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DISSOLUTION CHARACTERISTICS OF CAPSULE SHELLS AND DRUG RELEASE FROM COMMERCIAL TETRACYCLINE-HCl CAPSULES

A. El-Yazigi*
Department of Pharmaceutics, College of Pharmacy,
University of Riyadh, Riyadh, Saudi Arabia.

*Current Address: Cancer & Radiation Biology Research, King Faisal Specialist Hospital and Research Centre, PO Box 3354, Riyadh, Saudi Arabia.

ABSTRACT

The dissolution characteristics of the gelatin shells of four brands of tetracycline-HCl capsules were examined by measuring the shell rupture time (t_r) in a modified version of two-blade stirrer apparatus under various stirrer depth, ionic strength, and pH conditions. The dissolution rate of tetracycline-HCl from these capsules was also determined using the U.S.P. XIX dissolution apparatus. While no significant effect of stirrer depth on t_r was found, increasing the basket-stirrer distance from the bottom of the flask from 0.2 to 2 cm was found to increase the dissolution rate of tetracycline-HCl from capsules significantly ($p < 0.001$). As the ionic strength was increased, the dissolution rates of both gelatin shell and tetracycline-HCl content were increased, however, increasing the ionic strength from 0.6 to 1.5 failed to produce any further increase in

t_r. The pH of the dissolution fluid significantly ($p < 0.01$) influenced the dissolution rate of the capsule shell and t_r was longest at pH = 4. A linear, inverse relationship between pH and tetracycline-HCl dissolution rate constant (k_s) was obtained. While a good correlation between t_r and k_s was obtained under certain conditions, capsule shell and tetracycline-HCl content showed different dissolution behaviour under other conditions. It is expected therefore, that under the latter conditions capsule shells had their maximum effect on drug release from the capsules studied.

INTRODUCTION

Although the dissolution rate of drugs from capsules has been adequately studied (1-5), a little or no work has been reported on the dissolution rate of the capsule shell in relation to drug release from capsules under various conditions. A knowledge of this relationship may assist in understanding the influence of the gelatin shell on the drug release from capsules, and enable drug formulators to select the appropriate type of gelatin.

The present report describes a method for characterization of the dissolution of the capsule shell, and examines the dissolution rate of tetracycline-HCl from four capsule products under various stirrer depth, ionic strength, and pH conditions. The relationship between the capsule shell dissolution rate and the release of tetracycline-HCl from these formulations was also addressed.

METHODOLOGY

Materials

The products studied, capsules I, II, III, and IV, each containing 250 mg of tetracycline-HCl, were

purchased commercially. Tetracycline-HCl was used as obtained.

Methods

Determination of the Shell Rupture Time

The dissolution rate of the gelatin shell was determined by measuring the shell rupture time in a modified version of a two-blade stirrer dissolution apparatus (6). The capsule was placed in the vessel and a round, 10-mesh, stainless steel screen was anchored horizontally on the vessel wall so the distance between the vessel bottom and the screen was 1 cm. After stirring was initiated, the dissolution fluid was poured in and time commenced. This approach was used to prevent the capsule from floating when the fluid is added, and to limit the volume into which the capsule could move. The rupture time was determined visually at 25 rpm stirring rate. The stirrer was positioned 2 mm, 2 cm, or 7 cm from the center of the screen. Distilled water, HCl (pH = 1), acetate buffer (pH = 4; 0.1 M), and phosphate buffer (pH = 7; 0.1 M) were used as dissolution media. The effect of ionic strength (μ) was studied using aqueous solutions of sodium chloride at concentrations equivalent to $\mu = 0.25$, $\mu = 0.6$, and $\mu = 1.5$.

Determination of Dissolution Rate of Tetracycline-HCl from Capsules

The dissolution rate of tetracycline-HCl from the capsule used was determined using the U.S.P. XIX dissolution apparatus under the same dissolution conditions mentioned above. A stirring speed of 50 rpm was used. This apparatus could not be used for determination of the shell rupture time because the capsule can not be seen through the screen of the rotating basket.

Determination of the Dissolution Rate Constant

The data were well described by the following equation (7):

$$\ln \Delta A = -k_s(t-t_o) + \ln(A_\infty - A_o)(1-e^{-k_s \Delta t}) \quad \text{for } t \geq t_o$$

where ΔA is the successive increment in cumulative percent dissolved during the time interval Δt, A_∞, A_o are the cumulative percent dissolved at time (t) = ∞ and t = 0 respectively, k_s is a first-order rate constant for dissolution, and t_o is the time at which ΔA commences to decrease exponentially with time. The dissolution rate constant (k_s) was determined by plotting ln ΔA against ($t_{mid}-t_o$) where t_{mid} is the time at mid-interval using least square regression analysis. The slope of the resulting line is equal to $-k_s$. The values of k_s reflect mainly the dissolution rate of tetracycline-HCl from capsules since at $t = t_o$ most of the gelatin shell would be dissolved.

RESULTS AND DISCUSSION

A direct determination of dissolution rate of the gelatin capsule shell is practically infeasible, therefore, characterization of the shell dissolution behaviour is frequently achieved by incorporation of a dye into the gelatin during capsule shell preparation, and measuring the color intensity of the dissolution fluid as a function of time. Such an approach can not be employed for most commercial capsules since the shells of these formulations are not adequately colored to produce solutions of measurable color intensity without interference of the drug content dissolving in the medium. For such products, the determination of the shell rupture time as described here may represent a suitable tool to characterize the dissolution behaviour of the capsule shell.

The study of the relationship between the dissolution rate of the capsule shell and that of drug content should ideally be carried out using the same apparatus, however, since the determination of the shell rupture time can not be carried out in the U.S.P. XIX dissolution apparatus, a modification had to be devised to accommodate for that. This modification consisted of replacing the rotating basket with a two-blade stirrer and a capsule compartment which allows one to observe the dissolution process of both capsule shell and content, and determine t_r visually.

Dissolution Rate as a Function of Stirrer Depth

Table 1 lists the dissolution parameters obtained for the capsules tested at different stirrer depths. No significant differences in t_r and k_s were found as stirrer depth was changed, however, as shown in Table 1 the values of dissolution rate constant (k_s) at 2 mm were somewhat higher than those obtained at 2 or 7 cm basket depth. Evaluation of the effect of basket depth, based on the analysis of variance of the percent labeled content dissolved at 15 minutes (A_{15}), revealed that the basket depth significantly ($P < 0.01$) influenced the rate of dissolution of tetracycline-HCl from the capsules studied. It should be noted, however, that the difference in A_{15} at 2 cm and that obtained at 7 cm was not significant according to Tukey's W Procedure (8) at the 5% level of significance. A possible explanation for these findings is that the hydrodynamics of the liquid in the vessel may vary with the position of the basket in the vessel. The actual stirring and agitation of the fluid may increase as the basket approaches the bottom of the flask in the range .2 to 2 cm from the bottom. The difference in dissolution behaviour between drug content (as expressed by A_{15}) and capsule shell as a function of stirrer depth may be due to a

TABLE 1

Effect of Stirrer Depth on the Dissolution Parameters for the Capsules Tested in Distilled Water.

Formulation	Stirrer Depth[a] (cm)	A_{15}[b] (%)	t_r[c] (min)	k_s[d] (min^{-1})
I	0.2	106 (9.9)[e]	1.26 (0.14)	0.1859
I	2.0	107 (5.6)	1.45 (0.30)	0.1520
I	7.0	108 (4.5)	1.21 (0.19)	0.1695
II	0.2	64.8 (2.6)	1.16 (0.39)	0.1113
II	2.0	55.3 (8.7)	1.03 (0.28)	0.1077
II	7,0	37.3 (20.2)	0.93 (0.21)	0.0870
III	0.2	97.4 (7.8)	1.50 (0.14)	0.1317
III	2.0	73.6 (16.2)	1.60 (0.19)	0.1267
III	7.0	72.2 (8.1)	1.36 (0.17)	0.1304
IV	0.2	51.8 (14.5)	1.41 (0.35)	0.0975
IV	2.0	49.7 (12.5)	1.47 (0.20)	0.0872
IV	7.0	54.4 (5.9)	1.45 (0.17)	0.0905

[a] Distance between the stirrer and the bottom of the flask or screen.

[b] Percent of labeled content dissolved at 15 min.; n = 5.

[c] Shell rupture time; n = 5.

[d] First-order dissolution rate constant.

[e] Standard deviation.

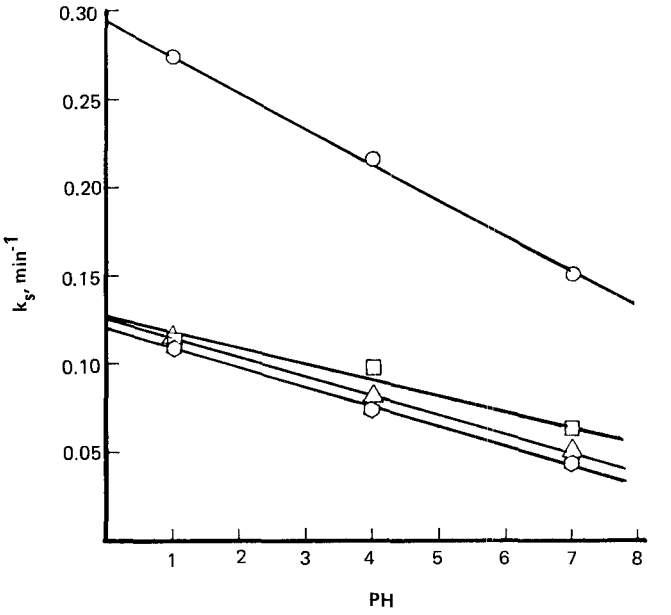

FIGURE 1

Effect of pH on the Dissolution Rate Constants for Capsule. Key: I (o), II (Δ), III (⬡), and IV (□).

TABLE 2

Effect of pH on the Shell Rupture Time for the Capsules Tested.

Formulation	Shell Rupture Time pH = 1	pH = 4	pH = 7
I	0.97 (0.24)	1.13 (0.10)	1.31 (0.08)
II	0.77 (0.07)	1.08 (0.17)	1.04 (0.20)
III	1.06 (0.29)	1.29 (0.14)	1.04 (0.17)
IV	0.85 (0.15)	1.60 (0.21)	1.29 (0.17)

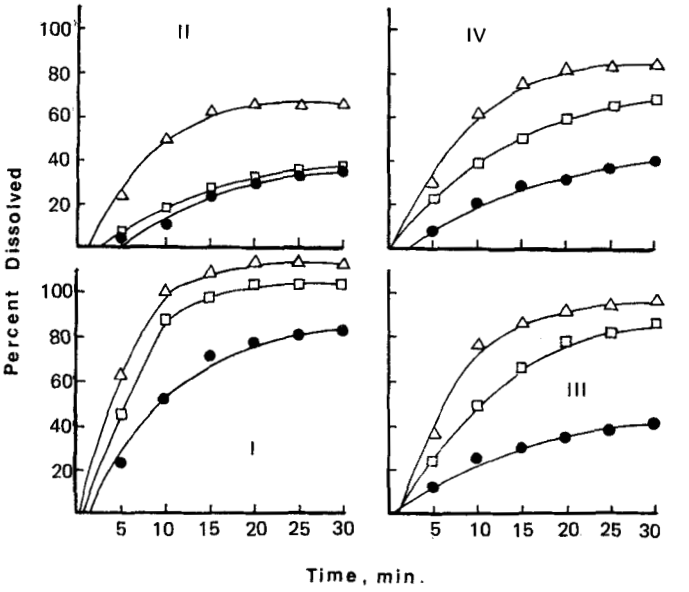

FIGURE 2

Effect of Ionic Strength on the Dissolution Profiles of Capsules Studied. Key: μ = 0.25 (Δ); μ = 0.6 (□); μ = 1.5 (●).

solubility difference between the tetracycline-HCl and gelatin, or to differences in the stirring pattern between the two dissolution apparatus used. The dissolution of the gelatin shell in water was possibly so rapid that a change in the stirrer depth failed to produce any effect.

The statistical discrepancy between A_{15} and k_s may be due to the nature of each parameter. While A_{15} is a single point parameter and a subject to experimental errors, k_s reflects the general behaviour of the dissolution data and is a subject to equation fitting errors.

Dissolution Rate as a Function of pH

Because the solubility of tetracycline hyrdochloride is much greater than that of tetracycline

TABLE 3

Effect of Ionic Strength on the Shell Rupture Time for the Capsules Tested.

Formulation	Shell Rupture Time (minutes) μ = 0.25	μ = 0.6	μ = 1.5
I	1.25 (0.14)	1.71 (0.23)	1.68 (0.24)
II	1.05 (0.24)	1.31 (0.08)	1.28 (0.10)
III	1.14 (0.11)	1.55 (0.29)	1.85 (0.54)
IV	1.10 (0.22)	1.58 (0.17)	1.36 (0.35)

base, the increase in pH may be expected to increase the ratio tetracycline/tetracycline-HCl, which leads to a decrease in the dissolution rate of tetracycline-HCl from capsules. Indeed, as can be seen in Figure 1, the dissolution rate constant (k_s) was inversely and linearly related to pH of the dissolution medium in the range 1 - 7. The effect of pH on the dissolution rate of the gelatin shell as indicated by t_r was also significant ($p < 0.01$), however, t_r was longest at pH = 4 (Table 2). The pH of the minimum dissolution of the capsule shell seems to be close to the iso-electric point of type B gelatin (pH 4.7 - 5.1) which may be the chief component of the capsule shells tested.

Dissolution Rate as a Function of Ionic Strength

Figure 2 demonstrates the dissolution profiles of tetracycline-HCl from the capsules tested. As shown in this figure, the dissolution rate of this drug decreased as the ionic strength increased from 0.25 to 1.5. Treatment of the results by the analysis of variance showed that the difference in A_{15} as a function

of ionic strength was significant ($p < 0.001$). This seems the result of "salting out" effect on the dissolution of both capsule shell and tetracycline-HCl content. Table 3 shows that the shell rupture time increased as ionic strength increased from 0.25 to 0.6, however, a further increase in μ did not yield any further increase in t_r. This may be attributed to the possibility that the "salting out" effect on the dissolution of the gelatin reaches a maximum at a certain value of ionic strength.

CONCLUSION

The method described here for the determination of the shell rupture time is simple, practical, and enable one to characterize capsule shell dissolution rapidly.

A good correlation between the dissolution rate of tetracycline-HCl and that of the capsule shell was obtained under certain conditions i.e. pH = 1, μ = 0.25 - 0.5, or stirrer depth = 2 cm. It is apparent, therefore, that under these conditions, capsule shells showed no influence on the drug release from the capsules studied, whereas, at other conditions e.g. pH = 4, the shell dissolution was the slowest relative to the other pH values used, therefore, one would think that at this pH capsule shell would have its maximum effect on tetracycline-HCl release from the capsules tested.

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