ORIGINAL ARTICLE

STUDY DESCRIBING THE FORMULATION AND THE RELEASE OF SOME ACTIVE PHARMACEUTICAL INGREDIENTS FROM HPMC HYDROPHILIC MATRIX TABLETS. NOTE I

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Abstract

For this study, hydroxypropylmethylcellulose (HPMC) matrix tablets were prepared by direct compression containing active pharmaceutical ingredients (APIs) from different biopharmaceutical classification system (BCS) classes, diclofenacum sodium (DicloNa) and phenytoin sodium (PheNa). For each API, three formulations were obtained, varying the amount of API and the concentration of HPMC matrix. After preparation, the tablets were submitted to pharmaco-technical tests and dissolution tests. The dissolution data was then fitted on different release models. Informations about the release kinetics from our tablets were obtained from these fittings.

Rezumat

Pentru acest studiu s-au obținut comprimate cu matriță hidrofilă bazată pe hidroxipropilmetilceluloză (HPMC) conținând substanțe active din clase BCS (sistemul de clasificare biofarmaceutică) diferite, diclofenac și respectiv fenitoină. Utilizând metoda comprimării directe, pentru fiecare substanță activă s-au realizat trei formulări, variind cantitatea de substanță activă și concentrația de HPMC. După preparare tabletele au fost supuse testelor farmacotehnice și testelor de dizolvare. Datele au fost apoi fitate pe diferite modele cinetice. Cu ajutorul fitărilor, s-au obținut rezultate referitoare la modul de cedare al substanțelor active din aceste comprimate.

Keywords: Phenytoin sodium, diclofenacum sodium, modified release, zero order kinetics, Korsmeyer-Peppas

Introduction

Although the modern concept of medicine included safety and efficacy surprisingly late, these two attributes became the fulcrum on which the drug product is balancing. Not surprisingly, the way in which the drug was evaluated changed quite a lot in less than one hundred years since tablets became available on the market. Regulatory agencies were interested in the active substance of a tablet (with regards to its purity and then quantity), the amounts found in the tablet, the time tablet breaks when are placed in a liquid, the time the actives need to be released in a standardized liquid in a certain percentage, in approximatively this chronology. Nowadays, a "good medicine" is becoming more and more a process than a product, as described by the quality by design concept. In order to check tablets, different fields are involved: chemistry, physics, physic chemistry and pharmacotechnics and, lately, the relatively new domain of biopharmaceutics. Slowly, the failure point moved from what's inside the product to its performance in intended usage, today's products being characterized by bioavailability/bioequivalence. This change of concept is not completely one way, however. Useful as they are, the *in vivo* studies are also expensive, so there is a lot of interest in either dropping them altogether when possible (in the

form of biowaivers), or at least reducing them as much as possible and using them as final check-points. To that effect, *in vitro* dissolution studies are very efficient tools. Things get even more complicated when modified release preparations are examined, release models, kinetics and fittings being involved [1].
Previous research [2, 3] revealed a quite strange release behaviour for similar formulations. To over-come the respective research's limitations (unusual tablet geometry; thin and lenticular), we redesigned the tablets using an optimised geometry; also different BCS classes of active ingredients were used, in order to obtain data regarding the influence of BCS class towards the release kinetics.
In the first part of this work we described the release from diclofenacum sodium (DicloNa) and phenytoin sodium (PheNa) hydrophilic matrix modified release tablets based on hydroxypropylmethylcellulose (HPMC).

Materials and Methods

Reagents
In addition to the APIs, the tablets contained Starch 1500 (Colorcon) as a diluent, HPMC - Methocel K15M Premium CR Grade (Colorcon), magnesium stearate, aerosile and talcum (Sigma Aldrich, Germany) as anti-frictional agents. The APIs were obtained from Sigma Aldrich.
Formulations
For each API, three formulations (F1, F2 and F3) were designed and presented in Table I.

Table I
Formulations

	F1		F2		F3	
	%	mg/tablet	%	mg/tablet	%	mg/tablet
API	33.33	200	22.17	133	33.33	200
HPMC	20	120	20	120	30	180
Starch 1500	45.52	273.1	56.68	340.1	35.52	213.1
Magnesium stearate	0.5	3	0.5	3	0.5	3
Aerosil	0.5	3	0.5	3	0.5	3
Talcum	0.15	0.9	0.15	0.9	0.15	0.9
Total	100	600	100	600	100	600

As it can be noted, there are two variables, the amount of API (either 33.33% or 22.17%) and the amount of HPMC (20% or 30%). Anti-frictional agents are at the same level all over the formulations and the diluent completes the formulation up to 100%.
The chosen method was the direct compression. For each formulation, the API, HPMC and diluent were sieved through a 400 mesh sieve and mixed for 12 minutes at 15 rpm. The lubricants were sieved through a 600 mesh sieve, added to the API mixture and further mixed for 6 minutes. The final mixture was then compressed using a Korsch EK-O type press, in order to produce 600 mg tablets. The dies/punches set were 12 mm wide, with flat faces.
Pharmacotehnical factors
Uniformity of mass, height, hardness and friability were checked before the dissolution tests. Tablet height and hardness were measured using a Vanderkampf VK 200 tester and the friability using a VanKel friabilator.
Dissolution assay
The dissolution system was a PTWS 100 with 6 compendial dissolution vessels, coupled with a programmable PTFC 2 Fraction Collector and Ismatec IPC peristaltic pump. The tests were carried on 6 tablets each. The conditions were as next presented [4, 5]. For phenitoyn sodium: *USP apparatus 2* (paddle), 50 rpm; medium: 900 mL purified and degassed water, automatic sampling (5 mL) with medium replacement, timing was 0.5 - 1.0 - 1.5 - 2.0 - 2.5 - 3.0 - 3.5 - 4.0 - (5.0) - 6.0 - 20.0 - 24.0 h after immersion. It was used a spectrophotometric assay with the next parameters: first derivative, d_1 = 222 nm, dilution factor 26: 2500 µL blank medium + 100 µL sample, only for samples during the 5 - 24 h interval. For diclofenacum sodium: *USP apparatus 2* (paddle), 50 rpm; medium: 900 mL degassed pH 7.5 phosphate buffer (USP37/NF32), automatic sampling (5 mL) with medium replacement, timing was 1.0 - 2.0 - 3.0 - 4.0 - 5.0 - 6.0 - 7.0 - 8.0 - 9.0 - 10.0 h after immersion. It was used a spectro-photometric assay with the next parameters: λ = 276 nm, dilution factor 3: 2000 µL blank medium + 1000 µL sample.

Results and Discussion

The data obtained after the evaluation of the pharmacotehnical factors are depicted in Table II.
As we can see from Table II, the tablets from each batch are uniform in regard to weight, height and mechanical resistance. For all tablets friability is less than the maximum allowed of 1%. Due both to equipment limitations and the different properties of the six powder mixes, the mechanical and physical properties are different; we tried to set up the tableting press in order to apply roughly the same force from batch to batch.

Table II

Pharmacotechnical factors (M ± SD)

API	Formulation	Mass (g)*	Height (mm)**	Hardness (kponds)**	Friability (%)
DicloNa	F1	0.6079 ± 0.0028	3.921 ± 0.0328	7.98 ± 0.8766	0.38
	F2	0.5972 ± 0.0049	3.889 ± 0.0172	9.81 ± 0.8319	0.32
	F3	0.6054 ± 0.0046	3.99 ± 0.0442	9.98 ± 0.7955	0.38
PheNa	F1	0.5993 ± 0.0056	4.087 ± 0.0478	10.18 ± 0.6613	0.37
	F2	0.5996 ± 0.0059	3.944 ± 0.0259	12.66 ± 0.9501	0.22
	F3	0.6072 ± 0.0044	4.362 ± 0.0520	11.85 ± 0.7487	0.19

*Average, n = 20; **average, n = 10.

For diclofenac sodium extended release tablets, the United States Pharmacopoeia 39 includes four individual dissolution tests as part of the individual monograph. All the procedures were based on the paddle method, with two levels of the stirring rates (50 rpm and, respectively 100 rpm) and correlated acceptance intervals (samples collected for 10 or 24 hours). One of the procedures recommends the use of sinkers, most probably added for the prevention of both sticking and floating phenomena. To be noted, the adherence to the bottom of the vessel reduces the surface available for release, whereas the gradual hydration may trigger the floating of the dosage unit, with consequent increase in the variability of the experimental data. The time points and related limits vary largely, which means that formulations with distinct *in vitro* dissolution behaviour have similar *in vivo* performance. The relevance of *in vitro* test results is depending upon the qualitative and quantitative composition, as well as on the impact of process variables. For swelling, erodible matrixes, the physiological factors, especially the peristaltic movements' specific to the gastro-intestinal environment, are key factors for the release. The hydrodynamics of the paddle apparatus has known limitations in simulating the concomitant swelling and erosion, therefore the relevance of *in vitro* testing may be claimed only after the demonstration of *in vitro – in vivo* relations or correlations, using the biobatch and side batches [6].

The model-independent assessment of the *in vitro* dissolution profiles indicated no significant differences between the three modified release formulations containing sodium diclofenac. While the dose-release proportionality was expected, considering that the same amount of the macromolecular agent was used for 200 mg and 133 mg strengths, the differences less than 3% between the mean fractions dissolved by 50% increase in the quantity of the matrix forming agent was intriguing. The results of the profile fitting confirmed that the specific index n of the Korsmeyer Peppas model, which provided the most adequate correlation between experimental and estimated release data (correlation coefficient higher than 0.999, Akaike information criterion between 1.71 and 10.23), was significantly different. For formulation F2, the diffusional control of the release was confirmed by values of 0.55, whereas a 10% increase was noted between F1 (n = 0.60) and F3 (n = 0.66). The non-Fickian model was consistent throughout the test duration, with presumable compliance with sink conditions requirements. The combined role of the diluent and hydroxypropyl-methylcellulose in the overall swelling process may explain the lack of significant differences in terms of absolute fraction release, as well as for the changes in release rate. Both excipients are responsible for the thickness and microstructural properties of the limiting gel barrier. A more intense stirring rate may be more discriminative for the non-similarities in the quantitative composition, but it is not clear whether they may change the *in vivo* performance.

For the formulations containing sodium phenytoin, the release was rather linear, the overall kinetics being described by a zero-order process for the first 6 hours. Considering that the only difference between the two groups of formulations is the API, it is obvious that the kinetic differences are triggered by two factors, i.e. the composition of the aqueous media and the physico-chemical properties of the drug. The use of water without the compendial buffer components may induce distinct swelling profiles, as well as significant differences in the diffusional resistance of the gel barrier. Moreover, water is not a good *in vitro* release medium, based on the lack of buffer capacity and large variation of characteristics between laboratories [7, 8]. The fractions released after 360 minutes are more discriminative with respect to the content of hydrophilic macromolecular agent. The dissolution was slower for F3 compared to F1, with differences higher than 10% at 24 hours while the kinetic model was consistent. The higher release rate for the 200 mg strength compared to 133 mg can be explained by the concentration gradient through the gel barrier, combined with a lower solubility of sodium phenytoin in water. As can be seen, phenytoin sodium F2 and F3 appear to be quite similar (Figure 2), while F1 shows a faster release. All three diclofenacum sodium formulations release the API quite similarly (Figure 1), but a bit slower than the phenytoin sodium formulations.

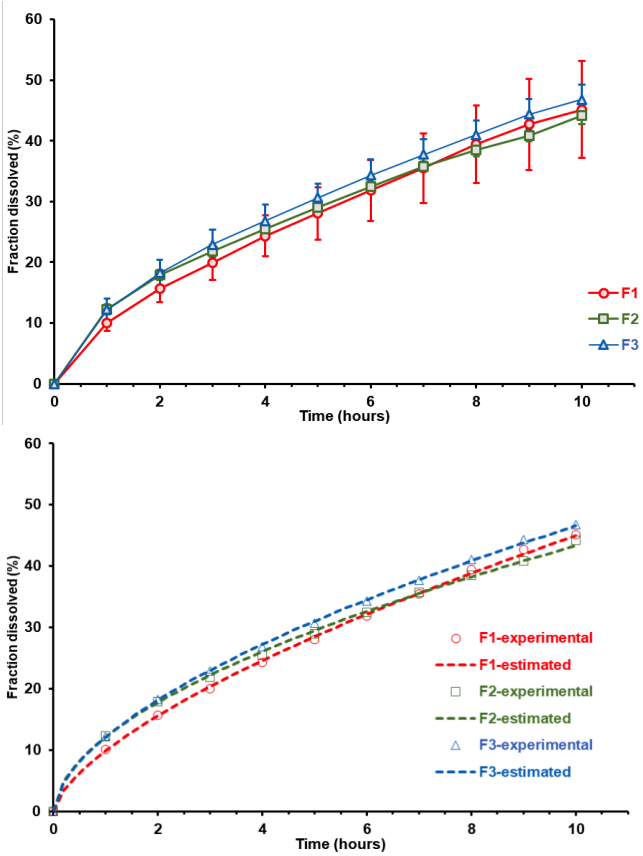

Figure 1.
DicloNa release, error bars (up), experimental *vs* estimate (down)

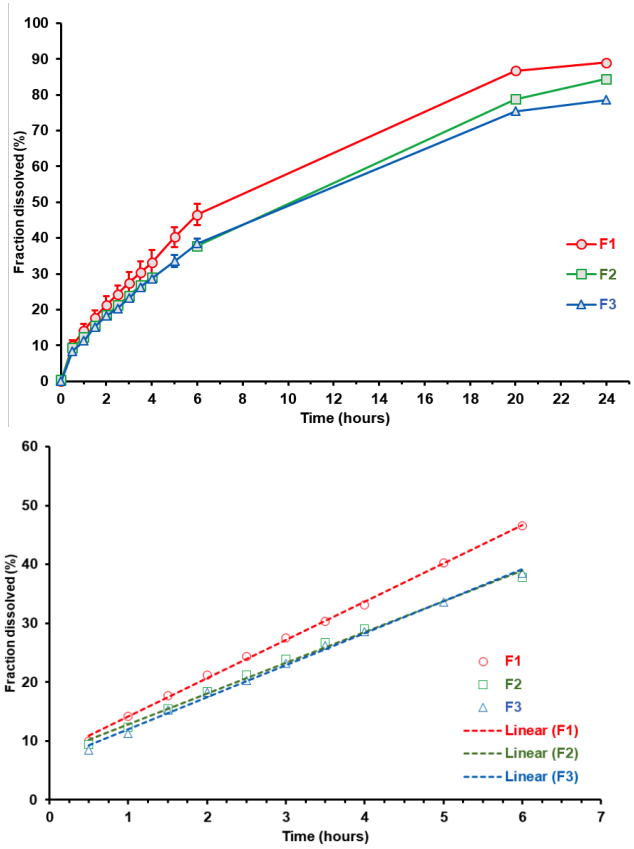

Figure 2.
PheNa release 24 hours (up), first 6 hours (down)

Phenytoin sodium, is more soluble than diclofenacum sodium, therefore at higher API concentration and lower HPMC concentration offered the fastest release from the six formulations presented. The decrease in phenytoin sodium concentration or the increase of HPMC concentration yielded quite similar release plots. The less soluble diclofenacum sodium showed a slower release from the hydrophilic matrix (Figure 3).

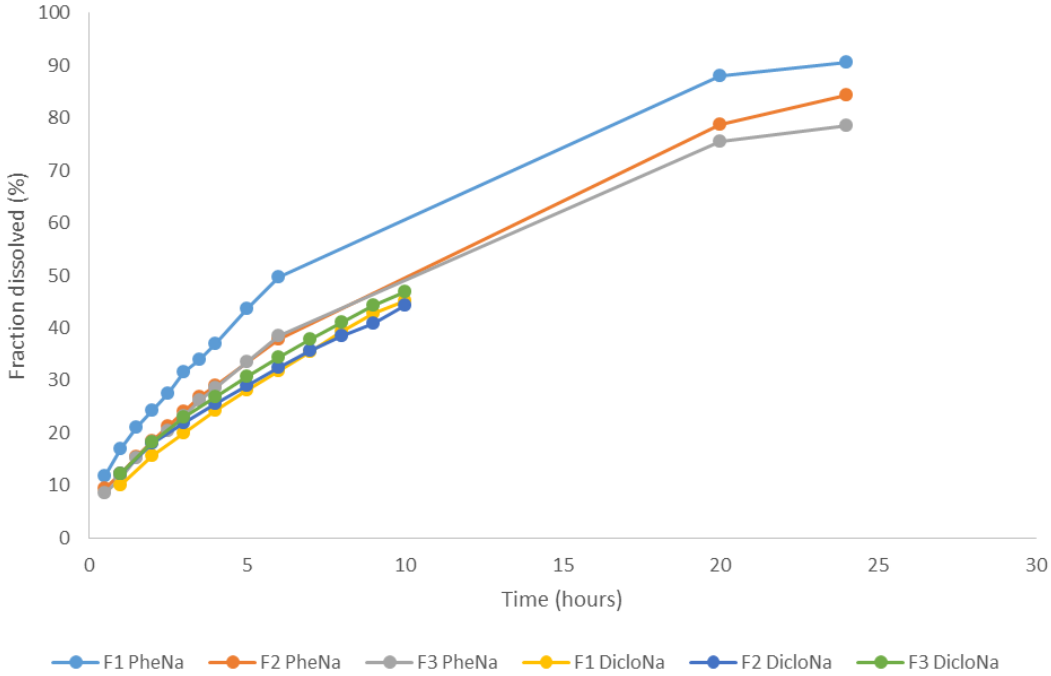

Figure 3.
Results (averages, overlaid, connected) for phenitoyn sodium and diclofenacum sodium

The calculation of compendial similarity metrics confirmed the preliminary conclusions. There were only two cases of difference, both suggested by the factor f1 for sodium phenytoin: 17.46 for strength comparison (F1 *vs.* F2) and 19.53 for the controlled variation in the quantity of macromolecular agent (F1 *vs.* F3).

When comparing the same formulation with different APIs, we must consider the most obvious sources of difference: the API itself (with regard to the substance solubility and dissolution rate) and the differences in manufacturing process (especially tableting pressure). Since the tableting press was not instrumented, data regarding compaction pressure is unavailable. The only evaluation regarding the compact can be done using the hardness results. However, the hardness results are influenced not only by the compaction pressure, but also by the characteristics of the powder mix. Although the other adjuvants are the same, the API is not - so it will influence the tablet properties by itself and by its interactions with the other components of the mix [9].

More information can be extracted by fitting the profiles on the more commonly used release models.

One of the most often used models to describe the release from a matrix system was described by Higuchi [10-12]. The simplified Higuchi equation states that the amount of drug released is proportional to the square root of time (Eq. 1). Assumptions apply to this model: the matrix contains a drug concentration much higher than the drug's solubility in the environment; diffusion is unidirectional; the thickness of the dosage form is much larger than the size of drug molecules; swelling is negligible; diffusion is constant; perfect sink conditions are attained in the environment. Examining the Higuchi plots and the regression trendline for the phenytoin sodium formulation, we found that the points are quite linear during the first 4 hours. After 4 hours, the linearity changed, however the R^2 coefficients are still good.

$$f_i = Q = K_H\sqrt{t} \quad \text{(Eq. 1)},$$

where: $f_i = Q$ – fraction of drug released on time t; K_H – Higuchi release constant.

Korsmeyer-Peppas [13, 14] (or Power Law) is a modification of the Higuchi model. It basically states that the amount released is proportional to the time raised to a power (called exponent of release, n) (Eq. 2). This equation is useful to study the release from polymeric systems with unknown or multiple mechanisms of release. Also, according to the value of the exponent of release, it can be classified [15] into Fickian model (n = 0.5, Case I), non-Fickian (n = 1, Case II), anomalous non-Fickian (n is between

0.5 and 1, anomalous Case) or Super Case II (n > 1). Considering the full data range, our formulations showed exponents of release around 0.6. However, it is recommended to use the range in which the amount released is less than 60%. In the case of diclofenacum sodium, all points are under 60%, but for phenytoin sodium we had to discard the last two points. However, the n values did not significantly change (Figure 4). For all formulations described, dissolution is anomalous, with n values close to 0.6, which indicates similar rates of solvent diffusion and polymeric matrix relaxation. Changing the nature of the API or the concentration of HPMC from 20% to 30% did not alter this characteristic, as expected.

$$f_i = \frac{M_i}{M_\infty} = Kt^n \quad \text{(Eq. 2)},$$

where: M_i – amount of drug released over time t; M_∞ – amount of drug at equilibrium state; K – release velocity constant; n – exponent of release.

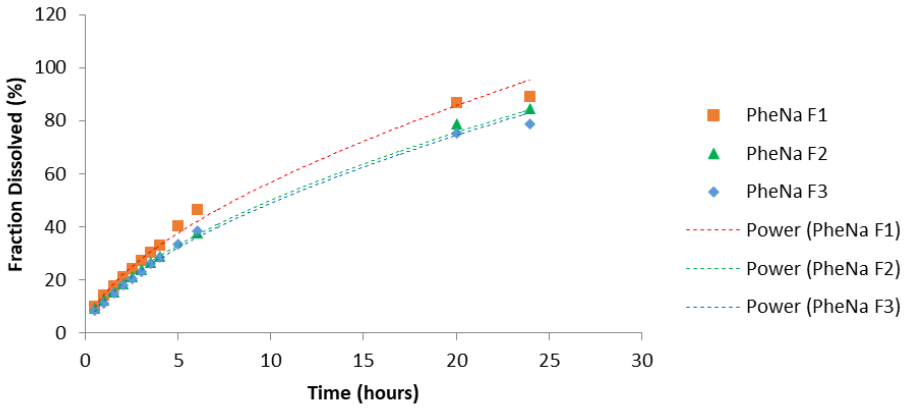

Figure 4.
PheNa Korsmeyer-Peppas fitting - points and trendline. Data until 6 hours lines up.

Hixon-Crowell model [16] states that the cubic root of the fraction of drug still unreleased is proportional to the time (Eq. 3). The assumptions are that the dosage form is quite flat and the dissolution happens in planes parallel to the surface; the tablet dimensions decrease with the maintenance of the geometry and that the limiting factor for the drug release is dissolution rate and not diffusion. Looking at the PheNa data (Figure 5), we noticed that the Hixon-Crowell plot war linear for the first 6 hours; in the case of F2, the linearity did not changed.

$$\sqrt[3]{1 - f_i} = 1 - K_\beta t \quad \text{(Eq. 3)},$$

where: K_β – release constant.

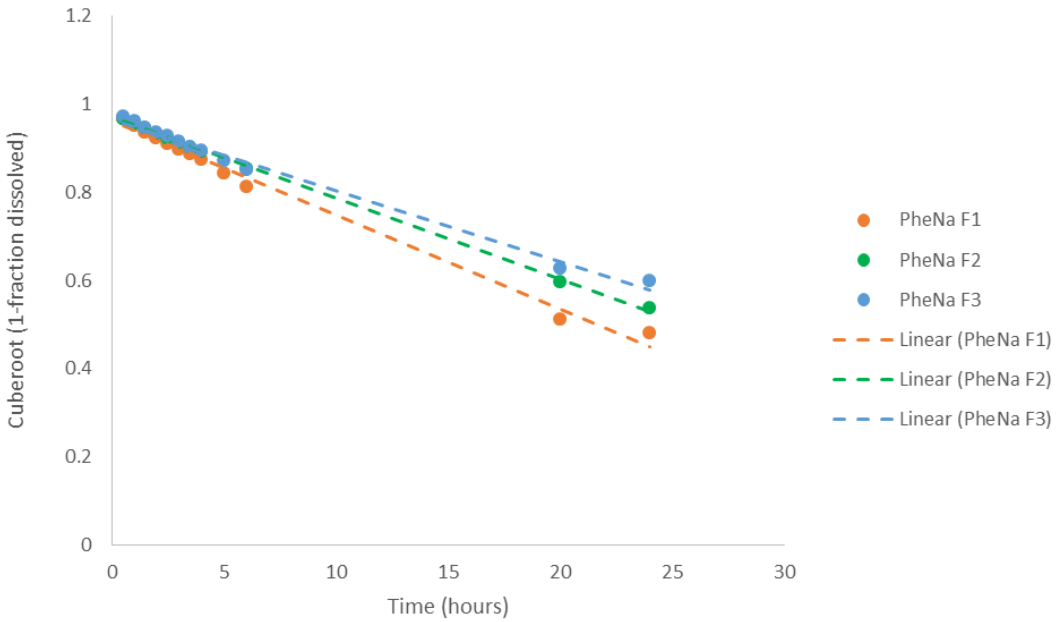

Figure 5.
PheNa Hixson-Crowell fitting – points and trendline. Good linearization for the first points.

Weibull equation [17, 18] (Eq. 4) is more useful in comparing drug release profiles than in characterizing a formulation. The a and b factors are not intrinsic to the dissolution of a drug. The Weibull equation is often rearranged (by taking the log) in a form that is easier to plot and read [19] (Eq. 5).

$$m = 1 - exp\left[\frac{-(t-T_i)^b}{a}\right] \quad \text{(Eq. 4)},$$

or

$$\log[\ln(1-m)] = b\log(t-T_i) - \log a \quad \text{(Eq. 5)},$$

where: m – accumulated drug fraction; T_i – localization parameter; latency time; a – scale parameter; b – form parameter.

The centralized data can be found in the Table III.

Table III

Model-fitting data

Model / Formulation	Zero order (up to 6 h)	Higuchi	Korsmeyer-Peppas			Hixson-Crowell	Weibull
	R^2	R^2	R^2	n	n (q < 60%)	R^2	R^2
PheNa F1	0.9984	0.9941	0.9947	0.592	0.618	0.9915	0.979
PheNa F2	0.9933	0.9963	0.9958	0.595	0.573	0.9987	0.9876
PheNa F3	0.9959	0.9964	0.9958	0.606	0.624	0.9907	0.9889
DicloNa F1	0.9947	0.9944	0.9992	0.658	-	0.9986	0.9986
DicloNa F2	0.9908	0.9971	0.9987	0.554	-	0.9963	0.9988
DicloNa F3	0.9908	0.9977	0.9995	0.585	-	0.9969	0.9985

Despite the initial linear release, the overall dissolution processes of sodium phenytoin from the three modified release formulation were of non-Fickian diffusional type, being accurately described by the Korsmeyer-Peppas model. The exponent values were very close, independent on the strength and on the composition variables.

Conclusions

For the studied formulation, it can be concluded that in the long timeframe the release is best described by the Korsmeyer-Peppas model. The *in vitro* process was non-Fickian and diffusion-controlled. However, for the first six hours, the PheNa release is almost linear, zero order model.

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