THE USE OF KINETIC N-ORDER MODEL IN DESCRIPTION OF ACTIVE SUBSTANCE RELEASE FROM VARIOUS DRUG FORMS. PART 1. PREMISES AND MATHEMATICAL ANALYSIS OF THE N-ORDER MODEL

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Abstract: The paper presents the premises and equations which are the basis of the mathematical n-order model, which contrarily to standard models based on the laws of chemical kinetics, i.e. 0-order and 1-order kinetics, enables categorization of the investigated process taking into account two parameters: the rate at which it occurs, and actual order, which it is distinguished by. Standard models, which assume in advance the kinetic order of the described processes, may be used with satisfactory accuracy to analyze only a low percentage of performed experiments. However, as shown in practice, the order of many physico-chemical processes, including those which are most interesting for us, active substance release from the drug form, may assume intermediate values, what is manifested as various types of “smooth non-linearities” in the obtained release profiles, which cannot be explained on the basis of assumed standard theories. N-order model may be numbered among the group of physical mathematical models based on the premises of chemical kinetics, possessing the analytical structure of internally non-linear function. It is characterized by two parameters: release rate constant $K$ and order coefficient $N$.

Keywords: mathematical models, chemical kinetics, pharmacokinetics, active substance release, diffusion, release rate, release kinetics, methylcellulose, gel, hydrogel, paracetamol, sodium diclofenac

Models based on the laws of chemical kinetics, together with physical diffusion models, are most commonly used in the description of processes of active substance release from drug form, as they combine two basic features of so-called good physical models: relatively simple mathematical structure, which facilitates practical use of the model, with a satisfactory theoretical basis strongly rooted in the laws of physics. Two of them are most commonly used in in vitro studies on pharmaceutical availability: model which obeys kinetics of 1-order and 0-order model (1).

The model which obeys 1-order kinetics may be used to describe almost all release profiles, but it is most commonly used in the description of active substance release from formulation with non-modified release rate, which is determined mainly by solubility of the active substance (2-4). Its basic advantage, despite often too low quality of fitting the actual empirical data, is its mathematical simplicity. It has the structure of a linear function with one estimated parameter – release rate constant $k_1$. This enables easy classification of all described release profiles on the basis of only one parameter – the rate at which the process occurs.

Active substance release from drug form with controlled release rate is usually described by means of a model obeying 0-order kinetics, as it assumes independence of the process rate on time. This model has recently gained a significant popularity as its premises fully reflect the main idea on which modern drug design is based, i.e. developing such a formulation which would allow active substance release with strictly determined and not changing in time rate (5, 6). Higher order total models, as well as a whole range of multicompartmental models, have much lower practical application, as it is often difficult to prove the physical legitimacy of their use. Moreover, their mathematical structure is less user-friendly, as it makes subsequent statistical analysis of the obtained results more difficult (7, 8).

A common feature of all the mathematical models obeying the laws of chemical kinetics, which differentiates them from diffusion models (9-13), is the purely theoretical assumption of full homogeneity of the system from which an active substance is released.

However, the practice shows that production of a fully homogenous drug form strictly fulfilling the
premises of so-far used kinetic models, is impossible and the actual order of the process of active substance release from such formulations may have various actual values, and not natural values as was assumed so far. Actual order of the process of active substance release from the drug form should depend on such factors as the size and physico-chemical properties of active substance molecules suspended or dissolved in the excipient or composition and spatial structure of the drug matrix. This observation was the starting point for the development of a simple linear kinetic \( n \)-order model, which is characterized by two parameters: release rate constant \( K \) and actual order of the release process \( n \). The model enables explanation in a relatively simple way on the grounds of chemical kinetics, and description of mathematically various types of non-linearities occurring in the course of numerous release profiles without the necessity to use multicompartmental models, which are not so clear and it is difficult to prove theoretically their use in in vitro studies on pharmaceutical availability.

The premises and mathematical structure of \( n \)-order model

The proposed \( n \)-order model is based on the premise that every actual course of the release process is the resultant outcome of a whole range of mutually overlapping physico-chemical factors, which in fact are difficult to be isolated and described mathematically. Those chaotic and heterogeneous systems imply non-linearities in the release profiles, which may be easily described assuming that the discussed system is characterized by a specific, intrinsic order. Thus according to the \( n \)-order model, the process of active substance release from the investigated formulation may be described by means of two parameters: release rate constant \( K \) and order \( n \), which is a certain measure of non-homogeneity of the investigated system.

The following differential equation fulfills the premises of \( n \)-order model:

\[
\frac{dC(t)}{dt} = -k \cdot C(t)^n
\]  

(1)

where \( C(t) \) is the concentration of the drug in the drug form in given time \( t \), \( k \) – release rate constant, and \( n \) – actual order of the process. Integrating equation (1), it is possible to obtain relation \( C = f(t) \), which describes given release profile by means of two parameters, \( k \) and \( n \):

\[
\int \frac{1}{C(t)^n} dC = \int -k dt,
\]

\[
\frac{C^{1-n}}{-n} = -k \cdot t + a_0.
\]  

(2)

Figure 1. Graphic interpretation of Equations (5) and (6) which are the basis of the proposed \( n \)-order model.
The value of integration constant \( a_0 \) may be determined defining the basic conditions, i.e.:

\[ t = 0, \ C = C_0. \]

Thus we obtain:

\[ a_0 = \frac{(C_0)^{1-n}}{1-n} \quad (3), \]

in which \( C_0 \) is the initial concentration of the active substance in the formulation.

Putting (3) into equation (2), we can obtain:

\[ \frac{C^{1-n}}{1-n} = -k \cdot t + \left(\frac{C_0}{1-n}\right)^{1-n}. \quad (4) \]

Substituting:

\[ n = N + 1, \]

we obtain equation (5), which is the base of the proposed n-order model:
where \( N \) is the so-called order coefficient.

Worth mentioning is the fact that investigating the pharmaceutical availability of a given product, it is a customary practice to determine the amount or percentage of the released active substance in time \( t \), and not the concentration of the active substance which remains in the drug form after time \( t \) (this situation is described by equation (5)). In this case equation (5) should take the following form:

\[
M_t = M_\infty \cdot N \cdot t^{1/N}
\]

where \( M_t \) according to Crank’s terminology (9) determines the amount of active substance released in time \( t \), and \( M_\infty \) – the amount which is released in infinitely long time (in practice \( M_\infty \approx C_0 \)).

Release rate \( K \) in equation (6) is given by the formula:

\[
K = k \cdot V^{N}
\]

where \( V \) is the volume in which the release process was carried out in vitro.

In the situation when we want to describe the relationship between the percentage of the active substance released (not its amount) and time \( t \), we should use the following equation:

\[
C\%(t) = 100 \cdot (100^N + K \cdot N \cdot t)^{-N}
\]

where \( C\%(t) \) is the percentage of the active substance released in time \( t \).

Figure 1. presents graphic interpretation of equations (5) and (6), which are the basis of the proposed \( n \)-order model.

Basing on the derived equations it is possible to determine the so-called release part-time \( t_{x\%} \), for \( n \)-order model, like for the first order kinetics, which is defined as time in which \( x\% \) of the active substance is released from the drug form.

Thus basing on equation (6), we can derive:

\[
\frac{M_t}{100} \cdot x\% = M_\infty \cdot ((M_\infty)^N + K \cdot N \cdot t_{x\%})^{1/N}
\]

Solving equation (9) in relation to \( t_{x\%} \), we obtain:

\[
t_{x\%} = \frac{-(M_\infty)^N + \left(M_\infty - M_\infty \cdot x\%\right)^N}{K \cdot N}
\]

If we assume that \( M_\infty = 100\% \), equation (10) can be simplified to the formula:

\[
t_{x\%} = \frac{-100\%^N + (100\% - x\%)^N}{K \cdot N}
\]

In a particular case we can also determine the so-called half-release time \( t_{50\%} \), i.e. time in which a half of the active substance is released from the drug form (\( x\% = 50\% \)).
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\[ t_{50\%} = \frac{(-1 + 2^N) \cdot (M_\infty)^{-N}}{K \cdot N} \quad (12) \]

further, if we assume, as above, that $M_\infty = 100\%$, we obtain:

\[ t_{50\%} = \frac{(1 + 2^N) \cdot 100^{-N}}{K \cdot N} \quad (13) \]

Opposite to models obeying 1-order kinetics, for which $t_{50\%}$ is a constant function depending only on the release rate constant $k_1$ (for 1-order kinetics $t_{50\%} = \ln 2/k_1$), in the $n$-order model the half-release time depends on two variables, $K$ and $N$. Figure 2B presents the effect of the magnitude of both parameters, $N$ and $K$, on the half-release time $t_{50\%}$ obeying the $n$-order model.

According to the premises of $n$-order model, parameter $K$ determines the release rate and may assume for it any value above 0. Parameter $N$, which is referred to as an order coefficient, determines in detail the profile of the investigated process and theoretically it may assume any actual value, also those below 0. The effect of actual values of $N$ on the shape of the active substance release from drug form profile in comparison to functions illustrating the course of zero order ($N = -1$) and first order ($N = 0$) processes is presented in Figure 3.

The effect of release rate constant $K$ on the course of function (4) with unchanged numerical values of $N$ parameter is presented in Figure 4.

Equations (5, 6 and 8) have internally non-linear structure, what means that it is not possible to reduce them to linear functions by means of simple mathematical transformations. For this reason, for the estimation of $N$ and $K$ parameters, which characterize $n$-order model, non-standard, non-linear algorithms enabling minimalization of the loss function by means of the least squares method should be used. One of the most effective is the quasi-Newton algorithm available in the basic statistical software modules STATISTICA PL.

The second part of this paper will present a comparative statistical analysis of $n$-order model with standard physical and semi-empirical models most commonly used in the description of active substance release from drug form. It is used for the mathematical description and detailed analysis of the release kinetics of sodium diclofenac and paracetamol from hydrogels with various viscosity based on methylcellulose. Moreover, the effect of viscosity, temperature and kind of active substance used in the studies on the release rate and actual order will be discussed.

**REFERENCES**