Original Article

ESTIMATION OF *IN VITRO* AND *IN VIVO* PERFORMANCE OF METRONIDAZOLE ORAL DOSAGE FORMS

JOSE RAUL MEDINA-LOPEZ, YONATAN JOCEL GOMEZ-VARGAS, HEDWYN RODOLFO MENDEZ-HERNANDEZ, FELIPE DINO REYES-RAMIREZ, JUAN CARLOS RUIZ-SEGURA, MARCELA HURTADO

Departamento Sistemas Biologicos, Universidad Autonoma Metropolitana-Xochimilco, Mexico City, Mexico
*Corresponding author: Jose Raul Medina-Lopez; *Email: rmlopez@correo.xoc.uam.mx

ABSTRACT

Objective: To estimate plasma concentrations-time profiles of metronidazole commercial tablets through *in vitro* dissolution data using the Inverse Release Function approach and a convolution method.

Methods: Dissolution profiles of metronidazole reference tablets (500 mg) were obtained using USP Apparatus 1 at 100 rpm, USP Apparatus 4 at 16 ml/min, and 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer as dissolution media. Additionally, three generic drug products were tested using USP Apparatus 1 and pH 4.5 acetate buffer. Drug was quantified at 278 nm until 60 min. Dissolution parameters such as mean dissolution time, area under the cumulative dissolution curve, and dissolution efficiency were calculated. Metronidazole plasma levels were predicted considering the *in vitro* release data and published information. Percent of prediction error (PE) for C_{max} and AUC_{0-inf} at each condition was calculated.

Results: When comparing dissolution profiles with common dissolution parameters (USP 1 *vs.* 4) significant differences were found (*P<0.05). Values of PE for C_{max} and AUC_{0-inf} were within range (±15%) only with USP Apparatus 1 and pH 4.5 acetate buffer. Using these conditions when comparing generic drug products *vs.* reference formulation, significant differences were found (*P<0.05) and values of PE for AUC_{0-inf} were out of the range.

Conclusion: The obtained information suggests using USP Apparatus 1 and pH 4.5 acetate buffer to predict the *in vivo* performance of metronidazole tablets. The impact of *in vitro* differences of all generic formulations was confirmed with differences in predicted *in vivo* performance.

Keywords: Convolution, Inverse release function, Metronidazole, Prediction error, Tablets

INTRODUCTION

An important objective of pharmaceutical product development is to gain a better understanding of the *in vitro* and *in vivo* drug performance. Through the successful development and application of an *in vitro/in vivo* correlation (IVIVC), *in vivo* drug performance can be predicted from its *in vitro* behavior [1]. Prediction of plasma concentration-time profiles can be established by a convolution approach. The convolution technique has some advantages: a) the procedure does not require an *in vivo* study for the test product to obtain pharmacokinetic parameters (bioavailability factor, F; volume of distribution, Vd; elimination rate constant, ke) since values of these parameters are available in the literature and b) it is not necessary to purchase sophisticated computer software since a simple spreadsheet software (MS Excel) may be used [2].

For immediate-release dosage forms, the successful development of IVIVC models may be limited to Class 2 and Class 3 compounds classified under the Biopharmaceutics Classification System (BCS). According to Food and Drug Administration (FDA) guidelines, biowaivers can also be requested for Class 1 compounds provided the drugs are solubilized in the gastric fluid sufficiently rapidly that gastric emptying does not become the rate-limiting step [1]. Gastric emptying time is 15-20 min under fasting conditions [3]. Metronidazole is a BCS Class 1, being a highly soluble and highly permeable drug [4]. The monograph states that a biowaiver for metronidazole solid immediate-release formulations is justified provided, among other characteristics: the test product and its comparator are both rapidly dissolving [4]. According to FDA guidance, immediate-release formulations are considered rapidly dissolving products when a mean of 85% or more dissolves within 30 min using USP basket apparatus (USP Apparatus 1) and dissolution media of pH 1.2 as well as pH 4.5 and pH 6.8 buffers [5].

Pharmacopeial dissolution test for metronidazole tablets suggests USP Apparatus 1 at 100 rpm with 900 ml of 0.1 N HCl as dissolution medium and not less than 85% of the labelled amount should be dissolved in 60 min [6]. On the other hand, the flow-through cell method (USP Apparatus 4) is an alternative to conventional USP dissolution testing apparatuses [7]. The USP Apparatus 4 offers several advantages over the USP Apparatus 1 and paddle apparatus (USP Apparatus 2). These include the ability to maintain *sink* conditions due to the continuous introduction of dissolution medium to the dissolution cell in an open system and the ease with which the composition and pH of the dissolution medium can be changed over the course of a dissolution test [8].

The influence of dose and USP apparatus in the *in vitro* release performance of metronidazole reference tablets as well as the pharmaceutical equivalence of metronidazole generic drug products with media of physiological relevance has been previously reported [9, 10]. Significant differences were found between the therapeutic dose of 250 and 500 mg using USP Apparatus 1 and 4 (*P<0.05). Some generic drug products showed different dissolution profiles than that observed with the reference formulation using 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer as dissolution media. Benzoyl metronidazole suspensions have also been studied with the USP Apparatus 4 and simulated gastrointestinal fluids [11]. Significant differences in the rate and extent of drug dissolution of generic and reference drug products were found (*P<0.05). Given the *in vitro* release conditions in which all formulations were tested, these differences could be of clinical implication.

The aim of this research is to predict the metronidazole plasma concentrations-time profiles through *in vitro* dissolution data using the Inverse Release Function approach [12] and to estimate the *in vivo* performance of metronidazole tablets with a convolution method [13]. Conditions included the use of the USP Apparatus 1 and 4 and dissolution media of physiological relevance (pH 1.2–pH 6.8). A first set of experiments included the *in vitro* release of reference formulation and when obtaining the conditions that best reflect the *in vivo* performance, the metronidazole generic drug products for sale in the local market will be evaluated.

MATERIALS AND METHODS

Reagents and chemicals

Metronidazole reference tablets (coded as R formulation) (Flagyl 500 mg, Sanofi-Aventis de México S. A. de C. V. Mexico City, Mexico) and three generic formulations (coded as A, B, and C drug products) with the same dose were used. Mexican health authorities have established Flagyl drug product as the reference formulation for dissolution and bioequivalence studies [14]. HCl, sodium acetate, and phosphate monobasic and dibasic salts were acquired from J. T. Baker-Mexico (Xalostoc, Mexico). Metronidazole standard was acquired from Sigma-Aldrich Co. (St. Louis MO, USA).

Uniformity of dosage units and assay

Uniformity of dosage units and assay tests were performed with all formulations according to the procedures described in the USP [6].

In vitro dissolution profiles

In the first part of the *in vitro* release studies, dissolution profiles of R formulation were obtained using a USP Apparatus 1 at 100 rpm (Sotax AT7-Smart, Sotax AG, Switzerland) and 900 ml of dissolution medium. Additionally, the USP Apparatus 4 (Sotax CE6, Sotax AG, Switzerland) at a laminar flow rate of 16 ml/min and 22.6 mm cells (i.d.) was used. In both dissolution apparatuses, 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer at 37.0±0.5 °C were used as dissolution media. In all cases, dissolution samples were taken at 10-, 20-, 30-, 45-, and 60-min using fiberglass filters (n = 12). The amount of dissolved metronidazole was determined by UV measurement at 278 nm with the support of a standard calibration curve in each dissolution medium. In the second part of release studies, dissolution profiles of R formulation and all generic drug products were determined using the USP Apparatus 1 at 100 rpm and 900 ml of pH 4.5 acetate buffer at 37.0±0.5 °C. Samples of dissolution medium were withdrawn at same sampling times of the first part of dissolution studies and dissolved metronidazole was calculated with a standard calibration curve in pH 4.5 acetate buffer (n = 12).

Data analysis

Common dissolution parameters such as mean dissolution time (MDT), area under the cumulative dissolution curve (AUCC), and dissolution efficiency (DE) were calculated and statistically compared. Dissolution parameters were determined with the Excel add-in DDSolver program [15]. After this, f_2 similarity factor was also calculated with the aim of comparing dissolution profiles. Similar profiles were considered if f_2 = 50-100 [16]. A first set of comparisons were considered with USP Apparatus 1 *vs.* 4 data (Student's t-test) while the second set of comparisons were A-C generic drug products *vs.* R formulation (one-way ANOVA followed by a Dunnett's multiple comparison test) with a model-independent approach [17]. Significant differences were considered if *P<0.05.

Prediction of metronidazole *in vivo* performance

Metronidazole plasma levels were calculated by the support of the Inverse Release Function approach proposed by Cardot *et al.* [12]. This methodology allows and adjustment in the time scale of the *in vitro* release performance to facilitate the establishment of a meaningful IVIVC. Once the new time scale of the dissolution profile is calculated, predicted plasma concentrations-time profiles were determined with a simple numerical convolution method proposed by Qureshi [13]. The method uses published metronidazole pharmacokinetic parameters such as bioavailability factor (F), elimination rate constant (k_e), and volume of distribution (V_d) [4]. From predicted plasma concentrations-time profiles, pharmacokinetic parameters such as peak concentration (C_{max}) and area under the concentration-time curve from zero to infinity (AUC_{0-inf}) were calculated by a compartmental method using the Excel add-in PKSolver program [18]. Reported data of a metronidazole bioequivalence study with R formulation (500 mg tablets) were used to estimate the predictability of the convolution method [19]. It has been established by the calculation of the percent of prediction error (%PE) for C_{max} and AUC_{0-inf} according to Eq. 1 (where %PE should not exceed 15%) [20-22].

$$(\%PE) = \frac{(observed\ value - predicted\ value)}{observed\ value} \times 100 \ ... \ Eq.\ (1)$$

RESULTS AND DISCUSSION

Uniformity of dosage units and assay

Metronidazole tablets were within USP limits. The mean±standard deviation (SD) of ten metronidazole reference tablets in uniformity of dosage units test was 104.36±0.30% (85-115% as USP limit); in assay test with three samples was 99.81%±0.70 (90-110% as USP limit) [6]. All generic drug products also met both pharmacopeia tests.

In vitro dissolution profiles

Dissolution profiles of metronidazole R formulation using USP Apparatus 1 and 4 are shown in fig. 1 and fig. 2, respectively. Dissolved drug (mean±SD) at 30 min, using USP Apparatus 1 and 900 ml of 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer, was 78.63±2.70%, 45.26±3.03%, and 41.74±1.89%, respectively. This formulation in no condition, was able to dissolve more than 85% of the drug at 30 min so R formulation cannot be considered as a rapidly dissolving product. The result differs from the reported solubility of metronidazole at 37 °C where at pH 1.0, pH 5.0 and pH 7.0 was 30.6, 12.8, and 11.6 mg/ml, respectively [4]. According to this information, the therapeutic dose used should have no problem to be completely dissolved from the oral dosage form; however, limited *in vitro* release was observed. Metronidazole reference tablets met the pharmacopoeia criteria as more than 85% of the dissolved drug was found at 60 min (98.78±2.96% with 0.1 N HCl). On the other hand, the use of USP Apparatus 4 significantly affected both rate and extent of released metronidazole, as the drug dissolved considerably slower. Dissolution parameters used to compare dissolution profiles and f_2 similarity factor (USP 4 *vs.* USP 1) are shown in table 1. In all cases, significant differences were found (*P<0.05) and all f_2 values were less than 50.

Estimation of *in vivo* plasma levels

To identify whether the conditions for the USP Apparatus 1 or USP Apparatus 4 reflected the *in vivo* performance of metronidazole in humans, it was necessary to predict the *in vivo* plasma concentration-time profiles from the *in vitro* dissolution data. An adjustment in the time scale of dissolution profiles, as well as the values of some metronidazole pharmacokinetic parameters, were used to estimate the *in vivo* performance of metronidazole commercial tablets. Plasma concentration-time profiles from USP Apparatus 1 and 4 dissolution data are shown in fig. 1 and fig. 2, respectively. Only using USP Apparatus 1 at 100 rpm and 900 ml of pH 4.5 acetate buffer as dissolution medium the values of PE for C_{max} and AUC_{0-inf} were<15%, indicating the validity of the convolution method [20] as well as the best *in vitro* conditions to predict the *in vivo* performance of metronidazole tablets.

Comparison of generics and reference

As the above result suggests the best conditions to test the *in vitro* release, three metronidazole generic drug products were studied, and dissolution profiles were compared with the dissolution profile of R formulation. Results are shown in fig. 3. At 30 min, all generic drug products released more than 85% of drug while R formulation dissolved 44.45±1.70%. At 60 min, all formulations dissolved more than 85% of metronidazole. Difference in *in vitro* release of all generic drug products and R formulation is evident even so, statistical comparison of MDT, AUCC, and DE parameters were carried out. Significant differences in all parameters were found (*P<0.05). Results are depicted in table 2. The calculation of the f_2 similarity factor confirms the differences between dissolution profiles (f_2<50). Predicted metronidazole plasma concentrations of all generic drug products and R formulations are shown in fig. 3. All PE values of AUC_{0-inf} from generic formulations were less than-15% (table 2). Therefore, it is considered that generic drug products would not have the same *in vivo* performance as the R formulation. On the other hand, PE values of C_{max} and AUC_{0-inf} of R formulation were in the range of±15% which maintains the prediction of the *in vivo* behavior of the R drug product used by us like that observed in the previously published bioequivalence study. It is known that metronidazole has a good bioavailability ≥90%) [23]; however, several complications have been documented such as absorption

problems [24], non-equivalence cases [25] and treatment ineffectiveness due to low plasma concentrations [26-28]. The results of the present *in vitro* release study could be related to

previously reported problems. On the other hand, some efforts have been made to obtain better and more effective metronidazole formulations [29, 30].
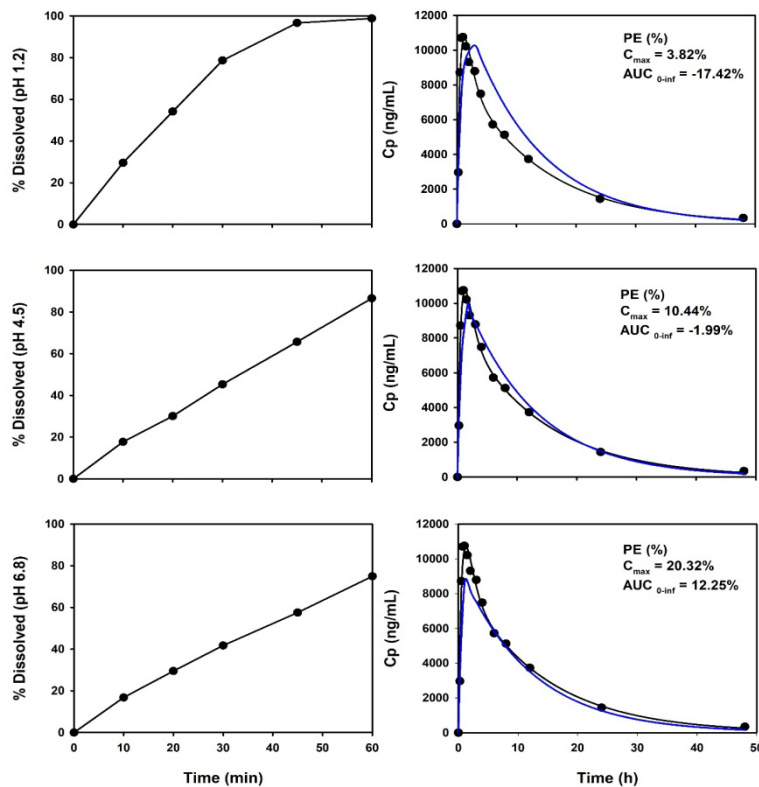

Fig. 1: Dissolution profiles of metronidazole tablets using USP apparatus 1 (left) and predicted plasma levels (blue line at right). Observed data (full circles) were reported by Herrera [19]. Data is given as mean, n = 12
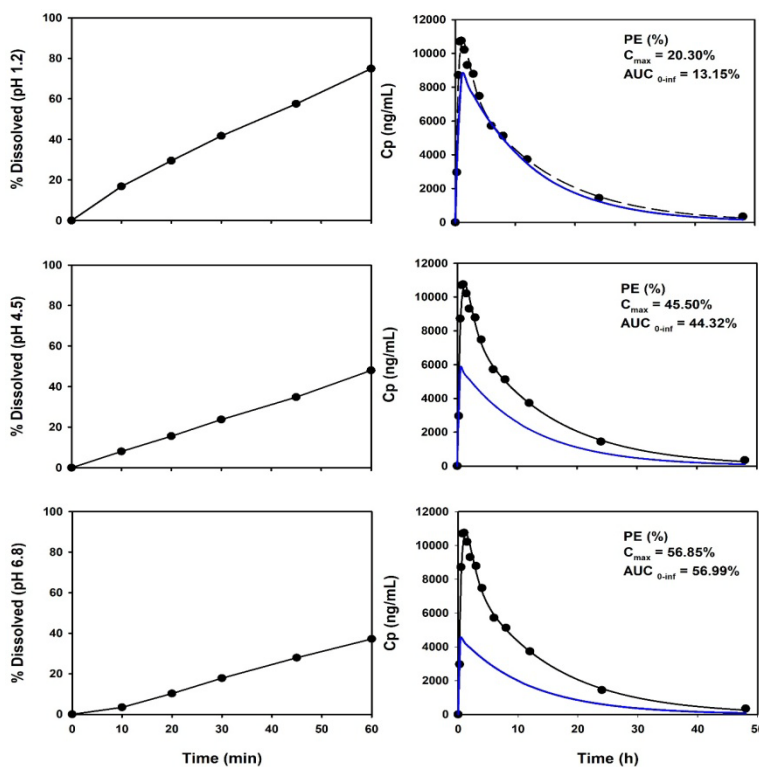

Fig. 2: Dissolution profiles of metronidazole tablets using USP apparatus 4 (left) and predicted plasma levels (blue line at right). Observed data (full circles) were reported by Herrera [19]. Data is given as mean, n = 12

Table 1: Dissolution parameters and f_2 similarity factors calculated to compare dissolution profiles (USP 4 *vs*. USP 1)

pH	MDT (min)	AUCC (%·min)	DE (%)	f_2
USP Apparatus 1				
1.2	19.38±0.29	4010.48±26.34	66.84±0.44	-
4.5	29.07±0.28	2676.30±45.73	44.61±0.76	-
6.8	27.84±0.28	2409.58±26.28	40.16±0.44	-
USP Apparatus 4				
1.2	30.47±0.23*	2440.86±32.97*	40.68±0.55 *	29.45
4.5	30.47±0.32*	1413.41±28.17*	23.56±0.47*	31.79
6.8	31.59±0.47*	1056.29±29.26*	17.60±0.49*	31.06

MDT: mean dissolution time, AUCC: area under the cumulative dissolution curve, DE: dissolution efficiency, Data is given as mean±SD, n = 12, *P<0.05
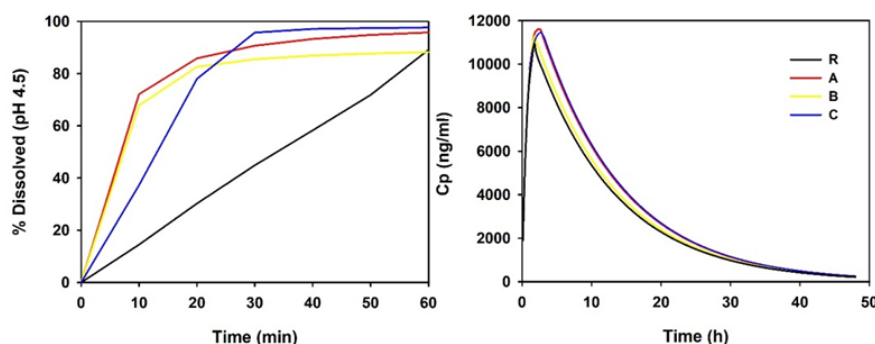

Fig. 3: Dissolution profiles of metronidazole reference (R) and generic formulations (A-C) using USP Apparatus 1 at 100 rpm and 900 ml of pH 4.5 acetate buffer (left) and their predicted plasma concentrations (right). Error bars were omitted for clarity. Data is given as mean, n = 12

Table 2: Dissolution parameters and f_2 similarity factors calculated to compare dissolution profiles (A-C *vs*. R formulations). Predicted errors for C_{max} and AUC_{0-inf}

Parameter	R	A	B	C
MDT (min)	30.35±0.23	9.37±0.44*	8.47±0.18*	13.46±0.24*
AUCC (%·min)	2640.90±34.12	4845.12±57.21*	4545.41±28.96*	4542.05±34.45*
DE (%)	44.01±0.57	80.75±0.95*	75.76±0.48*	75.70±0.57*
f_2	-	20.78	23.12	24.06
PE (%) for C_{max}	1.96	-7.32	-3.51	-7.17
PE (%) for AUC_{0-inf}	-11.62	-28.55	-17.47	-28.96

MDT: mean dissolution time, AUCC: area under the cumulative dissolution curve, DE: dissolution efficiency, PE: prediction error, R: reference, A-C: generic formulations, Data is given as mean±SEM, n = 12, *P<0.05.

CONCLUSION

The obtained information suggests using USP apparatus 1 at 100 rpm and 900 ml of pH 4.5 acetate buffer to predict the *in vivo* performance of metronidazole tablets. These dissolution conditions seem to be appropriate for the evaluation of metronidazole oral dosage forms. The impact of *in vitro* release differences of all metronidazole generic drug products was confirmed with differences in predicted *in vivo* performance. Human studies with these formulations are necessary to confirm the obtained results.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

REFERENCES

1. Lu Y, Kim S, Park K. *In vitro-in vivo* correlation: perspectives on model development. Int J Pharm. 2011;418(1):142-8. doi: 10.1016/j.ijpharm.2011.01.010, PMID 21237256.
2. Rastogi V, Yadav P, Lal N, Rastogi P, Singh BK, Verma N. Mathematical prediction of pharmacokinetic parameters-an *in vitro* approach for investigating pharmaceutical products for IVIVC. Future Journal of Pharmaceutical Sciences. 2018;4(2):175-84. doi: 10.1016/j.fjps.2018.03.001.
3. Alt A, Potthast H, Moessinger J, Sickmüller B, Oeser H. Biopharmaceutical characterization of sotalol-containing oral immediate release drug products. Eur J Pharm Biopharm. 2004;58(1):145-50. doi: 10.1016/j.ejpb.2004.02.007. PMID 15207548.
4. Rediguieri CF, Porta V, G Nunes DSG, Nunes TM, Junginger HE, Kopp S. Biowaiver monographs for immediate release solid oral dosage forms: metronidazole. J Pharm Sci. 2011;100(5):1618-27. doi: 10.1002/jps.22409, PMID 21374600.
5. Center for Drug Evaluation and Research (CDER). Food and drug administration guidance for industry: waiver on *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system; 2017. Available from: https://collections.nlm.nih.gov/catalog/nlm:nlmuid-101720038-pdf. [Last accessed on 12 May 2023]
6. United States Pharmacopeia. USP 44. NF. The United States of America Pharmacopeial Convention. Vol. II; 2021. p. 39.
7. Singh I, Aboul Enein HY. Advantages of USP apparatus IV (flow-through cell apparatus) in dissolution studies. J Iran Chem Soc. 2006;3(3):220-2. doi: 10.1007/BF03247211.
8. D'Arcy DM, Liu B, Bradley G, Healy AM, Corrigan OI. Hydrodynamic and species transfer simulations in the USP 4

dissolution apparatus: considerations for dissolution in a low velocity pulsing flow. Pharm Res. 2010;27(2):246-58. doi: 10.1007/s11095-009-0010-4, PMID 20012167.

9. Medina JR, Ortiz HD, Hurtado M, Domínguez Ramirez AM. Influence of dose and the USP basket and flow-through cell dissolution apparatuses in the release kinetics of metronidazole immediate-release products. Int J Res Pharm Sci. 2014;5(2):137-46.

10. Jimenez Flores Y, Hurtado M, Medina Lopez JR. Pharmaceutical equivalence of metronidazole tablets using the flow-through cell (USP Apparatus 4) and media of physiological pH range. Int J App Pharm. 2022;14(4):259-64. doi: 10.22159/ijap.2022v14i4.44759.

11. Medina JR, Hernandez J, Hurtado M. *In vitro* release studies of carbamazepine tablets and benzoyl metronidazole suspensions using the flow-through cell apparatus and simulated gastrointestinal fluids. Int J App Pharm. 2017;9(4):54-60. doi: 10.22159/ijap.2017v9i4.18929.

12. Cardot JM, Lukas JC, Muniz P. Time scaling for in vitro-in vivo correlation: the inverse release function (IRF) approach. AAPS J. 2018;20(6):95. doi: 10.1208/s12248-018-0250-5, PMID 30159772.

13. Qureshi SA. *In vitro-in vivo* correlation (IVIVC) and determining drug concentrations in blood from dissolution testing a simple and practical approach~!2009-10-30~!2010-01-04~!2010-04-29~!. Open Drug Deliv J. 2010;4(2):38-47. doi: 10.2174/1874126601004020038.

14. Comision Federal Para la Proteccion de Riesgos Sanitarios (COFEPRIS). Listado actualizado de medicamentos de referencia 2023/01. Mexico. Available from: https://www.gob.mx/cms/uploads/attachment/file/803597/lMR_2023-01_actualizaci_n_10_febrero_2023.pdf. [Last accessed on 12 May 2023]

15. Zhang Y, Huo M, Zhou J, Zou A, Li W, Yao C. DD Solver: an add-in program for modeling and comparison of drug dissolution profiles. AAPS J. 2010;12(3):263-71. doi: 10.1208/s12248-010-9185-1, PMID 20373062.

16. Moore JW, Flanner HH. Mathematical comparison of dissolution profiles. Pharm Technol. 1996;20(6):64-74.

17. Yuksel N, Kanik AE, Baykara T. Comparison of *in vitro* dissolution profiles by ANOVA-based, model-dependent and-independent methods. Int J Pharm. 2000;209(1-2):57-67. doi: 10.1016/s0378-5173(00)00554-8, PMID 11084246.

18. Zhang Y, Huo M, Zhou J, Xie S. PK Solver: an add-in program for pharmacokinetic and pharmacodynamic data analysis in microsoft excel. Comput Methods Programs Biomed. 2010;99(3):306-14. doi: 10.1016/j.cmpb.2010.01.007. PMID 20176408.

19. Herrera GL. Determinación de la bioequivalencia de dos formulaciones orales de metronidazol en voluntarios sanos; 2006. Available from: https://tesis.ipn.mx/bitstream/handle/123456789/3393/determinacionbioequiv.pdf?sequence=1&isAllowed=y. [Last accessed on 12 May 2023]

20. Center for Drug Evaluation and Research (CDER). Food and Drug Administration Guidance for Industry: extended release oral dosage forms: development, evaluation, and application of *in vitro/in vivo* correlations; 1997. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/extended-release-oral-dosage-forms-development-evaluation-and-application-vitroin-*in vivo*-correlations. [Last accessed on 12 May 2023].

21. Bendas ER. Two different approaches for the prediction of *in vivo* plasmaconcentration–time profile from *in vitro* release data of once-daily formulations of diltiazem hydrochloride. Arch Pharm Res. 2009;32(9):1317-29. doi: 10.1007/s12272-009-1918-2, PMID 19784589.

22. El-Masry SM, Helmy SA. Hydrogel-based matrices for controlled drug delivery of etamsylate: prediction of *in vivo* plasma profiles. Saudi Pharm J. 2020;28(12):1704-18. doi: 10.1016/j.jsps.2020.10.016, PMID 33424262.

23. Freeman CD, Klutman NE, Lamp KC. Metronidazole a therapeutic review and update. Drugs. 1997;54(5):679-708. doi: 10.2165/00003495-199754050-00003, PMID 9360057.

24. McGilveray IJ, Mousseau N, Brien R. Bioavailability of 23-canadian formulations of phenylbutazone. Can J Pharm Sci. 1978;13:33-9.

25. Boix Montanes A, Barrera Puigdollers MT. Sustitucion y seleccion de equivalentes terapeuticos. Farm Hosp. 1996;20(6):351-8.

26. McGilveray IJ, Midha KK, Loo JC, Cooper JK. The bioavailability of commercial metronidazole formulations. Int J Clin Pharmacol Biopharm. 1978;16(3):110-5. PMID 649227.

27. Itiola OA, Pilpel N. Studies on metronidazole tablet formulations. J Pharm Pharmacol. 1986;38(2):81-6. doi: 10.1111/j.2042-7158.1986.tb04516.x. PMID 2870167.

28. Idkaidek NM, Najib NM. Enhancement of oral absorption of metronidazole suspension in humans. Eur J Pharm Biopharm. 2000;50(2):213-6. doi: 10.1016/s0939-6411(00)00098-9, PMID 10962229.

29. Dey S, Samantha A, Roy K, Ghosh S, Ghosh A, De PK. Formulation and *in vitro* evaluation of oil entrapped buoyant beads for stomach-specific delivery of metronidazole. Int J Pharm Pharm Sci. 2014;6(9):407-10.

30. Chakravorty A, Chakravorty M, Sa B. Factors influencing delayed release followed by rapid pulse release of drugs from compression coated tablets for colon targeting. Int J Pharm Pharm Sci. 2016;8(8):330-6.