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Research Article

Study of the Influence of Formulation Variables in Bioadhesive Emulgels Using Response Surface Methodology

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Abstract. The aim of the present work was to study the main formulation variables that influence attributes of bioadhesive emulgels based on a combination of polymers, using response surface methodology (RSM). Bioadhesive products continue to gain attention in topical cutaneous administration as they allow long residence times on the application site, which is important when a long dermal action and a reduced product administration frequency are desired. A Box-Behnken design of experiments (DoE) was introduced to study the effect of formulation variables on quality attributes of the emulgels. The effects of concentration of carbomer interpolymer type A (Polym1), xanthan gum (Polym2) and mineral oil (Oil) on detachment force (Fdetch), spreadability (Spread), and phase separation by mechanical stress (PhSep) were investigated. RSM and desirability functions were applied for data analysis. Emulgels were further characterized by viscosity and extrudability measurements. Polym1 showed a positive effect on Fdetch, while the increase in concentrations of Polym2 and Oil decreased this property. Polym1 and Polym2 favored emulgel PhSep. However, their interaction effect decreased it. The combination of 0.4–0.6% of carbomer and 0.2–0.3% of gum was able to produce easy-to-spread bioadhesive emulgels with mineral oil as discontinuous phase in the presence of a low surfactant concentration. Based on the DoE results, value ranges for the variables, which could achieve for the experimental domain to get the critical quality attributes of emulgels jointly within the specification limits, were able to be identified using RSM supported by desirability functions.

KEY WORDS: bioadhesion; emulgels; polymers; response surface methodology.

INTRODUCTION

Bioadhesive products continue to gain attention in cosmetic and pharmaceutical topical cutaneous administration. They allow long residence times on the application site (1), maintaining a high local concentration of active ingredient in the surrounding tissues over an extended period, which is important when a long dermal action and a reduced product administration frequency are desired. Bioadhesive hydrogels, in general, are considered as good candidates, due to their high biocompatibility, low toxicity, good rheological properties, high capacity for drug loading, and modified-release behaviors (2). However, their hydrophilic nature is a strong limiting factor for its use as a vehicle of lipophilic active ingredients. To overcome this limitation, formulations under emulgel form, which are emulsions either of the oil-in-water or water-in-oil type, gelled by mixing with a gelling agent (3), can be an interesting alternative, providing appropriate vehicles for both hydrophilic and lipophilic active ingredients. Emulgels also present other advantages such as low surfactant content since the gelling agent can act as an emulsifier (4) and ability to aid in skin conditioning by oil emollient action (5). Moreover, they possess the properties of both emulsions and gels, and thus, emulgels act as dual control release systems. Emulsion internal phases act as reservoir of active ingredient and slowly release it in a controlled way through the external phase to the skin. Gels form cross-linked

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networks where they capture small active ingredient particles and can provide their release also in a controlled manner (6).

The polyacrylic acid derivatives have been widely used as gelling agents for their bioadhesive properties and a relevant amount of work has been done on their rheological and adhesive properties (7–10). Acrylic polymers as a group contain some of the strongest bioadhesives, polycarbophil, and carbomers (11). In delivery systems to apply on intact skin, acrylic polymers are usually employed as adhesives (12–14). One approach to improve adhesiveness on skin is by combining different polymers (15). Adhesion results of carbomer homopolymer hydrogels on hairless rat skin have been reported in literature (14). Many polysaccharides, in particular gums, have also been reported as effective bioadhesive gelling agents (16,17). For instance, xanthan gum has proved to enhance bioadhesion (17) when used in combination with carbomers such as carbomer homopolymer type C (18). Carbomers and xanthan gum are examples of agents extensively used in pharmaceutical, cosmetic, and food products and recognized as safe. Xanthan gum is GRAS listed (FDA) (19), and both polymers are included in the FDA Inactive Ingredient Database (20).

In order to ensure quality of new developed products, it is necessary to thoroughly understand the main and interaction effects of multiple factors on the critical quality attributes of these products. A systematic design of experiments (DoE) allows achieving more effectively this pursued knowledge, while reducing the number of experimental trials required (21). Having established those factors and interactions that determine a response or dependent variable, the same experiments can be used for a predictive purpose, namely, estimating the response at combinations of factors that have not been studied experimentally. This is precisely the role of the statistical method response surface methodology (RSM) (22), which finds its most extensive applications in the industrial world, particularly in situations where several input variables potentially influence some performance measure or quality characteristic of the product or process (23).

The aim of the present work was to study the main formulation variables that influence attributes of bioadhesive emulgels based on a binary combination of polymers, using RSM.

MATERIALS AND METHODS

Materials

Carbopol® Ultrez 10 (Lubrizol, USA) is an easy-to-disperse carbomer interpolymer type A, which is an attractive excipient characteristic in process escalation and commercial manufacturing. Xanthan gum (Weifang Ouchem, China) is an anionic polysaccharide commercially obtained by bacterial fermentation (24). Other excipients used were mineral oil, propylene glycol, polysorbate 60 (Tween® 60), sorbitan monostearate (Span® 60), methylparaben, propylparaben, FD&C blue no. 1 colorant, sodium hydroxide, and deionized water.

Preparation of Emulgels

Experimental Design

A Box-Behnken design was introduced to study the effect of formulation variables on the bioadhesive emulgels. A three-factor, three-level design with two center points was suitable for exploring response surfaces and constructing polynomial models with R language (25) and rsm package (26). The effects of concentration of carbomer interpolymer type A (Polym1), xanthan gum (Polym2), and mineral oil (Oil) on relevant quality attributes of the emulgels were investigated. Detachment force (Fdetch), spreadability (Spread), and phase separation (PhSep) by mechanical stress were the selected emulgel quality attributes. The investigated factors along with their levels and the corresponding responses are summarized in Table I. A design matrix comprising 14 experimental runs was constructed using qualityTools package (27), R language (25). The amounts of the formulation components were determined in preliminary studies. The total surfactant content was fixed at a low concentration (2%). The entire design of experiment (DoE) composition for all of the runs is given in Table II.

Manufacturing Process

Hydrogels were prepared dispersing the carbomer interpolymer type A followed by the xanthan gum by mechanical stirring (Servodyne 50003-45, Cole-Parmer Instrument Co., Vernon Hill, USA) in water in the presence of colorant. The mineral oil and the surfactants were mixed separately with the parabens previously dissolved in propylene glycol, at 70 ± 1 °C, and then added to the hydrogels (previously heated up to 30 to 32 °C) with the aid of mechanical stirring. Sodium hydroxide solution was added up to make the final pH 5.5, and emulgel final weight was completed with water. Finally, the emulgels were homogenized for 2 min by higher shear stirring (Ika Ultra-Turrax TV45, Janke & Kunkel KG, Staufen, Germany).

Characterization of Emulgels

The rationale followed in the characterization of the emulgels divided the product attributes between those considered relevant as dependent variables in the Box-Behnken design and those which were considered useful for further assessment. Above all, it is fundamental to select DoE responses closely related to product critical quality attributes. Finally, three responses for the DoE were selected (Table I). One response per each relevant quality aspect of the bioadhesive emulgels: adhesion, system stability, and ease of application.

Box-Behnken Responses

Adhesion Properties. Adhesion properties were evaluated at 32 ± 1 °C using a TA-XT Plus Texture Analyzer (Stable Micro Systems, Godalming, UK) with a load cell of 30 kg and set in "adhesive mode." Samples were placed in cylindrical containers stuck to the base of the analyzer. The probe (cylindrical, 40 mm diameter) was lowered to the

Table I. Factors and Responses Used in Box-Behnken Experimental Design

Factors	Levels (coded values)		
	Low (−1)	Medium (0)	High (1)
X_1: concentration of carbomer interpolymer type A (Polym1)	0.2%	0.4%	0.6%
X_2: concentration of xanthan gum (Polym2)	0.2%	0.4%	0.6%
X_3: concentration of mineral oil (Oil)	4.0%	7.0%	10.0%
Responses			
Y_1: detachment force (Fdetch) Y_2: spreadability (Spread) Y_3: phase separation (PhSep)			

surface of each sample at a speed of 1.0 mm/s, and after reaching the trigger force (0.049 N), intimate contact between probe surface and emulgel was assured by means of a constant downwards force of 0.5 N applied by the probe during 60 s. Afterwards, the probe was brought back through a return distance of 20 mm at a speed of 1.0 mm/s. Detachment force was measured automatically by the texture analyzer software, Texture Exponent 32 (Stable Micro Systems, Godalming, UK).

Spreadability. This test was based on a method proposed by Bachhav and Patravale (28). Briefly, 1 g of sample at 32 ± 1 °C was loaded on a glass plate placed over squared paper (in millimeters). A second glass plate was placed over the sample, and a weight of 100 g was allowed to rest on the upper glass plate for 1 min. The diameter after spreading of the emulgel was measured.

Accelerated Stability Studies (Phase Separation by Mechanical Stress). In this test, 10 g samples of each formulation were centrifuged at 3000 rpm during 15 min. At the end of the cycle, the samples were checked to see whether there was any change. The extent of phase separation was measured with a scale ruler (in millimeters).

Further Characterization of Emulgels

Viscosity Measurements. A rotary viscometer (Brookfield LVT, Stoughton, USA) with spindle no. 4 was used to measure the viscosity of the emulgels at different rotational speeds at 25 ± 1 °C. Each run involved gradually increasing the spindle speed from 0.3 to 60 rpm (0.3, 0.6, 1.5, 3, 6, 12, 30, and 60 rpm). Readings were taken at the third revolution at each speed. Viscosity was then calculated multiplying the dial reading by the spindle factor and the following formula was used for yield value (YV) calculation (29).

$YV = 2r_1(\eta_1 - \eta_2)/1000$, where η_1 and η_2 are the viscosity values at rotational speeds r_1 and r_2, respectively, with $r_2/r_1 = 2$.

Extrudability. This property was assessed in a group of promising formulations to evaluate delivery of the

Table II. Formulations and Measured Responses as Per the Box-Behnken Experimental Design

Run no.[a]	Polym1 (% *w*/*w*)	Polym2 (% *w*/*w*)	Oil (% *w*/*w*)	Fdetch (N)	Spread (cm)	PhSep (mm)
1	0.2	0.2	7.0	0.308	6.38	0
2	0.6	0.6	7.0	0.435	4.63	0
3[b]	0.4	0.4	7.0	0.472	5.68	2
4	0.4	0.2	10.0	0.462	5.50	4
5	0.4	0.2	4.0	0.554	5.68	0
6	0.6	0.2	7.0	0.477	5.05	0
7	0.2	0.4	10.0	0.291	6.50	6
8	0.4	0.6	10.0	0.442	5.40	5
9	0.2	0.6	7.0	0.261	6.85	5
10	0.6	0.4	10.0	0.500	5.08	5
11	0.6	0.4	4.0	0.532	5.20	0
12	0.4	0.6	4.0	0.462	5.75	0
13[b]	0.4	0.4	7.0	0.466	5.55	6
14	0.2	0.4	4.0	0.332	6.53	0

Polym1 carbomer interpolymer type A, *Polym2* xanthan gum, *Oil* mineral oil, *Fdetch* detachment force, *Spread* spreadability, *PhSep* phase separation

[a] Other components: 5.0% propylene glycol, 2.0% [polysorbate 60 (0.96%) + sorbitan monostearate (1.04%)], 0.2% methylparaben, 0.2% propylparaben, 0.001% colorant blue FD&C no. 1, 10% sodium hydroxide solution to make the final pH 5.5, and deionized water up to 100% (700 g)

[b] The center points of the design

Table III. Response Surface Models of Detachment Force, Spreadability, and Phase Separation

Model	F (lack of fit)	p (lack of fit)	Adjusted R^2 (regression)	F (regression)	p (regression)
Y_1 = 0.3045 + 2.0502 Polym1 − 0.3345 Polym2 − 0.0668 Oil +0.0298 Polym2.Oil − 1.9763 Polym1^2 + 0.0034 Oil^2	1.1985	0.3593	0.9429	75.35	0.00
Y_2 = 6.7037 − 5.1125 Polym1 + 3.7156 Polym2 − 5.6250 Polym1. + 4.2813 Polym1^2	1.3764	0.2803	0.8993	49.25	0.00
Y_3 = −17.7333 + 30.7500 Polym1 + 48.2500 Polym2 + 0.8333 Oil − 31.2500 Polym1. Polym2 − 27.5000 Polym1^2 − 40.0000 Polym2^2	1.4028	0.2768	0.7998	18.97	0.00

product from a typical primary container. The test adopted was based upon the quantity of product extruded from a plastic collapsible tube on application of weight in grams required to extrude at least 0.5 cm of emulgel in 15 s at 25 ± 1 °C (30). Extrudability was then calculated using the following formula

Extrudability = W/A, where W is applied weight (in g) to extrude emulgel from a tube, and A is area (in cm^2).

All the above mentioned tests were performed in duplicate 24 h after preparation of the emulgels, and average results are presented.

Data Analysis

Response-surface regression analysis was performed on Y_1, Y_2, and Y_3. Polynomial models were then constructed using the results, including interaction and quadratic terms, along with linear terms. The adequacy of the polynomial models to the experimental data was evaluated using analysis of variance (ANOVA), lack of fit test, the statistical significance of the coefficients, and the correlation of determination (R^2). Results were presented using three-dimensional response surface plots and corresponding two-dimensional contour plots.

The superimposition of contour plots was applied to identify areas in which the values of each response were acceptable.

For a more precise location of the optimum, desirability function, where a target value and a value (or values) which are unacceptable are attached to each response, was estimated using R-language (25) and desirability package (31). The partial desirability functions for each individual response were combined to give an overall desirability function, which is the geometric mean of all the partial functions and has a range of values from 0 to 1 (22). If this desirability index is near 1, then the responses are well within their requirements, while if it is near or equal to 0, one or more responses are outside of their requirements (32).

A checkpoint analysis was performed to confirm validity of the generated mathematical model for prediction of responses. The emulgel was prepared in duplicate and the mean responses determined.

All data analyses were performed using R-language (25).

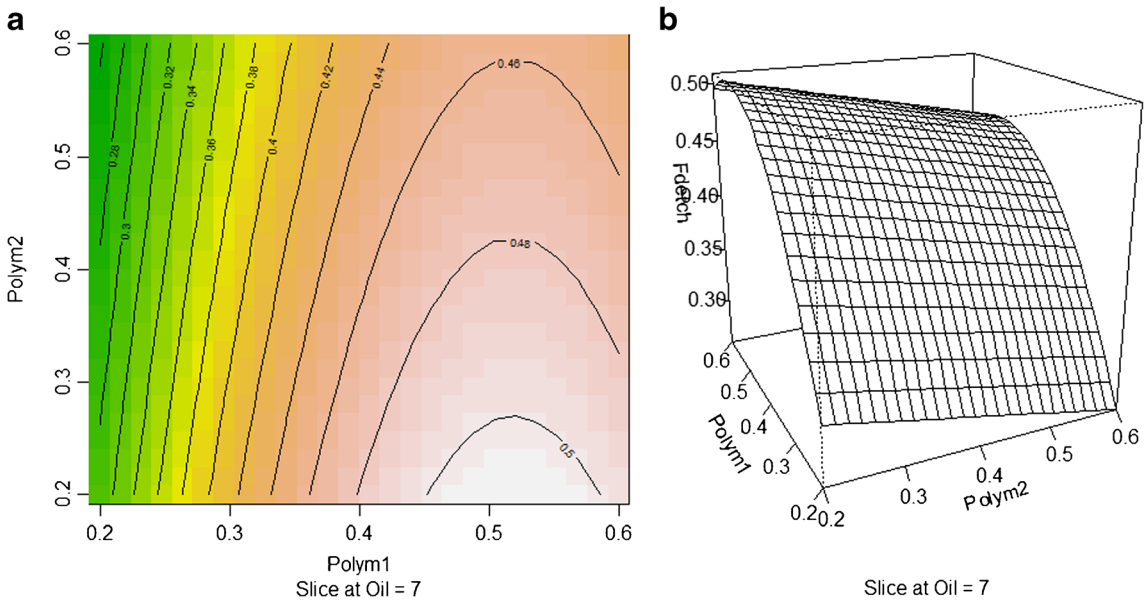

Fig. 1. Contour (**a**) and response surface (**b**) plots showing effect of carbomer concentration (*Polym1*) and xanthan gum concentration (*Polym2*) on detachment force (*Fdetch*) at fixed mineral oil concentration (*Oil*) of 7%

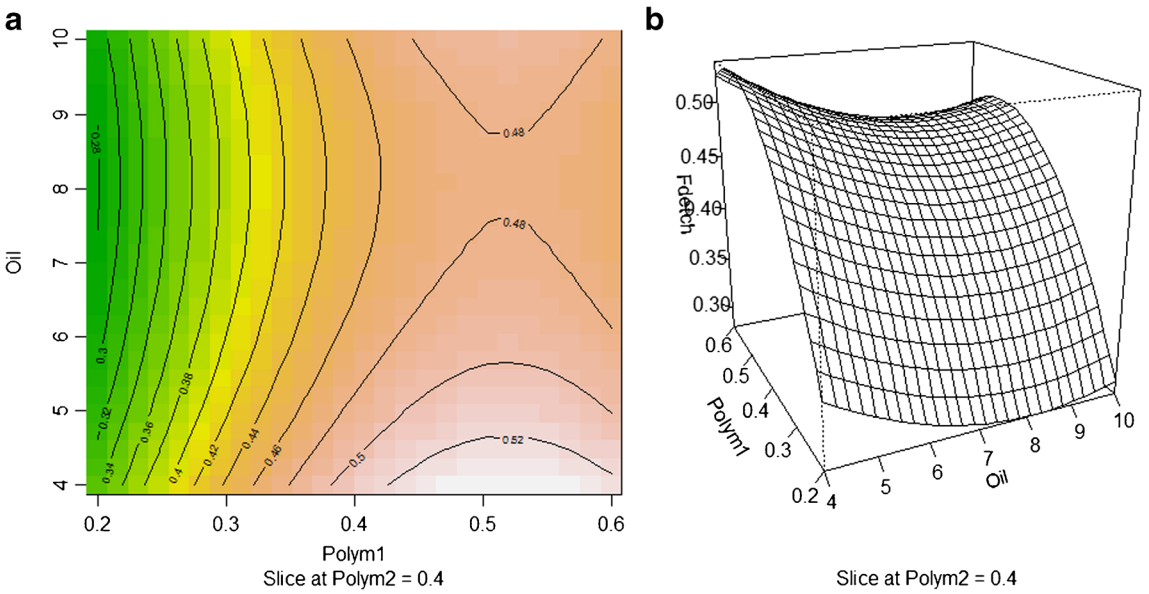

Fig. 2. Contour (**a**) and response surface (**b**) plots showing effect of carbomer concentration (*Polym1*) and mineral oil concentration (*Oil*) on detachment force (*Fdetch*) at xanthan gum concentration (*Polym2*) of 0.4%

RESULTS AND DISCUSSION

Characterization of Emulgels

Box-Behnken Responses

Adhesion and dispersed system stability were considered the main product attributes to enhance in the present research work. Therefore, the criteria selected to attain an optimized formulation were based on achieving maximum adhesion (maximum Y_1) and no phase separation by mechanical stress ($Y_3 = 0$), while constraining spreadability to ensure adequate administration of the product. Spreadability range of $4.5 < Y_2 < 7.0$ cm was based on a previous work with cosmetic gels within which ensures an adequate administration of the product (18).

Response data of emulgels are presented in Table II. *Response-Surface Analysis.* The model equations for Y_1, Y_2, and Y_3 are presented in Table III. Only statistically significant ($p < 0.05$) coefficients were included in the models. The large p values for lack of fit (>0.05) indicate that the lack of fit tests was insignificant, implying that significant model correlation existed between the formulation variables and the three critical quality attributes of the emulgels.

According to these equations, the concentration of carbomer favored the detachment force and the phase separation of the emulgels (positive coefficients), while decreased the spreadability (negative coefficient). The other

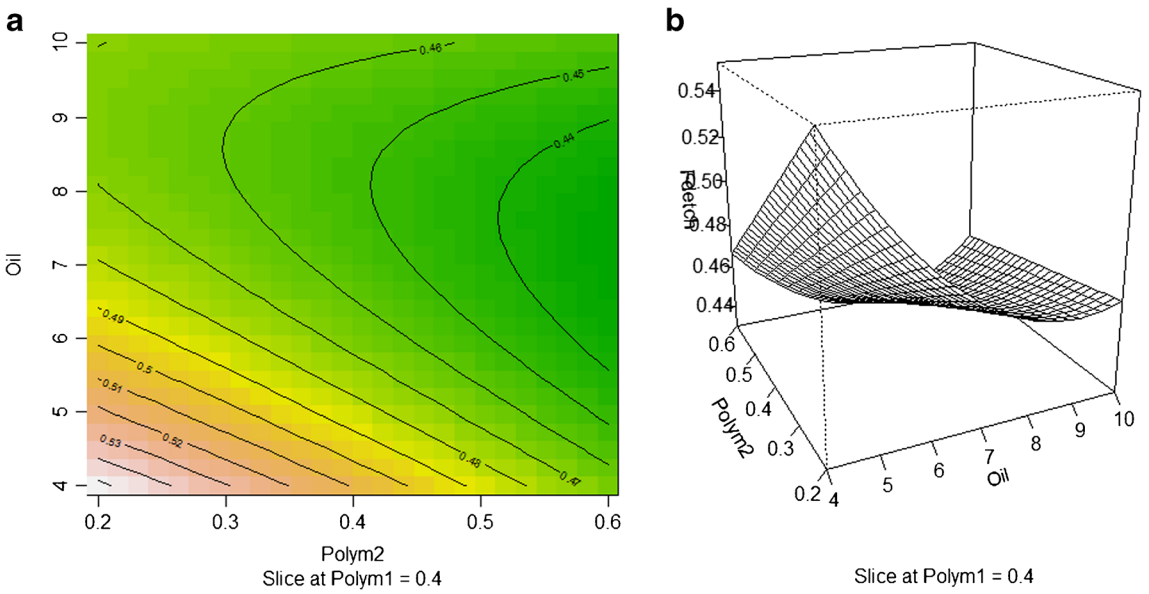

Fig. 3. Contour (**a**) and response surface (**b**) plots showing effect of xanthan gum concentration (*Polym2*) and mineral oil concentration (*Oil*) on detachment force (*Fdetch*) at fixed carbomer concentration (*Polym1*) of 0.4%

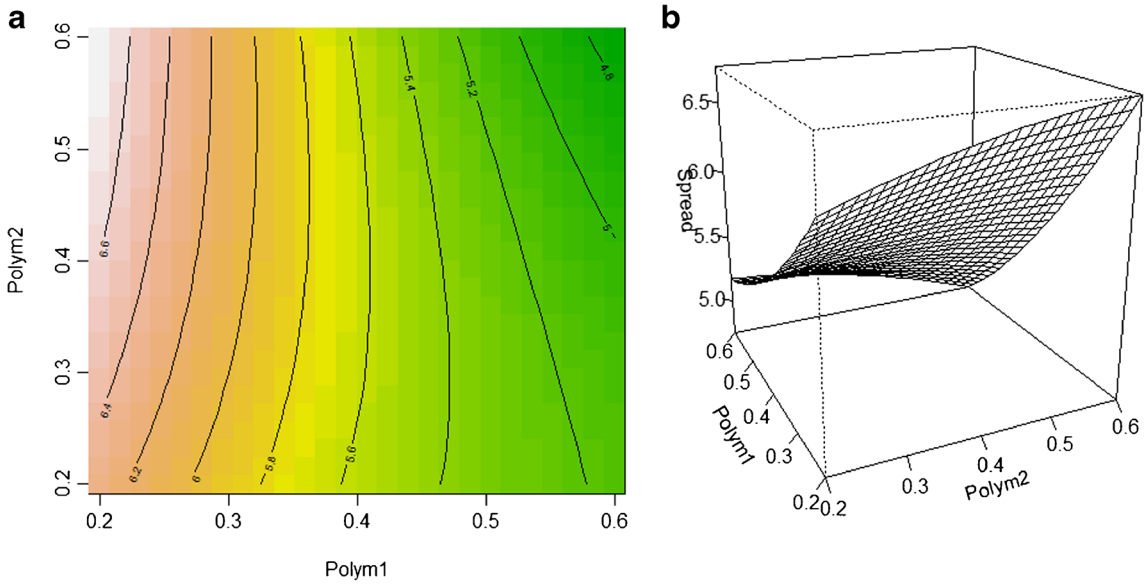

Fig. 4. Contour (**a**) and response surface (**b**) plots showing effect of carbomer concentration (*Polym1*) and xanthan gum concentration (*Polym2*) on spreadability (*Spread*)

two independent variables, concentration of xanthan gum and concentration of mineral oil, showed an inverse relationship with Y_1, but the effect of the mineral oil on Y_1 was about 5-fold less than the effect of the xanthan gum. However, their mutual interaction effect (Polym2.Oil) favored the adhesion. These results showed that the xanthan gum did not increase the adhesion of the carbomer interpolymer type A formulations in contrast to those described in a previous work where this gum was used in combination with carbomer homopolymer type C in a monophasic bioadhesive gel (18).

Furthermore, the gum concentration enhanced both Y_2 and Y_3, while mineral oil concentration did not produce a significant effect on Y_2, but also favored Y_3. However, its effect was almost 60-fold less pronounced than the effect of the gum. The interaction effect between bioadhesive polymers, carbomer, and gum (Polym1.Polym2) decreased both responses. The effect of this mutual interaction was about 1.5-fold more intense than the effect of the gum on Y_2, and 1.5-fold less intense in the case of Y_3.

Therefore, regarding stability of emulgels, an increase in either polymer concentration favored phase separation, while their mutual interaction decreased it. However, the effect of xanthan gum was 1.5-fold more pronounced than the effect of the carbomer. Similar results showing better physical stability of formulations containing low level of carbomer or combinations of carbomer with other gelling agents have been reported in literature (33). Additionally, high and negative quadratic effects of carbomer were observed on both Y_1 and Y_3, while high and positive on Y_2. Quadratic effect of xanthan gum was high and negative for Y_3.

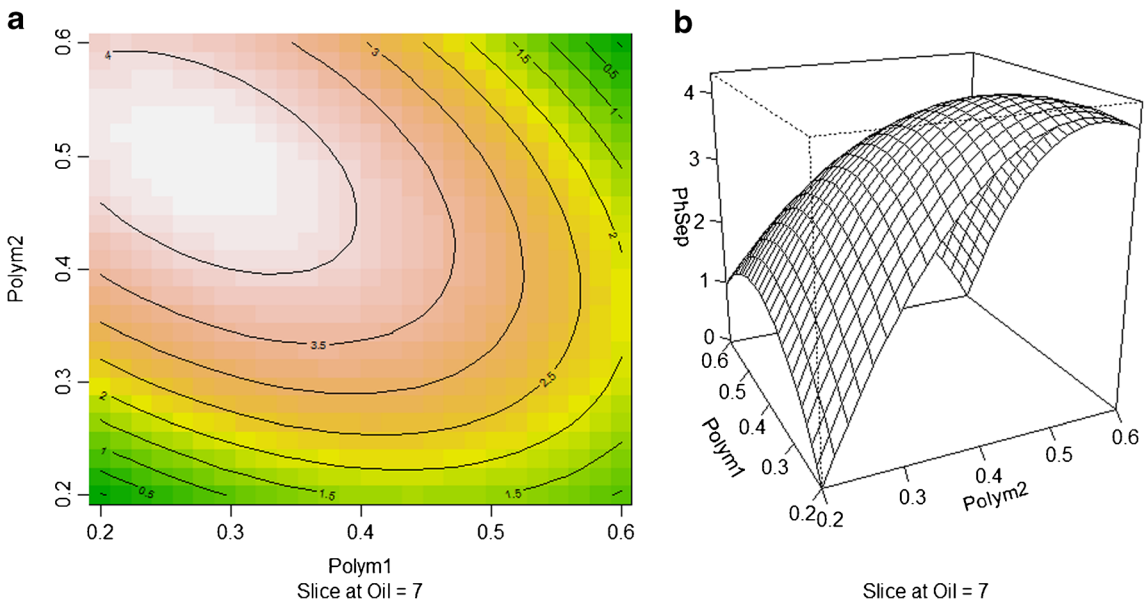

Fig. 5. Contour **a** and response surface **b** plots showing effect of carbomer concentration (*Polym1*) and xanthan gum concentration (*Polym2*) on phase separation (*PhSep*) at fixed mineral oil concentration (*Oil*) of 7%

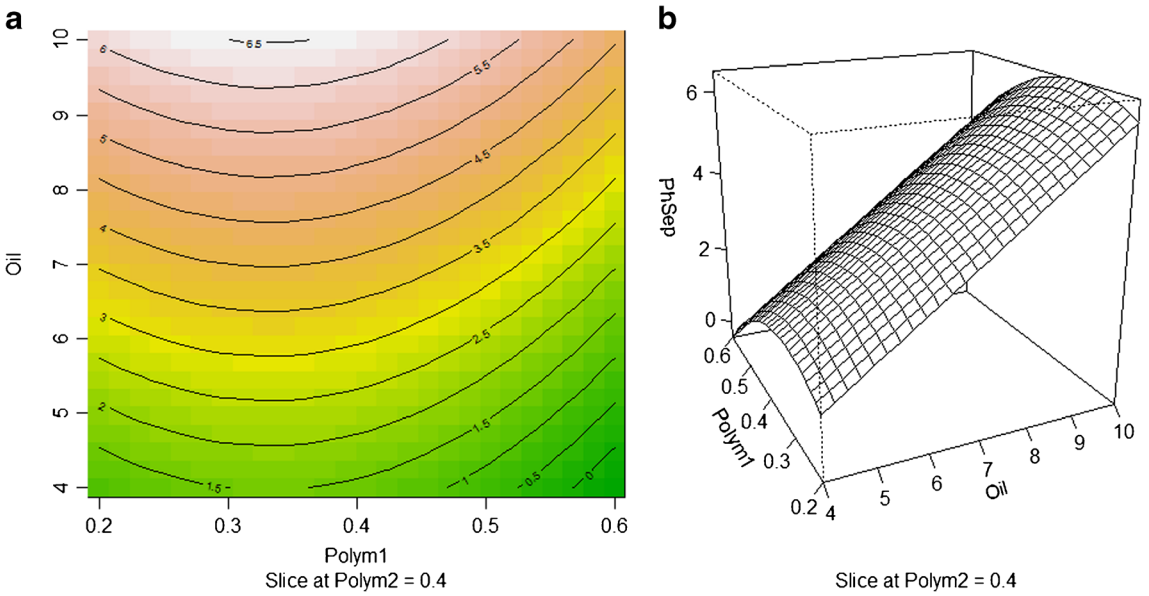

Fig. 6. Contour (**a**) and response surface (**b**) plots showing effect of carbomer concentration (*Polym1*) and mineral oil concentration (*Oil*) on phase separation (*PhSep*) at fixed xanthan gum concentration (*Polym2*) of 0.4%

Two-dimensional contour plots and three-dimensional surface plots were constructed based on the model polynomial functions and are presented in Figs. 1, 2, 3, 4, 5, 6, and 7. These plots were a useful tool for analyzing the effects of two factors at one time on each response, maintaining the third factor at a constant level.

All the relationships among the three variables were non-linear, although Figs. 1 and 2 exhibit a nearly linear relationship of factor Polym1 with factors Polym2 and Oil at low level of Polym1 concentration, respectively. At higher Polym1 concentrations, these relationships become non-linear. The factor Polym2 presented a nearly linear relationship with Oil up to medium levels of oil concentration (Fig. 3). The maximum Y_1 value of 0.55 N was observed at 0.4% Polym1, 0.2% Polym2, and 4% Oil (Fig. 3). Since 4% is a low mineral oil concentration, in the optimization step, an experimental region, where mineral oil concentration could be increased while adhesion was still kept high, should be found. The diminishing effect of Oil on Y_1 was more pronounced from the lowest to the medium level than from the medium to the upper level of mineral oil concentration (Figs. 2 and 3).

The response surface plot and contour plot (Fig. 4) show a steady decline in the value of Y_2, as the carbomer concentration increases. Nevertheless, the entire surface was within the acceptable spreadability range defined to optimize the emulgel formulation.

From analysis of Figs. 5 and 6, it was found that zero values of Y_3 were obtained when minimum or maximum levels (0.2 or 0.6%) of both polymer concentrations were

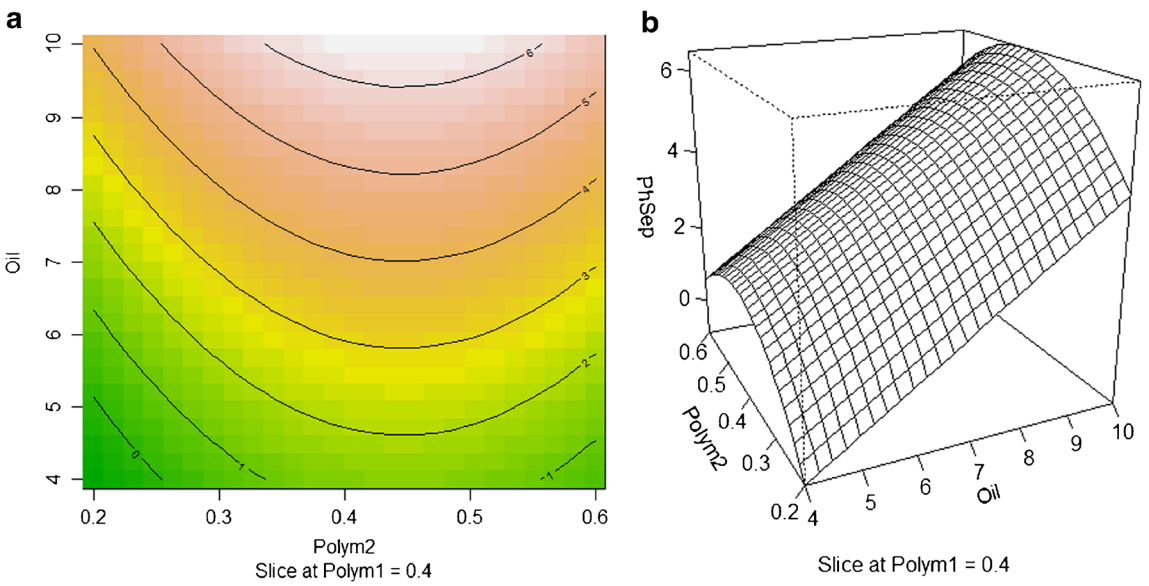

Fig. 7. Contour (**a**) and response surface (**b**) plots showing effect of xanthan gum concentration (*Polym2*) and mineral oil concentration (*Oil*) on phase separation (*PhSep*) at fixed carbomer concentration (*Polym1*) of 0.4%

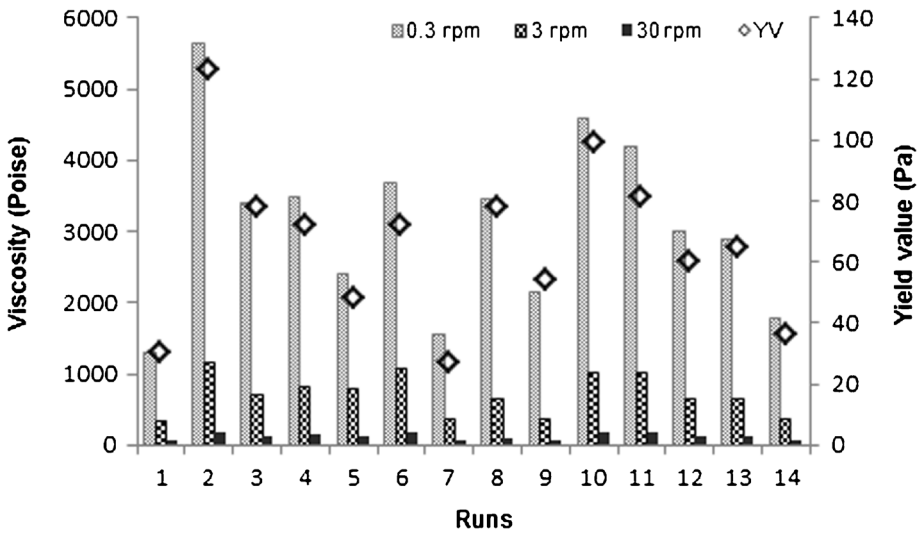

Fig. 8. Mean viscosity and yield values (*YV*) of emulgels at three rotational speeds

used in formulations containing low to medium concentrations of mineral oil. Previous works reported in literature have concluded that emulsified systems, which withstand a high mechanical load, generally showed more stability than those which did not show this property (34). It was not possible to avoid phase separation when emulgels were formulated containing 10% of Oil.

Further Characterization of Emulgels

Viscosity Measurements. Rheology impacts relevant product characteristics such as, ease of removal from containers, distribution on the skin, film-forming ability (35), and disperse system stability (36–37). YV, the minimum amount of force necessary to induce flow (38), is one of the main factors to consider that influences product stability (39). Viscosity measurements and yield values are plotted in Fig. 8. All of the emulgels showed a shear thinning flow behavior within the range of rotational speeds (0.3 a 60 rpm) used in Brookfield equipment. Viscosity and yield values increased with increasing carbomer concentration as expected (29,40).

The correlation matrix was performed to confirm the correlations among studied response variables. Pearson correlation coefficient between all pairs of variables was calculated. As expected, it was found that viscosity was inversely correlated with spreadability ($r = -0.94$; $p < 0.05$) and yield value ($r = -0.90$; $p < 0.05$). Lucero *et al.* (41) have already concluded about the relevance of spreadability and viscosity, two parameters that together would define the rheology of gelified disperse systems. Therefore, viscosity could be regarded as a useful quality attribute, which is easy to measure during production of emulgels.

Extrudability. Three formulations were selected for extrudability test since their compositions located them in promising areas of the contour plots, according to the results of the three critical quality attributes of these emulgels (see the "Optimization" section). The selected formulations were

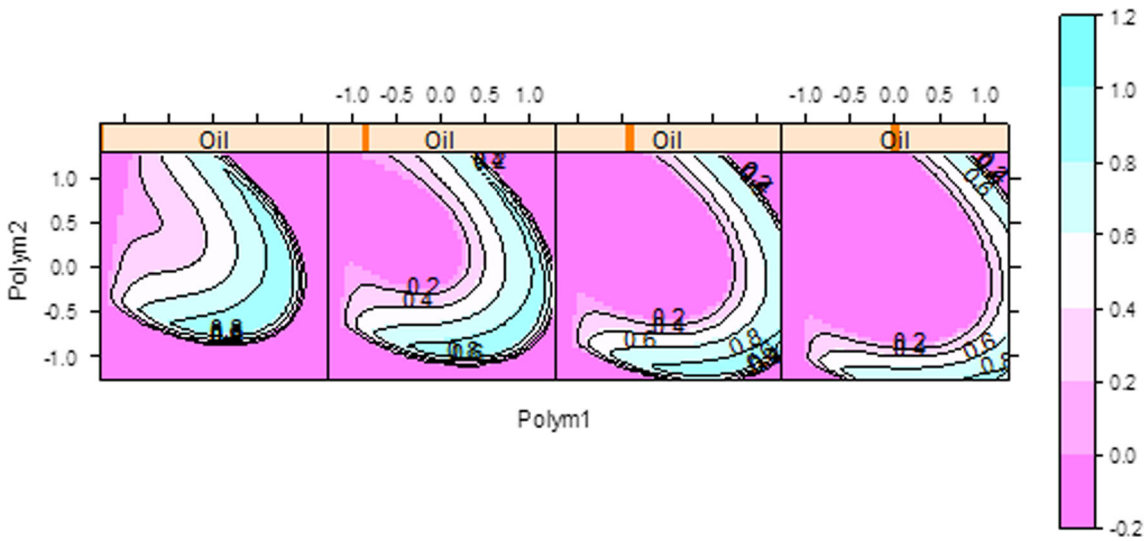

Fig. 9. Overall desirability contour plots (in coded units) at fixed mineral oil concentrations from 4 to 7%

Table IV. Formulation Settings, and Observed and Predicted Values of Responses Used in Checkpoint Analysis

X_1	X_2	X_3	Response	Observed Y ± SE	Predicted Y	Residual[a]	% RSD[b]
0.45%	0.20%	5%	Y_1 (N)	0.526 ± 0.006	0.540	0.015	2.729
			Y_2 (cm)	5.35 ± 0.17	5.51	0.16	2.85
			Y_3 (mm)	0 ± 0	0	0	0

SE standard error
[a] Residual: |Observed Y − Predicted Y|
[b] RSD: (Residual/Predicted Y) x 100

runs 5, 6, and 11, and their extrudability values were 93, 58, and 136 g/cm^2, respectively. Run 11 (containing higher total polymer concentration) showed the highest result. From preliminary trials (data not reported), it was found that extrudability values of emulgels within the range 50 to 200 g/cm^2 were acceptable, and a desirable zone was defined below 150 g/cm^2. Based on this data, these three extrudability results were within the desirable zone.

Optimization

The superimposition of contour plots identified spaces where values of each response are acceptable. The two identified regions restricted the desirable ranges of the factors to Polym1 = 0.4–0.6%, Polym2 = 0.2–0.4%, Oil = 4–6% and to Polym1 = 0.55–0.6%, Polym2 = 0.2–0.4%, Oil = 7%, respectively.

For a more precise location of a space which could achieve for the entire experimental domain to get the three critical quality attributes of emulgels (Y_1, Y_2, and Y_3) jointly within the specification limits, the desirability functions for each individual response were determined. Since in the case of Y_2, the entire contour surface was within the acceptable spreadability range, only desirability functions for the other two responses, Y_1 and Y_3, were computed. Y_1 was maximized for this determination, while Y_3 should be near the target value 0 mm, considering the applied constraints on Y_1 and Y_2. Afterwards, both functions were combined to give the overall desirability (Fig. 9).

In order to attain a sufficiently high desirability index (equal or over 0.8), the space had to be further reduced; thus, new desirable ranges of the factors were identified and restricted to Polym1 = 0.4–0.6%, Polym2 = 0.2–0.3%, and Oil = 4–6%.

Therefore, the following formulations should be able to produce bioadhesive emulgels with positive characteristics for cutaneous application and as vehicles of lipophilic active ingredients. Those emulgels, which contain 4% of mineral oil, should combine 0.50–0.55% of carbomer interpolymer type A with 0.30% of xanthan gum. In order to increase concentration of mineral oil to 5%, either 0.6% of the carbomer with 0.3% of the gum or 0.4–0.5% of carbomer with 0.2% of the gum should be used. And finally, to include 6% of mineral oil in the formulations, 0.6% of carbomer interpolymer type A should be combined with 0.2% of xanthan gum.

In order to evaluate the optimization capability of the generated models for prediction of responses, a new emulgel was prepared and evaluated. The optimized settings for the formulation variables used in this checkpoint are presented in Table IV. Comparison of the observed and predicted values for detachment force, spreadability, and phase separation indicated small residuals with RSD < 3% (Table IV), confirming validity of the mathematical models.

CONCLUSIONS

The binary combination of an easy-to-disperse carbomer interpolymer type A and xanthan gum was able to produce easy-to-spread bioadhesive emulgels with mineral oil as discontinuous phase in the presence of a low surfactant concentration. Regarding stability of emulgels, an increase in either polymer concentration favored phase separation, with the effect of xanthan gum 1.5-fold more pronounced than the effect of the carbomer. However, their mutual interaction effect decreased it, favoring product stability. Carbomer concentration showed a positive effect on the detachment force, while the increase in concentrations of xanthan gum and mineral oil decreased this adhesion property.

Based on the DoE results, value ranges for the three formulation variables, which could achieve for the entire experimental domain to get the critical quality attributes of emulgels jointly within the specification limits, were able to be identified using RSM supported by desirability functions.

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