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Research article

DEVELOPMENT AND EVALUATION OF MOUTH DISSOLVING FILM OF DEXTROMETHORPHAN HYDROBROMIDE AND CHLORPHENIRAMINE MALEATE

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Abstract

The combination of dextromethorphan (DXM) and chlorpheniramine maleate (CPM) offers a robust therapeutic strategy for managing cough and allergic symptoms, grounded in their complementary pharmacological mechanisms. The objective of the present investigation was to formulate a mouth dissolving film for the drug combination. A further objective was to mask the bitter taste of the drugs. Simultaneous equation method was used for analysis of the two drugs as they show absorbance at λmax of each other. Film was formulated using hydroxypropyl methyl cellulose E5 as film former and polyethylene glycol 400 as plasticizer. Face-centered factorial design was applied to optimize the amount of polymer and plasticizer so as to get high folding endurance coupled with minimum disintegration time. First order model for folding endurance and perfect quadratic model were selected for disintegration time. Mathematical models were generated for folding endurance and disintegration time. Contour plots were generated for both the response and overlayed to identify the desirable zone. Checkpoint batch was identified and the selected combination was used to prepare the film. The observed value was in agreement with the predicted value. This formulation was taken forward for taste masking using Sucralose and Aspartame. The final formulation was tested for taste masking using Brief Access Taste Aversion model which indicated better acceptance of formulation as compared to plain drug solution. The formulation was found to be stable over a period of 1 month at ambient conditions.

Keywords: Mouth dissolving film, Face centered factorial design, RStudio, Simultaneous equation method

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Introduction

Mouth dissolving films (MDFs) represent a state-of-the-art development in drug delivery systems, offering heightened bioavailability through the utilization of the oral mucosa for drug absorption. [1] This formulation type rapidly disintegrates upon interaction with saliva, allowing the drug to be absorbed directly through the mucosa of intraoral cavity. The oral mucosa, characterized by its extensive vascularization and high permeability, enables swift systemic circulation of the drug, bypassing the gastrointestinal tract and evading hepatic first-pass metabolism. [2] This mechanism significantly increases drug bioavailability and quickens the onset of therapeutic action, which is particularly beneficial for drugs with poor gastrointestinal stability, low solubility, or those exposed to substantial first-pass metabolism.[3]

MDFs are formulated with hydrophilic polymers that warrant quick disintegration, alongside plasticizers, superdisintegrants, and permeation enhancers to augment drug release and mucosal absorption.[4] This delivery system is especially valuable for drugs with narrow therapeutic index, as it allows for more precise dose control. MDFs are suitable for a wide range of therapeutic agents, including antihistamines, antiemetics, and cardiovascular drugs, offering better pharmacokinetic profiles compared to conventional oral dosage forms. [5] However, despite their several benefits, MDFs face certain limitations, such as restricted drug loading ability and sensitivity to environmental factors like temperature and humidity, which can affect stability.[6] Additionally, the challenge of taste-masking bitter drugs remains a noteworthy consideration in formulation. [7]

Dextromethorphan (DXM), a widely used antitussive agent in over-the-counter cough preparations, is highly suitable candidate for formulation as MDFs due to its physicochemical properties. [8] DXM has moderate aqueous solubility, which facilitates its dissolution in saliva and ensuing absorption via the oral mucosa. Its lipophilic nature, indicated by a Log P value of 3.23, augments its permeation through the lipid-rich mucosal membrane, thereby taming systemic bioavailability and confirming a rapid onset of action, crucial for effective cough management. Additionally, DXM's pKa of 9.36 suggests it largely exists in a non-ionized form at physiological pH, favouring its transmembrane diffusion.[9] Despite its mild bitter taste, MDFs can include taste-masking agents to enhance palatability. This formulation strategy not only optimizes DXM's therapeutic efficacy but also increases patient compliance by providing an alternate to conventional solid dosage forms, predominantly for individuals with dysphagia.[10]

Chlorpheniramine maleate (CPM), a first-generation antihistamine, is also a model candidate for mouth-dissolving films due to its physicochemical traits. Solubility profile of CPM, with a water solubility of 1 g/100 mL, ensures rapid dissolution in saliva and effective mucosal absorption. Its Log P value of 3.13 indicates sufficient lipophilicity to support permeability through the oral mucosa, facilitating quicker systemic absorption and dipping the onset time of action—key for prompt relief from allergic signs. [11] The pKa of CPM, approximately 9.2, means it is chiefly in its non-ionized form at physiological pH, enhancing its ability to diffuse across mucosa. Bitter taste of CPM can be overcome by inclusion of sweeteners and flavoring agents.

The amalgamation of DXM and CPM in a single formulation provides a robust therapeutic strategy for handling both cough and allergic symptoms. DXM acts as a non-opioid antitussive by modifying NMDA and sigma-1 receptors in the medullary cough center, effectively decreasing non-productive coughs.[12] Conversely, CPM, as an H1-antihistamine, antagonizes histamine receptors to lessen symptoms such as rhinorrhea, sneezing, and itching.[13] This complementary pharmacological action takes care of primary symptoms of upper respiratory conditions simultaneously, offering comprehensive symptomatic relief. The pharmacokinetic profiles of DXM and CPM are well-suited for oral administration, with DXM attaining peak plasma levels within 2-3 hours and CPM giving sustained antihistaminic effects due to its judicious absorption. Combining these drugs into a single formulation not only enhances patient compliance by simplifying dosing regimens but also reduces side effects associated with higher doses of individual drugs. This synergy expands treatment outcomes and adherence, particularly for patients experiencing collective cough and allergy symptoms.

Several commercial products combine DXM and CPM to deliver comprehensive relief from cough and allergy symptoms. Notable products include Tylenol® Cold Multi-Symptom, Dimetapp® Cold & Allergy, Delsym® Cough + Allergy and Robitussin® Cough & Allergy. These products are available as tablets, syrups, and lozenges, catering to different patient preferences. Tablets offer ease of administration and longer shelf life, syrups are chosen for ease of swallowing and faster action, and lozenges provide a portable choice.

In MDF formulations, aspartame and sucralose are important sweeteners used for taste masking. Aspartame, roughly 200 times sweeter than sucrose, counteracts bitterness effectively [14], while sucralose, approximately 600 times sweeter, offers powerful sweetness and stability across various conditions.[15] Both sweeteners enhance palatability and patient compliance by masking disagreeable drug flavors, making MDFs more satisfactory, especially for paediatric and geriatric population.

An attempt was made to combine DEX and CPM in the mouth dissolving film. The challenge lies in analysing the combination of drug by suitable analytical method and masking the taste of the two drugs. Simultaneous equation method was used to analyse the drugs. Aspartame and sucralose were used as sweeteners to overcome the bitter taste of drug. Effectiveness of taste masking was checked using Brief Access Taste Aversion model.

Materials

Chlorpheniramine maleate and dextromethorphan hydrobromide were obtained as gift samples from Reino Remedies Pvt Ltd. and Blue Cross Pvt Ltd., respectively. Additionally, excipients such as sucralose and aspartame were also received as gift samples from Reino Remedies Pvt Ltd. Polyethylene glycol 400 (PEG) and hydroxypropyl methylcellulose E5 (HPMC) were purchased from Oxford Lab Fine Chem LLP.

Methods

2.1. Analytical Method Development

Linearity and calibration graphs —Two serial dilutions of CPM and DEX were separately prepared by transferring

aliquots equivalent to 20–80 µg and 20–80 µg of CPM and DEX, respectively, from their standard solutions (100 µg/mL) into a two sets of 10 mL volumetric flasks and diluted to volume
with methanol. The absorption spectra of these dilutions were measured and recorded against methanol as a blank in the wavelength range from 200–400 nm.[16]

For the simultaneous equation method, the absorbance values of samples A1 and A2 measured at 260 nm (λmax of CPM) and 278 nm (λmax of DEX), respectively, were used for building two simultaneous equations from which the concentration of each drug (Cx for CPM and Cy for DEX) was calculated as follows:
$Cx = (A_2ay_1 - A_1ay_2) / (ax_2ay_1 - ax_1ay_2)$
$Cy = (A_1ax_2 - A_2ax_1) / (ax_2ay_1 - ax_1ay_2)$
where ax_1 and ax_2 are absorptivity values of CPM at 260 and 278 nm, respectively, and ay_1 and ay_2 are absorptivity values of DEX at 260 and 278 nm, respectively.

2.2. Drug Authentication

2.2.1. Melting Point Determination

Melting point of the drug was measured using capillary method.

2.2.2. FTIR of DEX and CPM

The Fourier transform infrared (FTIR) spectra of CPN and CPN loaded microemulsions were recorded using FTIR spectrophotometer (FTIR-8400S, Shimadzu, Kyoto, Japan). Samples were mixed with potassium bromide (FT-IR grade) and compressed into disks using hydraulic press before scanning from 4000 to 500 cm^{-1}

2.3. Formulation and Evaluation of film

2.3.1. Calculation of drug requirement

A single film unit (2*2 cm^2) should contain 10 mg of DEX and 5 mg of CPM. The film was prepared in a petridish having a radius of 3.4615 cm. The amount of drug required per petridish was calculated.

2.3.2. Preparation of film

The required amount of polymer (HPMC) was taken and mixed with 10 ml of the casting solvent, distilled water. This mixture was considered as [SOLUTION-1]. Then, the necessary amount of both drugs for one film-forming petridish was dissolved in 2 ml of ethanol, and this solution was labelled as [SOLUTION-2]. [SOLUTION-1] was then added to [SOLUTION-2], and the final volume was adjusted to 10 ml. A plasticizer (PEG 400) and sweeteners were incorporated into this final 10 ml solution. The resulting solution was poured into a film-forming petri dish and allowed to dry at room temperature for 24 hours.[17]

2.3.3. Evaluation of film [18]

2.3.3.1. Weight: The square film (4 cm^2) was placed on a calibrated analytical balance to accurately measure its weight. To ensure precision, the weighing process was repeated three times, and the average weight was calculated.[19]

2.3.3.2. Thickness: The film sample was positioned between the jaws of the Vernier caliper and gently closing the caliper's jaws until they just touched the film, ensuring not to compress or distort it. The thickness was measured at five different locations; one at each of the four corners and one at the center. The recorded measurements were noted for each location, and the average thickness was calculated.[20]

2.3.3.3. Folding endurance: The film was folded manually at the center, ensuring that the fold was precise and consistent each time. This folding process was repeated by bending the film back and forth at the same crease until the film cracked or broke. The number of times the film could be folded without breaking was recorded as the folding endurance value.[21]

2.3.3.4. Disintegration time: The film was placed in a petri dish. 10 ml of distilled water was gently poured into the petri dish to fully immerse the film. The time required for the film to completely disintegrate into smaller fragments or to dissolve completely was noted using a stopwatch. The endpoint of the disintegration process was when the film no longer exhibited any solid residue.

2.3.3.5. Drug content: The film unit was placed in 100 ml of methanol. After complete solubilization, the solution was diluted appropriately, filtered and analyzed at 261 and 278 nm for CPM and DEX respectively using UV-Visible Spectrophotometer. The average of three films was taken as the drug content.

2.3.3.6. In vitro Dissolution Study: The dissolution study was carried out using a beaker, at 37 C ± 0.5 C using 300 ml of simulated salivary fluid (pH 6.8) as a dissolution medium. The agitation rate of paddle was 50 rpm. Samples were withdrawn at 5 minutes and filtered through Whatman filter paper, diluted suitably, if required and analyzed spectrophotometrically at 261 and 278 nm for CPM and DEX respectively.

2.4. Optimization using 3^2 factorial design

The 3^2 factorial design is a statistical method used to conduct experiments where two factors are each established at three different levels. This design matrix consists of nine experimental runs, allowing researchers to systematically evaluate the main and quadratic effects of each factor and their interactions on the response variable. In this system, all possible combinations of factor levels are tested, ensuring a comprehensive analysis. The amount of HPMC and PEG were considered as two factors based on the preliminary experiments. Folding endurance and disintegration time for film formed in each run was taken as response variable.[22]

2.5. Characterization of best batch

2.5.1. In-vivo taste assessment - Brief Access Taste Aversion (BATA) model

Six adult Wistar Albino rats (175–200 g) were used for the study. Three rats each were housed in each cage maintained a 12-h light/dark cycle and an ambient temperature of around 22°C. Food and water were available as required except during the testing. Water intake was restricted during the testing phase. All procedures were approved by the Institutional Animal Care and Use Committee (IACUC) at K. B. Institute of Pharmaceutical Education and Research (KBIPER/2024/665). The animals were deprived of water for 6 hours and one group was allowed access to the solution formed from drug containing films and the other group was allowed access to plain drug solution in the same concentration as in the film solution.[23]

2.5.2. Stability Study:
FTIR of the drug combination, drug, and excipient was taken after storage for month. The final formulation film was kept at ambient temperature and monitored for physical appearance, drug content, disintegration time and folding endurance over 1 month.[24]

3. Result and Discussion

3.1. Spectral Characteristics

After recording the UV absorption spectra of both CPM and DEX (Figure 1), it was observed that direct simultaneous determination of CPM and DEX is very difficult due to severe overlap of their spectra. Simultaneous equation method is used in such case. The absorbance values of each drug at 260 nm and 278 nm were measured and are given in Table 1. The absorptivity values were calculated by taking the average of quotients of dividing absorbance values of each drug at each selected wavelength by its corresponding concentrations. (Table 2) The equation so formed was used for calculation of concentration of the two drugs.

Table 2: Regression for quantitative analysis of DEX and CPM by the proposed method

Parameter	CPM		DEX	
Wavelength (nm)	260	278	260	278
Linearity (µg/ml)	20-80	20-80	20-80	20-80
Slope	0.0141	0.0013	0.0018	0.0055
Intercept	0.0125	0.0275	0.0179	0.0276
Correl	0.9925	0.9622	0.9943	0.9988
R Square	0.9850	0.9259	0.9886	0.9976
Absorptivity	aX1	aX2	aY1	aY2
Average	0.014	0.002	0.002	0.006

Figure 1 A. Overlay spectra of DEX and CPM at A) 260 nm and B) 278 nm

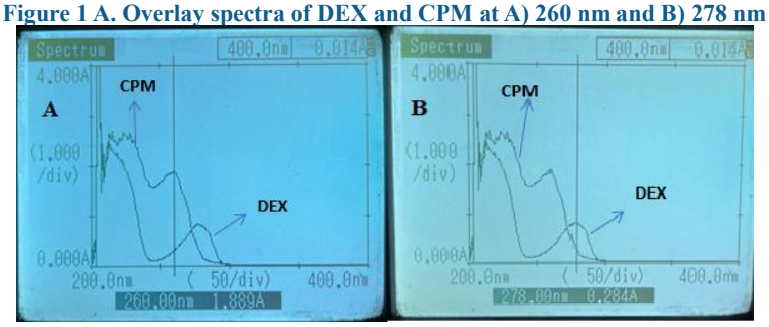


Figure 2: FTIR Spectra of A) DEX and B) CPM

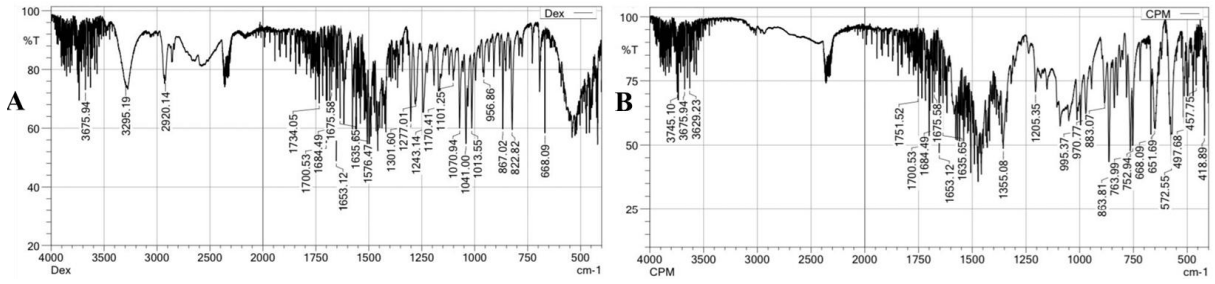


Table 1: absorbance of different concentration of both drug at each other's λ max

Concentration	Absorbance			
µg/ml	DEX		CPM	
	278	261	278	261
20	0.142	0.054	0.056	0.275
30	0.192	0.069	0.067	0.454
40	0.241	0.086	0.087	0.616
50	0.306	0.114	0.089	0.693
60	0.357	0.128	0.106	0.862
70	0.424	0.146	0.108	0.940
80	0.464	0.156	0.147	1.186

3.2. Authentication of the drug

3.2.1. Melting point

Melting point of DEX was found to be in the range of 125-130°C[25] and CPM between 130-135°C [26] which very well match with the literature data.

3.2.2. FTIR Analysis

Chlorpheniramine maleate exhibits characteristic FTIR peaks at approximately 3675 cm-1 for N-H stretching, 1635 cm-1 for aromatic C=C stretching, 1355 cm-1 for C-N stretching, and 763 cm-1 for C-Cl stretching, indicating its structural components.[27] (Fig.2A)Dextromethorphan hydrobromide exhibits characteristic FTIR peaks at approximately 2920 cm-1 for aliphatic C-H stretching, 1041 cm-1 for C-O-C stretching, 1301 cm-1 for C-H bending, and 761 cm-1 for aromatic C-H bending, reflecting its functional groups.[25] (Fig. 2B)

3.3. Formulation of Mouth dissolving films

Preliminary experiments (data not shown) were conducted to identify the polymer and plasticizer for the formulation of DEX and CPM films. HPMC and PEG 400 were identified as film forming polymer and plasticiser respectively. Face-centered factorial design was generated to identify the levels of the excipients to be used to formulate a film that had good folding endurance and minimum disintegration time. The composition and values of evaluation results are given in Table 4. Mathematical models were generated for folding endurance and disintegration time.

3.4. Optimization of the film forming formulation

Face-centered design matrix is given in Table 3. HPMC and PEG were considered as two formulation factors and their effect on folding endurance (Response Y1) and disintegration time (Y2) was determined. The number of runs was 9 including one center point batch. The results of the experimental runs are given in Table 3. The data so obtained was analysed using RStudio software.[28]

3.4.1. Response Y1 – Folding Endurance

ANOVA table was referred to identify the importance of main, two way interaction and quadratic terms. FO, TWI, and PQ terms are compared for their effects on the response variable, FoldEndur (Table 4). The p value of main effects (FO) demonstrate a significant main effect of HPMC and PEG on FoldEndur, with a sum of squares of 274.833 and a p-value of 0.03713. This indicates strong linear effects. In contrast, the Two-Way Interaction (TWI) has a sum of squares of 30.250 and a p-value of 0.20288, indicating no significant interaction effect between HPMC and PEG. Similarly, the pure quadratic effect (PQ) is insignificant, with a sum of squares of 42.500 and a p-value of 0.29931, showing that non-linear effects are minimal.

The linear model for the folding endurance is given by the following equation:

Folding Endurance = 16.67 - 6.67*HPMC + 1.17*PEG (R-squared: 0.7195, F-statistic: 7.694, p-value: 0.02208)

The contour plot (Fig. 3A) demonstrates a linear relationship between HPMC, PEG, and folding endurance, with contours increasing from the bottom-right to the top-left. This indicates that HPMC affects the folding endurance value negatively while PEG positively affects folding endurance. The straight, evenly spaced contours suggest no significant interaction between the two factors, confirming that their effects are primarily additive. The highest folding endurance value (22) occurs at lower levels of HPMC and higher level of PEG, highlighting the optimal region for formulation. Thus, increasing concentrations of PEG improves folding endurance, aligning with the assumption of first-order model and guiding effective formulation strategies.[29]

3.4.2. Response Y2 – Disintegration Time

The ANOVA results indicate that both the main effects and pure quadratic terms significantly impact disintegration time, with **p-values** of **0.003778** and **0.007963**, respectively (Table 5). The main effects reveal strong linear effects from HPMC and PEG, while the quadratic terms highlight their crucial contributions. In contrast, the TWI term is insignificant (**p-value = 0.326763**), suggesting minimal interaction effects between HPMC and PEG. Thus, while the main and quadratic effects are vital for understanding disintegration time, interaction is negligible, guiding formulation optimization towards focusing on linear and quadratic relationships. Based on the regression analysis coefficients, the mathematical equation for disintegration time can be formulated as follows:

$DT = 54.78 + 20.50 \times HPMC + 22.83 \times PEG + 4.83 \times HPMC^2 + 40.83 \times PEG^2$ (R-squared: 0.9779; F-statistic: 44.17, p-value: 0.001448)

The equation predicts DT using HPMC and PEG concentrations. The intercept is 54.78, representing the baseline endurance without HPMC or PEG. HPMC and PEG significantly enhance endurance, with coefficients 20.50 and 22.83, respectively, indicating substantial linear effects. Quadratic terms highlight the nonlinear influence of PEG, with PEG2^22 being highly significant (40.83), indicating a strong curvature effect. The HPMC2^22 term (4.83) is not significant. Overall, PEG significantly impacts folding endurance, with notable quadratic effects, while HPMC and its interaction play lesser roles.

The contour plot illustrates how HPMC and PEG concentrations influence disintegration time (Fig. 3B).

Figure 3: Contour plot for A) Folding Endurance and B) Disintegration time

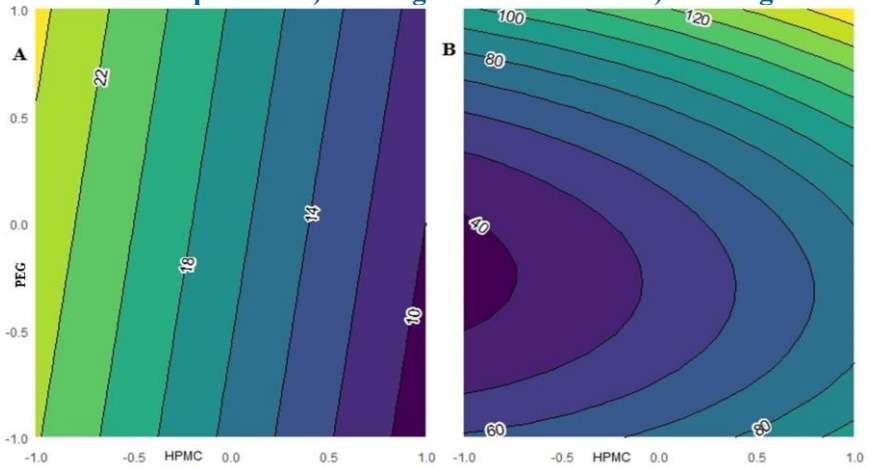


Table 3: Factorial Design Batches

	CODED VALUE		ACTUAL VALUE					
	X1	X2	HPMC (mg)	PEG 400 (mg)	Weight (mg)	Thickness (mm)	Folding Endurance	DT (sec)
F1	-1	-1	250	0.25	70	0.20	18	57
F2	-1	0	300	0.25	80	0.21	23	47
F3	-1	1	350	0.25	95	0.22	28	95
F4	0	-1	250	0.50	96	0.22	16	75
F5	0	0	300	0.50	100	0.20	22	51
F6	0	1	350	0.50	118	0.21	14	120
F7	1	-1	250	0.75	124	0.24	8	96
F8	1	0	300	0.75	120	0.23	14	76
F9	1	1	350	0.75	141	0.20	07	150

Table 4: ANOVA for Folding Endurance

Fold Endur	Df	Sum Sq	Mean Sq	F value	Pr(>F)
FO(HPMC, PEG)	2	274.833	137.417	11.9782	0.03713
TWI(HPMC, PEG)	1	30.250	30.250	2.6368	0.20288
PQ(HPMC, PEG)	2	42.500	21.250	1.8523	0.29931
Residuals	3	34.417	11.472		
Lack of fit	3	34.417	11.472	NaN	NaN
Pure error	0	0.000	NaN		

Table 5: ANOVA for Disintegration Time

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
FO(HPMC, PEG)	2	5649.7	2824.83	60.3406	0.003778
TWI(HPMC, PEG)	1	64.0	64.00	1.3671	0.326763
PQ(HPMC, PEG)	2	3381.4	1690.72	36.1151	0.007963
Residuals	3	140.4	46.81		
Lack of fit	3	140.4	46.81	NaN	NaN
Pure error	0	0.0	NaN		

Increasing HPMC generally increases disintegration time, especially at higher PEG levels. Optimal disintegration can be achieved with specific HPMC and PEG combinations. Disintegration time increases at higher HPMC concentrations, particularly at high level of PEG. These findings suggest that HPMC and PEG are crucial in controlling disintegration rate. The circular shape of the curve indicates the importance of quadratic terms of both the factors.

3.4.3. Checkpoint Batch

The checkpoint batch was identified in overlay region coloured yellow. (Fig. 4) The co-ordinate point chosen was -0.68, -0.8 which translates to 266 mg of HPMC and 0.3 ml of PEG. The predicted value of folding endurance is 20 which is close to 21 as observed and that for disintegration time is 50 sec which again is in close agreement with observed value of 49. Sucralose and aspartame were added to the check point composition (Table 6) for taste masking. The percentage drug release at the end of 5 min for DEX and CPM was 86 and 85 respectively.[30]

Figure 5: FTIR spectra of A) DEX and CPM and B) DEX+CPM+ Polymer

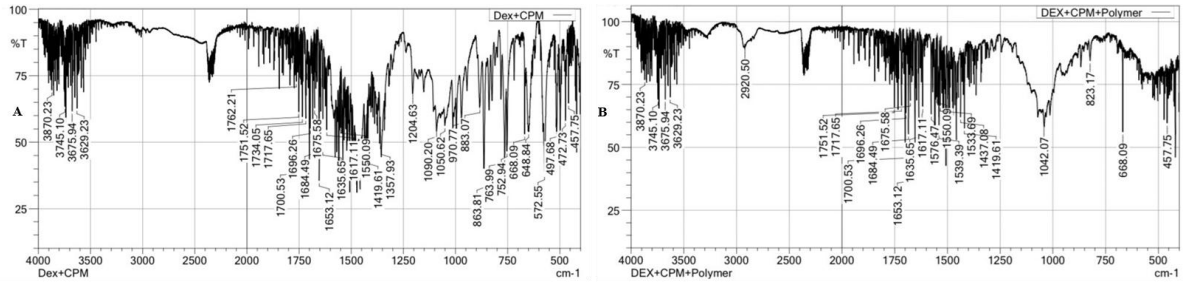


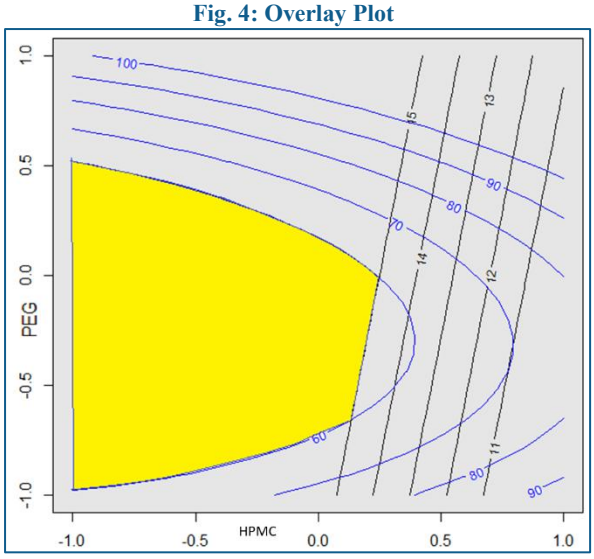
Table 6: Final Formulation

Ingredient	Quantity
DEX	94.05 mg
CPM	47.03
HPMC	266 mg (-0.68)
PEG 400	0.35 ml (-0.8)
Sucralose	150 mg
Aspartame	45 mg
Water to make	10 ml

Table 7: Water consumption using BATA model

	ml consumed from Film solution	ml consumed from Drug solution
DAY 1	3.00	1.00
DAY 2	2.67	1.67
DAY 3	1.67	1.33

Fig. 4: Overlay Plot



3.5. Taste masking

The amount of solution consumed by rats was noted down (Table 7). The volume of solution consumed by rat in film group was significantly more than drug solution indicating an agreeable taste of film. ($p<0.05$)

3.6. Stability Study

There was no interaction between two drugs (Fig. 5A) and drugs and polymer (Fig.5B) as indicated by the characteristic peaks of the two drugs. The films remained transparent and the values of disintegration time and folding endurance did not significantly change ($p<0.05$) at the end of stability period indicating a stable formulation.

Conclusion

Mouth dissolving film can be prepared used HPMC and PEG as film former and plasticizer respectively. The taste of the drugs can be masked using right amount of sucralose and aspartame.

References

1. Husain M, Agnihotri V V., Goyal SN, Agrawal YO. Development, optimization and characterization of hydrocolloid based mouth dissolving film of Telmisartan for the treatment of hypertension. Food Hydrocolloids for Health 2022;2. https://doi.org/10.1016/j.fhfh.2022.100064.
2. Shipp L, Liu F, Kerai-Varsani L, Okwuosa TC. Buccal films: A review of therapeutic opportunities, formulations & relevant evaluation approaches. Journal of Controlled Release 2022;352:1071–92. https://doi.org/10.1016/J.JCONREL.2022.10.058.
3. Zayed GM, Rasoul SA El, Ibrahim MA, Saddik MS, Alshora DH. In vitro and in vivo characterization of domperidone-loaded fast dissolving buccal films. Saudi Pharmaceutical Journal 2020;28:266–73. https://doi.org/10.1016/J.JSPS.2020.01.005.
4. Al-Mogherah AI, Ibrahim MA, Hassan MA. Optimization and evaluation of venlafaxine hydrochloride fast dissolving oral films. Saudi Pharmaceutical Journal 2020;28:1374–82. https://doi.org/10.1016/J.JSPS.2020.09.001.
5. Mady O, Hussien S, Abdelkader DH, El-Dahaby E. Metoclopramide loaded buccal films for potential treatment of migraine symptoms: in vitro and in vivo study. Pharm Dev Technol 2023;28:650–9. https://doi.org/10.1080/10837450.2023.2231076.
6. Jain P, Gupta A, Darwhekar G. An Detailed Overview on Mouth Dissolving Film. Journal of Drug Delivery and Therapeutics 2023;13:172–6. https://doi.org/10.22270/JDDT.V13I7.6121.
7. Khan Q ul ain, Siddique MI, Rasool F, Naeem M, Usman M, Zaman M. Development and characterization of orodispersible film containing

cefixime trihydrate. Drug Dev Ind Pharm 2020;46:2070–80. https://doi.org/10.1080/03639045.2020.1843477.
8. Moonesan M, Ganji F, Soroushnia A, Bagheri F. Fast-dissolving oral films containing dextromethorphan/phenylephrine for sinusitis treatment: formulation, characterization and optimization. Prog Biomater 2022;11:243. https://doi.org/10.1007/S40204-022-00191-W.
9. Bolger MB, Macwan JS, Sarfraz M, Almukainzi M, Löbenberg R. The Irrelevance of In Vitro Dissolution in Setting Product Specifications for Drugs Like Dextromethorphan That are Subject to Lysosomal Trapping. J Pharm Sci 2019;108:268–78. https://doi.org/10.1016/j.xphs.2018.09.036.
10. Visser JC, Wibier L, Mekhaeil M, Woerdenbag HJ, Taxis K. Orodispersible films as a personalized dosage form for nursing home residents, an exploratory study. Int J Clin Pharm 2020;42:436–44. https://doi.org/10.1007/S11096-020-00990-W/TABLES/2.
11. Kasim NA, Whitehouse M, Ramachandran C, Bermejo M, Lennernäs H, Hussain AS, et al. Molecular properties of WHO essential drugs and provisional biopharmaceutical classification. Mol Pharm 2004;1:85–96. https://doi.org/10.1021/MP034006H/ASSET/IMAGES/MEDIUM/MP034006HN00001.GIF.
12. [Silva AR, Dinis-Oliveira RJ. Pharmacokinetics and pharmacodynamics of dextromethorphan: clinical and forensic aspects. Drug Metab Rev 2020;52:258–82. https://doi.org/10.1080/03602532.2020.1758712.
13. [Rizvi SAA, Ferrer G, Khawaja UA, Sanchez-Gonzalez MA. Chlorpheniramine, an Old Drug with New Potential Clinical Applications: A Comprehensive Review of the Literature. Current Reviews in Clinical and Experimental Pharmacology 2024;19:137–45. https://doi.org/10.2174/2772432817666220601162006.
14. Bhatt P, Singh S, Sharma SK, Rabiu S. Formulation Development and Characterization of Rapid Mouth Dissolving Film of Frovatriptan Succinate. Int J Pharm Investig 2020;10:479. https://doi.org/10.5530/IJPI.2020.4.84.
15. Nagaraju T, Gowthami R, Rajashekar M, Sandeep S, Mallesham M, Sathish D, et al. Comprehensive Review On Oral Disintegrating Films n.d.
16. Abdelazim AH, Ramzy S, Shahin M. Application of Different UV Spectrophotometric Methods for Quantitative Analysis of Acotiamide and Esomeprazole. J AOAC Int 2022;105:1475–8. https://doi.org/10.1093/JAOACINT/QSAC041.
17. Bhatt P, Singh S, Sharma SK, Rabiu S. Development and Characterization of Fast Dissolving Buccal Strip of Frovatriptan Succinate Monoydrate for Buccal Delivery. Int J Pharm Investig 2021;11:69. https://doi.org/10.5530/IJPI.2021.1.13.
18. Yellanki SK, Jagtap S, Masareddy R. Dissofilm: A Novel Approach for Delivery of Phenobarbital; Design and Characterization. Journal of Young Pharmacists 2011;3:181–8. https://doi.org/10.4103/0975-1483.83756.
19. Vishvakarma P, Vishvakarma P. DESIGN AND DEVELOPMENT OF MONTELUKAST SODIUM FAST DISSOLVING FILMS FOR BETTER THERAPEUTIC EFFICACY. Journal of the Chilean Chemical Society 2018;63:3988–93. https://doi.org/10.4067/S0717-97072018000203988.
20. Maciej Serda, Becker FG, Cleary M, Team RM, Holtermann H, The D, et al. Enhancement of dissolution rate of rapidly dissolving oral film of meclizine hydrochloride by complexation of Meclizine hydrochloride with ß-cyclodextrine. J Appl Pharm Sci 2011;:150–3. https://doi.org/10.2/JQUERY.MIN.JS.
21. Shelke PV, Dumbare AS, Gadhave M V, Jadhav SL, Sonawane AA, Gaikwad DD. FORMULATION AND EVALUATION OF RAPIDLY DIS INTEGRATING FILM OF AMLODIPINE BES YLATE. Journal of Drug Delivery and Therapeutics 2012;2:72. https://doi.org/10.22270/JDDT.V2I2.85.
22. Farghaly DA, Afifi SA, Aboelwafa AA, Mohamed MI. Oral Dissolving Film of Rivastigmine: Optimization Using Factorial Design. J Pharm Innov 2023;18:1892–907. https://doi.org/10.1007/S12247-023-09743-4/FIGURES/9.
23. Rana H, Panchal M, Thakkar V, Gandhi T, Dholakia M. Investigating in-vitro functionality and in-vivo taste assessment of eco-friendly Tadalafil Pastilles. Heliyon 2024;10:e29543. https://doi.org/10.1016/J.HELIYON.2024.E29543
24. Bala R, Madaan R, Gupta R, Chawla R, Sahoo U. Formulation of Mouth Dissolving Strips of Metoprolol Succinate Using Locust Bean Gum. Egypt J Chem 2021;64:187–92. https://doi.org/10.21608/EJCHEM.2020.38329.2789.
25. Jassim* Z, Al-Kinani K, Alwan Z. Preparation and Evaluation of Pharmaceutical Cocrystals for Solubility Enhancement of Dextromethorphan HBr 2021.
26. de Oliveira GGG, Feitosa A, Loureiro K, Fernandes AR, Souto EB, Severino P. Compatibility study of paracetamol, chlorpheniramine maleate and phenylephrine hydrochloride in physical mixtures. Saudi Pharmaceutical Journal 2017;25:99–103. https://doi.org/10.1016/J.JSPS.2016.05.001.
27. [Afreen U, Fahelelbom KM, Shah SNH, Ashames A, Almas U, Khan SA, et al. Formulation and evaluation of niosomes-based chlorpheniramine gel for the treatment of mild to moderate skin allergy. J Exp Nanosci 2022;17:467–95. https://doi.org/10.1080/17458080.2022.2094915.
28. Swathy KK, Sarath Chandran S, Sourav K, Jafna MC, Raj A, Kappally S. Statistical Design of Experiments Using R Program for the Optimization of an Extended-Release Neem Oil Matrix Tablet. J Pharm Innov 2023;18:205–19. https://doi.org/10.1007/S12247-022-09640-2/METRICS.
29. Basha DC, Sudha BN. Box Behnken's Design of Fast-Dissolving Ondansetron Buccal Films and Assessing the Impact of Independent Variables on their Swelling and Folding Endurance Constraints. Indian Journal of Pharmaceutical Education and Research 2024;58:s412. https://doi.org/10.5530/IJPER.58.2S.44.
30. Sahoo S, Makwana A, Ranjan Sahu A, Keshri A, Dash V. FORMULATION AND EVALUATION OF SUBLINGUAL FILM OF ASENAPINE MALEATE BY USING 3 2 FULL FACTORIAL DESIGN n.d.