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RESEARCH PAPER

Development of a Topical Suspension Containing Three Active Ingredients

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ABSTRACT

The objective of this study was to develop a topical suspension that contains sarafloxacin hydrochloride (1 mg/mL), triamcinolone acetonide (1 mg/mL), and clotrimazole (10 mg/mL), and is stable at room temperature (15–28°C) for clinical usage. Due to the difference in the physicochemical properties and chemical stability profiles of these three active ingredients, it is a challenge to develop a stable suspension formulation containing these three drugs. In this study, the stability of these drugs in different buffer solutions was determined under different accelerated isothermal conditions. The Arrhenius equation was subsequently utilized to predict the room-temperature stability of these three drugs in these buffer solutions. By knowing the room-temperature solubility of the drugs in the buffer solution, the stability of the drugs in suspension was predicted. As a result, a 0.02 M phosphate buffer (pH 7.0) containing 0.02% (w/v)polysorbate 20, 1% (w/v) NaCl, and 0.1% (w/v) EDTA was determined to be an acceptable medium. In addition, 0.35% (w/v) high-viscosity carboxymethylcellulose (HV-CMC) was first selected as the suspending agent to enhance the redispersibility of the suspension. Stability data further supported that all three drugs were stable in the suspension containing HV-CMC with less than 5% potency loss for at least 6 months at 40°C and 12 months at 25°C. However, the viscosity drop of this HV-CMC formulation at 25°C and 40°C became a product stability concern. To improve the viscosity stability of the suspension, the medium-viscosity carboxymethylcellulose (MV-CMC) was selected to

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replace the HV-CMC as the suspending agent. The optimal combination of MV-CMC and sodium chloride in achieving the most desirable dispersion properties for the formulation was determined through the use of a 3^2 factorial design. The optimal formulation containing 1% MV-CMC and 1% sodium chloride has shown improved viscosity stability during storage and has been used for clinical studies.

Key Words: *Topical suspension; Sarafloxacin hydrochloride; Triamcinolone acetonide; Clotrimazole; Redispersibility; Viscosity; Chemical stability; High-viscosity carboxymethylcellulose; Medium-viscosity carboxymethylcellulose*

INTRODUCTION

Otic preparations are commonly used to treat diseases of the external ear and occasionally of the middle ear in dogs. Otitis externa, infection or inflammation of the external ear canal, is one of the most common diseases of the ear. Otitis externa can be caused by fungi, or bacteria such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

The majority of the existing otic products on the market are solution dosage forms containing either a combination of antibacterial and anti-inflammatory agents or antifungal and anti-inflammatory agents. In addition, most of the existing otic preparations require refrigeration storage (5–15°C). In this study, a new otic preparation was developed with a combination of an antibacterial, an antifungal, and an antiinflammatory agent to provide a broader spectrum of activity. This product was also formulated to meet the room-temperature storage requirements for more convenient product storage and use.

The major challenge in developing a topical suspension containing three active ingredients is to choose a liquid medium in which the three active drugs remain stable during storage. It has been reported that clotrimazole is stable in an alkaline medium, but degrades hydrolytically in an acidic medium (1). The decomposition of triamcinolone acetonide is minimal at pH ~3.4 in water–ethanol solutions; however, when the pH is above 5.5, the decomposition of triamcinolone accelerates and is directly related to the phosphate buffer concentration (2). Sarafloxacin HCl is very stable (<1.0 % degradation) in either an acidic solution (0.1 N HCl) or an alkaline solution (0.1 N NaOH). Since these three drugs have different stability profiles, the identification of a liquid medium for the suspension, providing the optimal stability for these three drugs, has been the focus of this formulation study.

In a suspension, the dispersed drug particles are not likely to undergo chemical degradation and only the small fraction of the drug dissolved in the continuous phase is susceptible to degradation. As the drug decomposes in solution, more drug is dissolved from the suspended particles, so that the soluble drug concentration remains constant. The concentration of the soluble drug in a suspension is actually the drug's equilibrium solubility in the liquid medium at a specific temperature. Theoretically, the degradation of a drug in a suspension can be described by an apparent zero-order equation (3):

$$k_0 = k[C]_s \tag{1}$$

where k is the first-order rate constant for drug degradation in solution, $[C]_s$ is the equilibrium drug solubility, and k_0 is the zero-order rate constant. Thus, the rate constant of drug degradation in a suspension at a specific temperature can be predicted by knowing its solubility and its rate constant in solutions. In this study, solutions of each drug were prepared and subjected to various elevated isothermal conditions. The degradation rate of the drug in a solution could be predicted by using the Arrhenius equation:

$$k = Ae^{-E_a/RT} \tag{2}$$

or

$$\ln k = \ln A - (E_a/RT) \tag{3}$$

in which k is the specific reaction rate constant, A is a constant known as the Arrhenius factor or frequency factor, E_a is the energy of activation, R is the gas constant (1.987 cal/mole-K), and T is the

absolute temperature. The constants, A and E_a, can be evaluated by determining k at several accelerated temperatures (60, 70, and 80°C in this study) and plotting $\ln k$ against $1/T$. As seen in Eq. (3), the slope of the linear plot so obtained is $-(E_a/R)$ and the y-intercept on the vertical axis is $\ln A$, hence E_a and A can be calculated from these two values. Thus, by determining the rate constants for drug degradation at elevated temperatures, the rate constant at a lower temperature such as 25°C or 40°C can be calculated by extrapolation. As a result, the apparent zero-order rate constant of drug degradation in a suspension at 25°C or 40°C can be calculated as the product of its predicted first-order rate constant and its solubility at the specific temperature (see Eq. (1)). The liquid medium producing the maximal drug stability was then determined by comparing the predicted degradation rate constant of the drug in the suspension.

The second goal of the formulation development work is to select a suitable suspending agent to enhance product redispersibility and to prevent caking in the product. After the preliminary screening of different suspending agents, a 3^2 factorial design was employed to determine the optimal levels of two formulation factors with respect to redispersibility and sedimentation volume of the suspension.

EXPERIMENTAL

Materials

All three bulk drugs—sarafloxacin HCl (Abbott Laboratories, North Chicago, IL), triamcinolone acetonide (Sicor, Milano, Italy), and clotrimazole (Fabbrica Italiana Sintetici, Vicenza, Italy)—were micronized to yield a mean particle size between 3 and 7 μm and with 90% of particles less than 11 μm. Sodium carboxymethylcelluloses with nominal viscosities 400–800 cps [medium-viscosity CMC (MV-CMC)] and 1500–3000 cps [high-viscosity CMC (HV-CMC)], methylcellulose with nominal viscosity 15 cps (MC), and hydroxypropylmethylcellulose (HPMC K4M) were purchased from Sigma, St. Louis, MO, and used as received. Other excipients, such as polysorbate 20, ethylenediaminetetraacetic acid (EDTA) disodium, monobasic and dibasic potassium phosphate, and NaCl were all reagent grades.

Methods

Suspension Preparation

The suspensions were prepared according to the following procedures. A predetermined amount of excipients (EDTA, NaCl, polysorbate 20) was dissolved in the buffer solution. The suspending agent (CMC or MC or HPMC) was subsequently added and stirred until it was completely hydrated. Triamcinolone acetonide, sarafloxacin HCl, and clotrimazole were later dispersed into the solution mixture using a Silverson® L4RT high-shear mixer (East Longmeadow, MA) at 7000 rpm to produce a uniform suspension.

Determination of Stability of Drugs in the Suspension Liquid Media

In this study, suspension liquid media without a suspending agent were used. The suspension was prepared by first dissolving the excipients in the buffer solution and subsequently dispersing the three active ingredients in the liquid medium by mechanical stirring. The resulting dispersion was then subjected to sonication (in a water bath) for 5 min and mechanically stirred at 40°C in a stability chamber overnight. The suspension was filtered through a 0.2-μm membrane filter (Nalgene® NYL 153-0020). The initial concentration of each drug in the filtrate was equal to its 40°C solubility in the medium of the suspension. This concentration also represented the initial drug concentration in the samples used for isothermal stability evaluation at elevated temperatures. The filtrate was placed in 10-mL glass vials and stored at 60, 70, and 80°C, respectively. The samples were withdrawn at predetermined time points and analyzed by using an HPLC method described below. The extent of drug degradation was monitored and the degradation rate constant was determined for these three accelerated conditions. Then, the degradation rate constants for the drug at 25°C and 40°C were predicted using the Arrhenius relationship.

Drug Analysis

A validated stability-indicating gradient HPLC method was used to assay the three active ingredients. The liquid chromatography system consisted of a Hewlett Packard Series 1100 HPLC system (Kennett Square, PA). Reversed-phase liquid

chromatography was accomplished on a Waters symmetry C18 column (5 μm, 25 cm × 4.6 mm I.D.). The injection volume was 25 μL and the mobile phase flow rate was set at 1.0 mL/min. The HPLC was run according to the gradient scheme described in Table 1. A pH 2.5 phosphate buffer for mobile phase was prepared by mixing 1800 mL water with 5 mL phosphoric acid (85%) followed by dilution to 2000 mL. The pH was adjusted with 2 N sodium hydroxide. The mobile phase A was prepared by mixing 500 mL acetonitrile with 2000 mL of pH 2.5 phosphate buffer and the mobile phase B was prepared by mixing 1200 mL acetonitrile, 600 mL tetrahydrofuran, and 100 mL water. Both mobile phases were filtered through a 0.45-μm filter. The column was kept at 25°C. Ultraviolet (UV) detection was performed at 260 nm.

For potency assay, a predetermined amount of sample was first dissolved in a mixture of mobile phase A and *N,N*-dimethylformamide (10 : 1) prior to injecting onto the column. While handling suspension samples, appropriate rinsing was performed in order to avoid the loss of drug due to the adhering of drug particles to the containers.

Formulation Optimization Using a 3^2 Factorial Design

Experimental Design

The objective of this study is to investigate the effect of NaCl and MV-CMC on redispersibility, sedimentation volume, and viscosity of the suspension. The levels of these two independent variables are given in Table 2; the design and the resulting response values are presented in Table 3.

Table 1

HPLC Gradient Scheme

Time (min)	Mobile Phase A (%)	Mobile Phase B (%)
0	100	0
8.0	100	0
10.0	70	30
17.0	70	30
19.0	0	100
24.0	0	100
26.0	100	0
35.0	100	0

Table 2

Level of Independent Variables

Independent Variables	Levels of Variables (%)		
	Low (−1)	Center (0)	High (1)
NaCl	0	0.5	1
MV-CMC	0.5	0.75	1

Determination of Suspension Redispersibility Using a Reciprocal Shaker

A 15-mL sample was stored in a 20-mL glass vial in a vertical position for 1 week after preparation. The glass vial was then placed horizontally on the reciprocal shaker platform (HS501 digital, IKA Laboratechnik, IKA Works, Inc., Wilmington, NC) with a speed setting at 300 stokes/min. This speed setting was chosen because it simulates human arm motion when shaking a bottle of suspension. The time required to clear all the sediments from the bottom of the vial was determined. The ease of redispersion is 100% when the time required for complete redispersion is less than 30 s: every additional 30 s required for redispersion would cause a 5% drop in the degree of redispersibility.

Determination of Viscosity

The viscosity of a suspension was measured in centipoise (cps) within 48 hrs of preparation using the Canon LV-2000 Viscometer. The viscosity of the suspension was measured at 25°C using spindle #4 with the speed of 12 rpm.

Determination of Sedimentation Volume

The sedimentation volume (V_u/V_0), expressed as percent, was measured after the suspension was settled 1 week after preparation in a 10-mL graduate cylinder. V_u is the ultimate volume of the sediment and V_0 is the initial volume of the suspension.

Data Analysis

DOEKISS®, version 97 (Digital Computations, Inc. and Air Academy Associates, LLC, Colorado Springs, CO) was used for data analysis. All the experimental data, model parameters and the response surfaces were generated according to a

Table 3

Design Factor Combinations and the Resulting Response Values

Run No.	Levels of Variables		Response Values		
	NaCl (X_1) %	CMC (X_2) %	Sedimentation Volume (%)	Redispersibility (%)	Viscosity (cps)
1	0.5	0.5	8.0	70	9.73
2	1	0.5	10.5	55	10.65
3	0	1	5.0	55	52.20
4	1	1	26.0	80	58.90
5	1	0.75	13.5	45	25.60
6	0	0.75	6.0	65	27.44
7	0	0.5	5.9	40	10.64
8	0.5	0.75	9.5	55	26.65
9	0.5	1	1.9	75	71.20

Table 4

Formulations for the Arrhenius Study

Ingredients	Formulation 1	Formulation 2	Formulation 3
NaCl	10 mg/mL	10 mg/mL	10 mg/mL
Phosphate buffer	0.01 M	0.01 M	none
Acetate buffer	None	none	0.01 M
pH	7.0	6.0	7.0

second-order polynomial model (Eq.(4)). Analysis of variance was used to determine the statistical significance of the coefficients in the equation:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad (4)$$

where, b_i is the estimated coefficient for the factor X_i, whereas Y_i is the measured response. The coefficients corresponding to the linear effect (b_1 and b_2), the interaction (b_{12}) and the quadratic effects (b_{11} and b_{22}) were determined using the experimental data.

RESULTS AND DISCUSSION

Prediction of Stability of Drugs in the Suspension Media Using the Arrhenius Relationship

Formulations prepared with various buffers and pHs are given in Table 4. All formulations contained 1 mg/mL of sarafloxacin HCl, 1 mg/mL of triamcinolone acetonide, 10 mg/mL of clotrimazole, 1 mg/ml of EDTA, and 2 mg/mL of polysorbate 20.

To study the effect of pH, Formulations 1 and 2 were prepared at pH 7 and 6. Also, acetate buffer instead of phosphate buffer was used in Formulation 3.

The predicted zero-order rate constant k_0 and the extent of degradation at 25°C and 40°C using the Arrhenius relationship is given in Table 5. In summary, triamcinolone acetonide was found to be more stable in a 0.01 M phosphate buffer and its degradation was enhanced when lowering the pH from 7.0 to 6.0. Clotrimazole was more stable at pH 7.0 than pH 6.0 in a phosphate buffer. For sarafloxacin HCl, its degradation was insignificant in all formulations. The stability of triamcinolone acetonide was only slightly improved using the acetate system. The above information indicated that a 0.01 M phosphate buffer (pH 7.0) was appropriate for the system.

Table 5

Predicted k and k_0, Drug Solubility and Predicted Extents of Degradation in Formulations 1–3

	Obtained Results	Sarafloxacin	Triamcinolone	Clotrimazole
Formulation 1	$k_{60°C}$ and (r^2)	N/A[a]	0.0081 (0.94)	0.0148 (0.85)
	$K_{70°C}$ and (r^2)	N/A[a]	0.0301 (0.98)	0.1246 (0.99)
	$K_{80°C}$ and (r^2)	N/A[a]	0.0694 (0.97)	0.2458 (0.99)
	E_a (kcal/mole)	N/A[a]	25.13	33.05
	ln A	N/A[a]	33.29	45.96
	r^2 (Arrhenius plot)	N/A[a]	0.99	0.93
	k_0 at 25°C (mg/mL · day)	N/A[a]	2.3×10^{-6}	1.0×10^{-6}
	k_0 at 40°C (mg/mL · day)	N/A[a]	2.6×10^{-5}	1.4×10^{-5}
	Degradation at 25°C, 24 months[b]	N/A[a]	0.17%	0.01%
	Degradation at 40°C, 6 months[b]	N/A[a]	0.47%	0.03%
Formulation 2	$k_{60°C}$ and (r^2)	N/A[a]	0.0146 (0.99)	0.0790 (0.98)
	$k_{70°C}$ and (r^2)	N/A[a]	0.0443 (0.99)	0.2413 (0.90)
	$k_{80°C}$ and (r^2)	N/A[a]	0.0264 (0.90)	0.2109 (0.76)
	E_a (kcal/mole)	N/A[a]	7.19	11.62
	ln A	N/A[a]	6.91	15.25
	r^2 (Arrhenius plot)	N/A[a]	0.31	0.67
	k_0 at 25°C (mg/mL·day)	N/A[a]	8.1×10^{-5}	4.4×10^{-5}
	k_0 at 40°C (mg/mL·day)	N/A[a]	3.0×10^{-4}	7.1×10^{-4}
	Degradation at 25°C, 24 months[b]	N/A[a]	5.83%	0.32%
	Degradation at 40°C, 6 months[b]	N/A[a]	5.40%	1.28%
Formulation 3	$k_{60°C}$ and (r^2)	0.0007 (0.94)	0.0041 (0.83)	0.0304 (0.92)
	$k_{70°C}$ and (r^2)	0.0082 (0.98)	0.0284 (0.96)	0.2194 (0.90)
	$K_{80°C}$ and (r^2)	0.0146 (0.99)	0.0572 (0.99)	0.2692 (0.94)
	E_a (kcal/mole)	35.21	30.85	25.67
	ln A	46.94	41.39	35.63
	r^2 (Arrhenius plot)	0.90	0.94	0.84
	k_0 at 25°C (mg/mL · day)	1.5×10^{-7}	1.0×10^{-6}	1.1×10^{-5}
	k_0 at 40°C (mg/mL · day)	1.0×10^{-5}	1.1×10^{-5}	1.4×10^{-4}
	Degradation at 25°C, 24 months[b]	0.01%	0.07%	0.08%
	Degradation at 40°C, 6 months[b]	0.18%	0.20%	0.25%

[a]N/A, not available due to the insignificant decomposition of sarafloxacin HCl over the testing period.
[b]Predicted percent degradation based upon the rate constant as listed.

Selection of a Suspending Agent

After an optimal buffer solution was identified for the formulation, the effect of various excipients on the physical stability of the suspension was evaluated by measuring its redispersibility.

Sodium chloride is used as a flocculating agent in this formulation. Polysorbate 20 is a nonionic wetting agent that is used to aid dispersion of hydrophobic drugs such as clotrimazole and triamcinolone acetonide in this formulation. MC, HPMC, and HV-CMC were evaluated as the suspending agent for the formulation (4).

The six suspensions listed in Table 6 all contained 1 mg/mL of sarafloxacin HCl, 1 mg/mL of triamcinolone acetonide, and 10 mg/mL of clotrimazole, but varied in the type and concentration of the suspending agents, polysorbate 20 and NaCl in a 0.01M phosphate buffer (pH 7.0). The redispersibility and physical appearance of these formulations were evaluated visually and manually. The evaluation criteria were the ease of redispersing the sediment from the bottom of the vials (settled for 1 week) by manual shaking and the extent of foaming after shaking.

Suspensions (Formulations A–C) containing 2.2% MC, 0.4% HPMC, or 0.35% HV-CMC

Table 6

Formulations for Redispersibility Evaluation

	Formulation					
Ingredient	A	B	C	D	E	F
Tween20	0.2%	0.2%	0.2%	0.02%	0.02%	0.02%
NaCl	1%	1%	1%	1%	—	1%
MC	2.2%	—	—	—	—	—
HPMC	—	0.4%	—	—	—	—
HV-CMC	—	—	0.35%	0.35%	0.35%	—
0.1% EDTA	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%

Note: All ratios are w/v.

yielded a viscosity close to ~25 cps. It is more meaningful to compare redispersibility of formulations with similar viscosities than to compare formulations with same concentration of the suspending agent. It was found that the suspension containing 0.35% HV-CMC (Formulation C) was much easier to redisperse than those containing MC or HPMC (Formulations A and B). Since MC and HPMC are both nonionic polymers, it was speculated that the anionic nature of HV-CMC might play a critical role in producing a redispersible suspension. The negatively charged CMC could interact with these three drugs, forming a loosely linked polymer network system within the suspension. On the other hand, the aggregates of drugs, with non-charged MC and HPMC were denser and more difficult to redisperse. Excess foaming was also seen in Formulation C (0.2% polysorbate 20) in comparison with Formulation D (0.02% polysorbate 20). It was later decided to reduce polysorbate 20 from 0.2% to 0.02% in the formulation. It was also noticed that the redispersibility of the suspension containing 1% NaCl (Formulation D) was relatively easier than that for the suspension with no NaCl added (Formulation E). Although Formulation F (1% NaCl but no suspending agents) exhibited the best redispersibility, a product viscosity target of 10–60 cps could not be attained without the addition of a suspending agent.

In summary, HV-CMC was chosen to be the suspending agent for the suspension. The final formulation consisted of the three active ingredients, 0.02% polysorbate 20, 1% NaCl, 0.35% HV-CMC and 0.1% EDTA in 0.01M phosphate buffer (pH 7.0). The chemical stability of the drugs in this suspension was further determined.

Stability Evaluation of the HV-CMC Suspension

The drug potency and pH of the HV-CMC suspension containing 0.01 M phosphate buffer (pH 7.0) were monitored for 3 months. Sarafloxacin, triamcinolone, and clotrimazole were stable in this formulation for at least up to 3 months at 25°C, as shown by data in Table 7. Also, the pH was maintained in the 25°C samples for at least up to 3 months. However, it was found that the pH declined from the initial of 6.98 to 6.68 at 3 months for samples stored at 40°C. A slight degradation of sarafloxacin (4.2 %) and triamcinolone (3.7 %) was also shown in these samples. The predicted degradation of sarafloxacin in this buffer alone (without addition of HV-CMC) was insignificant at 40°C for 3 months. At the same temperature, the degradation of triamcinolone was predicted to be about 0.24%. The cause for the discrepancy between the actual stability data and the predicted values was not clear. It is possible that the incorporation of HV-CMC could adversely affect the drug stability in the suspension medium. In an attempt to stabilize the product pH and reduce drug degradation, an increase in phosphate buffer concentration (0.02 M) was recommended for further evaluation.

The long-term stability of the HV-CMC suspension consisting of 0.02 M phosphate buffer was evaluated at 40°C for 6 months and 25°C for 12 months (Table 8).

Table 7

Drug Stability in the HV-CMC Suspension Based on 0.01 M Phosphate Buffer

	Percent Potency			
	Sarafloxacin	Triamcinolone	Clotrimazole	pH
Initial	100.1	101.0	98.0	6.98
3 months at 25°C	100.4	100.0	97.1	6.98
3 months at 40°C	95.9	97.3	96.1	6.68

Table 8

Drug Stability in the HV-CMC Suspension Based on 0.02 M Phosphate Buffer

	Percent Potency			
	Sarafloxacin	Triamcinolone	Clotrimazole	pH
Initial	98.2	100.5	100.1	6.76
12 months at 25°C	100.7	99.8	100.5	6.79
6 months at 40°C	100.8	99.4	101.9	6.74

The drug potency results indicated that sarafloxacin HCl, triamcinolone acetonide, and clotrimazole were stable—i.e., less than 1% degraded—at the two storage temperatures. The pH change in samples was found to be insignificant. These results showed that the pH should be maintained close to the initial value for long-term product stability by increasing the buffer concentration (buffer capacity) for long-term product stability.

In regard to redispersibility, the time required to redisperse a settled suspension was less than 10 min for all stability samples tested. While the redispersibility is considered to be acceptable, a drop in viscosity from 39 cps initially to 3 cps at 40°C and to 10 cps at 25°C was seen in samples after 6 months. This significant decline in product viscosity has caused concern about its effect on clinical efficacy of the product. It has been known that viscosity decline is caused by the decrease in the molecular weight of CMC. After complete hydrolysis, the resultant viscosity would be equal to the viscosity of the hydrolytic end-products in the solution. The rate of CMC degradation depends on the resistance of the polymer network to hydrolysis. It has been reported that the viscosity stability of solutions of linear polymers such as CMC generally varies inversely with the molecular weight of the polymer (5). The molecular weight of HV-CMC is ~700,000. Therefore, in an attempt to reduce CMC degradation, the MV-CMC (MW = 250,000) was used to replace HV-CMC.

Formulation Optimization of MV-CMC Suspension Using a 3^2 Factorial Design

In this study, a 3^2 factorial design was used to investigate the effect of two selected parameters—concentration of NaCl and MV-CMC—on redispersibility, sedimentation volume, and viscosity of the suspension. The objective of this study was to determine the optimal level of the formulation variables in producing a suspension with the most desirable dispersion properties.

The response values of sedimentation volume, viscosity, and redispersibility are given previously in Table 3 and the results of the multiple regression analysis are summarized in Table 9. The response surface plots are shown in Figs 1–3.

The polynomial equation did not provide a good fit to the sedimentation volume data ($r^2 < 0.9$, in Table 9). However, it was noteworthy that NaCl had a significant positive effect ($p < 0.1$) on the sedimentation volume. MV-CMC and the

Table 9

Summary of Regression Analysis Results for Measured Responses

Response		NaCl	CMC	NaCl·CMC	$NaCl^2$	CMC^2	r^2
Sedimentation volume	Coeff.	5.517	1.417	4.100	4.683	−0.117	0.775
	p	0.089	0.569	0.229	0.311	0.978	
Viscosity	Coeff.	0.812	25.213	1.673	−4.955	8.990	0.970
	p	0.777	0.002	0.639	0.355	0.142	
Redispersibility	Coeff.	−2.500	5.000	10.000	2.500	15.000	0.724
	p	0.633	0.367	0.182	0.780	0.1635	

Note: Coeff. = coefficient for the factor; $p = p$ value.

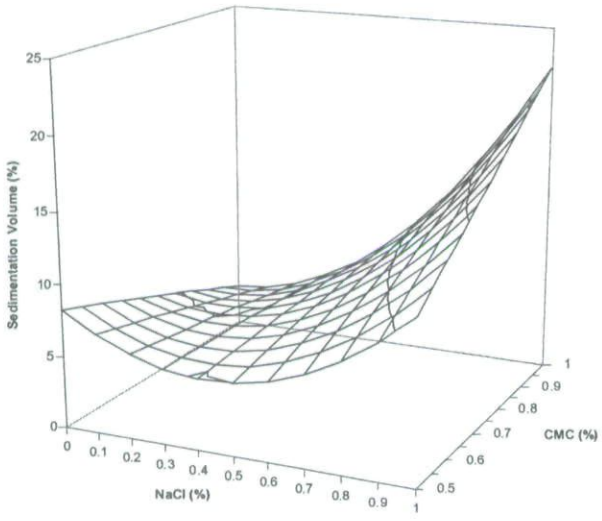

Figure 1. Effect of NaCl and MV-CMC on the sedimentation volume.

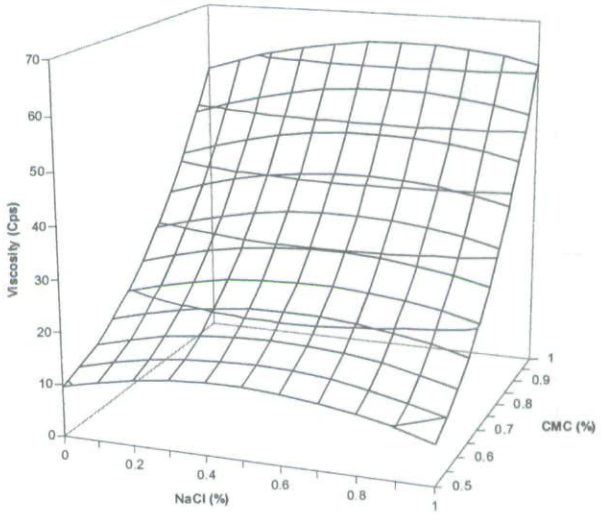

Figure 2. Effect of NaCl and MV-CMC on the viscosity.

interaction effect of NaCl and MV-CMC had no influence on the sedimentation volume. Also, the highest sedimentation volume (26%) can be obtained by using the maximum amount of NaCl (1%) and MV-CMC (1%) as shown in the response plot (Fig. 1) and by the measured response (Table 3).

In Table 9, an r^2 value of 0.97 was obtained for the model fitted with the viscosity data indicating a good fit of the polynomial equation to the viscosity data. CMC was found to be the only variable showing significant positive effect on the viscosity ($p = 0.002$ in Table 9). It was also apparent that the level of NaCl had no significant effect on the viscosity of the suspension (Table 9 and Fig. 2).

The effect of NaCl and CMC on the redispersibility of the suspension was not significant (with $p = 0.633$ for NaCl and $p = 0.367$ for MV-CMC, Table 9). However, as shown in the response surface plot (Fig. 3), the redispersibility of the suspension was relatively higher when the formulation contained no NaCl and 0.5% CMC or 1% NaCl and 1% CMC.

In summary, a suspension with a high redispersibility and a high sedimentation volume can be produced with a combination of 1% NaCl and 1% MV-CMC. This selected formulation exhibited a redispersibility (80%) higher than that (35%) of the HV-CMC formulation, even though the viscosity of this optimized formulation (~50–60 cps) was higher than that of the HV-CMC formulation (25 cps).

Table 10

Drug Stability in the MV-CMC Suspension

	Percent Potency			
	Sarafloxacin	Triamcinolone	Clotrimazole	pH
Initial	99.7	100.1	101.2	6.77
6 months at 25°C	100.1	110.8	102.3	6.83
6 months at 40°C	101.3	99.9	103.2	6.79

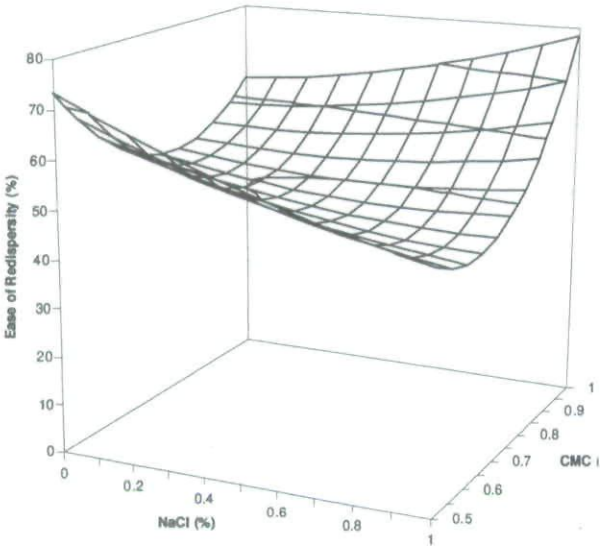

Figure 3. Effect of NaCl and MV-CMC on the redispersibility.

Stability Evaluation of the MV-CMC Suspension

In this study, the long-term stability of the suspension containing 1% MV-CMC and 1% NaCl was evaluated. The chemical composition of the HV-CMC and MV-CMC are the same except that the HV-CMC has longer polymer chains (a higher molecular weight) and the MV-CMC has shorter polymer chains (a lower molecular weight). Because of their similarities in chemical composition, the chemical stability of the MV-CMC formulation should be similar to that of the HV-CMC formulations, which were shown to be stable at 25°C and 40°C for at least 6 months. From this stability study it was found the drugs in this MV-CMC formulation were chemically stable at 25°C and 40°C for at least six months (Table 10). The physical stability of this formulation was also found to be acceptable; all stability samples exhibited high redispersibility. With respect to viscosity stability, it was found that viscosity drop was less drastic by using the MV-CMC instead of the HV-CMC. For the HV-CMC suspension, the viscosity was 39 cps initially, but dropped to 10 cps at 25°C and to 3 cps at 40°C after 6 months. The viscosity of the MV-CMC formulation showed an initial viscosity of 61 cps, and the viscosity dropped to 33 cps at 25°C and 9.5 cps at 40°C after 6 months. It is apparent that an improved product viscosity stability was achieved by replacing HV-CMC with MV-CMC.

CONCLUSIONS

In this formulation study, a 0.02 M phosphate buffer (pH 7.0) was identified to be an acceptable buffer for a topical suspension containing 1 mg/mL sarafloxacin HCl, 1 mg/mL triamcinolone acetonide, and 10 mg/mL clotrimazole. Long-term stability data indicate that these three drugs exhibited acceptable stability profiles in the suspension stored at 25°C and 40°C. MV-CMC was identified as the suspending agent because of its relatively stable viscosity profile upon long-term storage. A formulation containing 1% MV-CMC and 1% NaCl was determined to be an appropriate formulation for the product, due to its high redispersibility and sediment volume of the resultant suspensions.

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