

## BI-LAMINATED ORAL DISINTEGRATING FILM FOR SYMPTOMATIC TREATMENT OF VIRAL NASOPHARYNGITIS: FORMULATION, CHARACTERIZATION, TASTE MASKING, AND STABILITY STUDIES

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### ABSTRACT

**Objective:** Nasopharyngitis (NP) is one of the most common upper respiratory tract infections (URTIs) brought on by viral infections and requires symptomatic treatment. In this study, a new approach to delivering drugs was developed, which is a bi-laminated oral disintegrating film (ODF) containing dextromethorphan hydrobromide (DEX), phenylephrine hydrochloride (PE), and methylcobalamin (MeCbl) to support the symptomatic treatment of NP. Yet, the extreme bitterness of DEX and PE required a taste-masking technique before ODF formulation to enhance patient compliance.

**Methods:** Various complexing agents were tried at different ratios to mask the bitter taste of the drug(s). DEX-PE ODFs were formulated using the solvent casting procedure. A 3<sup>1</sup>.2<sup>1</sup> full factorial design was performed to characterize DEX-PE ODFs, where the effects of polymer grade and plasticizer type were evaluated on the disintegration time (DT) and the percentage of drugs released after 10 min (Q<sub>10</sub>).

**Results:** Complexation with maltodextrin (MD) and ion exchange resin (Kyron T-314) could successfully mask the bitter taste at a ratio of 1:2:2 of drugs, MD, and Kyron T-314, respectively. The ODF optimized formula (F4) recorded the least DT (5±0.5 s) and highest Q<sub>10</sub> (96.7±2.1%) and (97.4±1.9%) for DEX and PE, respectively. F4 was then combined with the second film layer containing MeCbl to develop the bi-laminated ODF (B1), which was later evaluated and subjected to stability studies.

**Conclusion:** In conclusion, a taste-masked, bi-laminated ODF could be successfully developed for the symptomatic treatment of NP.

**Keywords:** The oral disintegrating film, Taste masking, Ion-exchange resin, Bi-laminated, Stability studies

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### INTRODUCTION

Oral disintegrating film (ODF) is one of the most innovative oral drug delivery technologies that enhances patient acceptability. It dissolves rapidly in the mouth without chewing or drinking water. This method of administration is suitable, especially for the geriatric and pediatric populations that have difficulty swallowing traditional oral dosage forms [1, 2].

Nasopharyngitis (NP), generally known as the common cold, is among the most common upper respiratory tract infections (URTIs). NP's symptoms include weakness, nasal congestion, headache, cough, sore throat, and other symptoms. NP is caused by viral infections of the upper respiratory tract, and its treatment is primarily symptomatic [3, 4]. Dextromethorphan hydrobromide (DEX) is a non-narcotic antitussive drug that acts centrally on the cough center and alters the brain signals that cause the cough reflex. In 1958, the FDA approved it as an over-the-counter cough suppressant [5, 6]. According to the Biopharmaceutics Classification System (BCS), DEX is classified as a class II drug [7]. Phenylephrine hydrochloride (PE) treats nasal congestion and cough in URTIs, sinusitis, and rhinitis [8]. In the BCS classification, phenylephrine hydrochloride is a class I molecule [9]. Both drugs have an extremely bitter taste because of the amine functional group [6]. Methylcobalamin (MeCbl) is a water-soluble vitamin belonging to the B complex. It has crucial roles in the cardiovascular and circulatory systems, as well as in the control of the immune system and antiviral activities. Because of its role in neuromuscular diseases and its ability to act as an analgesic, vitamin B12 can be considered an adjuvant therapy for mild to severe respiratory viral infections because of its significant role in viral infections [10]. MeCbl, as a form of vitamin B12, is classified as BCS class three [11].

One of the biggest challenges in developing drug formulations is masking the bitter-tasting active pharmaceutical ingredients to achieve an acceptable level of palatability. Taste masking can be done using a variety of techniques, including the addition of sweeteners, flavoring agents, ion exchange resins, and complexing agents such as  $\beta$ -cyclodextrins (CDs) and maltodextrins (MDs) [12, 13].

This work aimed to formulate a taste-masked formula of DEX-PE to be incorporated into the first film layer of a bi-laminated ODF. Formulation and characterization of several DEX-PE ODFs were done by assessing the formulation factors impacting the ODF characteristics via a 3<sup>1</sup>.2<sup>1</sup> full factorial design using Design-Expert® software version 12. The optimized formula of DEX-PE ODF was combined with a second film layer containing MeCbl, which was evaluated to develop a bi-laminated ODF. The bi-laminated ODF was subjected to shelf and accelerated stability studies to ensure the stability of the final formula.

### MATERIALS AND METHODS

#### Materials

DEX, PE, and MeCbl were gifted by Eva Pharma (Giza, Egypt). Kyron T314 was supplied by Corel Pharma (Gujarat, India). The lemon flavor was purchased from Kamena (Cairo, Egypt). Sucralose was brought from Gangwal Healthcare Private Limited (Maharashtra, India). MD was purchased from Cargill (Delhi, India). CD was purchased from Shandong Binzhou Zhiyuan Biotechnology Co., Ltd. (Binzhou, China). HPMC E5, HPMC E15, and HPMC E50 were purchased from Colorcon Limited (Kent, England). PEG400 was purchased from Nitika (Nagpur, India). Propylene glycol (PG) was purchased from Basf Fine Chemicals (Ludwigshafen, Germany). Glycerin and sodium perchlorate monohydrate were purchased

from Merck (Steinheim, Germany). Distilled water. All other reagents and chemicals used were of analytical grade.

## Methods

### Preparation of the taste-masked formulae

Several trials were prepared to select the most taste-masked formula, where each trial was prepared inside a 200-ml glass

beaker containing 100 ml of distilled water, 0.5 g of DEX, 0.25 g of PE, 0.2 g of sucralose as a sweetener, and 0.1 g of lemon flavor as a flavoring agent. Then, different combinations of ion-exchange resin (Kyron T-314), CD, and MD as taste-masking agents were added at two ratios of (1:1) or (2:1) to the drug(s), as shown in table 1. Each preparation was stirred for 30 min using an Ika Eurostar 20 digital overhead stirrer (Staufen, Germany) [14].

**Table 1: The composition of taste-masked trials for DEX and PE**

Formula code	Ingredients in (g) per 100 ml of distilled water		
	CD	MD	Kyron T-314
T1	-	-	-
T2	0.75	-	-
T3	1.5	-	-
T4	-	0.75	-
T5	-	1.5	-
T6	-	-	0.75
T7	-	-	1.5
T8	0.75	-	0.75
T9	1.5	-	1.5
T10	-	0.75	0.75
T11	-	1.5	1.5

CD,  $\beta$ -cyclodextrin; MD, maltodextrin.

### In vivo evaluation of the taste-masked trials

Six healthy volunteers participated in the *in vivo* evaluation of the taste-masked trials. The Research Ethics Committee (REC-FOPCU) at the Faculty of Pharmacy at Cairo University, Egypt, gave the study protocol its permission (protocol No. PI (3189)). Participants were fully aware of the study's nature and goal before

it began, and they gave written consent. 1 ml of each prepared formula, equivalent to 5 mg of DEX and 2.5 mg of PE, was administered on the tongue of the six volunteers and then spit out after 5 seconds, followed by a mouth rinse with water before administering the next one. The bitterness degree was recorded to select the most taste-masked formula. The optimized taste-masked formula was subjected to further studies [6, 15].

**Table 2: A 3<sup>1</sup>.2<sup>1</sup> full factorial design for the optimization of layer 1**

Factors (independent variables)	Levels
X1 polymer grade	HPMC E5 HPMC E15 HPMC E50
X2 plasticizer type	PG+Glycerin PEG400+Glycerin
Response (dependent variables)	Desirability constraints
Y1: DT (s)	Minimize
Y2: % (DEX-PE) released after 10 min (Q <sub>10</sub> )	Maximize

HPMC, hydroxypropyl methylcellulose; PG, propylene glycol; PEG, polyethylene glycol; DT, disintegration time; DEX, dextromethorphan hydrobromide; PE, phenylephrine hydrochloride.

**Table 3: Different compositions of DEX-PE ODFs and the Bi-laminated ODF**

Formula code	DEX-PE ODFs' ingredients (mg)					PG: Glycerin (2:1)			PEG400: Glycerin (2:1)		
	HPMC E5	HPMC E15	HPMC E50	PG: Glycerin (2:1)	PEG400: Glycerin (2:1)	HPMC E5	HPMC E15	HPMC E50	PG: Glycerin (2:1)	PEG400: Glycerin (2:1)	
F1	T11*	50							10:5		
F2	T11*		50						10:5		
F3	T11*			50					10:5		
F4	T11*	50								10:5	
F5	T11*		50							10:5	
F6	T11*			50						10:5	

The formula of the bi-laminated ODF containing DEX, PE, and MeCbl (mg)

Formula code	DEX-PE Layer Ingredients (mg)					MeCbl Layer Ingredients (mg)				
	DEX	PE	HPMC E5	PEG400: Glycerin (2:1)	Kyron T314	MeCbl	HPMC E5	HPMC E15	HPMC E50	PEG400: Glycerin (2:1)
B1	5	2.5	50	10:5	15	0.5	50	50	50	10:5

\*The optimized taste-masked formula contains DEX (5 mg), PE (2.5 mg), Kyron T314 (15 mg), MD (15 mg), sucralose (2 mg), and lemon flavor (1 mg) per film. HPMC, hydroxypropyl methylcellulose; PG, propylene glycol; PEG, polyethylene glycol; DEX, dextromethorphan hydrobromide; PE, phenylephrine hydrochloride; MeCbl, methylcobalamin; MD, maltodextrin.

### Evaluating the effect of different ODF formulation variables using a full factorial design

Polymer grade (X1) with three levels (HPMC E5, HPMC E15, and HPMC E50) and plasticizer type (X2) with two levels (PG+glycerin and PEG400+glycerin) were investigated as two independent

variables using a 3<sup>1</sup>.2<sup>1</sup> full-factorial design via Design-Expert® software version 12 Stat-Ease, Inc., Minneapolis, MN, USA).

The dependent variables were disintegration time (DT) (Y1) and percent released after 10 min (Q<sub>10</sub>) (Y2), as shown in table 2. The compositions of the six formulae developed are shown in table 3.

### Formulation of DEX-PE ODFs

DEX-PE ODFs were formulated via the solvent casting procedure using three different polymer grades (HPMC E5, HPMC E15, or HPMC E50) and two different plasticizer combinations (PEG400+glycerin or PG+glycerin), where the polymer and the plasticizers were weighed and dissolved in distilled water to form a polymeric solution. Then, DEX and PE were dissolved in distilled water and stirred with Kyron T314, MD, lemon flavor, and sucralose for 30 min to be transferred to the previous polymeric solution. The preparation was left for 24 h to remove all air bubbles and transferred for coating using an ODF coating machine (Optimags, Germany). The drying process was performed at 60 °C at a speed of 3 m/h. The film was peeled off and cut to the desired size (2 x 3 cm<sup>2</sup>), then stored in an aluminum foil pouch until evaluation [16].

### Characterization of DEX-PE ODFs

#### Visual examination

The homogeneity and color of all the prepared DEX-PE ODFs were assessed visually [17].

#### Film thickness

As the thickness of the film directly influences the uniformity of the drug(s) content, it is crucial to maintain uniformity in the film's thickness. Using a digital thickness gauge meter (Shanghai, China), the thickness of each film was measured in different areas. The average thickness and the standard deviation (SD) were then determined [18].

#### Surface pH

The ODF was placed on a petri dish and moistened with 0.5 ml of simulated saliva fluid (SSF) of pH 6.8 for 30 s. A pH meter was used to record the pH. The results were presented as the mean±SD [19].

#### Drug content

Drug content analysis was performed to confirm the drug loading in the film using high-performance liquid chromatography (HPLC) coupled with an ultraviolet-visible (UV-VIS) detector [20]. One film (2 x 3 cm<sup>2</sup>) was dissolved in 200 ml of SSF, followed by a dilution of 20 ml into 100 ml of SSF to get a final concentration of 5 µg/ml and 2.5 µg/ml of DEX and PE, respectively. The sample is filtered through an Agilent PTFE 0.45 µm syringe filter to be analyzed by HPLC. Chromatographic separation was carried out at a 200 nm wavelength on an Inertsil C18 (4.6 mm x 15 cm, 5 µm) column at a temperature of 40 °C, using a mobile phase composed of 2% acetonitrile and 98% buffer that is prepared by dissolving 3g of sodium perchlorate monohydrate in 1000 ml of distilled water and adjusted to pH 3 by orthophosphoric acid. A membrane filter with a 0.45 µ pore size was used to filter the mobile phase. The analysis was performed at a 1 ml/min flow rate and an injection volume of 100 µl. All measurements were done in triplicate, and the values were represented as the mean±SD.

#### Construction of a standard calibration curve for DEX and PE

Serial concentrations of 2, 3, 4, 5, 6, 7, 8, and 9 µg/ml for DEX and 1, 1.5, 2, 2.5, 3, 3.5, 4, and 4.5 µg/ml for PE were prepared using SSF. The peak area responses of the prepared solutions were measured by HPLC at the above-mentioned chromatographic conditions. The measured peak area responses were plotted against the corresponding concentrations. The linearity correlation coefficient ( $r^2$ ) and % RSD for peak area response for lower and higher concentrations were calculated.

#### Folding endurance

It was repeatedly folding the film 180 degrees in the same spot more than 100 times until it broke. The value of folding endurance was determined [21].

#### In vitro disintegration time (DT)

The pharmacopeial disintegration apparatus was used to carry out the disintegration test. Separately, six films were put into the tubes of the USP apparatus, which were then allowed to move up and down in the

disintegration medium (phosphate buffer, pH 6.75 at 37±1 °C) at a rate of 30 times per minute, and the time taken for the films to start disintegration was recorded. The average and SD were determined [22].

#### In vivo evaluation of ODF disintegration time

Six healthy volunteers participated in the evaluation of the *in vivo* disintegration time of ODFs. The Research Ethics Committee (REC-FOPCU) at the Faculty of Pharmacy at Cairo University, Egypt, gave the study protocol its permission (protocol No. PI (3189)). Participants were fully aware of the study's nature and goal before it began, and they gave written consent. Participants were instructed to put the film on their tongues, gently slide it on the hard palate of their mouths, and let it dissolve. The lack of the tongue's sensory detection of the films indicated their full disintegration, which was also confirmed by the researcher's monitoring of their absence. The participants were then instructed to wash their mouths with a glass of water. The disintegration time was recorded for each formula [23].

#### In vitro drug release

The test was done via the USP dissolution system, Agilent (California, USA), USP Apparatus 5 (paddle over disc) at 37±0.5 °C at a speed of 50 rpm using 900 ml of SSF (pH 6.8). Samples were withdrawn at 5, 10, 15, 20, and 30-minute intervals. The percentage of drugs released was measured by HPLC [24].

#### Optimization of DEX-PE ODFs

An efficient approach for selecting the optimized formula was to use Design Expert® software version 12. The optimum formula was chosen as the ODF with the fastest DT and highest Q<sub>10</sub>.

#### Drug-excipient compatibility testing

Testing for drug-excipient compatibility can be performed using various techniques to determine any incompatibility between drug and excipient combinations. A trustworthy result is produced using HPLC technology coupled with a UV-Vis detector in assessing drug excipient compatibility [24]. Drug-excipient blends (1:1) underwent isothermal stress testing (IST), which promotes any incompatibilities and speeds up drug interactions with the excipients by being heated to a high temperature (>50 °C) for about 3–4 w [25].

#### Simultaneous determination of DEX, PE, and MeCbl by HPLC

Chromatographic separation of DEX, PE, and MeCbl in SSF was carried out by HPLC equipped with a UV-Vis detector at the same chromatographic conditions mentioned earlier. A standard calibration curve of MeCbl was constructed where serial concentrations of 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, and 0.9 µg/ml of MeCbl were prepared using SSF. The measured peak area responses were plotted against the corresponding concentrations. The  $r^2$  value and % RSD for peak area responses for lower and higher concentrations were calculated.

#### Bi-laminated ODF formulation comprising DEX, PE, and MeCbl

The DEX-PE optimized ODF (F4) and the MeCbl-ODF layer formed the composition of the bi-laminated ODF (B1), as shown in table 3. The solvent casting method, as explained earlier, was used to develop each layer using the ODF Coating Machine (Optimags, Germany). The first layer (DEX-PE) was cast and dried at a temperature of 60 °C and a speed of 3 m/h, followed by releasing the second layer (MeCbl) over the first one at a temperature of 40 °C and a speed of 3 m/h to form the bi-laminated ODF (B1), which was subsequently cut and subjected to further evaluation [26]. When DEX, PE, and MeCbl were combined into one film as an initial formula (U1), the temperature required for drying the whole film was 65 °C. This could be explained by the higher thickness of the initial formula (U1) than that of the MeCbl layer. Since MeCbl is known to undergo thermal degradation [27], It was recommended to develop a bi-laminated ODF that contained DEX and PE in one layer and MeCbl in the second, with drying temperatures of 60 °C and 40 °C, respectively. Both trials were subjected to further stability studies.

#### Bi-laminated ODF (B1) characterization

The bi-laminated ODF (B1) was tested using the same characterization tests and procedures previously done on the DEX-PE ODFs.

### Stability studies of the bi-laminated ODF (B1)

Since any pharmaceutical formulation's performance is significantly influenced by its stability, the optimized bi-laminated ODF formula (B1) and the initial formula (U1) were packed in sealed triple-laminated aluminum pouches and kept for three months in Thermolab Walk-In Stability Chambers (Thermolab House, Maharashtra, India) at shelf stability conditions (25 °C, 60% relative humidity (RH)) and accelerated stability conditions (40 °C, 75% RH) by the International Council on Harmonization guidelines. After three months, they were examined for their surface pH, folding endurance, film thickness (mm), drug content (%), DT, and  $Q_{10}$  [28, 29].

### Statistical analysis

The experimental findings of DEX-PE ODFs' characterization were analyzed using GraphPad Prism 5.01 statistical software (GraphPad Software, Inc., La Jolla, CA, USA). A one-way analysis of variance

(ANOVA) was performed, followed by Tuckey's test, to assess the significance among the formulated (DEX-PE) ODFs regarding the dependent variables (DT and  $Q_{10}$ ). Additionally, the *in vitro* and *in vivo* DT results were tested for each formula to determine the *in vitro/in vivo* correlation. The significance or non-significance of stability studies' results on B1 ODF and U1 ODF were also analyzed. The results are considered statistically significant when (\* $p < 0.05$ ).

### RESULTS AND DISCUSSION

#### *In vivo* taste evaluation of DEX and PE

Table 4 shows the findings of the taste evaluation. The bitterness degree was recorded for each formula. The drug(s) alone in T1 had an extremely bitter taste. In contrast, no bitterness was perceived in T11, which indicates successful taste masking of both DEX and PE using a combination of MD and ion-exchange resin (Kyron T-314) at a ratio of 1:2:2 of drugs: MD: Kyron T-314, respectively.

Table 4: *In vivo* taste evaluation of the taste-masked formulae

Formula code	Drug(s)/CD/MD/Kyron T-314	Drug(s): CD/MD/Kyron T-314 ratio	Bitterness degree
T1	Drug(s)	-	xxx
T2	Drug(s)/CD	1:1	xxx
T3	Drug(s)/CD	1:2	xx
T4	Drug(s)/MD	1:1	xxx
T5	Drug(s)/MD	1:2	x
T6	Drug(s)/Kyron T-314 resin	1:1	xx
T7	Drug(s)/Kyron T-314 resin	1:2	x
T8	Drug(s)/CD/Kyron T-314 resin	1:1:1	xx
T9	Drug(s)/CD/Kyron T-314 resin	1:2:2	x
T10	Drug(s)/MD/Kyron T-314 resin	1:1:1	x
T11	Drug(s)/MD/Kyron T-314 resin	1:2:2	+

xxx: extremely bitter; xx: bitter; x: slightly bitter; +: no bitterness. CD,  $\beta$ -cyclodextrin; MD, maltodextrin.

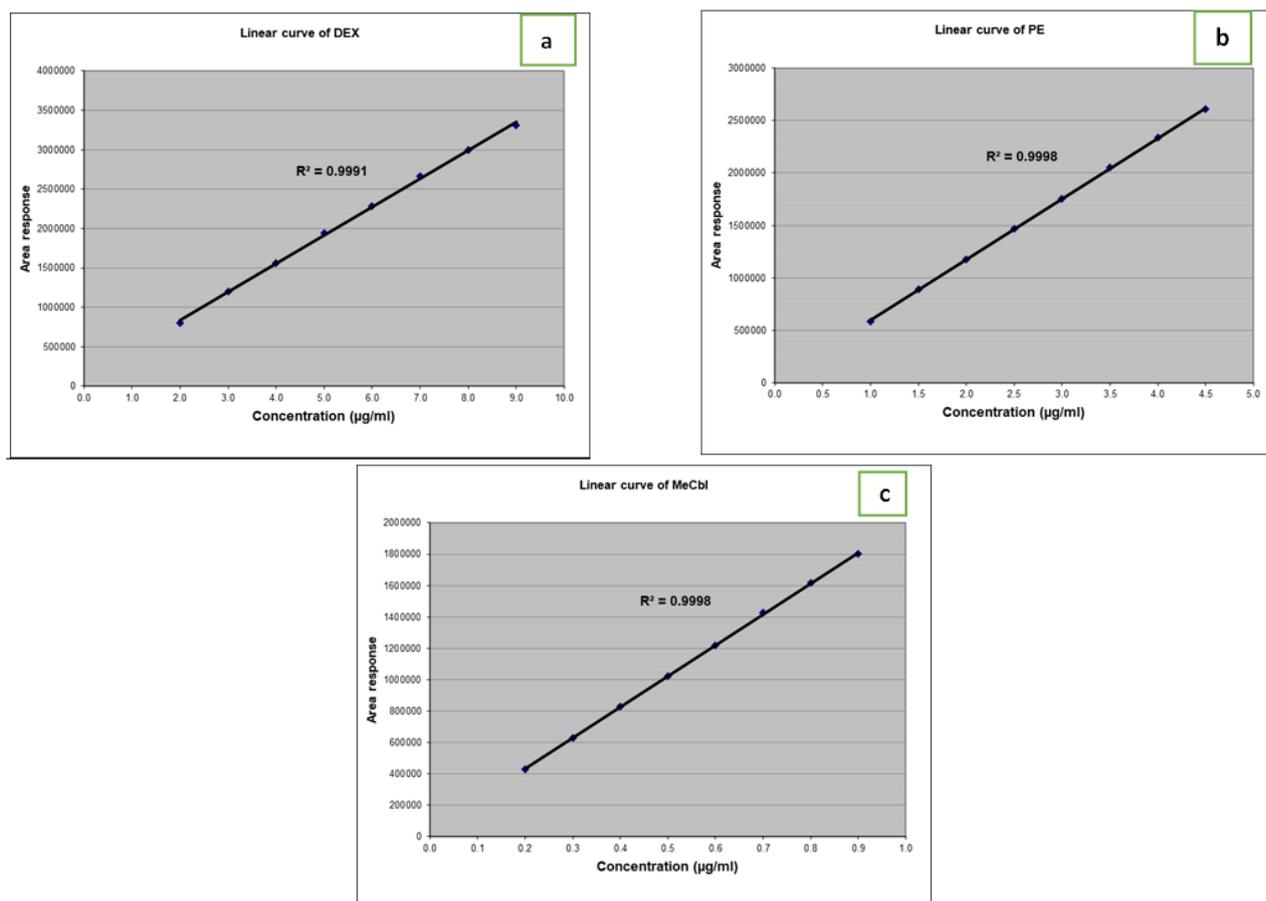


Fig. 1: Standard calibration curve of (a) DEX, (b) PE, and (c) MeCbl in SSF

### Standard calibration curves of DEX, PE, and MeCbl

The calibration curve plots demonstrate linearity over a range of 40 to 180% of working level concentration, as shown in fig. 1, with  $r^2$  values of 0.9991, 0.9998, and 0.9998 for DEX, PE, and MeCbl, respectively, and % RSD of 1.41%, 0.52%, and 0.63% for DEX, PE, and MeCbl, respectively.

### Characterization of DEX-PE ODFs

Table 5 shows the results of the formulated DEX-PE ODFs. The films were white, thin, and smooth, as shown in fig. 2. The DEX-PE ODFs had thickness values ranging from 0.115 mm $\pm$ 0.01 mm for F1 to 0.125 mm $\pm$ 0.01 mm for F6 and a surface pH ranging from 6.78 $\pm$ 0.05 for F5 to 6.89 $\pm$ 0.05 for F3, which was close to the salivary pH (6.8). All the films exhibited values for folding endurance up to 300 folds, demonstrating the films' good flexibility [21]. The drug content of the prepared DEX-PE ODFs was found within the pharmacopeia specifications in all the formulae, ranging from 98.5 $\pm$ 0.8% to 100.6 $\pm$ 0.5% and from 98.7 $\pm$ 0.3% to 99.8 $\pm$ 0.3% for DEX and PE, respectively, and this shows that the drug(s) were distributed uniformly throughout the film [21]. Fig. 3 and 4 reveal the effect of formulation variables on the results of DT and  $Q_{10}$  of DEX-PE ODFs. The grade of the polymer (X1) and the type of

plasticizer (X2) had a statistically significant effect on DT and  $Q_{10}$  of DEX-PE ODFs (\*\* $p$ <0.01), where ODF (F4), formulated by HPMC E5 and PEG400, recorded the shortest DT (5 $\pm$ 0.5 s) and the greatest  $Q_{10}$  (96.7 $\pm$ 2.1% for DEX and 97.4 $\pm$ 1.9% for PE). On the other hand, ODF (F3) based on HPMC E50 and PG recorded the longest DT (42 $\pm$ 1.2 s) and the least  $Q_{10}$  (61 $\pm$ 2.5% for DEX and 67.4 $\pm$ 2.9% for PE). This could be explained by the fact that as the molecular weight and viscosity of the polymer increase, the disintegration time increases, and thus the release rate ( $Q_{10}$ ) decreases. The polymer grades can be arranged according to their molecular weight and viscosity, from lowest to highest: HPMC E5<HPMC E15<HPMC E50 [30, 31]. The surface of the HPMC E5-based films was porous and developed a network-like structure that allowed rapid disintegration and dissolution by Jadhav *et al.* [32]. It was observed that films with PEG400 had faster disintegration and a higher dissolution rate than those with PG. PEG400 had an essential function in the process of dissolution as it not only acted as a plasticizer but also a dissolution-enhancing agent, which could contribute to the strong polarity of PEGs because of the terminal hydroxyl and ether groups in their structure [32, 33]. Additionally, PEG400 has a good dissolution ability owing to its low molecular weight. It causes rapid drug(s) release as it augments the dissolution, which is in harmony with Chopade *et al.* [34].

Table 5: Characterization of DEX-PE ODFs and the bi-laminated ODF (B1)

Formulae code	Thickness (mm)	Surface pH	Folding endurance (Number of folds)	Drug content (%)	DT (s)
DEX-PE ODFs characterization					
F1	0.115 $\pm$ 0.01	6.79 $\pm$ 0.05	293 $\pm$ 1.0	DEX: 99.8 $\pm$ 0.7, PE: 98.7 $\pm$ 0.3	11 $\pm$ 0.5
F2	0.120 $\pm$ 0.01	6.83 $\pm$ 0.05	299.6 $\pm$ 0.5	DEX: 99.6 $\pm$ 0.4, PE: 99.2 $\pm$ 0.5	22 $\pm$ 0.8
F3	0.123 $\pm$ 0.01	6.89 $\pm$ 0.05	294.2 $\pm$ 0.5	DEX: 100.6 $\pm$ 0.5, PE: 99.7 $\pm$ 1	42 $\pm$ 1.2
F4	0.122 $\pm$ 0.01	6.82 $\pm$ 0.05	298 $\pm$ 1.0	DEX: 99.6 $\pm$ 0.5, PE: 99.8 $\pm$ 0.3	5 $\pm$ 0.5
F5	0.124 $\pm$ 0.01	6.78 $\pm$ 0.05	298.6 $\pm$ 0.5	DEX: 98.5 $\pm$ 0.8, PE: 98.8 $\pm$ 0.6	16 $\pm$ 1.0
F6	0.125 $\pm$ 0.01	6.81 $\pm$ 0.05	295.3 $\pm$ 0.5	DEX: 99.1 $\pm$ 1, PE: 99.5 $\pm$ 0.7	31 $\pm$ 1.5
Bi-laminated ODF (B1) characterization					
B1	0.190 $\pm$ 0.05	6.77 $\pm$ 0.05	297 $\pm$ 2.0	DEX: 99.8 $\pm$ 0.5, PE: 99.5 $\pm$ 0.3, MeCbl 101.9 $\pm$ 0.6	7 $\pm$ 1.0

Data are shown as mean $\pm$ SD, n = 3. ODF, oral disintegrating film; DT, disintegrating time; DEX, dextromethorphan hydrobromide; PE, phenylephrine hydrochloride; MeCbl, methylcobalamin.

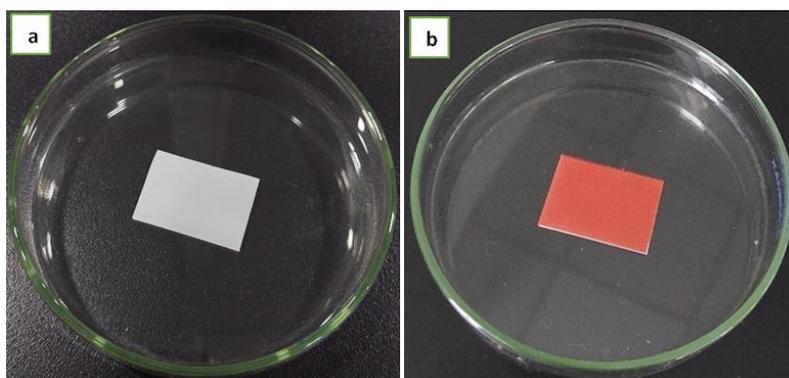


Fig. 2: Photograph of (a) DEX-PE ODF cut into 2 x 3 cm<sup>2</sup> and (b) the bi-laminated ODF (B1)

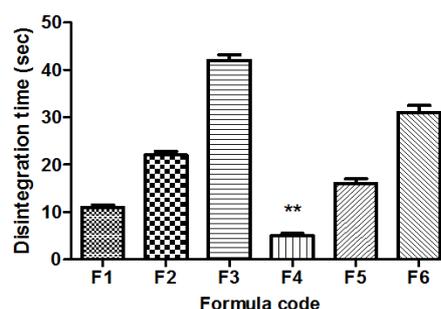


Fig. 3: Disintegration time of DEX-PE ODFs. Data are presented as mean $\pm$ SD, n = 3. At  $p$ <0.01, \*\*F4 significantly differs from the other formulae

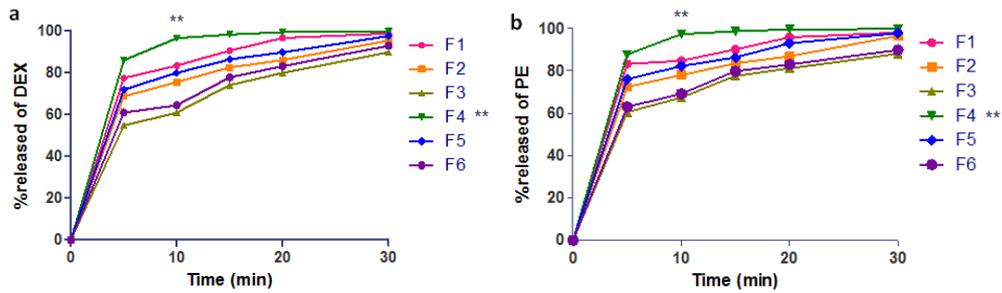


Fig. 4: *In vitro* release profiles of (a) DEX and (b) PE from DEX-PE ODFs. Data are presented as mean±SD, n = 3. At p<0.01, \*\*F4 significantly differs from the other formulae

**The *in vivo* evaluation of DT**

The *in vivo* DT of each formula was recorded, as shown in fig. 5. The *in vitro* and *in vivo* DT of the films were statistically analyzed. It was found that the results of the *in vitro* DT were not significantly different from those of the *in vivo* DT (p>0.05), which confirms the *in vitro/in vivo* correlation of DT.

**Optimization of DEX-PE ODFs**

The F4 formula was chosen by Design Expert® software version 12 to be the optimum formula with the shortest DT (5±0.5 s) and the greatest Q<sub>10</sub> (96.7±2.1%) and (97.4±1.9%) for DEX and PE, respectively.

**Drug-excipient compatibility testing by HPLC**

Fig. 6 presents HPLC chromatograms of the bi-laminated ODF excipients, the drug(s) in combination with the excipients initially, and the drug(s) combined with the excipients after being stored under IST for four weeks. No changes were detected in the peak area responses

between the initial analysis and after IST. The chromatograms show good resolution with no interference between the drugs and the excipients, indicating no interactions or incompatibilities.

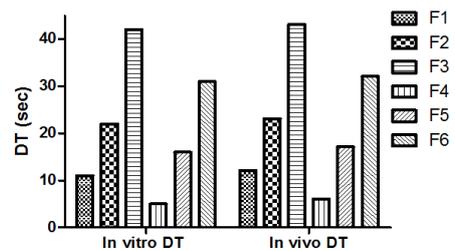


Fig. 5: Bar chart of *in vitro* and *in vivo* DT of DEX-PE ODFs. There was no significant difference between the *in vitro* and *in vivo* DT in all the formulae (p>0.05)

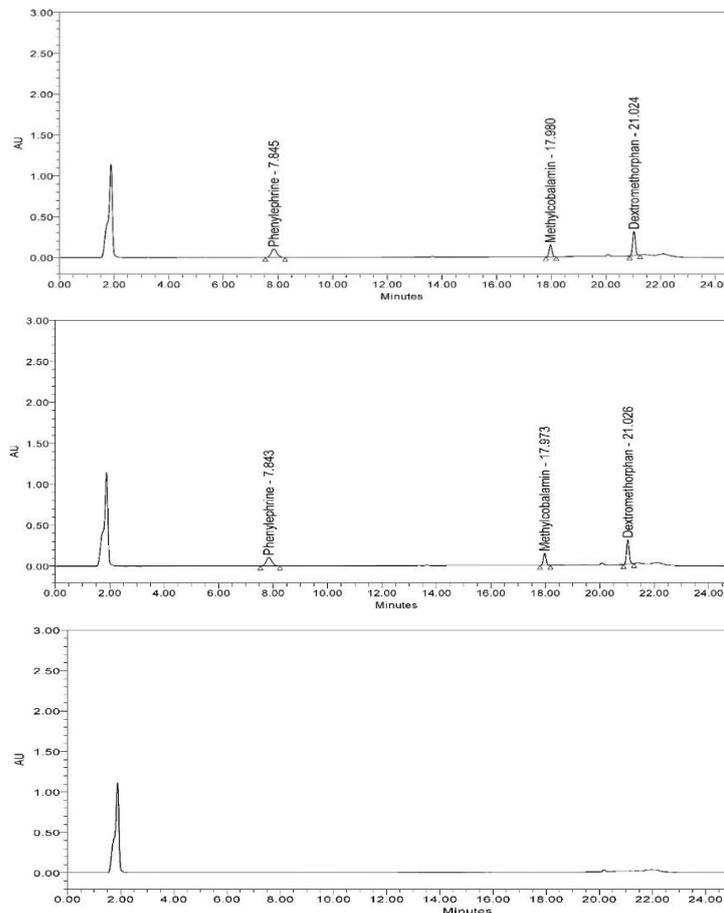


Fig. 6: HPLC chromatogram of (a) DEX, PE, and MeCbl in combination with the excipients (initially), (b) DEX, PE, and MeCbl in combination with the excipients (after IST), and (c) the bi-laminated ODF excipients (after IST)

### Simultaneous determination of DXM, PE, and MeCbl by HPLC equipped with a UV-VIS detector

Fig. 6(a) shows the chromatographic separation of DEX, PE, and MeCbl under the chromatographic conditions mentioned earlier in the Methods. PE, MeCbl, and DXM retention times were determined at around 7.8 min, 17.9 min, and 21.0 min, respectively.

### Characterization and evaluation of the Bi-Laminated ODF (B1)

Table 5 shows the results of the characterization tests performed on the bi-laminated ODF (B1). The DEX-PE layer (F4) was a smooth, thin, and white layer, whereas the MeCbl layer was red since the drug itself has a red color, as shown in fig. 2. B1 ODF has a folding endurance of up to 300 folds, which ensures the bi-laminated film's flexibility. The drug content (%) of the drugs was accepted within the pharmacopeia specifications. The *in vitro*

release ( $Q_{10}$ ) of DEX, PE, and MeCbl in B1 was 96.2%, 96.7%, and 97.1%, respectively.

### Stability studies of the bi-laminated ODF (B1)

The optimized formula (B1) was packed in triple-laminated aluminum pouches. The results over the specified time under accelerated stability conditions are shown in table 6, where visual examination, surface pH, film thickness, folding endurance, DT, and  $Q_{10}$  were not significantly impacted. The drug content (%) decreased from 99.8% to 98.6% for DEX and from 99.5% to 98.8% for PE (p-value>0.05). Drug content (%) of MeCbl decreased from 101.9% to 97.1% and from 98.8% to 92.3% in B1 and U1, respectively, indicating a statistically significant difference (\*p<0.05) between B1 and U1 for MeCbl. This demonstrates that the optimized formula B1 was stable over the three months and confirms its preference over the initial formula U1 regarding MeCbl stability.

Table 6: Stability study of the Bi-laminated ODF (B1)

Tests	Initial	Three months (Shelf)	Three months (Accelerated)
Surface pH	6.82±0.03	6.8±0.05	6.75±0.05
DT (s)	5.0±0.5	5.2±0.7	5.25±0.3
Film Thickness(mm)	0.190±0.003	0.189±0.0035	0.189±0.0038
Folding endurance	298±1.0	297±1.0	297±2.0
Drug content (%): DEX	99.8±0.5	98.9±0.3	98.6±0.7
Drug content (%): PE	99.5±0.3	99.1±1.5	98.8±0.8
Drug content (%): MeCbl	101.9±0.3	99.6±0.4	97.1±0.7
( $Q_{10}$ )-DEX	96.7±0.9	95.8±0.5	95.5±0.5
( $Q_{10}$ )-PE	97.4±1.6	96.6±0.5	96.3±0.6
( $Q_{10}$ )-MeCbl	97.1±0.8	96.2±1.2	95.9±1.6

Data are shown as mean±SD, n = 3. ODF, oral disintegrating film; DT, disintegrating time; DEX, dextromethorphan hydrobromide; PE, phenylephrine hydrochloride; MeCbl, methylcobalamin;  $Q_{10}$ , % drug released after 10 min

### CONCLUSION

A taste-masked, bi-laminated ODF could be successfully developed for the symptomatic treatment of NP. The taste-masking technique before ODF formulation was achieved by the complexation of DEX and PE with MD, along with the use of ion exchange resin (Kyrion T-314) at a ratio of 1:2:2 of drugs: MD: Kyrion T-314, respectively. A 3<sup>1</sup>.2<sup>1</sup> full factorial design was performed to formulate and characterize DEX-PE ODFs. The optimized ODF (F4), based on HPMC E5, PEG400, and glycerin, recorded the least DT and highest  $Q_{10}$ . The optimized formula (F4) was then combined with the second film layer containing MeCbl to develop the bi-laminated ODF (B1), which was later evaluated and subjected to shelf and accelerated stability studies to ensure the stability of the final formula.

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### AUTHORS CONTRIBUTIONS

Merna A. Rizk: Conceptualization, project administration, Methodology, Investigation, writing-original draft, Resources, Funding acquisition, Formal analysis. Mahmoud H. Teaima: project administration, Supervision, Writing-review and editing, methodology, visualization. Rehab Abdelmonem: Writing-review and editing, visualization, Software. Mohamed A. El-Nabarawi: Conceptualization, project administration, Supervision, Writing-review and editing, validation. Sammar Fathy Elhabal: Data curation, writing review and editing, Methodology, visualization, Software, validation.

### CONFLICT OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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