

THE *IN VITRO* RELEASE MECHANISM OF IBUPROFEN FROM CONVENTIONAL AND SPECIAL DOSAGE FORMS

DOINA DRĂGĂNESCU¹, ELENA POPA DANIELA², DUMITRU LUPULEASA³, GEORGE TRAIAN ALEXANDRU BURCEA DRAGOMIROIU², SIMONA MIRON DALIA¹, ADRIAN COSMIN ROȘCA^{4*}, RAZVAN-DANIEL CHIVU⁵

University of Medicine and Pharmacy „Carol Davila” Bucharest, Faculty of Pharmacy, 6th Traian Vuia street, 020956, Bucharest, Romania.

¹*Department of Pharmaceutical Physics and Informatics,*

²*Department of Drug Control,*

³*Department of Pharmaceutical Technology and Biopharmaceutics,*

⁴*Ovidius University Constanta, Faculty of Pharmacy, Department of Drug Control, Constanta, Romania*

⁵*University of Medicine and Pharmacy „Carol Davila” Faculty of Medical Midwifery and Nursing Bucharest, Romania*

**corresponding author: cosmin_rosca13@yahoo.com*

Abstract

Six pharmaceutical dosage forms (sugar coated tablets, hard and soft gelatin capsules, oral suspension and rectal suppositories), containing various concentrations of ibuprofen as single active ingredient, were evaluated *in vitro*, based on the available compendial recommendations. Several methodological adaptations were implemented, in order to adequately address the particularities of the formulations and the rate-limiting step of the release process. The analysis of the mean dissolution profiles was focused on applicability of different kinetic models, possible explanations for observed similarities or non-similarities and on the foreseen limitations in applicability of the test conditions, in the context of biowaiver.

Rezumat

Șase forme farmaceutice (drajeuri, capsule gelatinoase moi și tari, suspensie orală și supozitoare rectale), conținând diferite concentrații de ibuprofen ca unic principiu activ, au fost evaluate *in vitro*, pe baza recomandărilor compendiale disponibile. Au fost implementate mai multe adaptări metodologice, în concordanță cu particularitățile de formulare și etapele limitante ale procesului de cedare. Analiza profilelor medii de dizolvare a fost axată pe aplicabilitatea unor diferite modele cinetice, posibile explicații pentru similaritățile sau non-similaritățile observate și limitări previzibile ale aplicabilității condițiilor de testare, în contextul exceptării de la evaluarea *in vivo*.

Keywords: ibuprofen, modeling, *in vitro* dissolution test.

Introduction

Ibuprofen, one of the safest non-steroidal anti-inflammatory drugs [1], has been the center of considerable debate in terms of its biopharmaceutical properties and the prospected applicability of the biowaiver principles, based on the initial [2] and specific subsequent development [3] of the Biopharmaceutical Classification System (BCS, [4]). The acido-basic characteristics (pK_a 4.5 – 4.6 [5]) limit the fraction dissolved from orally administered, solid dosage forms. As for many other highly permeable, weak acid drugs, the high solubility profile at the major site of absorption, the small intestine, generated a new, yet unofficial, subgroup of BCS class II, i.e. the “intermediate solubility class” [6]. The wide range of pH values and the non-relevant nature and volume of fluid are incriminated in the conservative attitude of the regulatory authorities. The “too strict” definition of this critical biopharmaceutical property could be considered as a prudent approach in granting biowaiver for several drugs products.

The new guidance of European Medicine Agency [3] apparently addressed the pressing need for more permissive cut-off values and parameters, widening the framework of BCS-based exemptions from clinical trials. The very rapid release pattern (>85% of the label claimed amount, dissolved in 15 minutes or less, in all three media) is now requested for oral solid dosage forms of immediate-release oral dosage forms containing BCS class III drugs [7,8]. A similar criterion would not be feasible for BCS class II drugs, since the low solubility in the acidic media will frequently lead to non-sink conditions, incomplete release and lower sensitivity of *in vitro* methodology to the formulation factors. Nevertheless, the acidic stage is an essential, sometimes crucial stage for the *in vivo* evolution and biopharmaceutical outcome of oral formulations. Alternative pH intervals have been proposed, for this category of weak highly ionizable acid drugs (5 to 6.8 or 7.5), as well as a higher volume of fluid (500 mL)[6]. Moreover, the lack of biorelevance of simple aqueous buffers was mentioned [9], since the endogenous surfactants play an important role in the dissolution and absorption processes [10].

In addition to the previously mentioned difference in definitions and acceptance criteria, the regulatory guidance issued by Food and Drug Administration, European Medicine Agency or World Health Organization [11] have distinct recommendations for the experimental conditions for dissolution testing: the volume of fluid varies from 500 to 900 mL, whereas the paddle or basket apparatus are set to 50 or 75 rpm. The biowaiver monograph for ibuprofen published in 2005 [12] pointed out the fact that

compendial methodology, i.e. the use of 900 mL phosphate buffer and 75 rpm, is able to predict the *in vivo* performance of immediate release, oral solid dosage forms. Other reports suggested that bioequivalent products displayed non-similar *in vitro* dissolution [13], probably due to the overly discriminatory test conditions. The main concern is that the differences in the release are most probably transposed into distinct peak exposure, as estimated by the maximum concentration, with unknown therapeutic consequences [14]. A more complex issue comes from the availability of several strengths and types of dosage forms delivering ibuprofen at various levels of the gastro-intestinal tract (film coated tablets, soft and hard gelatin capsules, oral suspensions or rectal suppositories). In some instances, the extrapolation of the *in vivo* results from higher to lower strength proved to be problematic. The aim of the present paper was to evaluate the extent to which the current compendial methodology for dissolution testing of ibuprofen dosage form is able to detect a distinct mechanism of release, the mathematical models that describe adequately the *in vitro* profile and the prospected consequence for waived registration.

Materials and Methods

Six conventional and special dosage forms containing ibuprofen as a single active pharmaceutical ingredient were evaluated *in vitro*, according to current compendial recommendations. The assigned codes and qualitative composition are provided in Table I.

Table I

Identification and qualitative compositions of tested ibuprofen dosage forms

Code	Dose, dosage form	Composition ¹	Batch
N400T	400 mg, sugar coated tablet ²	crosscarmellose sodium, stearic acid, sodium citrate, sodium lauryl sulphate, silica, acacia, carmellose sodium, sugar, talc, titanium dioxide, macrogol, Opacode S-1-9460 HV Brown	20Y
N200T	200 mg, sugar coated tablet ²	crosscarmellose sodium, stearic acid, sodium citrate, sodium lauryl sulphate, silica, acacia, carmellose sodium, sugar, talc, titanium dioxide, macrogol,	33X
P200C	200 mg, hard gelatin capsules ²	lactose, potato starch, povidone, silica, talc, magnesium stearate	05083070
N200G	200 mg, soft gelatin capsules ³	macrogol, vitamin E polyethylene glycol succinate, povidone, gelatin, maltitol, sorbitol, Ponceau 4R (E124), Opacode S-1-7020 or Opacode NS-78-18011	7Y
N100/5	100 mg / 5 mL, oral suspension ³	polisorbate 80, glycerin, maltitol, sodium saccharine, citric acid, sodium citrate, Xanthan gum, sodium chloride, Orange flavor 2 M 16014, domiphen bromide, purified water	911821
N125S	125 mg, rectal suppositories ²	semisynthetic triglycerides	124

¹ the name of excipients was standardized, according to table provided in the biowaiver monograph [12];

² conventional dosage forms, according to [15];

³ special dosage forms, according to [15].

The tests were performed on an Erweka DT 600 dissolution tester (Erweka, Germany), equipped with paddle or basket apparatus (40 mesh, for lipophilic rectal suppositories), using a stirring rate of 75 rpm and 900 mL of phosphate buffer pH=7.2, 100 mM. The media was degassed by filtration under vacuum and heated to 37°C. The dosage forms were added sequentially in each vessel. For hard gelatin capsules, in-house made stainless steel sinkers were used for immersion. Samples of 5 mL were collected manually at 5, 10, 20, 30, 45, 60 minutes and filtrated through 0.45 μm pore size, 15mm diameter regenerated cellulose syringe filters (PhenexTM, Phenomenex, batch no. 80349103). Replacement with an equal volume of pre-heated blank media was performed.

The quantitative analysis of ibuprofen in the collected samples was performed, using a validated spectrophotometric method (on a double fascicle, UV/Vis Jasco spectrophotometer model V-530, Jasco Inc., Japan). The quantification was performed at $\lambda_{\text{max}}=222$ nm, after appropriate dilution, with the blank release media used as compensation liquid.

For the evaluation of *in vitro* dissolution profiles, the variability at each sampling point, as well as the values of difference (f_1) and similarity factors (f_2) were considered. Specific mathematical models (zero and first order kinetics, Higuchi model) were applied for the assessment of the release pattern. The modeling of the experimental data was performed using DDSolver platform [16], with or without considering a specific lag-time, based on the particularities of the pharmaceutical dosage form (opening or rupture of the capsule, erosion of the coating layer, melting of the fat base etc.).

All reagents and the analytical standard of ibuprofen were purchased from Sigma-Aldrich. The purified water was generated by a SGW Ultraclear UV PlusTM system.

Results and Discussion

The *in vitro* release profiles presented a high variability of the fraction dissolved at the first sampling point, although the coefficient of variation was below the limit value of 20%. Particularly for sugar coated tablets (N400T and N200T), the processes occurring between 20 and 30 minutes from the debut of the test seem to generate a considerable dispersion of the experimental data, probably associated with the complete erosion of the coating layer and disintegration of the nucleus. The fastest release was observed for the hard gelatin capsules (P200C), the opening of the shell occurring before the first sampling. The dissolved fraction exceeded the 85% cut-off within 20 minutes. Almost supposable profiles were obtained

for suppositories and soft gelatin capsules (N125S and N200G), whereas an atypical, linear pattern corresponded to the oral suspension (N100/5) (Figure 1).

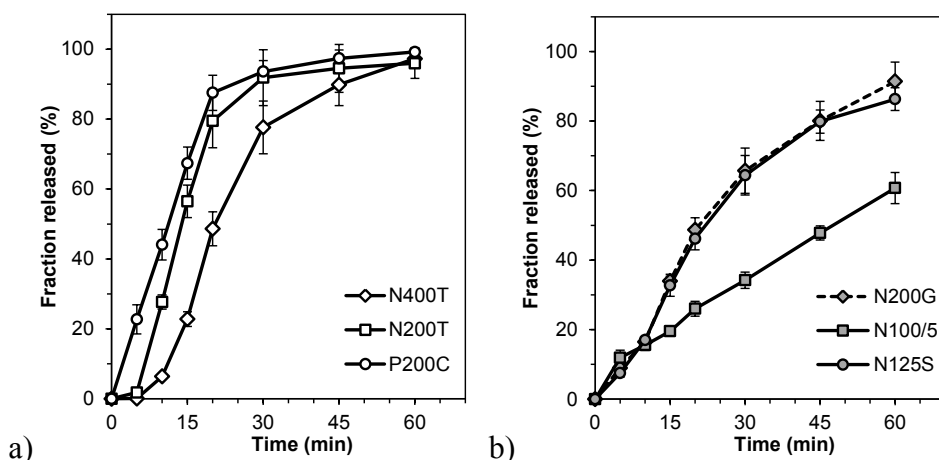


Figure 1

Mean *in vitro* dissolution profiles of ibuprofen (error= ± 1 SD, n=6)

a) conventional dosage forms ($\diamond$ -sugar coated tablets, 400 mg; $\square$ -sugar coated tablets, 200 mg; $\circ$ -hard gelatin capsules)

b) special dosage forms ($\diamond$ -soft gelatin capsules, 200 mg; $\square$ -oral suspension, 125 mg / 5 mL; $\circ$ -rectal suppositories, 125 mg)

In vitro non-similarity was concluded between the profiles of the two different strengths of sugar coated tablets, the average difference being higher than 10% during the first 30 minutes ($f_1=65.45$; $f_2=33.47$). Considering the remarkable qualitative similarity of the composition and the compendial testing methodology providing adequate sink conditions, a possible explanation could be the proportionality between the dose strength and the thickness or quantity of coating layer.

In fact, modeling procedures conducted on the average dissolution profiles indicated that, despite considerable difference in the values of the lag-time (6.9 minutes for N200T, respectively 10.2 minutes for N400T), the release data are best fitted by the same model - first order kinetics (correlation coefficient, $R^2 > 0.98$). The first sampling point was excluded from the analysis, since it has been associated with the highest variability, as previously mentioned, and a single point after the 90% release levels was considered. The smallest lag-time was reported for hard gelatin capsules (3.2 minutes), corresponding to the fastest observed disintegrations. For the oral suspension, the zero-order kinetics seem to adequately describe the

entire dissolution profile ($R^2 > 0.999$), the fraction released achieving 60% at the end of the test (Figure 2).

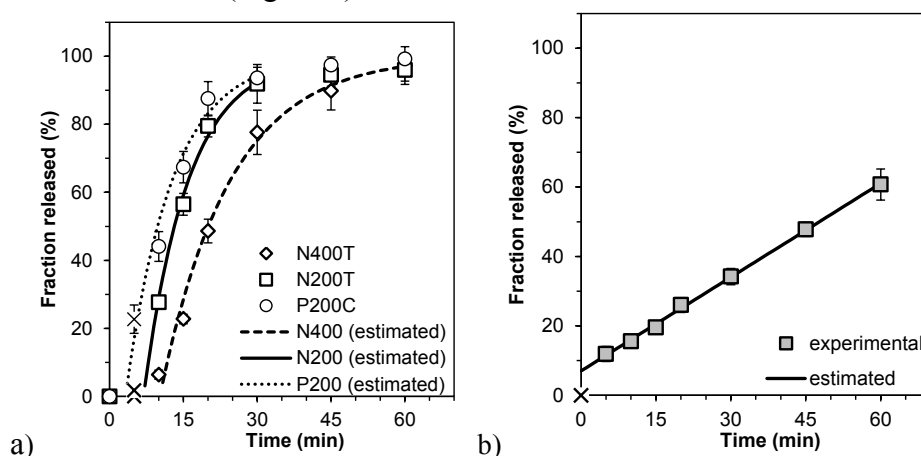


Figure 2

Experimental and estimated *in vitro* release profiles of ibuprofen from: a) conventional dosage forms (first order kinetics with lag time) and b) oral suspension (zero order kinetics). Cross markers correspond to points excluded from analysis.

Noteworthy, the apparent initially dissolved amount corresponds to two independent operational factors. The first one is the addition of the semisolid sample, performed by slowly placing it at the bottom the vessels, in the region underneath the paddle, after standardized re-suspension and volumetric measurement (5 mL). The stirring of the paddle was initiated after insertion of samples in all six vessels, therefore a small fraction of ibuprofen was probably dissolved by the time of test debut. The second factor is the particular shear stress initially acting on the suspension. Enforced by the hydrodynamics of the paddle apparatus, it may be distinct and difficult to assess kinetic consequences, compared to the steady state. Subsequently, the hydration and further dispersion of the macromolecular agent was the rate-limiting step.

The dissolution profiles of suppositories (N125S) and soft gelatin capsules (N200G) were surprisingly similar, despite the clear differences in the nature of the pharmaceutical vehicle, but also in the type of apparatus and correlated flow pattern of the surrounding aqueous buffer system. Both profiles were adequately described by the Higuchi (square root low) model ($R^2 > 0.98$; figure 3), probably due to the nature and structure of the lipid matrix in which ibuprofen is either dissolved or dispersed. The lag-time value varied between 6 and 8.4 minutes, corresponding to the melting of the

suppository base, respectively to the rupture of the gelatin shell and release of the oil-phase. Both represented the initial rate-limiting processes and were followed by a slow partition between the lipid and aqueous phase (dominated by their relative volume ratio and by the high value of the partition coefficient of ibuprofen, 3.6 [12]).

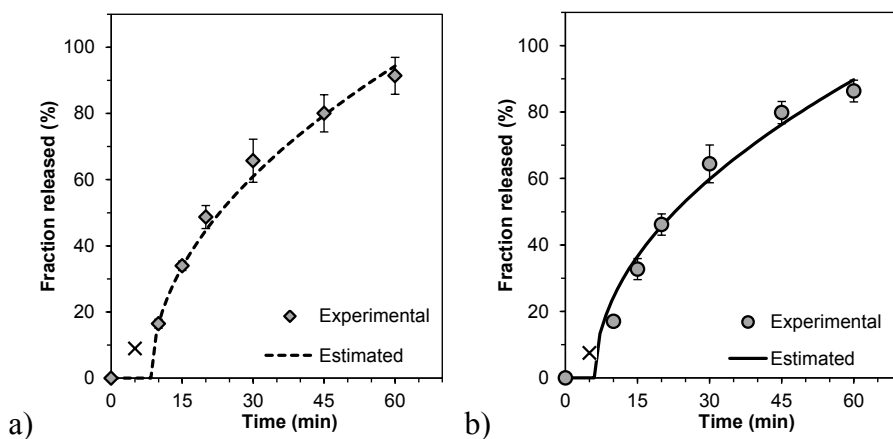


Figure 3

Experimental and estimated *in vitro* release profiles of ibuprofen (Higuchi model with lag-time) from: a) soft gelatin capsules and b) rectal suppositories. Cross markers correspond to points excluded from analysis.

The compendial *in vitro* methodology seems to adequately discriminate the particular formulation factors and the designed mechanism of release, imposed by the intended route of administration and absorption site. Nevertheless, the consequences on the *in vivo* performance are difficult to predict. It has been previously reported that, although the consequence on the safety profile is probably minor, the lack of biological relevance of the dissolution procedures and its acceptance for biowaiver purposes could lead to approval of orally administered drug products essentially differing in the maximum exposure [17]. The equivalence of total exposure can be assumed, based on the biopharmaceutical properties of ibuprofen and on the long intestinal transit times. This provisionally limits a successful therapeutic outcome. The slower *in vitro* release from soft gelatin capsules, usually considered as adequate for a fast onset of drug action, can be added as a supplementary argument. But this fact does not invalidate the potential use of dissolution test as surrogate of *in vivo* studies. It points out that methodological refinements are needed in order to adequately assess the key product characteristics that generate optimal performance.

Conclusions

Conventional and special dosage forms containing ibuprofen were evaluated *in vitro*, based on compendial recommendations. The methodology was able to discriminate the differences in qualitative and quantitative composition, as well as in design mechanism of release, imposed by the intended route of administration and absorption site. The rate-limiting steps of the dissolution process were identified and used for explaining the distinct kinetic models fitting the experimental data. In order to be used as a biorelevant test, supporting the biowaiver procedures, the methodology needs future refinements.

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