Research Article

Development and Validation of IVIVR Models for Managing Formulation Changes in Immediate-Release Drug Products: A Case Study on LOSARTAN Potassium 100 mg Tablets

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ABSTRACT

The aim of the present study was to develop a tool to ensure that formulation changes do not compromise the quality or efficacy of a drug product. The study focused on the bioequivalent generic product LOSARTAN Potassium 100 mg immediate-release (IR) tablets. Prior to implementing changes to the marketed product, a validated mathematical modeling approach was employed to establish the relationship between in vivo and in vitro parameters. Specifically, the models were developed to link C_{max} to % dissolution and AUC_{0-t} to % dissolution. The robustness of the developed IVIVR models was confirmed through successful validation and sensitivity testing. Sensitivity was assessed using five in-house IR formulations, with variations in the amount (0.5–8% w/w) of Sodium Starch Glycolate (SSG), a super-disintegrant, as well as Microcrystalline Cellulose and Maize Starch in the formulation of the marketed product. The results demonstrated that the IVIVR approach effectively detected formulation changes and provided reliable predictions of their impact. Consequently, this approach represents a highly relevant tool for controlling formulation modifications in marketed products for which bioequivalence studies have been conducted.

Keywords: Losartan potassium; in vitro in vivo relationship (IVIVR); dissolution; predictability.

INTRODUCTION

Losartan potassium is an orally active, non-peptide angiotensin II (**AII**) receptor antagonist. It is the first of a new class of drugs to be introduced for clinical use in treating hypertension. Losartan potassium is readily absorbed from the gastrointestinal tract after oral administration. It is a Biopharmaceutics Classification System (BCS Class – III) drug with a high aqueous solubility and low permeability [1]. At pH 6.8, losartan exists predominantly in its ionized form (pKa ≈ 4.7 (4.5–5)), ensuring maximum solubility crucial for dissolution testing [2]. Phosphate buffer at this pH, widely accepted by regulatory agencies (FDA, EMA), serves as a standard medium for drugs targeting intestinal absorption. This physiologically relevant medium enables standardized comparisons of dissolution profiles across losartan potassium formulations, supporting both development and regulatory submissions.

In regulatory terms, a change in product is considered a variation to the terms of the marketing authorization and must be authorized and approved by the regulatory health authorities. Regulatory authorities such as the EMA and FDA require criteria to be verified to prove that the product's quality and efficacy have not been affected by the change [3,4]. For major changes these criteria generally include validating the manufacturing process and conducting stability studies [5]. These parameters are qualitative, providing information on the preservation of product quality rather than on the preservation of efficacy. To solve this problem, it is logical to consider repeating the bioequivalence studies to ensure the product remains bioequivalent after the change. However, cost and time constraints prevent bioequivalence studies from being repeated after every change. Therefore, this study aims to develop a novel tool that, based on previously conducted bioequivalence studies, can provide assurance of the quality and efficacy of a marketed product after modifications. Specifically, the objective is to establish a validated, linear in vitro–in vivo relationship (IVIVR) that links the in vitro parameter, % dissolution, to the pharmacokinetic (PK) parameters from bioequivalence studies, namely C_{max} and AUC_{0-t} [6,7]. To validate the robustness of the proposed approach, the model's established relationship between PK parameters (*Cmax*, *AUC_(0–t)*) and % dissolution was applied to five in-house immediate-release (IR) formulations (F1, F2, F3, F4, F5) with varying levels of three critical excipients: a super-disintegrant, a diluent, and a binder [8,9].

MATERIALS AND METHODS

Tablet formulations

LOSARTAN Potassium 100 mg Tablets under study was obtained by direct compression of a mixture of Losartan potassium (33.33%), Maize Starch, microcrystalline cellulose, Talc, Colloidal Anhydrous Silica, Sodium Starch Glycolate and Magnesium Stearate. The composition of the five in-house formulations is described in Table 1.

Dissolution testing

Dissolution testing was performed for 100 mg LOSARTAN potassium 100 mg Tablets potassium formulations with automated dissolution tester (SOTAX AT7 smart) employing the USP paddle method with 900 mL (± 1 %) of buffer phosphate (pH 6.8) at a temperature of 37 ± 0.5ºC. Each

tablet was immersed into the medium, and the apparatus operated at 75 rpm. After 10, 15, 20, 30, 45 min, 5 mL of solution was withdrawn, filtered and diluted in 50 mL of phosphate buffer (pH 6.8). The solutions were analyzed using a UV/VIS spectrophotometer (PerkinElmer Lambda 25) at λ: 247 nm. Under these experimental conditions, the dissolution profiles of 12 tablets from both the test and reference products were assessed and compared using the similarity factor (f_2). [10]

Table 1: Composition of in-house formulations of LOSARTAN potassium 100 mg subject of change.

Ingredients	F1 %	F2 %	F3 %	F4 %	F5 %
Losartan potassium	33.33	33.33	33.33	33.33	33.33
Maize Starch	6.66	6.66	6.66	15	6.66
Microcrystalline cellulose	55.25	53.08	47.75	44.75	55.75
Talc	*	*	*	*	*
Colloidal anhydrous silica	*	*	*	*	*
Sodium starch glycollate	0.5	2.66	8	2.66	0
Magnesium stearate	*	*	*	*	*

(*) confidential amounts

Bioequivalence study

This study aimed to compare the bioequivalence of two formulations: the test drug, LOSARTAN potassium 100 mg Tablets (Batch number 12619001, manufactured by the IBERMA laboratory), and the reference drug, COZAAR® 100 mg (Batch number S006754, produced by MSD laboratory). The study was conducted as a randomized, crossover design with two administrations per drug. It involved 28 healthy male and female volunteers, each completing four administration periods[10]. Blood samples (4 mL) were collected at the following times: 0 (h), 0.25h, 0.5h, 0.66h, 0.83h, 1h, 1.16h, 1.33h, 1.5h, 1.75h, 2h, 2.5h, 3h, 3.5h, 4h, 5h, 6h, 8h, 12h and 24h and centrifuged. PK parameters (C_{max}, T_{max}, AUC_{0-t} , AUC(0-∞)…) were then calculated.

IN VITRO release model

Analysis of the in vitro dissolution profiles of LOSARTAN Potassium 100 mg described a release following a first-order reaction and Weibull model [11].The time profile of in vitro release is represented by the following equation (Eq. 1) :

$$Q_{diss} = \mathbf{Dose} \times (\mathbf{1} - \mathbf{e}^{-\mathbf{kd} \times \mathbf{t}}) \quad \text{(Eq.1)}$$

Where:

Q_{diss} is amount dissolved

kd is dissolution rate constant

Dose is the initial amount of losartan potassium in tablet at t_0, before dissolving reaction

IN VITRO Data analysis

The aim was to develop a mathematical model representing "%Dissolution" of Test product (LOSARTAN Potassium 100 mg Tablets) as a function of time capable of matching the first-order reaction (Eq. 1) with an acceptable confidence interval (95%).

The data (Table 2) shows the regression representing the variation of dissolution data as a function of time (Figure 1).

Table 2: Dissolution Profile of LOSARTAN Potassium 100 mg Tablets (Batch 12619001, Manufactured and Tested by IBERMA Laboratory)

Time_Diss (h)	% Dis_pH 6.8*
0	0
0.17	68.69
0.25	92.36
0.33	95.63
0.50	97.29
0.75	97.63

% Dis_pH6.8* is the average of the dissolution results from 12 dosage units,

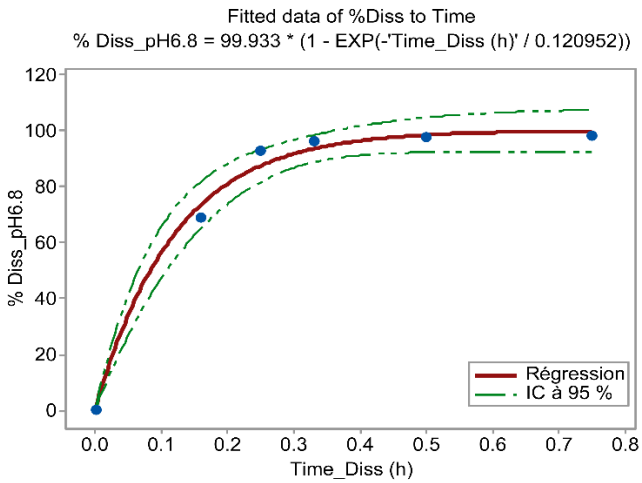

Figure 1: Fitted Data of %Diss to time of LOSARTAN Potassium 100 mg Tablets (Batch 12619001, Manufactured and Tested by IBERMA Laboratory)

IN VITRO Data model

According to the previous results, the regression equation representing IN VITRO model for LOSARTAN Potassium 100 mg Tablets is (Eq. 2):

$$\%\mathbf{Diss} = 99.93 \times (1 - e^{-t/0.121}) \quad \text{(Eq.2)}$$

***In Vivo* release model**

The PK parameters, C_{max} and AUC_{0-t}, were estimated from the plasma concentration time data.

C_{max} Data analysis

To obtain a relationship between C_{max} and %Dissolution, we used T_{max},the time parameter representing C_{max}. Using T_{max}, (Eq. 2) was applied to calculate %Dissolution and subsequently establish the relationship between C_{max} and %Dissolution. Data from the bioequivalence study carried out on LOSARTAN Potassium 100 mg (Table 3) were used to establish the relationship between C_{max} and %Dissolution. Using the grouping method (Figure 2), each group of values with the same % dissolution value is represented by the mean C_{max} of the group (Table 3). The grouping obtained (Table 4) provides the relationship between C_{max} and % Dissolution (Figure 3), the relationship which is a linear regression with r^2 = 94.1% and regression equation (Eq. 3):

$$C_{max} = 2914 - 24.10 \times \%\mathbf{Diss}$$

Table 3: % Dissolution results corresponding to C_{max} of LOSARTAN Potassium 100 mg Tablets (Batch 12619001, Manufactured by IBERMA Laboratory)

Volunteer	Administration 1**			Administration 2		
	Tmax h	Cmax ng/mL	%Diss_pH6.8	Tmax h	Cmax ng/mL	%Diss_pH6.8
V1	0.4	1021.64	96.27	0.15	1194	71.02
V2	1.3	213.16	99.93	0.3	373.5	91.57
V3	0.4	671.13	96.27	0.4	421.59	96.27
V4	0.4	587.62	96.27	0.5	519.45	98.33
V5	5	424.34	99.93	8	113.47	99.93
V6	0.4	596.92	96.27	0.3	513.97	91.57
V7	1	459.45	99.91	0.5	389.32	98.33
V8	0.4	564.98	96.27	0.4	667.61	96.27
V9	1.45	463.13	99.93	0.3	815.11	91.57
V10	1	1025.63	99.91	0.5	664.64	98.33
V11	2	205.98	99.93	0.5	221.67	98.33
V12	0.3	1187.84	91.57	1.1	643.34	99.92
V13	0.3	467.65	91.57	0.3	874.12	91.57
V14	0.3	1197.64	91.57	1	930.17	99.91
V15	0.3	528.69	91.57	1.45	368.54	99.93
V16	0.4	520.24	96.27	0.4	1160.89	96.27
V17	0.3	532.85	91.57	0.4	216.52	96.27
V18	1.2	261.36	99.93	0.4	404.34	96.27
V19	0.5	473.42	98.33	0.3	563.28	91.57
V20	1.3	806.13	99.93	0.4	728.77	96.27
V21	1.3	418.71	99.93	1.45	135.47	99.93
V22	0.4	920.2	96.27	0.4	1435.14	96.27
V23	5	212.28	99.93	2.3	266.6	99.93
V24	1.3	424.48	99.93	1	509.62	99.91
V25	0.3	785.59	91.57	3	177.46	99.93
V27	0.3	888.58	91.57	0.3	997.97	91.57
V28	0.4	391.11	96.27	0.3	739.87	91.57

*V26: Eliminated from the study because he vomited during administration

** Administration (1 and 2) refers to the controlled process of delivering the drug to volunteers, where each participant received the test product, LOSARTAN Potassium 100 mg tablets (Batch 12619001), on two separate occasions.

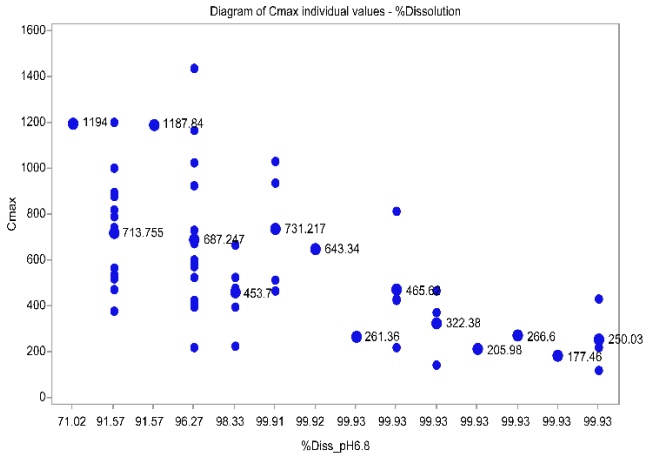

Figure 2: Diagram C_{max} - % Dissolution of LOSARTAN Potassium 100 mg Tablets (Batch 12619001).

Table 4: Grouping C_{max} - % Dissolution of LOSARTAN Potassium 100 mg Tablets (Batch 12619001)

*Cmax (ng/mL)	%Diss_pH 6.8
1194	71.02
713.755	91.57
687.247	96.27
453.7	98.33

*Cmax (ng/mL) : Mean C_{max} of each group

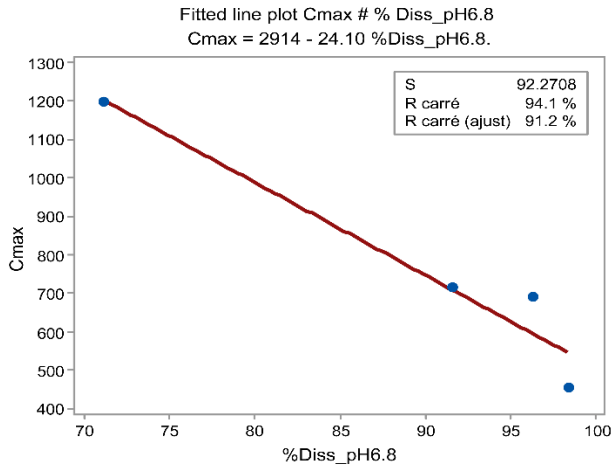

Figure 3: Relationship of C_{max} determined by IN VIVO analysis and % Dissolution IN VITRO analysis of LOSARTAN Potassium 100 mg Tablets (Batch 12619001).

IVIVR C_{max} - %Dissolution Model

For any change made to the original formulation of LOSARTAN Potassium 100 mg, we could predict, using developed the IVIVR C_{max}- %Dissolution Model, the C_{max} of the formulation changed. C_{max} (predicted) was compared with C_{max} of the original formulation to evaluate the percentage error of predictability (%PE). The %PE, which had to be less than 15% [11], enabled us to assess the impact of this change on the original formulation of the marketed product which has been approved by the bioequivalence studies.

AUC_{0-t} Data analysis

The mathematical model representing the AUC_{0-t} of the test product (LOSARTAN Potassium 100 mg Tablets) as a function of time, based on PK data (Table 5), is represented by (Eq. 4):

$$\mathbf{AUC_{0-t}} = \mathbf{851.38} \times (\mathbf{1} - \mathbf{e^{-t/2.0865}}) \quad (4)$$

Table 5: PK Data of AUC_{0-t} of LOSARTAN Potassium 100 mg Tablets (Batch 12619001, Manufactured by IBERMA Laboratory)

Time (h)	AUC_{0-t} (ng.h/mL)
0	0
0.25	63.683
0.5	132.169
0.66	204.437
0.83	267.649
1	318.391
1.16	364.485
1.33	404.496
1.5	454.264
1.75	495.539
2	560.566
2.5	610.285
3	648.105
3.5	676.475
4	726.305
5	764.837
6	803.712
8	832.815
12	846.604
24	846.604

The AUC_{0-t} as a function of time curve is fitted with an acceptable confidence interval (95%) (Figure 4).

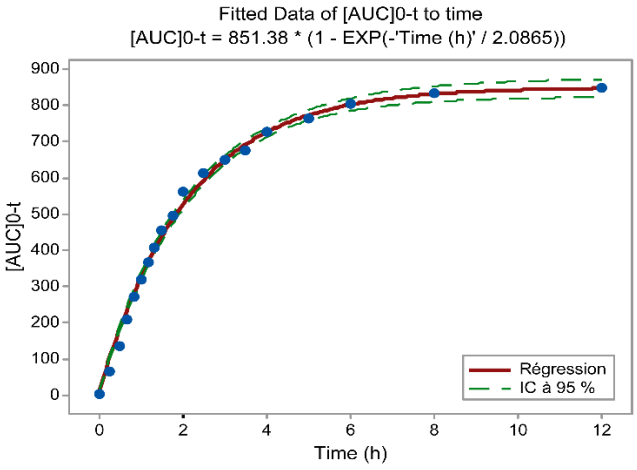

Figure 4: Fitted Data of AUC_{0-t} to time of LOSARTAN Potassium 100 mg Tablets (Batch 12619001)

The challenge was to find a linear relationship between AUC_{0-t} and time taking into account the % Dissolution parameter. The idea was to exploit the basic formula for AUC_{0-t} [11] :

$$\mathbf{AUC_{0-t} = \frac{1}{2}\sum_{i=1}^{n}(C_{i-1} + C_i)(t_i - t_{i-1})}$$

We can see that AUC_{0-t} is a function of concentration $(C_{i-1} + C_i)$, which can be replaced by dissolved dose (%Dissolution *100 mg) and multiplied by a time factor, with 100mg of active pharmaceutical ingredient (API) in a tablet. The relationship found is a linear regression (Figure 5) with perfect r^2 = 99.5% and regression equation (Eq. 6):

$$\ln\left(\frac{1}{\left(1-\frac{AUC_{0-t}}{851.38}\right)}\right) = 0.05604 + 0.000045 \times \%Diss \times 100mg \times Time$$

The data results of this relationship are presented in (Table 6).

Table 6: Data from the (Eq. 6) application of LOSARTAN Potassium 100 mg Tablets (Batch 12619001)

Time (h)	AUC_{0-t} ng.h/mL	LN(1/(1-(AUC_{0-t}/851.38)))	*%Diss_pH6.8	%Diss×100mg×Time
0	0	0	0	0.00
0.25	63.683	0.078	87.28	2182.10
0.5	132.169	0.169	98.33	4916.60
0.66	204.437	0.275	99.51	6567.43
0.83	267.649	0.377	99.83	8285.76
1	318.391	0.468	99.91	9990.74
1.16	364.485	0.559	99.93	11591.44
1.33	404.496	0.645	99.93	13290.87
1.5	454.264	0.763	99.93	14989.89
1.75	495.539	0.872	99.93	17488.27
2	560.566	1.074	99.93	19986.60
2.5	610.285	1.262	99.93	24983.25
3	648.105	1.432	99.93	29979.90
3.5	676.475	1.583	99.93	34976.55
4	726.305	1.918	99.93	39973.20
5	764.837	2.286	99.93	49966.50
6	803.712	2.883	99.93	59959.80
8	832.815	3.826	99.93	79946.40
12	846.604	5.183	99.93	119919.60

*%Diss_pH6.8: %Dissolution calculated by the (Eq. 6)

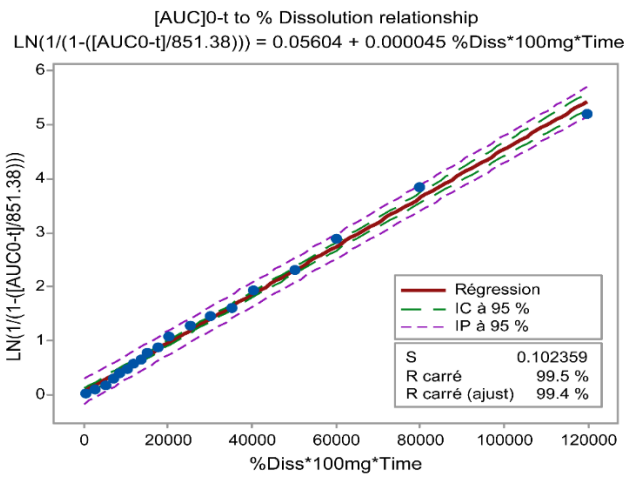

Figure 5: Relationship of AUC_{0-t} determined by IN VIVO analysis and %Dissolution IN VITRO analysis of LOSARTAN Potassium 100 mg Tablets (Batch 12619001, Manufactured by IBERMA Laboratory)

IVIVR AUC_{0-t} - % Dissolution Model

The IVIVR AUC_{0-t} - %Dissolution model developed enabled us to determine the predicted AUC_{0-t} for any formulation that has undergone a change. The %PE in relation to the AUC_{0-t} of the original formulation, which had to be less than 15% [11], was used to assess the effect of this change on the marketed product that has successfully passed bioequivalence studies.

RESULTS AND DISCUSSION

Results

Validation of the IVIVR models

To ensure the reliability of our IVIVR model, its validation was necessary. So, the aim of this phase was to challenge the results obtained with real bioequivalence studies on LOSARTAN potassium 100 mg (batch number AUS5004) manufactured by IPCA Laboratories Limited, with a formulation similar to the test product (LOSARTAN

potassium 100 mg, batch number 12619001), and two different batches of the reference product (COZAAR batch numbers S006754 and H754). The results of the dissolution profiles in 6.8 pH Phosphate buffer of each product were used to calculate C_{max} (pred) and AUC_{0-t} (pred). The predictive values of C_{max} and AUC_{0-t} were compared with the observed values, which are the results of the bioequivalence studies carried out on the above-mentioned products [10,11]. %PE of the IVIVR models was calculated with regard to C_{max} and AUC_{0-t} (Formulas (Eq. 7), (Eq. 8)). According to relevant FDA regulatory guidance [12,13,14], the permissible %PE values should be less than 15 % for each product and less than 10 % for the average.

$$\%PE(C_{max}) = [\{C_{max}\ (Obs) - C_{max}\ (Pred)\} / C_{max}\ (Obs)] \times 100 \quad \text{(Eq.7)}$$

$$\%PE\ (AUC_{0-t}) = [\{AUC_{0-t}\ (Obs) - AUC_{0-t}\ (Pred)\} / AUC_{0-t}\ (Obs)] \times 100 \quad \text{(Eq.8)}$$

According to the values obtained from Table 7 and Table 8, we can see that the IVIVR models developed to predict C_{max} and AUC_{0-t} of a Losartan potassium formulation based on IN VITRO dissolution data is valid since the %PE calculated for both parameters for each product is less than 15% and the average of the three %PE(C_{max}) is 7.32% and for three %PE(AUC_{0-t}) is 6.85% (less than 10%).

Table 7: IVIVR models results of LOSARTAN Potassium 100 mg Tablets (Batch AUS5004, Manufactured by IPCA Laboratories Limited) and two distinct batches of the reference product (COZAAR batch numbers S006754 and H754)

	COZAAR S006754			**LOSARTAN potassium100mg AUS5004**			**COZAAR H754**		
Time (h)	**%Diss**	**C_{max} *(Pred)*** ng/mL	**AUC_{0-t} *(Pred)*** ng.h/mL	**%Diss**	**C_{max} *(Pred)*** ng/mL	**AUC_{0-t} *(Pred)*** ng.h/mL	**%Diss**	**C_{max} *(Pred)*** ng/mL	**AUC_{0-t} *(Pred)*** ng.h/mL
0.17	51.14	1681.526	76.690	40.54	1936.986	70.506	49.48	1721.532	75.724
0.25	80.02	985.518	192.389	63.31	1388.229	172.245	70.88	1205.792	183.820
0.33	93.35	664.265	343.970	-----	-----	-----	-----	-----	-----
0.50	99.78	509.302	552.241	93.59	658.481	371.497	95.57	610.763	385.971
0.75	102.38	446.642	833.821	96.00	600.400	640.674	99.24	522.316	661.480
1	-----	-----	-----	96.82	580.638	971.378	100.74	486.166	1001.288

Table 8: IVIVR model validation results of LOSARTAN Potassium 100 mg Tablets (Batch AUS5004, Manufactured by IPCA Laboratories Limited) and two distinct batches of the reference product (COZAAR batch numbers S006754 and H754)

COZAAR S006754			**LOSARTAN potassium 100 mg AUS5004**			**COZAAR H754**		
C_{max} [M] (Pred) ng/mL	**C_{max} [M] (Obs)** ng/mL	**%PE**	**C_{max} [M] (Pred)** ng/mL	**C_{max} [M] (Obs)** ng/mL	**% PE**	**C_{max} [M] (Pred)** ng/mL	**C_{max} [M] (Obs)** ng/mL	**%PE**
532.63	567.31	**6.11**	612.298	563.823	**8.60**	537.275	579.283	**7.25**
AUC_{0-t} (Pred) ng.h/mL	**AUC_{0-t} (Obs)** ng.h/mL	**%PE**	**AUC_{0-t} (Pred)** ng.h/mL	**AUC_{0-t} (Obs)** ng.h/mL	**% PE**	**AUC_{0-t} (Pred)** ng.h/mL	**AUC_{0-t} (Obs)** ng.h/mL	**%PE**
833.821	857.95	**2.81**	971.378	1093.77	**11.19**	1001.288	1071.31	**6.54**

***C_{max} (Pred)** cannot be valued until after the % Dissolution has reached its maximum, at which point we can speak of maximum absorption, since the tablet has released the maximum dose of the active ingredient it contains. In this case, from 85% minimum. **C_{max} [M] (Pred)** is the geometric Mean of **C_{max} (Pred)** for which %Dissolution is greater than 85%.

***AUC_{0-t} (Pred)** is the cumulative value corresponding to the end-of-dissolution timing.

***C_{max} [M] (Obs)** and **AUC_{0-t} [M] (Obs)** are the mean observed values obtained from bioequivalence studies.

Sensitivity study of the IVIVR models

The objective of this stage was to determine if the developed and validated IVIVR was sensitive to any formulation changes made and could measure the impact of the change in terms of tolerable deviation from the initial PK parameters C_{max} and AUC_{0-t} corresponding to LOSARTAN potassium 100 mg Tablets, batch number 12619001 (Test product). This allowed us to predict the behavior of the modified formulation and whether it called for a possible second bioequivalence study imposed by the type of change made. [3,4]

To this end, five in-house (IR) formulations (F1, F2, F3, F4, F5) were carried out with varying amounts of three excipients: (Super-disintegrant, Diluent, and Binder), as shown in Table 1. The rationale for the change was to vary the amount of super-disintegrant Sodium Starch Glycollate (SSG) in the range (0.5 - 8% w/w) and compensate it with the amount of diluent Microcrystalline Cellulose in the range (44.75 - 55.75%) [15,16]. Dissolution profiles were carried out on tablets from each formulation, enabling the developed IVIVR models to calculate C_{max} and $AUC_{0-t}$for each formulation (Table 9). The results found were compared with the C_{max} and AUC_{0-t} values of the LOSARTAN potassium 100 mg, batch number 12619001 (Test product) by evaluating %PE (Table 10). Whenever the %PE was greater than 15%, the change was deemed to have a serious impact on the marketed bioequivalent formulation, indicating a high risk of failure for a subsequent bioequivalence study and the notable financial investment of the sponsor laboratories.

To confirm this hypothesis, the similarity factor f_2 [17] which had to be greater than 50 (50-100) [18,19], was used for each dissolution profile to reinforce decisions regarding the level of change and its impact on the product. The concordance of the values of f_2 and those of the %PE is quite obvious, each time the %PE is nearing the limit of 15%, f_2 is nearing the lower limit 50 [20]. This demonstrates a strong link between IN VIVO and IN VITRO performance, further justified by the f_2 test. [21]

Table 9: Responses C_{max} and AUC_{0-t} of formulations of LOSARTAN potassium 100 mg subject of change.

		Time (h)				
		0.17	**0.25**	**0.33**	**0.50**	**0.75**
F1	**%Diss**	63.73	78.78	89.4	94.16	95.54
	$\mathbf{C_{max}}$ ***(Pred)*** ng/mL	1378.107	1015.402	759.46	644.744	611.486
	$\mathbf{AUC_{0-t}}$ ***(Pred)*** ng.h/mL	83.97	198.643	346.065	546.152	814.425
F2	**%Diss**	76.15	90.79	91.95	93.02	92.83
	$\mathbf{C_{max}}$ ***(Pred)*** ng/mL	1078.785	725.961	698.005	672.218	676.797
	$\mathbf{AUC_{0-t}}$ ***(Pred)*** ng.h/mL	91.085	215.645	365.754	564.169	827.084
F3	**%Diss**	75.98	90.28	95.05	93.46	94.57
	$\mathbf{C_{max}}$ ***(Pred)*** ng/mL	1082.882	738.252	623.295	661.614	634.863
	$\mathbf{AUC_{0-t}}$ ***(Pred)*** ng.h/mL	90.988	215.131	368.493	567.555	833.915
F4	**%Diss**	78.53	91.58	94.77	94.17	94.48
	$\mathbf{C_{max}}$ ***(Pred)*** ng/mL	1021.347	706.962	629.963	644.543	637.032
	$\mathbf{AUC_{0-t}}$ ***(Pred)*** ng.h/mL	83.97	209.174	362.247	562.347	828.53
F5	**%Diss**	49.63	58.53	74.93	89.92	90.72
	$\mathbf{C_{max}}$ ***(Pred)*** ng/mL	1717.917	1503.427	1108.187	746.928	727.648
	$\mathbf{AUC_{0-t}}$ ***(Pred)*** ng.h/mL	75.812	173.508	305.484	499.329	758.038

Table 10: IVIVR models sensitivity results.

	$\mathbf{C_{max}}$ **[M] (Pred) ng/mL**	$\mathbf{*C_{max}}$ **[M] (Obs) ng/mL**	**% PE**	$\mathbf{AUC_{0-t}}$ **(Pred) ng.h/mL**	$\mathbf{*AUC_{0-t}}$ **(Obs) ng.h/mL**	**% PE**	$\mathbf{f_2}$
F1	671.9	598.1	12.34	814.425	861.62	5.48	52
F2	682.34	598.1	14.08	827.084	861.62	4.01	65
F3	639.92	598.1	6.99	833.915	861.62	3.22	67
F4	637.18	598.1	6.53	828.53	861.62	3.84	62
F5	860.92	598.1	43.94	758.038	861.62	12.02	30

*C_{max} [M] (Obs) = 598.1 is the mean C_{max} reported by the bioequivalence study of the marketed formulation of LOSARTAN potassium 100 mg Tablets, batch number 12619001 (Test product).

*AUC_{0-t} (Obs) = 861.62 is the AUC_{0-t} reported by the bioequivalence study of the marketed formulation of LOSARTAN potassium 100 mg Tablets, batch number 12619001 (Test product).

DISCUSSION

In this study, we succeeded in developing an IVIVR model based on an immediate-release formulation, which is innovative compared to other published studies that primarily concern extended-release formulations. The model developed is simple, and based on a significant linear relationship linking the two important IN VIVO parameters C_{max} and AUC_{0-t} to IN VITRO %Dissolution. As observed with the IVIVR developed for three formulations (LOSARTAN potassium 100 mg Tablets/Batch: US5004, COZAAR 100mg/Batch: S006754, COZAAR 100mg/Batch: H754), each model accurately estimated the C_{max} and AUC_{0-t} values (justified by the %PE values).

To demonstrate the robustness of the developed models, validation and sensitivity analyses were conducted. The validation results were consistent with the observed bioequivalence outcomes obtained for similar formulations of Losartan Potassium 100 mg Tablets (Batch AUS5004, manufactured by IPCA Laboratories Limited) and two distinct batches of the reference product COZAAR (Batch S006754 and Batch H754).

The sensitivity of the models to changes was assessed on five in-house formulations prepared for this purpose. The developed IVIVR models accurately predicted C_{max} and AUC_{0-t} of the drug from the immediate-release formulation. The prediction errors for C_{max} and AUC_{0-t} were all less than 10% for all formulations used to develop the IVIVR, with a mean prediction error for all formulations no greater than 15%.

The IVIVR models developed in this study have proven effective in identifying formulation changes that could significantly impact the quality and efficacy of the marketed bioequivalent product. Any change resulting in a percentage prediction error (%PE) exceeding 10% is deemed unacceptable, as it poses a high risk of compromising the product's bioequivalent status. In our analysis, the modified formulations F1, F2, and F5 exhibited %PE values greater than this threshold, highlighting their potential risk. Conversely, formulations F3 and F4 demonstrated no significant impact, with %PE values below 10%. Furthermore, a strong correlation was observed between the outcomes of the IVIVR models and the similarity factor (*f2*) values, reinforcing the reliability of the proposed approach.

On the basis of these results, we conclude that the IVIVR models developed are valid, and predictive for the immediate release formulation LOSARTAN potassium 100 mg tablets. In addition, they are sensitive for detecting possible formulation changes and determining its impact.

CONCLUSION

The results of this study underscore the robustness and practicality of the IVIVR models developed for the immediate-release formulation of LOSARTAN Potassium 100 mg tablets. By establishing a predictive and validated mathematical relationship between *in vitro* dissolution profiles and key pharmacokinetic parameters (C_{max}, AUC_{0-t}), this study provides a critical tool for evaluating the impact of formulation changes without the need for repeated bioequivalence studies.

The sensitivity analysis demonstrated the models' ability to reliably detect formulation modifications and their potential impact on the quality and bioequivalence status of the drug product. This capability is invaluable for regulatory and industrial applications, offering a cost-effective and time-efficient alternative to traditional bioequivalence testing while maintaining compliance with stringent regulatory standards.

This approach represents a significant advancement in pharmaceutical development, particularly for BCS Class III drugs, by ensuring the consistent quality and efficacy of marketed products.

Future research should focus on extending this methodology to other drug classes and formulations to further enhance its applicability and utility in the fields of drug formulation development and pharmaceutical quality management.

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