INFLUENCE OF SOME FORMULATION FACTORS ON THE RELEASE OF PHENYTOIN SODIUM FROM HYDROPHILIC MATRIX TABLETS

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Abstract

The aim of this study was the formulation and evaluation of extended release sodium phenytoin tablets based on hydroxypropylmethylcellulose (HPMC) hydrophilic matrix. Different ratios of active ingredient, HPMC and fillers were used. Methocel® K15M Premium CR Grade was the chosen HPMC sort, while Starch 1500 was chosen as filler, both materials showing swelling properties when wet. The formulations were mechanically evaluated, then a set of *in vitro* release tests were performed on the tablets. For each formulation, dissolution was carried out at three stirring speeds and in two types of vessels. Dissolution profiles were obtained for each experiment and that data was fitted on the usual release models. It was discovered that certain combinations of excipients can result in a change of release kinetics.

Rezumat

Scopul acestui studiu a fost formularea şi evaluarea unor tablete cu cedare extinsă conţinând fenitoină sodică bazate pe matriţe hidrofile cu hidroxipropilmetilceluloză (HPMC). În studiul formulării, s-au folosit diverse proporţii de substanţă activă, HPMC şi diluant. Methocel® K15M Premium CR Grade a fost tipul de HPMC ales ca formator de matriţă hidrofilă, iar amidonul pregelatinizat Starch 1500 ca diluant, ambele materiale prezentând proprietăţi de îmbibare. Formulările au fost întâi evaluate mecanic, iar apoi testate din punctul de vedere al cedării *in vitro*. Testele de dizolvare s-au realizat pentru fiecare formulare la trei viteze diferite de agitare şi în două tipuri diferite de vase. În cazul fiecărui test s-au obţinut profile de dizolvare, iar datele au fost fitate pe modelele de cedare uzuale. S-a stabilit că anumite combinaţii de excipienţi pot conduce la modificarea cineticii de dizolvare.

Keywords: Sodium phenytoin, modified release, *in vitro* dissolution, Peak vessels, modeling

Introduction

Phenytoin (diphenylhydantoin) is a commonly used antiepileptic from the hydantoin's class. It is prescribed and used mainly in epilepsy, *grand mal* seizure; it is also classified as a class Ib antiarrhythmic and is also considered an option in trigeminal neuralgia.

The aim of this study was to evaluate the possibility of formulating prolonged release tablets containing sodium phenytoin. Modified release tablets allow a smaller number of daily administrations, improve the patient compliance and favour more linear plasma concentrations of the active ingredient pharmaceutical (API) [6, 9]. At the time of the study, there was only one extended release phenytoin formulation available worldwide, which consisted of one or two extended release minitablets within a capsule**.**

In order to modify the release, we chose to manufacture hydrophilic matrix tablets, based on hydroxypropylmethylcellulose (HPMC), which is one of the most used hydrophilic matrix forming polymers [4, 5].

The aim of the study was to find out the influence of some of the factors involved in the formulation and evaluation of extended release sodium phenytoin tablets based on HPMC hydrophilic matrix, as far as pharmacotechnical properties and release kinetics are concerned [1, 3, 7, 8]. The experimental protocol offered the opportunity to screen the interaction between qualitative and quantitative composition, a model hydrophilic drug and *in vitro* testing parameters.

Materials and Methods

Materials: Active pharmaceutical ingredient (API): Phenytoin sodium, hydrophillic matrix former: Methocel® K15M Premium CR Grade (Colorcon), dilluant: Starch® 1500 (Colorcon), Lubricants: Magnesium Stearate (Undesa Union Derivain SA), Aerosile® (Degussa GmbH).

Preparation: Three formulations (named F1, F2, F3) were designed based on direct compression tablet manufacturing methods. F1 was based on Methocel® usage recommendations, in order to evaluate the API behaviour in hydrophilic matrix tablets, F2 contained less API than F1, in order to evaluate formulation robustness and F3 contained more Methocel® than F1, in order to indicate how the matrix-forming agent influences the API release. The three formulations are shown in Table I.

Table I.
Phenytoin sodium formulations

Formulation	F1		F2		F3	
Excipient	%	mg/tablet	%	mg/tablet	%	mg/tablet
Phenytoin sodium	33.33	200	22.17	133	33.33	200
Methocel®	20.00	120	20.00	120	30.00	180
Starch	45.67	274	56.83	341	35.67	214
Magnesium stearate	0.50	3	0.50	3	0.50	3
Aerosile®	0.50	3	0.50	3	0.50	3
Total	100.00	600	100.00	600	100.00	600

The API, Methocel® and filler were mixed for 15 minutes in a cubic mixer at about 15 rpm, then the lubricants were added and the mixing was further continued for 10 minutes. The powder was then compressed using a Triowin® tabletting machine, with 15 mm punches, resulting in 600 mg double convex tablets. Tablet size and shape were imposed by available punches/dye sets.

The three batches were first mechanically tested (mass, hardness, friability) and then the dissolution tests were performed. The three experimental formulations were subject to an *in vitro* dissolution testing protocol with two factors of variation concerning the experimental parameters. Firstly, due to the nature of the dosage forms and the intended mechanism of release, the dissolution testing focused on the development of an abbreviated procedure, assessing the release profile over a 6 hours' time interval. The stirring rate varied in the compendial recommended interval, i.e. 50, 75 and 100 rpm. Two types of dissolution vessels were used, round bottom, USP compliant, 1000 mL vessels and Peak™ vessels, Vankel Technologies Inc., US. The latter design has two compendial applications, both methodologies addressing the variability associated with the cone formation, described as the accumulation of a high quantity of dispersed particle in the region underneath the paddle. In this case, the moulded, inverted cone placed at the bottom of the vessel was used as an element of hydrodynamic alterations, therefore exposing the pharmaceutical formulation to a high share rate profile depend on the *in vitro* release fluid. Secondly, according to previous evaluation using similar vessels, the formulations are also exposed to peripheral erosion, which theoretically corresponds to a phenomenon typically occurring in the gastro-intestinal environment, following *in vivo* administration. Based on the solubility profile of sodium phenytoin, 900 mL of purified water was used as dissolution media, previously degassed by filtration under vacuum.

Samples of 5 mL were collected at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0 and 6.0 hours after introduction of the tablets. The sampled volume was immediately replaced with an equal amount of fresh media. Each evaluation was performed in triplicate. The quantitative analysis of sodium phenytoin was performed spectrophotometrically (λ_{max} = 258 nm).

As a general procedure, the mean dissolution profiles were analysed using compendial metrics f_1 and f_2 (difference and, respectively, similarity factor, the calculation formulas given below). Various kinetic models (zero and first order kinetics, Higuchi and Korsmeyer-Peppas), currently used for the analysis of modified release profiles, were applied to the mean values of the fraction dissolved, in order to adequately identify the changes in the release mechanism induced by the differences in composition.

The individual dissolution profiles (expressed as fraction released per time unit) were analysed. The mean profiles were calculated only if the values of the coefficient of variation were lower than 20% for earlier time points and lower than 10% for the remaining samples. The comparison was performed based on the currently recommended difference (f1) and similarity (f2) metrics:

$$f_1 = \frac{\sum_{i=1}^{n} |\mu_{ri} - \mu_{ti}|}{\sum_{i=1}^{n} \mu_{Ri}} x100 \quad , \qquad f_2 = 50 \log \left\{ \left[1 + \frac{\sum_{i=1}^{n} (\mu_{ri} - \mu_{ti})^2}{n} \right]^{-1/2} * 100 \right\} ,$$

where:

n = number of sampling points

μ_{ri} = mean fraction released at t_i point for the reference formulation

μ_{ti} = mean fraction released at t_i point for the reference formulation.

Similarity was concluded for f_1 <15 and f_2 >50.

Only a single point after 85% was considered.

Notably, the evaluations of similarity were further conditioned by the existence of the same kinetic pattern between the two compared formulations.

Results and Discussion

Mechanically, the tablets performed well. The results are shown in Table II.

Table II.
Mechanical results

Formulation	Friability (%)	Hardness (kiloponds)
F1	0.42	7.6
F2	0.39	8.8
F3	0.43	5.9

The plots for the dissolution profile are shown in Figure 1.

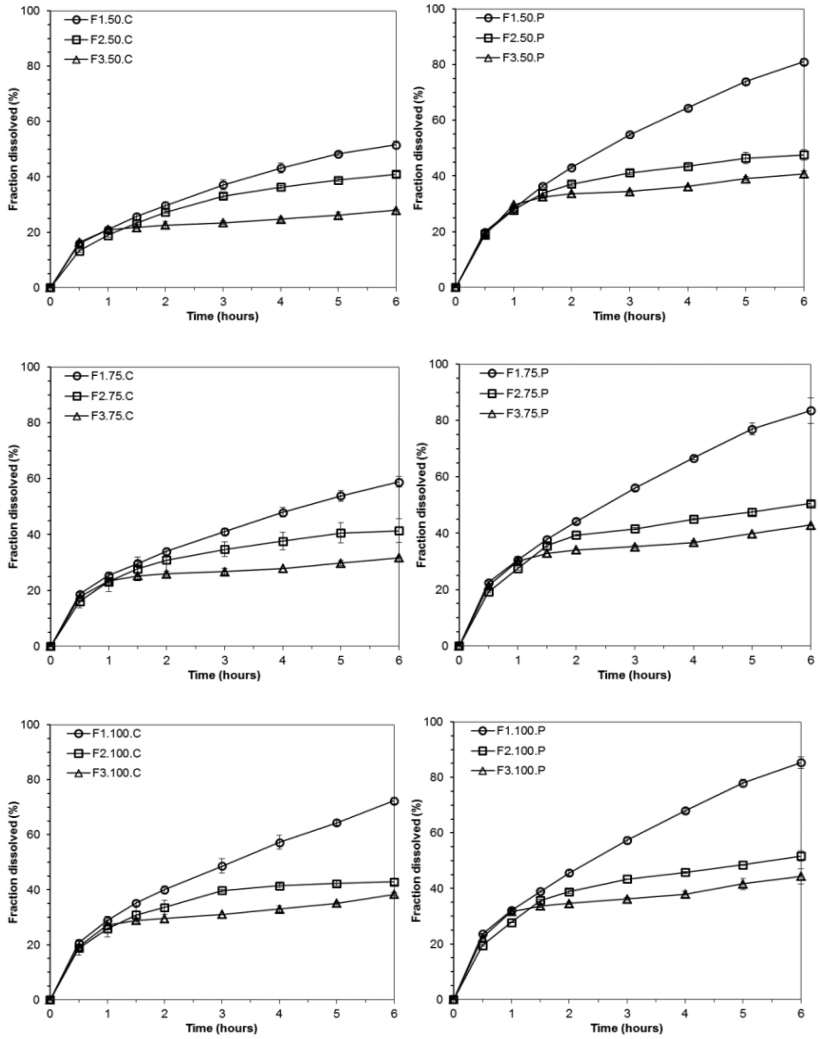

Figure 1.
Mean *in vitro* release profiles of sodium phenytoin in water from formulations F1, F2 and F3, in 900 mL water using conventional - C (round bottom) and Peak^{TM} - P vessels, at a) 50 rpm, b) 75 rpm and c) 100 rpm

Although the results for the mechanical testing are less than stellar, they meet the compendial demands. We consider that the relatively high friability values and the relatively low hardness values are due to the shape and size of the punches used in the tableting machine which yielded quite thin and wide biconvex tablets. Even so, the compendial demands were met [10, 11, 12].

It is noteworthy that the formulation variations between F1, F2 and F3 are not straightforward. In most cases, when it is wanted to obtain tablets containing different amounts of the same API, the formulation is scaled up (or down), meaning that the percentage between the components is constant. In our study, the total weight of the tablet was kept constant, thus varying the percentages of API, HPMC and filler.

Release kinetics fitting to usual models in show in Table III.

Table III.

Dissolution fitting. (coding: Fi – formulation number; C – classical, P – Peak vessel; 50, 75, 100 – rotation speed – rpm)

Test	R square			
	Linear	Higuchi	Kormeyer-Peppas	Weibull
F1 C 50	0.9776	0.9979	0.9969	0.9984
F1 C 75	0.9852	0.9988	0.9978	0.9974
F1 C 100	0.9873	0.9977	0.9985	0.9937
F2 C 50	0.9238	0.9829	0.9903	0.9992
F2 C 75	0.8847	0.9618	0.9753	0.9992
F2 C 100	0.8215	0.9203	0.9587	0.9993
F3 C 50	0.8696	0.9259	0.9434	0.9998
F3 C 75	0.8292	0.9007	0.9269	0.9997
F3 C 100	0.8538	0.9117	0.9241	0.9994
F1 P 50	0.9839	0.9988	0.9992	0.9893
F1 P 75	0.9888	0.9963	0.9963	0.9879
F1 P 100	0.9898	0.9965	0.9961	0.9863
F2 P 50	0.8469	0.9371	0.9581	0.9988
F2 P 75	0.8426	0.9294	0.9476	0.9986
F2 P 100	0.8605	0.9438	0.9597	0.9985
F3 P 50	0.7419	0.8357	0.8587	0.9993
F3 P 75	0.8271	0.8962	0.9159	0.9992
F3 P 100	0.8429	0.9036	0.9163	0.999

Two kinetic models were found to adequately describe the *in vitro* release profile, Higuchi (square root law) and Korsmeyer-Peppas (exponential release or power law) models.

The Higuchi model ($F\%=kt^{0,5}$, where F is the fraction of active pharmaceutical ingredient released, k is a constant and t is the time) is used for fitting *in vitro* data in case of a semisolid matrix controlling the release

through diffusional resistance. The Korsmeyer Peppas model [4] ($F\%=kt^n$, where F is the fraction of active pharmaceutical ingredient released, k and n are model dependent constants) describes an exponential function, the n parameter being an indicator of the mechanism of release, depending also on the geometry of the matrix. For non-Fickian (anomalous) release from spherical particles, the release is dependent on both diffusion processes and relaxation of macromolecules (n between 0.43 and 0.85). Values of n = 0.43 indicate a Fick-type (transport type I) mechanism, while n higher than 0.85 corresponds to super case II type.

When compendial metrics where applied, the similarity was concluded between F1 and F2, based on *in vitro* data theoretically providing the most discriminatory conditions (conventional vessels, 50 rpm) (f_1=14.88; f_2=62.00). F3 was found to be non-similar with both F1 (f_1=32.86; f_2=43.36) and F2 (f_1=25.23; f_2=54.24), based on 50% increase in the relative concentration of the macromolecular agents. This further generated different kinetic models. The release profiles of F1 and F2 were adequately described by the Higuchi model (k=0.021, respectively 0.019; R^2>0.997), indicating that, after an initial lag-time, the gel barrier formed on the surface of the tablet formulation is controlling the access of the solvent to the solid particles of the active ingredient. The higher concentration of the gel-forming cellulose derivative led to a more complex dissolution pattern, including the previously mentioned macromolecular relaxation. Therefore, Korsmeyer-Peppas model adequately fitted the experimental data throughout the entire 6 hours profile (n=0.18; R^2=0.991). It is to be mentioned that after an initial 4 hours' time interval, the hydration process generated a considerable increase in volume of the solid formulation, which further determined the floating to the upper region of the vessel. Although the correlated variation in the hydrodynamics is considerable, this didn't generate a variability of experimental data. Nevertheless, it seems that the release was limited to a specific level (apparent low release rate) for formulation F3, or the release profile is actually composed of two distinct regions for F2 (the first 4 hours with Fickian behaviour and the remaining segment, probably with zero-order kinetics) (Figure 2).

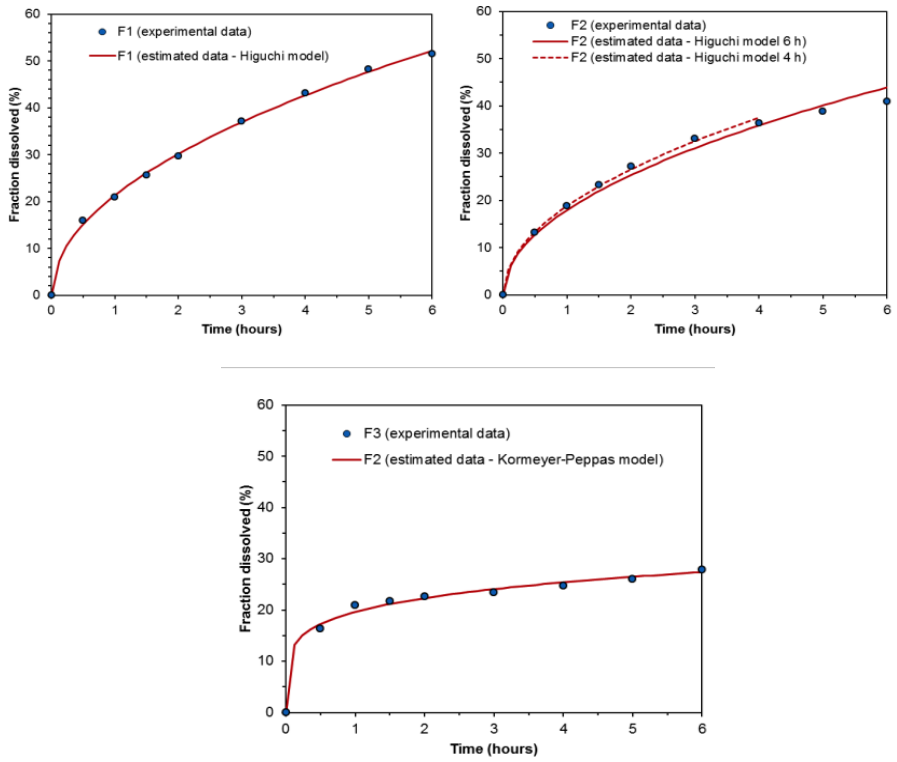

Figure 2.
Modeling of the *in vitro* mean dissolution profiles

Increasing the stirring rate provided a more rapid hydration of the matrix, registering a marked increase of the fraction dissolved for F1 and F3. For formulation F2, the amount released after 6 hours was almost independent on the hydrodynamic pattern, in case of the conventional vessels (varying between 40.9 and 42.8). A possible explanation could be a complex interplay between HPMC and starch, leading to a constant diffusional resistance of gel-barrier.

Noteworthy, the impact of the stirring rate was minimal in the case of Peak^{TM} vessels. The formulations were exposed to a high share rate pattern, most probably generating similar hydration profiles and consequently, constant release rates.

Conclusions

Three hydrophilic matrix extended release tablets formulations containing sodium phenytoin were produced, using HPMC as matrix

forming polymer. The tablets were mechanically evaluated and then submitted to *in vitro* dissolution tests, both on classical and Peak^{TM} vessels, at different stirring speeds. It was found out that all three formulations yielded tablets able to release the API for more than 6 hours. It was also found out that F3 formulation exhibited a different release kinetic than F1 and F2.

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