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IN VITRO DRUG RELEASE FROM MATRIX TABLETS CONTAINING A SILICONE ELASTOMER LATEX

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ABSTRACT

A silicone elastomer latex was evaluated as a wet-granulating agent in preparing controlled release matrix tablets containing a water soluble active ingredient. A one-half fractional factorial statistical design was used to investigate the effect of five different formulation and non-formulation variables on the in vitro release characteristics of the drug from the matrix tablets. Tablets containing a high percent of fumed colloidal silica exhibited a faster drug release rate. A high drug to polymer ratio in the tablets was also shown to result in a faster release of the drug. Granules

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dried at a higher temperature (80°C vs. 60°C) produced tablets with a slower drug release rate. The release of the drug was shown to be pH dependent. A higher drug release rate was obtained in a dissolution medium with a lower pH (1.2 vs. 6.8).

INTRODUCTION

Oral controlled release dosage forms continue to maintain a significant presence in the development of controlled release medications because they are relatively inexpensive to prepare and oral administration is one of the most convenient routes of administration. Although technological advances have been made with various oral controlled release systems, the role of tablet matrix for controlled drug delivery remains vital, because tablet production is economical and tableting technology and equipment are readily available to most pharmaceutical manufacturers.

A variety of aqueous colloidal dispersions of polymers have been developed for controlled release film coating (1). Recent studies have shown that these polymer dispersions can be employed in the manufacture of controlled release matrix tablets using the wet granulation method (2). During tablet compression, drug particles are embedded in a fine network of thin polymer layers, which control the penetration of dissolution fluid into the matrix and the subsequent diffusion of the dissolved drug through the porous structure of the matrix. Aqueous polymer dispersions currently available for tablet matrix formation primarily include the latex and pseudolatex of acrylate copolymers and ethylcellulose (2).

Because of the physiological inertness and excellent biocompatibility, silicone elastomers have had a long history of biomedical applications. Currently, silicone elastomers have become indispensable in many controlled drug delivery systems. The silicone elastomer latex evaluated in the present study is composed of a cross-linked hydroxyendblocked polydimethylsiloxane (PDMS). The use of this latex for controlled release tablet film coating has been reported (3). The purpose of this study was to investigate the use of this latex as a wet-granulation agent to form controlled release matrix tablets containing dextromethorphan hydrobromide as a model water soluble drug. Factors controlling the drug release from the tablet matrix were also evaluated.

EXPERIMENTAL

Materials:

The silicone elastomer latex was supplied by Dow Corning Company, Midland, Michigan. The latex had a mean particle size of 0.2 μm and a pH of 8.2. The amorphous fumed silica (EH-5) was obtained from Cabot Corporation, Tuscola, Illinois. It had a mean particle size of 0.007 μm. Dextromethorphan hydrobromide, USP, was obtained from Sigma Chemical Company, St. Louis, Missouri.

Methods:

Experimental Design

Factorial experimental design offers the possibility of evaluating the influence of individual variables and their interaction at the same time with a minimum number of experiments (4). This method has been

extensively used in pharmaceutical formulation and clinical research (5). However, as the number of independent variables increases, the large number of experiments required will render a complete factorial design inefficient. With the help of certain assumptions, the fractional factorial designs can efficiently reduce the number of experiments and still obtain the desired information (4). In the present study, a one-half fractional factorial design was used to evaluate the influence of five different variables on the release of drug from matrix tablets formed with a silicone elastomer latex. The dependent variable was the slope from the plot of cumulative percent drug released versus square root time. Each of the five independent variables evaluated was coded and set at a high and low level as shown in Table 1. By setting the identity I = ABCDE, all main effects have aliases of four factor interactions, and all two factor interactions have three factor interactions as aliases. Therefore, by assuming the three-way and four-way interaction effects as insignificant, the main effect and the two-way interaction effect can be evaluated. The treatment combinations evaluated in the design are listed in Table 2. One batch of tablets was prepared for each treatment combination and two replications were done for four of the sixteen treatment combinations. Totally, twenty batches of tablets were prepared and tested.

Preparation of Tablets

A predetermined amount of silicone elastomer latex was diluted with an adequate amount of water and mixed with fumed silica to form a thick slurry using a mortar and pestle. The active ingredient was subsequently

Table 1. The independent variables and their levels for evaluation.

Variable	Level High	Low
Compression Force (a)*	3,000 lb	1,500 lb
Drying Temperature (b)	80 °C	60 °C
Drug to Polymer Ratio (c)	1/3	1/4
Silicone to Silica Ratio (d)	1/2	1/4
pH of Dissolution Medium (e)	6.8	1.2

* Small letters represent the independent variable.

Table 2. Treatment Combinations for Tablets Evaluated in the Experiment Design.

Treatment Combination	Compression Pressure,lb	Drying Temp. °C	Drug/ Polymer	Silicone/ Silica	pH
(1)*	1,500	60	1/4	1/4	1.2
ab**	3,000	80	1/4	1/4	1.2
ac	3,000	60	1/3	1/4	1.2
ad	3,000	60	1/4	1/2	1.2
ae	3,000	60	1/4	1/4	6.8
bc	1,500	80	1/3	1/4	1.2
bd	1,500	80	1/4	1/2	1.2
be	1,500	80	1/4	1/4	6.8
cd	1,500	60	1/3	1/2	1.2
ce	1,500	60	1/3	1/4	6.8
de	1,500	60	1/4	1/2	6.8
abcd	3,000	80	1/3	1/2	1.2
abce	3,000	80	1/3	1/4	6.8
abde	3,000	80	1/4	1/2	6.8
acde	3,000	60	1/3	1/2	6.8
bcde	1,500	80	1/3	1/2	6.8

* represents the treatment combination for all variables at their low level.

** represents the treatment combination with the variables a and b at the high level and the other three at the low level.

added and mixed with the silicone-silica base to ensure a uniform distribution of the active ingredient. The final wet mass was dried in an oven at a specific temperature overnight. The dried mass was milled in a stainless steel Warning blender. The milled granules were passed through a 80 mesh standard sieve and subsequently blended with 1% of magnesium stearate using a miniature V-blender. An amount of granules containing 60 mg of dextromethorphan hydrobromide was weighed and compressed into a 5/16" standard concave tablet using a laboratory Carver press (Model C) at a specific compression load.

Determination of Tablet Surface Area

Since two different drug to polymer ratios were used in this study, in order to prepare tablets containing the same amounts of drug (60 mg), a higher tablet weight was used for formulations with a low drug to polymer ratio. At the same compression load, tablets with a higher weight were probably formed with a larger surface area. Therefore, it was necessary to know the tablet surface area so that a drug release rate corrected for the tablet surface area could be determined and used for comparison. The surface area of a tablet was calculated using the following equation (6).

$$\text{Tablet surface area } (cm^2) = \pi[4RC + 2L(D-L) + D(T-2C)] \qquad \text{Eq. 1}$$

where R = radius of curvature,
D = diameter,
C = cup depth,
T = thickness,
L = land width.

Dissolution Test

Three tablets for each treatment combination were used in the dissolution test. The in vitro release profiles of dextromethorphan from the tablets were determined using the standard USP Dissolution Method II-the paddle method. The apparatus used was a six-unit dissolution tester (Vanderkamp 600). The dissolution medium was 900 mls of degassed USP simulated gastric fluid and intestinal fluid (without enzyme) respectively. The paddle stirring rate was set at 100 rpm. The dissolution medium was circulated through a UV spectro-photometer (Perkin-Elmer Lambda 38) which was interfaced with the Lambda 3 Data Station equipped with the Perkin-Elmer PR-100 Printer. The absorbance (at 278 nm) of dextromethorphan in the dissolution medium was measured and recorded at half hour intervals for twelve hours. The amount of dextromethorphan hydrobromide released was calculated by means of a calibration curve. The plotting of the cumulative percent released against square root of time elapsed gave the square root time release profile. The slope of the profile was determined using the least squares method. The regression was not forced through the origin and drug release data up to 75% of the total amounts drug released were used in the regression, but the zero time point was not included. In order to correct for the difference in surface area of each tablet tested, the calculated slope was divided by the surface area of the tablet to give the release rate with a unit of % per $cm^2 \cdot hr^{1/2}$.

RESULTS AND DISCUSSION

Commercial latex and pseudolatex products commonly used for film coating have been used in the manufacture of controlled-release tablets using wet granulation method (2). The total solids content of these products were about 30% by weight. The amount of polymer that may be added in a wet granulation process is always limited because a large volume of dispersions may make the granulations too damp for processing. In some cases, a double or even triple granulation procedure has been employed to produce granules with high content of polymer from dispersions (7). However, this procedure was very time consuming and inefficient. The use of the silicone elastomer latex in wet granulation eliminates the above problems. The silicone elastomer latex contains up to 50% polymer solids and the fumed silica, which was added to the latex as a filler, has a very high liquid adsorption capacity. Therefore, a large volume of silicone elastomer latex can be added to the fumed silica and the drug, to form wet granulations without the problem of overwetting. In this study, wet granulations of dextromethorphan HBr containing silicone elastomer solids, as high as 80% of the total dry weight, were prepared by a single granulation procedure.

Figure 1 shows the drug release profiles for four different tablet formulations. The release of the active ingredient was characterized by a fast initial release phase followed by a gradual decrease in release rate. The replotting of the data shown in Figure 1 against the square root of time, yielded straight lines with different slopes (Figure 2). This indicates

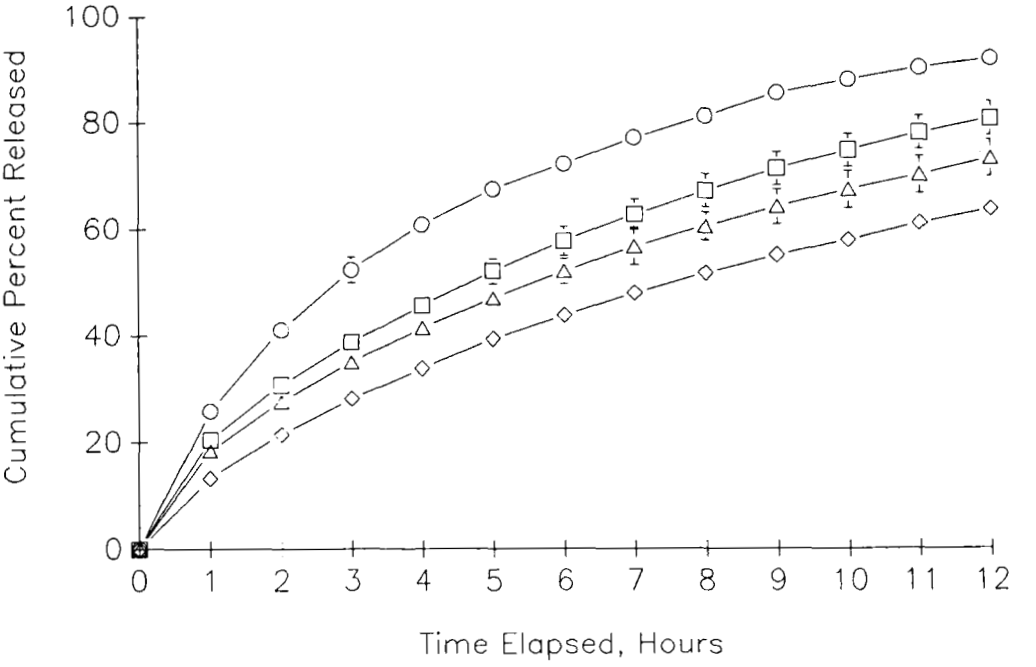

FIGURE 1

The release profile of dextromethorphan HBr from four different matrix tablets. Key: ○ bc, □ ad, △ de and ◇ abde. Each treatment is defined in Table 2.

that the release of dextromethorphan HBr from the silicone elastomer tablet matrix followed a diffusion controlled mechanism as described by Higuchi (8). The linear square root time plots for the drug release data allowed the determination of the drug release rate for the tablet matrix, which was subsequently used as the responsible variable in the statistical analysis of the five formulation variables evaluated in this study. Table 3 presents the release rate for dextromethorphan HBr from different matrix tablets. These data were further analyzed to determine the significance of

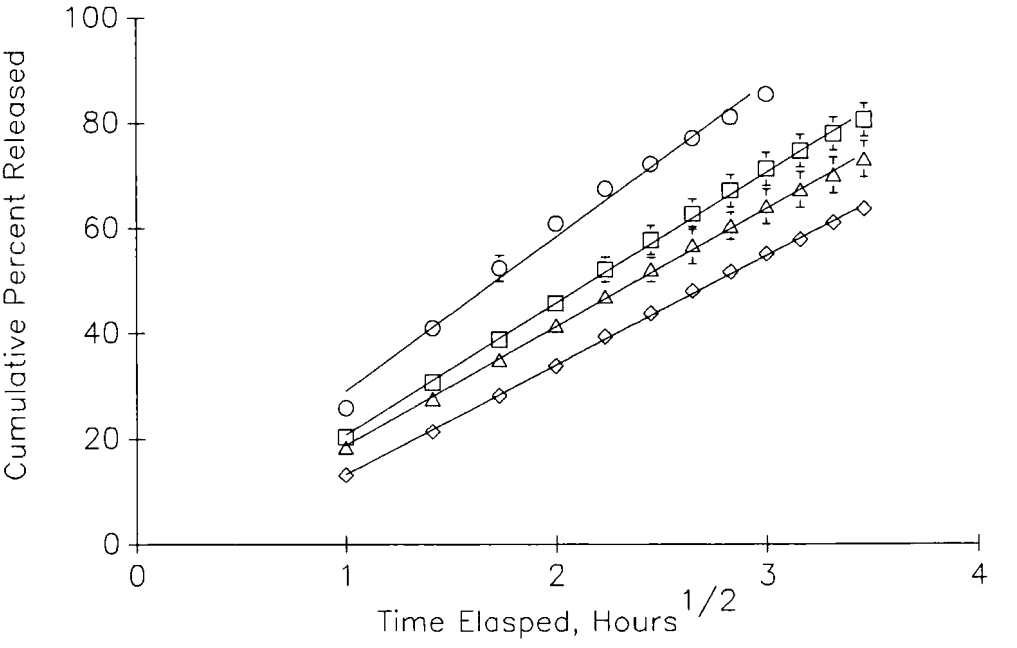

FIGURE 2

The square root time plots showing the release profile of dextromethorphan HBr from four different matrix tablets. Symbols are the same as defined in Figure 1.

the independent variables by using the GLM procedures in SAS (Statistical Analysis System). The ANOVA results are presented in Table 4. The compression loads used for compression of the matrix tablets did not show any significant effect on the release behavior of the tablets (α = 0.05). The effect of compression pressure on the release characteristics of a matrix tablet has been related to its impact on the matrix porosities and the tablet surface area (9). Since the drug release rates were corrected for the difference in tablet surface area, it was not surprising to find that

Table 3. Drug Release Rate (% per $cm^2 \cdot hr^{1/2}$) for the Tablets Evaluated in Experimental Design.

Treatment Combination	Release Rate*
(1)	11.01 (0.89)
(1)-1**	11.22 (0.78)
ab	10.69 (0.31)
ab-1	10.12 (0.25)
ac	12.84 (0.35)
ad	9.57 (0.51)
ae	8.65 (0.61)
ae-1	8.18 (0.77)
bc	11.56 (0.71)
bd	9.96 (0.43)
be	8.09 (0.23)
be-1	8.65 (0.31)
cd	11.83 (0.57)
ce	11.64 (0.69)
de	8.13 (0.72)
abcd	10.89 (0.81)
abce	10.77 (0.74)
abde	7.75 (0.48)
acde	10.26 (0.59)
bcde	9.46 (0.60)

* Mean and standard deviation for three tablets from the same batch.
** Replication.

an increase of compression load from 1,500 lb to 3,000 lb did not significantly alter the drug release rate from the silicone elastomer matrix .

The main effects of drying temperature and silicone to silica ratio of the elastomer were found to be significant ($\alpha = 0.05$). A comparison of the sample means of the release rate for tablets prepared from granules dried at two different temperatures (80°C and 60°C) indicates that

Table 4. Analysis of Variance Results.

Source*	DF	SS	F Value	PR > F
A	1	0.18394	1.69	0.2634
B	1	1.50591	13.84	0.0205***
C	1	15.80212	145.24	0.0003***
D	1	3.68579	33.88	0.0043***
E	1	16.54744	152.09	0.0002***
A x B**	1	0.56156	5.16	0.0855
A x C	1	0.22412	2.06	0.2245
A x D	1	0.02068	0.19	0.6853
A x E	1	0.00053	0.00	0.9480
B x C	1	0.62160	5.17	0.0751
B x D	1	0.10571	0.97	0.3801
B x E	1	0.01761	0.16	0.7080
C x D	1	0.14535	1.34	0.3121
C x E	1	0.86847	7.98	0.0476***
D x E	1	0.00109	0.01	0.9251
Error	4	0.43540	-	-

* Capital letters represent the effect of the independent variable.
** Interaction effect.
*** Significant at $\alpha = 0.05$ level.

granules dried at a higher temperature resulted in tablets with a slower release rate. It has been well documented that the coalescence of latex particles is facilitated at a higher temperature (10). Therefore, it is likely that, at a drying temperature of 80°, the drug containing silicone elastomer granules would be formed with a more coherent matrix structure which would exert a greater retardant effect on the release of drug from the resultant tablets. An analysis of the effect of silicone to silica ratio in the matrix on the drug release rate reveals that tablets

containing a lower silicone to silica ratio (a higher silica content) exhibited a faster drug release rate. The understanding of the interaction between silica and silicone elastomer in the formation of granules may provide a plausible explanation for the effect of silica content on the drug dissolution behavior of the tablet matrix. During the wet granulation process, the silicone elastomer latex and fumed silica was first mixed to form a moistened mass prior to the addition of the active ingredient. The uniform dispersion of the silica in the latex allowed an intimate contact between the particles of these two components. Upon the removal of water, a strong filler-polymer interaction occurred between the free silicone polymer chains on the surface of the latex particles and the surface hydroxyl groups of the colloidal silica. Due to the vast difference in their particle size, it is possible that silicone elastomer particles were actually coated by the much smaller silica particles. As the amounts of silica in the formulation increased, the coalescence of silica particles probably gave rise to a separate hydrophilic silica solid phase within the elastomer networks as suggested by Saam and his coworkers (11). Therefore, the release mechanism for a water soluble ingredient from a silicone elastomer tablet matrix may be identified as a dissolution-diffusion process. First, the drug molecules dissolve in the penetrating medium and then diffuse out of the matrix. The formation of a hydrophilic gel of silicone elastomer in the matrix is unlikely because of the hydrophobic nature of PDMS. However, due to the very polar nature of silica, the rehydration of the silica by water penetrating into the matrix may actually

give rise to hydrophilic gel-like microstructures of silica within the matrix. Thus, the mass transfer of the dissolved drug molecules inside the matrix probably takes place through these hydrophilic regions consisting of hydrated silica. An expanding hydrophilic silica phase in the matrix is thought to be responsible for the higher release rate of a water soluble ingredient from tablets containing a higher percent of silica. Although an increase of silicone content (a higher silicone to silica ratio) in the matrix resulted in a greater retardant effect on the release of the drug from tablets, the silicone to silica ratio should not exceed 1/2; otherwise, the granules formed would be non-compressible because of the extremely elastic nature of silicone elastomer.

From the ANOVA results listed in Table 4, it can be concluded that both the main effect and interaction effect between the drug to polymer ratio and pH of dissolution medium are significant. Since the interaction effect is significant, the Newman-Keuls test was used to compare the sample means for the four different combinations of these two variables. The results of the test showed that the fastest release rate ($\alpha = 0.05$) was obtained with tablets having a drug to polymer ratio of 1/3 in the pH 1.2 dissolution medium. The drug release rate in a pH 1.2 medium from tablets with a drug to polymer ratio of 1/4 did not significantly differ from that exhibited by tablets having the higher drug to polymer ratio (1/3) in a pH 6.8 medium; however, both were significantly lower than the fastest rate. In a pH 6.8 medium, tablets with the low drug to polymer ratio (1/4) released the active ingredient at the slowest rate. Since

dextromethorphan HBr is a water soluble salt, an increase in the percent of this drug in a silicone elastomer matrix is expected to reduce the retardant effect of the hydrophobic silicone polymer and enhance the drug release. Furthermore, the increase in tablet porosity due to the dissolution of this water soluble ingredient is more pronounced in tablets with a higher drug to polymer ratio. This may also enhance drug release from the tablets. Dextromethorphan HBr, which has a pK_a of 4.24, is a water soluble salt of a slightly water soluble weak base, dextromethorphan. The solubility of such a salt is affected by the pH of the medium. The aqueous solubility (37°C) of dextromethorphan HBr at pH 1.2 and pH 6.8 were determined by measuring the drug concentration in its saturated solution (37°C) with the pH adjusted to 1.2 with 1.0 N HCl and 6.8 with 1.0 N NaOH. The aqueous solubility was 31.1 mg/ml at pH 1.2 and 28.4 mg/ml at pH 6.8. The lower water solubility at pH 6.8 is due to the lower degree of ionization of the drug at this pH. In theory, the drug release from a heterogeneous matrix is dependent on the equilibrium solubility of the drug in the dissolution medium (8). However, there have been studies in which the release of a drug having a pH dependent solubility was shown to be quite insensitive to differences in pH of the dissolution fluid (12). The pH-independent release was explained by the fact that the pH inside the matrix controls the solubility of the drug and, therefore, the release rate. The volume of the dissolution fluid penetrating into the matrix is small, so that the capacity of the penetrating fluid to buffer a concentrated solution of the drug is exceeded. Thus, the pH inside the

matrix remains virtually constant and solubility of the drug in the fluid (inside the matrix) is independent of the pH of the external dissolution medium. Although the water solubility of dextromethorphan HBr at pH 1.2 is about 10% higher than that at pH 6.8, the pH-dependent solubility of the drug is unlikely to be the major contributing factor for the pH sensitive release characteristics of the silicone elastomer matrix. As proposed previously, the penetrating of the dissolution medium into the matrix and the diffusion of the drug through the hydrated silica phase are the major controlling steps in drug release from the silicone elastomer matrix. It may be possible that both these processes are affected by the pH of the medium. From these results, it may be proposed that both processes take place at a faster rate at a lower pH (1.2).

CONCLUSION

This study has demonstrated that the silicone elastomer latex can be used to prepare matrix tablets for controlled release of a water soluble ingredient by a wet granulation method. Owing to the high liquid adsorption capacity of fumed silica, granulations containing a high percent of silicone elastomer can be prepared in a single granulation procedure. The release rate of the active ingredient from the matrix is affected by the formulation of the tablets, the processing conditions as well as the drug release environment. The use of a higher silica and/or drug content in the formulation produced tablets with a faster drug release rate. A higher drying temperature for the granules and a higher pH (6.8) dissolution medium resulted in a slower drug release rate. The retardant effect of

the matrix to drug release appears to be related to the rate of water penetration into the matrix and the diffusion rate of the dissolved drug through the hydrated silica regions of the matrix.

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REFERENCES

1. R.K. Chang, C.H. Hsiao, and J.R. Robinson, Pharm. Technol., 11(3), 56 (1987).

2. Y. Kawashima, H. Takeuchi, T. Handa, W.J. Thiele, D.P. Deen, and J.W. McGinity, "Aqueous-Based Coatings in Matrix Tablet Formulations", in "Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms", J.W. McGinity eds., Marcel Dekker, Inc. New York, 1989.

3. L.C. Li and G.E. Peck, Drug Dev. Ind. Pharm., 15(4), 499 (1989).

4. V.L. Anderson and R.A. McLean, "Design of Experiments, a Realistic Approach", Marcel Dekker, Inc. New York, 1974.

5. S. Bolton, "Pharmaceutical Statistics, Practical and Clinical Applications", 2nd Ed., Marcel Dekker, Inc. New York, 1990.

6. G. Stetsko, G.S. Banker, and G.E. Peck, Pharm. Technol., 7(11), 50 (1983).

7. G.H. Klinger, E.S. Ghali, S.C. Porter, and J.B. Schwartz, Drug Dev. Ind. Pharm., 16(9), 1473 (1990).

8. T. Higuchi, J. Pharm. Sci., 52, 1145 (1963).

9. H. Fessi, J.P. Marty, F. Puisseux, and J.T. Carstensen, J. Pharm. Sci., 71, 749 (1982).

10. F.W. Goodhart, M.R. Harris, K.S. Murthy, and R.U. Nesbitt, Pharm.Technol., 8(4), 64 (1984).

11. J.C. Saam, D. G. Ravier, and M. Baile, Rubber Chemistry and Technology, 54, 976 (1981).

12. S.S. Jambhekar and J. Cobby, J. Pharm. Sci., 74, 991 (1985).