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Research Article

DESIGN AND STATISTICAL OPTIMIZATION OF MOUTH DISSOLVING SUBLINGUAL FILM OF FIXED DOSE COMBINATION OF DOXYLAMINE SUCCINATE AND PYRIDOXINE HYDROCHLORIDE USING DESIGN OF EXPERIMENT IN THE TREATMENT OF NAUSEA AND VOMITING IN PREGNANCY

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ABSTRACT

Objective: The present research aims at formulating a mouth dissolving sublingual film of fixed dose combination of doxylamine succinate (DS) and pyridoxine hydrochloride (PH) that would provide faster onset of action and hence relief from the condition of nausea and vomiting in pregnancy.

Methods: Mouth dissolving films were prepared using a solvent casting technique. A 2^3 full-factorial design of eight formulations was set up with three independent variables: X1 - polymer 1 HPMC E15 concentration, X2 - polymer 2 HPMC E5 concentration, and X3 - plasticizer PEG 400 concentration. The responses, i.e., dependent variables measured for the study were Y1 disintegration time in seconds, Y2 tensile strength in kg/cm^2, Y3 drug release in the percentage of DS, and Y4 drug release in the percentage of PH. All the formulations were evaluated for physicochemical parameters such as clarity, weight, thickness, folding endurance, surface pH, and content. The design expert software 11.0 trial version was used for statistical analysis of the responses.

Results and Conclusion: All the film formulations were found to be transparent, non-tacky, and easily peelable having the satisfactory tensile strength and folding endurance. The concentration of polymer 1 and 2 was found to have a significant effect on disintegration time and drug release of mouth dissolving films. The best film formulation DP1 was found to have a disintegration time of 77.66 s and found to release 96.22% of DS and 95.43% of pyridoxine HCl in 21 min.

Keywords: Sublingual film, Mouth dissolving film, Doxylamine succinate, Pyridoxine hydrochloride.

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INTRODUCTION

Nausea, a feeling of impending vomiting, is common in pregnancy [1]. Around 70–80% of the women, during their first trimester in pregnancy, suffer from nausea and vomiting. Nausea and vomiting in pregnancy (NVP) can be mild to moderate. Severe NVP may indicate a condition of hyperemesis gravidarum [2]. Hyperemesis gravidarum is characterized by persistent vomiting, dehydration, ketonuria, electrolyte abnormalities (hypokalemia), and weight loss of more than 5%. This deteriorates the pregnant woman's quality of life [3]. The American College of Obstetricians and Gynecologists recommend the administration of pyridoxine hydrochloride (PH) or combination with doxylamine succinate (DS) for the prevention and treatment of NVP [4]. This combination of PH (Vitamin B6) and DS is given as first-line treatment as it is found to be safe and effective. Antiemetic drugs, PH, is chemically 5-hydroxy-6-methyl-3,4-pyridinedimethanol hydrochloride (Fig. 1) and DS is N,N-dimethyl-2[1-phenyl-1-(2-pyridinyl) ethoxy]-butanedioate (Fig. 2) [4].

Antiemetic drugs, DS and PH, are a synergistic combination available in the market as a delayed release tablet. The drugs are released and absorbed in the intestine, which results in delay in the onset of action, and as such, the pregnant women are required to take this medication at night so that morning sickness can be prevented. There is a need to provide faster onset of action to pregnant women who require relief from this condition. Sublingual route is rich in blood supply, and the absorption is 3–10 times greater than conventional oral route. It bypasses hepatic metabolism and provides for drug absorption directly in the systemic circulation [5]. The present study attempts to exploit the advantages of sublingual route by the administration of DS and PH in the form of sublingual film that would provide faster bioavailability and onset of action and use of the film only if the symptom of nausea exists.

METHODS

DS was obtained as a gift sample from Indoco Remedies, Verna, Goa. PH was obtained as a gift sample from Merck India Ltd., Usgao Tisk Goa. HPMC E15, E5, and E3 were provided as a gift sample from Colorcon Asia Pvt. Ltd., Verna, Goa. Ascorbic acid was purchased from Avra synthesis Pvt. Ltd., and sucralose was obtained as gift sample from J K Sucralose. PEG 400 was purchased from Hi-Media Pvt., Ltd. Citric acid and raspberry syrup were purchased from SD Fine Chemicals. Distilled water prepared using in-house plant was used for the research work.

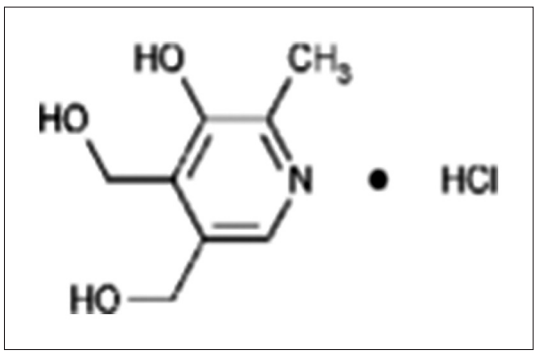

Fig. 1: Pyridoxine hydrochloride

Analysis of drug

Simultaneous equation method was used in the estimation of drugs DS and PH. 10 ppm solution of both the drugs was prepared in simulated salivary fluid (SSF), and their spectra were recorded using ultraviolet (UV) spectrophotometer (UV 1800 Shimadzu). From the overlay spectra, the wavelength selected for estimation was the absorption maxima of both the drugs 260.6 nm and 324 nm, respectively, for DS and PH. The equations used are as given follows:

$$Cx = \frac{(A2ay1 - A1ay2)}{(ax2ay1 - ax1ay2)} \text{ and}$$

$$C_Y = \frac{(A1ax2 - A2ax1)}{(ax2ay1 - ax1ay2)}$$

CX = concentration of DS A1 = absorbance of samples at 260.6 nm ax1 = absorptivity of DS at 260.6 nm and ax2 = absorptivity of DS at 324 nm CY = concentration of PH A2 = absorbance of samples at 324.0 nm ay1 = absorptivity of PH at 260.6 nm and ay2 = absorptivity of PH at 324 nm.

Preliminary screening of polymers and plasticizers

Experimental trials were carried out to find the film-forming capacity of various HPMC polymers, namely E15, E6, E5, and E3. The polymer HMPC E15 gave good films in the concentration range between 3 and 7%, while E3, E6, and E5 gave at above 5%. The results of the placebo batches indicated HPMC E15 and E5 used in combination gave good transparent, non-tacky films of adequate stiffness with PEG 400 as plasticizer. Preliminary trials were carried out for the selection of plasticizer from PEG 400, glycerine, and propylene glycol. Glycerine produced tacky films while propylene glycol films were not easy to peel. PEG 400 when used produced easily peelable non-tacky films and was hence selected for the formulation.

Experiment design

An experimental design of eight formulations was set up using three factors at two levels. The factors as independent variable chosen were the concentration of HPMC E15 (X1), concentration of HPMC E5 (X2), and concentration of PEG 400 (X3). The responses, disintegration time in seconds (Y1), tensile strength measured in kg/cm^2 (Y2), and drug release in percentage (%) of the drug DS (Y3) and PH (Y4) were chosen as dependant variables. Table 1 gives the layout of the experimental design.

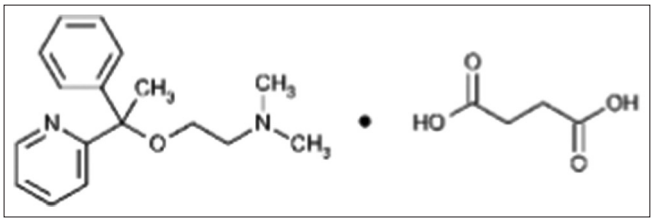

Fig. 2: Doxylamine succinate

Table 1: Three factor two-level factorial experimental designs

Code	Coded values			Actual values in percentage (%)			Dependent variables			
	X1	X2	X3	X1	X2	X3	Y1	Y2	Y3	Y4
DP1	−1	−1	−1	3	0.5	2	77.66	77.04	96	90.26
DP2	+1	−1	−1	5	0.5	2	94	139.12	89	84.54
DP3	−1	+1	−1	3	1	2	109.33	84.07	75.75	81.91
DP4	+1	+1	−1	5	1	2	130	141.9	68.35	59.51
DP5	−1	−1	+1	3	0.5	4	100.66	43.32	97.64	94.28
DP6	+1	−1	+1	5	0.5	4	165	101.53	90.21	85.27
DP7	−1	+1	+1	3	1	4	138.33	52.39	82.82	75.82
DP8	+1	+1	+1	5	1	4	174.66	108.27	78.95	69.27

X1 is % of HPMC E15 X2 is the % HPMC E5, X3 is % of PEG 400 Y1 is disintegration time in seconds, Y2 is tensile strength in kg/cm^2, Y3 and Y4 are drug release at 21 min of DS and PH, respectively

Method of preparing film

The dose of DS and PH is 10 mg each. The area of 9-cm diameter Petri plate is 63.585 cm^2. Amount of drug present in film of 4 cm^2 is 10 mg, so total amount of each drug to be added to the 10 mL solution is 63.585 × 10/4 = 158.96 mg.

The polymers were placed overnight for hydration in half the amount of water. Then, the polymer solution was made homogeneous by stirring it using magnetic stirrer (Remi Mumbai). Then, raspberry syrup, sucralose, citric acid, and ascorbic acid were added. Both the drugs were dissolved in water and added to the polymer solution. Once uniform, the formulation was casted on 9-cm diameter Petri plate which was previously lubricated with glycerine. The films were dried in oven at temperature of 38°C. The films when dried were peeled off using a sharp knife and then cut in 2 cm × 2 cm size. The films were then wrapped in aluminum foil and stored in desiccators.

Drug excipient compatibility

The compatibility of the formulation in the solid state was checked using differential scanning calorimetry (DSC) of making Universal V4SA TA Instrument in a nitrogen atmosphere with a heating rate of 1°C/min at a temperature between −100 and 400°C.

Evaluation

The prepared films were evaluated for physical appearance, weight, thickness surface pH, disintegration time, drug content, folding endurance, tensile strength, *in vitro* release, and *ex vivo* permeation studies. The physical appearance of the film such as homogeneity, color, transparency, and tackiness of the films was checked by visual inspection. Three films were weighed using Sartorius electronic balance (Shimadzu, Japan), and average and standard deviation were calculated. The thicknesses of the three films at three locations per film were determined using micrometer (Mitutoyo, Japan). The average and standard deviation were recorded. Surface pH was determined by placing a drop of water on the film and determined the pH by placing an electrode on it [6]. The disintegration time was determined using the disintegration test apparatus IP (Veego Instruments, Mumbai India). For the drug content, the film was dissolved in SSF, and then, dilutions were made and absorbance recorded and drug content was determined using UV spectrophotometer (UV 1800 Shimadzu, Japan) by method developed using simultaneous equation method. Folding endurance was determined by folding the cut films in the same plane until they developed cracks and the times it is folded without causing crack are recorded as folding endurance. Tensile strength was determined using the formula load at fracture multiplied by hundred divided by the product of film thickness and film width. *In vitro* drug release was determined using a modified dissolution method (Veego Instruments, Mumbai India) as stated in Dinge *et al*. using 20 mL of SSF as dissolution medium with speed of 50 rpm and temperature of 37°C [7].

Statistical analysis

The data obtained are analyzed using Design Expert 11.0 Software Trial version from Stat ease Inc. The contribution of each factor and its effect on response is obtained using ANOVA and response surface graphs. The significance level was considered to be $p<0.05$ [8].

***Ex vivo* permeation**

The study was carried out for the best-optimized formulation using the excised buccal mucosa of goat using modified Franz diffusion cell. The buccal mucosa of freshly killed goat was obtained from the local slaughterhouse. The mucosa was evenly trimmed and then washed with Ringer's solution. The modified Franz diffusion cell consisted of

a beaker containing 20 ml of SSF warmed at 37°C which served as a receptor compartment. A test tube with 2 cm diameter was cut to obtain a cylinder which was open on both the ends to which the treated buccal mucosa was attached which acted as a donor compartment. The assembly was placed on a magnetic stirrer (Remi make). The film was placed on the inner side of the buccal mucosa which was mounted between the donor and receptor compartment. To the donor compartment containing the film, 1 mL of SSF was added. The receptor medium was stirred using magnetic bead. Samples of 2 mL were withdrawn at 3, 6, 9, 12, 15, 18, 21, and 24 min and replaced with 2-ml SSF at each time point. The absorbance was measured at 260.6 nm and 324 nm, and the drug permeation across the buccal mucosa was estimated using simultaneous equation method [8].

Stability study was done on the optimized formulation. The films were wrapped in aluminum foil and stored at room temperature and 40°C ± 2°C and 75% ± 5% RH for 3 months. They were evaluated for appearance, weight, thickness, folding endurance, disintegration time, drug content, and drug release.

RESULTS AND DISCUSSION

Method for the estimation of drugs

The wavelength selected for simultaneous equation method is as shown in Fig. 3.

- Two simultaneous equations using absorptivity coefficients were formed as follows:
- $A_1 = 00.00956C_1+0.00015C_2$
- $A_2 = 0.01545C_1+0.0352C_2$, where A_1 and A_2 are absorbances of solution and C_1 and C_2 concentrations of DS and PH in mcg/mL. Hence, concentration of the drug can be calculated as follows:

$$C_{DS} = \frac{A2\ (0.01545)\ -\ A1\ (0.0352)}{-\ 0.0003341}$$

$$C_{PH} = \frac{A1\ (0.00015)\ -\ A2\ (0.00956)}{-0.0003341}$$

Preliminary trials

Trials carried out of placebo films depict that HPMC E15 produced good peelable films in comparison to HPMC E5 and E3 when used alone but had low tensile strength at the lowest concentration of 3%. Combination of HPMC E15 and E5 with HPMC E15 at high concentration of 3% and HPMC E5 at low concentration 0.5–1% gave better results than the reverse combination, respectively. Results of the trials are tabulated in Table 2.

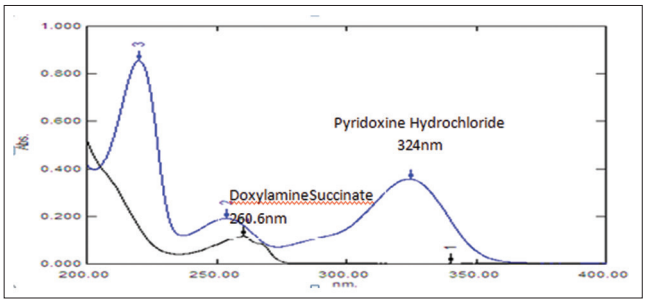

Fig. 3: Overlay spectra of doxylamine succinate and pyridoxine hydrochloride in simulated salivary fluid

Table 2: Preliminary trial of placebo films

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
HPMC E15	3	-	-	0.5	3	3	0.5	1	3
HPMC E5	-	3	-	-	0.5	1	3	3	-
HPMC E3	-	-	3	3	-	-	-	-	0.5
PEG400	2	2	2	2	2	2	2	2	2
Water	10	10	10	10	10	10	10	10	10
Film property	+++	++	+	+	+++	+++	++	++	++

+++: Good peelable films with good tensile strength. ++: Peelable films having low tensile strength. +: Films difficult to peel

Optimized factorial design

Based on the trials of placebo batch, the concentration of HPMC E15, E5, and Plasticizer PEG400 at two levels was chosen as factors for experimental design as shown in Table 1.

Drug excipient compatibility

The DSC spectra of the pure drugs DS, PH combination of drugs DS-PH, and combination of both drugs with excipients are as shown in Figs. 4-7, respectively. The spectra of the pure drug DS and PH show sharp endothermic peak at 100.90°C and 206.7°C, respectively. The combination of DS-PH spectra shows a slight shift in endothermic peak of DS at 102.48°C and PH at 210.80°C. The spectra of a combination of DS-PH and excipients show endothermic peak of DS at 100.27°C and PH at 197.54°C. The slight shift in the endothermic peak of PH may be due to change in glass transition temperature of polymers. There is no major change in spectra which rules out the possibility of any drug excipient incompatibility.

Evaluation of films

The prepared films were evaluated for weight, thickness, folding

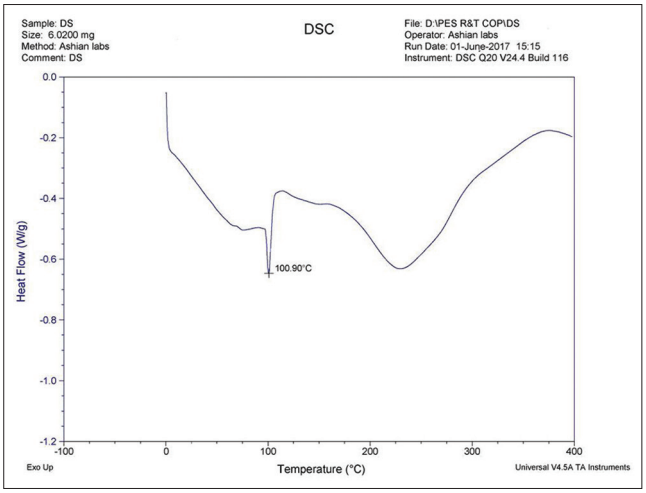

Fig. 4: Differential scanning calorimetry spectra of doxylamine succinate

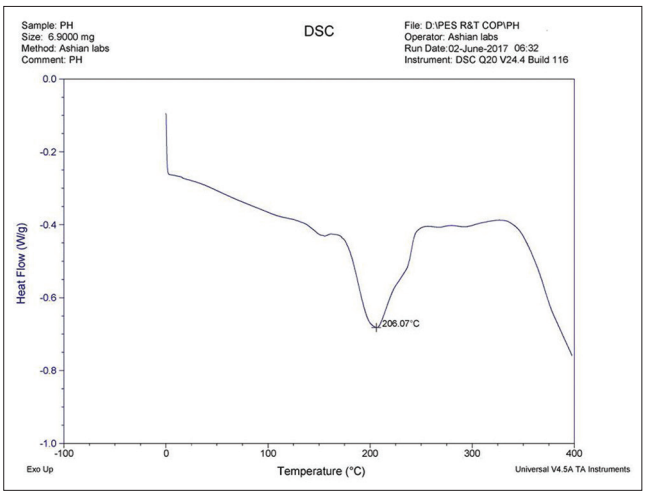

Fig. 5: Differential scanning calorimetry spectra of pyridoxine hydrochloride

Table 3: Physicochemical evaluation of films

Code	Weight (mg)[a]	Thickness[a] (mm)	Folding endurance[a]	Percent elongation[a]	Assay (%) DS[a]	Assay (%) PH[a]
DP1	145.66±3.055	0.246±0.011	898.0±3.0	1.25±0	97.65±0.963	100.65±1.035
DP2	161.0±2.0	0.316±0.005	932.33±2.516	3.33±0.72	98.41±0.870	99.06±0.697
DP3	146.0±3.0	0.25±0.01	980.0±2.00	2.5±1.25	100.95±2.053	97.49±0.212
DP4	154.66±1.527	0.266±0.005	1053.66±3.21	3.75±1.25	98.95±0.843	98.3±1.433
DP5	167.03±1.732	0.29±0.01	1154.0±2.0	5±3.30	97.46±0.848	98.99±0.681
DP6	166.33±2.309	0.306±0.011	1207.33±2.516	6.25±0	100.74±1.087	97.84±0.371
DP7	171.66±1.527	0.29±0.017	1247.33±2.516	2.08±1.44	99.88±1.147	98.21±1.232
DP8	180.0±0.001	0.326±0.011	1274.0±3.60	4.16±1.44	100.99±1.532	98.40±0.829

[a]Mean±SD n=3

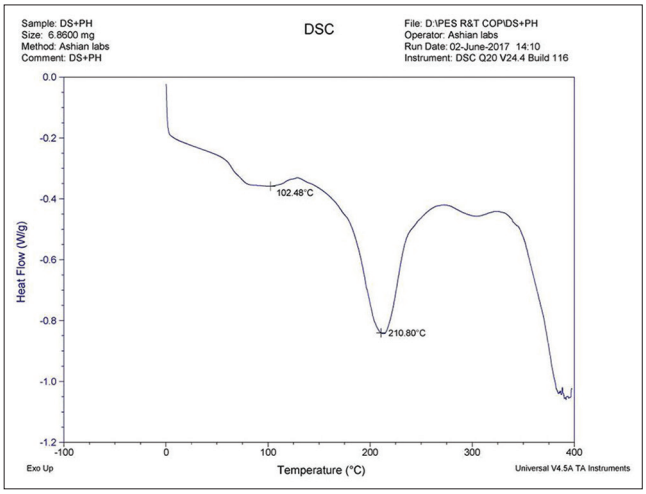

Fig. 6: Differential scanning calorimetry spectra of doxylamine succinate and pyridoxine hydrochloride

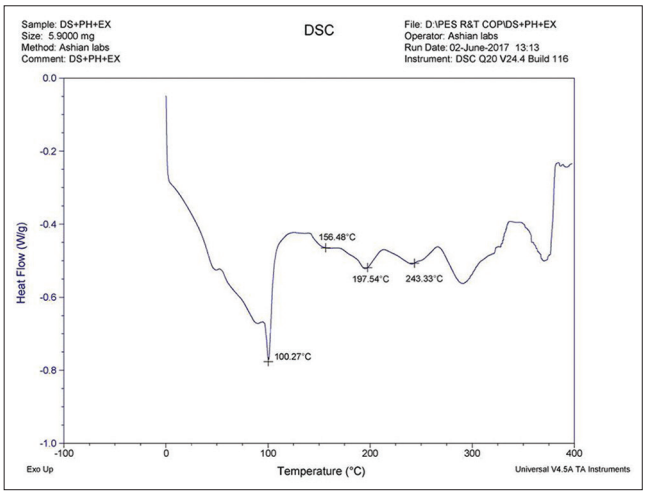

Fig. 7: Differential scanning calorimetry spectra of combination of doxylamine succinate, pyridoxine hydrochloride, and excipients

endurance, percent elongation. and assay of film; the results are tabulated in Table 3. All the mouth dissolving sublingual films were found to be homogenous, transparent, non-tacky, easy to peel, and having adequate tensile strength. The films were found to weigh in the range of 145.66–180 mg. The thickness of the films was found to be between 0.246 mm and 0.326 mm. The folding endurance of all the formulations was found to be very good, i.e., between 898 and 1247, which indicate they are very robust. The percent elongation of the films was found to be in the range of 1.25–6.25%. The drug content in the films was found to be between 97.46% and 100.99% for DS and 97.49% and 100.65 for PH. The surface pH of the films was found to be between

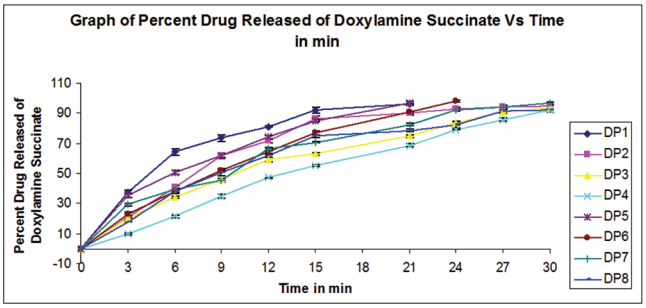

Fig. 8: Drug release of doxylamine succinate from mouth dissolving film formulations DP1-8

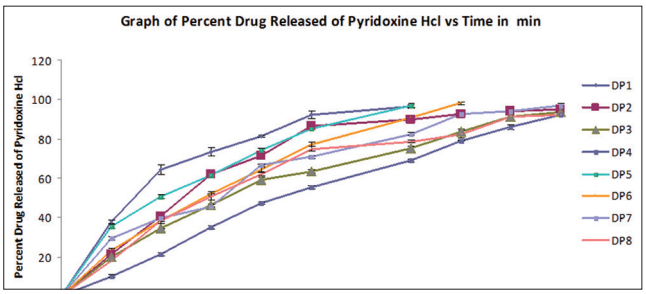

Fig. 9: Drug release of pyridoxine hydrochloride from mouth dissolving film formulations DP1- DP8

6.0 and 6.9. The drug release profile of the film formulations is shown in Figs. 8 and 9 for DS and PH, respectively. The formulation DP1 and DP5 were found to release the drug completely in 21 min and DP6 in 24 min, while all other formulations showed complete release in 30 min. DP1 and DP5 were found to release around 74–80% drug in 12 min.

Statistical analysis

Effect of formulation variables on disintegration time

The polynomial equation generated as per coded factors for response 1 that is disintegration time in second is as given follows:

$$Y1 = +44.3575 - 6.6625 *X1 + 57.50*X2 - 10.87250*X3 + 7.9575*X1*X3 \quad (1)$$

Where X1 is a concentration of polymer 1, X2 is a concentration of polymer 2, and X3 is concentration of plasticizer. The p value was found to be 0.0130 which is <0.05 (Table 4) that indicates that model is significant and the X1, X2, and X3 were found to be significant model terms as their p value was found to be <0.05. The effect of independent variables on disintegration time is shown in response surface plot (Figs. 10 and 11). The disintegration time of the films increased with increase in the concentration of HPMC E15 and E5. The concentration of HPMC E15 was found to have a greater effect than HPMC E5 on disintegration time. Similarly, increase in the concentration of PEG400 and HPMC E15 was found to increase the disintegration time of films.

Effect of formulation variables on tensile strength

The polynomial equation generated as per coded factors for response 2 that is tensile strength in kg/cm^2 is as given below:

$$Y2 = +18.08 + 29.25 *X1+12.81*X2-17.07750*X3 \quad (2)$$

The model for the response was found to be significant as the p value was <0.05 (Table 4). The terms X1, X2, and X3 were found to be significant model terms as their p value was found to be <0.05. The effect of independent variables on tensile strength is shown in response surface plot (Figs. 12 and 13). The tensile strength of the films increased with increase in the concentration of HPMC E15 and E5. The concentration of HPMC E15 was found to have greater effect than HPMC E5 on tensile strength. However, increase in the concentration of PEG400 with HPMC E15 was found to decrease the tensile strength of films.

Effect of formulation variables on drug release

The polynomial equation generated as per coded factors for response 3 [Y3] and 4 [Y4] that is percent drug released for the drug DS and PH, respectively, is as given below:

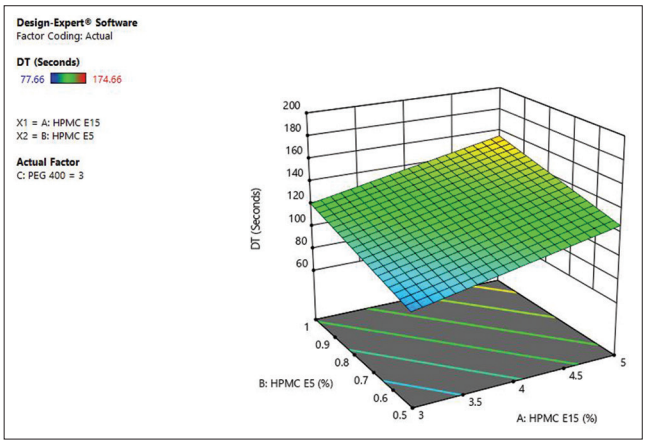

Fig. 10: Response surface plot for the influence of polymer on disintegration time

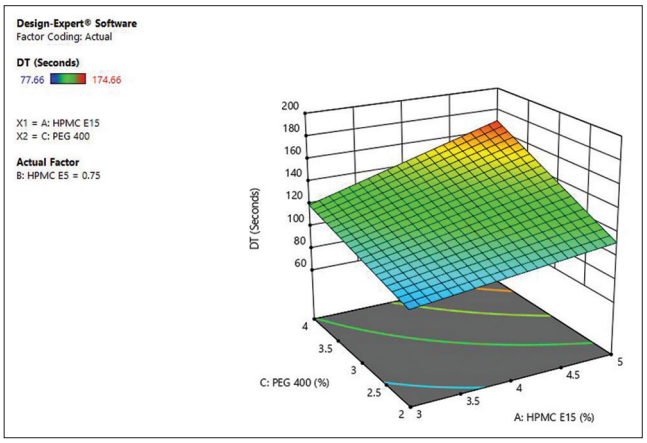

Fig. 11: Response surface plot for the influence of polymer and plasticizer on disintegration time

$$Y3 = +132.885–2.84*X1-58.36*X2–3.61*X3+7.95*X2*X3 \quad (3)$$

$$Y4 = +131.78750–5.96*X1-35.92*X2 \quad (4)$$

The model for drug release was found to be significant as the p value was <0.05 (Table 4). The terms X1, X2 X3, and X2*X3 were found to be significant model terms for Y3 as their p value was found to be <0.05 while for Y4, X1, and X2 were found to be the significant model terms. In equation Y3, X1, X2, and X3 were found to have an antagonistic effect on drug release as shown by the negative value in the equation −2.84, 58.36, and −3.61 for X1, X2, and X3, respectively, while factors X2 and X3 in combination were found to have synergistic effect on drug release as shown by positive value +7.95 in the equation [9]. The influence of independent variables on drug release is shown in response surface plot (Figs. 14-17). HPMC is a hydrophilic polymer known for controlling the release of drugs. The drug release of the films decreased with increase in the concentration of HPMC E15 and E5. Increase in concentration of PEG400 with HPMC E15 was found to decrease the release of drug

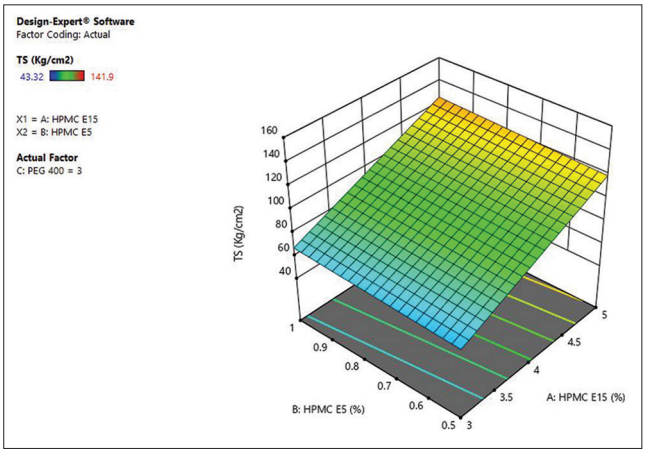

Fig. 12: Response surface plot for the influence of polymer on tensile strength

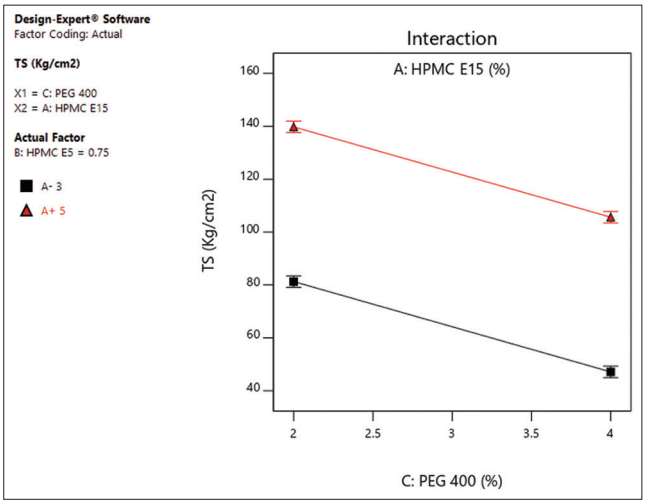

Fig. 13: Interaction plot of effect of plasticizer on tensile strength

Table 4: Model summary statistics of ANOVA analysis

Response	p value	R^2	Adjusted R^2	Predicted R^2	Adequate precision	SD	CV%
Y1	0.0130	0.9696	0.9290	0.7835	14.4875	9.17	7.42
Y2	00001	0.9984	0.9972	0.9937	73.3102	1.91	2.04
Y3	0.0005	0.9967	0.9924	0.9767	38.9447	0.8977	1.06
Y4	0.0019	0.9179	0.8851	0.7899	11.9711	4.08	5.03

from the films. Hence, lower concentration of polymer and plasticizer would form an ideal combination to increase the release of drug from the films.

The statistical data obtained from ANOVA are given in Table 4. The coefficient of variation is <10% for all the responses which indicates that the model is reasonably reproducible [10]. The predicted R^2 value was found to be in reasonable agreement with adjusted R^2, i.e., <2 for all the responses that explain the reliability of the model [11]. All the responses in this study show adequate precision value >4 which indicates adequate signal, and hence, the model is significant [10].

Optimization

Design expert software provides an option for the optimization of formulation by choosing a desired goal for each factor and response. The goal for the present study was to have minimum disintegration time and maximum drug release with an optimum tensile strength within a range for the mouth dissolving sublingual film. Based on the goals set for the responses, the software provided various solutions having desirability between zero and one. From the various solutions provided based on the response, one solution provided by software was of formulation DP1 having the desirability of 0.981, which would give a disintegration time of 79.12 s, tensile strength of 78.08 kg/cm^2, and drug release of 95.915% for DS and 95.947% for PH. Hence, it was chosen and it provided results similar to that predicted by the software thatbest-optimized formulation would give, fulfilling all the goals.

Ex vivo permeation study of the optimized film formulation DP1 was carried out the results of which are demonstrated in Fig. 17. The films showed more than 80% drug permeation in time period of 15 min.

Stability test

The optimized formulation did not show any visual change in appearance and the results of all the tests conducted are tabulated in Table 5 which were found to be within limits which indicates the stability of the formulation.

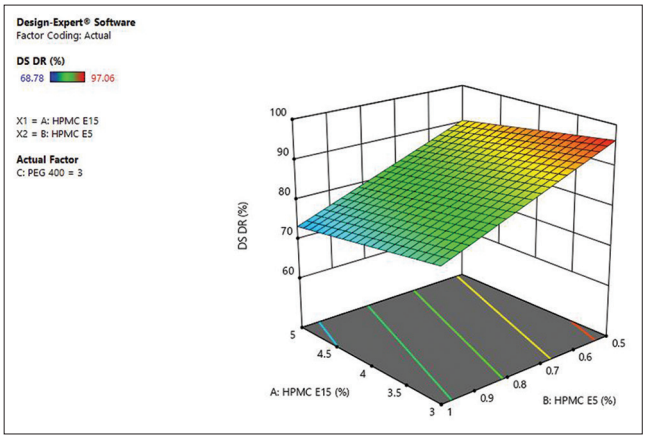

Fig. 14: Response surface plot for the influence of polymer on drug release of DS

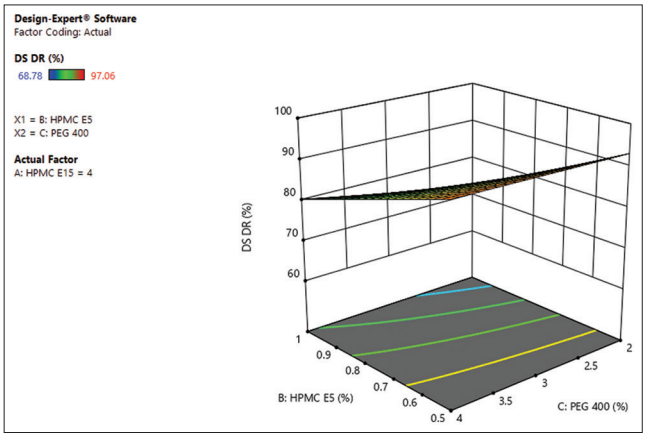

Fig. 15: Response surface plot for the influence of polymer and plasticizer on drug release of DS

CONCLUSION

In the present study, the use of design of experiment has helped to identify the influence of formulation variables on the performance

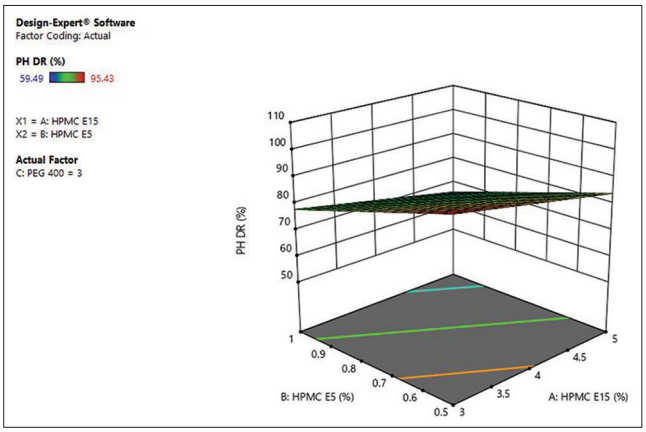

Fig. 16: Response surface plot for the influence of polymer on drug release of PH

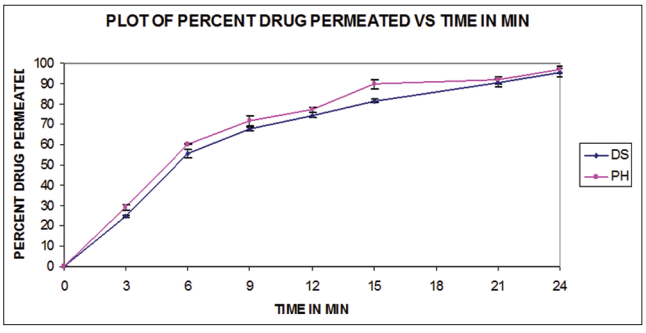

Fig. 17: *Ex vivo* drug permeation

Table 5: Stability test results of optimized batch

Testing	Room temperature ambient humidity	40°C and 75% RH
Description	Transparent, non-tacky films	Transparent, non-tacky films
Folding endurance	900±3.5	896±2.0
Disintegration time (s)	72.56±2.61	75.0±1.92
Tensile strength (kg/cm^2)	77.46±1.02	78.02±1.76
Drug release (%) of DS	97.21±1.59	98.33±1.87
Drug release (%) of PH	99.09±2.81	96.20±0.71

of mouth dissolving film. The prepared films were found to be homogenous, non-tacky, transparent, and easy to peel. Formulation variables and concentration of HPMC E15 and HPMC E5 were found to influence the disintegration time, tensile strength, and drug release from films. DP1 was found to be the best formulation having disintegration time of 77.66 s, tensile strength of 77.04 kg/cm^2, and providing the drug release of 96.00% DS and 90.26% pyridoxine HCl. Mouth dissolving sublingual film of DS and pyridoxine HCl can be an effective alternative to provide rapid action and relief from NVP to already distressed pregnant women.

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AUTHORS' CONTRIBUTION

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CONFLICTS OF INTEREST

All the authors have none to declare.

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