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# Formulation And Characterization Of Buccal Patches Of Dapagliflozin Using Box–Behnken Design

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## Introduction

Buccal drug delivery has emerged as a promising approach for the systemic delivery of various therapeutic agents, offering several advantages over conventional oral administration routes (Dhiman et al., 2020). Buccal patches, in particular, provide controlled release of drugs, enhanced bioavailability, avoidance of hepatic first-pass metabolism, and improved patient compliance. Dapagliflozin, a selective sodium-glucose co-transporter 2 (SGLT2) inhibitor, is widely used in the management of type 2 diabetes mellitus.
Formulation and characterization of buccal patches of dapagliflozin represent a novel strategy to enhance drug delivery and therapeutic efficacy. The development of optimized buccal patches can address challenges associated with the oral administration of dapagliflozin, such as variable absorption, gastrointestinal side effects, and dosing frequency.
The Box-Behnken design, a statistical experimental design methodology, offers a systematic approach for optimizing formulation parameters and evaluating their effects on the performance characteristics of buccal patches (Senthil et al., 2018). By systematically varying factors such as polymer composition, plasticizer concentration, and drug loading, Box-Behnken design facilitates the identification of optimal formulation conditions to achieve desired drug release kinetics, adhesive properties, and mechanical strength of buccal patches.
Several studies have demonstrated the successful formulation and characterization of buccal patches for various drugs using Box-Behnken design (Patel et al., 2019). These studies highlight the effectiveness of this experimental design approach in optimizing formulation parameters and enhancing the performance of buccal drug delivery systems.
In this study, we aim to formulate and characterize buccal patches of dapagliflozin using Box-Behnken design methodology. By systematically exploring the effects of formulation variables on patch properties, such as drug release profile, mucoadhesive strength, and mechanical integrity, we seek to develop optimized buccal patches capable of providing sustained and controlled release of dapagliflozin for improved therapeutic outcomes in the management of type 2 diabetes mellitus.

## Materials and Methods

### Formulation of buccal patches of dapagliflozin

A mucoadhesive layer was formulated through the solvent casting technique. The experimental design was based on a $2^3$ full factorial design using Design Expert (Version 8.0.4.1, Stat-Ease Inc., Minneapolis, MN, USA). Diverse concentrations of polymer solutions were meticulously blended according to the specified ratios outlined in Table 4.1. HPMC K4, Sod. alginate, and Eudragit RLPO polymers were individually dissolved in ethanol (95%) and subsequently amalgamated. This polymeric dispersion underwent stirring on a magnetic stirrer (Remi Equipments Ltd., India) for one hour to achieve a homogeneous, clear solution,

followed by a 15-minute sonication period. Propylene glycol 4000 (PEG) was introduced as a plasticizer, and stirring persisted for an additional 30 minutes. The drug solution, equivalent to 120mg (resulting in a total of 12 patches, each containing 10mg of the drug), was then added, thoroughly mixed, and left undisturbed for several hours to allow the escape of entrapped air.

To facilitate controlled solvent evaporation, the mold was covered with an inverted funnel. Subsequent to a careful examination, the dried patches were scrutinized for imperfections or air bubbles and subsequently cut into 2.5cm diameter patches. These patches were meticulously packed in aluminum foil and stored in a glass container at room temperature for future use (Koland et al., 2010; Chopra et al., 2007).

**Optimization of formulation**

A $2^3$ randomized full factorial design was employed in this study. Three factors, each at two levels, were evaluated and experimental trials were performed on all nine possible combinations Table 4.2. The amount of HPMC K4 (A), Sod. Alginate (B) and Eudragit RLPO (C) the amount of were selected as independent variables. The Cumulative drug release (R1), folding endurance (R2) and Drug content (R3) were selected as dependent variables. Amount of Propylene glycol 4000 (PEG) was remain constant. Regression polynomials for the individual dependent variables were calculated with the help of Design Expert 11.0.4.0 software and applied to approximate the response surface and contour plots. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

**Table 1: Formulation run using DOE for buccal patches of Dapagliflozin**

| Std | Run | Factor 1 A: HPMC K4 (mg) | Factor 2 B: Sod. Alginate (mg) | Factor 3 C: Eudragit RLPO (mg) | PEG 4000 (ml) |
|---|---|---|---|---|---|
| 17 | 1 | 1000 | 350 | 100 | 0.5 |
| 16 | 2 | 1100 | 350 | 100 | 0.5 |
| 13 | 3 | 1200 | 350 | 100 | 0.5 |
| 10 | 4 | 1000 | 500 | 50 | 0.5 |
| 6 | 5 | 1200 | 350 | 50 | 0.5 |
| 9 | 6 | 1000 | 200 | 50 | 0.5 |
| 12 | 7 | 1000 | 500 | 150 | 0.5 |
| 15 | 8 | 1000 | 400 | 100 | 0.5 |
| 2 | 9 | 1200 | 200 | 100 | 0.5 |
| 3 | 10 | 800 | 500 | 100 | 0.5 |
| 4 | 11 | 1200 | 500 | 100 | 0.5 |
| 14 | 12 | 1000 | 500 | 100 | 0.5 |
| 5 | 13 | 800 | 350 | 50 | 0.5 |
| 7 | 14 | 800 | 350 | 150 | 0.5 |
| 11 | 15 | 1000 | 200 | 150 | 0.5 |
| 8 | 16 | 1200 | 350 | 150 | 0.5 |
| 1 | 17 | 800 | 200 | 100 | 0.5 |

**Table 2: The factors selected for the formulation of buccal patches containing dapagliflozin were as follows**

| Factor | Name | Unit | Min. | Max. |
|---|---|---|---|---|
| A | HPMC K4 | mg | 800.00 | 1200.00 |
| B | Sod. Alginate | mg | 200.00 | 500.00 |
| C | Eudragit RLPO | mg | 50.00 | 150.00 |

**Final equation in terms of coded factors**

Cumulative drug release = +93.16 -1.17 A+1.06 B-3.11C-0.7650 AB3.50 AC+6.85 BC-0.4760 $A^2$-0.4760 $A^2$+0.0290 $B^2$-6.20 $C^2$

**Final Equation in terms of actual factors**

Cumulative drug release = +31.55186+0.207633 HPMC K4-0.155199 Sod. Alginate-0.043328 HPMC K4 * Sod. Alginate +0.000112 HPMC K4 * Eudragit RLPO-0.000076 Sod. Alginate * Eudragit RLPO-0.000132 HPMC $K4^2$+0.000187 Sod. $Alginate^2$-0.000458 Eudragit $RLPO^2$

**Final Equation in terms of coded factors**

**Folding Endurance** = +247.00-9.75A-11.50 B-10.00 C-12.00 AB+8.00 AC+31.00 BC-2.25 $A^2$+7.75 $B^2$-36.25 $C^2$

**Final equation in terms of actual factors**

**Folding Endurance** = +268.19444+0.123750 HPMC K4-0.331111 Sod. Alginate+0.453333 Eudragit RLPO-0.000400 HPMC K4 * Sod. Alginate+0.000800 HPMC K4 * Eudragit RLPO+0.004133 Sod. Alginate * Eudragit RLPO-0.000056 HPMC $K4^2$+0.000344 Sod. $Alginate^2$-0.014500 Eudragit $RLPO^2$

**Final equation in terms of coded factors**

**Drug Content** = +97.49-0.4900 A+0.2550 B+1.18 C+0.0275 AB+1.58 AC-0.0175 BC+0.6187 $A^2$+0.3487 $B^2$-1.71 $C^2$

**Final equation in terms of actual factors**

**Drug content** = +123.586670.049533 HPMC K4-0.009833 Sod. Alginate+0.002717 Eudragit RLPO+9.16667E-07 HPMC K4 * Sod. Alginate+0.000158 HPMC K4 * Eudragit RLPO2.33333E-06 Sod. Alginate * Eudragit RLPO+0.000015 HPMC $K4^2$+0.000015 Sod. $Alginate^2$-0.000682 Eudragit $RLPO^2$

**Characterization of prepared mucoadhesive patches**

**Weight and thickness of the patch**

The average weight of each formulation was determined by individually weighing 10 samples using a Digital Balance (Wensar PGB 200). Additionally, the thickness of each formulation was assessed by measuring 10 samples at three different locations with a vernier caliper (Patel et al., 2007). The mean thicknesses were subsequently calculated for each set of 10 samples.

**Folding endurance**

Folding endurance was assessed by repetitively folding a single patch at the same location until it either broke or reached a maximum of 250 folds without breaking. The folding endurance value was determined based on the number of times the film could be folded at the same spot without experiencing a break (Vashmi et al., 2007).

**Surface pH determination**

The patches were allowed to undergo a swelling process for 3 hours on an agar plate. The agar plate was prepared by dissolving 2% (m/v) agar in a simulated human saliva (SHS) solution with a pH of 6.8. The SHS solution was composed of NaCl (0.126 g), KCl (0.964 g), KSCN (0.189 g), $KH_2PO_4$ (0.655 g), and urea (0.200 g) dissolved in 1 L of distilled water (Verma et al., 2007). The preparation involved stirring the solution and pouring it into a Petri dish until gelling occurred at room temperature.

**Drug content uniformity**

Patches, each having a diameter of 25 mm and designed to contain 55 mg of LP, were dissolved through homogenization in a solution comprising 5 ml of ethyl alcohol and 2 ml of dichloromethane (Nafee et al., 2003). This dissolution process was conducted for 5 hours with intermittent shaking and was later diluted to a total volume of 50 ml with distilled water. Following this, the solution underwent filtration to eliminate insoluble residue. Subsequently, 1 ml of the filtrate was further diluted to 10 ml using simulated human saliva (SHS) with a pH of 6.8.

**Percent moisture absorption**

Accurate weighing of the buccal patches was performed, followed by placement in desiccators containing 100 ml of a saturated solution of aluminum chloride. The desiccators were maintained at relative humidity levels of 76% and 86%. After duration of 3 days, the patches were removed from the desiccators, and their weights were recorded (Semalty et al., 2005).

**Percent moisture loss**

Accurate weighing of the buccal patches was conducted, and subsequently, they were placed in desiccators containing anhydrous calcium chloride. Following 3-day duration, the patches were retrieved, and their weights were recorded. The percentages of moisture absorption and moisture loss were then calculated using the appropriate formula:

$$SI\% = \frac{\text{Inital weight} - \text{Final weight}}{\text{Initaial weight}} x100$$

**Tensile strength measurement**

The assessment of patch tensile strength was conducted using a tensiometer (Erection and Instrumentation, Ahmedabad) equipped with two load cell grips. The lower grip remained fixed, while the upper one was movable. Film strips measuring 2.5 × 2.5 cm were securely positioned between these grips, and a gradual force application ensued until the film reached the point of breakage. Tensile strength values were directly obtained from the dial reading, measured in kilograms (Patel and Poddar, 2009).

**Swelling study**

The assessment of the bioadhesive polymer's degree of swelling plays a crucial role in determining adhesion characteristics. To evaluate the swelling rate of the mucoadhesive patch, the patches were immersed in simulated human saliva (SHS) solution with a pH of 6.8 at 37°C ± 1. For each formulation, three patches were cut, weighed, and the average weight (W1) was calculated (Satishbabu and Srinivasan, 2008).

$$SI(\%) = \frac{W2 - W1}{W1} X100$$

**Ex-vivo bioadhesion strength**

The muco-adhesive strength of the buccal film was measured by the Modified Physical Balance. In this method porcine buccal membrane as the model mucosal membrane. The fresh porcine buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. The both pans were balanced by adding an appropriate weight on the left- hand pan. A piece of the mucosa was tied to the surface of the beaker and placed below the right pan which was moistened with phosphate buffer pH 6.8. The film was sticky to the lower side of right pan with glue. Previously weighed beaker was placed on the left-hand pan and water (equivalent to weight) was added slowly to it until the film detaches from the mucosal surface. The weight required to detach the film from the mucosal surface gave the muco- adhesive strength. The experiment was performed in triplicate and the average value was calculated (Park, Robinson, 1987).

**Ex-vivo bioadhesion time**

The ex-vivo residence time was determined using a locally modified USP disintegration apparatus. The disintegration medium was composed of 500 mL pH 6.8 phosphate buffer maintained at $37^0$C. The porcine buccal tissue was glued to the surface of a glass slab, vertically attached to the apparatus. The buccal film was hydrated from one surface using 0.5 ml of pH 6.8 phosphate buffers and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to run test. The time necessary for complete erosion or detachment of the film from the mucosal surface was recorded. The experiments were performed in triplicate and mean was determined (Ramana, Nagada, Himaja 2007).

**In vitro drug release study**

The drug release study from the patches was conducted utilizing a USP 23 Type-2 rotating paddle dissolution test apparatus (Electrolab). The dissolution medium consisted of 250 ml of simulated human saliva (SHS) solution at a pH of 6.8, maintained at a temperature of 37°C ± 5°C, with a stirring rate set at 50 rpm (Korsmeyer et al., 1983).

A patch, measuring 2.5 cm in diameter, was affixed to a glass disc using cyanoacrylate adhesive. This disc was positioned at the bottom of the dissolution vessel, ensuring the patch remained on the upper side of the disc. Samples (5 ml) were withdrawn at predetermined intervals of 30 minutes and replaced with an equivalent volume of the dissolution medium. The withdrawn samples were then filtered through a 0.45 mm filter, appropriately diluted with SHS solution (pH 6.8), and spectrophotometrically measure the absorbance.

**Results and Discussion**

The formulation and characterization of buccal patches of Dapagliflozin utilizing Box-Behnken design present an innovative approach to enhance drug delivery efficacy. Table 3 outlines the formulation development process, demonstrating variations in cumulative drug release, folding endurance, and drug

content among different formulations (F1 to F17). These parameters serve as critical indicators of the patch's performance, influencing its therapeutic effectiveness and patient acceptability.

Table 4 showed experimental results with predicted responses, offering insights into the accuracy and reliability of the Box-Behnken design in optimizing formulation parameters. Notably, formulation F10 exhibits close agreement between predicted and experimental values for cumulative drug release, folding endurance, and drug content, indicating the robustness of the experimental design approach in predicting patch characteristics.

Upon characterization of the optimized formulation (F10) in Table 5, key parameters such as weight, thickness, surface pH, moisture absorption, tensile strength, swelling, ex-vivo bioadhesion strength, and bioadhesion time are evaluated. These results provide a comprehensive understanding of the patch's physical and mechanical properties, essential for ensuring its suitability for buccal drug delivery.

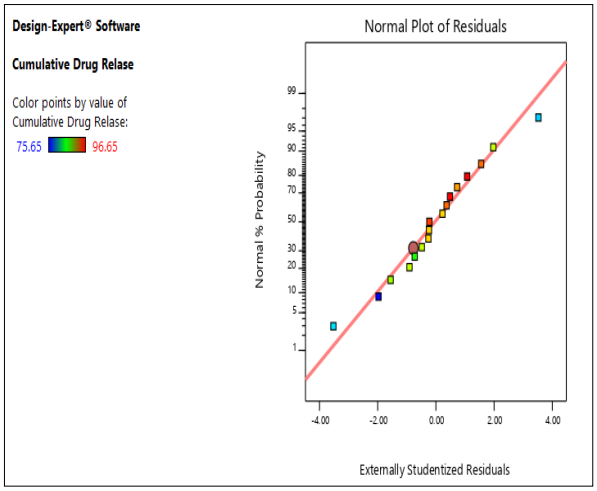
The in-vitro drug release study depicted in Table 6 illustrates the sustained release profile of Dapagliflozin from the optimized formulation (F10) over a period of 12 hours. The cumulative drug release steadily increases over time, reaching 96.65% at the end of the dissolution study, indicative of controlled drug release kinetics.

Furthermore, the release kinetics regression values presented in Table 7 elucidate the drug release mechanism of formulation F10. High correlation coefficients for zero order, Higuchi, and Korsmeyer-Peppas models suggest that the drug release follows a combination of diffusion and erosion mechanisms, characteristic of matrix-type buccal patches.

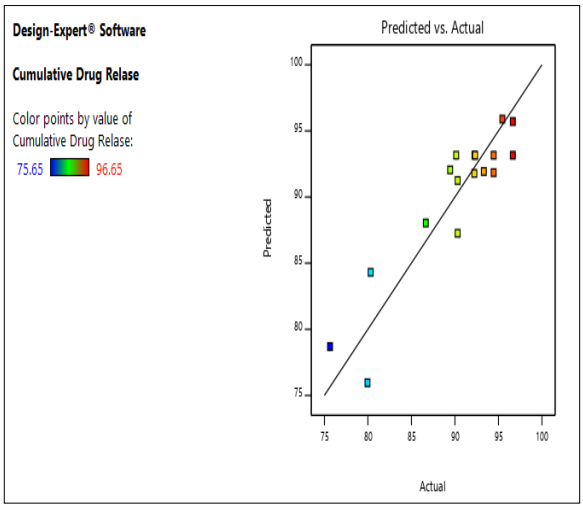
**Table 3: Formulation and development of buccal patch of Dapaglifloxin**

| F. Code | Response 1: Cumulative Drug Release | Response 2: Folding Endurance | Response 3: Drug Content |
|---|---|---|---|
| F1 | 92.32 | 241 | 97.85 |
| F2 | 92.25 | 245 | 97.05 |
| F3 | 96.65 | 240 | 98.32 |
| F4 | 80.32 | 165 | 94.45 |
| F5 | 93.32 | 205 | 93.32 |
| F6 | 95.45 | 278 | 94.45 |
| F7 | 92.23 | 221 | 97.78 |
| F8 | 94.45 | 269 | 96.45 |
| F9 | 90.31 | 255 | 97.74 |
| F10 | 96.65 | 274 | 99.12 |
| F11 | 94.45 | 236 | 98.85 |
| F12 | 90.14 | 240 | 97.78 |
| F13 | 90.31 | 246 | 98.12 |
| F14 | 86.65 | 196 | 96.32 |
| F15 | 79.95 | 210 | 97.85 |
| F16 | 75.65 | 187 | 97.85 |
| F17 | 89.45 | 245 | 98.12 |

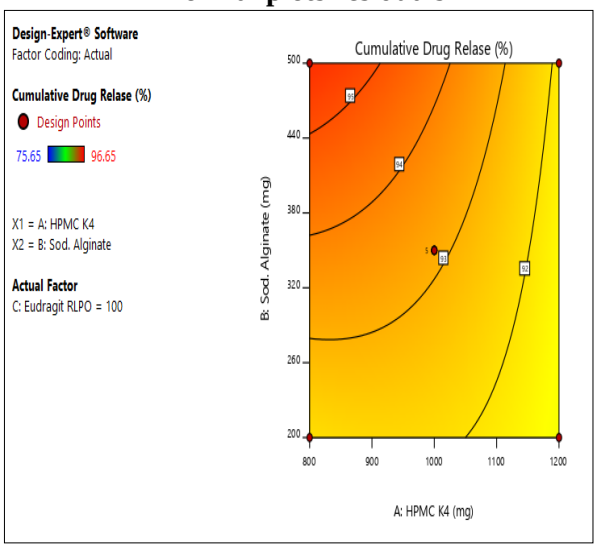
## Graphs for cumulative drug release



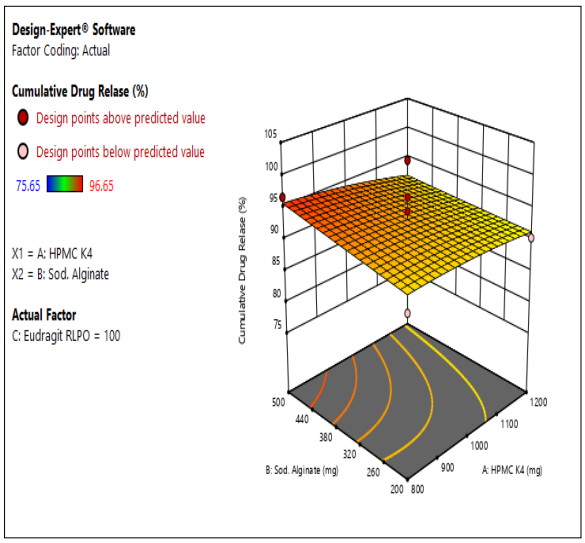

**Normal plots residuals**




**Predicted vs. Actual release**

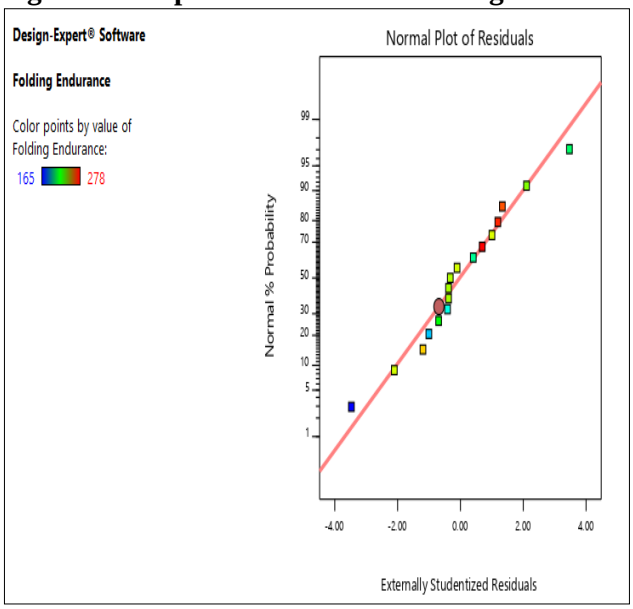



**ontour plots for HPMC K4 and Sod. Alginate**

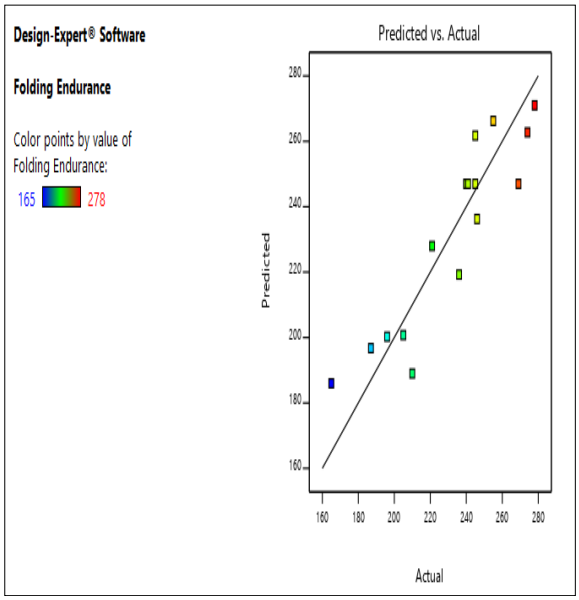



**3D surface plots for HPMC K4 and Sod. Alginate**

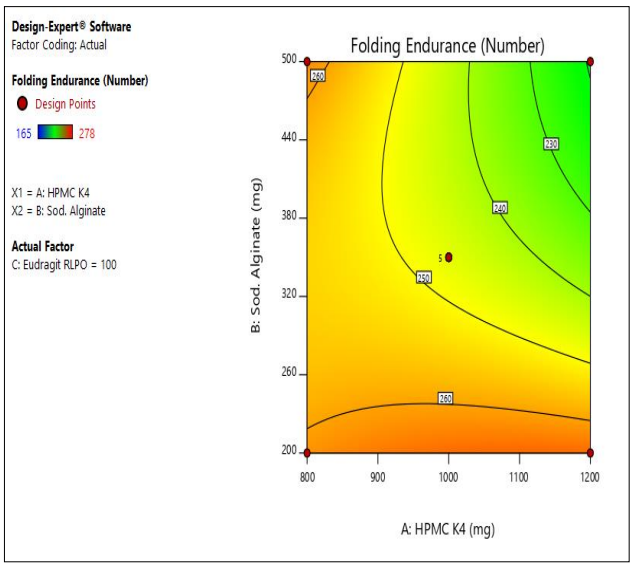
**Figure 1: Graphs for cumulative folding endurance**



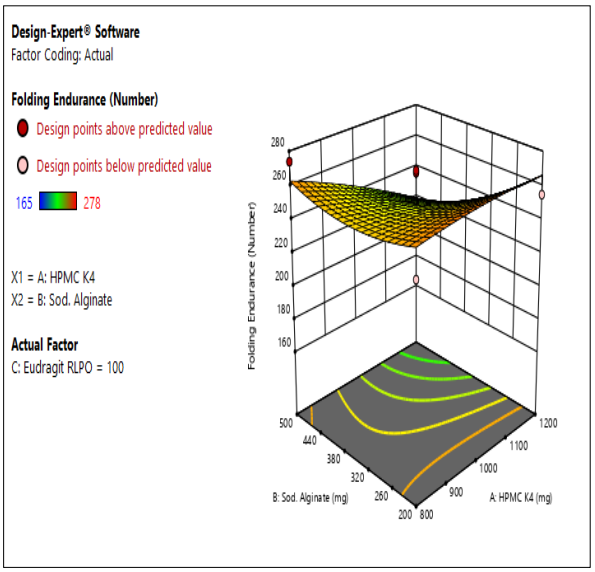

**Normal plots residuals**




**Predicted vs. Actual**

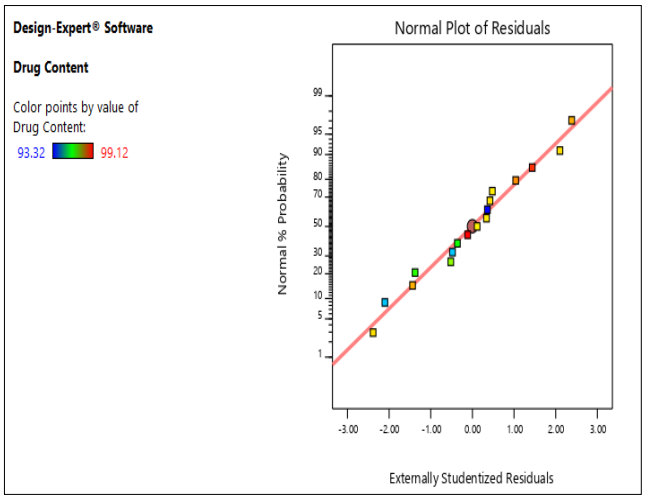



**Contour plots for HPMC K4 and Sod. Alginate**

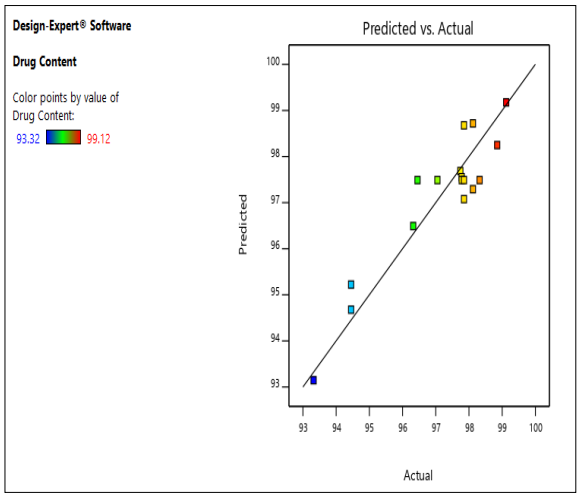



**3D surface plots for HPMC K4 and Sod. Alginate**

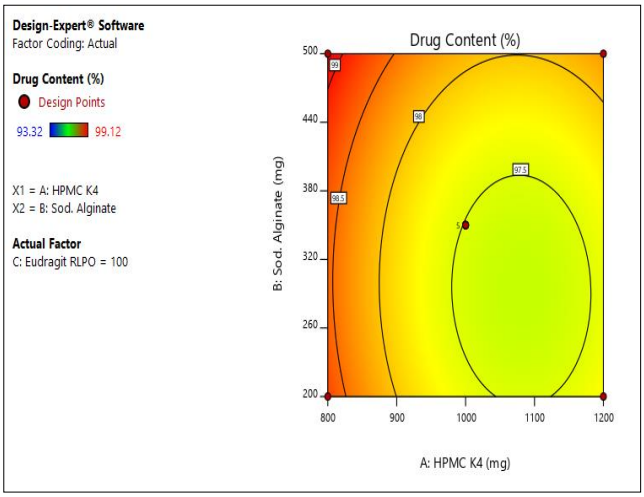
**Figure 2: Graphs for folding endurance**



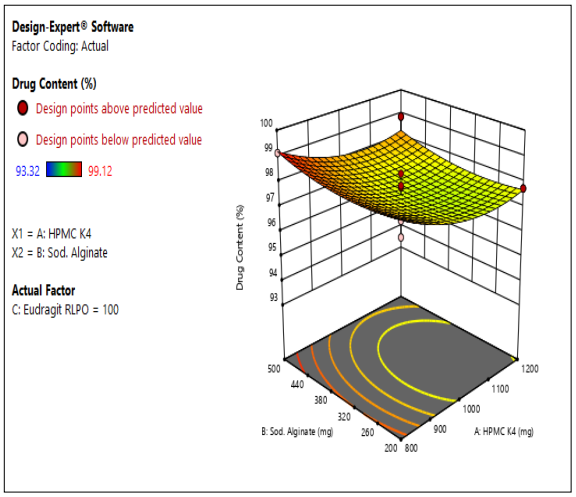

**Normal plots residuals**




**Predicted vs. Actua**




**Contour plots for HPMC K4 and Sod. Alginate**




**3D surface plots for HPMC K4 and Sod. Alginate**

**Figure 3: Graphs for drug content**

**Experimental results with predicted responses:** On the basis of DOE formulation four formulations is selected as optimized formulation for preparation of buccal patches the results of experimental values for composition of patches are more similar to the predicted values and also these are within limit.

**Table 4: Experimental results with predicted responses**

| Formulation (Run order 10) | Composition HPMC K4/Sodium Alginate/Eudragit RLPO/ | Response | Predicted value | Experimental value |
|---|---|---|---|---|
| **F10** | 800/500/100 | Cumulative Drug Release | 95.71 | 96.65 |
| | | Folding Endurance | 262.75 | 274 |
| | | Drug Content | 99.17 | 99.12 |

**Table 5: Results of characterization of optimized formulation of buccal patches (F10)**

| S. No. | Parameters | Results* |
|---|---|---|
| 1 | Weight (mg) | 125±3 |
| 2 | Thickness of the patch (mm) | 0.12±0.02 |
| 3 | Surface pH determination | 6.74±0.12 |
| 4 | Moisture absorption (%) | 1.25±0.15 |
| 5 | Moisture loss (%) | 3.85±0.15 |
| 6 | Tensile strength measurement kg/cm$^2$ | 0.85±0.08 |
| 7 | Swelling study (%) | 113±6.00 |
| 8 | Ex-vivo bioadhesion strength (gm) | 24.5±0.30 |
| 9 | Ex-vivo bioadhesion time (Hrs.) | 8±0.50 |

*****Average of three determinations (N=3)

**Table 6: In-vitro drug release study of optimized formulation F10**

| S. No | Time (Hrs.) | F10 |
|---|---|---|
| 1 | 0.5 | 16.65 |
| 2 | 1 | 22.32 |
| 3 | 2 | 33.65 |
| 4 | 4 | 47.78 |
| 5 | 6 | 56.67 |
| 6 | 8 | 69.98 |
| 7 | 10 | 88.12 |
| 8 | 12 | 96.65 |

**Table 7: Release kinetics regression values of formulation F10**

| Formulation code | Zero order | First order | Higuchi | Korsmeyer peppas |
|---|---|---|---|---|
| **F10** | 0.991 | 0.874 | 0.980 | 0.991 |

## Conclusion

In conclusion, the formulation and characterization of buccal patches of Dapagliflozin using Box-Behnken design offer a systematic and effective approach to optimize patch properties and enhance drug delivery efficiency. The comprehensive evaluation of formulation parameters, coupled with in-vitro drug release studies, provides valuable insights into the performance and potential therapeutic utility of the developed buccal patches for the management of type 2 diabetes mellitus.

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