ORIGINAL ARTICLE

THE INFLUENCE OF SPLITTING ON THE *IN VITRO* RELEASE OF METOPROLOL SUCCINATE FROM SCORED TABLETS

GEORGE TRAIAN ALEXANDRU BURCEA DRAGOMIROIU[1], OCTAV GINGHINĂ[2], DALIA SIMONA MIRON[3]*, MARIA BÂRCĂ[1], DANIELA ELENA POPA[1], MIRCEA HÎRJĂU[4], DUMITRU LUPULEASA[4], FLAVIAN ŞTEFAN RĂDULESCU[5]

[1]*University of Medicine and Pharmacy "Carol Davila" Bucharest, Faculty of Pharmacy, Department of Drug Control, 6 Traian Vuia street, 020956, Bucharest, Romania*
[2]*University of Medicine and Pharmacy "Carol Davila" Bucharest, Faculty of Dental Medicine, Department of Oncological Surgery, „Sf. Ioan" Hospital, 13 Vitan-Bârzeşti street, 042122, Bucharest, România*
[3]*University of Medicine and Pharmacy "Carol Davila" Bucharest, Faculty of Pharmacy, Department of Pharmaceutical Physics and Informatics, 6 Traian Vuia street, 020956, Bucharest, Romania*
[4]*University of Medicine and Pharmacy "Carol Davila" Bucharest, Faculty of Pharmacy, Department of Pharmaceutical Technology and Biopharmaceutics, 6 Traian Vuia street, 020956, Bucharest, Romania*
[5]*University of Medicine and Pharmacy "Carol Davila" Bucharest, Faculty of Pharmacy, Department of Drug Industry and Pharmaceutical Biotechnologies, 6 Traian Vuia street, 020956, Bucharest, Romania*

**corresponding author: dalia_simona_m@yahoo.com*

Manuscript received: October 2014

Abstract

The paper presents the results of *in vitro* release tests applied for assessing the impact of mechanical splitting on the performance of sustained release oral solid formulations containing metoprolol succinate. Ten multiparticulate drug delivery systems of the same manufacturer available on the European market, with dose strengths between 23.75 to 190 mg, were evaluated according to the conditions specified in the United States Pharmacopoeia monograph for six hours. The similarity of the mean *in vitro* release profiles was concluded between the split and finished drug product, respectively the corresponding lower dose. A higher variability of the experimental data was noted for the divided lower strength, probably due to the reduced reproducibility of the splitting in terms of surface area and morphology. The results demonstrated that the mechanical splitting didn't alter the mechanism nor the amount released.

Rezumat

Lucrarea prezintă rezultatele testelor de cedare *in vitro* aplicate pentru analiza impactului fragmentării mecanice asupra performanţelor formulărilor solide orale cu cedare susţinută conţinând metoprolol succinat. Zece sisteme de cedare multiparticulate ale aceluiaşi producător disponibile pe piaţa europeană, având concentraţii cuprinse între 23,75 şi 190 mg, au fost evaluate în condiţiile specificate de monografia din Farmacopeea Statelor Unite, timp de şase ore. Concluzia privind similaritatea profilelor medii de cedare *in vitro* a fost obţinută între produsul divizat şi cel finit, respectiv nivelul inferior de doză disponibil. O variabilitate mai mare a datelor experimentale a fost observată pentru fragmentele generate de produsul conţinând doza minimă, fiind asociată probabil cu reproductibilitatea redusă a ariei şi morfologiei suprafeţei induse. Rezultatele au demonstrat că divizarea mecanică nu a alterat mecanismul de cedare sau cantitatea de substanţă medicamentoasă eliberată.

Keywords: metoprolol succinate, scored tablets, mechanical splitting, *in vitro* release

Introduction

The scored tablets are often subject to splitting procedures, the main reasons being the facilitated oral administration in case of patients exhibiting swallowing difficulties or the lack of appropriate, registered dose for special populations [1]. Despite solving these significant issues and reducing the costs of healthcare, the frequent practice of splitting the dosage forms raised major concerns about the impact of manipulation procedures on the pharmaceutical quality parameters and consequently, on the *in vivo* performance [2, 3]. An available review of literature data suggests a case-by-case influence on safety and efficacy profiles, depending among other factors on the therapeutic range of the active pharmaceutical ingredient and on its half-life [4]. The drug authorities issued guidances and regulatory documents in an attempt to develop a general approach for the evaluation of specific quality attributes of fragments resulted after splitting. Several specific tests and acceptance criteria for weight variation, dose uniformity, loss of mass, stability and dissolution have been proposed and adopted to a variable extent [5]. The alteration of the release mechanism was considered to have a particular relevance, based on the possible

incidence of dose-dumping phenomena. Food and Drug Administration (FDA) has established the term of "functional scoring", integrating the characteristics of the fragments resulted by splitting procedures evaluated during the review process [6]. The dissolution testing should be performed according to the available methodology, either compendial or developed and validated for the finished product. *In vitro* similarity should be demonstrated between the whole, modified release (MR) solid oral dosage form and fragments generated by splitting.

It must be considered that the *in vitro* dissolution data indicating significant changes in the amount of drug released for the divided, scored dosage forms are not always correlated with the *in vivo* outcome [7]. Slightly faster released is initially observed, due to the increase of the surface area of the dosing unit exposed to the media [8]. In case of multiparticulate drug dosage systems, the integrity of the coating film may be compromised for the beads located in the rupture region [13], particularly when mechanical splitting is applied (metal blade devices). Considering the general approaches in performing the dissolution tests and assessing the significance of the results, the procedure applied in case of scored tablets is distinct. The dosage unit is manipulated before its introduction into the media, i.e. its integrity is intentionally altered. The FDA guidance specifically indicates that fragments should be generated by both mechanical and non-mechanical methods [6], because the outcome can be highly different in terms of weight variation or characteristics of the surface (roughness, morphology). Comparative dissolution must be performed on the solid dosage forms at both extreme values of the hardness interval. It has been proposed that adjusted, reduced requirements should be implemented [10]. For example, since splitting impacts mainly the initial stages of release and safety concerns have been raised due to dose dumping, especially for tablets produced by matrix technology, short term evaluation might be relevant. At the same time, the *in vitro* similarity should have been demonstrated between the divided dosing and the corresponding lower strength of the same product, as initially suggested [10].

The aim of the current paper was to evaluate the impact of mechanical splitting on the *in vitro* dissolution profiles for sustained release solid oral dosage forms containing metoprolol succinate. The consistency of the *in vitro* performance was assessed on a wide range of dose strengths for the innovator product, tested as whole and halved scored tablets.

Materials and Methods

The experimental protocol was applied on prolonged release formulations of metoprolol succinate, purchased from community pharmacies in four EU countries. The tested products were bisected, oval or round white tablets, details on the dose strength, batch number and assigned codes being provided in Table I. According to the summary of product characteristics, the microencapsulated delivery system consists of compressed film coated beads, each acting as a depot unit. All dosage units had a minimum 20 months shelf life at the time of testing.

Table I

Description of the tested prolonged release formulations

Code	Strength (mg)*	Shape	Dimensions (mm)	Batch number
A	23.75	oval	5.5 x 10	P57B
B				ABHU
C	47.5	round	9	UBFP
D				UBFT
E				UAZT
F	95	round	10	R257A
G				VAKX
H				VAKS
I				VAGZ
J	190	oval	8.5 x 17	R133C

* metoprolol succinate

The splitting of scored tablets was performed mechanically along the superficial score, using a commercially available metal blade device. The resulting fragments were weighed after division and the individual mass was recorded.

The *in vitro* testing procedures were performed according to the individual monograph available in the United States Pharmacopeia [14]. Briefly, the paddle method was applied at 50 rpm using 500 mL phosphate buffer pH = 6.8, degassed by filtration under vacuum. The samples were collected manually for 6 hours, using polypropylene cannula filters mounted on resident rodes and having a mean pore size of 10 μm. The sampling procedure was followed by the replacement with an equal volume of blank media. Each *in vitro* release test was performed in triplicate, at 37 ± 0.5°C, on a Hanson SR8+ dissolution apparatus (Hanson Research Inc., United States). Whole and halved tablets of each product were analysed during the same run.

The quantitative analysis of the active pharmaceutical ingredient was performed by using a spectrophotometric method (λ_{max} = 274 nm) on undiluted samples (Agilent 8453 UV-Vis Spectrophotometer, Agilent Instruments,

Germany). For the fragments resulting after mechanical splitting, even distribution of drug was assumed and the dose applied into each vessel was considered proportional to the individual mass. The dissolution tests were performed within 30 minutes after division. The experimental data was analysed for variability and *in vitro* similarity was assessed using compendial metrics (whole *versus* half tablets, respectively resulting fragments *versus* corresponding lower strength).

All the reagents were of analytical grade and were commercially available (potassium dihydrogen phosphate anhydrous, Sigma Aldrich; sodium hydroxide, Riedel-de Haen). Metoprolol succinate (batch MTS00311) was a gift from Microsin SRL, Bucharest, Romania. The purified water was obtained using an Ultra Clear™ TWF System with ultraviolet oxidization (SG Wasseraufbereitung und Regenerierstation GmbH, Germany) and had a conductivity of 0.055 µS/cm.

Results and Discussion

The fragments obtained by mechanical splitting procedure had weights within 85 to 115% of the average values. The standard deviations were between 2.1 and 14.2%, with higher variations obtained for the extreme dose, oval tablets. In these cases, the surface of the splitting zone was rough and uniform, but didn't lead to loss of mass higher than 2%. The mean *in vitro* release profiles displayed a reduced variability for the early sampling time points, with a coefficient of variation lower than 20%. Moreover, the fraction release was not significantly different between the whole and split tablets. The manipulation of the dosage units didn't determine an initial burst in release and, consequently, a biphasic profile. Except for the divided 23.75 mg metoprolol succinate tablets, the fraction of drug released into the media increased linearly in time, throughout the 6 hours of the test (Figure 1).

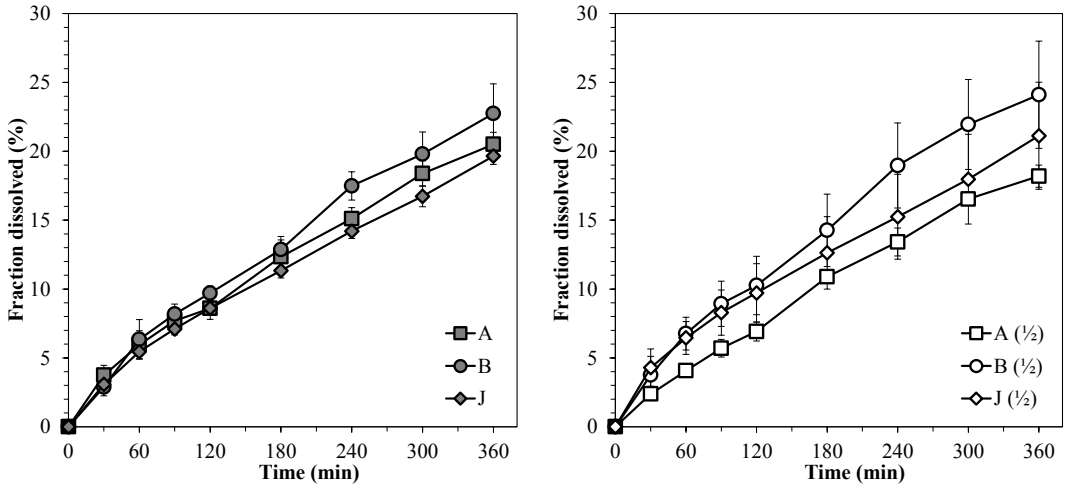

Figure 1.
In vitro release profiles of metoprolol succinate from whole (grey symbols) and split (white symbols) sustained release, oval tablets (23.75 and 190 mg; mean ± standard deviation, n = 3)

Within a short time interval after introduction of the tablets into the medium and debut of the agitation, the dosage units underwent a rapid disintegration process, generating a mass of granules and excipients grouped at the bottom of the vessel, under the paddle. The conning effect didn't alter significantly the release, probably due to the high solubility profile of the active pharmaceutical ingredient in the aqueous buffer system. For the 47.5 and 95 mg dose strength, the mean release profiles were more consistent between the various products and within the same product, before and after splitting (Figure 2). It is to be mentioned that this observation corresponded to the low variability of individual mass (5.3 to 9.6% of the average value), but also to the shape of the tablets. Most of the devices available on the market, including the one used for division in the present study, have a V shape holder, more suitable for round tablets. Based on the obvious similarity of the mean *in vitro* profiles, it can be assumed that the release mechanism was not altered. Due to the presence of a deep scoring, the metal blade induced a fracture similar to that obtained by non-mechanical, hand splitting. Presumably, the particles controlling the release of the drug were not altered by neither compression nor disruption of the coating film.

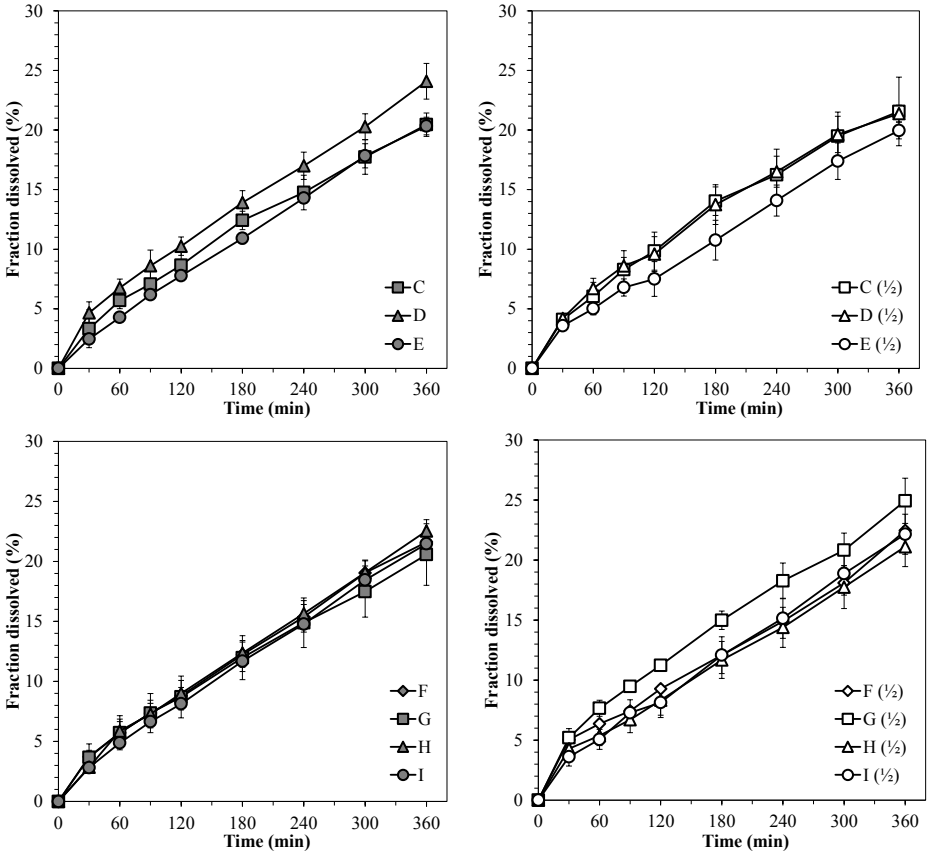

Figure 2.

In vitro release profiles of metoprolol succinate from whole (grey symbols) and split (white symbols) sustained release, round tablets (47.5 and 95 mg; mean ± standard deviation, n = 3)

Table II

The values of the similarity factor, f2, calculated for the mean *in vitro* release profiles (n = 3)

	A (½)	B (½)	C (½)	D (½)	E (½)	F (½)	G (½)	H (½)	I (½)	J (½)	Split tablet
A	**85.27**	69.74	**92.78**	**92.60**	**93.23**	-	-	-	-	-	**A (½)**
B	89.24	**90.58**	**94.45**	**94.72**	**81.92**	-	-	-	-	-	**B (½)**
C	98.66	87.28	**90.43**	99.05	83.69	**92.97**	**76.64**	**97.45**	**95.01**	-	**C (½)**
D	84.77	93.61	82.81	**92.64**	83.35	**88.14**	**94.05**	**82.42**	**86.31**	-	**D (½)**
E	91.63	82.57	93.88	77.96	**97.22**	**86.88**	**72.50**	**94.23**	**92.01**	-	**E (½)**
F	97.88	92.29	96.24	87.75	90.74	**95.85**	80.94	94.96	94.60	**95.93**	**F (½)**
G	98.66	87.20	99.41	82.91	93.42	96.16	**76.75**	76.12	78.98	**96.10**	**G (½)**
H	94.45	94.66	93.53	89.11	89.03	98.02	93.16	**92.55**	96.02	**93.52**	**H (½)**
I	95.38	87.65	96.48	82.67	96.57	96.44	95.90	95.31	**97.81**	**91.18**	**I (½)**
J	94.19	82.71	96.64	78.53	95.09	90.83	97.05	88.35	93.40	**91.00**	**J (½)**
Whole tablet	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	

Note: the bolded values on grey background were calculated for the split tablets (symbol ½ assigned to the tablet code) compared to the finished product, respectively with the corresponding dose (half dose strength).

For the evaluation of *in vitro* similarity, we applied the official model-independent approach, based on the calculation of difference (f_1) and similarity (f_2) metrics. The inclusion of a wide dose range of the same product, presumably manufactured in different site, offered the opportunity to comparatively assess the performance both between and within each strength. The results of the analysis are synthetically presented in Table II. The *in vitro* similarity was concluded in each instance, with

values of the f_2 factor between 69.7 and 99.4. On one hand, these results demonstrate the consistency in release for sustained release products for which the differences between various strengths is obtained by varying the quantity of drug-containing particles. The kinetics are essentially similar, under the diffusional control of the coating film and not influenced by the nature and amount of the diluents or other external excipients. On the other hand, the manipulation of the dosage units didn't alter critically the release. The highest differences were obtained at the level of the lowest strength (e.g. between fragments of product A and B), due to the considerable difficulties in generating uniform fragments.

The initial approaches in the development of the guidance and monograph chapter specifically addressing included the *in vitro* comparative assessment of the split tablets versus the corresponding strength of the same product [10]. The question was how to evaluate the divided lower strength, because no equivalent finished product is available (corresponding to the minimum therapeutic dose). Therefore, a comparison within product was selected in the final guidance, as being more relevant [6]. The current reports underline the role of the shape and release mechanism of the constitutive particles, correlated with the nature of the procedure selected for the division of the dosage units [9]. Perhaps it will be feasible to adopt a release limit after short time interval, e.g. within 30 or 60 minutes after debut of the test, together with a short term, abbreviated assessment of the *in vitro* performance. This will provide more detailed information on the degree of alteration of the particles resident at the site of compression and consecutive division. The first part of the mean release profiles can be considered as more relevant, similarly to the alcohol dissolution testing adopted for modified release formulations [12].

The *in vitro* release test demonstrated that no difference in the *in vivo* performance is likely to be observed, but some limitations of the methodology must be pointed out. The similarity was assessed based on a model independent approach, as recommended in current guidance [6]. It still remains to be established if a model dependent procedure of comparison will be more adequate for modified release oral solid dosage forms. Last but not least, meeting the same (compendial) requirements is debatable, at least from the point of view of the *in vitro* testing. The reduced biorelevance of the quality control tests has been previously reported [13, 14]. Perhaps the profile evaluation should consider the gradient pH in which the formulations evolve [8]. The interactions between formulation factors and medium could be evaluated in at least two stages, e.g. the acid and buffer stages of the general procedures for non-immediate release formulations, even though the drug has a high solubility profile.

Conclusions

The impact of mechanical splitting on the *in vitro* release of metoprolol succinate from sustained release, multiparticulate oral formulations was evaluated according to the compendial methodology. The results demonstrated a consistence in the performance, the kinetics being controlled by the film-coated beads which seems not to be altered during the dividing procedure. The size and shape of the finished product generated a reduced reproducibility of the splitting surface and of the mass in case of the lower strength. The *in vitro* similarity concluded for each product (whole versus split tablet), as well as between the fragments and the corresponding dose of the finished product, confirmed the label-claimed functional scoring.

Acknowledgements

This work was supported by the Sectorial Operational Programme Human Resources (SOP HRD) 2007-2013, financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/159/1.5/S/133377, beneficiary "Gr. T. Popa" University of Medicine and Pharmacy, „Program de excelenţă în cercetare doctorală şi postdoctorală multidisciplinară în bolile cronice" ("Program of excellence in doctoral and postdoctoral multidisciplinary research in chronic disease") and by PN-II-PT-PCCA-2013-4-1903. The results have been partially presented at the National Congress of Pharmacy from Romania, XVth edition, 10th Symposium of Biopharmacy and Pharmacokinetics, Iaşi, Romania, September 24-27, 2014.

References

1. van Santen E., Barends D.M., Frijlink H.W., Breaking of scored tablets: a review. *Eur. J. Pharm. Biopharm.*, 2002; 53(2): 139-145.
2. Mandal T.K., Effect of tablet integrity on the dissolution rate of sustained-release preparations. *J. Clin. Pharm. Ther.*, 1996; 21(3): 155-157.
3. Ishitsuka K., Onuki Y., Takayama K., Change in the drug release behavior of theophylline sustained-release tablets after division into two halves. *Yakugaku Zasshi*, 2012; 132(2): 225-230.
4. Burnham T., Tablet splitting. Annotated bibliography of publications. National electronic Library for Medicines. Medicines Management Overview. March 2013.
5. Food and Drug Administration, Advisory Committee for Pharmaceutical Sciences and Clinical Pharmacology. Tablet scoring: discussion

of guidance and compendial development. August 9, 2012.
6. U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Guidance for Industry. Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation. March 2013.
7. Simons K.J., Frith E.M., Simons F.E., Dissolution and bioavailability studies of whole and halved sustained-release theophylline tablets. *J. Pharm. Sci.*, 1982; 71(5): 505-511.
8. Shah V.P., Yamamoto L.A., Schuirman D., Elkins J., Skelly J.P., Analysis of *in vitro* dissolution of whole *vs*. half controlled-release theophylline tablets. *Pharm. Res.*, 1987; 4(5): 416-419.
9. Popa D.E., Lupuliasa D., Stănescu A.A., Bârcă M., Burcea-Dragomiroiu G.T.A., Miron D.S., Rădulescu F.S., Simulation of the in vivo exposure to ibuprofen based on *in vitro* dissolution profiles from solid dosage forms. *Farmacia*, 2014; 62(3): 483-493.
10. Green G., Berg C., Polli J.E., Barends D.M., Stimulli for revision process. Pharmacopeial Standards for the Subdivision Characteristics of Scored Tablets. *Pharm. Forum.*, 2009; 35(6): 1598-1612.
11. Hîrjău M., Lupuliasa D., Rădulescu F.S., Miron D.S., The study of piroxicam dissolution from eudragit rs-coated pellets. *Farmacia*, 2013; 61(5): 845-855.
12. Qureshi S.A., Developing discriminatory drug dissolution tests and profiles: some thoughts for consideration on the concept and its interpretation. *Diss. Tech.*, 2006; 11: 18-23.
13. Zhao N., Zidan A., Tawakkul M., Sayeed V.A., Khan M., Tablet splitting: Product quality assessment of metoprolol succinate extended release tablets. *Int. J. Pharm.*, 2010; 401(1-2): 25-31.
14. United States Pharmacopeia and National Formulary (USP 36-NF 31). Volume 2. Rockville, MD: United States Pharmacopeia Convention; 2013.