DOI: 10.12923/cipms-2026-0002

Curr. Issues Pharm. Med. Sci., Vol. 39, No. 1, Pages 7-13

Current Issues in Pharmacy and Medical Sciences

Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA

journal homepage: https://czasopisma.umlub.pl/curipms

A 3% topical gel formulation of tenofovir disoproxil fumarate (TDF) for the treatment of human immunodeficiency virus (HIV) by experimental approach

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ARTICLE INFO

Received 05 November 2022
Accepted 05 February 2026

Keywords:
ex vivo;
Design-Expert®;
tenofovir disoproxil fumarate;
topical gel;
spreadability.

ABSTRACT

Tenofovir disoproxil fumarate (TDF) is widely used in the treatment of HIV-infected adults and is also approved for the management of chronic hepatitis B in adults, where it is administered in combination with other antiretroviral agents. The present study employed Design-Expert® software to investigate the effects of Kolliphor®P188 (g), Methocel®K100 Premium LV (g), and polyethylene glycol (mL) concentrations on the drug release characteristics of a topical TDF gel formulation. Eight formulations, including three center points, were prepared and evaluated for physical appearance, spreadability, syringibility, washability, pH, and *ex vivo* drug release. The interactions between formulation variables and drug release were also assessed. The results demonstrated statistically significant differences among formulations ($p < 0.05$). The findings indicate that polymer concentration is a critical formulation variable that must be carefully optimized to achieve a topical gel with desirable performance characteristics.

INTRODUCTION

Tenofovir disoproxil fumarate (TDF) is classified as a highly soluble, poorly permeable drug substance and belongs to Biopharmaceutics Classification System (BCS) Class III. Chemically, TDF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Oral TDF tablets were first approved in 2001 for the treatment of human immunodeficiency virus (HIV) infection and chronic hepatitis B. The TDF free base exhibits a pKa of 3.75, an intrinsic solubility of approximately 15.3 mg/mL at room temperature, and a log *p* value of 1.25.

Recent literature reports indicate that alternative dosage forms such as vaginal films have emerged as promising delivery systems, offering controlled drug release through single-stage processes [1]. Tenofovir-loaded films have been shown to release the drug gradually in vaginal fluid, with accelerated release observed in the presence of seminal fluid [2]. Topical gel formulations and oral emtricitabine/tenofovir combinations have demonstrated effectiveness in HIV prophylaxis, and future research directions have been extensively discussed [3-6]. Furthermore, the *in vitro* performance of implant-based delivery systems, including poly(ε-caprolactone) (PCL) matrices, has been shown to influence the daily release rates of TDF [7-9].

The efficacy and safety of tenofovir formulations, including 1% vaginal gel preparations for HIV prevention in women, have been well documented [10-12]. Various pharmaceutical dosage forms, such as gels, vaginal rings, films, and tablets are currently available for the vaginal or rectal administration of water-soluble compounds [12]. In addition, mucoadhesive films for vaginal delivery of tenofovir have been explored as a viable strategy to enhance localized drug retention and therapeutic efficacy [13].

Advances in topical and transdermal drug delivery systems have also been reported for other therapeutic agents. Studies investigating nanoemulgel systems containing essential oils demonstrated enhanced transdermal permeability of diclofenac sodium using high-pressure homogenization techniques [14-16]. Similarly, pharmacokinetic profiles, safety, and acceptability of novel gel formulations, such as OB-002H, have been evaluated [17]. Quality by Design (QbD) approaches have been successfully applied to develop topical hydrogels with reduced surfactant concentrations, including ketoconazole-loaded systems [18]. Additional

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research has examined econazole-loaded nanosponge hydrogels for the treatment of dermatological conditions, employing β-cyclodextrin-based nanosponges [18,19].

Recently, organogels and nanoemulsion-based systems have attracted considerable attention as rapid-acting and efficient drug delivery vehicles for hydrophobic drugs [20]. Ethosomal gel formulations have also been optimized for enhanced topical delivery of active pharmaceutical ingredients [21]. Numerous statistical optimization studies have demonstrated the individual and combined effects of formulation variables on drug release and performance characteristics [22-39].

In this context, the objective of the present study was to develop and optimize a 3% TDF topical gel formulation using a factorial experimental design. The independent formulation variables included Kolliphor® P188 (X_1; 0.5 and 1 g), Methocel® K100 Premium LV (X_2; 1 and 1.5 g), and polyethylene glycol (X_3; 1 and 1.5 mL). The low (-) and high (+) levels of each variable were selected to evaluate their individual and interactive effects on gel performance and drug release characteristics.

MATERIALS AND METHODS

Materials

Tenofovir disoproxil fumarate (TDF) was obtained from Laurus Labs Pvt. Ltd., Visakhapatnam. Methocel® K100 Premium LV (HPMC) was sourced from Colorcon, Kolliphor® P188 from IMCD Pvt. Ltd., Mumbai, and polyethylene glycol (PEG 400), hydrochloric acid, and methanol were purchased from MERCK Specialties Pvt. Ltd., Mumbai. All reagents were of analytical grade.

Gel formulation

The tenofovir 3% gel formulation is presented in Table 1. The gel was prepared by accurately weighing Kolliphor P188 and HPMC K100 Premium LV, which were dispersed in purified water up to 25 mL with moderate-speed stirring. The pH was adjusted to 6-6.5. Tenofovir was then mixed with propylene glycol and incorporated into the gel base. The resulting drug-gel mixture was stirred thoroughly and continuously, then left at room temperature for 24 hours. After this period, entrapped air bubbles settled, yielding the final gel formulation.

Table 1. Formulae of gel prepared

Name of ingredients	T1	T2	T3	T4	T5	T6	T7	T8	Optimized
Tenofovir disoproxil (mg)	500	500	500	500	500	500	500	500	500
Kolliphor-p188 (mg)	0.5	1	0.5	1	0.5	1	0.5	1	0.75
Methocel K 100 Premium LV (mg)	1.5	1.5	2	2	1.5	1.5	2	2	1.75
Polyethylene glycol (ml)	1.5	1.5	1.5	1.5	3	3	3	3	2.25
Water (Q.s)	25	25	25	25	25	25	25	25	25

Physical evaluation

All formulations were evaluated for physical appearance, color, texture, phase separation, homogeneity, and immediate skin feel. Additionally, a small sample of each gel was assessed for stiffness, grittiness, and greasiness.

Spreadability

A set of Petri dishes was prepared, and the gel formulations were placed on the lower dish. A 200 mg sample of the gel was spread on the upper Petri dish so that, when pressed, the gel formed a uniform layer between the two dishes. A 200 g weight was carefully placed on the upper dish. The time required for the gel to travel a specified distance and separate from the lower dish under the influence of gravity was recorded.

Syringability

The syringeability of the gel was evaluated using a 5 mL gel sample at room temperature. The gel was loaded into a 5 mL syringe fitted with an 18 G needle and supported vertically. The time required for the gel to be completely expelled from the syringe under constant pressure was recorded.

Washability

Washability was assessed by applying the gel formulation to the skin and subsequently removing it with water. A formulation was considered satisfactory if it could be easily washed off the skin without leaving a residue.

Skin irritation test

The gel was applied to a defined area of the forearm of 10 volunteers aged 20-22 years for 24 hours. Skin irritation was monitored by observing any changes in color, morphology, or signs of inflammation during and after the test period.

pH measurement

The pH of the gel formulations was determined using a calibrated pH meter.

Ex Vivo drug release study

the drug release from the gel formulations was evaluated using a modified Franz diffusion cell. Female goat skin was carefully excised, cleaned, and placed between the donor and receptor compartments of the diffusion cell. The receptor compartment was filled with 0.1 N hydrochloric acid, and the temperature was maintained at 32°C. The assembly was continuously stirred using a magnetic stirrer to ensure uniform distribution.

Aliquots of the receptor medium (at suitable intervals of 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, and 4.5 hours) were withdrawn and replaced with an equal volume of fresh medium to maintain sink conditions. The amount of Tenofovir released was quantified using a UV-visible spectrophotometer at 260 nm.

DATA ANALYSIS

The release kinetics of Tenofovir from the gel formulations were analyzed using zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. Statistical analysis, including analysis of variance (ANOVA), was performed using Design-Expert® software to evaluate the influence of formulation variables on drug release.

1. Physical examination

The prepared gel formulations were visually inspected for color, homogeneity, appearance, consistency, phase separation, and immediate skin feel. All formulations exhibited satisfactory physical characteristics, as summarized in Table 2. Stiffness, grittiness, and greasiness were also assessed, confirming the gels' suitability for topical application.

Table 2. General characteristics

Formulation	Physical appearance	Color	Texture	Phase separation	Homogeneity	Immediate skin feel
T1	Transparent	Colorless	Smooth	No	Observed	Cool, layer formation observed
T2	Transparent	Colorless	Smooth	No	Observed	Cool, layer formation observed
T3	Transparent	Colorless	Smooth	No	Observed	Cool, layer formation observed
T4	Transparent	Colorless	Smooth	No	Observed	Cool, layer formation observed
T5	Transparent	Colorless	Smooth	No	Observed	Cool, layer formation observed
T6	Transparent	Colorless	Smooth	No	Observed	Cool, layer formation observed
T7	Transparent	Colorless	Smooth	No	Observed	Cool, layer formation observed
T8	Transparent	Colorless	Smooth	No	Observed	Cool, layer formation observed
Optimized	Transparent	Colorless	Smooth	No	Observed	Cool, layer formation observed

2. Spreadability

Spreadability values ranged from 36.6 to 50 g·cm/sec, indicating that the gels spread easily on the skin, which can enhance drug absorption (Table 3).

Table 3. Spreadability

Formula	Spreadability (g·cm/sec)
T1	50.0
T2	46.6
T3	42.0
T4	40.0
T5	49.6
T6	47.0
T7	38.3
T8	42.0
Optimized	42.0

3. Washability

Washability was evaluated by applying the gel to the skin and removing it with water. All formulations were easily washable, demonstrating good user compliance and suitability for topical use (Table 4).

Table 4. Washability

Formulation	Properties
T1	Easy
T2	Easy
T3	Easy
T4	Easy
T5	Easy
T6	Easy
T7	Easy
T8	Easy
Optimized	Easy

4. Syringability

The time required to expel the gel completely from a syringe ranged from 29 sec to 1.17 min, confirming that all formulations could be efficiently administered via a syringe (Table 5).

Table 5. Syringability

Formula	Syringability (min.sec)
T1	1.17
T2	0.29
T3	1.30
T4	0.41
T5	0.50
T6	1.29
T7	1.80
T8	0.43
Optimized	0.59

5. *Ex vivo* drug release

The drug release from the gel formulations was evaluated using zero-order and Higuchi models (Table 6). Higuchi analysis indicated that drug release from all gels was diffusion-controlled (Figure 1). In the Korsmeyer-Peppas model, the release exponent (n) ranged from 0.013 to 1.6, indicating that formulations T1-T6 followed Fickian diffusion, while T7 and T8 exhibited super case-II transport (Figure 2).

The cumulative release profiles (Figure 3) showed the following results:

- T1: 100% release in 2.4 h,
- T2: 100% release in 2.5 h,
- T3: 100% release in 4.5 h,
- T4: 100% release in 3.5 h,
- T5: 100% release in 3.5 h,
- T6: 100% release in 1 h,
- T7: 100% release in 1.5 h,
- T8: 100% release in 3 h.

The order of drug release was:

- T6 > T7 > T1 > T2 > T8 > T4 = T5 > T3.

The Tenofovir 3% gel formulations were prepared with the following compositions:

- X1: Kolliphor P188 (0.5-1 g)
- X2: Methocel K100 Premium LV (1.5-2 g)
- X3: Polyethylene glycol (1.5-3 ml)

Table 6. Correlation-Coefficient (r) value of formulations

Formulation	Zero-order	First-order	Higuchi	Peppas
T1	0.989	0.7073	0.8343	0.7144
T2	0.9810	0.906	0.9280	0.9356
T3	0.949	0.924	0.9335	0.8625
T4	0.9260	0.8560	0.9515	0.8315
T5	0.9589	0.9412	0.9780	0.7684
T6	0.8663	0.7180	0.8761	0.9015
T7	0.8001	0.7470	0.8708	0.9267
T8	0.8120	0.7237	0.6335	0.8940
Optimized	0.9120	0.8170	0.9810	0.9110

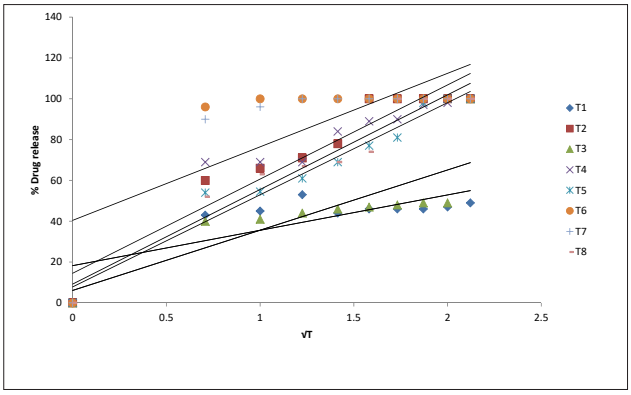

Figure 1. Drug release profile of various gel formulations fitted to the Higuchi model

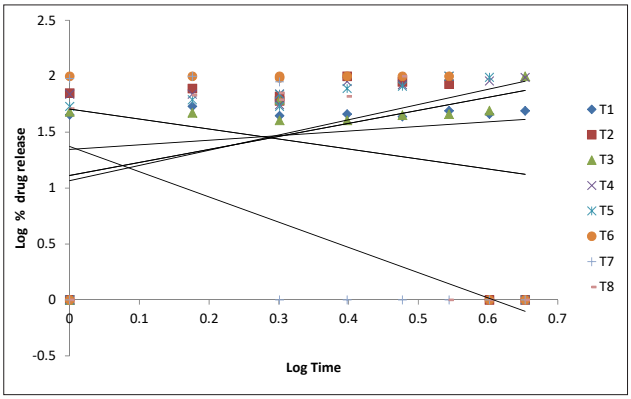

Figure 2. Korsmeyer-Peppas model. Drug release profiles of various gel formulations

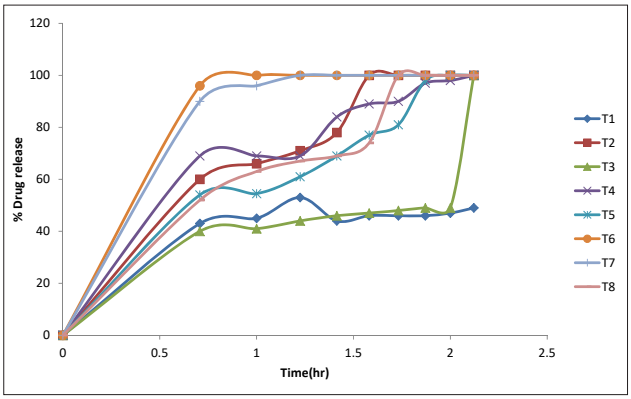

Figure 3. *Ex vivo* drug release profile of various gel formulations.

Statistical analysis

Table 7. Analysis of variance (ANOVA) of responses Q100 and DR 2hr

Source	S.S	df	M.S	F	p	Remark
Q100						
Model	404.32	7	57.76	38.43	0.0062	Significant
A-Kolliphor p-188	62.16	1	62.16	41.36	0.0076	
B-Methocel K100 Premium LV 100	39.16	1	39.16	26.06	0.0145	
C-Propylene glycol	86.46	1	86.46	57.53	0.0048	
AB	82.56	1	82.56	54.94	0.0051	
AC	55.65	1	55.65	37.03	0.0089	
BC	39.16	1	39.16	26.06	0.0145	
ABC	39.16	1	39.16	26.06	0.0145	
Residual	4.51	3	1.50			
Lack of Fit	4.51	1	4.51			
Pure Error	0.0000	2	0.0000			
Cor Total	408.83	10				
DR 2hr						
Model	9.50	7	1.36	63.09	0.0030	Significant
A-Kolliphor p-188	2.16	1	2.16	100.67	0.0021	
B-Methocel K 100 Premium LV 100	0.3254	1	0.3254	15.14	0.0301	
C-Propylene glycol	4.02	1	4.02	187.18	0.0008	
AB	0.5767	1	0.5767	26.82	0.0140	
AC	0.9510	1	0.9510	44.23	0.0069	
BC	0.2323	1	0.2323	10.80	0.0462	
ABC	1.22	1	1.22	56.82	0.0048	
Residual	0.0645	3	0.0215			
Lack of Fit	0.0645	1	0.0645			
Pure Error	0.0000	2	0.0000			
Cor Total	9.56	10				

The experimental data were analyzed using Design -Expert software, and the results are summarized in Table 7. Two response variables were considered:

- Y1: Time required for 100 % drug release (Q100):
  Based on the polynomial equation described below:
  Y1 = 5.05–2.79X1–2.21X2–3.29X3+3.21X1X2+2.64 X1X3+2.21X2X3–2.21 X1X2X3
- Y2: Drug released at 2 hours (Dr 2h):
  Based on the polynomial equation described below:
  Y2 = 8.04+0.5202X1–0.2017X2+0.7093X3–0.2685X1X2 –0.3448X1X3–0.1704 X2X3–0.3908 X1X2X3.

A plus sign indicates a positive a positive effect of the factors, while a minus sign indicates a decreased response. Figure 4 shows the optimization results: Y1 is 2.120 hours, Y2 is 60.69%, and the desirability is 1.000 (Figure 4). Figure 5 shows contour and response surface plots, while Figure 4 shows the optimized formulation [40–45].

CONCLUSIONS

The tenofovir 3% gel formulation was prepared using Kolliphor P188 (0.5 mg and 1 mg), Methocel K100 Premium LV (2 mg and 1.5 mg), and Polyethylene glycol (3 ml and 1.5 ml).

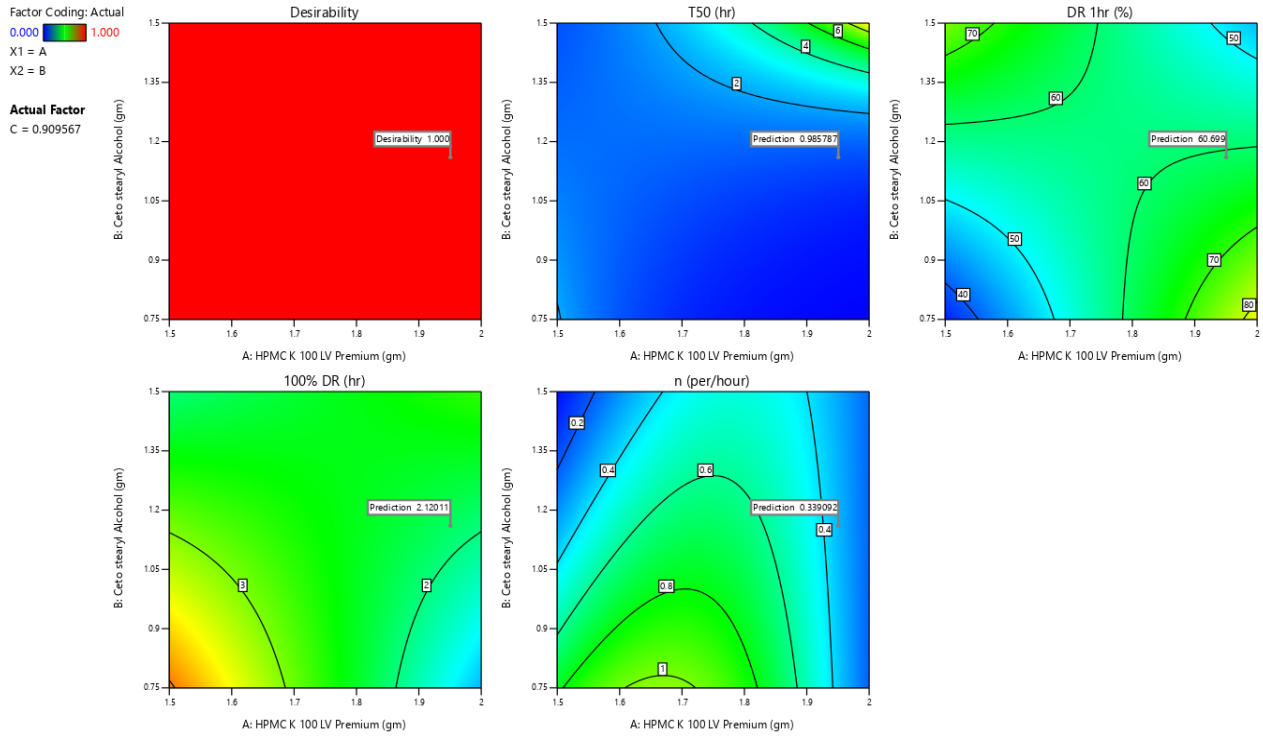

Figure 4. Desirability and optimization counterplots

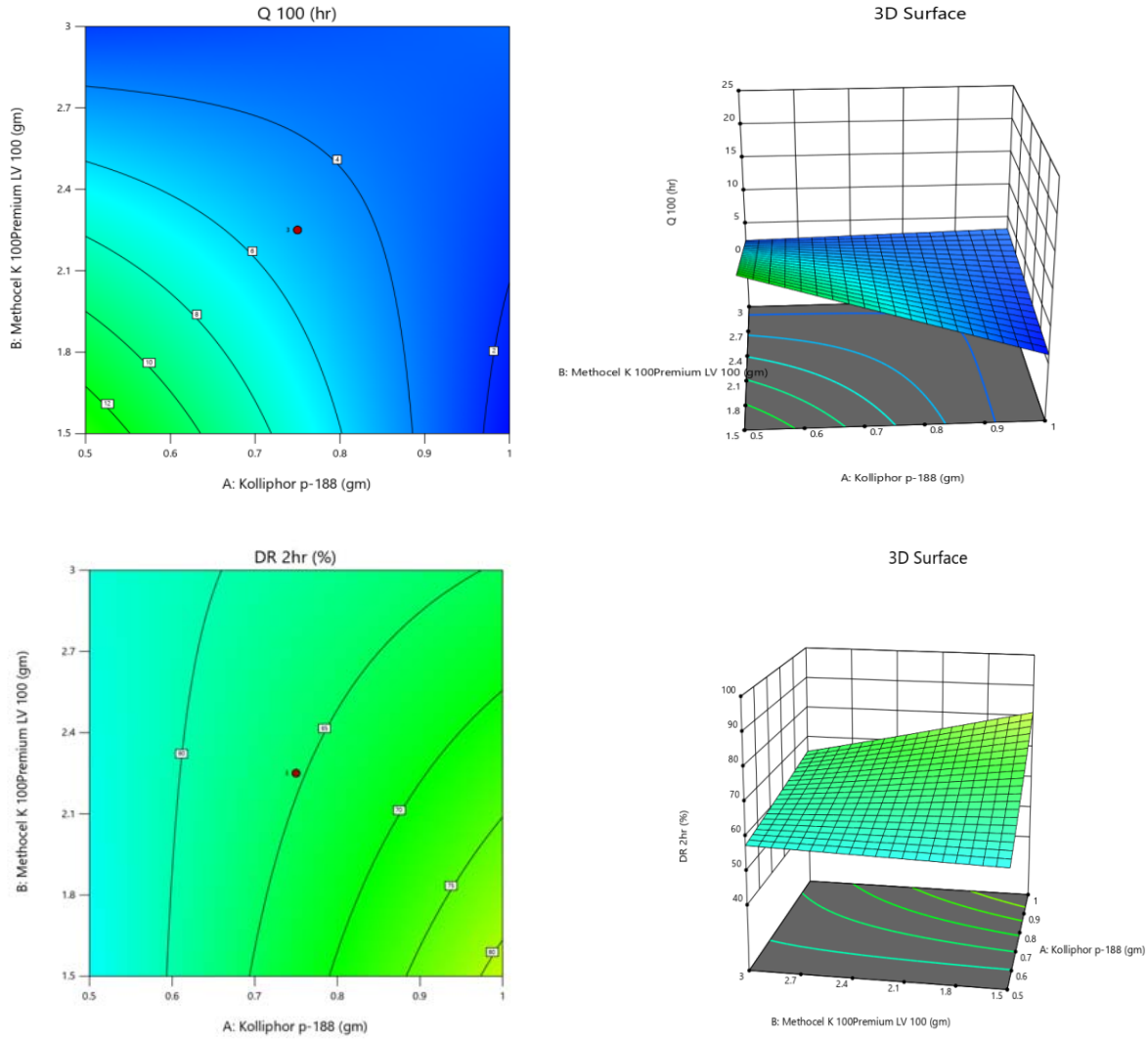

Figure 5. Counterplots (A & C) and 3D surface plots (B & D) of Q100 and DR 2hr

The formulation has good spreadability and washability and does not cause skin irritation. All prepared gel formulations demonstrated favorable physical properties. The *ex vivo* drug release study of tenofovir gel showed that it followed zero-order kinetics. This is due to a higher correlation coefficient than first-order kinetics. Drug release from T6 gave 100% release within one hour. Drug release follows Fick's diffusion due to the release exponent (n) of the optimized formula, T6. In recent years, all the above formulations were evaluated using a quality by design (QBD) approach, which was helpful for factorial design using software tools like Design-Expert to determine significance.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Sri Venkateswara College of Pharmacy for providing the facilities and support necessary for this research.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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