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Formulation and Characterization of Liposomal Gel with Povidone-Iodine for Wound Healing Activity by Using Box-Behnken Design

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Abstract

This work was focused on the optimization and characterization of liposomal gel based on PVP-Iodine. Poloxamer 188 and span 80 were used as a surfactant/cosurfactant for the topical delivery of PVP-Iodine liposomal gel. Seventeen runs of PVP-Iodine liposomal gel were composed of cholesterol, poloxamer 188 and span 80. A 3-factor, 5-level Box-Behnken design was used to optimize the process parameters including Cholesterol (A), Gelling agent and surfactant ratio (B) and Diethyl ether volume (C). Five dependent variables particle size, viscosity, percentage of available iodine content, gel strength, and spreadability was measured as responses. **P-values** less than 0.0500 indicate all model terms are significant.

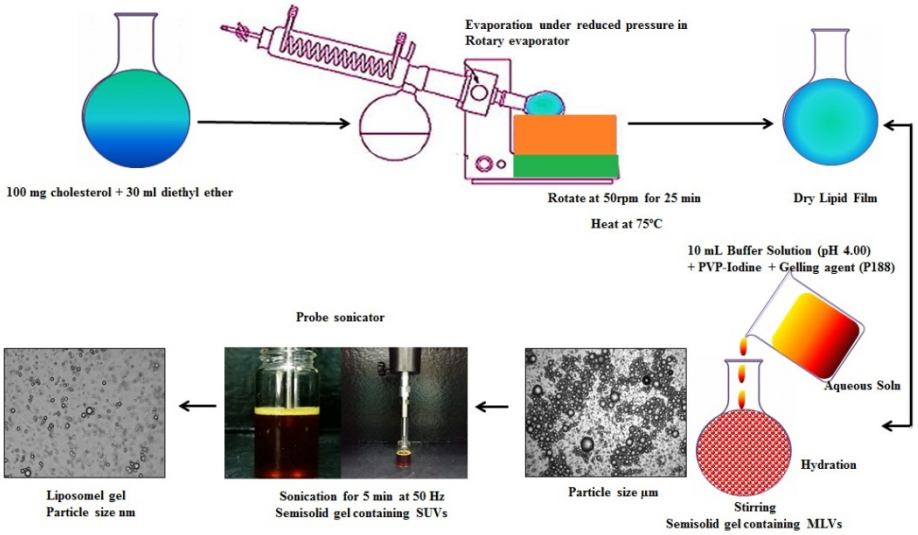
Keywords: Liposomal gel, Povidone-Iodine, Wound healing activity, Box-behnken design

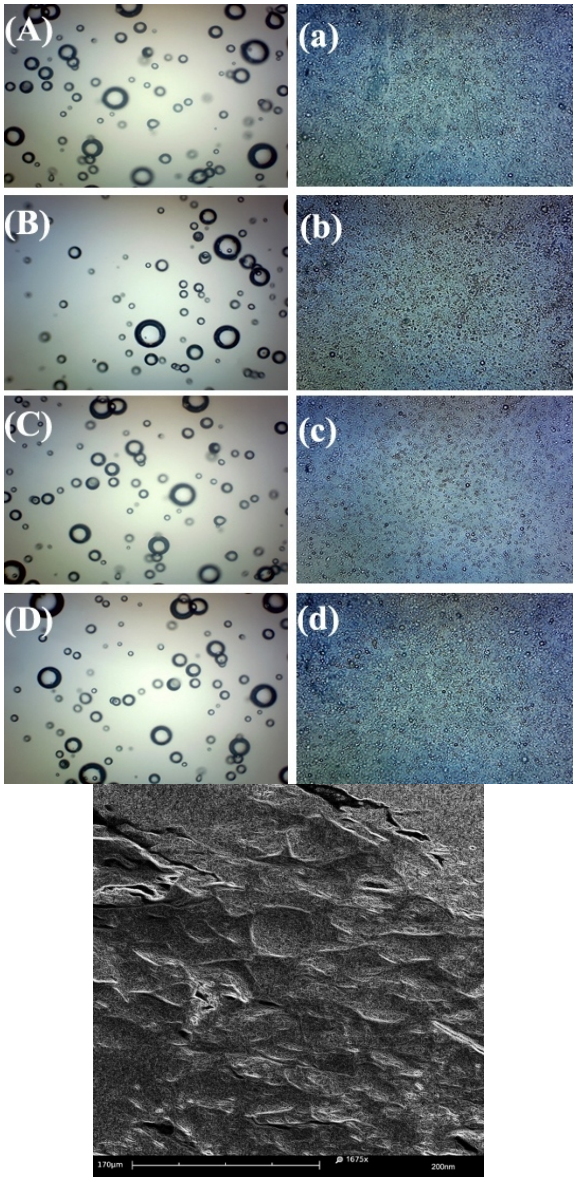
INTRODUCTION

Iodine has been used in wound treatment for more than 150 years. Povidone–iodine (PVP–I) has been popular since its discovery in 1955 because of its broad anti-microbial spectrum, versatility in wound treatment and lack of microbial resistance [1]. Furthermore, cell viability has been demonstrated at bactericidal concentrations of PVP–I in vitro [2], suggesting that it may not inhibit the wound healing process, unlike many other antiseptic solutions. The incorporation of PVP–I into liposomes was found to be very beneficial. PVP–I in a hydrogel base (PVP–ILH, hydrosome) combines the broad-spectrum antimicrobial activity of the antiseptic with the drug delivery and moisturizing properties of the liposomes and the hydrogel, thus presenting an innovative approach for wound healing [3,4,5].

Liposomal drug products provide topical activity and are generally considered less toxic than conventional drug formulations.[6] A wide variety of liposomal drugs are currently marketed.[7]Liposomes are composed of concentric phospholipid bilayers and can enhance the penetration of drugs into skin and mucus membranes. These multilamellar vesicles also act as microreservoirs to prolong the release of active ingredient.[6] Liposomal polyvinylpyrrolidone (PVP)-iodine (3%) hydrogel (Repithel®/Repigel®, [Mundipharma GmbH, Limburg, Germany] marketed in Germany, Switzerland, and South Korea) combines the antiseptic activity of PVP-iodine with the drug delivery properties and moisturizing effects of liposomes.[6] PVP-iodine is an established antiseptic and has been used as a skin cleanser in atopic dermatitis and acne vulgaris.[8,9] PVP-iodine ointment has also been shown to reduce inflammation (oxidative stress) and wound healing times in patients with burns,[10] and to have an anti-inflammatory effect when used in periapical surgery which was attributed to an inhibitory effect on leukocyte chemotaxis and extravasation.[11] The antimicrobial activity of PVP-iodine arises from its strong oxidizing effects which cause coagulation of nuclear material and pore formation in cells walls of bacteria and fungi.[12] This mechanism of action explains why PVP-iodine is not associated with development of bacterial resistance.[13] In contrast, resistance is commonly observed with antibiotics which act via specific biochemical pathways due to de novo mutations or acquisition of resistance genes from other organisms which overcome the antibiotic mechanism of action.[14] PVP-iodine has clinical activity against a range of antibiotic-resistant bacteria and at therapeutic concentrations is superior to several other antiseptic agents.[15] Liposomal PVP-iodine (3%) hydrogel has been shown to be well tolerated, effective against biofilm formation, and have wound healing properties.[16–18]

The aims of this study were to develop PVP- iodine loaded liposomal gel for topical delivery, perform particle size, viscosity, percentage of available iodine content, gel strength, and spreadability and wound healing activity of liposomal gels in rats.





Available iodine contents (IP, 2007)

Transfer 1.0 gm of PVP iodine *in situ* gel system into a round bottom stoppered iodine flask containing 150 ml of water and stir for 1 hour. Add 0.1 ml of diluted acetic acid and titrate against 0.01M sodium thiosulphate using starch solution as indicator towards the end.

1ml of 0.1M sodium thiosulphate is equivalent to 12.69 mg of available iodine.

$$\frac{\text{Titre volume} \times \text{Molarity factor of sodium thiosulphate} \times \text{equivalent factor} \times 100}{\text{Weight taken in (gm) sample}} = \%\ \text{gm of available iodine}$$

Name	Units	Low	High
Cholesterol	mg	90	100
Gelling agent and surfactant 1:3	mg	3000	3500
Diethyl ether	ml	8	10
Particle size	nm	220	275
Viscosity	cps	1180	1322
Available iodine content	%	94.8	98.6
Gel strength	seconds	69	98
Spreadability	g.cm/sec	10.2	18.3

Experimental Design:

Our research is focused on the development of PVP-Iodine liposomal gel through preliminary experiments, Cholesterol (A), Gelling agent and surfactant ratio (B) and Diethyl ether volume (C) were identified as the most significant variables influence the particle size, viscosity, percentage of available iodine content, gel strength, and spreadability. Among various design approaches, the Box-Behnken (BBD) has good and reliable design properties as shown in table 1. Seventeen runs were performed for response surface methodology based on the box-behnken design. Based on the experimental design, the factor combinations produced different responses as presented in Table 1. These results clearly indicated that all the dependent variables were strongly dependent on the selected independent variables as they showed a wide variation among the 17 runs.

Table-1: Factorial design of PVP-Iodine liposomal gel.

Run	A:Cholesterol (mg)	B:Gelling agent and surfactant 1:3 (mg)	C:Diethyl ether (ml)	Particle size (nm)	Viscosity cps	Available iodine content (%)	Gel strength (seconds)	Spreadability (g.cm/sec)
1	95	3250	9	234	1200	97.1	80	10.2
2	95	3500	8	260	1278	97.6	87	10.7
3	95	3000	10	258	1250	97.1	78	10.3
4	95	3250	9	230	1200	97.3	84	10.5
5	100	3500	9	270	1322	98.5	98	18.3
6	100	3250	10	275	1311	98.2	96	18.1
7	95	3000	8	258	1253	96.8	79	10.4
8	90	3500	9	225	1181	96	80	17.3
9	100	3000	9	270	1295	98.6	90	17.8
10	100	3250	8	274	1320	98.5	93	18.1
11	95	3250	9	233	1210	97.2	82	10.7
12	95	3500	10	260	1275	97.3	88	12.5
13	95	3250	9	234	1208	97.5	81	10.4
14	90	3000	9	255	1180	96.1	69	11.9
15	90	3250	8	220	1188	94.8	81	17.5
16	90	3250	10	222	1187	95.4	79	17.4
17	95	3250	9	234	1205	97.5	85	10.3

Table-2: ANOVA for Quadratic model for the response particle size

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	5601.31	9	622.37	10.04	0.0030	significant
A-Cholestrol	3486.12	1	3486.12	56.26	0.0001	
B-Gelling agent and surfactant 1:3	84.50	1	84.50	1.36	0.2811	
C-Diethyl ether	1.13	1	1.13	0.0182	0.8966	
AB	225.00	1	225.00	3.63	0.0984	
AC	0.2500	1	0.2500	0.0040	0.9511	
BC	0.0000	1	0.0000	0.0000	1.0000	
A^2	121.64	1	121.64	1.96	0.2039	
B^2	1163.75	1	1163.75	18.78	0.0034	
C^2	370.07	1	370.07	5.97	0.0445	
Residual	433.75	7	61.96			
Lack of Fit	421.75	3	140.58	46.86	0.0014	significant
Pure Error	12.00	4	3.00			
Cor Total	6035.06	16				

Table-3: ANOVA for Quadratic model for the response **Viscosity**

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	42908.30	9	4767.59	229.05	< 0.0001	significant
A-Cholestrol	32768.00	1	32768.00	1574.30	< 0.0001	
B-Gelling agent and surfactant 1:3	760.50	1	760.50	36.54	0.0005	
C-Diethyl ether	32.00	1	32.00	1.54	0.2550	
AB	169.00	1	169.00	8.12	0.0247	
AC	16.00	1	16.00	0.7687	0.4097	
BC	0.0000	1	0.0000	0.0000	1.0000	
A^2	790.27	1	790.27	37.97	0.0005	
B^2	2890.27	1	2890.27	138.86	< 0.0001	
C^2	4641.01	1	4641.01	222.97	< 0.0001	
Residual	145.70	7	20.81			
Lack of Fit	62.50	3	20.83	1.00	0.4784	not significant
Pure Error	83.20	4	20.80			
Cor Total	43054.00	16				

Table-4: ANOVA for Quadratic model for the response % **available iodine content**

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	17.88	9	1.99	23.16	0.0002	significant
A-Cholestrol	16.53	1	16.53	192.70	< 0.0001	
B-Gelling agent and surfactant 1:3	0.0800	1	0.0800	0.9326	0.3664	
C-Diethyl ether	0.0113	1	0.0113	0.1311	0.7279	
AB	0.0000	1	0.0000	0.0000	1.0000	
AC	0.2025	1	0.2025	2.36	0.1683	
BC	0.0900	1	0.0900	1.05	0.3398	
A^2	0.2579	1	0.2579	3.01	0.1265	
B^2	0.2179	1	0.2179	2.54	0.1550	
C^2	0.5084	1	0.5084	5.93	0.0451	
Residual	0.6005	7	0.0858			
Lack of Fit	0.4725	3	0.1575	4.92	0.0789	not significant
Pure Error	0.1280	4	0.0320			
Cor Total	18.48	16				

Table-5: ANOVA for Quadratic model for the response **gel strength**

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	817.81	9	90.87	21.24	0.0003	significant
A-Cholestrol	578.00	1	578.00	135.09	< 0.0001	
B-Gelling agent and surfactant 1:3	171.13	1	171.13	40.00	0.0004	
C-Diethyl ether	0.1250	1	0.1250	0.0292	0.8691	
AB	2.25	1	2.25	0.5259	0.4919	
AC	6.25	1	6.25	1.46	0.2660	
BC	1.0000	1	1.0000	0.2337	0.6435	
A^2	39.17	1	39.17	9.15	0.0192	
B^2	6.06	1	6.06	1.42	0.2727	
C^2	13.64	1	13.64	3.19	0.1173	
Residual	29.95	7	4.28			
Lack of Fit	12.75	3	4.25	0.9884	0.4830	not significant
Pure Error	17.20	4	4.30			
Cor Total	847.76	16				

Table-6: ANOVA for Quadratic model for the response **spreadability**

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	201.92	9	22.44	26.54	0.0001	significant
A-Cholestrol	8.41	1	8.41	9.94	0.0161	
B-Gelling agent and surfactant 1:3	8.82	1	8.82	10.43	0.0145	
C-Diethyl ether	0.3200	1	0.3200	0.3785	0.5579	
AB	6.00	1	6.00	7.10	0.0323	
AC	0.0025	1	0.0025	0.0030	0.9582	
BC	0.9025	1	0.9025	1.07	0.3359	
A^2	169.91	1	169.91	200.98	< 0.0001	
B^2	0.8432	1	0.8432	0.9973	0.3512	
C^2	4.23	1	4.23	5.01	0.0603	
Residual	5.92	7	0.8454			
Lack of Fit	5.77	3	1.92	51.98	0.0012	significant
Pure Error	0.1480	4	0.0370			
Cor Total	207.84	16				

Particle size analysis of liposomal gel was found to be in the range of 220 - 275 nm as shown in Table 1. The **Model F-value** of 10.04 implies the model is significant. There is only a 0.30% chance that an F-value this large could occur due to noise. **P-values** less than 0.0500 indicate model terms are significant. In this case A, B^2, C^2 are significant model terms as shown in table 2. The two main prerequisites of liposomal gel are viscosity and gelling capacity. To instill easily at the affected site the formulation must possess optimum viscosity. The accurate model produced for viscosity was found to be significant with F-value of 229.05 ($p < 0.0001$). In this case A, B, AB, A^2, B^2, C^2 are significant model terms as shown in table 3.

The mathematical model generated for % available iodine content was found to be significant with F-value of 23.16 ($p < 0.0001$) and R^2 value of 0.9257. The independent variables A, B, C and the quadratic term of A and C^2 have significant effects on the % available iodine as shown in table 4.

Gel strength is important because strong gels will support a much higher pressure than weak gels before they are washed out of the particular site. The gel strength of runs 1 to runs17 (69 to 98 sec) exhibited good gel strength among all PVP-Iodine liposomal gel formulation which may be due to the increase in concentration of gelling agent (P188) and cholesterol as shown in table 5.

Table-7: Coefficients in Terms of Coded Factors for Particle size

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	233.00	1	3.52	224.68	241.32	
A-Cholestrol	20.87	1	2.78	14.29	27.46	1.0000
B-Gelling agent and surfactant 1:3	-3.25	1	2.78	-9.83	3.33	1.0000
C-Diethyl ether	0.3750	1	2.78	-6.21	6.96	1.0000
AB	7.50	1	3.94	-1.81	16.81	1.0000
AC	-0.2500	1	3.94	-9.56	9.06	1.0000
BC	0.0000	1	3.94	-9.31	9.31	1.0000
A^2	5.38	1	3.84	-3.70	14.45	1.01
B^2	16.63	1	3.84	7.55	25.70	1.01
C^2	9.37	1	3.84	0.3038	18.45	1.01

Table-8: Coefficients in Terms of Coded Factors for Viscosity

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	1204.60	1	2.04	1199.78	1209.42	
A-Cholestrol	64.00	1	1.61	60.19	67.81	1.0000
B-Gelling agent and surfactant 1:3	9.75	1	1.61	5.94	13.56	1.0000
C-Diethyl ether	-2.00	1	1.61	-5.81	1.81	1.0000
AB	6.50	1	2.28	1.11	11.89	1.0000
AC	-2.00	1	2.28	-7.39	3.39	1.0000
BC	0.0000	1	2.28	-5.39	5.39	1.0000
A^2	13.70	1	2.22	8.44	18.96	1.01
B^2	26.20	1	2.22	20.94	31.46	1.01
C^2	33.20	1	2.22	27.94	38.46	1.01

Table-9: Coefficients in Terms of Coded Factors for **Available iodine content**

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	97.32	1	0.1310	97.01	97.63	
A-Cholestrol	1.44	1	0.1036	1.19	1.68	1.0000
B-Gelling agent and surfactant 1:3	0.1000	1	0.1036	-0.1449	0.3449	1.0000
C-Diethyl ether	0.0375	1	0.1036	-0.2074	0.2824	1.0000
AB	0.0000	1	0.1464	-0.3463	0.3463	1.0000
AC	-0.2250	1	0.1464	-0.5713	0.1213	1.0000
BC	-0.1500	1	0.1464	-0.4963	0.1963	1.0000
A^2	-0.2475	1	0.1427	-0.5850	0.0900	1.01
B^2	0.2275	1	0.1427	-0.1100	0.5650	1.01
C^2	-0.3475	1	0.1427	-0.6850	-0.0100	1.01

The values of spreadability indicate that the gel is easily spreadable by small amount of shear. The spreadability range of formulation run1 to run17 (10.2-18.3 gm.cm/sec) was found to be optimum in the PVP-iodine liposomal gel. This indicates spreadability of liposomal gel containing PVP-iodine having optimum concentration of cholesterol was good as compared with high concentration of cholesterol as shown in table 6.

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-colinearity, the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable. The coefficients in terms of coded factors are shown in table 7,8,9,10,11 and 12.

The 2D response surfaces and the 3D contour plots of the response R1, R2, R3, R4 and R5 are shown in Figure 1 and 2 to depict the interactive effects of independent variables on response R1to R5, one variable was kept constant while the other two variables varied in a certain range.

Table-10: Coefficients in Terms of Coded Factors for Gel strength

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	82.40	1	0.9250	80.21	84.59	
A-Cholestrol	8.50	1	0.7313	6.77	10.23	1.0000
B-Gelling agent and surfactant 1:3	4.63	1	0.7313	2.90	6.35	1.0000
C-Diethyl ether	0.1250	1	0.7313	-1.60	1.85	1.0000
AB	-0.7500	1	1.03	-3.20	1.70	1.0000
AC	1.25	1	1.03	-1.20	3.70	1.0000
BC	0.5000	1	1.03	-1.95	2.95	1.0000
A^2	3.05	1	1.01	0.6663	5.43	1.01
B^2	-1.20	1	1.01	-3.58	1.18	1.01
C^2	1.80	1	1.01	-0.5837	4.18	1.01

Table-11: Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	82.40	1	0.9250	80.21	84.59	
A-Cholestrol	8.50	1	0.7313	6.77	10.23	1.0000
B-Gelling agent and surfactant 1:3	4.63	1	0.7313	2.90	6.35	1.0000
C-Diethyl ether	0.1250	1	0.7313	-1.60	1.85	1.0000
AB	-0.7500	1	1.03	-3.20	1.70	1.0000
AC	1.25	1	1.03	-1.20	3.70	1.0000
BC	0.5000	1	1.03	-1.95	2.95	1.0000
A^2	3.05	1	1.01	0.6663	5.43	1.01
B^2	-1.20	1	1.01	-3.58	1.18	1.01
C^2	1.80	1	1.01	-0.5837	4.18	1.01

Table-12: Coefficients in Terms of Coded Factors for spreadability

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	10.42	1	0.4112	9.45	11.39	
A-Cholestrol	1.02	1	0.3251	0.2563	1.79	1.0000
B-Gelling agent and surfactant 1:3	1.05	1	0.3251	0.2813	1.82	1.0000
C-Diethyl ether	0.2000	1	0.3251	-0.5687	0.9687	1.0000
AB	-1.22	1	0.4597	-2.31	-0.1379	1.0000
AC	0.0250	1	0.4597	-1.06	1.11	1.0000
BC	0.4750	1	0.4597	-0.6121	1.56	1.0000
A^2	6.35	1	0.4481	5.29	7.41	1.01
B^2	-0.4475	1	0.4481	-1.51	0.6121	1.01
C^2	1.00	1	0.4481	-0.0571	2.06	1.01

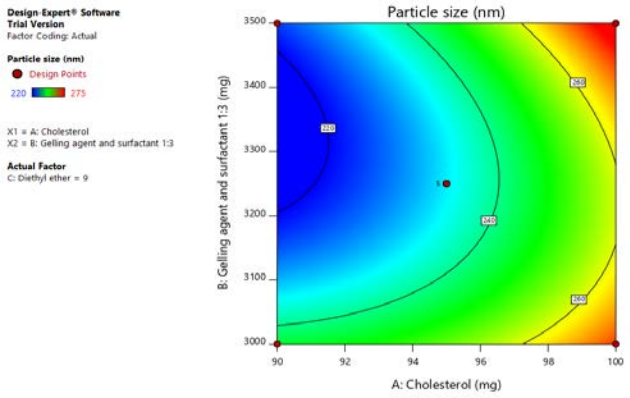


Figure-11: 2D contour plot presenting the interaction between the cholesterol and gelling agent/ surfactant ratio affecting the particle size at constant level of C.

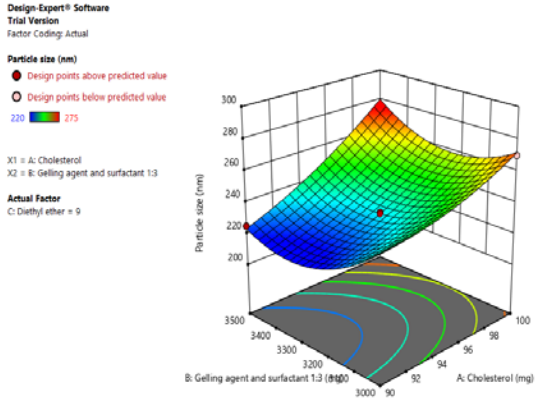
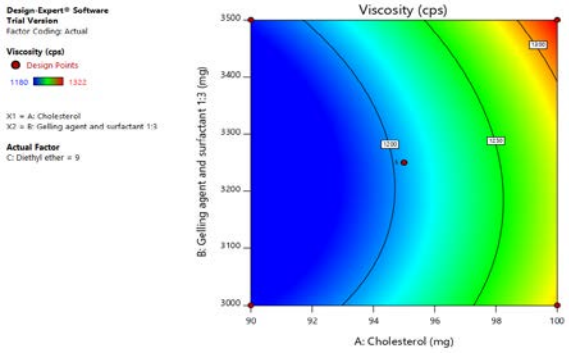


Figure-11: 3D contour plot presenting the interaction between the cholesterol and gelling agent/ surfactant ratio affecting the particle size at constant level of C.



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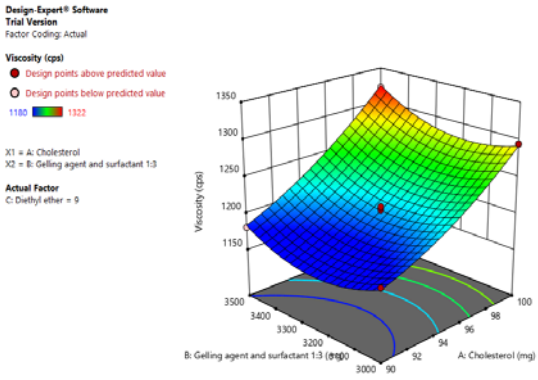

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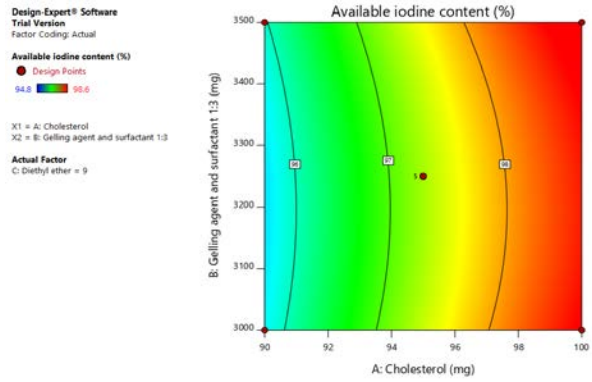

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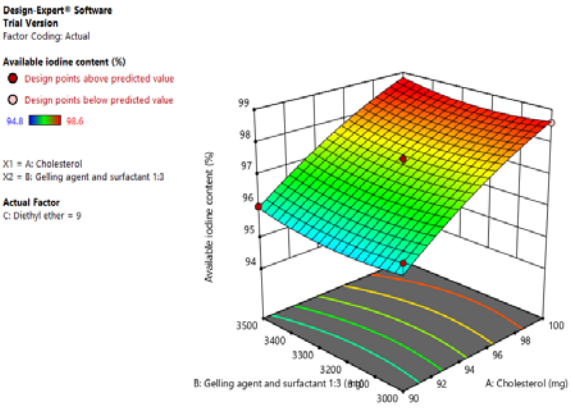

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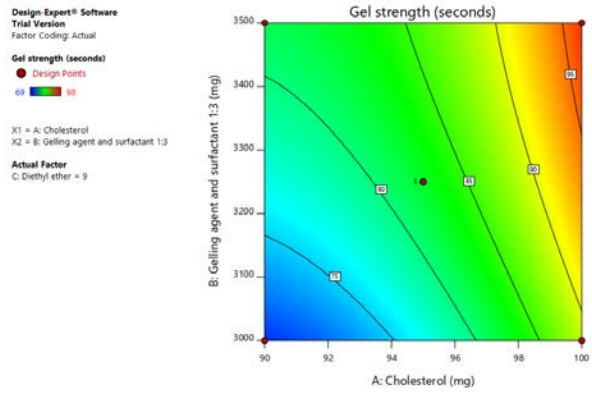

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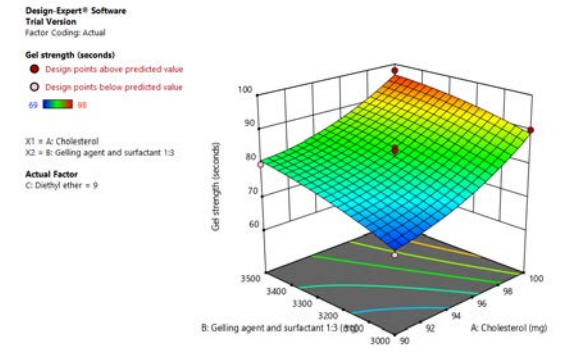

Figure-11: 3D contour plot presenting the interaction between the cholesterol and gelling agent/ surfactant ratio affecting the particle size at constant level of C.

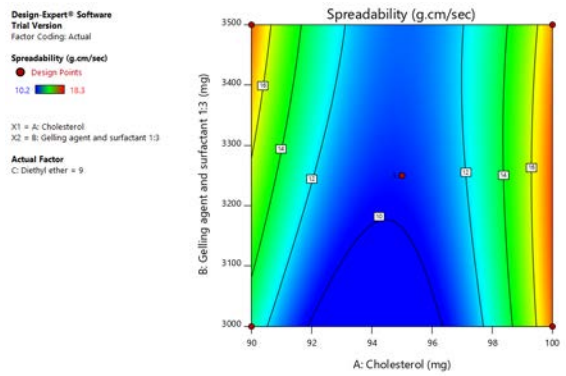

Figure-11: 2D contour plot presenting the interaction between the cholesterol and gelling agent/ surfactant ratio affecting the particle size at constant level of C.

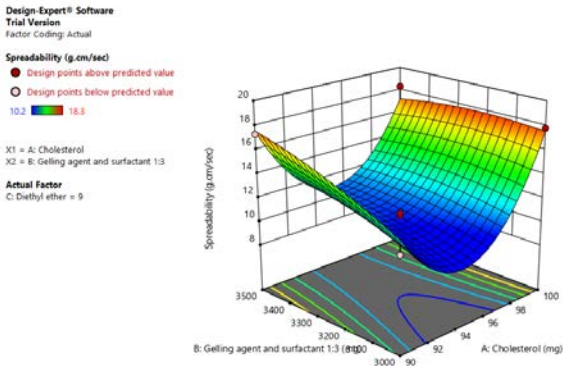

Figure-11: 3D contour plot presenting the interaction between the cholesterol and gelling agent/ surfactant ratio affecting the particle size at constant level of C.

CONCLUSION

In conclusion, our results in infected MSGs show a trend for more effective bacterial removal and more rapid re-epithelialization (by physician assessment and photoplanimetry) with 10% PVP–I ointment, which may be the initial treatment of choice for infected MSGs. Liposomal 3% PVP–I hydrogel achieved better scores in subjective assessments of quality of wound healing, and may be preferred as a dressing for non-infected MSGs.

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