24. *IN VITRO* DISSOLUTION TESTING FOR SOLID DOSAGE FORMS

24.1. Zero Order Kinetic Model

The equation of zero order model is given in the following:

$C = C_o - k_o t$

C : the amount of undissolved active substance at time t

C_o: the initial amount of active substance

k_o : zero order release constant

t : time

In zero order kinetics when C values are plotted versus time, a straight line with a slope 'k_o' is obtained. According to this kinetics, the amount of active substance released into the solution at each time interval from the dosage form is constant. In many dosage forms in which release rate is modified, especially controlled release / extended release dosage forms it is intended to be substantially compatible with this type of dissolution kinetics.

24.2. First Order Kinetic Model

The equation of first order model is given in the following:

$\ln C = \ln C_o - kt$

C : the amount of undissolved active substance at time t

C_o : the initial amount of active substance

k : first order release constant

t : time

In first order kinetics when lnC values are plotted versus time, a straight line with a slope 'k_o' is obtained. In first-order kinetics, the amount of active substance that dissolves over time decreases exponentially. Most of the conventional dosage forms show this dissolution mechanism, and also the extended release formulations conform to this type of dissolution process.

24.3. Hixson-Crowell Cube-Root Law

Hixson and Crowell developed the 'cube-root law' based on the following assumptions:

a) Dissolution occurs perpendicular to the surface of the particle and against the entire surface area of the solid, the mixing effect is the same.

b) The spherical shape of the solid particle usually retains its shape during the dissolution process.

c) The dissolved particle does not need to be in a specific geometric shape and therefore no further measurements except for weight are required.

d) Under these conditions, differences in dissolution rates from different surfaces are insignificant because they all contribute to a combined process to generate an average speed.

e) There is intense mixing around the particle; thus in this region there is no static liquid layer causing the diffusion to slow down.

The equation of cube-root law is given in the following:

$W_o^{1/3} - W^{1/3} = k_4 t$

W_o : the initial amount of active substance

W : the amount of undissolved active substance at time t

k_4 : specific release constant

t : time

In this kinetic model when $W_o^{1/3} - W^{1/3}$ values are plotted versus time, a straight line with a slope 'k_4' is obtained. This equation is especially suitable for particulate drug delivery systems.

24.4. Weibull Distribution Model

It is another model that is used for the linearization and identification of the dissolution data.

$\log[\ln(1/1-Q)] = \beta\log\tau - \beta\log\tau_d$

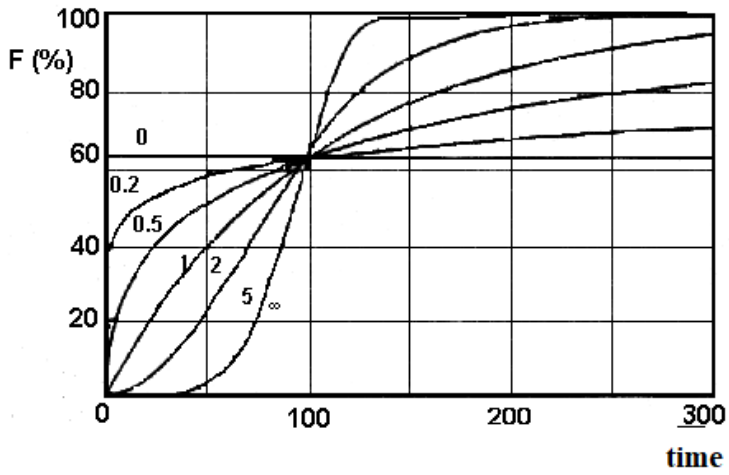
Q : percentage of dissolved active substance

β : shape parameter

τ : time - minute

τd : time for dissolution of 63.2% of active ingredient

In this equation $x = \log\tau$ and $y = \log[\ln(1/1-Q)]$. The slope of the line is β and the ordinate intersection is $\beta\log\tau_d$. The two important parameters that define the system are τ_d and β parameters. The β parameter characterizes the shapes of the original dissolution profiles numerically. Comparison of the different curves obtained by plotting the active substance percentages (F%) versus time (t) by means of β parameter is shown in the figure below.



$\beta > 1$ defines the curves that rapidly reach a plateau following the slow release patern of the active substance. When $\beta \leq 1$, it is possible to reach the plateau in accordance with the simple first order curve following the rapid release of the active substance at the beginning.

24.5. Higuchi Equation

Most of the modified release dosage forms are in the form of a matrix system. T.Higuchi theoretically examined the mathematical relationships determining the release rates of active substances dispersed in controlled release solid matrices. The equation is implemented in the follows:

$$Q = k\, t^{1/2}$$

Q : the amount of active substance released at time t

k : Higuchi release constant

t : time

This equation is known as the 'square root law'. When the amount of the active substance is plotted versus square root of time, if the active substance release is controlled by diffusion, a straight line with the slope of the k constant is obtained.

24.4. Comparison of *In Vitro* Dissolution Profiles : f_1 – Difference Factor and f_2 – Similarity Factor

Two equations have been proposed to evaluate the difference / similarity between the percetage of released active substance from the two formulations identified as the test and the reference.

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} X100$$

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum_{i=1}^{n} (R_t - T_t)^2 \right)^{-0.5} X100 \right\}$$

f_1 : difference factor

f_2 : similarity factor

R_t : % dissolved of reference formulation at time t

T_t : % dissolved of test formulation at time t

n : number of sampling times during dissolution test

For the acceptance of dissolution profiles as similar, f_1 values should be between 0 -15 and f_2 values should be between 50 - 100.

24.7.1. Experimental Procedure

900 ml of the dissolution medium (0.1 N HCl solution) is put into the vessel (dissolution cuvette) and waited until the temperature reaches 37 ° C. The experiment is then started by dropping a tablet into the vessel and determining the time. At certain time intervals, a certain volume of samples is taken with the injector (in this study, at 5, 10, 15, 20, 25, 30 minutes, 5 ml samples will be taken into pre-numbered tubes). After each sample is taken out, the same volume of solution is added into the vessel. The active substance amount in the samples is determined by a suitable assay method.

24.7.2. Quantitation of Active Substance

Depending on the active substance to be assayed, the quantitation method to be used is determined.

24.7.3. Calibration Curve

Calibration Curve is drawn appropriately using known concentration solutions of active substance in the dissolution medium.

24.7.4. TABULATION OF DISSOLUTION DATA

n	T (min)	A	$C_{mg/ml}$ [1]	S.F [2]	C_nxSF	C_ixSFx5 [3]	C_nxSF x900 [4]	$\sum_{i=1}^{n-1} C_i xSFx5 + C_n xSFx900$ [5]	% dissolved	% undissolved
1	5									
2	10									
3	15									
4	20									
5	25									
6	30									

1: This is calculated by substituting the A value in the equation of the calibration curve of the active substance.
2: Diluted solution volume / sample volume
3: Amount of active substance (µg) in 5 ml sample
4: Amount of active substance (µg) in the dissolution medium (900 ml)
5: At previous t times, the amount of active substance withdrawn in a 5 ml sample is added to the amount of active substance in the dissolution medium at the next t time.

24.7.5. Evaluation of the Results

1. Plot the percentage of active substances dissolved from the tablets versus t time.
2. Apply linear regression to each dissolution data for each mathematical model and draw the graphs. Calculate the parameters of each mathematical model and tablulated with r^2 values.
3. Take the results of dissolution data and mathematical models from your other group mates and show them in a table with your own results.
4. Calculate the f_1 and f_2 factors from the dissolution data by taking your own group's data as the referance and the other group's data as the test.

Questions:

1. Which model does the dissolution of the active substance from your tablet fit into, why?
2. Define the shape of your dissolution profile according to the calculated β value.
3. Do you find a difference when you compare the results of other group's compliance with mathematical models to your group's? If you find, explain why.
4. Write down the results according to the factors f_1 and f_2.