

RELEASE KINETIC MODELLING

8. WEEK

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- ❖ There are large variety of formulations devoted to oral controlled drug release, and also the varied physical properties that influence drug release from these formulations.
- ❖ The release patterns can be divided into those that release drug at a slow zero or first order rate and those that provide an initial rapid dose, followed by slow zero or first order release of sustained component.
- ❖ For this context, there are number of kinetic models, which described the overall release of drug from the dosage forms. These models are based on different mathematical functions, which describe the dissolution profile.

The basic kinetic models used are

- Zero order model,
- First order model,
- Higuchi model,
- Hixson-Crowell model.

1. Zero-Order Model

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$Q_0 - Q_t = K_0 t$$

Rearrangement of this equation yields:

$$Q_t = Q_0 - K_0 t$$

$$Q_t = Q_0 + K_0t$$

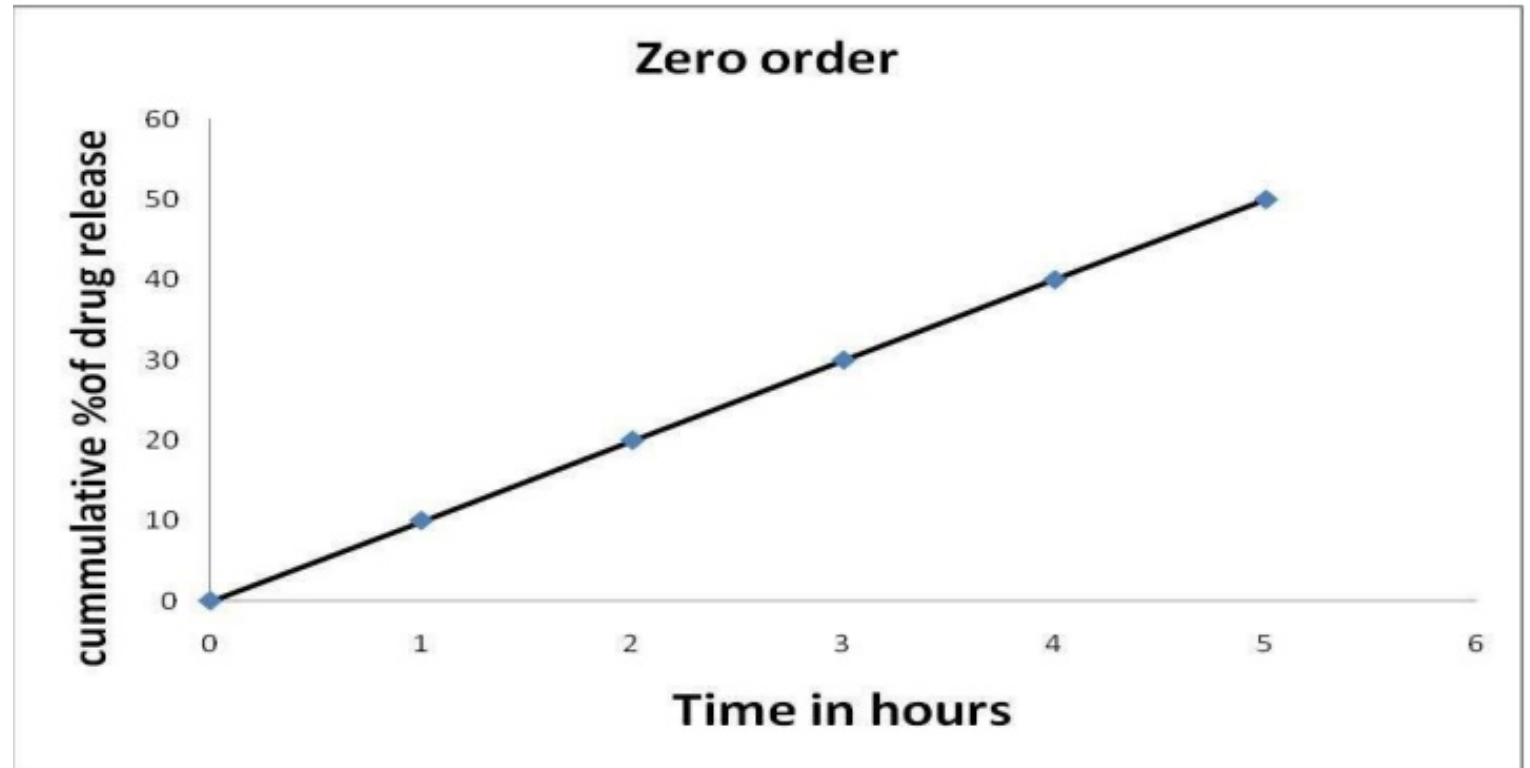
where

- Q_t is the amount of drug dissolved in time t ,

- Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and

- K_0 is the zero order release constant expressed in units of concentration/time.

To study the release kinetics, data obtained from in vitro drug release studies were plotted as cumulative amount of drug released versus time.



A graph is plotted between the time taken on x-axis and the cumulative percentage of drug release on y-axis and it gives a straight line.

This relationship can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of controlled release systems such as some transdermal systems, as well as matrix tablets with low soluble drugs in coated forms, osmotic systems, etc.

2. First-Order Model

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first order kinetics can be expressed by this equation:

$$\frac{dC}{dt} = -Kc$$

where K is first order rate constant expressed in units of time^{-1} .

This equation can be expressed as:

$$\log C = \log C_0 - Kt / 2.303$$

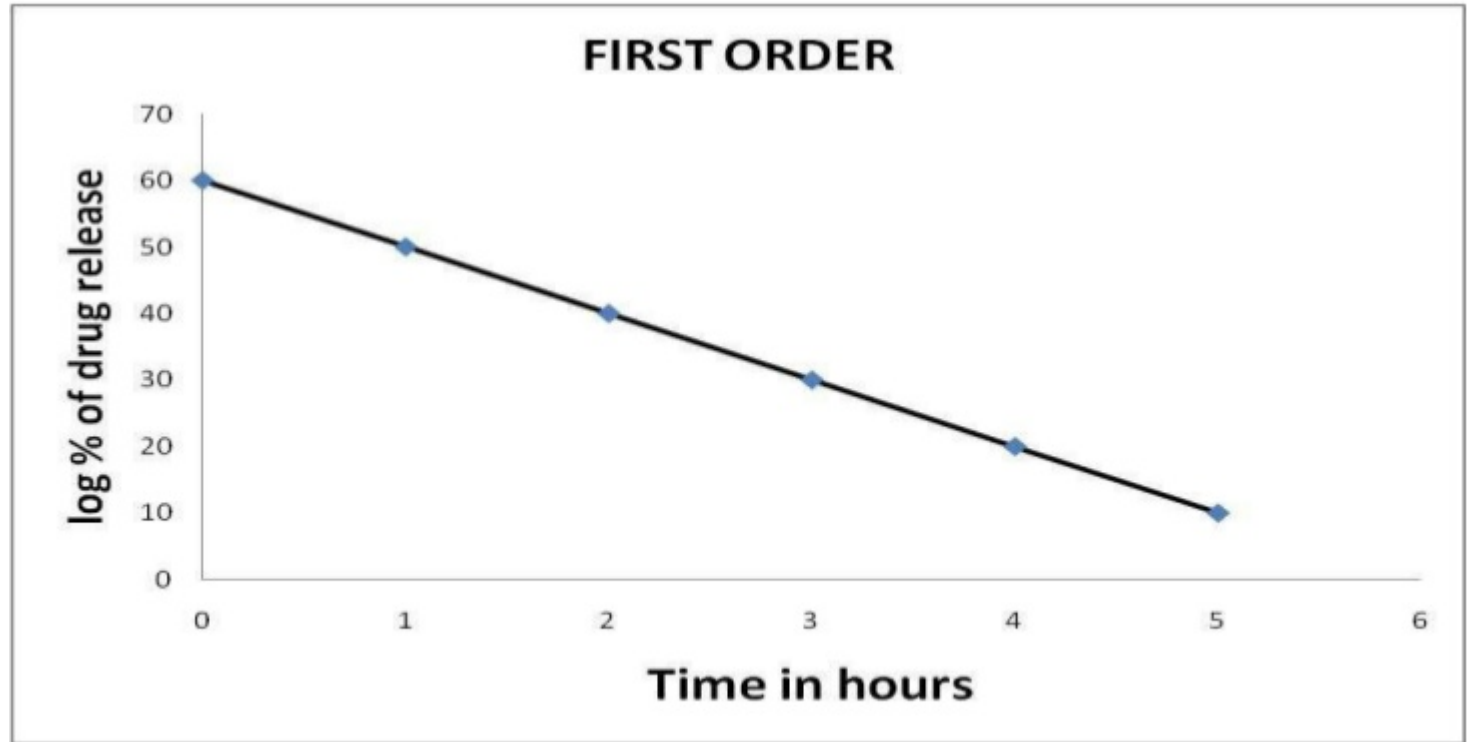
where

- C_0 is the initial concentration of drug,

- k is the first order rate constant,

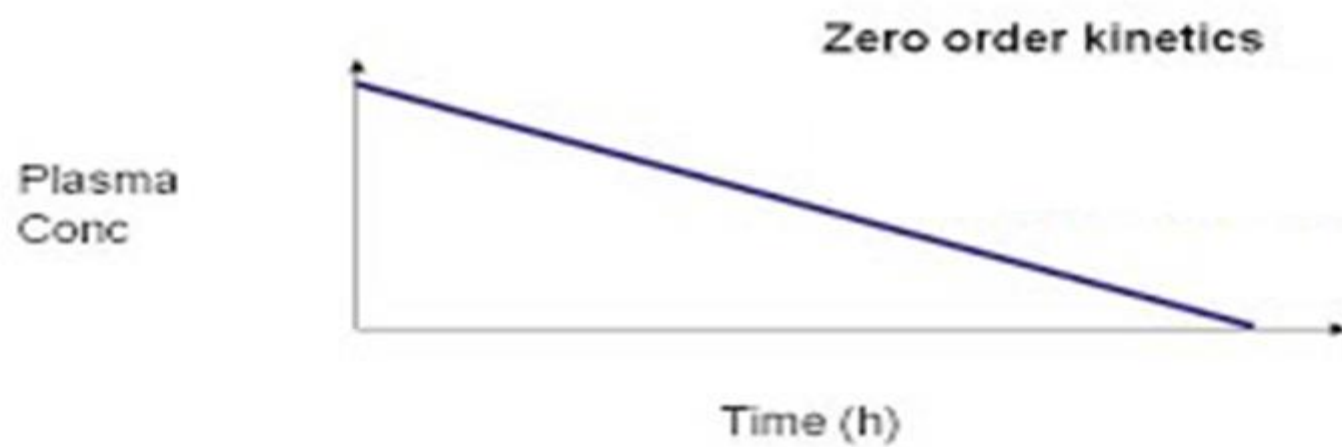
- t is the time.

The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of $-K/2.303$.

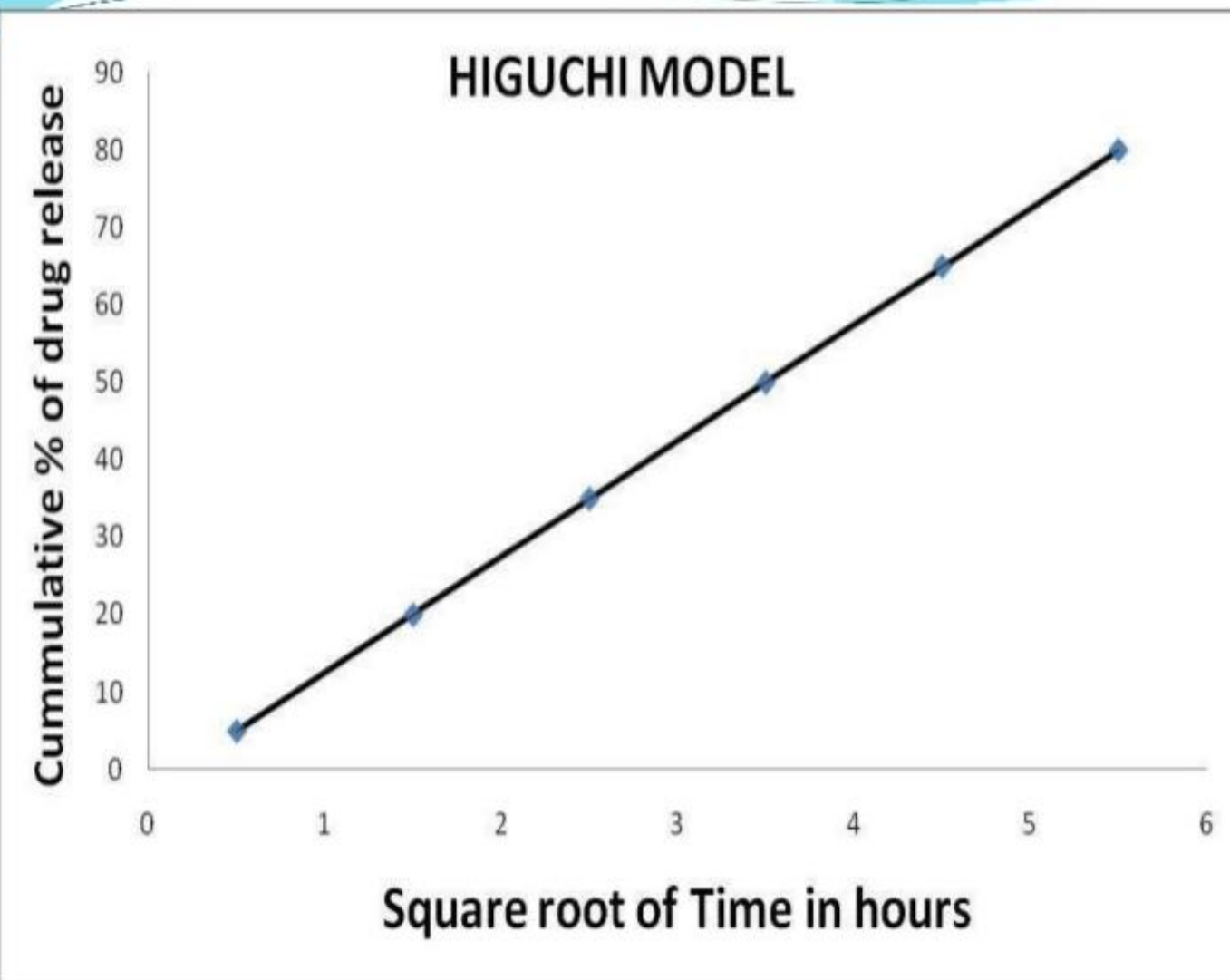


A graph is plotted between the time taken on x-axis and the log cumulative percentage of drug remaining to be released on y-axis and it gives a straight line.

This relationship can be used to describe the drug dissolution in conventional pharmaceutical dosage forms such as tablets, capsules,



3. Higuchi Model



- ❖ The first example of a mathematical model aimed to describe drug release from a matrix system was proposed by Higuchi in 1961.
- ❖ Initially conceived for planar systems, it was then extended to different geometrics and porous systems.

- ❖ This model is based on the hypotheses that
 - (i) initial drug concentration in the matrix is much higher than drug solubility;
 - (ii) drug diffusion takes place only in one dimension (edge effect must be negligible);
 - (iii) drug particles are much smaller than system thickness;
 - (iv) matrix swelling and dissolution are negligible;
 - (v) drug diffusivity is constant; and
 - (vi) perfect sink conditions are always attained in the release environment.

Accordingly, model expression is given by this equation:

$$Q = A \sqrt{D(2C - C_s) C_s t}$$

where

Q is the amount of drug released in time t per unit area A ,

C is the drug initial concentration,

C_s is the drug solubility in the matrix media and

D is the diffusivity of the drug molecules (diffusion coefficient)

in the matrix substance.

- ❖ This relation is valid during all the time, except when the total depletion of the drug in the therapeutic system is achieved.
- ❖ To study the dissolution from a planar heterogeneous matrix system, where the drug concentration in the matrix is lower than its solubility and the release occurs through pores in the matrix, the expression is given by the below equation:

$$f_t = Q = \sqrt{\frac{D\delta}{\tau} (2C - \delta C_s) C_s t}$$

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where

D is the diffusion coefficient of the drug molecule in the solvent,

δ is the porosity of the matrix,

τ is the tortuosity of the matrix and

Q, A, C_s and t have the meaning assigned above.

- ❖ Tortuosity is defined as the dimensions of radius and branching of the pores and canals in the matrix.

In a general way it is possible to simplify the Higuchi model as (generally known as the simplified Higuchi model):

$$Q=K_H t^{1/2}$$

where

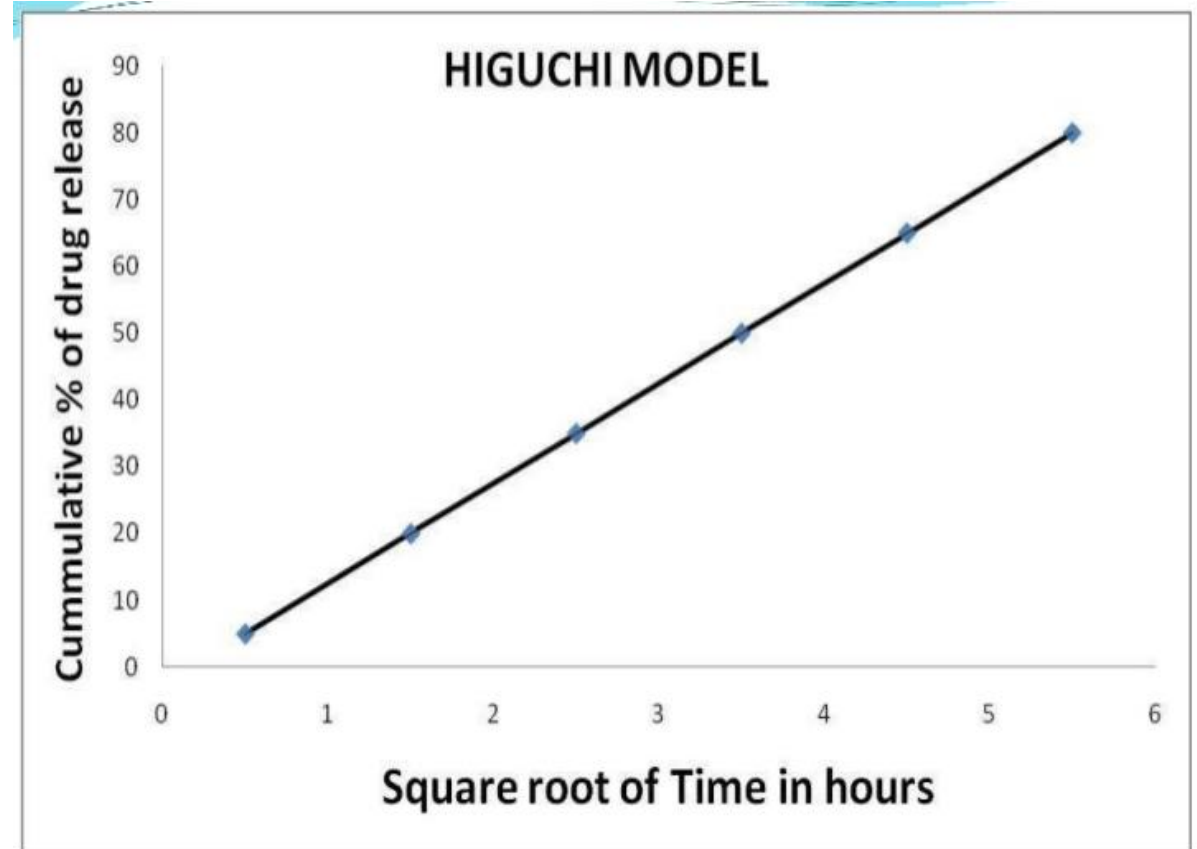
Q is cumulative amount of drug release at time «t»,

K_H is Higuchi constant,

t is time in hours.

- ❖ The Higuchi equation suggests that the drug release by diffusion.

- The data obtained were plotted as cumulative percentage drug release versus square root of time.
- This relationship can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs.



4. Hixson-Crowell Model

Hixson and Crowell (1931) recognized that the particles' regular area is proportional to the cube root of its volume. They derived the equation:

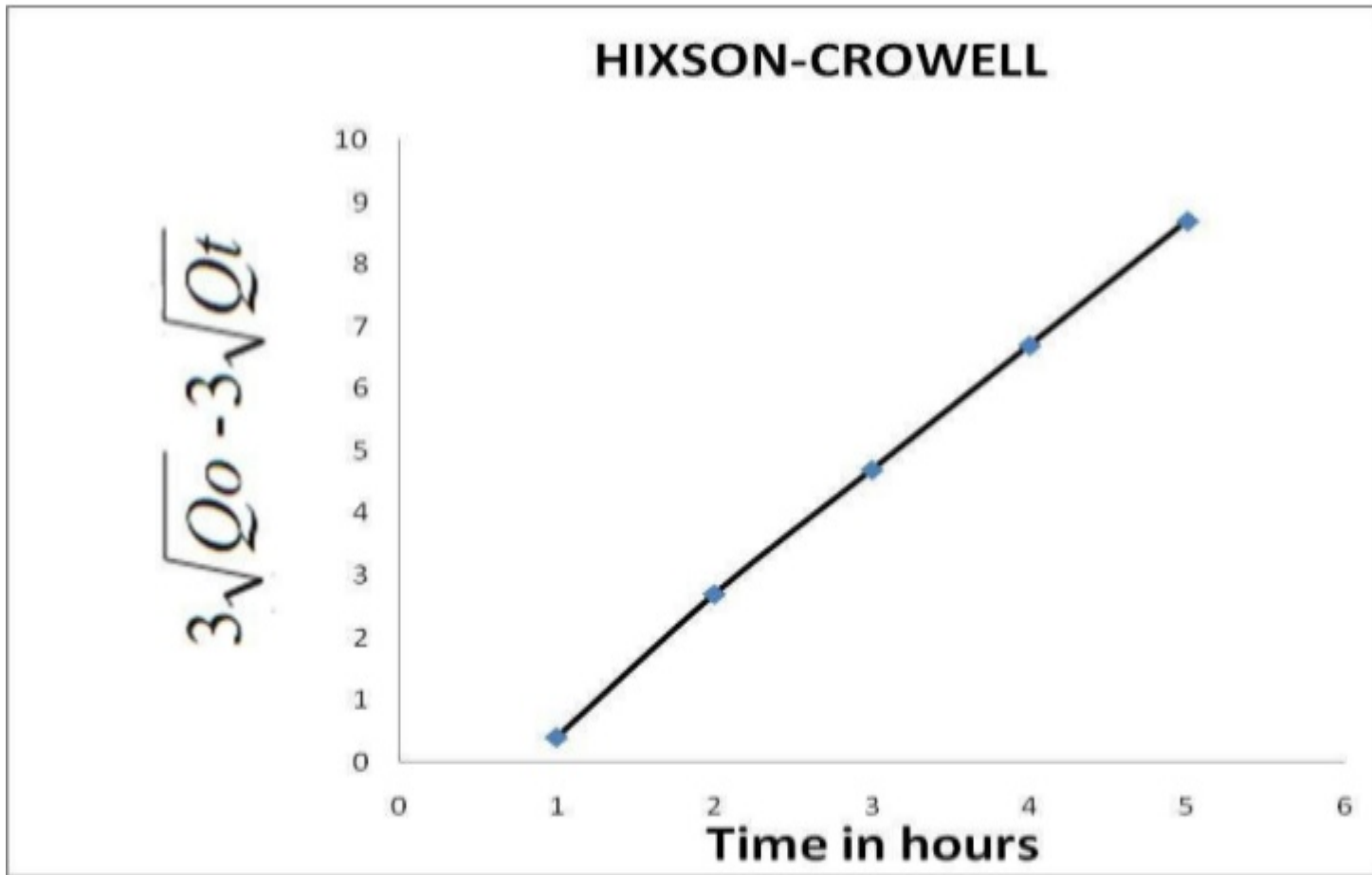
$$W_0^{1/3} - W_t^{1/3} = \kappa t$$

where

W_0 is the initial amount of drug in the pharmaceutical dosage form,

W_t is the remaining amount of drug in the pharmaceutical dosage form at time t and

κ (kappa) is a rate constant incorporating the surface-volume relation.¹⁹



A linear plot of the cube root of the initial concentration minus the cube root of percent remaining versus time in hours for the dissolution data in accordance with the Hixson-Crowell equation.

The equation describes the release from systems where there is a change in surface area and diameter of particles or tablets. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cube root of drug percentage remaining in matrix *versus* time.

This expression applies to pharmaceutical dosage forms such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time.