

SOFT GELATIN CAPSULES III: AN ACCELERATED METHOD FOR EVALUATING  
THE DISSOLUTION STABILITY OF VARIOUS GEL FORMULATIONS

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ABSTRACT

A rapid method has been developed for the evaluation of the dissolution stability of various preformulation gels. Freshly prepared gel samples, after proper drying, were stored over a drying agent at above room temperatures. Periodically the dissolution of a stability sample in % dissolved for a given time was determined spectrophotometrically. In this manner, various preformulation gels could be evaluated in a relatively short time by changes in their dissolution rates from a slope values versus time plot for a given storage condition. Other applications of the method were in screening various plasticizers and additives for their solubility enhancing or protective properties.

INTRODUCTION

In the formulation of soft elastic gelatin capsules or other pharmaceutical products, especially for controlled release, an accelerated test for evaluating dissolution stability of

preformulation gels is useful. A method to study the relationship between various factors influencing the dissolution rate of capsule shell was reported<sup>1</sup>. The present investigation deals with the modification and application of this method for evaluating the dissolution stability of various gel formulations. The previously derived:

$$W = KSC_s t \quad (\text{Eq. 1})$$

$$W_t = A_t M / A_{\infty} \quad (\text{Eq. 2})$$

where  $W$  is the amount dissolved,  $t$  is the time,  $K$  is the solution rate constant,  $S$  is the surface area of the dissolving solid,  $C_s$  is the concentration of the dissolving solid at the liquid-solid interface,  $W_t$  is the amount dissolved at time  $t$ ,  $A_t$  is the absorbance at time  $t$ ,  $M$  is the initial weight of the solid and  $A_{\infty}$  is the absorbance when all the solid has dissolved may be used. Since  $M$  may be assigned a value of 100%, Equation 2 may be rewritten:

$$W_g = A_t \text{ 100\%} / A_{\infty} \quad (\text{Eq. 3})$$

$$W_g = m t \quad (\text{Eq. 4})$$

where  $W_g$  is the percent dissolved at time  $t$ . A plot of  $W_g$  versus time approximates a straight line with slope ( $m$ ) proportional to the solution rate constant provided there is little or no change in the dissolving surface area. Under these experimental conditions, the slope values may be used to measure the insolubilization zero order rate constant  $k$  of various gel formulations after storage at several temperatures by the use of the Arrhenius equation.

$$k = F \exp^{-E_a/RT} \quad (\text{Eq. 5})$$

where  $F$  is the frequency factor,  $E_a$  is the activation energy,  $R$  is the gas constant and  $T$  is in absolute temperature.

### EXPERIMENTAL

Materials - Gelatin USP type B, 150 Bloom grams from the same lot (Rousselot Corp.) was used. Glycerin USP, sorbitol solution USP, FD & C certified Blue No. 1 (Hilton-Davis Chemical Co.), and reagent grades of semicarbazide hydrochloride, L-histidine monohydrochloride and anhydrous calcium chloride were also used without further purification.

Preparation of Sample - Capsule shell disks measuring 0.3 cm thick and 2 cm in diameter were prepared containing approximately 0.3% on dry basis of FD & C Blue No. 1, 25% either glycerin or sorbitol, 47% gelatin, water and 1% additive, if any. These components were mixed in a filtering flask and the pressure of the system was reduced to deaerate the contents. The system was heated on a steam bath and swirled to mix and to obtain a flowable mass. The flask was then vented and the content was poured on a clean glass plate. The mass was leveled with a constant level blade. The gel was allowed to set for one hour and was stored at room temperature and 32% relative humidity ( $RT - 32\% RH$ ). Gel disks were cut the following day.

Dissolution Apparatus and Dissolution Medium - The USP XX dissolution apparatus 1 set at 50 rpm and simulated gastric fluid T.S. without pepsin at  $37 \pm 0.5^\circ\text{C}$  were used<sup>2</sup>.

Storage Conditions - Constant temperature chambers, desiccators

containing anhydrous calcium chloride and saturated aqueous solution of calcium chloride at room temperature (RT - 32% RH) were used<sup>3</sup>.

Dissolution Procedure - A gel disk was placed flatly on the bottom of the stainless steel dissolution basket, and secured with fine wires inserted crosswise immediately above the sample. The basket was assembled to the dissolution apparatus. Five hundred ml of simulated gastric fluid T.S. without pepsin was added to vessel and maintained at  $37^{\circ} \pm 0.5^{\circ}\text{C}$ . The basket was lowered to a predetermined level and dissolution was started by turning on the stirring motor at 50 rpm. At appropriate time intervals the absorbance of the dissolution medium was determined at 630 nm versus water in a suitable spectrophotometer. By the use of Equation 3 the percent of solid dissolved for a given time was calculated. Results are from two or more determinations.

#### RESULTS AND DISCUSSION

Figure 1 shows two typical plots of % dissolved versus time in minutes. One is from a gel made with glycerin and the other with sorbitol as plasticizer. As can be seen they are straight lines but do not go through the origin as predicted by Equation 4. Both have lag times. It seems the lag time depends on the nature of the dissolving solid and the degree of agitation. The faster the stirring rate the smaller the lag time. In any event the slopes may be used as a direct reflection of the relative dissolution rate of a given gel sample. Here, the slopes in % dissolved per minute for the gels made with glycerin and sorbitol

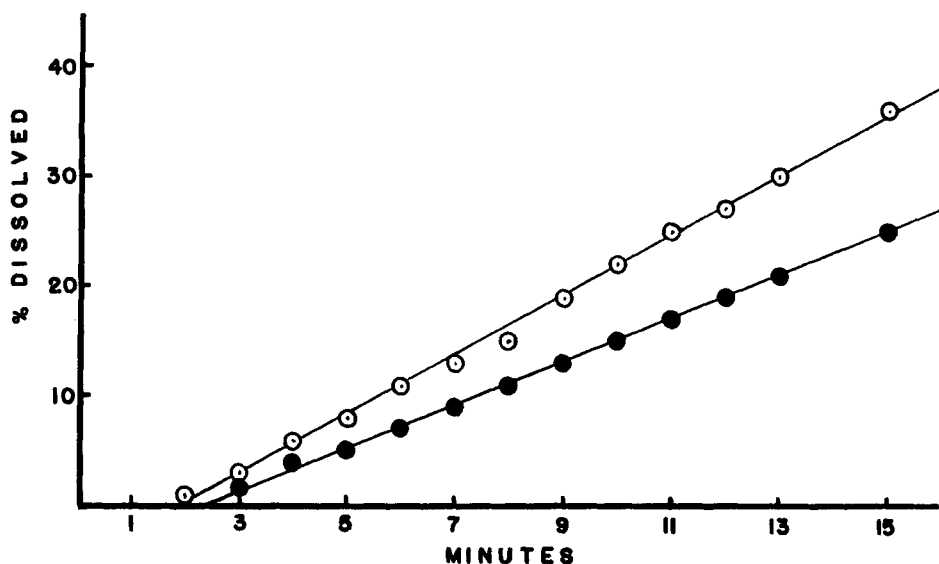


FIGURE 1

Two representative dissolution plots of gels made from glycerin (●) and sorbitol (○) as plasticizer with slope values of 1.89 ( $r^2 = 1.00$ ) and 2.67 ( $r^2 = 1.00$ ) respectively.

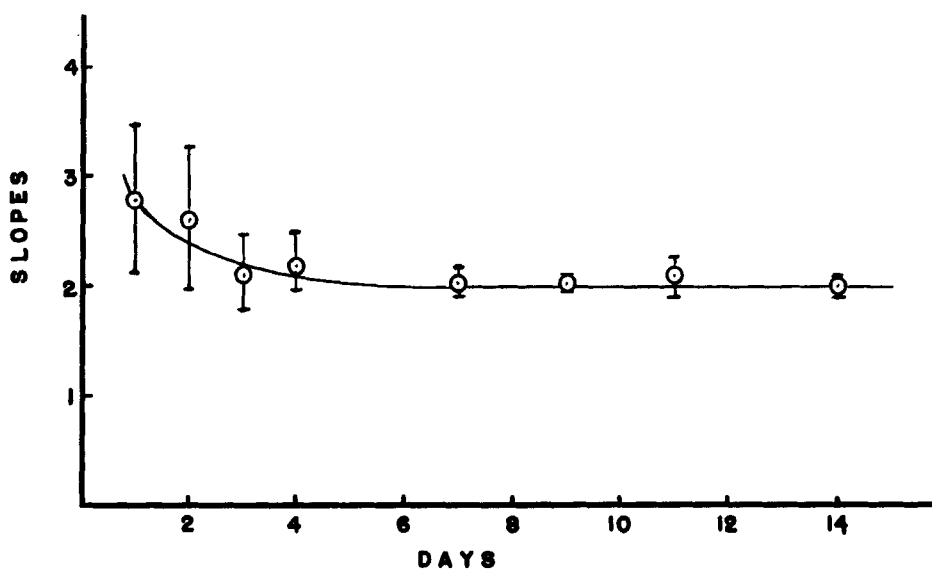


FIGURE 2

Glycerin gel dissolution slope values  $\pm$  standard deviation as a function of the time in days drying at RT - 32% RH after production.

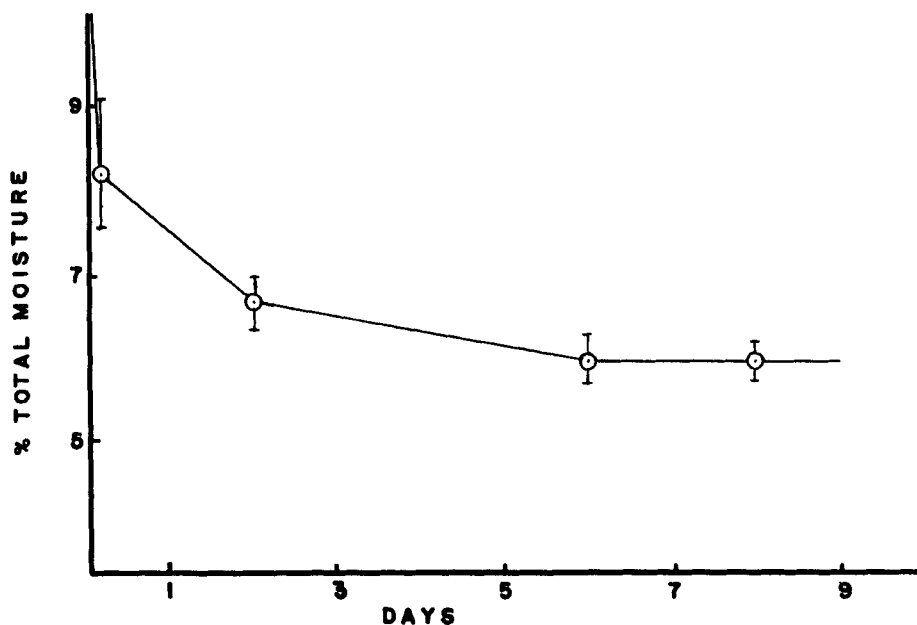


FIGURE 3

Percent total moisture  $\pm$  S.D. of a glycerin gel capsule drying at RT - 32% RH in days after production.

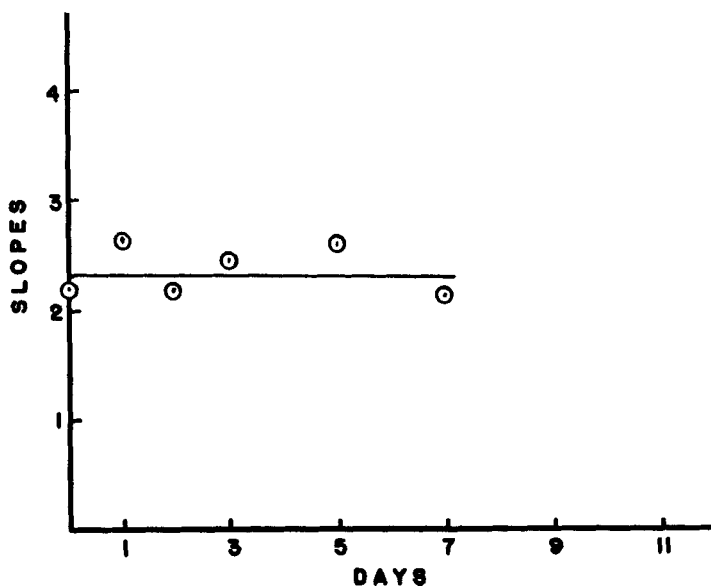


FIGURE 4

Dissolution slope values of a glycerin gel dried for 14 days at room temperature over anhydrous calcium chloride versus days of rehydration at RT - 32% RH. Linear regression slope = 0.01 ( $r^2 = 0.01$ ).

are 1.89 ( $r^2=1.00$ ) and 2.67 ( $r^2=1.00$ ) respectively. The coefficient of determinations indicate good correlations for the first 15 minutes of dissolution.

Since capsule shells are made from a water solution of plasticizer and gelatin it may be postulated that a freshly made one has a higher dissolution rate. Fig. 2 shows this is the case in a plot of slope values versus time in days after production of the shell and storing at RT - 32% RH. It appears a relatively constant rate is reached in about five to six days under the storage conditions. This equilibration time seems to parallel the drying process. Fig. 3 is a plot of the % total moisture as determined by the toluene method<sup>2</sup> of a capsule versus time in days after production of the capsule and drying at RT - 32% RH. Many factors affect the capsule drying but in this particular case the capsule is termed "dry" in six days. Even though the capsule is "dry" it still contains some water. For this matter even the raw material gelatin due to the manufacturing process has about 10% water<sup>4</sup>. This residual water creates melting problems in higher temperature tests. For this reason the capsule residual water is removed in the accelerated test by storing it over anhydrous calcium chloride. In this manner the capsule may be heated to 60°C without melting or becoming sticky. Fig. 4 shows the results for two-week storage at room temperature over anhydrous calcium chloride then stored at RT - 32% RH for possible rehydration rate effect has on glycerin gel. Linear regression of the data yielded a slope value of -0.009 with a correlation

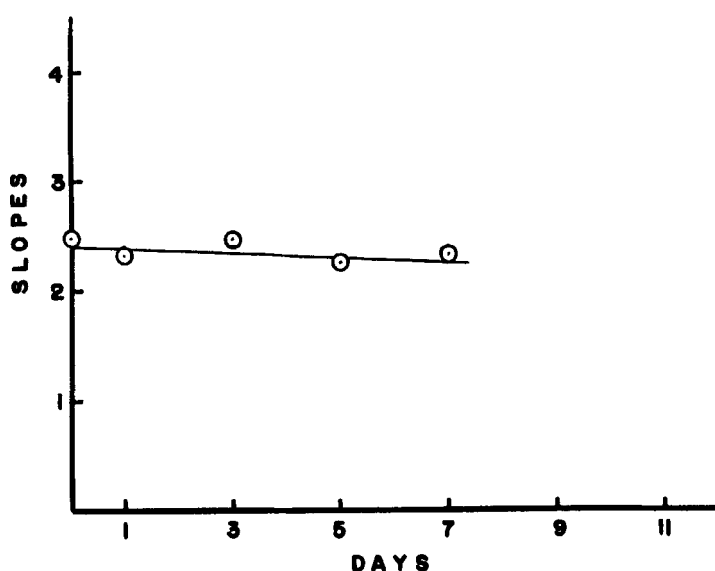


FIGURE 5

Dissolution slope values of a sorbitol gel stored for 14 days at 60°C over anhydrous calcium chloride versus days of rehydration at RT - 32% RH. Linear regression slope = -0.02 ( $r^2 = 0.37$ ).

coefficient of  $r^2 = 0.009$  indicating little or no change in dissolution rate when plotted versus time in days at RT - 32% RH.

Apparently the storage over anhydrous calcium chloride is not detrimental to the sample nor is there a rehydration problem.

Fig. 5 shows the results for two-week storage at 60°C over anhydrous calcium chloride then stored at RT - 32% RH for possible rehydration rate effect has on a sorbitol gel. Surprisingly the sorbitol gel appears to be stable under this condition as gleaned from a comparison to the initial value. There is also little or no rehydration rate problems as evidenced by the relatively flat plot.



TABLE I

Mean glycerin gel dissolution slope value  $\pm$  standard deviation for samples stored in days in air over anhydrous calcium chloride at 24, 40, 50 and 60  $\pm$  0.5°C.

Storage Time Days	60°C	50°C	40°C	24°C
0.0	2.69 $\pm$ 0.22	1.79 $\pm$ 0.99	2.61 $\pm$ 0.06	2.69 $\pm$ 0.22
0.3	1.92 $\pm$ 0.68	-	-	-
1.0	1.68 $\pm$ 0.56	1.63 $\pm$ 0.74	1.08 $\pm$ 0.75	-
1.3	-	-	2.24 $\pm$ 0.26	-
2.0	0.70 $\pm$ 0.32	0.51 $\pm$ 0.26	1.77 $\pm$ 1.21	-
3.0	0.15 $\pm$ 0.04	0.16 $\pm$ 0.05	1.50 $\pm$ 1.08	-
7.0	-	-	1.04 $\pm$ 0.85	-
21	-	-	-	1.83 $\pm$ 0.78
41	-	-	-	0.18 $\pm$ 0.30
44	-	-	-	0.34 $\pm$ 0.12
k	-0.795	-0.601	-0.166	-0.058
r <sup>2</sup>	0.957	0.919	0.427	0.968

Table I gives the mean glycerin gel dissolution slope values and their standard deviations for samples stored in air over anhydrous calcium chloride at 24, 40, 50 and 60  $\pm$  0.5°C. Linear regression of the data yielded the glycerin gel insolubilization rate constant k and their correlation coefficient ( $r^2$ ). Figure 6 shows the results in an Arrhenius plot. Linear regression

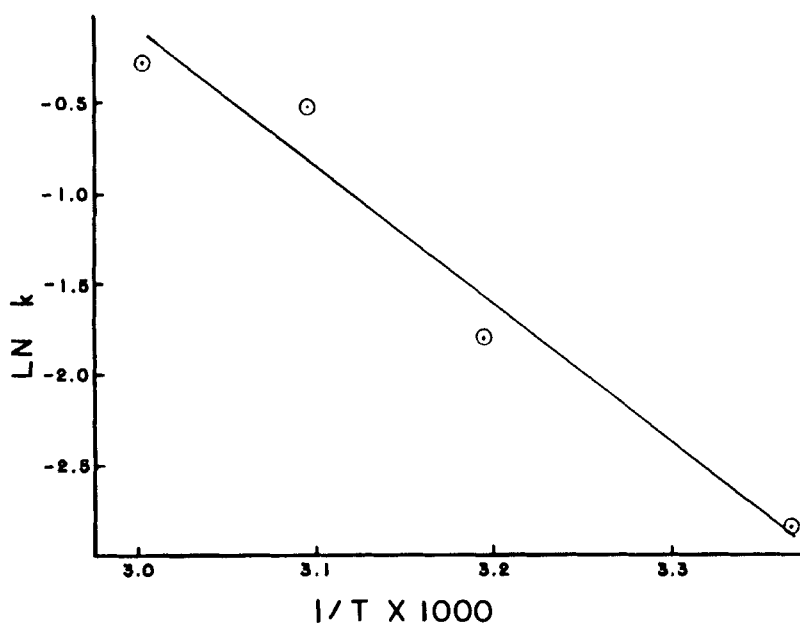


FIGURE 6

Arrhenius plot showing the effect of temperature on the glycerin gel insolubilization rate constant. Linear regression slope = -7639 ( $r^2 = 0.963$ ).

yields a straight line with a -7639 slope value and a 0.963 correlation coefficient. By use of the Arrhenius equation the calculated activation energy of 15.2 kcal/mole is in line with the value of 15.1 kcal/mole from earlier dissolution study<sup>1</sup>. At this activation energy level the relative insolubilization rate would be about sixteen times faster for a glycerin gel sample stored at 60°C as compared to one stored at 24°C.

In repeating the experiment in the absence of air by the 60°C storage test, there was no detectable insolubilization of the glycerin gel samples. However, glycerin gel samples when stored in low humidity (over anhydrous calcium chloride) air at  $60 \pm 0.5^\circ\text{C}$

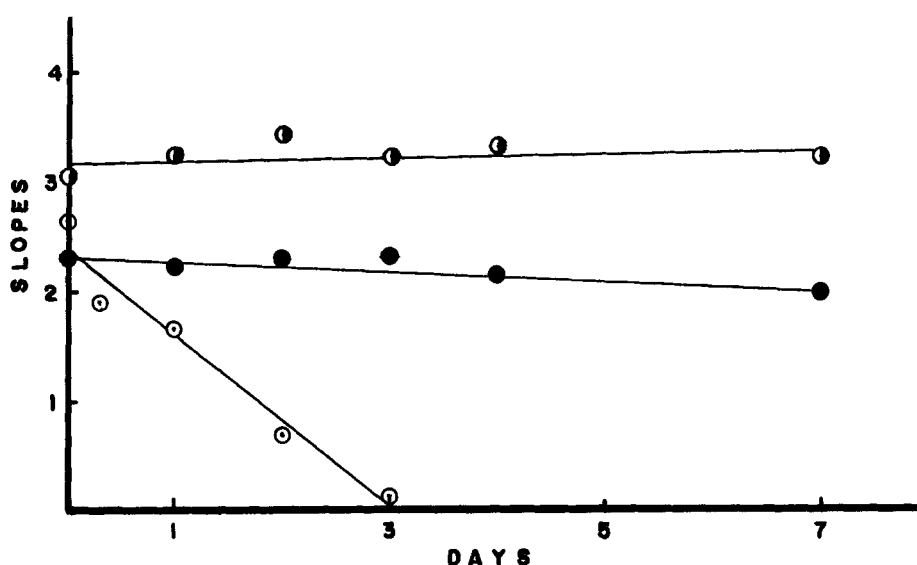


FIGURE 7

Dissolution slope values of a glycerin gel as control (○) and with 1% semicarbazide hydrochloride (◐) and 1% L-histidine hydrochloride (●) added as a function of storage time in days at 60°C over anhydrous calcium chloride. Linear regressions yield slopes of  $-0.795$  ( $r^2 = 0.957$ ),  $0.012$  ( $r^2 = 0.053$ ) and  $-0.044$  ( $r^2 = 0.754$ ) respectively.

become more insoluble with time except the ones containing small amounts of additives such as shown in Figure 7 (semicarbazide or L-histidine). Also it was observed that the addition of 0.5% ferric chloride accelerated the glycerin gel insolubilization rate; the addition of 1% citric acid slowed the rate. These accelerated test results seem to support an oxidative mechanism of glycerin gel insolubilization. Perhaps, the drying rate and/or the combination of higher temperature and oxygen from the air caused oxidation of glycerin on the surface of the gel to glyceraldehyde which in turn reacts with gelatin to form a layer of relatively insoluble

polymer, a pellicle. Marks et al<sup>5</sup> investigated the phenomenon of gelatin insolubility by heating in a closed system at 75°C for one week observed that the rate of insolubilization depends on the gelatin fraction obtained from the manufacturing process and the moisture content of the gelatin. Certain fractions and higher moisture content gave faster rates.

### SUMMARY AND CONCLUSIONS

An accelerated method is described for evaluating the dissolution stability of various preformulation gels. In order to circumvent possible melting problems at above room temperature tests the samples are stored over anhydrous calcium chloride. The method entails the modification and application of a formerly reported use of the USP dissolution apparatus 1. The percent of the solid dissolved for a given time is calculated from spectrophotometric readings of the dissolution medium. The linearity of the Arrhenius plot (24 to 60°C) facilitates accelerated temperature test as a convenient method to evaluate gel formulations and to study factors governing capsule shell dissolution behavior.

### ACKNOWLEDGMENTS

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