR spectra of (A): CLM, (B): PEG 6000, (C): physical mixture of CLM: PEG 6000, and (D): solid dispersion of CLM /PEG 6000 at a weight ratio of 1:1. (E) sucrose, (F) CH, and (G) formula F-3.

Figure 4: The solid dispersion of CLM/PEG 6000 medicated lozenges

In vitro drug release studies

Table 5 and Figures 5, 6, and 7 depict the results of the *in vitro* release studies on the solid dispersion of CLM/PEG 6000 medicated lozenges. Solid dispersions in PEG 6000 considerably increased CLM solubility and dissolution in these lozenges. Formulations containing CH (F-1: 99.56% ±0.31, F-2: 103.25% ±0.55, and F-3: 100.83% ±0.68) and SA (F-7: 97.69% ±0.11, F-8: 99.59% ±0.14, and F-9: 101.32% ±0.21) showed faster drug release in 10 to 20 minutes compared to those containing MC, which provided approximately complete dissolution of 98.09% ±0.11 within 60 minutes (F-6). However, only 48.99% ±0.07 (F-4) and 80.15% ±0.47 (F-5) of the CLM were dissolved after 60 minutes.

Statistical analysis of the applied design on the in vitro release

This study used a central composite design to investigate the effect of CH, MC, and SA on the *in vitro* release behavior of the solid dispersion of CLM/PEG 6000 medicated lozenges. Table 6 illustrates the optimal model for assessing the relationship between the independent factors (A and B) and the response (Y). The higher-order model, the cubic model, was aliased, indicating that it was unsuitable for response prediction. The quadratic model provided the best fit for the response (R^2 = 0.9960). The predicted R^2 of 0.9554 was in good agreement with the adjusted R^2 of 0.9894; the difference was less than 0.2. The ANOVA results for the quadratic model (Table 7) demonstrated a significant effect of polymer type (A) and concentration (B) on the *in vitro* release rate of CLM ($p < 0.001$). The final equation in terms of coded factors for the coefficients of actual independent factors (A: polymer type and B: polymer concentration) and the dependent response factor (Y: % release at 10 minutes) is:

$$Y = 69.44 + 16.98\,A + 10.29\,B - 4.85\,AB + 8.16\,A^2 - 0.5317\,B^2$$

The estimated coefficients represent that the release rate of CLM from the solid dispersion of CLM/PEG 6000 medicated lozenges depends on the polymer's nature (CH > SA > MC) [45]. It was evident that an increase in hydrophilic polymers in all formulations resulted in an increased CLM release from the medicated lozenges.

Table 5: The in vitro release of the prepared solid dispersion of CLM/PEG 6000 medicated lozenges (F-1-F-9)

Time (minutes)	Drug Released (%), mean ±S.D								
	F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F--7**	**F-8**	**F-9**
5	67.91 ±0.79	75.56 ±0.15	83.70 ±1.33	33.82 ±0.21	41.85 ±0.25	61.52 ±0.49	39.33 ±0.40	47.03 ±0.28	53.68 ±0.36
10	88.44 ±0.16	93.41 ±0.09	100.83 ±0.68	44.11 ±0.42	60.80 ±1.97	75.91 ±0.39	59.62 ±0.24	70.44 ±0.13	77.20 ±1.21
15	99.56 ±0.31	103.25 ±0.55		49.23 ±0.20	67.17 ±1.83	83.36 ±0.17	74.97 ±1.29	99.59 ±0.14	101.32 ±0.21
20				50.07 ±0.25	76.04 ±0.05	86.51 ±0.35	97.69 ±0.11		
25				48.88 ±0.16	79.18 ±0.11	88.46 ±0.06			
30				49.05 ±0.20	77.00 ±0.66	89.72 ±0.27			
45				50.30 ±0.03	75.41 ±0.02	93.21 ±0.12			
60				48.99 ±0.07	80.15 ±0.47	98.09 ±0.11			

This highlights the multifunctional role of polymeric agents in pharmaceutical formulations and the importance of selecting appropriate excipients for improved oral drug delivery. These findings were consistent with those from the formulations of lidocaine [46] and cetirizine lozenges [47]. Figure 8 shows the predicted versus the actual value, contour plot of the drug release, and surface plot of the drug release. The lozenges are solid sugar syrups that dissolve slowly and uniformly over 5–10 minutes without disintegration, allowing for excellent medication delivery [48]. The optimal formulation was F-3, with 1.5% CH and a drug release rate of 100.83% ±0.68 within 10 minutes. It was selected for further studies to evaluate the antifungal activity of CLM against *Candida albicans*.

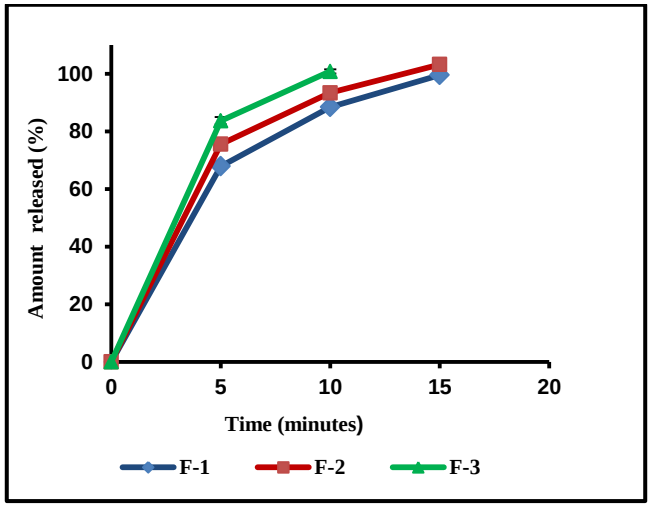

Figure 5: The in vitro release of CLM from the medicated lozenges fabricated with chitosan (CH)

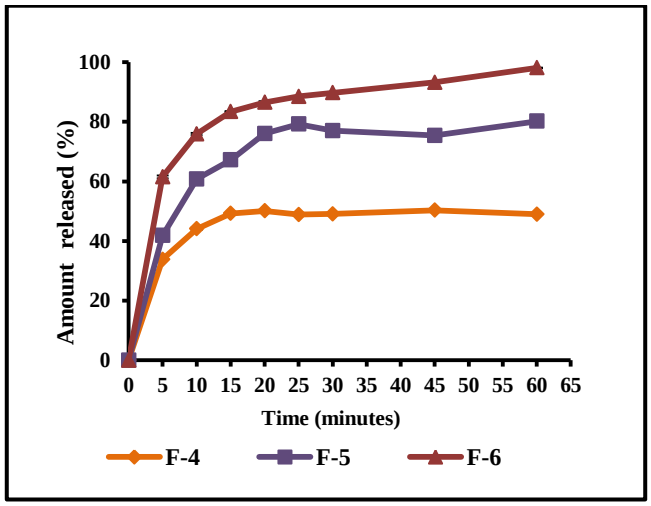

Figure 6: The in vitro release of CLM from the medicated lozenges fabricated with methyl cellulose (MC)

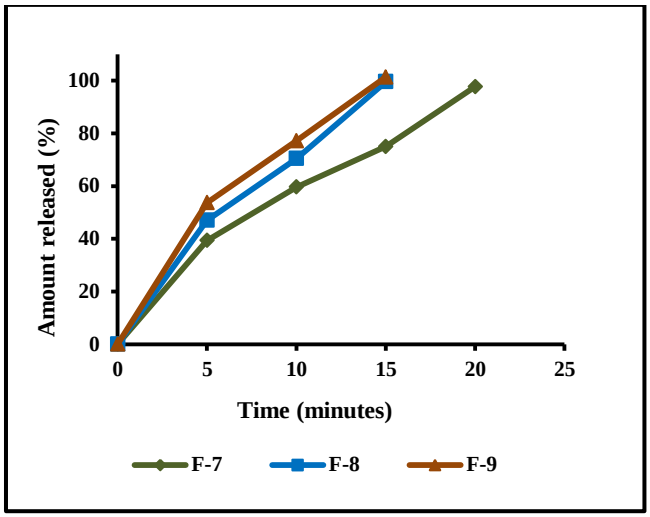

Figure 7: The in vitro release of CLM from the medicated lozenges fabricated with sodium alginate (SA)

Table 6: Fit summary for response (Y: release at 10 minutes)

Model	R^2	Sequential p-value	Adjusted R^2	Predicted R^2	
Linear	0.9084	0.0008	0.8779	0.7635	
2FI	0.9446	0.1306	0.9114	0.7834	
Quadratic	**0.9960**	**0.0193**	**0.9894**	**0.9554**	**Suggested**
Cubic	0.9991	0.4648	0.9931	0.8429	**Aliased**

Table 7: ANOVA results for the quadratic model for response (Y)

Source	Sum of square	DF	Mean square	F-value	p-value	
Model	2593.20	5	518.64	149.70	0.0009	significant
A	1729.24	1	1729.24	499.13	0.0002	
B	635.92	1	635.92	183.55	0.0009	
AB	94.19	1	94.19	27.19	0.0137	
A^2	133.28	1	133.28	38.47	0.0084	
B^2	0.5653	1	0.5653	0.1632	0.7133	
Residual	10.39	3	3.46			
Correlation Total	2603.59	8				

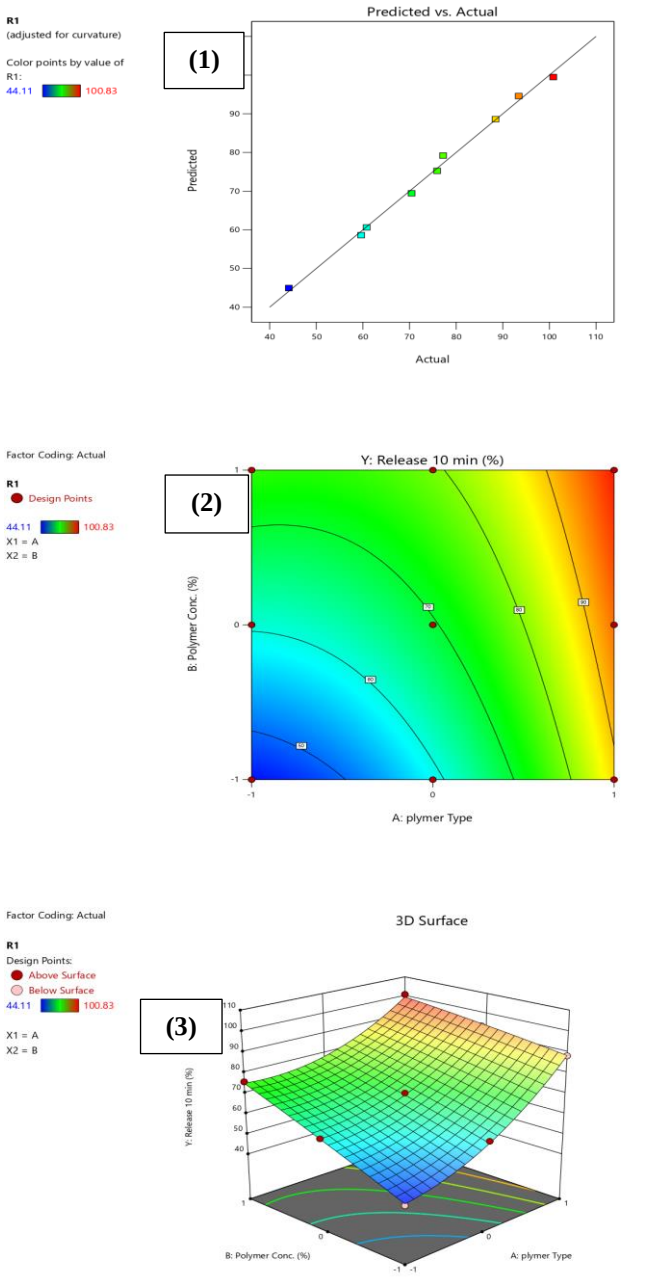

Figure 8: The effect of polymer type (A) and concentration (B) on the release of CLM at 10 minutes (Y) from the solid dispersion of CLM/PEG 6000 medicated lozenges. (1): the predicted versus the actual value (2): Contour plot of the drug release and (3): surface plot of the drug release

Antifungal activity of the solid dispersion of CLM/PEG 6000 medicated lozenges

The optimized formulation F-3 had a drug dissolving rate of 100.83% ±0.68 after 10 minutes, making it suitable for testing antifungal efficacy against *Candida albicans*. This formula was compared to pure CLM (St) and saliva-simulating buffer at pH 6.8 (Ct). Table 8 displays the findings for determining the diameter of the zone of growth inhibition. The findings for medicated lozenges F-3 were 32 mm, while pure CLM yielded 23 mm. Compared to pure CLM, medicated lozenges F-3 had a higher zone of growth inhibition ($p < 0.05$), showing superior antifungal activity. These results indicated that the dissolution improvement by the solid dispersion method was efficient for delivering CLM for treatment of the infection by *Candida albicans*. No inhibitory impact of saliva imitating buffer at pH 6.8 was noticed. As illustrated in Figure 9, there is a substantial difference in the fungi's sensitivity to CLM when administered as a solid dispersion versus a pure drug. CLM's efficacy against candida species increased as its low water solubility and bioavailability improved. Overall, increasing the solubility of CLM has been proven to greatly improve its efficacy against *Candida albicans*. This suggests that formulation solutions that include complexation techniques or solubility enhancers could improve CLM's antifungal activity [10, 12]. However, in other studies, when its solubility was not improved by any approach for enhancing drug dissolution before it was incorporated into dosage forms, the zone of inhibition remained identical for the pure drug [16,49].

Table 8: The antifungal activity of the solid dispersion of CLM/PEG 6000 medicated lozenges, F-3 (T), pure CLM (St) and saliva simulating buffer at pH 6.8 (Ct) (n=6)

Formulation code	Inhibition Zone (mm)	P- value
T	32	< 0.05
St	23	
Ct	-	

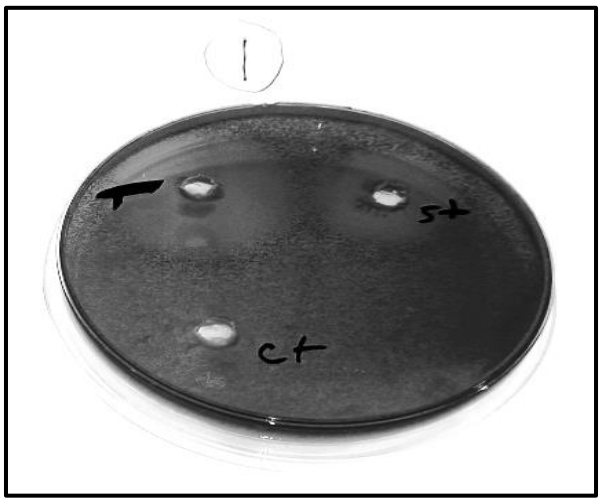

Figure 9: *The inhibition zone of growth of* Candida albicans in the agar well diffusion method. (T): *the solid dispersion of CLM/PEG 6000 medicated lozenges*, F-3, (St): pure CLM and (Ct): *saliva simulating buffer at pH 6.8*

Conclusion

In conclusion, to improve CLM dissolution efficiency, a solid dispersion containing PEG 6000 and PVP at various ratios was made. The dissolving efficiency of 1:1 CLM to PEG 6000 exceeded that of the pure drug. This solid dispersion of CLM and PEG 6000 was effectively made into lozenges. The optimized formulation completely released the drug within 10 minutes and had strong antifungal action against Candida albicans. This solid dispersion of CLM/PEG 6000 medicated lozenges may reduce the need for frequent dosing, minimize drug side effects, and provide patients with better convenience, compliance, and comfort during administration..

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Disclosure

The authors declare no conflict of interest in the manuscript.

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بحث علمي

صياغة وتقييم أقراص الاستحلاب العلاجية التي تحتوي على التشتت الصلب لكلوتريمازول/PEG 6000 لعلاج داء المبيضات الفموي

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الملخص

تهدف الدراسة إلى صياغة كلوتريمازول (CLM) على شكل أقراص استحلاب علاجية صلبة ذات ذوبان معزز لعلاج داء المبيضات الفموي البلعومي. وهي مناسبة للعديد من المرضى وسهلة الاستخدام. في هذه الدراسة تم استخدام طريقة التبخر بالمذيبات لتحضير مشتتات صلبة من CLM باستخدام البولي إيثيلين جلايكول 6000 والبولي فينيل بيروليدون بنسب وزن مختلفة من الدواء إلى الناقل. وجدت الدراسة أن البولي إيثيلين جلايكول 6000 ، عند استخدامه بنسبة وزن 1:1، أدى إلى تحسن كبير في ذوبان الكلوتريمازول. كما أظهرت نتائج دراسات FTIR أن الدواء كان منتشرًا في البولي إيثيلين جلايكول 6000، كما لم يكن هناك أي تفاعل دوائي مع السواغات المستخدمة في تركيبات أقراص الاستحلاب العلاجية. تم استخدام تصميم مكون من 32 عاملًا لتطوير وتحسين وتقييم تسع تركيبات من التشتت الصلب للمعينات المعالجة بـ الكلوتريمازول / البولي إيثيلين جلايكول 6000 لتحسين النتائج العلاجية. لقد قمنا بتصنيع المعينات باستخدام عوامل التبلور البوليمرية المتوافقة حيويًا (الكيتوزان، وسليلوز الميثيل، والجينات الصوديوم) على ثلاثة مستويات مختلفة (0.5، 1، و1.5%). كانت جميع أقراص الاستحلاب العلاجية موحدة في الوزن ومحتوى الدواء ضمن حدود دستور الأدوية الأمريكي، مع معدلات إطلاق دوائية كاملة تتراوح بين 10-20 دقيقة لتركيبات الشيتوزان الجينات الصوديوم، مقارنة بـ 60 دقيقة لسليلوز الميثيل. وأظهرت النتائج أن نوع البوليمر وتركيزه له أثر بشكل كبير على إطلاق الدواء. أظهرت الصيغة المحسنة، F-3، التي تحتوي على 1.5% CH، إطلاقًا دوائيًا بنسبة 100.83% ±0.68 في نهاية 10 دقائق. حيث أظهرت نشاطًا مضادًا للفطريات بشكل كبير ضد المبيضات البيضاء ($P < 0.05$)، مما يجعله مناسبًا لتوصيل الدواء إلى تجويف الفم.

مفاتيح البحث

التسليم : 29 يونيو 2024

القبول : 16 أغسطس 2024

كلمات مفتاحية :

كلوتريمازول، المشتتات صلبة، أقراص استحلاب علاجية، إطلاق الدواء في المختبر، المبيضات البيضاء.