Research Article

Quality by Design (QbD) Empowered by IVIVR Modeling: A Predictive Approach for Drug Formulation Development

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ABSTRACT

This study demonstrates how integrating validated In Vitro–In Vivo Relationship (IVIVR) modeling within a Quality by Design (QbD) framework empowers predictive, robust, and regulatory-compliant drug formulation development. Using losartan potassium 100 mg immediate-release tablets as a case study, factorial Design of Experiments (DoE), sensitivity analyses, and predictive modeling were applied to identify and prioritize critical quality attributes (CQAs) and critical process parameters (CPPs). A scientifically justified Design Space was established and experimentally validated, achieving prediction errors below 10% across all CQAs, confirming the reliability and scalability of the model. By reducing reliance on in vivo studies and accelerating the optimization of formulation parameters, this IVIVR-QbD integration offers a forward-looking strategy that aligns with ICH Q8, Q9, Q10 and Q14 guidelines, supporting efficient lifecycle management, cost reduction, and consistent therapeutic performance.

Keywords: IVIVR, QbD, Design Space, critical quality attributes (CQAs), critical process parameters (CPPs), dissolution, Cmax, AUC(0-t), Design of Experiment (DoE).

INTRODUCTION

Quality by Design (QbD) has established itself as a systematic, science-driven, and risk-based paradigm for pharmaceutical developmen[1–4,16–21] , where product quality is built into the formulation from its inception rather than verified solely through end-product testing. In parallel, In Vitro–In Vivo Relationship (IVIVR) modeling serves as a powerful predictive tool, linking in vitro dissolution behavior to in vivo pharmacokinetic responses with quantitative accuracy[1–4,9–11,14,15]. By integrating IVIVR modeling into the QbD framework[1–4,16–21], formulation scientists gain a deeper mechanistic understanding of the interplay between critical quality attributes (CQAs), critical process parameters (CPPs), and clinical performance. This synergy not only enables the development of a scientifically justified and robust Design Space[22,24–27], but also allows for informed formulation adjustments without the need for extensive bioequivalence studies[5,6]. The present work exemplifies this integrated IVIVR–QbD approach through the case study of losartan potassium 100 mg immediate-release tablets[15], demonstrating how predictive modeling can streamline formulation optimization, ensure bioequivalence, and support lifecycle management.

MATERIALS AND METHODS

In this study, a Quality by Design (QbD) framework empowered by In Vitro–In Vivo Relationship (IVIVR) modeling was applied to define and optimize a robust Design Space for formulation adjustments of immediate-release losartan potassium 100 mg tablets[14,15,30,33]. The approach was based on previously validated predictive IVIVR models[7,9–11,14,15], which enhanced the mechanistic understanding of the relationship between in vitro dissolution behavior[12,13] and in vivo pharmacokinetic performance. The integration of IVIVR within the QbD strategy[1–4,16–21] enabled a science-driven evaluation of critical quality attributes (CQAs) and critical process parameters (CPPs) [22,24–27], ensuring formulation robustness, consistent bioequivalence[5,6], and clinical relevance. The overall methodology was structured and implemented through the following sequential steps:

1. **Identification of CQAs**: As part of the IVIVR framework, Critical Quality Attributes (CQAs) refer to the in vivo parameters that must be controlled to ensure the drug product's performance. These include indicators such as bioavailability, release kinetics, absorption, and various pharmaco-technical parameters (e.g., mass and mass uniformity, friability, hardness, and disintegration) [12,13]. The Quality by Design (QbD) approach[1–4,16–21] begins with the identification of these essential CQAs. In this study, the selected CQAs included disintegration time, percentage friability, tablet hardness, percentage dissolution, similarity factor (f_2), Cmax, and AUC(0–t).

2. **Selection of Critical Process Parameters (CPPs)**: CPPs are in vitro parameters that have a direct impact on the Critical Quality Attributes (CQAs) [22,24–27]. Within the IVIVR framework[7,9–11,14,15], these may include factors such as raw material composition, dissolution rate, permeability, and solubility characteristics[8]. In this study, the sensitivity analysis[23,25,26], aimed at evaluating the impact of formulation changes, was leveraged to identify key CPPs. Specifically, the proportions of sodium starch glycolate and microcrystalline cellulose[15,28,29] in the formulation were

identified as CPPs due to their significant influence on product performance.

3. Design of Experiment (DoE): A factorial design approach[22–25] was used to generate multiple formulations, with systematic variation of excipient levels[15,28,29]. The impact on CQAs was statistically analyzed using Minitab®18. By employing the Design of Experiments (DoE) approach (Table 3) as an experimental design tool, the Critical Process Parameters (CPPs) can be systematically varied to assess their impact on the Critical Quality Attributes (CQAs)[23–27]. This methodology enables the quantification of relationships between in vitro characteristics and in vivo performance[15].

4. **IVIVR Modeling**: Previously validated IVIVR models[15] (Eq. 1, Eq. 2) relating "% dissolution" to pharmacokinetic parameters (Cmax and AUC(0–t)) were applied to predict in vivo performance of new formulations[9,10,15]:

IVIVR Models

Cmax Model: Eq. 1

$$C_{max} = 2914 - 24.10 \times \%\text{Diss} \quad \text{(Eq.1)}$$

AUC_0–t Model: Eq. 2

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

5. Design Space Definition and Optimization: Based on model predictions[12,15] and desirability functions[23–27], optimal compositions were proposed and experimentally validated[15]. The design of the experimental plan began with the confirmation of the selected Critical Quality Attributes (CQAs)[1,19–22]. It was evident that disintegration time, friability, hardness, percent dissolution, and similarity factor (f_2) were all significantly influenced by variations in formulation composition. However, the responses of Cmax and AUC(0–t)—two in vivo CQAs—remained unclear in relation to changes in the levels of two key excipients, sodium starch glycolate and microcrystalline cellulose, identified as Critical Process Parameters (CPPs). To address this, a preliminary impact study[23,25,26] was conducted to evaluate the influence of these CPPs on Cmax and AUC(0–t)[15,30,33]. Data generated from the development of five formulations (F1–F5) (Table 1) were used to define and optimize the appropriate Design Space[15].

Table 1: Composition (% w/w) of in-house LOSARTAN potassium 100 mg formulations (F1–F5)

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 quantity (not disclosed)

The objective was to identify the most suitable formulation composition in terms of sodium starch glycolate and microcrystalline cellulose capable of achieving the target pharmacokinetic parameters: Cmax of 598.1 ng/mL and AUC(0–t) of 861.62 ng·h/mL, corresponding to the marketed bioequivalent product[15]. Sodium starch glycolate and microcrystalline cellulose were selected as independent variables, whereas maize starch, serving as a binder, was found to have a negligible effect on drug release[28,29].

Using the Quality by Design (QbD) framework outlined in ICH Q8 guidelines[1] and Minitab® 18 software, we assessed the influence of excipient variations on the two pharmacokinetic parameters (Figure 1 and Figure 3). The impact study revealed that the Design Space required to achieve the target Cmax of 598.1 ng/mL corresponds to a formulation containing 7.81315 % sodium starch glycolate and 44.9574 % microcrystalline cellulose, predicting a Cmax of 598.71 ng/mL and a prediction error (%PE) of 0.1 % (<10 %) (Figure 1). Similarly, the Design Space needed to reach the target AUC(0–t) of 861.62 ng·h/mL corresponds to 7.78499 % sodium starch glycolate and 45.0348 % microcrystalline cellulose, with a predicted AUC(0–t) of 847.715 ng·h/mL and a %PE of 1.61 % (<10 %) (Figure 3).

This impact study confirmed the sensitivity of Cmax and AUC(0–t) to variations in the quantities of sodium starch glycolate and microcrystalline cellulose. To validate these findings, an optimization study[27] was carried out (Figure 2 and Figure 4), showing that the optimal formulations identified through optimization were consistent with those derived from the impact assessment, further supporting the reliability of both defined Design Spaces.

The primary objective of this study was to define a Design Space that ensures control over formulation changes through the integration of IVIVR and QbD principles. A subsequent step aimed to define a unified Design Space capable of simultaneously achieving both target pharmacokinetic values within ±5 % tolerance limits [Cmax (598.1 ± 5 %) and AUC(0–t) (861.62 ± 5 %)][15]. Based on this

analysis (Figure 5), the global Design Space was defined as a formulation containing 7.79987 % sodium starch glycolate and 44.9431 % microcrystalline cellulose, predicting a Cmax of 598.683 (%PE = 0.1 %) and an AUC(0–t) of 848.004 (%PE = 1.6 %). Final validation through an additional optimization run (Figure 6) proposed a Design Space at 8 % sodium starch glycolate and 45.046 % microcrystalline cellulose, yielding predicted values of Cmax = 598.1023 (0.0 % PE) and AUC(0–t) = 848.5162 (1.5 % PE), again confirming strong alignment between the predicted and optimized values[15].

A Position of the Resulting "Design Space" Relative to the Various Formulations (Table 2) showed that formulations F3 and F4 exhibited relatively low %PE values compared to the optimized Design Space: F3 (6.89 % for Cmax and 1.66 % for AUC(0–t)), and F4 (6.43 % for Cmax and 2.30 % for AUC(0–t)). These were the closest to the defined Design Space. However, the significant difference in excipient levels between these formulations limits the rational selection between them[28,29]. Additionally, formulations containing 7.8 % to 8 % sodium starch glycolate may present risks to product quality and efficacy due to the known risk of gelatinization associated with concentrations above 8 %[28,29].

This lack of clear decision-making between F3 and F4 is acceptable given the primary aim of this phase—to demonstrate the sensitivity of Cmax and AUC(0–t) to variations in the selected CPPs[23–29]—which was effectively achieved. The integration of other CPPs, as per the extended Design of Experiments (Table 3), will allow for a more comprehensive and robust formulation strategy to resolve this limitation[23–25].

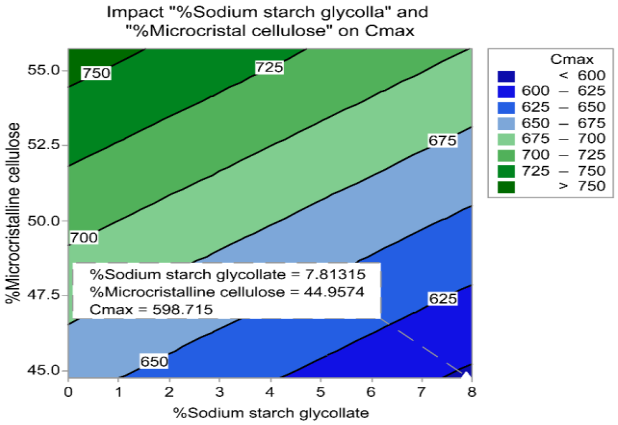

Figure 1: Impact of "%Sodium starch glycollate" and "%Microcrystalline cellulose" variation on C_{max}

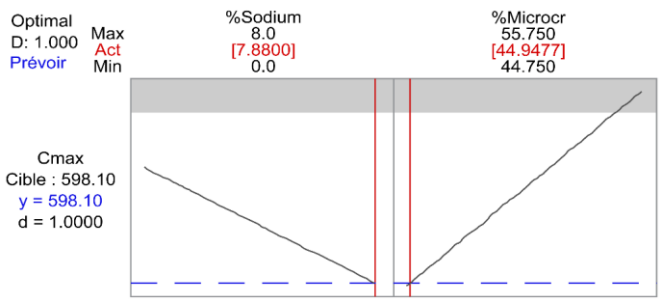

Figure 2: Optimization plot formulation focus C_{max} target

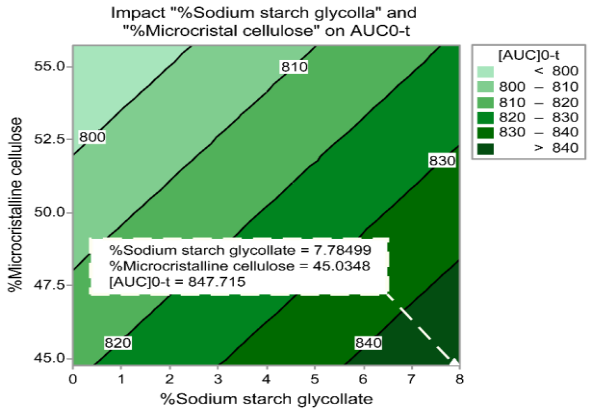

Figure 3: Impact of "%Sodium starch glycollate" and "%Microcrystalline cellulose" variation on AUC_{0-t}

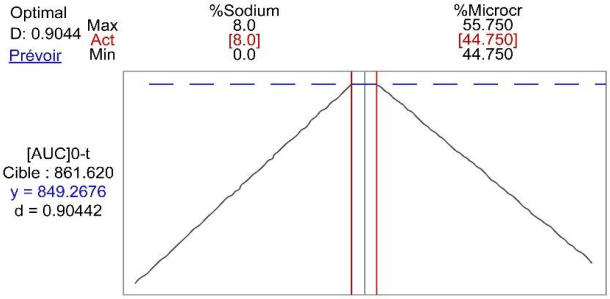

Figure 4: Optimization plot formulation focus AUC_{0-t} target

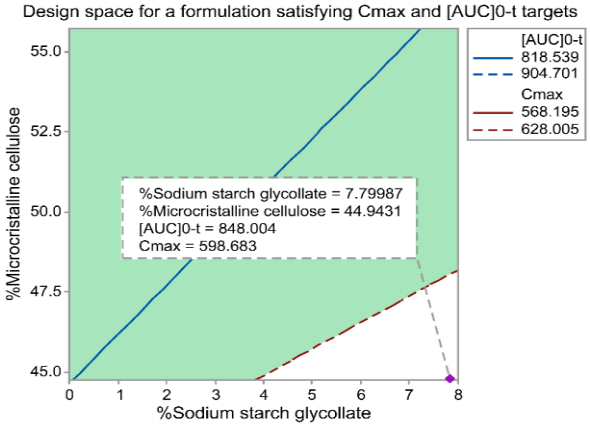

Figure 5: Design space for a formulation satisfying C_{max} and AUC_{0-t} targets.

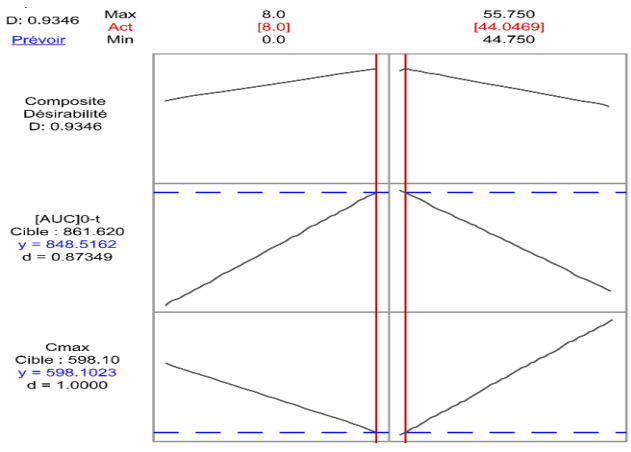

Figure 6: Optimization plot formulation focus C_{max} and AUC_{0-t} targets

Table 2: Position of the Resulting ''Design Space'' Relative to the Various Formulations

Formulation	% sodium starch glycolate	% microcrystalline cellulose	C_{max}	%PE_C_{max} / *DS	AUC_{0-t}	%PE_AUC_{0-t} /DS
Design Space	7.8	44.94	598.683	-----	848.004	------
Optimized formulation	8	45.05	598.102	-----	848.516	------
F1	0.50	55.25	671.90	12.23	814.425	3.96
F2	2.66	53.06	682.34	13.97	827.084	2.47
F3	8.00	47.75	639.92	6.89	833.915	1.66
F4	2.66	44.75	637.18	6.43	828.530	2.30
F5	0.00	55.75	860.92	43.80	758.038	10.61

*DS: Design space

Table 3: Design of Experiments (DoE)

				CPPs		CQAs								
Ordre.Std	Ord.Essai	Pt. Centr	Blocs	%microcrystalline cellulose	% sodium starch glycolate	Disintegration time (mn)	%Friability	Hardness (N)	%Dissolution	f2	Cmax	[AUC]0-t	%PE_Cmax	%PE_[AUC]0-t
4	1	1	1	55.25	0.5	8	0.07	69.98	95.54	52	671.90	814.425	12.34	5.48
1	2	1	1	53.08	2.66	6	0.18	62.46	92.83	65	682.34	827.084	14.08	4.01
2	3	1	1	47.75	8	4	0.12	37.61	94.57	67	639.92	833.915	6.99	3.22
3	4	1	1	55.75	0	10	0.09	58.86	90.72	30	860.92	758.038	43.94	12.02

RESULTS AND DISCUSSION

Results

Following the establishment of a relationship between in vitro characteristics (CPPs) and in vivo performance parameters (CQAs), the next step involved adjusting the CPPs to optimize the targeted CQAs[1,16–21]. This phase includes the identification of acceptable value ranges for the CPPs[23–27] (Table 4) that ensure the desired performance of the drug product, as specified in targeted performance ranges for drug product CQAs (Table 5).

The application of a design of experiments (DoE) approach[23–25], developed under optimization and adjustment conditions for both CPPs and CQAs, enabled the generation of the final Design Space. This Design Space incorporates both in vitro and in vivo performance criteria[15]. The optimized formulation (Fopt), as determined through the optimization plot (Figure 7), is defined by the composition presented in Table 6.

Table 4 : CCPs Adjustment

CCP	Lower Limit	Upper Limit
% Microcrystalline cellulose	47.75	55.75
% Sodium starch glycolate	0	8

Table 5: Targeted Performance Ranges for Drug Product CQAs

CQA Response	Goal	Lower Limit	Target	Upper Limit	Weight	Importance
[AUC]0-t	Target	758.038	**861.62**	947.782	1	1
Cmax	Target	538.290	**598.10**	687.815	1	1
f2	Target	50.000	**70.00**	77.000	1	1
%Dissolution	Target	90.720	**97.00**	106.700	1	1
Hardness (N)	Target	37.610	**50.00**	65.000	1	1
%Friability	Target	0.070	**0.20**	0.220	1	1
Disintegration time (mn)	Target	4.000	**5.00**	10.000	1	1

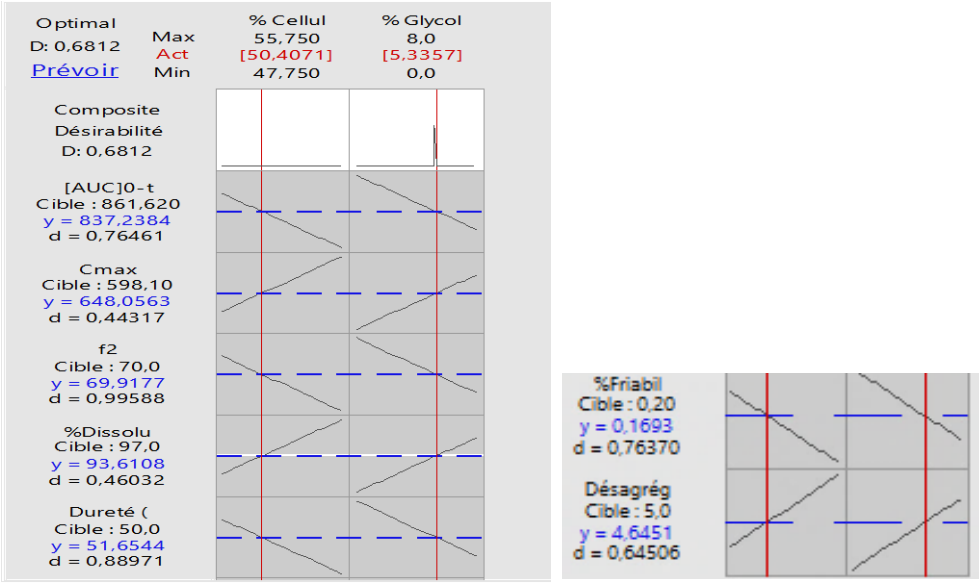

Figure 7: Optimization plot formulation focus *CQAs* targets

Table 6: Design Space Visualization for optimized formulation (Fopt)

Design space	
% Microcrystalline cellulose	50.4071
% Sodium starch glycolate	5.3357
Quality–Efficacy Rating of Fopt	
AUC_{0-t}	837.20
C_{max}	648.00
f2	69.90
%Dissolution	93.61
Hardness (N)	51.65
%Friability	0.17
Disintegration time (mn)	4.65

DISCUSSION

The experimental validation of the developed Design Space is proved by the statistically robust and scientifically satisfactory results obtained[15,23–27]. However, adopting the proposed Design Space at an industrial scale without prior testing remains a significant risk that must be mitigated. To address this, an experimental formulation (Fopt-Experimental) was prepared and evaluated at the laboratory scale[15]. A comparison between the predicted outcomes (Fopt-Theoretical) and the experimental results is presented in Table 7.

With prediction errors (%PE) below 10 %, and approaching 0 % for certain CQAs, the experimental results demonstrated excellent concordance with the theoretical predictions derived from the developed Design Space. Based on this agreement, confidence in the robustness and reliability of the Design Space is reinforced, supporting its potential use in scale-up strategies for product improvement and manufacturing process optimization without compromising product quality or therapeutic efficacy[1–4,16–21].

Table 7: Experimental vs. Theoretical Results of Fopt

CQA	Fopt-Theoretical	Fopt-Experimental	%PE
[AUC]0-t	837.20	785.00	6.24
Cmax	648.00	677.84	4.60
f2	69.90	69.00	1.29
%Dissolution	93.61	93.62	0.01
Hardness (N)	51.65	52.65	1.94
%Friability	0.17	0.10	------
Disintegration time (mn)	4.65	6.00	------

Optimization plots and prediction error (PE) values confirmed the robustness of the IVIVR–QbD integration. An optimized formulation with 5.34 % sodium starch glycolate and 50.4 % microcrystalline cellulose delivered Cmax and AUC(0–t) values within acceptable limits, with experimental PE < 10 %[1,5,6,14,15,19].

Comparative evaluation between predicted and experimental outcomes showed high concordance, supporting the validity of the derived Design Space[1,5,6,14,15,19].

By integrating the IVIVR approach within the QbD framework, pharmaceutical companies aim to enhance the predictability of in vivo drug performance, reduce the risk of non-compliance, and optimize development, formulation, and manufacturing processes. This integration can also contribute to reducing the reliance on costly in vivo studies by supplementing them with more targeted and meaningful in vitro experiments.

CONCLUSION

The successful integration of In Vitro–In Vivo Relationship (IVIVR) modeling within the Quality by Design (QbD) framework has demonstrated a powerful, science-based strategy for managing formulation changes in immediate-release oral drug products. Using losartan potassium 100 mg tablets as a case study, a robust and optimized Design Space was established by systematically varying key Critical Process Parameters (CPPs)—specifically sodium starch glycolate and microcrystalline cellulose—through factorial Design of Experiments (DoE), sensitivity analyses, and statistical optimization tools.

This approach enabled the identification and prioritization of the most influential Critical Quality Attributes (CQAs), including Cmax, AUC_{0-t}, dissolution, hardness, friability, and disintegration time. The validated IVIVR models effectively predicted the impact of formulation changes on in vivo performance, providing a mechanistic understanding of the formulation–performance relationship.

Experimental validation of the optimized formulation (Fopt: 5.34% sodium starch glycolate, 50.41% microcrystalline cellulose) confirmed excellent agreement with model predictions, with prediction errors consistently below 10% across all CQAs. These findings affirm the predictive reliability, robustness, and industrial applicability of the defined Design Space, offering a sound basis for formulation adjustments and scale-up without the need for additional in vivo studies.

By embedding IVIVR within the QbD approach, this study:

- Enhances formulation robustness and predictability.
- Reduces reliance on costly clinical studies by leveraging validated in vitro dissolution data and predictive pharmacokinetic models.
- Aligns with global regulatory guidelines (ICH Q8–Q10, Q14) on lifecycle and risk-based pharmaceutical development.
- Supports proactive and flexible quality management throughout the product lifecycle.

In conclusion, the IVIVR-QbD integration provides a pragmatic and efficient roadmap for pharmaceutical manufacturers aiming to implement safe, rapid, and cost-effective formulation modifications while ensuring consistent product quality, bioequivalence, and therapeutic efficacy.

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