

The effect of splitting on the quality and *in vitro* release of metformin hydrochloride from extended-release (XR) tablets

O efeito da divisão na qualidade e na liberação *in vitro* de cloridrato de metformina de comprimidos de liberação prolongada (XR)

El efecto de la división sobre la calidad y la liberación *in vitro* del clorhidrato de metformina de las tabletas de liberación prolongada (XR)

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Abstract

Metformin hydrochloride (MetCl) is used worldwide in the treatment of type-2 diabetes mellitus. Although extended-release (XR) tablets containing 500 mg, 850 mg, and 1000 mg of MetCl are marketed, it is not uncommon to split the tablet when the dosage form of the required strength is not available commercially. The aim of work was to evaluate the effects of splitting on the *in vitro* performance of XR tablets containing MetCl. We performed quality control assays and comparative dissolution profile studies among several medicines containing 500 mg and 1000 mg of MetCl, marketed in Brazil and Argentina. Tablets containing 1000 mg of MetCl were halved (test samples) and compared with whole tablets of products containing 500 mg of MetCl (reference samples). The halved tablets were more fragile and presented lower uniformity of mass and dosage unit as compared to the whole ones. However, it was evidenced by the F2 bootstrapping parameter that splitting MetCl XR tablets did not significantly impact the *in vitro* drug release profiles

as compared to the whole tablets. In addition, nor the drug release mechanism neither the release kinetics were significantly affected. The XR tablets containing 1000 mg of metformin hydrochloride might be eligible for division, however, manufacturers could provide appropriate scores in the tablets surfaces to make the splitting proper and safer for the patients.

Keywords: Metformin hydrochloride; Drug release; Dissolution; Quality control; Diabetes mellitus.

Resumo

O cloridrato de metformina (MetCl) é usado mundialmente no tratamento do diabetes mellitus tipo 2. Embora os comprimidos de liberação prolongada (XR) contendo 500 mg, 850 mg e 1000 mg de MetCl sejam comercializados, não é incomum dividir o comprimido quando a dosagem necessária não está disponível comercialmente. O objetivo do trabalho foi avaliar os efeitos da divisão no desempenho *in vitro* de comprimidos XR contendo MetCl. Realizamos ensaios de controle de qualidade e estudos de perfil de dissolução comparativos entre diversos medicamentos contendo 500 mg e 1000 mg de MetCl, comercializados no Brasil e na Argentina. Comprimidos contendo 1000 mg de MetCl foram divididos pela metade (amostras de teste) e comparados com comprimidos inteiros de produtos contendo 500 mg de MetCl (amostras de referência). Os comprimidos reduzidos ao meio são mais frágeis e apresentam menor uniformidade de massa e unidade de dosagem em relação aos inteiros. No entanto, foi evidenciado pelo parâmetro de F2 bootstrapping que a divisão dos comprimidos de MetCl XR não afetou significativamente os perfis de liberação do fármaco *in vitro* em comparação com os comprimidos inteiros. Além disso, nem o mecanismo de liberação do fármaco nem a cinética de liberação foram significativamente afetados. Os comprimidos XR contendo 1000 mg de cloridrato de metformina podem ser elegíveis para divisão, no entanto, os fabricantes devem fornecer sulcos adequadas nas superfícies dos comprimidos para tornar a divisão adequada e mais segura para os pacientes.

Palavras-chave: Metformina; Liberação controlada de fármacos; Dissolução; Controle de qualidade; Diabetes mellitus.

Resumen

El clorhidrato de metformina (MetCl) se utiliza en todo el mundo para el tratamiento de la diabetes mellitus tipo 2. Aunque se comercializan tabletas de liberación prolongada (XR) que contienen 500 mg, 850 mg y 1000 mg de MetCl, no es raro dividir la tableta cuando la forma de dosificación de la concentración requerida no está disponible comercialmente. El objetivo del trabajo fue evaluar los efectos de la división en el rendimiento *in vitro* de tabletas XR que contienen MetCl. Realizamos ensayos de control de calidad y estudios comparativos de perfil de disolución entre varios medicamentos que contienen 500 mg y 1000 mg de MetCl, comercializados en Brasil y Argentina. Las tabletas que contenían 1000 mg de MetCl se dividieron a la mitad (muestras de prueba) y se compararon con tabletas enteras de productos que contenían 500 mg de MetCl (muestras de referencia). Las tabletas partidas a la mitad eran más frágiles y presentaban menor uniformidad de masa y unidad de dosificación en comparación con las enteras. Sin embargo, el parámetro de arranque F2 demostró que la división de las tabletas de MetCl XR no tuvo un impacto significativo en los perfiles de liberación de fármacos *in vitro* en comparación con las tabletas completas. Además, ni el mecanismo de liberación del fármaco ni la cinética de liberación se vieron afectados significativamente. Las tabletas XR que contienen 1000 mg de clorhidrato de metformina podrían ser elegibles para la división, sin embargo, los fabricantes deber proporcionar surcos apropiados en las superficies de las tabletas para que la división sea adecuada y más segura para los pacientes.

Palabras clave: Metformina; Liberación de fármacos; Disolución; Control de calidad; Diabetes mellitus.

1. Introduction

Tablet splitting is a very common practice in clinical routine worldwide, especially in the geriatric and psychiatric communities, as a way of drug adjustment and/or to reduce the cost of treatment (Carey & Fondriest, 2017; Elliott et al., 2014; Gracia-Vásquez et al., 2017). In Brazil, for instance, the prevalence of such practice in a tertiary hospital has shown to be of 4.5% (de Melo et al., 2020). However, the tablet splitting not necessarily results in uniform halves in terms of weight, physical strength, chemical stability, contents of active substances, and release performance (Abu-Geras et al., 2017; Eserian & Lombardo, 2017; Faelelbom et al., 2016; Helmy, 2015; Teixeira et al., 2017).

Over the last few years, studies have shown that this practice can impact the effectiveness of the treatment, especially for drugs with a narrow therapeutic index (Chou et al., 2015; Mascarenhas Starling et al., 2015; Nidanapu et al., 2016). It is also an eminent cause of medication error when the patients are taking two or more medications with similar shape and color (Tranchard et al., 2016). Studies regarding the evaluation of the clinical effects caused by the practice of tablet splitting showed no difference in the management of psychiatric disorders, thyroid cancer, and patient compliance (Ashrafpour et al., 2018; Freeman et al., 2012). Nonetheless, there is still scanty clinical evidence about this practice with respect to other drugs widely

used in the treatment of diabetes and metabolic syndrome like oral hypoglycemic, hypolipidemic, and antihypertensive medicines (Elliott et al., 2014; Freeman et al., 2012).

The metformin hydrochloride (MetCl), an oral hypoglycemic agent belonging to the biguanide class, is marketed worldwide due its favorable toxicity profile and clinical efficacy in the pharmacological management of type-2 diabetes mellitus (DM2) (Nasri & Rafieian-Kopaei, 2014). Its oral bioavailability varies between 16% and 55%, being absorbed predominantly by the small intestine (Graham et al., 2011). In addition, MetCl has a wide therapeutic window, ranging from 1000 to 2000 ng/mL (Balan et al., 2001; Idkaidek et al., 2011). Although immediate and extended-release (XR) tablets containing 500, 750, 850 or 1000 mg of MetCl can be found, is not uncommon in clinical practice that patients ask their physicians and pharmacists about the appropriateness of splitting XR tablets containing 1000 mg of MetCl and take each half whenever the XR tablets containing 500 mg are not commercially available at the moment.

The tablet splitting however, can destroy the extended-release mechanism provided by the drug delivery technology and the functional architecture of the dosage forms. As consequence, the disruption of the gastro-resistant coating or the limiting coatings for the nucleus hydration can directly affect the *in vitro* and *in vivo* performance of the formulation (Abu-Geras et al., 2017; Gracia-Vásquez et al., 2017; Wilczyński et al., 2016).

Motivated by this technological and clinical paradox, our team sought to provide scientific evidence to aid in the decision-making process as regards the practice of splitting MetCl XR tablets. Henceforth, we report the results of quality control assays and comparative dissolution profile studies conducted on six batches of XR tablets containing 500 mg and 1000 mg of MetCl available in the Brazil and Argentine markets.

2. Materials and Methods

2.1 Metformin hydrochloride formulations

We have performed a quantitative experimental research (Hussain et al., 2019). Six batches of non-scored MetCl XR tablets were evaluated: two reference products marketed in Brazil with dose strengths of 500 mg (AR) and 1000 mg (AT), two similar products marketed in Argentina with dose strengths of 500 mg (BR) and 1000 mg (BT), and two reference products marketed in Argentina with dose strengths of 500 mg (CR) and 1000 mg (CT). All batches were within the expiration date, the reference batches consisted of uncoated oblong tablets, whereas the similar tablets were rounded with polymeric coating (nonfunctional).

2.2 Standard and chemicals

MetCl reference standard was acquired from the United States Pharmacopeia (Rockville, USA). All other chemicals were analytical grade and obtained from the local suppliers. Ultrapure water from a from a Milli-Q® system (Millipore, Bedford, MA, USA) was used throughout this study.

2.3 Tablet splitting and quality control tests

The tablet splitting was performed on samples of products AT, BT, and CT, using a knife in order to mimic popular usage (Van Riet-Nales et al., 2014). The tablets and the split portions were submitted to the following tests according the United States Pharmacopeia (The United States Pharmacopeia and National Formulary - USP 42, 2019): hardness, friability, dissolution (Test 1), and uniformity of dosage unit by weight variation method.

The uniformity of mass for single-dose preparations was conducted according to the International Pharmacopoeia (World Health Organization (WHO), 2019) and the content of API in each batch was assessed according to the Brazilian Pharmacopeia (Brasil, 2019). Briefly, twenty tablets were weighed and powdered. An amount of powder equivalent to 100 mg

of MetCl was transferred to a 100 mL volumetric flask and dissolved with 70 mL of water by sonication for 15 min. The volume was completed with the same solvent and filtered. Further, 10 mL of the filtrate was transferred to a 100 mL volumetric flask, and the volume was completed with water. Successive dilutions were performed until reaching a concentration of 0.001% (w/v), using water as a solvent. The absorbances from the samples and that from the MetCl reference standard solution were recorded at 232 nm using a PERSEE T7DS spectrophotometer (Auburn, California, USA). The assay was carried out in triplicate and the result expressed as average (mg) \pm standard deviation (SD).

The halved tablets were also submitted to the splitting test as stated in the chapter <705> “Quality attributes of tablets labeled as having functional scores” from the United States Pharmacopeia (The United States Pharmacopeia and National Formulary - USP 42, 2019). Concisely, it was determined according **equation 1**

$$\frac{MS_{Cal}}{MS_{Exp}} \times 100 \quad (1)$$

wherein, MS_{Cal} is the mass of the split portion of the tablet accurately weighted and MS_{Exp} is the expected mass of the split portion determined dividing the whole-tablet weight by the number of portions, which in this study was 2 halves. According to the test, the weight of not less than 28 split portions from 30 tablets should be between 75% to 125% of the expected weight. Finally, the average weight of the whole and halved tablets was also determined.

2.4 Dissolution profiles

The whole or halves tablets of each brand ($n = 12$) were placed randomly and separately in the vessels of the dissolutor Sotax AT7 Smart (Sotax AG, Switzerland) containing 1000 mL of phosphate buffer (pH 6.8 ± 0.1) as dissolution medium, set at $37 \pm 0.5^\circ\text{C}$. The dissolution was carried using the paddles apparatus adjusted to 100 rpm and the samples (10 mL) were withdrawn at 1, 2, 4, 6, 8, and 10 h. The same volume was replaced with fresh dissolution medium at $37 \pm 0.5^\circ\text{C}$ to keep the sink condition. The samples were filtered and after appropriate dilution in phosphate buffer they were analyzed for MetCl at 232 nm as already stated. The data were expressed as mean values (% released) \pm SD.

The similarity factor (F_2) calculated by the bootstrap method (Paixão et al., 2017) was used to compare the dissolution profiles (**equation 2**):

$$F_2 = 50 \times \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^n (Rt - Tt)^2 \right]^{-0.5} \times 100 \right\} \quad (2)$$

wherein n is number of sampling times, Rt is the percent amount of drug dissolved at t time, obtained for the reference sample (whole tablets), Tt – percent amount of drug dissolved at t time, obtained for the test sample (halved tablets). Pair of dissolution profiles with values of $F_2 > 50$ were considered similar.

Additionally, the release kinetics of MetCl from XR tablets were evaluated using the depended models of Higuchi, Weibull, Korsmeyer-Peppas, zero-, and first-order (Simionato et al., 2018). The best model was selected based on the adjusted coefficient of determination ($R^2_{adjusted}$) and on the model selection criteria (MSC) (Zhang et al., 2010). The regression and linear correlation analysis of the kinetic models and release mechanisms were performed using the Microsoft Office Excel[®] supplement DDSolver[®] (Zhang et al., 2010; Zuo et al., 2014). Finally, the dissolution half-life (T_{50}) was determined from the equations defined by the mathematical models that have a more significant correlation coefficient (Simionato et al., 2018).

2.5 Data analysis

Pair-wise comparison were done by Student's t-test, while for three or more data set, the one-way Analysis of Variance (ANOVA) followed by the Tukey test were performed using the GraphPad v. 5.0 software (GraphPad Software Inc., CA, USA). In all analyzes, p values below 5% ($p < 0.05$, 95% confidence interval) were considered significant.

3. Results and Discussion

3.1 The effects of the splitting on the quality attributes of the XR tablets

Although XR MetCl tablets do not have functional scores, the administration of a halved portion of a 1000 mg of MetCl XR tablet as surrogate of a XR tablet with the half of the dose strength (500 mg) is not uncommon in clinical practice. Therefore, this study evaluated, for the first time, the quality parameters of the halved portions of XR tablets of MetCL (1000 mg) marketed in Brazil and Argentina as well as their *in vitro* dissolution performances which were further characterized and compared with those from whole XR tablets containing 500 mg of the MetCl. The only tablet-splitting technique used in this study was a knife because in preliminary tests we have found that splitting both the oblong and rounded non-scored tablets by hand or with sharp instruments such as splitting devices yield quite deformed halves.

The quality parameters of whole and halved tablets are presented on Table 1. Regarding the uniformity of mass, the references batches comprised with the requirements of the International Pharmacopeia (World Health Organization (WHO), 2019) since the percentage of weight variability of each unit remained between $\pm 5\%$ of average weight. On the other hand, none of the halved tablets fulfilled such specifications. Results are detailed in the panel of control charts showcased in Figure 1.

The mean weight loss verified after splitting the batches AT, BT, and CT were 0.4%, 0.06%, and 0.23%, respectively. It should be noted that none of these products had scores on their surfaces to guide and facilitate the splitting, however the values were lower than those already reported (Fahelbom et al., 2016; Teixeira et al., 2017). Moreover, among the samples tested, the tablets from BT batch with rounded shape and coating showed the lowest mass loss compared to those from batches AT and CT which were oblong and uncoated. The split portions fulfilled the requirements of the split test, since their weights remained between 75% to 125% of the expected weight (AT: 82.5-115.4%; BT: 80.8-119.0%; CT: 78.2-118.9%).

The halves showed a reduced mechanical resistance when compared to the whole tablets, which was evidenced by their smaller values of hardness and higher friability. This can be attributed to the fact that the mechanical force applied during tablet splitting weakened the intermolecular interactions changing the arrangement of their internal structures and making them less resistant to the application of subsequent breaking forces (Teixeira et al., 2017). Although coated tablets are not required to be submitted to the friability as demonstrated by the results of whole tablets which did not present any loss of mass after the test, to better demonstrate the effect of splitting on the mechanical strength of the halves, we have performed this assay. As observed, in all cases the friability values of the split portion of the three batches were no more than 1% which complies with the USP 42 requirements (The United States Pharmacopeia and National Formulary - USP 42, 2019).

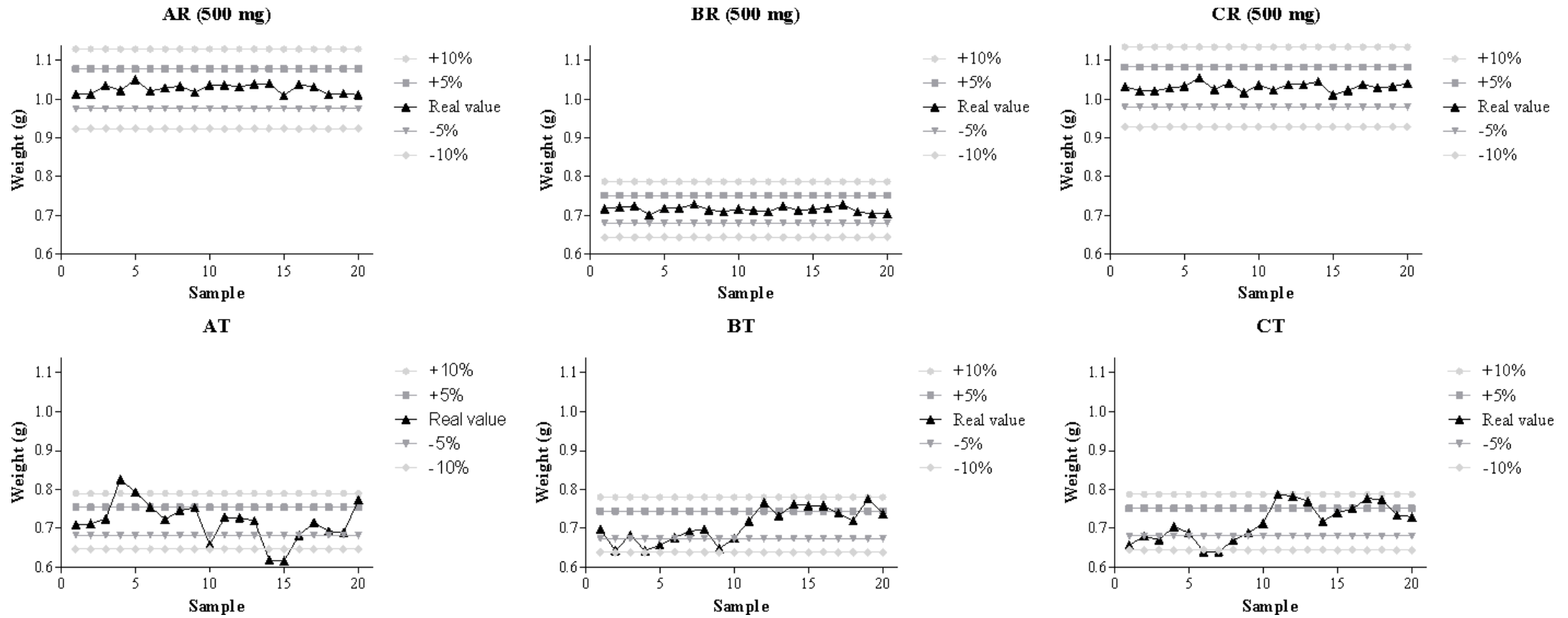
Most of the samples fulfilled the S1 stage (n= 6) requirements for the dissolution test, in which none result is outside the specification (The United States Pharmacopeia and National Formulary - USP 42, 2019). Only the samples C(R) and C(T) underwent to S2 stage (n= 12). To be approved, the sample must fulfil all the following requirements: i) the average value of the 12 units lies within each of the stated ranges and is not less than the stated amount at the final test time; ii) none is more than 10% of labeled content outside each of the stated ranges; and iii) none is more than 10% of labeled content below the stated amount at the final test time (The United States Pharmacopeia and National Formulary - USP 42, 2019). The average percentages of MetCl released from the C(R) and C(T) batches after 10 h of dissolution were 85.0% and 87%, respectively. No statistical difference was observed among the batches for each time sampling, demonstrating that the split did not affect the extension of drug release.

Table 1 – Quality parameters of the six batches of metformin hydrochloride (MetCl) XR tablets. The dissolution results are expressed as the minimum and maximum percentage of drug release. The results of AT, BT, and CT were obtained using one halved of the tablets containing 1000 mg of MetCl.

Test	Uniformity of mass (n= 20)	Hardness, N (mean ± SD, n= 10)	Friability (%) (mean, n= 10)	Dissolution (%) [#] (Buffer pH 6.8, n= 6-12)	Uniformity of dosage unit (weight variation)	Assay, (mean ± SD; n= 3)
Specifications	NMT 2 units outside ± 5% of the average weight (World Health Organization (WHO), 2019)	*	≤ 1.0% (The United States Pharmacopeia and National Formulary - USP 42, 2019)	1h – 20-40% 3h – 45-65% 10h - ≥ 85% (The United States Pharmacopeia and National Formulary - USP 42, 2019)	AV ≤ 15 (L1), n= 10 AV ≤ 25 (L2), n= 30 (The United States Pharmacopeia and National Formulary - USP 42, 2019)	90 - 110% of the labeled amount (BRASIL, 2019)
AR (500 mg)	Passed	87.7 ± 27.5	0.0	1h – 29.5 - 32.1 3h – 51.5 - 56.3 10h – 88.1 - 94.3	9.0	91.1 ± 1.1
AT (1000 mg; halved)	Failed	61.3 ± 21.8 ^a	0.9 ^b	1h – 28.7 - 32.9 3h – 52.9 - 60.8 10h – 85.3 - 98.9	23.6	88.1 ± 3.1 (failed)
BR (500 mg)	Passed	116.2 ± 2.2	0.0	1h – 32.3 - 34.2 3h – 57.8 - 59.3 10h – 93.4 - 96.6	5.5	93.6 ± 0.6
BT (1000 mg; halved)	Failed	97.3 ± 20.9 ^a	0.2 ^a	1h – 34.1 - 39.2 3h – 61.0 - 67.8 10h – 86.9 - 100.3	18.2	91.0 ± 1.8
CR (500 mg)	Passed	116.7 ± 0.3	0.0	1h – 26.1 – 27.2 3h – 46.2 - 53.0 10h – 78.7 - 91.8*	11.4	89.1 ± 1.0 (failed)
CT (1000 mg; halved)	Failed	84.8 ± 23.7 ^b	1.0 ^b	1h – 31.1 - 36.8 3h – 57.0 - 63.1 10h – 79.1 - 95.3*	24.5	85.7 ± 1.0 ^a (failed)

NMT: No more than; ^ap < 0.05, ^bp < 0.01 e ^cp < 0.001 as compared to their respective reference product; *after stage S2; 12 units tested. Source: Authors.

Figure 1 - Control charts for the results of the uniformity of mass test for six batches of metformin hydrochloride XR tablets (Int. Pharm, 9th ed.);



R, whole tablets containing 500 mg of metformin hydrochloride (Reference); T, halved tablets containing metformin hydrochloride (Test); Source: Authors.

The results of the uniformity of dosage unit test suggest that the API was homogeneously distributed among the batches units since all of them complied with the USP requirements, although one can observe that the halves presented higher acceptance values (AV). Although the splitting affected the dose uniformity between the halves, it was within of an acceptable level.

The spectrophotometric assays revealed that the content of MetCl remained within the limits of 90%-110% of the labeled amount only in the batches AR, BR, and BT. This finding may be justified in part by loss of mass that normally occurs during the process of splitting, however reasons for the quality deviation found in CR batch remains unclear.

3.2 Halved tablets had similar *in vitro* drug dissolution profiles as compared to whole tablets

The Figure 2 presents the dissolution profiles of MetCl from whole (R) and halved (T) XR tablets. The results of the kinetic parameters of dissolution are shown in Table 2. As can be seen, for all whole and halved tablets analyzed, both the Higuchi (pseudo First-order) and the Weibull mathematical models can be applied to describe the drug release kinetics. Furthermore, the velocity of drug release was determined by the dissolution half-life (T50). It is possible to state that splitting the tablets of the products A and C significantly increased the rate of metformin hydrochloride dissolution (approximately 10% and 16%, respectively). For the product B there was no statistically significant difference for this parameter.

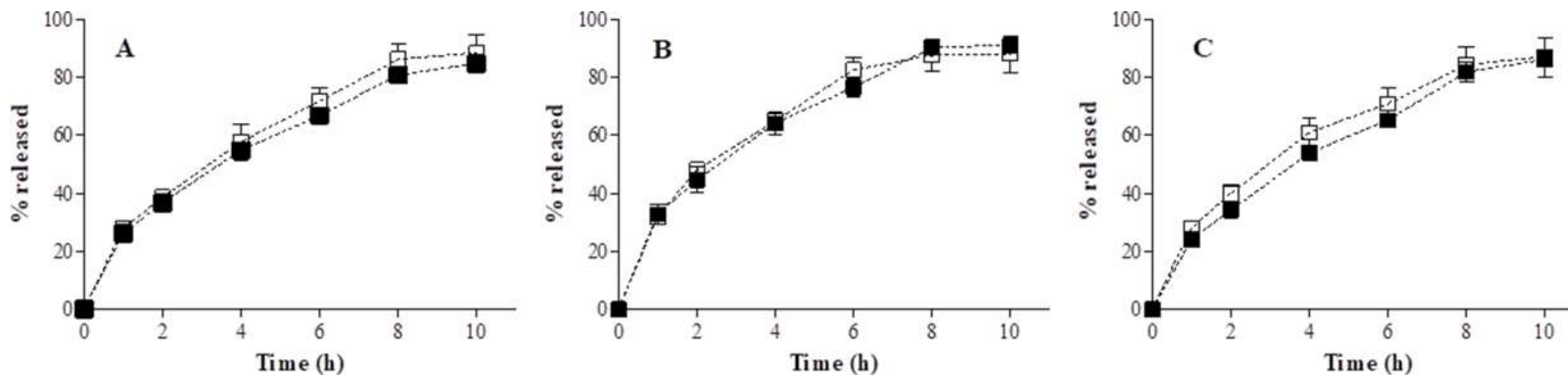
The drug release mechanism from hydrophilic polymeric matrices was determined by the diffusion coefficient (n), obtained by mathematical models of Korsmeyer and Peppas (Korsmeyer & Peppas, 1981). Based on the results presented in Table 2, regardless of the product, the release mechanism can be attributed to anomalous transport ($0.45 < n < 0.89$), i.e., the drug release depends on the diffusion through the polymeric matrix as well as its swelling (hydration) and bulk erosion (Lopes et al., 2005). Thus, the changes caused to the tablet surfaces due to the splitting did not significantly affect the release mechanism. In all cases, according to the labeled information described by the manufacturers, the adjuvant responsible for matrix formation is hydroxypropyl methylcellulose, a hydrophilic polymer with high hydration/swelling capacity and slow erosion (Siepmann & Peppas, 2012).

The MetCl dissolution profiles from the halved XR tablets were considered similar to their respective reference batches once the F2 bootstrapping values were greater than 50 (AR/AT: 72.17, BR/BT: 74.76; CR/CT: 66.97). Therefore, differently from what is stated in the literature (Abu-Geras et al., 2017; Gracia-Vásquez et al., 2017; Wilczyński et al., 2016) the splitting of MetCl XR tablets did not significantly impair the *in vitro* release behavior and, likewise, may not affect its bioavailability and bioequivalence. Noteworthy, our findings do not enable drawing clinical conclusions, since no clinical outcomes were assessed.

To be considered appropriate for tablet splitting a medication should be comprised by a drug with long half-life and broad therapeutic window, and the dosage form should be of large size and preferably scored (Helmy, 2015). Although MetCL tablets comprise most of these requirements, these formulations are not scored. Modification on the shape of the XR tablets containing 1000 mg of MetCl to include scores with adequate design might be an alternative to make the splitting more accurate and feasible by the patients. Indeed, suitable scoring of XR tablets exerts a key role in the physical and physicochemical features of the halves (Vranić & Uzunović, 2007, 2009). However, it is worth of note to mention that patients should be counseled to split the tablets in the moment of the administration and to do not store the second halve during long periods since the stability and the performance of the formulation can be affected (Teixeira et al., 2017).

The splitting has affected some quality parameters of the halves especially the assay, probably because the absence of scores. However, it did not compromise the dissolution behavior, which may encourage future *in vitro/in vivo* correlation studies using scored test formulations to further investigate if halved portions of 1000 mg MetCl XR tablets can surrogate the 500 mg XR tablets.

Figure 2 - Dissolution profiles of metformin hydrochloride from whole (Reference, filled squares) and halved (Test, empty squares) extended-release tablets of batches AR and AT (**A**), BR and BT (**B**), and CR and CT (**C**).



1000 mL of phosphate buffer, pH 6.8 ± 0.1 , type-II apparatus (paddle), 100 rpm, 37.0 ± 0.5 °C. Values represent mean \pm SD, n= 12. Source: Authors.

Table 2 - Results of the kinetic models and dissolution mechanism of metformin hydrochloride from whole and halved extended-release (XR) tablets (500 mg). Results were expressed as average \pm standard deviation (SD) (n= 12).

Model	Metformin hydrochloride XR tablet batches											
	AR		AT		BR		BT		CR		CT	
	R ² _{adjusted}	MSC	R ² _{adjusted}	MSC	R ² _{adjusted}	MSC	R ² _{adjusted}	MSC	R ² _{adjusted}	MSC	R ² _{adjusted}	MSC
Zero-order	0.9172	0.8383	0.8039	0.7782	0.7162	0.3455	0.6463	0.0557	0.8636	1.1882	0.7680	0.5674
First-order	0.9814	3.1363	0.9758	3.0698	0.9785	2.9748	0.9606	2.5453	0.9879	3.6380	0.9766	3.0477
Higuchi	0.9962	4.7608	0.9886	3.9336	0.9852	3.5958	0.9729	2.6691	0.9901	3.8474	0.9926	4.1113
Korsmeyer-Peppas	0.9960	4.6125	0.9869	3.6863	0.9908	3.6753	0.9783	2.7627	0.9942	4.3025	0.9904	3.7410
Weibull	0.9913	3.7666	0.9847	3.5765	0.9909	3.8091	0.9930	3.9220	0.9900	3.7491	0.9941	4.1777
T ₅₀ (h)	3.35 \pm 0.16		3.01 \pm 0.39 [#]		2.30 \pm 0.31		2.17 \pm 0.23		3.34 \pm 0.18		2.79 \pm 0.40 ^{##}	
n	0.53 \pm 0.01		0.53 \pm 0.02		0.47 \pm 0.05		0.46 \pm 0.02		0.57 \pm 0.01		0.51 \pm 0.02 [*]	

R: whole tablets containing 500 mg of metformin hydrochloride (Reference); T: halved tablets containing metformin hydrochloride (Test); R²_{adjusted}: Adjusted determination coefficient, MSC: Model selection criteria; T₅₀: time to release 50% of the labeled amount of metformin hydrochloride; n: difusional coefficient obtained by the Korsmeyer-Peppas model; ^{*}p < 0.05 as compared to AR (Paired T-Test); ^{##}p < 0.01 as compared to CR (Paired T-Test); ^{*}p < 0.05 as compared to CR (Paired T-Test); Bold values correspond to the most significant mathematical models. **Source:** Authors.

4. Conclusions

Splitting metformin hydrochloride XR tablets (1000 mg) significantly affected their physical quality attributes, decreasing the average weight and hardness, and increasing the friability. Regarding the assay, the splitting compromised the drug content. For all brands, the partitioning of the tablets led to greater variation in the uniformity of dose unit test, although all products met the test specifications. Suitable scoring the tablets surfaces would be useful to circumvent these quality deviations. There was no significant difference in the dissolution of the drug between whole and halved tablets, all of which fulfilled the test requirements. In addition, the splitting did not modify mechanism of drug release. The 1000 mg metformin hydrochloride XR tablets might be eligible for splitting, however future *in vitro* and *in vivo* studies using scored test formulations should be conducted to clarify this issue. In fact, the effects of splitting XR tablet either in the pharmacokinetics of metformin hydrochloride and glycemic control in animal models of type-2 diabetes mellitus will be investigated by our research team.

Conflicts of interest statement

None.

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Author's contributions

LGFS, FSM, YKH and MPK acquired, treated and analyzed data; as well as wrote the first draft of the manuscript. OF aided in the conceptualization of the study and revised the manuscript. MPF and ACFS revised data and writing. ROC, WVC and AIS conceptualized the research; as well as coordinated all data collection, treatment, analysis and wrote the final version of the manuscript.

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