

# MODELLING OF RELEASE KINETICS OF MEBENDAZOLE FROM SOLID DISPERSION BASED FORMULATIONS IN SIMULATED GASTRIC FLUID

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## Abstract

**Background.** Mebendazole (MBZ) is the main treatment of human echinococcosis caused by the larval forms of the parasite *Echinococcus granulosus* or *E. multilocularis*, which enter in blood and contaminate internal organs, and has been shown active also in various cancer types. Due to its poor solubility in intestinal fluid, in both cases its bioavailability is a critical factor in determining the extent and duration of effect.

**Methods.** Tablets based on solid mebendazole dispersions in polyethylene glycol 6000 (PEG) by melting method were prepared in the ratios of 1: 1 and 1: 2.5, with croscarmellose and Ludiflash as excipients, in order to increase its bioavailability. In vitro release assays were performed in simulated gastric fluid. The release was performed using USP apparatus 2 (paddles) model using an ERWEKA DT800 HH device at a rotational speed of 75 rpm. The resulting samples were quantitatively analyzed using a validated HPLC method. Release kinetics was performed using Noyes-Whitney, Higuchi, Siepmann Peppas, Weibull and Immediate Release in Semi-infinite Medium model (IR-SIM).

**Results.** Swelling and disaggregation excipients led to a release in two, well separated, phases: pre-disaggregation and post- disaggregation. Release after three hours decreased following inclusion of MBZ as solid dispersion in PEG from 100 % in absence of PEG to approximately 50 % in case of 1:1 MBZ-PEG proportion and to some, 20 % in case of 1: 2.5 MBZ-PEG proportion. In both phases, the kinetics of release fitted well the law of the radical and the law of Noyes Whitney.

**Conclusions.** Since the site of the action / absorption of mebendazole is not at the gastric but at the intestinal level, as well as the fact that mebendazole has the tendency to precipitate in the passage from the gastric fluid to the intestine fluid, it was considered that the slower gastric release may partially cancel out its tendency to precipitate. Square root type behavior can appear in case of dissolution of active substance in solvent penetrating the tablet matrix (Higuchi model) or in case of release outside the matrix acting as an infinite reservoir. Since Noyes Whitney model suppose the release in a limit layer outside the matrix, it was considered an argument for IR-SIM model. The

conclusion has a general methodological significance in conditions of quasi-total acceptance in literature of Higuchi model even in conditions far of those used in its deduction.

Key words: Mebendazole PEG solid dispersion, release kinetics in simulated gastric fluid, Infinite Reservoir – Semi-infinite Medium model

## **Introduction:**

Mebendazole (MBZ) has been considered since 1975 for local action in the gut, for the treatment of parasitic worm infestations, being included in the List of Essential Medicines of the World Health Organization. However, there are larval forms which enter in blood and contaminate internal organs (Albonico, 1999; Safioleas, 2000), Consequently, long-term treatments with formulations providing a significant absorption of MBZ are required. MBZ has been shown more recently active in various cancer types such as colon cancer (Nygren, 2013), brain tumors (De Witt, 2017), as well as gastric tumors (Pinto, 2015).

Following its low solubility, MBZ has a slow and incomplete release in gastrointestinal tract, an incomplete absorption (Petri 2011) and consequently an unfavorable pharmacokinetic (Chaudhary, 2014). Hence, increasing bioavailability of MBZ was from the beginning a problem which remains and is not yet satisfactory solved (Zimmermans, 2018).

A high number of technological solutions to increase MBZ solubility and to ensure an appropriate release kinetics were proposed. For modulating the solubility of MBZ, present paper focuses on its formulation as solid dispersions.

Solid dispersion of poorly water-soluble drug in a hydrophilic carrier or matrix in different ratios can be prepared by the melting (fusion) method, solvent method or melting solvent method (Vasconcelos, 2007). Solid dispersions using polyglycolized glycerides and polyethylene glycol (PEG) were reported (Abdul Fattah 2002, Damian 2000). PEG is recommended following its ease of melting, as it has a low melting point (Sharma et al. 2014a), surfactant property (Sharma et al. 2014b) and oral safety (Singh et al. 2014).

In this study is presented the preparation of solid dispersion tablets of mebendazole with poly ethylene glycol (PEG) 6000 by melting method, evaluation of release kinetics in simulated gastric fluid and selection of a mathematical model appropriate for analysis of experimental data.

Modelling of heat and mass transfer has more than two hundred years history, starting with Joseph Fourier (Fourier, 1822) which predicted the heat transfer, both as function of time and space. Thirty years later Fick applied the equation of heat to mass transfer (Fick 1855). First dissolution study was performed by chemists Noyes and Whitney from Massachusetts Institute of Technology (Noyes, 1897) but the paper had not echo in pharmaceutical literature. It was only 50 or so years ago that pharmacists and medical doctors realized the importance of release processes in assuring the absorption of drugs. Practically in all cases, therapeutic effect is determined by the plasma levels of drug. In particular case of lipophilic drugs, for which the absorption process from the gastrointestinal tract is rapid, the rate of release of that drug can be the step which controls its appearance in blood.

The beginning of modeling of drug release was the Higuchi model published in 1961 (Higuchi, 1961). He solved the diffusion equation in particular initial and boundary conditions corresponding to release of active substances from ointments and from tablets with insoluble matrix and found that the released amount is proportional with square root of time.

Later other researchers added to diffusion phenomena in release kinetics, the relaxation and erosion of matrices, introducing more complex “power laws” models.

Ten years later mathematical models begin to be less considered. FDA introduced “official dissolution tests”, which are an important criterion in defining the quality of a drug product and reproducibility of manufacturing processes, but reducing release kinetics to only dissolution is an oversimplification, good in standardization but less productive in further progress of science.

More recently it was understood that the final goal is to ensure absorption and it was tried to develop “biorelevant dissolution tests. The first direction was assuring dissolution conditions more similar to gastric and intestinal media in the fasted state (Dressman, 1998). Also, media mimicking the fed state conditions in the human intestinal fluid were proposed (Dressman, 1998; Galia, 1998; Kostewicz, 2002; Persson, 2005). The other direction was to correlate in vitro release with in vivo absorption deduced by deconvolution from pharmacokinetics.

Unfortunately, as was put in evidence by a recent review (Mircioiu, 2019), almost all correlations use mathematical models without verifying the phenomenological and mathematical conditions used in deriving the model, application having a rather empirical character.

## **Materials**

Mebendazole was a gift sample from Iraqi Pharmaceutical Industry (IPI) Company (Baghdad – Iraq). Polyethylene glycol 6000 was purchased from Merck (Schuchardt – Germany), whereas all other chemicals are of high analytical grade. Croscarmellose from AC-DI-SOL FMC Biopolymers and Ludiflash from BASF

## **Methods**

### *Preparation of solid dispersions*

For studying the effect of active substance: polymer ratio on mebendazole release kinetics, two different ratios, respectively 1: 1 and 1: 2.5, respectively, were prepared and evaluated.

The preparation of solid dispersions was carried out using the melting method and included the following steps: firstly, the MBZ and the polymer (PEG 6000) were mixed in various mass ratios (1: 1, 1: 2.5), and heating at  $70 \pm 2$  ° C for 5 minutes with continuous stirring. The obtained molten mixture was subjected to rapid solidification on an ice bath, and was subsequently maintained at -20 ° C for 24 hours. The resulted solid mass was milled, in order to obtain a fine powder. Particles with a diameter of 1-1.5 mm were separated from those with a diameter of less than 1 mm.

### Tablet preparation

Tablets were obtained by direct compression after mixing of the solid dispersion with Ludiflash (BASF), croscarmellose, talc and magnesium stearate in the proportions shown in Table 1.

Table 1. Composition of the prepared experimental tablets

	<b>1:1</b>	<b>1:2,5</b>	<b>Control 1:0</b>
<b>Ingredients:</b>	mg/cpr.	mg/cpr.	mg/cpr.
<b>Mebendazole:PEG 6000 1:1</b>	200	-	-
<b>Mebendazole:PEG6000 1:2.5</b>	-	350.0	-
<b>Mebendazole</b>	-	-	100
<b>Ludiflash (BASF)</b>	376	226.0	476.0
<b>Sodium Croscarmellose</b>	<b>12.0</b>	12.0	<b>12.0</b>
<b>Talcum</b>	6	6.0	6.0
<b>Magnesium stearate</b>	6	6.0	6.0
<b>Total</b>	<b>600</b>	<b>600</b>	<b>600</b>

### Dissolution experiments.

In vitro release assays were performed in simulated gastric fluid containing surface active agents (0.1N HCl containing 1% sodium lauryl sulfate). The release was performed using the USP 2 (paddle) apparatus, with an ERWEKA DT800 HH device at a rotational speed of 75 rpm. 2 ml samples were taken at 5, 10, 15, 30, 45, 60, 90, 120, and 180 minutes after the start of the test. The resulting samples were quantitatively analyzed using a validated HPLC method with UV detection at 254 nm. All determinations were performed in triplicate.

### Modeling the MBZ release kinetics.

In order to model dependence on time of the cumulative amount of mebendazole, several mathematical models were applied and compared.

Noyes-Whitney model (NW). Equation associated to model is used in in this paper in the form of a linear implicit function:

$$-\ln(1 - r(t)) = kt$$

where  $r(t)$  is the fraction of drug released at time  $t$ .

Delivery is considered across a limit stationary layer in the dissolution media, adjacent to the matrix of drug formulation, of thickness ( $h$ ). The concentration of molecules in the immediate neighborhood of interface is considered to be equal to a maximum value -  $c_s$

Initial and boundary conditions corresponding to phenomenological conditions for  $c(x,t)$  are  $c(0,t) = c_s$  and  $h,t) = c_h(t)$  for  $x \geq h$

Higuchi square root law (H). Higuchi model assumes that the solvent penetrates and wash layer by layer the active component from drug matrix. The external solvent is supposed to act as a

perfect sink, under pseudo steady-state conditions. Since the assumptions of the model are valid only in the first part of the release process, the model is applicable only for the first 60% of the release curve. The law can be written in the form:

$$r(t) = \sqrt{DC_s(2C_0 - C_s)t} = k_H t^{1/2}$$

where,  $D$  is the diffusion coefficient,  $C_0$  is the initial drug concentration in the matrix and  $C_s$  the solubility of the drug.

The Power-Law (SP). A series of authors tried to take into consideration simultaneously both the effects of diffusion and erosion, the results being very complex equations. An empirical, more simple form proved to be applicable in such cases, in the form of “Peppas law”:

$$r(t) = \alpha t^\beta$$

Weibull model (W). Weibull model is a very general, probabilistic models, being applicable to processes running in several steps with constant rate of inter-transfer. Dependence of released fraction  $r$  on time is applied in this paper in the implicit form:

$$\ln(-\ln(1 - r(t))) = \ln \alpha + \beta \ln t$$

$\alpha$  and  $\beta$  being empirical constants.

The model was applied for the first time for describing the dissolution of drugs from pharmaceutical formulations by Langerbucher (Langerbucher 1972).

Infinite Reservoir – Semi-infinite Medium model (IR-SIM). Another square root law was proposed to describe the release kinetic of active components from a pharmaceutical formulation, which was considered as an infinite reservoir toward dissolution medium, which was assimilated with a semi-infinite solution (Mircioiu, 2013a; Mircioiu, 2013b, Mircioiu, 2019; Paolino, 2019). The concentration of active component inside dissolution medium as function of time and distance between the interfaces between formulation and solvent, was found to be described by the following equation:

$$c(y, t) = c_s \left( 1 - \operatorname{erf} \left( \frac{y}{\sqrt{4Dt}} \right) \right)$$

where,  $y$  is the distance from the interface and  $\operatorname{erf}(z)$  is the error function

$$\operatorname{erf}(z) = \int_0^z \frac{2}{\sqrt{\pi}} e^{-x^2} dx$$

The integration of flux in the interface in the range between 0 and  $t$  further provided the following square root equation:

$$m(t) = \frac{2}{\sqrt{\pi}} A c_s \sqrt{Dt}$$

where,  $A$  is area of interface between reservoir and diffusion medium.

The quantity of active substance released is proportional to the square root of time, but the law was deduced under initial and boundary conditions very different from those of the Higuchi square root law.

## **Results**

### *Release experiments*

Whatever the composition of formulations, release was characterized by two distinct phases: pre and post disintegration. In the first phase of the dissolution experiment:

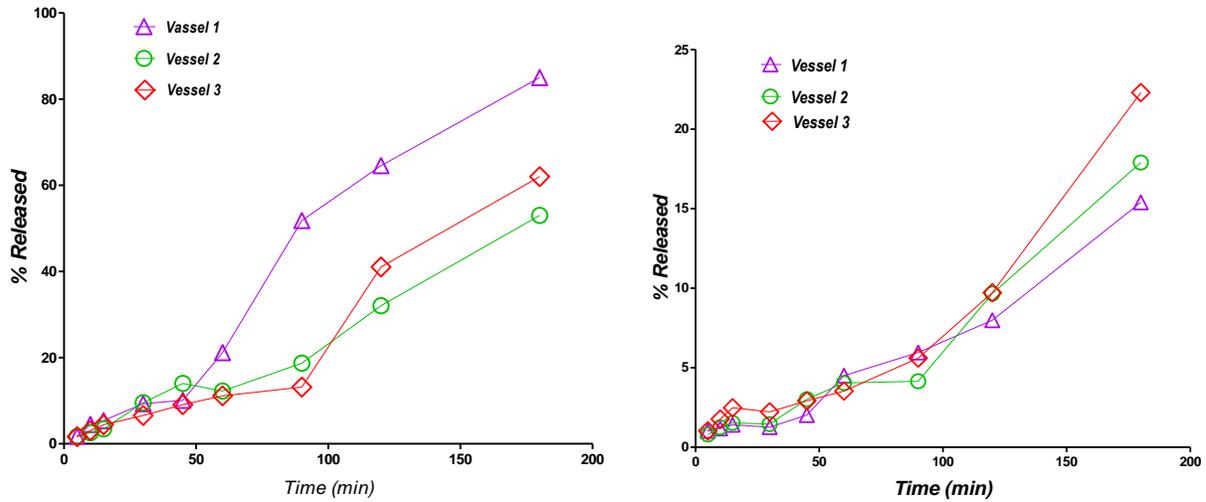


**Figure 1.** Swelling of the tablet by solvent

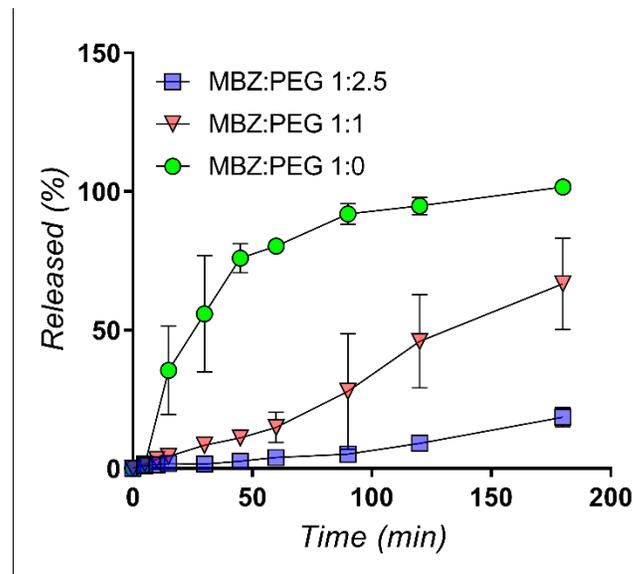
Tablets were swollen by water, increasing of their volume being visible with naked eye, as can be seen in Figure 1. After disintegration the system became a coarse suspension.

### *Release in simulated gastric fluid*

Release in simulated gastric fluid within three hours was moderately variable in case of 1:1 and less variable in case of 1:2.5 MBZ-PEG ratio (Figure 2). Areas under release curves decreased following inclusion of MBZ as solid dispersion in PEG from 100 % in absence of PEG to approximately 50 % in the case of 1:1 MBZ-PEG ratio and to approximately 20% in case of 1:2.5 MBZ-PEG ratio (Figure 3).



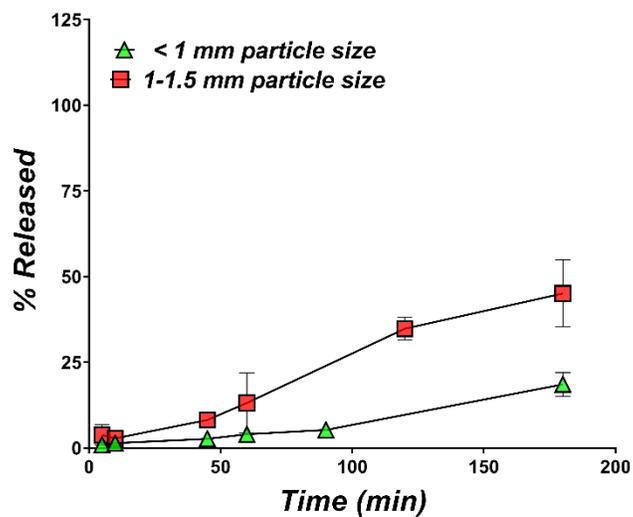
**Figure 2.** Release in simulated gastric fluid. A. 1:1 solid dispersion; B 1: 2.5 solid dispersion



**Figure 3.** Release curves in the absence of PEG (1:0) and in cases of 1:1 and 1:2.5 MBZ:PEG ratios

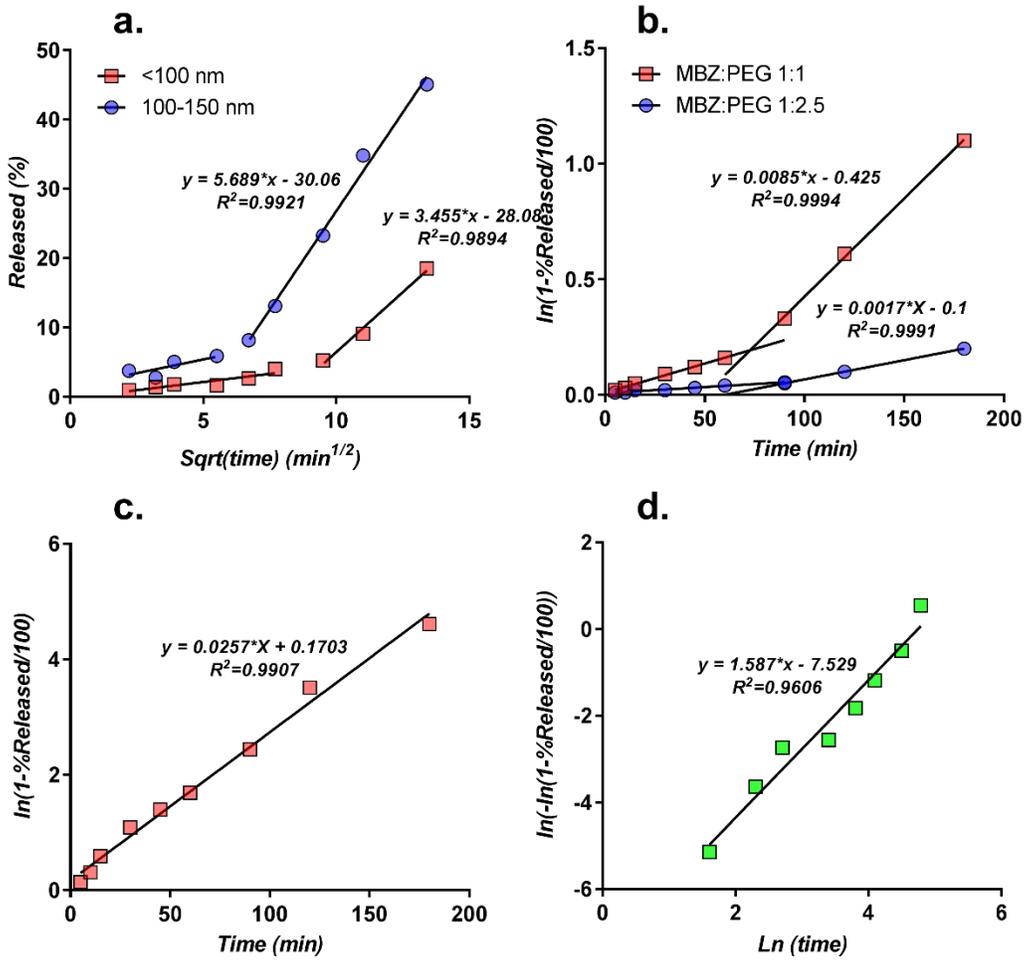
At three hours, the released amount was lower in the case of dispersion with a higher proportion of PEG. This effect is contrary to that from dissolution of the same solid dispersions in fasted state simulated intestinal fluid (Sandulovici, 2019).

The effect of decreasing availability may be rather temporary because after one hour, the release from 1:1 dispersion has a significant acceleration. Thus, the primary effect of increasing PEG concentration could be rather a delay than a decrease in release.



**Figure 4.** Influence of particle diameter of mebendazole: PEG6000 solid dispersion on the release of MBZ

For the 1:2.5 solid dispersion, the impact of particle size on MBZ release kinetics was also investigated. Increasing particle size in the range 100-150 nm led to an increased MBZ release rate and extent (Figure 4).

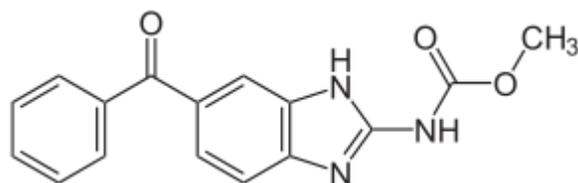


**Figure 5.** Fitting of the experimental release data with theoretical models. a. two steps modeling with Higuchi model of 1:2.5 dispersion; b. two-steps fitting of data with Noyes Whitney (NW) model for the 1:1 and 1:2.5 solid dispersions; c. NW modeling of release data from control formulation d. fitting with Weibull model of the 1:2.5 dispersion

In case of control tablets (containing crystalline MBZ, and not solid dispersion), NW model proved to be applicable on the entire interval (Figure 6c). Since, as what observed with naked eye, in a first phase tablets were swelled and later disaggregated, it was applied a two-phase modeling of release data (Mircioiu, 2012). Results were excellent for NW and H models, as can be seen in fig 5a and 5b. The same was the case for modeling using SP model (data not shown).

## Discussions

Mebendazole (MBZ), chemically methyl-5-benzoyl benzimidazole-2-carbamate (Merck Index), is changing in acid medium into a water soluble, salt form.



The presence of PEG 6000 as dispersion medium in a fairly large proportion leads to a decrease in the rate at which mebendazole is delivered to the stomach level in comparison to tablets containing not PEG. The marked hygroscopicity of PEGs and their plasticizing properties prevented rapid disintegration of the tablets in SGF, leading to a slower release of mebendazole. In fact, PEG is commonly used in pharmaceutical technology in formulating controlled release products as a result of its swelling ability in concentrations over 5% to result in slow release of the active substance from the formulation.

However, given that the site of action / absorption of mebendazole is not at the gastric but intestinal level, as well as the tendency to precipitate in the intestine (having a weak basic structure), the lower gastric level does not have a negative impact on the bioavailability of the product but, on the contrary, it may partly cancel out its precipitation tendency and increase its bioavailability.

#### *Modeling of the Release Kinetics*

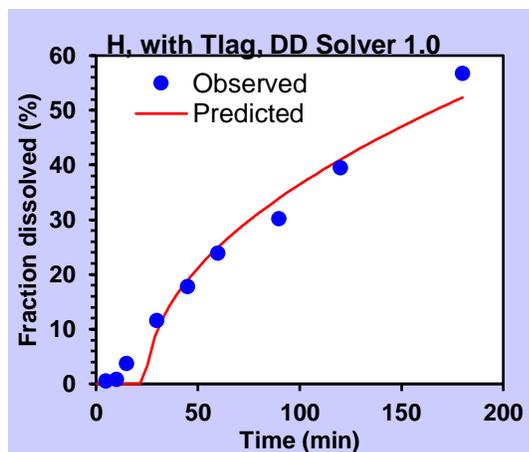
Relaxation of the polymer in the "swelling phase" is visible with the naked eye and it is possible to play a part, but a smaller one, in the second phase also.

Weibul model fitted well enough the data on entire interval, but this model has two parameters and implicit has a more power to reduce the errors. On other hand, from mathematical considerations (Sandulovici, 2009) connected with the stability of predictions, it is to prefer the models with lower numbers of parameters, in our case Higuchi and NW models.

An alternative approach is to consider a lag-time and after this to start the fitting data with the model. If this lag-time is established after examination of data with naked eye the approach is phenomenological. It is possible also to deduce this lag-time such to optimize the fitting performance, like presented in Figure 6. It is seen that such software approach suffers of two limitations.

First is that in the 0 – 20 minutes time interval, the model considers that release is absent but, as can be seen in Figure 2, this is not true.

The second aspect is that calculation of time lag by least square methods of fitting, represents the introduction of a new parameter in the model.



**Figure 6.** Fitting release data from the 1:1 dispersion, using DD Solver 1.0 program , with consideration of time-lag as parameter

Other aspect, much more fundamental, concerns the methods for comparison of the performances of models and selection of optimal ones. Most frequently it is used as criteria the correlation and regression performance (Simion 2018, Seher 2019, Nadejde 2019) A more complex analysis adds to this the informatics criteria of Akaike, Schwartz or Imbimbo (Prasacu, 2009) which introduce a penalty for increasing of the number of parameters. A more recent approach (Mircioiu, 2019; Paolino, 2019) is based on the phenomenological conditions and their translation in initial and boundary conditions for resolving differential equations associated to mathematical models. Phenomenological models are preferred to empirical ones, since give information about release mechanism.

In our case for example a good two steps fitting using square root model was obtained. This result was considered as being an argument for Higuchi model. Noyes Whitney model proved to be suitable, in the same context. But here a contradiction appears. Higuchi model assumes dissolution of active substance in the solvent which swells and washes layer by layer the matrix of the tablet, whereas NW model assumes release outside the matrix across the interface with the solvent. If we consider that NW is the true model, then the square root fitting corresponds to IR-SIM model, which considers, similar to the NW model, release across drug-solvent interface. Consequently, the interpretation that square root law good fitting represent applicability of Higuchi model is less reliable than the assumption of release following the IR-SIM model (Figure 7).

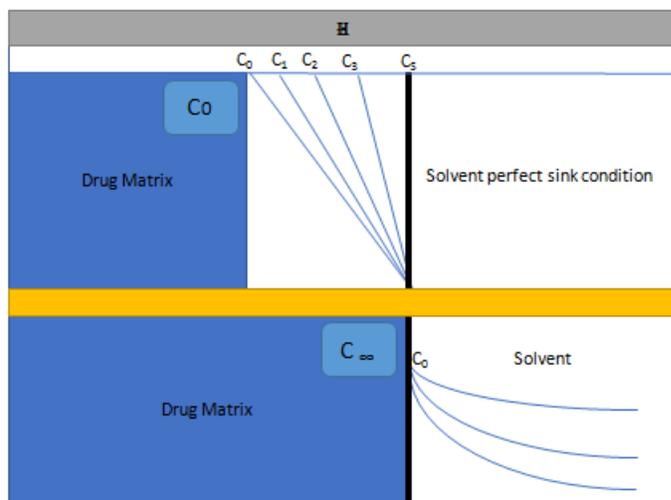


Figure 7. Release mechanisms according to Higuchi and IR-SIM models

The most important aspect concern biorelevance, i.e. correlation with in vivo dissolution, estimated by deconvolution from pharmacokinetics of active compound (Mircioiu, 2005, Preda, 2012). Other aspects as for example stability of estimated theoretical curves following small changes in composition of release medium (Pahomi, 2012), or metrics on spaces of curves, have to be examined. In essence, the problem of selection of the best model is, first of all, a problem of phenomenological analysis and only in the second step, a statistical and informational problem.

## CONCLUSIONS

1. Tablets based on solid mebendazole dispersions in PEG were realized in the ratio of 1: 1 and 1: 2.5, respectively. No higher ratios were used because, to obtain tablets containing 100 mg of mebendazole as dispersions, would require very large tablet masses and would contain large amounts of PEG 6000.
2. Swelling and disaggregation excipients led to a release in two, well separated, phases: pre-disaggregation and post- disaggregation.
3. Since the site of the action / absorption of mebendazole is not at the gastric but at the intestinal level, as well as the fact that mebendazole has the tendency to precipitate in the passage from the gastric fluid to the intestine fluid (having a weak basic structure), it was considered that the lower gastric level does not have a negative impact on the bioavailability of the product, but on the contrary, it may partially cancel out its tendency to precipitate.

4. Models square root and Noyes Whitney fitted well the release data, but separate, in predisintegration and postdisintegration phases.

5. Square root type behavior can appear in case of dissolution of active substance in solvent penetrating the tablet matrix (Higuchi model) or in case of release outside the matrix acting as an infinite reservoir. Fact that Noyes Whitney model suppose the release in a limit layer outside the matrix, it is an additional argument for IR-SIM model. The conclusion has a highly relevant methodological significance in conditions of quasi-total acceptance in literature of Higuchi model as most appropriate in case of release from supramolecular systems.

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