

# Epoxy Resin Beads as a Pharmaceutical Dosage Form II: Dissolution Studies of Epoxy-Amine Beads and Release of Drug

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**Abstract** □ The dissolution behavior of two different resins obtained by condensing epoxy compound with 2-amino-2-ethyl-1,3-propandiol (amine) in various acidic buffer solutions has been studied. The concentration of amine in these resins and pH as well as ionic strength of the buffer solutions were observed to have a significant effect on the dissolution of the resins. Chloramphenicol used as embedded drug model had no effect in lower concentrations on the dissolution behavior of these bead formulations. However, at higher concentrations, it retarded dissolution of the resins and hence release of drug.

**Keyphrases** □ Epoxy resin beads—dosage form □ Apparatus—dissolution studies □ 2-Amino-2-ethyl-1,3-propandiol-epoxy beads, dissolution behavior

In a previous report (1) the method of preparation of the epoxy resins in bulk and bead forms and the possibilities for their use in pharmaceutical technology has been discussed. In selecting the polymeric materials for application as protective or enteric coating or as sustained-release matrix, their dissolution rates *in vitro* in different buffer solutions, besides toxicity, *etc.*, have to be examined. The effects of various additives to the polymers on their dissolution rates may serve as an important guide for further formulations of such polymers during the early stages of development. The present investigation was designed to determine the influence of the following major factors on the *in vitro* dissolution rate of basic resin beads obtained by condensing epoxy compound with 2-amino-2-ethyl-1,3-propandiol (amine) (1):

1. Concentrations of 2-amino-2-ethyl-1,3-propandiol in the beads.
2. pH and ionic strength of the buffer solutions.
3. Concentrations of chloramphenicol USP in the beads.

## EXPERIMENTAL

**Apparatus**—The dissolution rate of the beads was determined in a modified USP tablet disintegration apparatus consisting of six glass cylinders (each 20 cm. long and having 3-cm. diameter) which could be closed at both ends with polyethylene caps as illustrated in Fig. 1. The tubes filled with buffer solutions were placed on the platform in a water bath and maintained at  $37 \pm 0.5^\circ$ . This platform was raised and lowered 30 times per minute through a height of 5 to 6 cm.

**Beads Used**—The materials and the method of preparation have already been reported (1). The composition of the beads used in this study was as follows: Preparation 1: epoxy compound 67.3%, 2-amino-2-ethyl-1,3-propandiol 32.7% and Preparation 2: epoxy compound 72.0%, 2-amino-2-ethyl-1,3-propandiol 28.0%. Beads of Preparations 1 and 2 in presence of 20, 35, and 50% chloramphenicol USP are designated as 1.1, 1.2, 1.3., and 2.1, 2.2., 2.3., respectively.

**Dissolution Buffers**—For studying the dissolution of these beads, buffer solutions of pH 1.2 (HCl/NaCl), 2.2, and 3.2 (phosphates), respectively, each with ionic strengths 0.1, 0.2, and 0.3 were used

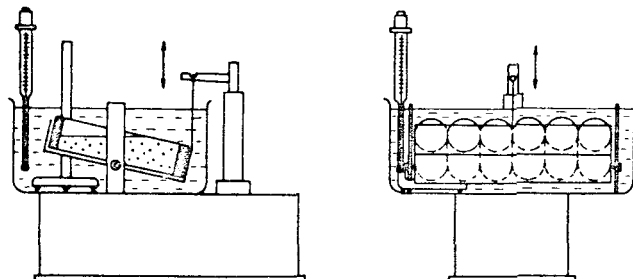


Figure 1—Apparatus of dissolution studies.

as eluting liquids. The ionic strength, if required, was adjusted by addition of extra sodium chloride. All the substances used were of analytical quality. To calculate the necessary quantities of buffer substances, the following equations were used (2).

$$\text{pH} = \text{pK}_n + \log \frac{(\text{salt})}{(\text{acid})} - \frac{A(2n-1)\sqrt{\mu}}{1 + \sqrt{\mu}} \quad (\text{Eq. 1})$$

$$\mu = \frac{1}{2} \sum C_i Z_i^2 \quad (\text{Eq. 2})$$

where all the symbols have the same meaning as in Reference 2.

**Dissolution Procedure**—One bead of known weight and diameter was exposed to 50 ml. of buffer solution. At time intervals selected according to the resin and the buffer solution used, the amount of the dissolved resin was determined spectrophotometrically as well as gravimetrically. As no significant difference was observed in the results obtained by these two methods, the gravimetric method was adopted for general use due to its convenience. After drying, the diameter of the undissolved bead was also determined with a micro-gauge of up to  $1\text{-}\mu$  accuracy. This procedure was repeated several times by putting the same bead in 50 ml. of fresh buffer solution until the bead size was reasonably small.

**Assay Procedure for Chloramphenicol from These Beads**—As the maximum UV absorption of chloramphenicol and the resins (1) in acidic buffer solutions were almost on the same wavelength ( $277\text{--}278\text{ m}\mu$ ), the spectrophotometric values were determined at two different wavelengths. The amounts of chloramphenicol and the resins dissolved were calculated from these readings using simultaneous equations.

## RESULTS AND DISCUSSION

Hixon and Crowell (3) derived a law for the dissolution rate of a particle using the formula of Noyes and Whitney (4) in which the surface area and concentration were allowed to change in the solution with time. For practical purposes the equation was further simplified and the surface area was replaced by weight under the assumption that density and volume shape factor remained constant during the dissolution of the particle. This meant that the dissolution took place perpendicular to all the planes and, therefore, during the dissolution process shape remained unchanged. The equation (3) was written as:

$$W_0^{1/3} - W^{1/3} = k \cdot a \cdot t \quad (\text{Eq. 3})$$

where,

- $W_0$  = initial weight of the particle
- $W$  = weight of the particle at time  $t$
- $k$  = dissolution rate constant of the substance
- $a$  = surface weight factor
- $t$  = time

**Table I**—Dissolution Equations of Epoxy-Amine Beads<sup>a</sup>

Prep. No.	Dissolution Buffers $\mu$	pH		
		1.2	2.2	3.2
1	0.1	$y = 3.8994 - 0.3151 x(3.7925)$ $y = 3.9263 - 0.2944 x(3.8338)$	$y = 3.3519 - 0.1372 x(3.3217)$ $y = 3.2784 - 0.1410 x(3.2560)$	$y = 3.9996 - 0.0139 x(3.8809)$ $y = 4.0306 - 0.0140 x(3.9485)$
	0.2	$y = 3.4878 - 0.2583 x(3.4186)$ $y = 4.2030 - 0.2421 x(4.1631)$	$y = 3.1277 - 0.1574 x(3.0917)$ $y = 2.9038 - 0.1564 x(2.9040)$	$y = 3.1761 - 0.02745 x(3.1312)$ $y = 3.3189 - 0.02591 x(3.2970)$
	0.3	$y = 3.9482 - 0.1581 x(3.9465)$ $y = 3.7664 - 0.1598 x(3.7301)$	$y = 3.3275 - 0.1882 x(3.3982)$ $y = 2.8452 - 0.2058 x(2.7655)$	$y = 3.4325 - 0.03634 x(3.3548)$ $y = 3.3428 - 0.03864 x(3.1055)$
2	0.1	$y = 4.6526 - 0.2550 x(4.5830)$ $y = 4.8339 - 0.2444 x(4.7666)$	$y = 3.4354 - 0.09646 x(3.4148)$ $y = 3.0699 - 0.1136 x(3.0384)$	$y = \text{No dissolution}$
	0.2	$y = 3.1615 - 0.2395 x(3.1144)$ $y = 3.5275 - 0.2286 x(3.5180)$	$y = 3.2770 - 0.1246 x(3.1302)$ $y = 2.7289 - 0.1377 x(2.5484)$	$y = 3.3160 - 0.01324 x(3.2875)$ $y = 3.0292 - 0.01477 x(2.9653)$
	0.3	$y = 3.4365 - 0.1786 x(3.3186)$ $y = 3.0967 - 0.2022 x(3.0474)$	$y = 3.8424 - 0.1508 x(3.6332)$ $y = 3.3310 - 0.1664 x(3.0835)$	$y = 3.1760 - 0.02362 x(3.0293)$ $y = 2.9033 - 0.02407 x(2.7655)$

<sup>a</sup> In above equations:  $y$  = cube root of weight (mg.) at time  $x$ ;  $x$  = time in minutes;  $\mu$  = ionic strength; ( ) = experimental cube root of weight at time zero.

Since  $a$  and  $k$  of the Eq. 3 are constant for a substance of a particular shape, the above equation may be written as:

$$W_0^{1/3} - W^{1/3} = -K \cdot t \quad (\text{Eq. 4})$$

Hence, if the cube root of the residual weight is plotted against time, a straight line should result having slope  $-K$ . This  $-K$  can be an adequate means of comparing the various factors effecting the dissolution of the particle.

In this study, Eq. 4 was used for comparing the dissolution behavior of epoxy-amine beads in various buffer solutions. To control whether the shape of the bead remained spherical or not from the beginning to the end of the dissolution study, the multiple regression (5) was used. The volume of the spherical bead was obtained from the geometrical mean diameter measured at each interval. Since no significant change in the ratio of  $w/v$  of the beads at dif-

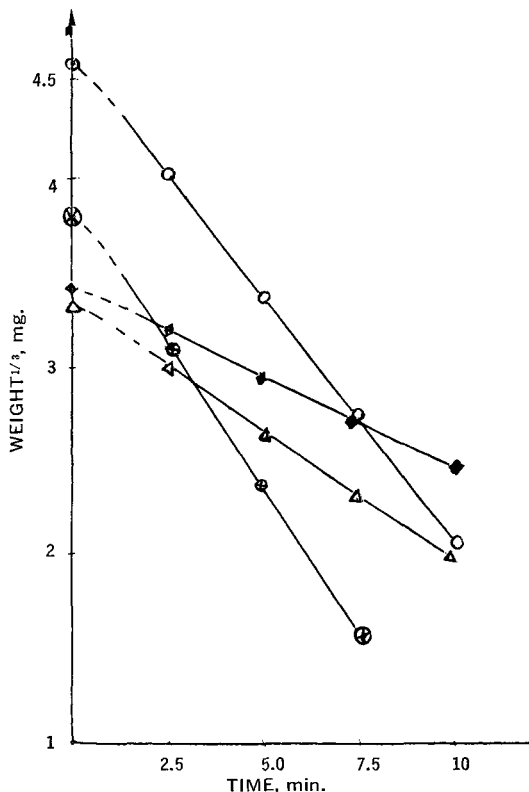
ferent times could be observed during the dissolution process, it was concluded that the bead maintained its shape and density.

The best fitting equations for the regression of the cube root of weight against time were calculated using orthogonal polynomials (6). For these calculations, the zero-time data have not been included. The regression coefficients of higher order were not significant. The linear equations obtained for the bead formulations in different buffer solutions are shown in Table I.

It may be observed from Table I that the cube roots of the weights at time extrapolated to time zero were lower than the values determined before the experiment. These differences were always significant. Therefore, it must be concluded that at the beginning of the dissolution process a curvature exists before the data obey the Hixon-Crowell law. Figure 2 further illustrates this for the beads of Preparations 1 and 2 in buffer solutions of pH 1.2, and 2.2, having ionic strength 0.1. This curvature or the slower dissolution of the beads at the beginning may be due to traces of silicone oil left on the surfaces after preparation (1) which hindered the wetting of the beads for the first few seconds.

**Influence of 2-Amino-2-ethyl-1,3-Propandiol Content in Epoxy Beads and pH and Ionic Strengths of Buffer Solutions on the Dissolution Behavior**—To ascertain the influences of the titled factors on the dissolution rates of the epoxy-amine beads, an analysis of variance (5) has been calculated (Table II).

From Table II, it may be concluded that the two preparations containing different amounts of amine behaved differently from each other if the ionic strength and pH of the buffer solutions were changed. Preparation 1 containing a higher amount of amine dissolved in all the buffer solutions more quickly than Preparation 2. Hence, the increase of the amine content in the resin enhances the dissolution rate in the buffer solutions.



**Figure 2**—Dissolution rates of epoxy-amine beads in various buffer solutions of 0.1 ionic strength and varying pH. Key: Preparation 1:  $\odot$ , pH = 1.2;  $\Delta$ , pH = 2.2; preparation 2:  $\circ$ , pH = 1.2;  $\blacklozenge$ , pH = 2.2.

**Table II**—Influence of Amine Content, pH, and Ionic Strengths of Buffer Solution on Epoxy-Amine Beads<sup>a</sup>

Source	Sum of Squares	Degree of Freedom	Significance Level, F test
Factor A	0.00342801	1	<1%
Factor B	0.00052085	2	≤5%
Factor C	0.27222984	2	<1%
Interactions A·C	0.00105405	2	≤1%
Interactions A·B	0.00078661	2	<5% >1%
Interactions B·C	0.02861400	4	<1%
Interactions A·B·C	0.00274454	4	<1%
Residual	0.00124184	18	—
Total	0.31061974	35	

<sup>a</sup> Residual mean square = 0.00006899, A = amine content in preparation; B = ionic strength of buffer solution ( $\mu$ ); C = pH of the buffer solution.

**Table III**—Effect of pH and Ionic Strength of Buffer Solutions on the Dissolution Rate of Preparation 1<sup>a</sup>

Source	Sum of Squares	Degree of Freedom	Significance Level, <i>F</i> test
Factor <i>B</i>			
Linear	0.0013830974	1	<1%
Quadratic	0.0000300487	1	>5%
Factor <i>C</i>			
Linear	0.1347302592	1	<1%
Quadratic	0.0041766060	1	<1%
Interactions			
<i>B</i> · <i>C</i>	0.0143380178	1	<1%
<i>B</i> · <i>C</i> <sup>2</sup>	0.0094438403	1	<1%
<i>B</i> <sup>2</sup> · <i>C</i>	0.0002028854	1	>5%
<i>B</i> <sup>2</sup> · <i>C</i> <sup>2</sup>	0.0003846613	1	<5% >1%
Residual	0.0005135189	9	—
Total	0.1652029350	17	

<sup>a</sup> Residual mean square = 0.0000570576; and *B* + *C* = same as Table II.

But since the two- as well as three-factor interactions are also highly significant, the influence of ionic strength and pH of the buffer solutions on the dissolution rate are systematically different for the two bead preparations. Therefore, Preparations 1 and 2 were handled separately in the subsequent calculations, Tables III and IV, respectively, at the quantitative analysis of variance.

From Table III, it may be observed that the linear term of the main effect of ionic strengths and linear and quadratic terms of the effects of pH are highly significant. This indicates that a simple linear relationship exists between ionic strength and dissolution rate, whereas equations of higher orders will be necessary for an adequate representation of the dependency of dissolution rate and pH. On the other hand, the significant interaction terms show that the effects of one factor are not independent of the levels of the other factor. The interaction *B*<sup>2</sup>·*C*<sup>2</sup> term which is only significant at a *p* of 0.05 indicates a tendency of nonlinearity of ionic strengths effects at certain pH levels.

The results are shown in Figures 3 and 4 for the effect of ionic strengths and pH on the dissolution rate, respectively. The change in quantitative and qualitative behavior of the dissolution rate can be seen from these.

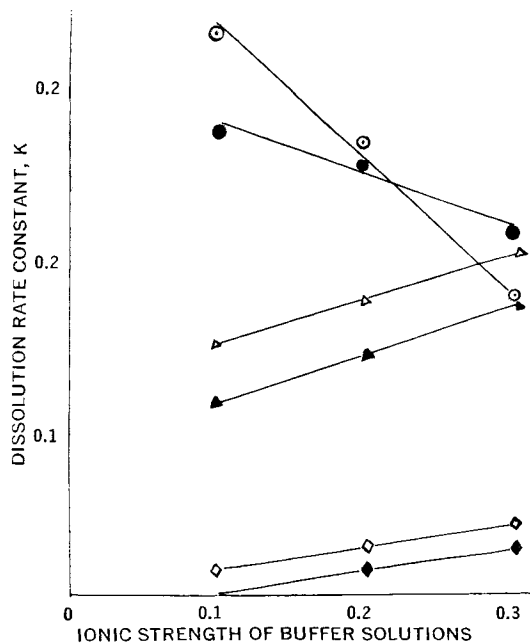
From Table IV, it may be seen that the linear and quadratic term of the effect of pH are highly significant and hence the equations of higher orders will be required as for Preparation 1 to have an adequate representation of the dependency of dissolution rate on pH of buffer solution. On the other hand, though ionic strength is not significant at any term, the significant interaction terms *B*·*C* and *B*<sup>2</sup>·*C*<sup>2</sup> show that the effects of one factor are not independent of the levels of the other factor.

These higher order interactions of the pH and ionic strength seen in Tables III and IV and reverse effect on the dissolution rate from

**Table IV**—Effect of pH and Ionic Strength of Buffer Solutions on the Dissolution Rate of Preparation 2<sup>a</sup>

Source	Sum of Squares	Degree of Freedom	Significance Level, <i>F</i> test
Factor <i>B</i>			
Linear	0.0000716385	1	>5%
Quadratic	0.0000888620	1	>5%
Factor <i>C</i>			
Linear	0.1334807227	1	<1%
Quadratic	0.0006265843	1	>1% <5%
Interactions			
<i>B</i> · <i>C</i>	0.0032497922	1	<1%
<i>B</i> · <i>C</i> <sup>2</sup>	0.0035580220	1	<1%
<i>B</i> <sup>2</sup> · <i>C</i>	0.0001242150	1	>5%
<i>B</i> <sup>2</sup> · <i>C</i> <sup>2</sup>	0.0000580683	1	>5%
Residual	0.0007281893	9	
Total	0.1419860943	17	

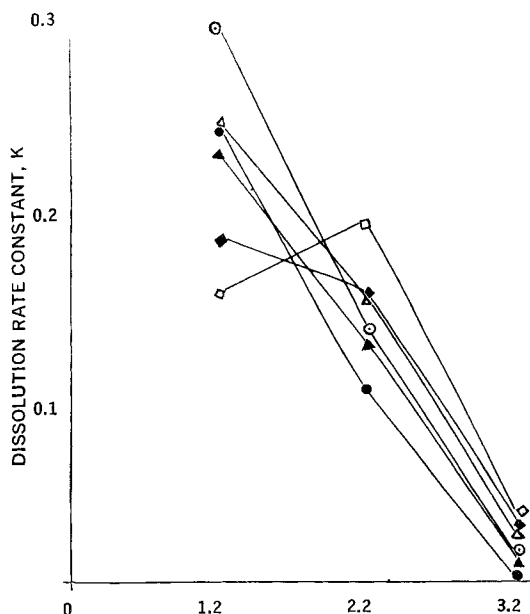
<sup>a</sup> Residual mean square = 0.0000809099; *B* and *C* = same as Table II.



**Figure 3**—Effect of ionic strengths of buffer solutions on dissolution rate of epoxy-amine beads. Key: Preparation 1: ○, pH 1.2; △, pH 2.2; ◇, pH 3.2; preparation 2: ●, pH 1.2; ▲, pH 2.2; ◆, pH 3.2.

pH 1.2 to pH 2.2 and 3.2 at different ionic strengths (Fig. 3) may be due to the different ionic species in the relative buffer solution of HCl/NaCl and phosphate, respectively. The buffer ions may have formed different salts with the amine groups of the resins so changing the solubility.

Furthermore the dissolution rate of the preparations decreases in the buffer solution of pH 1.2 with increasing ionic strengths and increases in the buffer solutions of pH 2.2 and 3.2. Thus it is possible to have the buffer solution of either pH 2.2 and pH 3.2 with higher ionic strength where dissolution rate may be faster for these epoxy-amine resins than in the buffer solution of pH 1.2 with same higher ionic strength. Such effect has been observed for the dissolution rate of Preparation 1 in the buffer solution of pH 2.2 with ionic strength 0.3 (Fig. 4).



**Figure 4**—Effect of pH of buffer solution on dissolution rate of epoxy-amine beads. Key: Preparation 1: ○, ionic strength 0.1; △, ionic strength 0.2; ◇, ionic strength 0.3; preparation 2: ●, ionic strength 0.1; ▲, ionic strength 0.2; ◆, ionic strength 0.3.

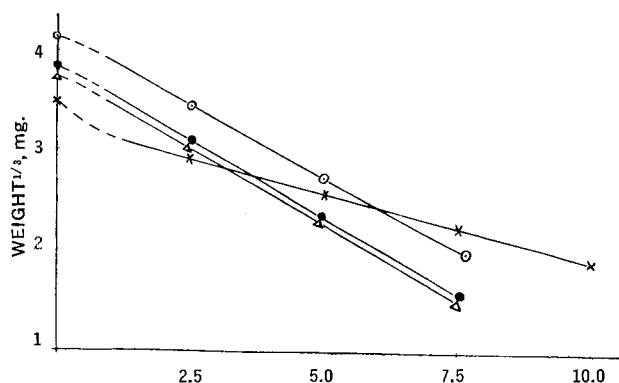
**Table V**—Dissolution Equations of Epoxy-Amine Beads Containing Chloramphenicol in Buffer Solution of pH = 1.2 and Ionic Strength = 0.1

Preparation No.	Equation	Weight <sup>1/3</sup> Beginning at
1.	$y^a = 3.8994 - 0.3151 x^b$	3.7925
	$y = 3.9263 - 0.2944 x$	3.8338
1.1.	$y = 4.1299 - 0.2806 x$	4.0916
	$y = 4.0719 - 0.2906 x$	3.9918
1.2.	$y = 3.9224 - 0.3269 x$	3.7157
	$y = 4.8307 - 0.2822 x$	4.7874
1.3.	$y = 3.2592 - 0.1278 x$	3.5263
	$y = 3.5259 - 0.1779 x$	3.6508
2.	$y = 4.6526 - 0.2550 x$	4.5830
2.1.	$y = 4.6509 - 0.2829 x$	4.5586
	$y = 3.7627 - 0.2786 x$	3.7121
2.2.	No dissolution	
2.3.	No dissolution	

<sup>a</sup>  $y$  = cube root of weight at Time  $x$ . <sup>b</sup>  $x$  = time in minutes.

**Influence of Chloramphenicol Embedded in Epoxy-Amine Beads on Dissolution Rate**—As the epoxy-amine resins are soluble in acidic buffer solutions the release of the chloramphenicol embedded in these resins should be governed by the dissolution behavior of the latter. The homogeneity of the drug in resin beads and the process of the drug release from the beads were demonstrated by plotting the percent release of drug determined by spectrophotometric method against percent release of drug by gravimetric method. Straight lines passing through the origin were obtained. These show that the drug is uniformly distributed in the beads and that the release of the drug is completely due to dissolution of the carrier resins and not due to any other process.

As chloramphenicol is also soluble in the aqueous buffer solution, the cube root of the residual weight of bead against time should



**Figure 5**—Dissolution curves of epoxy-amine with chloramphenicol beads in buffer solution of pH 1.2 and ionic strength 0.1. Key: ●, Preparation 1; ○, preparation 1.1; △, preparation 1.2; ×, preparation 1.3.

characterize the dissolution behavior of the beads containing this drug. Leaving zero-time value aside, the statistical linearity of the cube root of the residual bead weight against time for the experimental data could be proved. The equations obtained for all the preparations are given in Table V and graphically represented in Fig. 5 for Preparation 1.

Preparation 1 showed no significant difference in dissolution rate in buffer solution (pH = 1.2 and ionic strength = 0.1) when up to 35% of chloramphenicol was incorporated in this resin (Fig. 5). However, inclusion of 50% chloramphenicol retarded the dissolution significantly. Preparation 2 with 20% chloramphenicol showed no significant difference in the dissolution rate compared to resin beads without drug. But the same resin with 35 and 50% chloramphenicol (Preparations 2.2. and 2.3.) did not dissolve anymore in that buffer solution.

This change of behavior of the resins in the presence of higher concentrations of chloramphenicol may be due to the formation of a net-work by the drug with the polymers which at this moment is not fully understood.

## SUMMARY

1. *In vitro* dissolution behavior of epoxy-amine resin beads and release of drug (chloramphenicol) embedded in these resins have been studied.
2. With the increase of concentration of 2-amino-2-ethyl-1,3-propanediol in the epoxy resins dissolution rate was enhanced.
3. pH and ionic strength of the buffer solution had significant effect on the dissolution of these resins.
4. Low concentrations of chloramphenicol in such resins did not have any effect on the dissolution rate of these, however, dissolution rate decreased as concentration of chloramphenicol increased.

## REFERENCES

- (1) S. C. Khanna and P. Speiser, in press.
- (2) A. N. Martin, "Physical Pharmacy," Lea & Febiger, Philadelphia, Pa., 1960, pp. 202, 264.
- (3) A. W. Hixon and J. H. Crowell, *Ind. Eng. Chem.*, **23**, 923 (1963).
- (4) A. Noyes and W. Whitney, *J. Am. Chem. Soc.*, **19**, 930 (1897).
- (5) O. L. Davies, "Statistical Methods in Research and Production," Oliver and Boyd, London, England 1961, p. 208.
- (6) O. L. Davies, "Design and Analysis of Industrial Experiment," 2nd ed., Oliver and Boyd, London, England 1961, p. 304.

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