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DETERMINATION AND APPLICATION OF BIORELEVANT DISSOLUTION MEDIA TO MEET THE *IN-VIVO* PERFORMANCE IN VALSARTAN AND CHLORTHALIDONE IN SOLID DOSAGE FORM

Sebnem Sarisan *, Gul Gonul Kayar, Mine Gokalp, Udaya Kumar Dude, Zdravka Knezevic, Nilden Dayan and Cem Onal

Abdi Ibrahim Pharmaceuticals, Abdi Ibrahim Production Facilities, Esenyurt, 34538 Istanbul, Turkey.

Keywords:

Valsartan, Chlorthalidone, Biorelevant Media, Dissolution, *In-vitro in-vivo* correlation

Correspondence to Author:
Sebnem Sarisan

Abdi Ibrahim Pharmaceuticals, Abdi Ibrahim Production Facilities, Research and Development Department, Esenyurt - 34538 Istanbul, Turkey.

E-mail: sebnem.sarisan@abdiibrahim.com.tr

ABSTRACT: Dissolution testing with biorelevant media is used in the pharmaceutical industry as a predictive tool for the estimation of drug formulation's *in-vivo* performance in bioequivalence studies. The objective of this study was to determine the biorelevant dissolution media enabling the prediction of *in-vivo* performance of Valsartan and Chlorthalidone in solid oral dosage form as new fixed drug combination. Dissolution profiles were performed in different pH medias for the evaluation of Valsartan/Chlorthalidone film-coated tablets. The validation studies of the used dissolution method were conducted by performing the parameters specified in the ICH (The International Conference on Harmonization) Q2 (R1) Guideline and the results met the acceptance criteria. Although *in-vitro* dissolution test findings showed the similarity of release profile of test and mono reference drug products, the *in-vivo* results demonstrated that they are not similar. For this reason, biorelevant media was investigated and defined. This media proved to be biorelevant and has the potential to be further used to establish *in-vitro in-vivo* correlation (IVIVC) during the development of Valsartan and Chlorthalidone in solid dosage form.

INTRODUCTION: Valsartan (2S)-3-Methyl-2-[pentanoyl1 [[2′(1H-tetrazol-5-yl) biphenyl-4yl] methyl] amino] butanoic acid is a discriminating antagonist of the angiotensin II type 1 receptor. Valsartan is an angiotensin II receptor blocker used alone or in combination with other agents for curing hypertension and reduction of cardio-vascular mortality after myocardial infarction [1, 2, 3].

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This drug has constituted antihypertensive influences and also is correlated with progression in cardiac function (reduced left ventricular mass), endothelial function (improved basal nitric oxide availability, reduced the formation of reactive oxygen species, reduced C-reactive protein levels) and lipid profiles [4].

Valsartan is the BCS class III drug demonstrating low permeability and high drug solubility [5]. Chlorthalidone 2-chloro-5-[(IRS)-I-hydroxy-3-oxo-2,3-dihydro-lH-isoindol-l-yl]Benzenesulphonamide is considered a thiazide-like diuretic [6]. Diuretics are drugs that increase the production of urine, thereby removing excess water from the body. Indications of Chlorthalidone include high blood pressure,

congestive heart failure and edema treatment (fluid retention). Chlorthalidone is effective in keeping high blood pressure under control. Chlorthalidone is the BCS class IV drug demonstrating low permeability and low drug solubility [7].

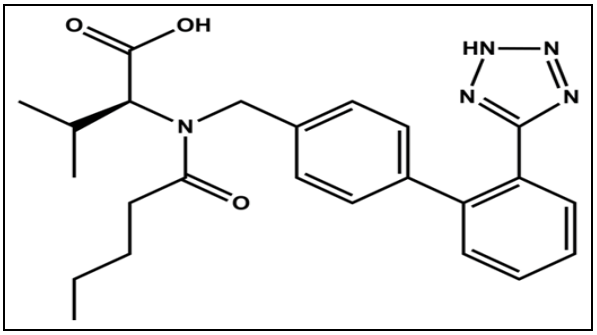

FIG. 1: CHEMICAL STRUCTURES OF VALSARTAN

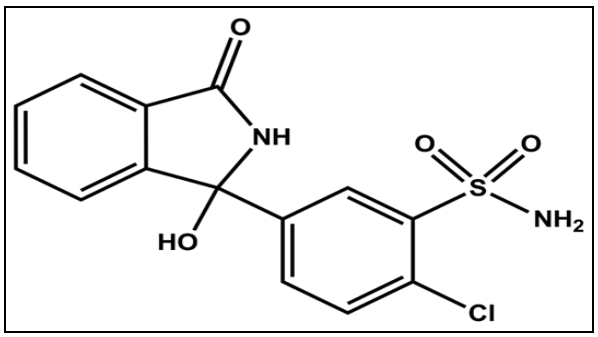

FIG. 2: CHEMICAL STRUCTURES OF CHLORTHALIDONE

For a generic drug product to be approved by regulatory authorities, this drug product needs to demonstrate the same pharmacokinetic profile when applied with and/or without food (fasted and/or fed states Bioequivalence study respectively) and compared to original drug [8]. A bioequivalence study is also mandatory for Valsartan and Chlorthalidone when applied as fix dose combination (FDC solid dosage form). In such study, objective is to compare the proposed new fix dose combination to the concomitant administration of individual mono reference drug products. The comparative *in-vitro* release profile of the new combination with individual mono reference drug products when performed in biorelevant media provides valuable data for prediction of outcome of the *in-vivo* bioequivalence study thus minimizing risk for *in-vivo* failure.

The essential objective in pharmaceutical development of dosage forms is correctly understanding the *in-vitro* and *in-vivo* performance of the dosage forms [9]. Based on the type of data used to establish the relationship between *in-vitro* and *in-vivo*, three main levels are defined by FDA [10]. These main levels are included in **Table 1**.

TABLE 1: VARIOUS PARAMETERS USED IN IVIVC DEPENDING ON THE LEVEL

Level	*In-vitro*	*In-vivo*
A	Dissolution curve	Input(absorption) curves
B	Statistical moments: MDT	Statistical moments: MRT, MAT, *etc.*
C	Disintegration time, time to have 10, 50, 90% dissolved, dissolution rate, dissolution efficiency	C_{max}, T_{max}, K_a, time to have 10, 50, 90% absorbed, AUC (total or cumulative)

Level A correlation reflects a point-to-point relationship between *in-vitro* dissolution and the *in-vivo* input rate and usually linear. In a linear correlation, the *in-vitro* dissolution and *in-vivo* input curves may be directly or indirectly superimposable using a scaling factor [11]. The Level B statistical moments analysis is to the calculation of mean (*in-vivo*) dissolution time (MDT) and means absorption time (MAT) from plasma level of drug versus time data [11, 12]. Level C is a single point comparison of dissolution time point to one pharmacokinetic parameter (*e.g.* C_{max}, area under the curve (AUC) and T_{max} time of the maximum plasma concentration) [13].

The aim of this study was to determine the biorelevant dissolution media enabling the prediction of the *in-vivo* performance of the new FDC product of Valsartan and Chlorthalidone (formulated as solid dosage form) in comparison with mono reference drug products. Initially, dissolution methods were developed for Valsartan and Chlorthalidone solid dosage form as Valsartan dissolution method and Chlorthalidone dissolution method. Then, *in-vitro* dissolution studies were performed with reference and test product (USP pH 6.8 phosphate buffer, pH 4.5 acetate buffer and 0.1 N HCl) [14]. Although, the developed product's multimedia results were suitable *in-vitro* dissolution studies, *in-vivo* results were not acceptable for Valsartan. Therefore, biorelevant dissolution media for Valsartan's research studies was performed.

MATERIALS AND METHODS:

Chemicals: Valsartan and Chlorthalidone film-coated tablets were produced in Abdi Ibrahim Pharmaceuticals, R & D center, in Istanbul,

Turkey. Valsartan has been respectively purchased from Alembic Pharmaceutical Limited, India. Chlorthalidone was obtained from IPCA Pharmaceutical Limited, India. All chemicals and solvents had analytical reagent grade. Acetonitrile was purchased from J. T. Baker Company. Potassium dihydrogen phosphate, sodium hydroxide, sodium acetate, hydrochloric acid, trifluoroacetic acid, acetic acid anhydrous and orthophosphoric acid were purchased from Merck.

Chromatographic Equipment and Conditions: A reversed-phase UPLC system (Waters, USA) consisting of autosampler, pump, oven, and UV/PDA detector. UV/PDA detection was carried out with set to 270 nm. Data were acquired and processed using Empower 2 software. The chromatographic separation was performed on a reversed-phase Waters BEH Phenyl 50 mm × 2.1 mm, 1.7 µm column at 25 °C. The system was operated with gradient programmed using mobile phase A (Water: Acetonitrile: Trifluoroacetic acid 900: 100: 1) and mobile phase B (Water: Acetonitrile: Trifluoroacetic acid 100: 900: 1) at a flow rate 0.2 ml/min. The injection volume was modified to 2 µl.

Standard Preparations: The working standard solution containing 0.36 mg/ml Valsartan was prepared by dissolving in the diluent. The standard solution was filtered through 0.22 µm PVDF filter.

Sample Preparations: The dissolution test was performed using a Varian VK7010 dissolution system with USP Apparatus II (paddle). A volume of 900 ml of dissolution medium was maintained at 37ºC ± 0.5 ºC. 6 tablets were used in each media analysis at 50 rpm paddle speed. From each media, samples collected at 5^{th}, 10^{th}, 15^{th}, 20^{th}, 30^{th}, 45^{th} and 60^{th} min and filtered through 0.22 µm PVDF filter.

RESULTS AND DISCUSSION:

Validation of the Method: A dissolution test method was developed for Valsartan and Chlorthalidone film-coated tablets. The method was validated in accordance with the FDA and ICH guidelines using the parameters of system suitability, specificity, linearity, range, accuracy, precision, and robustness. Validation of the method was completed with successfully. All the results met the limit requirements. The method could be able to detect differences in Valsartan from varied tablet formulations.

Dissolution Test in Different pH Media: The dissolution test for the Valsartan and Chlorthalidone formulated tablets was performed in pH 6.8 phosphate buffer, pH 4.5 acetate buffer and 0.1 N HCl. The *f2* (Similarity Factor) was calculated statistically by using SUPAC formula [15].

$$f_2 = 50 \cdot \log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n} w_t (R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

The *f2* value greater than 50 meant adequate similarity between compared products.

The United States Pharmacopeia (USP), the FDA dissolution methods database suggests pH 6.8 phosphate buffer as the dissolution media of Valsartan [16, 17]. Therefore the dissolution test for the FDC of Valsartan and Chlorthalidone tablets was performed in pH 6.8 phosphate buffer with 50 rpm. The results are shown in **Table 2** and **Fig. 3**.

TABLE 2: pH 6.8 PHOSPHATE BUFFER MEDIUM (50 RPM) DISSOLUTION PROFILE FOR VALSARTAN

% Dissolution Valsartan (50 rpm) pH 6.8 Phosphate Buffer Medium		
Time	**Reference Product**	**Test Product**
0	0	0
5	83.2	73.8
10	92.8	89.2
15	94.6	94.7
20	94.8	96.6
	f_2	*

* According to EMA guideline, calculation of f_2 value is not required and the dissolution profiles are considered similar in case of dissolutions for the products are higher than 85 % in 15 min (CPMP/EWP/QWP/1401/98Rev.01/Corr).

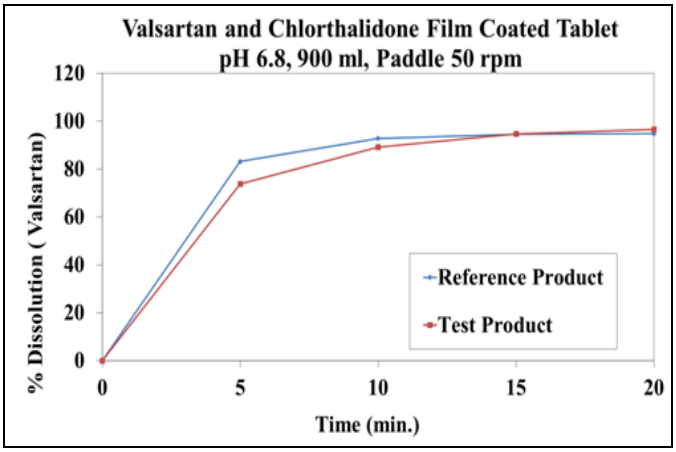

FIG. 3: pH 6.8 PHOSPHATE BUFFER MEDIUM (50 RPM) DISSOLUTION PROFILE FOR VALSARTAN

The dissolution test for the FDC of Valsartan and Chlorthalidone tablets was performed in 0.1N HCl with 50 rpm. The results are shown in **Table 3** and **Fig. 4**.

TABLE 3: 0.1N HCl MEDIUM (50 RPM) DISSOLUTION PROFILE FOR VALSARTAN

% Dissolution Valsartan (50 rpm) 0.1 N HCl Medium		
Time	**Reference Product**	**Test Product**
0	0	0
5	2.1	4.7
10	2.5	7.8
15	3.3	10.2
20	4.7	12.0
30	7.2	13.8
45	9.9	15.0
60	11.6	16.0
	f_2	60.7

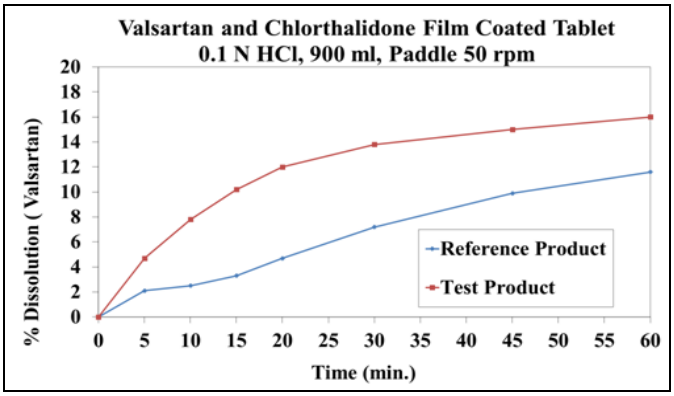

FIG. 4: 0.1N HCl MEDIUM (50 RPM) DISSOLUTION PROFILE FOR VALSARTAN

The dissolution test for the FDC of Valsartan and Chlorthalidone tablets was performed in pH 4.5 acetate buffer with 50 rpm. The results are shown in **Table 4** and **Fig. 5**.

A summary of f_2 value for Valsartan reference and Valsartan released from FDC Product in 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer are shown in **Table 5**.

TABLE 4: pH 4.5 ACETATE BUFFER MEDIUM (50 RPM) DISSOLUTION PROFILE FOR VALSARTAN

% Dissolution Valsartan (50 rpm) pH 6.8 Phosphate Buffer Medium		
Time	**Reference Product**	**Test Product**
0	0	0
5	28.7	35.5
10	43.9	51.6
15	55.1	60.7
20	62.7	67.1
30	73.8	75.0
45	83.4	82.2
60	88.2	86.5
	f_2	67.3

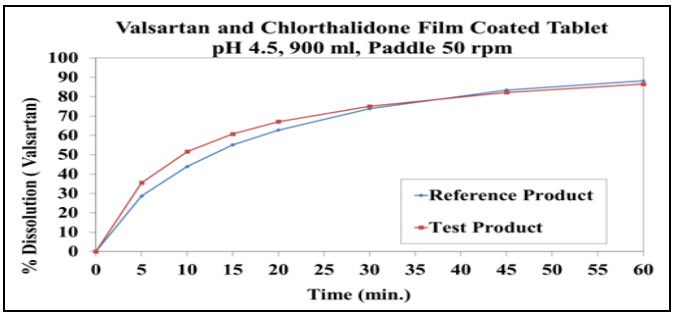

FIG. 5: pH 4.5 ACETATE BUFFER MEDIUM (50 RPM) DISSOLUTION PROFILE FOR VALSARTAN

TABLE 5: SUMMARY OF *f2* VALSARTAN IN DIFFERENT DISSOLUTION MEDIA

	Valsartan (50 rpm)		
	0.1 N HCl	**pH 4.5 acetate buffer**	**pH 6.8 phosphate buffer**
f_2	60.7	67.3	*

* According to EMA guideline, calculation of f2 value is not required and the dissolution profiles are considered similar in case of dissolutions for the products are higher than 85 % in 15 min (CPMP/EWP/QWP/1401/98Rev.01/Corr).

Although the similarity of two products *in-vitro* was proven, *in-vivo* bioequivalence study results demonstrate dissimilarity. The bioequivalence study results for Valsartan reference and Valsartan from FDC Product are shown in **Table 6** and **Fig. 6**.

TABLE 6: 1st BEQ STUDY RESULTS FOR VALSARTAN

Parameter	**T/R Ratio**	**90% Confidence Intervals**	
		Lower limit	**Upper limit**
C_{max}	115.40	99.26	134.15
AUC(0-t)	106.20	93.46	120.67

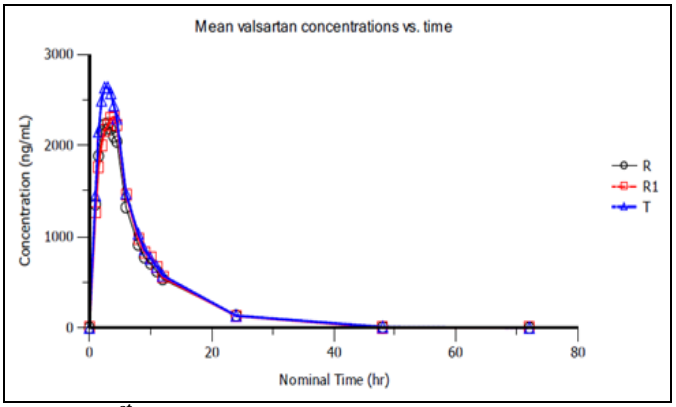

FIG. 6: 1st BEQ STUDY RESULTS FOR VALSARTAN

Biorelevant Dissolution Media Development: Clearly dissolution methodology needed more research to correlate it with obtained *in-vivo* data. Different pH Buffer solution and paddle speed were tested for determining the biorelevant media

that would enable the prediction of the *in-vivo* performance of Valsartan. First, we observed the change in the paddle speed. The dissolution test for the FDC of Valsartan and Chlorthalidone tablets was performed in pH 4.5 acetate buffer with 35 rpm. The f_2 values for Valsartan were calculated. The results for Valsartan revealed f_2 values of 70.3, respectively **Fig. 7** and **Table 7**.

TABLE 7: pH 4.5 ACETATE BUFFER MEDIUM (35 RPM) DISSOLUTION PROFILE FOR VALSARTAN

% Dissolution Valsartan (35 rpm) pH 4.5 Acetate Buffer Medium		
Time	**Reference Product**	**Test Product**
0	0	0
5	18.6	19.7
10	28.2	28.8
15	35.1	34.5
20	40.6	38.6
30	47.5	44.1
45	54.3	48.8
60	57.9	51.5
	f_2	70.3

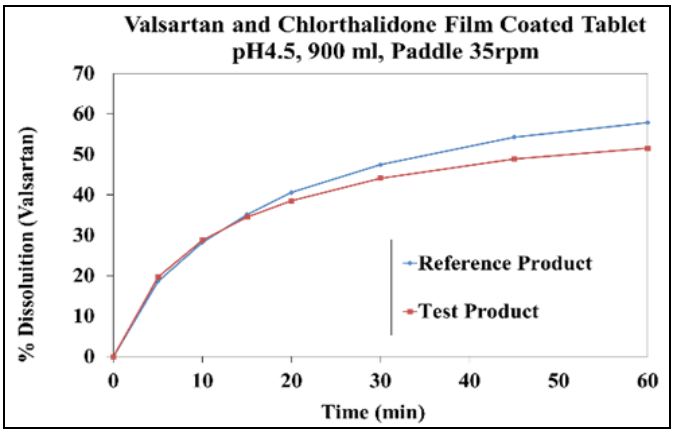

FIG. 7: pH 4.5 ACETATE BUFFER MEDIUM (35 RPM) DISSOLUTION PROFILE FOR VALSARTAN

The dissolution results in these conditions demonstrated that the test product is similar to the reference product. However, according to the *in-vivo* results, the test product was proven not to be similar. The change in paddle speed did not reflect *in-vivo* results.

Second, the pH change was attempted since the change in the paddle speed was not effective. The dissolution test for the Valsartan and Chlorthalidone tablets was performed in 4.0 acetate buffer with 50 rpm [14]. The f_2 values for Valsartan were calculated. The results for Valsartan revealed f_2 values of 76.7, respectively **Fig. 8** and **Table 8**.

TABLE 8: pH 4.0 ACETATE BUFFER MEDIUM (50 RPM) DISSOLUTION PROFILE FOR VALSARTAN

% Dissolution Valsartan (50 rpm) pH 4.0 Acetate Buffer medium		
Time	**Reference Product**	**Test Product**
0	0	0
5	12.9	15.8
10	22.3	26.0
15	29.3	32.9
20	34.8	37.5
30	42.3	44.9
45	50.0	52.0
60	56.0	57.1
	f_2	76.7

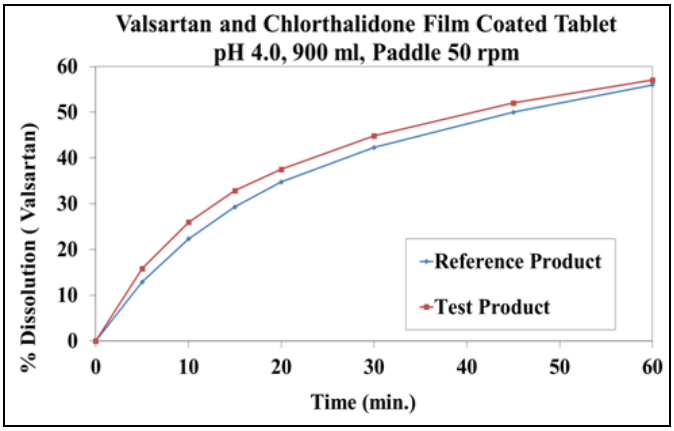

FIG. 8: pH 4.0 ACETATE BUFFER MEDIUM (50 RPM) DISSOLUTION PROFILE FOR VALSARTAN

The dissolution conditions of 900 ml of pH 4.0 phosphate buffer at 37 ± 0.5 °C and a paddle speed of 50 rpm showed similar f_2 values, and these values were not in correlation with in vivo results.

Valsartan's structure comprises two acidic functions, with the pKa values being 3.9 and 4.7 and one asymmetric center [18]. The solubility in water at room temperature of Valsartan is 0.18 g/l. The formation of the di-anion salt in a buffered solution increases the solubility of Valsartan [19]. Based on this information, the next experiment was performed with pH 3.8 citrate buffer, just below pKa value.

The pH 3.8 citrate buffer medium was prepared by a mixed 0.1 M citric acid solution and 0.1 M sodium citrate solution (63.5%: 36.5% v/v) [14]. The dissolution test for the Valsartan and Chlorthalidone tablets was performed in pH 3.8 citrate buffer with 50 rpm. The f_2 values for Valsartan were calculated. The results for Valsartan revealed f_2 values of 48.7, respectively **Fig. 9** and **Table 9** and most importantly results *in-vitro* were reflecting *in-vivo* results.

Valsartan component from FDC Tablets had faster dissolution in pH 3.8 around 10-15% (point by point), and same had T/R ratio for C_{max} at a level of 115% (see **Table 6**).

TABLE 9: pH 3.8 CITRATE BUFFER MEDIUM (50 RPM) DISSOLUTION PROFILE FOR VALSARTAN

% Dissolution Valsartan (50 rpm) pH 3.8 Citrate Buffer medium		
Time	**Reference Product**	**Test Product**
0	0	0
5	1.8	8.3
10	5.4	15.2
15	9.4	20.7
20	12.9	24.0
30	18.7	29.8
45	25.2	35.7
60	30.8	40.2
	f_2	48.7

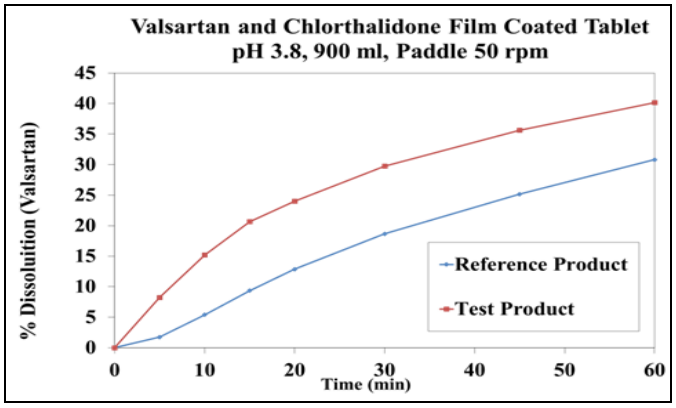

FIG. 9: pH 3.8 CITRATE BUFFER MEDIUM (50 RPM) DISSOLUTION PROFILE FOR VALSARTAN

Reference and Test products are not similar according to *in-vivo* results. f_2 is less than 50 for Valsartan in pH 3.8 citrate buffer medium since Test Product is having slower dissolution profile. Such result reflects results obtained *in-vivo* where C_{max} parameter was higher for test products.

As shown in **Table 6**, the ratio of C_{max} value to the reference product of the test product is about 115.4%. According to this information, pH 3.8 citrate buffer dissolution results submit the dissimilarity between test and reference product in line with *in- vivo* measured data. pH 3.8 Citrate buffer medium was proven to be biorelevant dissolution media for Valsartan by evaluating f_2 values and in comparison to *in-vivo* data.

Dissolution Profile for New Formulation: New FDC tablet formula was further developed using pH 3.8 citrate buffer medium dissolution results as a lead tool for reformulation process. The relevant *in-vitro* dissolution f_2 values for the new tablet formula are included in **Table 10**.

TABLE 10: SUMMARY OF f_2 VALSARTAN IN DIFFERENT DISSOLUTION MEDIA

	Valsartan			
	0.1 N HCl	**pH 3.8 citrate buffer**	**pH 4.5 acetate buffer**	**pH 6.8 phosphate buffer**
f_2	77.1	78.5	47.0	*

* According to EMA guideline, calculation of f_2 value is not required and the dissolution profiles are considered similar in case of dissolutions for the products are higher than 85 % in 15 min (CPMP/EWP/QWP/1401/98Rev.01/Corr).

TABLE 11: pH 3.8 CITRATE BUFFER MEDIUM (50 RPM) DISSOLUTION PROFILE FOR NEW TABLET FORMULA WAS DEVELOPED WITH USING pH 3.8 CITRATE BUFFER MEDIUM

% Dissolution Valsartan (50 rpm) from FDC Tablet pH 3.8 Citrate Buffer medium		
Time	**Reference Tablet**	**New Formula Tablet**
0	0	0
5	1.8	3.0
10	5.4	8.6
15	9.4	12.5
20	12.9	15.3
30	18.7	21.3
45	25.2	27.3
60	30.8	31.6
	f_2	78.5

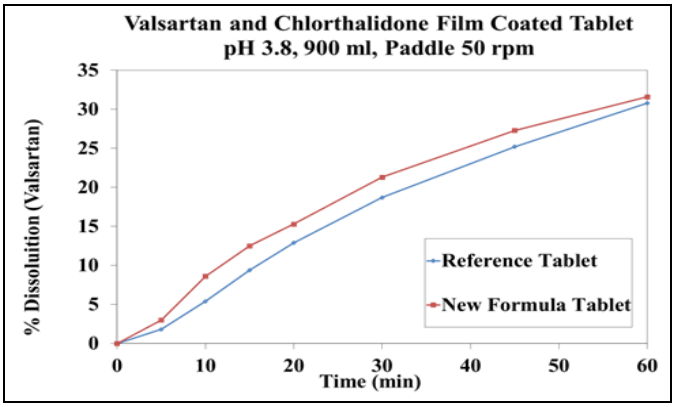

FIG. 10: DISSOLUTION PROFILES OF VALSARTAN IN pH 3.8 CITRATE BUFFER MEDIA FOR NEW TABLET FORMULA WAS DEVELOPED WITH USING pH 3.8 CITRATE BUFFER MEDIUM

TABLE 12: 2ND BEQ STUDY RESULTS FOR VALSARTAN

Parameter	T/R Ratio	90% Confidence Intervals	
		Lower limit	**Upper limit**
C_{max}	100.39	93.35	107.96
AUC(0-t)	101.21	95.09	107.73

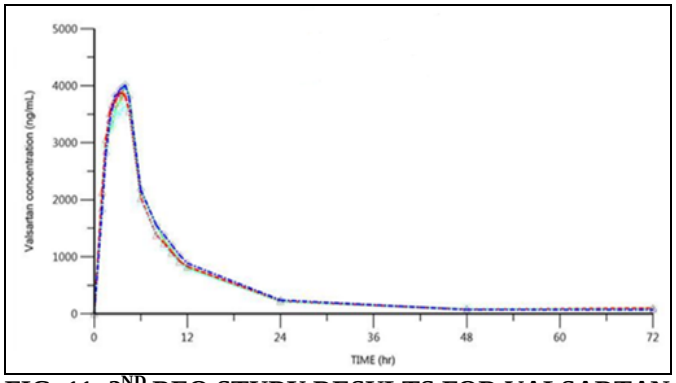

FIG. 11: 2ND BEQ STUDY RESULTS FOR VALSARTAN

The similarity of two products *in-vitro* was proven with f_2 values and *in-vivo* bioequivalence study was conducted accordingly. The second bioequivalence study results for Valsartan reference and FDC (test) products are shown in **Table 12** and **Fig. 11**.

Results clearly demonstrate that study was successful: T/R ratio for C_{max} and AUC is practically at a 100% level. Accordingly, similarity of profiles at pH 3.8 for Valsartan proved to be biorelevant and secured similar pK profile of compared products [20].

CONCLUSION: The development of biorelevant dissolution medium mainly used as *in-vitro* substitute for *in-vivo* performance. The compendial dissolution medium is unable to simulate the dissolution of *in-vivo* consequently; the development of biorelevant dissolution medium is necessary. The effect of changing paddle speed, pH of buffer and buffer type were observed for the determination of biorelevant media for Valsartan in Valsartan and Chlorthalidone solid dosage form.

The paddle speed (35 rpm) and the pH of the buffer (pH 4.0 acetate buffer) conversions did not provide any difference in$f_2$value but failed in the BEQ study. When the buffer type and pH value were changed together (pH 3.8 citrate buffer), f_2 value was observed the difference in line with *in-vivo* data. The new FDC Product for Valsartan and Chlorthalidone (solid dosage form) was developed with using pH 3.8 citrate buffer medium dissolution results as the guiding tool able to predict *in-vivo* performance of Valsartan from FDC product.

Developed method with pH 3.8 citrate buffer media could be also used for performing *in-vitro in-vivo* correlation (IVIVC) during the development of new fix dose combination of Valsartan and Chlorthalidone solid dosage form. The same is intention of our next study.

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CONFLICT OF INTEREST: Authors declare no conflict of interest.

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