

ADJUSTMENTS OF THE BIORELEVANT DISSOLUTION TESTING IN CASE OF OXICAMS ORAL SOLID DOSAGE FORMS

ION-BOGDAN DUMITRESCU¹, IOANA DUMITRA DRĂGOICEA²,
DUMITRU LUPULEASA³, DOINA DRAGANESCU¹, DRAGOȘ
FLORIAN CIOLAN⁴, DALIA SIMONA MIRON^{1*}, FLAVIAN ȘTEFAN
RĂDULESCU⁵

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

¹*Department of Pharmaceutical Physics and Informatics,*

²*Clinical Emergency Hospital, Department of Plastic and Reconstructive
Microsurgery,*

³*Department of Pharmaceutical Technology and Biopharmaceutics,*

⁴*Department of Pharmaceutical Chemistry,*

⁵*Department of Drug Industry and Pharmaceutical Biotechnologies.*

**corresponding author: dalia_simona_m@yahoo.com.*

Abstract

The paper presents the results of *in vitro* dissolution testing for oral solid dosage forms containing three representative oxicams in blank or standard, fast and fed state simulated intestinal fluids (FaSSIF/FeSSIF). Non-compendial PeakTM vessel were used in combination with an adapted composition of biorelevant media (1:2 dilution with the corresponding aqueous buffer system). The results revealed a significant contribution of the improved stirring profile to the release process in FeSSIF, counterbalancing the decreased concentration of endogenous tensioactive compounds. The dissolution efficiency was comparable for the two blank media. The implemented changes in composition of the biorelevant media and experimental design led to comparable variability of data, but request further evaluation of the discriminatory character for internal, formulation-controlled factors.

Rezumat

Lucrarea prezintă rezultatele testelor de dizolvare *in vitro* pentru forme farmaceutice solide orale conținând trei oxicami reprezentativi, în medii intestinale simulate, pre și postprandial, blank sau standard (FaSSIF/FeSSIF). Au fost folosite vase necompendiale PeakTM, cu adaptarea compozițiilor mediilor biorelevante (diluare 1:2 cu sistemul tampon apos corespunzător). Rezultatele au indicat contribuția semnificativă a profilului de agitare îmbunătățit pentru FeSSIF, contracarând scăderea concentrației de compuși tensioactivi endogeni. Eficiența dizolvării a fost comparabilă pentru cele două medii blank. Modificările de compoziție implementate pentru mediile simulate și design-ul experimental au condus la o variabilitate comparabilă a datelor, dar sunt încă necesare evaluări suplimentare asupra caracterului discriminatoriu față de factorii de formulare.

Keywords: biorelevant media, PeakTM vessels, meloxicam, piroxicam, tenoxicam.

Introduction

The dissolution tests are extensively applied for their utility as quality control (QC) tools or predictive methodology for the *in vivo* release of drugs from a wide variety of pharmaceutical vehicles. Usually, the aqueous buffer systems fail to accurately indicate the performance of the drug product in the biological conditions, since they simulate only a single physiological parameter, e.g. pH. The biorelevant fluids have been developed mainly for more in-depth understanding of the release mechanism of a formulation under development in the gastric or intestinal environment. Critical physiological characteristics, such as buffer capacity, osmolarity and surface tension have been adjusted to the values previously reported during clinical studies [1]. The addition of natural surfactants, sodium taurocholate (representative for the group of bile acid and salts) and lecithin, had triggered difficulties in terms of media preparation and standardization of composition. Nevertheless, another key issues limiting their application in routine dissolution procedures is the high price of these two endogenous components.

If the experimental devices and operating parameters are considered, the current recommended volume for both fasted and fed state simulated intestinal fluids (FaSSIF/FeSSIF) is considerably high (500 and 1000 ml, respectively). These values were presumably selected based on the common, compendial conditions for dissolution testing, especially the hydrodynamics specific to the paddle apparatus combined with 1000 ml vessels. A major factor influencing to the overall variability of *in vitro* release data is media degassing [2]. The recommended procedures are difficult to be performed on fluids containing surface-active agents, due to the foaming phenomenon. The regulatory authorities have a conservative attitude in adopting a wider variety of product-specific equipments and device. The producers of dissolution testers have develop several adaption of the official pharmacopoeial standards (United States Pharmacopoeia, USP), but their use is limited in most instances to the research and development phases. There are reports claiming benefits compared to the official design. Particularly, the PeakTM vessels (Varian Inc. Dissolution System [3]), including an inverted cone under the paddle region, have been developed for prevention of inhomogenous stirring generated by initial disintegration of solid oral dosage forms containing high quantities of excipients [4]. The low shear rate generated at the bottom of the compendial vessel (coning effect) can be eliminated by increasing the stirring rate within the recommended range (correlated with the type of USP apparatus). This further leads to low

sensitivity to composition or process variables, invalidating the use as a discriminatory QC tool [4].

The current paper present the evaluation of dissolution in biorelevant fluid for three oxicams formulated as tablet dosage forms. The analysis focused on the impact of media composition (blank buffer system with or without addition of endogenous tensioactives in official or reduced concentration) and vessel design. The active pharmaceutical ingredients represented typical hydrophobic drugs (included in the class 2 of the Biopharmaceutical Classification System, BCS [5]), the dissolution being the limiting step of the absorption processes.

Materials and Methods

The dissolution tests were performed on a standard dissolution equipment (Hanson SR8 Plus, Hanson Research Inc, US), using paddle apparatus at 75 rotations per minute. The two biorelevant media were prepared according to the current recommendations (adjustment of the aqueous buffer system to the specified pH value - 6,5 for fast state (FaSSIF_b) and 5 for fed state (FeSSIF_b); dispersion of sodium taurocholate under mild stirring and heating to 40°C; adding lecithin and continuing stirring for 4 hours). When Peak vessels were used, the standard FaSSIF and FeSSIF media were further diluted 1:2 with the corresponding blank buffer. All the in-vitro drug release tests were performed on triplicate, at 37°C, using 500 ml and, respectively, 1000 ml of media. Samples of 5 ml were collected manually at 5, 10, 15, 20, 30, 45 and 60 minutes after introduction of the tablet formulations, using resident stainless steel tubes with regenerated cellulose syringe filters (0,45 µm pore size, PhenexTM, Phenomenex. The quantitative analysis of oxicams was performed as previously reported [6, 7].

The comparison of dissolution profiles was based on the calculation of compendial difference and similarity metrics (f_1 and f_2) [8]. Rescigno indexes (ξ_1 and ξ_2) were evaluated according to the following formula [9]:

$$\xi_i(n) = \left[\frac{\int_0^n |F_R(t) - F_T(t)| \cdot dt}{\int_0^n |F_R(t) + F_T(t)| \cdot dt} \right]^{1/i}$$

where F_R and F_T are the fractions released for the reference and, respectively, test profiles, at time t , considering n experimental points.

The release pattern generated in standard FaSSIF and FeSSIF media were considered as reference. The mean profiles were fitted with a Weibull function [9]:

$$F(\%) = 100 \cdot [1 - e^{-(t/T_d)^b}]$$

where $F(\%)$ is the fraction of drug dissolved, t is the time, T_d is time corresponding to the release of 63,2% of the labeled amount and b is a shape parameter.

The contribution of media composition and of hydrodynamic variations to the in-vitro dissolution process was also assessed based on the calculation of dissolution efficiency ($DE\%$) [10].

The immediate release tablet formulations (Meloxicam LPH[®], tablets containing 15 mg meloxicam, batch 7072042287, LaborMed Pharma; Piroxicam LPH[®], tablets containing 20 mg piroxicam, batch 8060010566 LaborMed Pharma; Tilcotil[®], film coated tablets containing 20 mg tenoxicam, batch B1058B01, Roche), were purchased commercially. Sodium hydroxide pellets (Riedel-de Haen), sodium phosphate dibasic dihydrate, sodium phosphate monobasic monohydrate, sodium chloride, acetic acid 100%, sodium acetate (Sigma Aldrich), sodium taurocholate hydrate (Fluka) and lecithin (Roth) were of analytical grade. A SGW Ultraclear UV PlusTM system was used for water purification.

Results and Discussion

The dissolution data in the simulated intestinal fluids revealed the high impact of the endogenous tensioactives on the fraction released at the end of test. Independent on the physico-chemical properties of the hydrophobic drug, the presence of sodium taurocholate and lecithin determined an increased rate of released, especially during the first 15 minutes. The total amount of drug dissolved is double compared to the blank buffer system, for meloxicam (28 vs. 55%) and piroxicam (46 vs. 89%). In the case of tenoxicam, it seems like the pH-pKa relationship is the key determinant, the in-vitro profiles in fasting simulated fluids being essentially similar after disintegration of the solid dosage form (despite the absence or low concentration of tensioactives, without a significant contribution of the hydrodynamic parameters) (figure 1).

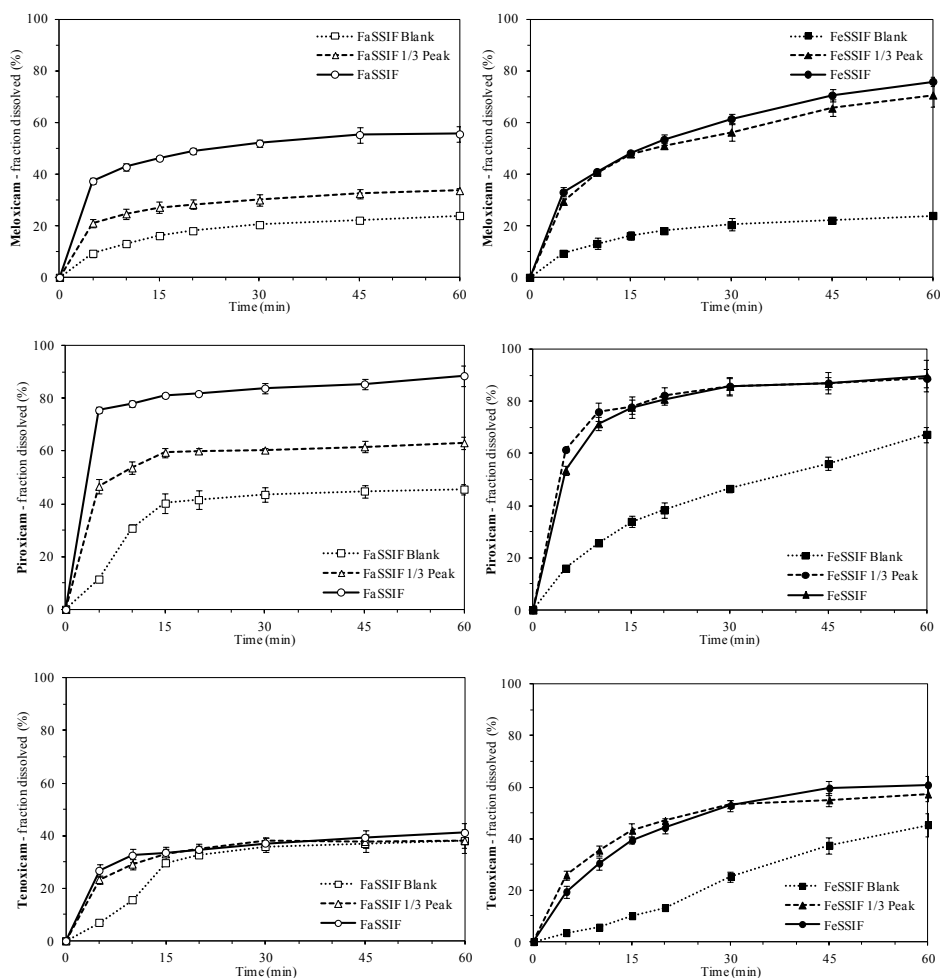


Figure 1

Mean dissolution profile of solid dosage forms containing oxicams
in biorelevant fluids

The most interesting aspects were revealed by the profiles generated in fed conditions. The higher volume, combined with a lower pH induced a net increased of the fraction dissolved, with small differences (less than 5%) between the standard formula of the biorelevant media and their diluted adaption. The decrease of sodium taurocholate concentration from 15 to 5 mM is compensated by generation of relative high shear rate region around the inverted cone. All the dissolution metrics confirmed the obvious similarity of the mean profiles (data not shown). Except for meloxicam, the most lipophilic compound in the evaluated group, the release process seems to be rather rate-limited than solubility-limited.

Furthermore, the dissolution efficacy tends to be a better indicator of the overall impact of test parameters. Its value is calculated based on area under dissolution curve, therefore model independent. The blank systems induced the lowest differences between the fast and fed stages, as a combined effect of double volume and solubility drop on the 1.5 pH-units. The Weibull model didn't described accurately the corresponding profiles (table I), suggesting a possible different mechanism of release. As previously mentioned, the volume of dissolution media is not determined by the general operating conditions of in-vitro release tests, without physiological analogy. For the stirring rate, there is no official recommendation. The apparent contradictory conclusion of similarity based on DE_{60} correlates with the lack of food-effect in terms of extent of exposure to oxicams [11]. In terms of physico-chemical properties, the absorption process for typical BCS class II drugs is limited by the solubility, whereas the permeability (when passive diffusion is considered) is controlled by the high values of distribution coefficient (figure 2).

Table IDissolution efficiency (DE_{60}) and fitting parameters for the Weibull model

Compound	Parameter	FaSSIF _b	FeSSIF _b	FaSSIF _{1/3}	FeSSIF _{1/3}	FaSSIF	FeSSIF
Meloxicam	DE_{60}	18.26	17.03	28.19	53.19	48.27	56.83
	b	0.38	0.73	0.22	0.48	0.23	0.53
	T_d	1693.68	269.99	3518.83	39.96	125.42	31.88
	R^2	0.9900	0.9985	0.9988	0.9978	0.9982	0.9985
Piroxicam	DE_{60}	38.05	43.23	56.71	78.95	79.64	77.79
	b	0.41	0.72	0.17	0.34	0.16	0.44
	T_d	139.93	55.05	47.19	4.55	0.67	7.15
	R^2	0.8844	0.9970	0.9908	0.9954	0.9994	0.9926
Tenoxicam	DE_{60}	29.90	23.53	33.61	46.58	34.78	46.45
	b	0.52	1.25	0.22	0.40	0.20	0.57
	T_d	186.77	86.62	1179.71	74.02	1471.06	56.31
	R^2	0.8886	0.9932	0.9819	0.9852	0.9975	0.9883

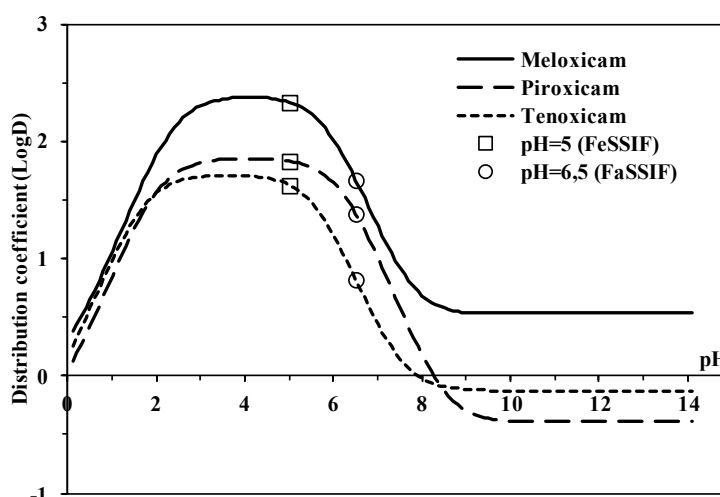


Figure 2

Estimated pH-dependence of the distribution profile for oxicams
(GastroPlus, Simulation Plus Inc.)

The difference in kinetic model between blank and standard biorelevant media could be explained, at least in part, by two major processes. The first one is the disintegration of the solid oral dosage forms. The tensioactive agents increase the penetration rate of the solvent, accelerating the disintegration of the tablets. The difference in the initial dissolution rates can be considered as a proof of subsequent swelling of particles [12], which compendial disintegration test fail to evaluate. The second process involves the specific interaction between endogenous component and drug or excipients particles [13]. Electrostatic or lipophilic interactions have been mentioned to support the selective effect on drug solubility [14]. Available reports made a clear distinction between weak acids and weak bases, mainly based on the relationship with relative negative charge of the major components of simulated fluids at the specific pH. The arguments rely on determinations of equilibrium solubility (e.g. an excess of drug substance was maintained in contact with a given aqueous system for 24 hours or longer). The hydrodynamics of dissolution process can have a dramatic impact on the dimension of the limiting boundary layer, surrounding the pharmaceutical formulation and, consecutively, the drug particles [15]. This explains why similar profiles were obtained for fed state by altering the flow pattern (PeakTM vessels), with a significant decrease of concentration for endogenous compounds. Theoretically, the results make

feasible the cost reduction in biorelevant testing, but further evaluations are needed in order to prove what groups of active pharmaceutical ingredients can be addressed. Nonetheless, it is not clear if this methodology can discriminate the critical changes in the qualitative and quantitative composition of the formulation.

Conclusions

The dissolution profiles for oral solid dosage forms containing oxicams have been evaluated in simulated intestinal fluids. The use of non-compendial PeakTM vessels combined with a reduction to one third of the concentration for endogenous tensioactives had a different impact on in-vitro release for the fast and fed conditions. Similar profiles were obtained only for the standard and modified fed stages, proving a significant contribution of the improved hydrodynamic pattern. For the fast state simulated intestinal fluid, despite the similar kinetic profile, the decreased amount of sodium taurocholate and lecithin generated a correlated reduction of the fraction released for meloxicam and piroxicam. The implemented changes in composition of the biorelevant media and experimental design led to comparable variability of data, but request further evaluation of the discriminatory character for internal, formulation-controlled factors.

Acknowledgements

This paper was partially supported by the Sectoral Operational Programme Human Resources Development, financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/89/1.5/S/64153. Portions of these results were generated by GastroPlusTM software provided by Simulations Plus, Inc., Lancaster, California, USA.

References

1. Jantravid E, Janssen N, Reppas C, Dressman JB: Dissolution media simulating conditions in the proximal human gastrointestinal tract: an update. *Pharm Res*. 2008, 25(7):1663-76.
2. Beckett AH, Quach TT, Kurs GS: Improved hydrodynamics for USP apparatus 2. *Diss Tech* 1996, 5:7-18.
3. Beckett AH, Swon JE, Hofer HZ: Device maximizing dispersion of aggregate in liquid dilluent. US Patent 5700087A, 1997.
4. Collins CC, Nair RR: Comparative evaluation of mixing dynamics in USP apparatus 2 using standard USP vessels and PeakTM vessels. *Diss Tech* 1998, 5:7-21.
5. Dahan A, Miller JM, Amidon GL: Prediction of solubility and permeability class membership: provisional BCS classification of the world's top oral drugs. *AAPS J* 2009, 11(4):740-746.

6. Radulescu FS, Voicu V, Miron DS, Mitu MA, Arsene AL: The solubility of oxycams, antifungal azoles and selected psychotropic drugs in simulated gastro-intestinal fluids and the consequences on their biopharmaceutical classification. *Farmacia* 2011, 59(3):432-439.
7. Radulescu FS, Dumitrescu IB, Miron DS, Lupuleasa D, Andries A, Draganescu D: The *in vitro* release profiles of nimesulide from oral solid dosage forms, in compendial and modified physiological media. *Farmacia* 2010, 58(4):502-508.
8. Zhang Y, Huo M, Zhou J, Zou A, Li W, Yao C, Xie S: DDSolver: an add-in program for modeling and comparison of drug dissolution profiles. *AAPS J* 2010, 12(3):263-271.
9. Vertzoni M, Symillides M, Iliadis A, Nicolaides E, Reppas C: Comparison of simulated cumulative drug versus time data sets with indices. *Eur J Pharm Biopharm* 2003, 56(3):421-428.
10. Khan KA: The concept of dissolution efficiency. *J Pharm Pharmacol* 1975, 27(1):48-49.
11. Olkkola KT, Brunetto AV, Mattila MJ: Pharmacokinetics of oxicam nonsteroidal anti-inflammatory agents. *Clin Pharmacokinet* 1994, 26(2):107-120.
12. Anwar S, Fell JT, Dickinson PA: An investigation of the disintegration of tablets in biorelevant media. *Int J Pharm* 2005, 290(1-2):121-127.
13. Luner PE, VanDer Kamp D: Wetting characteristics of media emulating gastric fluids. *Int J Pharm* 2001, 212(1):81-91.
14. Ottaviani G, Gosling DJ, Patissier C, Rodde S, Zhou L, Faller B: What is modulating solubility in simulated intestinal fluids? *Eur J Pharm Sci* 2010, 41(3-4):452-457.
15. Baxter JL, Kukura J, Muzzio FJ: Shear-induced variability in the United States Pharmacopeia Apparatus 2: modifications to the existing system. *AAPS J*, 2005, 7(4):E857-864.

Manuscript received: June 3rd 2011