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Study of *in vitro* Therapeutic Equivalence of the 5 mg Glibenclamide Multi-source Tablets Respecting the Reference Medicine Product

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in vitro *in vivo*

in vitro

tested pHs. Dissolution efýciency was 68.66% (pH 1.2), 56.59% (pH 4.5) and 95.98% (pH 6.8). The mean of *in vitro* dissolution time was 28.56 min (pH 1.2), 39.97 min (pH 4.5) and 4.54 min (pH 6.8).

According to the similarity factor (f2) and the efýciency of dissolution, it is concluded that the multisource

readings were made in duplicate at a wavelength of 300 nm, using the dissolution media as a target [26].

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As a statistical indicator of the "*in vitro* therapeutic equivalence" of the multi-source medicine with the referent, the similarity factor (f2) was used and calculated with the following equation: 5.19

$$f_2 = 50xLog\{[1+(1/n)\sum_{t=1} n(R_t - T_t)^2]^{-0.5} x100\}$$

e e ciency of the solution (EF%) was calculated from the values obtained in the area under the curve (AUCot) of the dissolution pro les applying the trapezoids method and calculated with the following equation:

$$EF\% = \frac{AUC_0^t}{Q_\infty T} \cdot 100$$

To characterize the dissolution pro le of the drug, the mean dissolution time (MDT) was used and calculated with the following equation:

$$MDT = \frac{\sum_i ti \triangle Q(ti)}{Q_\infty}$$

Figure 1 shows the average values of the dissolution pro le of the generic glibenclamide compared to that referring to three pH. It can be seen that both drugs, at pH 1.2 and pH 4.5 do not dissolve at least 85% in 15 minutes, according to the Food and Drug Administration (FDA), or in 30 minutes, according to the Pharmacopoeia of the States United (USP); but at pH 6.8, both drugs meet this criterion. So that the similarity factor analysis (f2) is not applied, they must be dissolved in the three means of dissolution, according to the FDA; and according to the criteria of the USP, to consider them as fast-dissolving drugs and apply the bio exception, at least 85% of the drug must be dissolved in 30 minutes using the device 2 and to three dissolution media of di erent pH.25 Our results, con rm that the limiting factor for the absorption of glibenclamide, is its lack of dissolution due to its limited solubility, and that it could be one of the factors of therapeutic failures in clinical practice. Already in 2007, Pereda and Martínez, had demonstrated the de ciency of release of the drug, reporting that the drug referring Daonil dissolves in 50% at 30 minutes, and 32% nationally produced drugs, so that they did not meet the condition established by the FDA for *in vitro* equivalence studies [25]. In another study conducted by El-Sabawi et al., it was reported that the Daonil reference in Jordan and the generic drugs did not release a signi cant percentage of the drug in the rst 30 minutes, in this case the Daonil showed the lowest percentage of release (20%), while the other products varied in a range of 35 to 65%. ese studies were carried out in a medium of phosphate bu er solution at pH 6.8.19 Wei H and Löbenberg R., 2006, showed that the dissolution media have an impact on the solubility of glibenclamide [16]. Azharshekoufeh et al., demonstrated that the dissolution speed of glibenclamide is optimal with a combination of liquid-solid and co-grinding technologies [27,28]. Mor et al., have reported that the GLI: POL2 granule fusion provides a higher dissolution rate (85.11%) compared to other polymers [29]. Applying the ANOVA and the multiple comparison test of Tukey's, results in

			2.39	0.479			0.783	
				0.724		4.97		
		39.30	2.37	0.932				
				1.579				
		59.48		1.968	59.25		1.259	
			3.39	2.199		2.07	1.357	
7	90	98.89	0.71	0.700				

		87.32		1.067	83.27	0.97		
		98.43			95.69		0.966	
				0.809	99.70	0.92	0.918	
			0.70	0.699		0.79	0.809	
		100.37		0.639	100.71			
				0.609		0.98	0.984	
7	90				100.72			

					59.2			96.4	
		68.7				39.9		95.9	

The mean dissolution time (MDT) *in vitro* was calculated in order to characterize the rate of dissolution of the drug. In pharmaceutical forms of immediate release, it indicates the average time required for the dissolution of the drug, being in our study of 4.54 minutes for the multi-source T, and for the reference of 3.34 minutes at a pH of 6.8; while at pH 1.2 both drugs T and R, have a dissolution speed of 28 minutes, and at pH 4.5, their speed is between 56.59 to 59.24 minutes, which correlates with the profile of dissolution. This parameter is very relevant, as mentioned by Mady O., since it is used to establish an *in vitro* and *in vivo* correlation [13], due to the fact that the average gastric residence time (T50%) is 15-20 minutes. under fasting conditions. If the solution is slower than gastric emptying, a dissolution profile with multiple time points in multiple media is recommended, and in any case carry out relative bioavailability studies to demonstrate the bioequivalence and interchange ability of the multi-source drug.

e present study reveals signi cant di erences in the dissolution pro les at two pH, but can be considered similar to the reference drug R according to the similarity factor (f2) and bio pharmaceutically equivalent depending on the e ciency of dissolution (EF%). However, it is recommended to carry out properly controlled relative bioavailability studies to demonstrate if they are bioequivalent and interchangeable.

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