ORIGINAL ARTICLE

Formulation and Evaluation of Perindopril Erbumine Mouth Dissolving Film Using 32 Factorial Design

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Abstract

Introduction: The aim was to develop and optimize fast dissolving film of Perindopril Erbumine (PDP) by two-factor, three-level factorial design as the two independent variables inclusive of X1 Hydroxypropyl methylcellulose (HPMC) and X2 propylene glycol (PG) has been decided on the idea of the initial studies done earlier than the experimental design is being implemented. **Materials and Methods:** HPMC E5 LV and PG were used respectively as a film former and a plasticizer, to increase the physicochemical properties of the films, organized by the solvent casting method. **Result and Discussion:** Structured or reaction variables included % drug release in 10 min (Y1), disintegration time (Y2), and refolding strength (Y3). Basic reaction diagrams were drawn, statistical validity of polynomials was established to identify optimized method compositions. The films have undergone *in vitro* drug release studies which have confirmed 90.97–99.36% drug release within 10 min. *Ex vivo* studies of optimized formulation confirmed 86% permeation of the drug through the oral mucosa of sheep within 15 min and no cellular necrosis was found for the duration of the histological study. The stability of optimized batch was found to be stable for 6 months under specified stability conditions. **Conclusion:** PDP mouth dissolving film was formulated evaluated by using 3^2 factorial design.

Key words: Histopathology, Hydroxypropyl methylcellulose, Mouth dissolving film, Oral mucosa, Perindopril erbumine, Solvent casting, Three-level factorial design, Two-factor

INTRODUCTION

Buccal drug delivery is an appealing alternative to more standard techniques of systemic drug delivery since the oral mucosa is unexpectedly porous and has a plentiful blood supply, making it an ideal location for drug absorption.[1] It is a rather static expanse of smooth muscle and mucosa that is eventually good for retentive dose forms.[2,3] The basal membrane, also known as the lamina propria, lies beneath the epithelial layer and can be seen through the submucosa. The lamina propria is densely packed with blood veins and capillaries that open into the internal jugular vein. Medicines can bypass first-pass hepatic metabolism and enter the systemic circulation directly through the internal jugular vein, resulting in excellent bioavailability.[4,5] Around 330 million people in the developed world and 640 million people in the developing world suffer from high blood pressure. According to the World Health Organization, high blood pressure is one of the main causes of premature death worldwide, and the situation is getting worse. By 2025, 1.56 billion adults are expected to have high blood pressure.[6] Perindopril Erbumin is quickly absorbed, reaching peak plasma concentrations in less than an hour after oral administration. Bioavailability is between 65% and 75%. After absorption, perindopril is hydrolyzed to perindoprilat, which has a bioavailability of 20%. Food, on the other hand, reduces peridoprilat bioavailability by 35% by inhibiting the degree of biotransformation.[7] Hydroxypropyl methylcellulose E-five LV is water-soluble polymer with moderate hydroxypropyl substitution and high methoxy content. The use of Hydroxypropyl methylcelluloses

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(HPMC) E-five LV, propylene glycol (PG), and PG as film-former and plasticizer, respectively, were chosen to increase physicochemical properties of films using the solvent casting method is an alternative route for increasing Perindopril Erbumine (PDP) bioavailability. To begin with, it will provide rapid drug release into the oral cavity, as well as absorption of the medication through the oral mucosa, avoiding primary pass metabolism.[8]

MATERIALS AND METHODS

Materials

PDP was obtained as a gift sample from Glenmark (Nashik-India). HPMC E-5 LV Premium, Sodium acetate (AR) and Citric acid LobaChemiePvt. Ltd. (Mumbai). PG, glacial acetic acid, and sodium hydroxide flakes obtained from Research-Lab Fine Chem (Mumbai-India) as a gift sample.

Methods

Preformulation studies

FTIR-ATR

The IR spectra of PDP and PDP-excipients determined using a FTIR-4100 series spectrophotometer (Jasco, Japan) equipped with a deuterated triglycine sulfate detector and diffuse reflectance attachment unit (Jasco, Japan) using KBr Disc method. The scanning range was from 400 to 4000 cm^{-1} with resolution of 4 cm^{-1}[5].

UV spectroscopic method

Analytical method of PDP using UV method (labIndia) with the help of standard curve of PDP (Y = 0.012× + 0.052; r^2= 0.997), range 10–50 ppm, absorbance measured at 213 nm performed.

Preparation of mouth dissolving films

PDP mouth dissolving films were prepared by solvent casting method. Aqueous solution A prepared by dissolving HPMC-E5 LV polymer in 20 mL cool water with stirring to produce solution and kept for 24 h to remove air bubbles to obtained clear solution.[9] Aqueous solution B was prepared by dissolving PDP, sweetener, citric acid and plasticizer in specific proportion in distilled water. The aqueous solutions A and B mixed and stirred for 1 h. The solutions had been cast directly to 9 cm diameter Petri dish and dried within side the oven at 45°C for 24 h. Obtained films cautiously eliminated from the Petri dish and checked for any imperfection and cut in line with length required for testing (square film 1 cm length, 1 cm width) so that each film contained 4 mg of the drug. Composition of mouth dissolving films is given in Table 1.

Characterization of oral film

PDP mouth dissolving film evaluated for various parameters as.

Film weight and thickness

The films weights, three films of each components have been taken and weighed individually on a weighed on analytical balance (EQ-610/Equiptronics), and the average weights calculated. Film thickness become measured through way of means of the use of a micrometer screw gauge (Digimaticcaliper, Mitutoyo) from five distinct positions and the imply value become calculated.[9,10]

Surface pH of films

The pH become decided through way of means of dissolving a film in 2 ml of distilled water after which the pH of the acquired answer become measured through way of means of pH meter (Equip-Tronics, EQ-610, India). The common become taken for 3 determinations of every component.[11,12]

Drug content uniformity

A film with a diameter of 2 cm is shrunk and placed in a beaker. 10 mL of phosphate buffer solution (pH 6.8) is poured into the container. To disintegrate the film, the contents were swirled in a magnetic stirrer. The liquid has been poured into a volumetric flask (10 ml). At 213 nm, the absorbance of the solution is measured in comparison to a blank solution. A blank solution was made in a similar manner using a blank polymer film. The experiments were done 3 times and the average value was calculated.[13]

Tensile strength

The pressure at tearing and elongation became measured all through tensile check through a common testing apparatus

Table 1: Composition of mouth dissolving films

Drug/ Polymers	Formulations (Qty in mg)								
	A1	A2	A3	A4	A5	A6	A7	A8	A9
PDP	4	4	4	4	4	4	4	4	4
HPMC-E5 LV	0.9	0.9	0.9	1.05	1.05	1.05	1.2	1.2	1.2
PG	0.18	0.20	0.22	0.18	0.20	0.22	0.18	0.20	0.22
Sucralose	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Citric Acid	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

(H10KM, Hess, Sonsbeck, Germany) the usage of a load cell of 1000 N. Tensile strength is the most pressure carried out to some extent at which the strip specimen breaks. It is calculated with the aid of using the carried out load at rupture divided with the aid of using the cross-sectional place of the strip as given within side the equation (1).[14]

$$\text{Tensile strentgh} = \frac{\text{Force at break}\,(\text{N})}{\text{Initial cross sectional area}\,(\text{mm}^2)} \quad (1)$$

Percent elongation

Percent elongation became evaluated the use of Universal Tensile Strength Testing Machine (LS5, Lloyd Instruments Limited, UK). Films have been held among clamps placed at distance of 3.0 cm. During measurement, the strips have been pulled via way of means of the top clamp at a rate of 80 mm/min; the pressure and elongation measured while the film broke.[14]

$$\%\,\text{elongation} = \frac{\text{Increase in length of strip}}{\text{Initial length of strip}} \times 100 \quad (2)$$

Folding endurance

A strip of film turned into reduces frivolously and time and again folded on the equal area until it broke. The range of instances the movie will be folded on the equal area without breaking gave the precise value of folding endurance.[15]

In vitro drug release studies

The release rate of PDP from rapid dissolving film become decided the usage of USP Dissolution Test Apparatus (Type II). The dissolution take a look at become carried out the usage of 900 ml of Phosphate Buffer Solution (pH 6.8), at 37 ± 0.5°C with the paddle velocity of 50 rpm. Aliquot (10 ml) of the solution become collected from the dissolution apparatus at time interval of 2 min and have been changed with identical quantity of fresh dissolution medium. Absorbance of the filtrates becomes measured at 213 nm. Aliquots have been withdrawn from a region halfway among the surface of dissolution medium and the top of rotating paddle now no longer much <1 cm aside from the vessel wall. Cumulative percent drug release becomes calculated the usage of an equation acquired from a standard curve. Release research has been carried out in triplicate. All formulations information have been subjected to numerous mathematical kinetic fashions like Zero-order, First-order, Higuchi and Korsmeyer–Peppas, for expertise release styles and establishing mechanism accompanied through PDP release from film matrix. The model with the very best correlation coefficient become taken into consideration because the pleasant becoming one.[16,17]

Ex vivo drug permeation studies

The optimized components A5 batch was subjected to permeation research thru the fresh sheep oral mucosa inside 10 min of the killing of the animal. *Ex vivo* permeation of PDP become done though "oral" mucosa carried out using Franz diffusion cell and the movie become positioned on oral mucosa. Receptor compartment contained 15.5 ml simulated saliva solution of pH 6.8, even as donor compartment full of 1 ml simulated saliva. The Franz diffusion cell become non-stop stirred at 50 rpm, and temperature 37 ± 0.5°C. Aliquots of 1 ml have been withdrawn at regular intervals (each 3 min) for 15 min and filtered. The quantity of drug permeated become quantified the usage of UV technique and calculated Permeation flux steady state flux (Jss), apparent permeability coefficient (Papp), and Steady state diffusion coefficient.[18,19]

Oral mucosa sensitivity test

The optimized system A5 subjected for oral mucosa sensitivity test. The sections of manipulate and sample mucosa (dealt with very last optimized system) located below digital microscope, the histopathological assessment of sections confirmed that mobile membrane became intact and there has been no harm to the epithelial layer. Cell necrosis became now no longer located and therefore it concluded that, system is secure for chronic oral administration of PDP[20]

Stability test

Film prepared became stored in an aluminum bundle at 25°C with 50–60% humidity (ordinary condition) and at 40°C with 75% humidity (elevated condition) location in a stability chamber (BRI 22D/Biotechnics), for 6 months, respectively. Then assessment examined for organoleptic properties and drug content material became performed.[21,22]

RESULTS AND DISCUSSION

Films weight and thickness

The average weight and thickness of all the films are given in Table 2. Weight variation values (mg) of different PDP films were found to be in the range of 71 ± 0.057 to 104 ± 0.040 mg.

Surface pH measurement

Surface pH of film becomes determined to test whether the film causes irritation to the mucosa. The pH of all of the films become observed to be within side the range of that of ordinary pH 6.88 ± 0.02 to 7.11 ± 0.03 is given in Table 2.

Drug content uniformity

The percent drug content material changed into determined with the aid of using UV spectroscopy technique the use of the standard calibration curve and the identical manner changed into repeated for three films of every components proven in Table 2.

Table 2: Physicochemical evaluation of PDP films

FC	Weight uniformity[b] (mg)	Thickness[b] (mm)	Surface pH[b]	Drug content uniformity[b] (mg)	Folding endurance[b]
A1	71±0.057	0.15±0.04	6.88±0.02	3.98±0.02	178±1.02
A2	76±0.050	0.15±0.03	7.02±0.02	3.80±0.02	185±1.45
A3	80±0.036	0.16±0.03	6.95±0.01	3.96±0.03	220±2.03
A4	84±0.050	0.16±0.02	6.79±0.01	3.99±0.02	247±1.94
A5	89±0.050	0.16±0.01	7.11±0.03	3.95±0.03	259±2.13
A6	91±0.032	0.17±0.03	7.05±0.05	4.02±0.01	276±1.92
A7	95±0.047	0.18±0.03	6.83±0.04	3.88±0.03	280±1.45
A8	99±0.037	0.18±0.02	7.04±0.02	3.92±0.03	289±1.78
A9	104±0.040	0.19±0.02	6.99±0.03	3.96±0.02	297±1.52

[b]All values are mean±SD, n=3

Folding endurance

The variety of folding required to break or crack a film turned into taken because the folding endurance. The folding endurance turned into found to be elevated with an increasing concentration of HPMC-E5 LV and PG. All the films confirmed exact value of folding endurance in Table 2. Indicate no breakage of film for the duration of its use.

Tensile strength

The tensile strength of optimized formulations became 8.160 N/mm2. It became observed that tensile strength multiplied with an increasing quantity of HPMC-E5 LV and growing quantity of PG.

Percent elongation

We found that increase in the concentration of polymer displays the modifications in all different variables. Specifically within side the case of the polymer we found that because the concentration of polymers increase, viscosity of the solvent system which turned into to be casted turned into will increase. It influences thickness and brittleness of the film. A end result confirmed that because the concentration of polymer will increase, tensile strength of mouth dissolving film will increase. A result confirmed that because the concentration plasticizer will increase tensile strength and % elongation of mouth dissolving film additionally will increase.

In Vitro drug release studies

In vitro drug release profiles are proven in Figure 1. *In vitro* drug release have a look at consequences confirmed that because the concentration of polymer increases, drug release of mouth dissolving films decreases. An immediate drug release changed into correctly discovered for all HPMC films.[23]

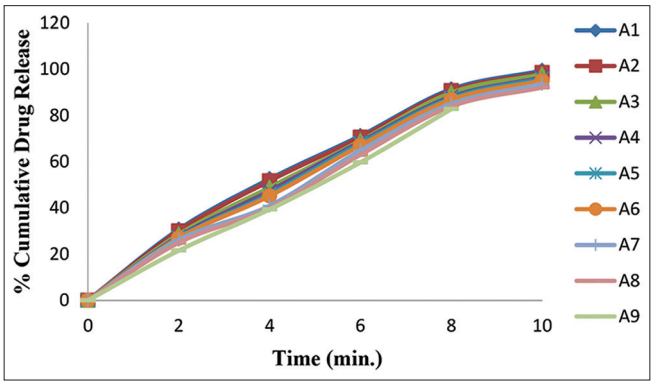

Figure 1: Comparative *in vitro* drug dissolution profiles of PDP films

Optimization of formulation

Optimization of PDP mouth dissolving film was carried out using 3^2 randomized full factorial designs. This design was also utilized to study the concentration effect of HPMC- E5 LV and PG on film physicochemical characteristics. The selection of independent variables, in this study is depends on quantity of (%) of film former polymer HPMC- E5 LV (X_1) and the quantity (%) of plasticizer PG (X_2) were selected as. Using three levels these two factors were evaluated. The actual units of higher is 0.9%, middle is 1.05%, and lower is 1.2% levels of factor X_1 and for factor X_2 were 0.18% (higher), 0.20% (middle), and 0.22% (lower). The coding was given as +1, 0, and -1, respectively, for higher, middle, and lower levels of each factor. The dependent or response variables included percentage (%) drug release in 10 min (Y_1), disintegration time (Y_2), and folding endurance (Y_3).

Effect of formulation variables on % drug release in 10 min

PDP is a used in hypertension, to avoid first pass metabolism and for quick effect in 10 min. is considered as suitable time for desired therapeutic. Therefore, % drug release

in 10 min forms an important parameter to be studied and hence was selected as dependent variable for the purpose of optimization. *In vitro* drug release profiles of all formulations are shown in Figure 1. The model for response Y_1 (% drug release in 10min) is as follows:

$$Y_1 = +95.54 - 3.17X_1 - 0.93X_2 \quad (3)$$

In Equation.3 Negative (–) sign of X_1 indicates that factor X_1 (concentration of HPMC-E5 LV) has negative effect, and Negative (–) sign of X_2 indicates that factor X_2 (concentration of PG) has negative effect on response Y_1 (% drug release in 10 min). That is, the percent drug release in 10 min falls when the HPMC-E5 LV concentration rises, as does the PG concentration.

The drug is released from the film at the concentration of HPMCE5 LV employed because when HPMCE5 LV comes into contact with the dissolution medium (buffer), it swells to form a gel, which acts as a barrier to drug diffusion. The solvent penetrates the dry matrix, the polymer gelatinizes, the drug dissolves, and the solubilized drug diffuses through the gel layer, resulting in drug release from the drug HPMC matrix. In a process called as erosion, the outer layers of the film completely hydrate and dissolve at the same time.[24,25]

The decrease in the drug release rate may be explained due to an extensive swelling property of HPMC to form gel. As the proportion of HPMC-E5 LV was increased in the formulation, erosion of the film slowed down. So formulations containing lowest amount of HPMC-E5 LV (0.9%) got eroded first. This in turn affected drug release rate. A1 formulation which contained lowest amount of HPMC-E5 LV (0.9%) and lowest concentration of PG (0.180%) showed highest drug release in 10 min [Figure 2].

The combined effect of HPMC-E5 LV and PG concentrations on percent drug release in 10 min is shown in the contour plot and 3D response surface plots. In this example, the results showed that the negative effect of HPMC-E5 LV concentration was greater than the beneficial effect of PG concentration on response. That is, at the same level of PG, a substantial decrease in percent drug release in 10 min was found with an increase in HPMC-E5 LV concentration.

Disintegration time is affected by formulation variables: The film's disintegration time ranges from 34 s (formula-1) to 62 seconds (formula-9) depending on the impartial factor combinations used [Table 3] The Model F-value of 971.70 indicates that the version is large. An F-value of this magnitude has a 0.01% chance of arising due to noise. Prob> F values <0.0500 indicate that version terms are significant.

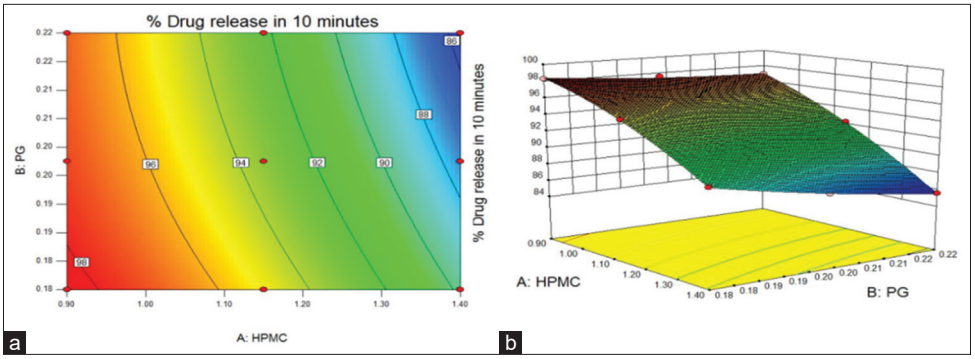

Figure 2: (a) Two-dimensional contour plot (b) three-dimensional (3D) response surface plots for Y_1 (% drug release in 10 min)

Table 3: Experimental design layout of PDP mouth dissolving film formulations

Run	FC	Factor X_1 (HPMC)	Factor X_2 (PG)	Response 1 (Y_1)	Response 2 (Y_2)	Response 3 (Y_3)
		Coded levels of variables		% Drug release at 10 min	Disintegration time (second)	Folding endurance
1	A1	–1	–1	99.36	34	178
2	A2	–1	0	98.51	38	185
3	A3	–1	1	97.85	41	220
4	A4	0	–1	96.44	46	247
5	A5	0	0	95.96	50	259
6	A6	0	1	95.03	53	276
7	A7	1	–1	93.61	55	280
8	A8	1	0	92.10	58	289
9	A9	1	1	90.97	62	297

X1 and X2 are significant version terms in this case. Values >0.10 indicate that the version phrases are not significant. The disintegration time response could be described using the quadratic equation below.

$$Y_2 = + 49.78 + 10.33X_1 + 3.50X_2 + 0.00X_1X_2 - 1.67X_1^2 - 0.1793X_2^2 \quad (4)$$

The positive sign (+) of X1 and X2 in equation. Four implies that the factors X1 (HPMCE5 LV concentration) and X2 (PG concentration) have a positive effect on the reaction Y2 (disintegration time). This suggests that as the concentration of HPMCE5 LV and PG increases, the decay time reduces. The minus sign (–) denotes a negative impact on decay time.

HPMCE5 LV and PG have a direct relationship with disintegration time. The level of polymer in the outermost hydrated layers drops with time as the hydrophilic matrix in the HPMC-containing film absorbs water and swells. Individual chains gradually detach from the matrix and diffuse into the bulk solution as the outermost layer of the matrix dilutes. The polymer chains separate from the matrix when the surface concentration of polymer exceeds a critical polymer concentration for macromolecular disentanglement or surface erosion. The polymer concentration at the matrix's surface is defined as the disentangling concentration of the polymer.

A high concentration of HPMC could cause gel formation and prolong the disintegration time of the film. A higher level of independent variable slowed the breakdown of the film into particles and the generation of the effective disintegration force, resulting in a longer decay time [Figure 3]. The quadratic term of the independent components X1 and X2 has a statistically significant influence (P = 0.05) on the decay time.[26,27]

Effect of formulation variables on flexural strength

PG acts as a plasticizer because it is able to lower the glass transition temperature (Tg). Lowering the Tg increases chain mobility and this, in turn, increases flexural strength.

The following quadratic equation could describe the bending strength response

$$Y_3 = + 257.78 + 47.17X_1 + 15.17X_2 - 6.25X_1X_2 - 20.17X_1^2 + 5.83X_2 \quad (5)$$

In equation 4, the positive sign (+) of X1 and X2 indicates that the factor X1 (concentration of HPMCE5 LV) and X2 (concentration of PG) has a positive effect on the response Y3 (resistance to folding), respectively. This is an increase in folding strength with an increase in HPMC and PG concentration. The negative sign () indicates a negative effect on folding strength.

The model's F-value of 119.60 indicates that it is significant. Due to noise, there is only a 0.12% probability that such a high F value will occur. The model terms are significant if the Prob > F<0.05. X1, X2, and X12 are important model terms in this scenario. The model terms are not significant if the values are bigger than 0.1000.

Plasticizers have been used to reduce the Tg of polymers and increase their mold ability. According to the free volume theory, the presence of a plasticizer lowers the polymer's Tg. The internal space accessible in a polymer matrix is measured by free volume. Polymer end group movement, polymer side group movement, and polymer internal movement are the three main sources of free volume in the polymer.[28]

More room or free volume is available for the movement of the molecular or polymer chain as the free volume grows, improving its process ability, flexibility, and elasticity. Plasticizers' principal function as non-volatile, low-molecular-weight additions is to improve polymer flexibility and process ability by lowering the second-order transition temperature (Tg, Tg). The presence of a plasticizer can be used as a criterion for determining how effective plasticization is shown in Figure 4.[29]

Ex vivo drug permeation studies

The permeation profiles of A5 formulation, without penetration enhancer, and across sheep oral mucosa are shown in Figure 5. The P_{app}, J_{ss}, and the steady state diffusion coefficient (D) of PDP through the mucosa were found to be 7.90 cm min^{-1}, 3.95 µg cm^{-2} min^{-1}, and 9.18 cm^2 min^{-1} × 10^{-2}, respectively.[30,31]

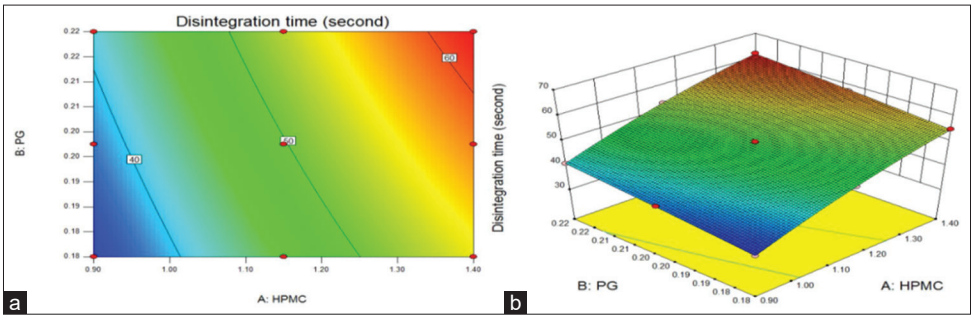

Figure 3: (a) Two-dimensional contour plot (b) three-dimensional (3D) response surface plots for Y_2 (Disintegration time)

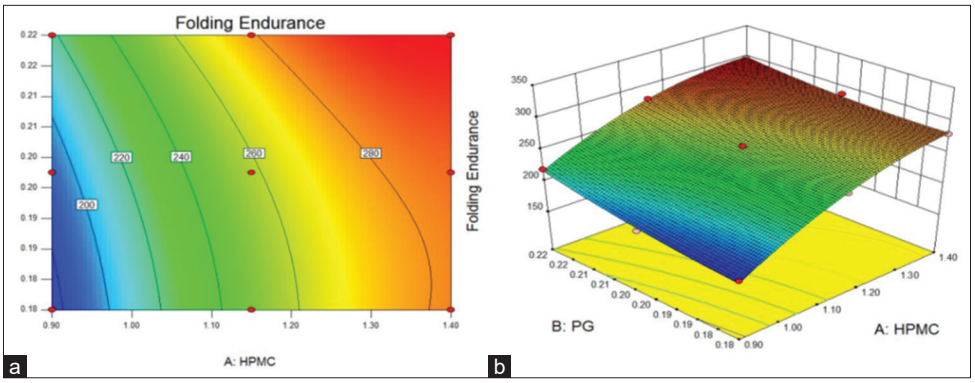

Figure 4: (a) Two-dimensional contour plot (b) three-dimensional (3D) response surface plots for Y_3 (folding endurance)

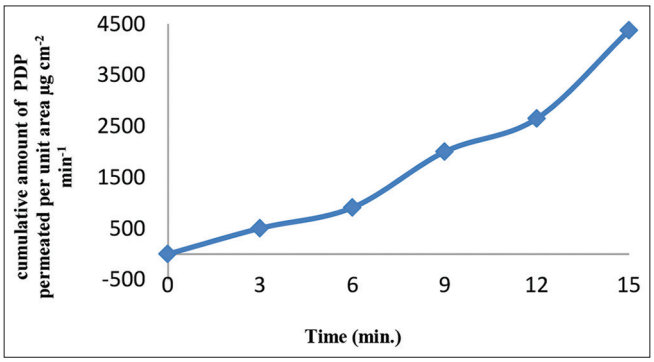

Figure 5: *Ex vivo* permeation of PDP in sheep oral mucosa

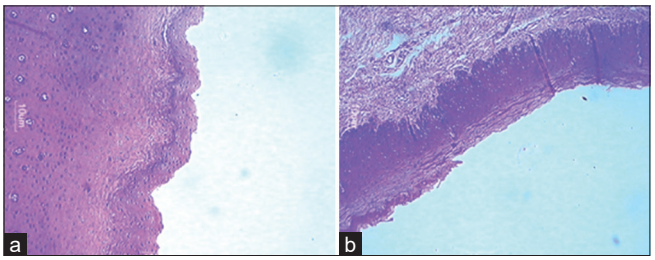

Figure 6: Sections of sheep oral mucosa for histopathological investigation (a) control (b) sample oral mucosa (treated with formulation A5)

Oral mucosa sensitivity test

The optimized A5 formulation has been tested for oral mucosal sensitivity. Control sections and mucosa sample (treated with final optimized formulation) viewed under a digital microscope (Motic, B1 Advanced series) [Figure 6]. Histopathological evaluation of the sections showed that the cell membrane was intact and there was no damage to the epithelial layer.[32,33]

Accelerated stability studies

Table 4 shows the results of stability tests performed on batch A5.

DISCUSSION

The entire mouth dissolving film had an average thickness of 0.15 0.04–0.19 0.02 mm. As a result, the weight of the films increased in proportion to the thickness of the films. The thickness and weight uniformity values for the films in each formulation type group were consistent. Due to the possibility of *in vivo* side effects, no mucosal irritation was expected from these produced films. Because an acidic or alkaline pH can irritate the oral mucosa, its best to keep the pH of the surface as neutral as possible. Because the drug content values of the formulations were not significantly different, it is considered that the medication was uniformly distributed in the films and that the patient received an accurate dose.

All of the films had good kink resistance and no signs of breaking during use. The tensile strength measurements indicated that the films' mechanical strength was sufficient to withstand the stresses encountered during transit and administration. The optimized formulas have a percent elongation of 120%. In general, as the amount of plasticizer in the film increases, the elongation of the film increases. The regression coefficient for the zero-order model was found to be the highest of all formulations, indicating that the release mechanism follows the Korsmeyer–Peppas model. For all formulations, the diffusion exponent n was determined to be smaller than 0.5, indicating virtually Fickian drug diffusion through the films.

Using the factorial design, the software proposed a quadratic model, which was determined to be significant with a F value of 226.98. A p0>F" value <0.05 suggests that the model terms are significant in this circumstance. X1 and X2 are important terms in the model. It was discovered that the drug's release is influenced by the swelling or gelation factor. With increasing PG concentration, drug release from the film increased, resulting in a higher drug release rate. After 10 min, the drug content and percent drug release had dropped, but not dramatically. Because no cellular necrosis was seen, the formulation can be considered safe for long-term oral administration of PDP. After 3 months of testing, it was discovered that there was no change in the appearance

Table 4: Stability studies at 40°C±2°C and 75%±5 RH of optimized batch A5.

Parameters	0 day	30 days	60 days	90 days
Appearance	No change	No change	No change	No change
Drug content (mg)	3.88	3.81	3.76	3.41
% Drug release	96.64	96.40	96.23	96.20
Surface pH	7.02	7.01	6.94	6.89

of the films and a small change in pH and mucoadhesive strength in accelerated stability studies.

CONCLUSION

In pH 6.8 phosphate buffer solutions and distilled water, the medication had a maximum absorbance of 213 nm, and its melting point was 126–128°C. The peaks in the drug's IR spectrum were also visible in the mixture drug excipients, indicating that the drug was compatible with all excipients. The medicine was also found to be compatible with all excipients in differential scanning calorimetry testing. All of the created films were smooth and elegant, with no visible cracks; they were homogeneous in weight, thickness, and drug content; and they exhibited good percent elongation. The films in the optimized batch (A5) had an excellent percent elongation of 120%. The concentration of HPMC and PG had a substantial effect on dependent variables such as percent drug release, disintegration time, and kink resistance after using the optimization technique. The magnitude of the disintegration time of the films increased as HPMC and PG levels increased. Batch A9 had a maximum disintegration duration of 62 s, and optimized batch A5 had a disintegration time of 50 s in an optimal interval of <1 min. *In vitro* drug release experiments on Batch A5 originally revealed rapid drug release (96.64% within 10 min), with the drug release mechanism being essentially Fickian (nandlt; 0.5 or 0.2557). The medication release rate was shown to rise with higher HPMC concentrations and decrease with higher PG concentrations. With an increase in HPMC and PG content, flexural strength improves. The effect of HPMC and PG on flexural strength was found to be positive. A9 had the highest flexural strength (297), whereas the improved batch A5 had an excellent flexural strength of 259. The oral mucosa permeability of the improved formulation sheep was substantial in achieving the therapeutic effect, and histological examinations revealed minimal injury to the oral mucosa. As a result, the final film containing 1.05 mg of HPMC and 0.2 mg of PG, as well as citric acid and sucralose, was optimized for buccal dissolving of PDP. Stability tests on the final improved formulation demonstrated no significant changes in physical parameters while stored at 40 degrees Celsius and 75% relative humidity (RH).

Finally, the findings revealed that HPMCE5 LV has the ability to alter drug release rates and has strong film and bioadhesive qualities. It showed promising initial drug release within 10 min (99.37%) and resistance to refolding when combined with PG. As a result, an economical and widely accessible semi-synthetic cellulose derivative can be employed as a potential drug release, flexibility, and process ability polymer modifier for successful formulation of oral PDP dissolving films, which may disrupt metabolism. Because it is necessary to achieve maximum medication penetration through the oral mucosa. According to the findings of this work, HPMCE5 LV-based PDP oral dissolving films may be successfully made with excellent stability and bioavailability.

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Consent for publication

All the authors approved the manuscript for publication.

Availability of data and material

All required data are available.

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