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Research Article

Comparative Study of Itopride Hydrochloride *in-Vitro* Drug Release in Various Brands of Sustained Release Capsules By RP-HPLC

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Abstract:

Background: The World Health Organisation has advocated the use of generic medicines to make them accessible and affordable but studies have revealed that marketed products do not produce same therapeutic effects and hence are not interchangeable. Dissolution testing of generic solid dosage forms serves as a valuable tool for acquiring dissolution profiles and for assessing the similarity or dissimilarity between the formulations under examination.

Objectives:

1. To evaluate the in-vitro drug release profiles of different generic brands of Itopride Sustained release capsules that are commercially available in Indian market and compare them with the innovator product using model dependant and as well as model independent methods.
2. To determine whether same medicine manufactured by different brands are interchangeable.

Materials & Methods: In this study Eight generic brands of Itopride 150mg sustained release capsules available in the Indian market were evaluated using dissolution test with the aim to assess their bioequivalence with the innovator product (Ganaton OD). Dissolution studies were performed using USP type II apparatus at 100 rpm in 900 ml 0.1N HCl while maintaining a temperature of 37±0.5 ºC. The samples were estimated by a validated HPLC method.

Dissolution test results were statistically evaluated by employing both model dependant and model independent methods. In model dependant experimental data obtained for each dissolution profile were transformed by applying the equations of different kinetic models and the best-fit model was

selected whereas in model independent approach fit factors, dissolution efficiency and mean dissolution times were calculated.
Results: The Weibull model best explained the release of drugs from all the brands. Upon statistical evaluation of dissolution test results its was found that while similarity factor f2 was within the limits for all generic brands, difference factor f1 of two brands was out of acceptable range thus questioning their bioequivalency with the innovator product. Also the dissolution efficiency of four out of the brands was out of acceptable limits.
Keywords: bioequivalence, difference factor (f1), similarity factor (f2), dissolution profile, comparison and evaluation..

Introduction

Dissolution or mass transfer is the kinetic process by which a solid solutes dissolve in a solvent to yield a solution. The dissolution process is crucial in releasing the active ingredient from its formulation, rendering it accessible for successive absorption within the gastrointestinal system. Conducting a dissolution experiment is a fundamental requirement for all solid oral dosage forms across various stages of product development and stability assessment [1]. It plays significant role in identifying the necessity for conducting bioequivalence studies, particularly concerning Scale-Up and Post Approval Changes (SUPAC). Simultaneously, it functions as a tool for detecting drug products that are unacceptable or below standard quality levels [2,3]. Furthermore, it can be employed to provide evidence of the bioavailability of a new drug product or to establish the bioequivalence of a product that is essentially similar or exhibits variations to become confident in substitution of branded with generics for affordability and to achieve therapeutic efficacy [4-6].

Dissolution analysis of pharmaceutical solid dosage forms holds great significance, as it can serve as highly sensitive tool for distinguishing among various formulations of the same medicinal substance [7]. The dissolution test must be sensitive, robust and reproducible enough to highlight or discriminate significant alterations in manufacturing changes as well as product performance. Selection of the relevant *in-vitro* conditions that simulate the *in-vivo* environment could lead to the development of a reasonable *in-vitro/ in-vivo* correlation [8,9].

Oral solid dosage forms represent the most commonly employed formulations for both new and established sustained release products, and they remain the favoured method of administration for numerous medications. sustained release systems present numerous clinical benefits, such as decreased dosing frequency, which contributes to better patient adherence, minimized fluctuations in drug plasma levels, a reduced likelihood of adverse effects, and the potential for improved efficacy. The primary objective of solid dosage forms is to deliver a drug to the human body at a predetermined rate, and in a precise quantity through the gastrointestinal tract which ensures that the drug can generate its intended pharmacological effects effectively. In practice, despite the presence of legislations for bioequivalence, generic products might differ significantly from the reference drug [10].

Many studies on bioavailability of drugs revealed that, marketed products did not give the same therapeutic effects causing debates on the safety and efficacy of generics on international level thereby casting shadow on their quality [5,11-21]. This primarily stems from inadequate dissolution and subsequent

absorption of the drug within the gastrointestinal tract (GIT). As a result, conducting in-vitro drug release studies on solid dose formulations becomes a critical assessment of the quality of product.

A pharmaceutical product comprises both an active drug substance and various excipients. The ratio between these components, the specific excipients employed, and the manufacturing process used for the final product are determined by factors such as the drug's composition, its physicochemical properties, its bulk characteristics, and its absorption properties. Collectively, these factors influence the dissolution characteristics of each individual product. Consequently, the dissolution of a drug from its dosage form is influenced by numerous factors, these encompass not solely the physicochemical attributes of the drug but also extend to the formulation of the dosage form itself and the intricacies of the manufacturing process [22,23]. Throughout the various developmental stages of a new drug product, the quality of the dosage form is consistently enhanced. The dissolution test serves as a dependable tool for assessing formulation and processing variables that could impact the drug's bioavailability [24].

Continuous monitoring of tablets available in the market by government agencies, manufacturers, and independent research organizations is crucial. This surveillance helps prevent issues like dose dumping and ensures that high-quality medicines remain readily available to the public. Dose dumping is defined as the “unintended, rapid drug release in a short period of time of the entire amount or a significant fraction of the drug contained in a modified release dosage form” [25].

Itopride sustained release capsules are not officially listed in the Indian Pharmacopoeia (IP), British Pharmacopoeia (BP), or United States Pharmacopeia (USP) till now. Nevertheless, the market presents both branded versions and generic alternatives of these capsules, despite their absence from these recognized pharmacopoeias. The World Health Organisation (WHO) advocates the use of generics to increase access to medicines as well as to make the treatment economical for the patient [26,27]. There is currently no established official method for conducting a dissolution study of Itopride sustained release capsules. Generic alternatives can serve as substitutes for branded versions, but this is only recommended if they have been demonstrated to be bioequivalent with the innovator brand and meet the standards for strength, purity, quality and identity [28,29]. When a generic product has the same active component as the innovator brand in the same dosage formulation and there is no discernible distinction in the rate and extent of the active drug's entry into systemic circulation, the product is deemed bioequivalent to the innovator brand [30]. Hence, it becomes crucial to analyse the dissolution profile of the available Itopride Sustained release capsules in the market in order to determine their bioequivalence.

Bioequivalence studies encompass both *in-vivo* (within the living organism) and *in-vitro* (outside the living organism) studies. However, since how bioavailable a medication can be is contingent on factors such as gastrointestinal permeability and dissolution of the drug, in-vitro dissolution testing plays a critical role in evaluating bioequivalence. Apart from serving as a surrogate for bioavailability and bioequivalence, in vitro dissolution tests can be used to guide formulation developments, identify critical manufacturing variables, monitor batch to batch formulation quality, predict the in vivo performances [31,32]. Therefore, an initiative was undertaken to assess the dissolution profiles of

commercially available Itopride sustained release capsules to determine whether same medicine manufactured by different brands are interchangeable.

MATERIALS AND METHODS

Reagents and Chemicals

Itopride IPRS (Indian Pharmacopoeia Reference Standard) was provided by Indian Pharmacopoeia Commission. Methanol and Acetonitrile were of HPLC grade. Potassium dihydrogen orthophosphate, dipotassium hydrogen orthophosphate and other reagents were of analytical-reagent grade, water was deionised and double distilled.

Itopride Capsule Samples

Eight generic brands of Sustained Release (150mg) were purchased from local market of Ghaziabad, Uttar Pradesh, India and were codified as A, B, C, D, E, F, G and H. The samples underwent thorough inspection to verify their manufacturing license numbers, batch numbers, as well as their production and expiry dates as shown in table 1. All the brands used were within their shelf life as at the time of study. The description of samples used is given in

Table 1: General characteristics of brands included in the study

Product	Mfg. Date	Exp. Date	Appearance
Ganaton OD (Innovator Product)	12/2021	11/2023	White color body and red color cap containing white colored pellets, hard gelatin capsule.
A	06/2022	11/2023	Dark blue color body and light blue color cap containing white and brown colored pellets, hard gelatin capsule.
B	08/2022	07/2024	Light pink color body and cap containing white and brown colored pellets, hard gelatin capsule.
C	07/2022	06/2024	White color body and light pink color cap containing white colored pellets, hard gelatin capsule.
D	11/2023	12/2021	Red color body and cap containing white and brown colored pellets, hard gelatin capsule.
E	11/2022	07/2024	Yellow color body and light blue color cap containing white and light blue colored pellets, hard gelatin capsule.
F	05/2022	04/2024	Purple color body and black color cap containing white and light blue colored pellets, hard gelatin capsule.

G	10/2022	09/2024	Dark blue color body and red color cap containing white and light blue colored pellets, hard gelatin capsule.
H	11/2022	10/2024	White color body and red color cap containing 1 yellow colored enteric coated and 2 white colored film coated round brown tablet, hard gelatin capsules.

Dissolution test

A validated dissolution by HPLC method was provided by Indian Pharmacopoeia Commission. The dissolution test was performed on tablet dissolution tester (DS 8000, Lab India) in 6 replicates for each brand using USP type 2 paddle apparatus with a rotation speed of 100 rpm. 900ml 0.1N HCl was employed as Dissolution media. The temperature of the medium was carefully maintained at 37 ± 0.5°C.

During each experiment, a 14 ml aliquot (comprising 10 ml of the sample and 4 ml of rinse) from the dissolution sample was extracted at time intervals of 1, 3, 6, 14 hours. To ensure the maintenance of sink conditions, this withdrawn volume was promptly replaced with an equal volume. Samples were filtered through 0.45µ nylon and assayed by HPLC method to determine the dissolution rate.

Chromatographic conditions

Chromatographic analysis was performed on C18 column (4.6mm x 50 mm) having particle size 2.7µ at ambient temperature in reverse phase mode. A mixture of Phosphate buffer (pH 7.2) and Acetonitrile in the ratio 70:30 was employed as mobile phase with a flow rate of 0.7 ml/min and detection was carried out on 260nm.

Data analysis

Model-independent Methods

Fit Factors: In order to judge whether these differences in dissolution profiles were significant, all dissolution profiles were compared to that of the originator (Ganaton OD) using fit factors or similarity indices f1 and f2.

The difference factor, denoted as f1, represents the average percentage disparity between two curves at each time point. It serves as a metric for assessing the relative error between these two curves. The similarity factor (f2) is derived from a logarithmic reciprocal square root transformation applied to the sum of squared errors. It serves as a quantification of the resemblance in the percent (%) dissolution between the two curves. The subsequent equations were utilized to compute f1 (the difference factor) and f2 (the similarity factor). [33,34].

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} X100$$

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum_{i=1}^{n} (R_t - T_t)^2 \right)^{-0.5} X100 \right\}$$

In these equations, "n" represents how many time points are being considered, "Rt" signifies value of the reference product's dissolution at time "t", and "Tt" represents the

dissolution value for the test product at the same time point "t."

The similarity factor, f2, has been endorsed by regulatory authorities such as the WHO (World Health Organization), European Agency for the Evaluation of Medicinal Products (EMEA), specifically by Committee for Proprietary Medicinal Products (CPMP), and the FDA (Food and Drug Administration). It is recommended as a criterion for comparing dissolution profiles [35-38]. Similarity factor f2 is included by the Centre for Drug Evaluation and Research (CDER) in their guidelines such as guidance on dissolution testing of immediate release solid oral dosage forms (FDA, 1997) and guidance on Waiver of In-Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (FDA, 2000). [39,40]

Dissolution profiles are deemed similar and bioequivalent when the difference factor (f1) falls within the range of 0 to 15 and the similarity factor (f2) is within the range of 50 to 100 [39,41].

Dissolution Efficiency (DE): DE is the area under the dissolution curve within a time range expressed as a percentage of the dissolution curve at maximum dissolution, over the same time frame [42]. is calculated as the percentage ratio of the area under the disolution curve up to time t to that of the area of the rectangle described by 100% dissolution at the same time point, and is defined as follows:

$$DE\% = \frac{AUC_0^T}{Q_{100.T}} 100$$

$$AUC = \sum_{i=1}^{i=n} \frac{(t_1 - t_{i-1})\,(y_{i-1} + y_i)}{2}$$

Where t_i is the i^{th} time point, y_i is the percentage of dissolved product at time t_i.

The reference and the test product can be said to be equivalent if the difference between their dissolution efficiencies is within appropriate limits (± 10%, which is often used) [42].

Mean Dissolution Time (MDT): MDT was calculated to characterize the dissolution rate of the drug in each dissolution profile using Equation (4), where t_i is a midpoint between two sampling time, ΔQ_i is the amount of drug dissolved in every interval of time, and Q_∞ represents the maximum of drug dissolved [43].

$$MDT = \frac{\sum\left[t_i \times \Delta Q_i\right]}{Q_\infty}$$

Mean dissolution time (MDT) characterizes the drug substance release from the dosage form and the retarding efficiency of the polymer. A higher value of mean dissolution time indicates the lowest rate of drug release from the dosage form. This in turn leads to the slow onset of action and higher drug-retaining ability of the polymer and vice versa [44].

Model Dependant Methods

Six model-dependent approaches were used to compare the Itopride Hydrochloride dissolution profiles. The model-dependent approaches included the zero order, the first order, the Higuchi, the Korsmeyer-Peppas, the Hixson-Crowell and the Weibull models.

Results and Discussion

The profiles of in-vitro drug release for different generic brands versus the innovator product are shown in Fig.1.

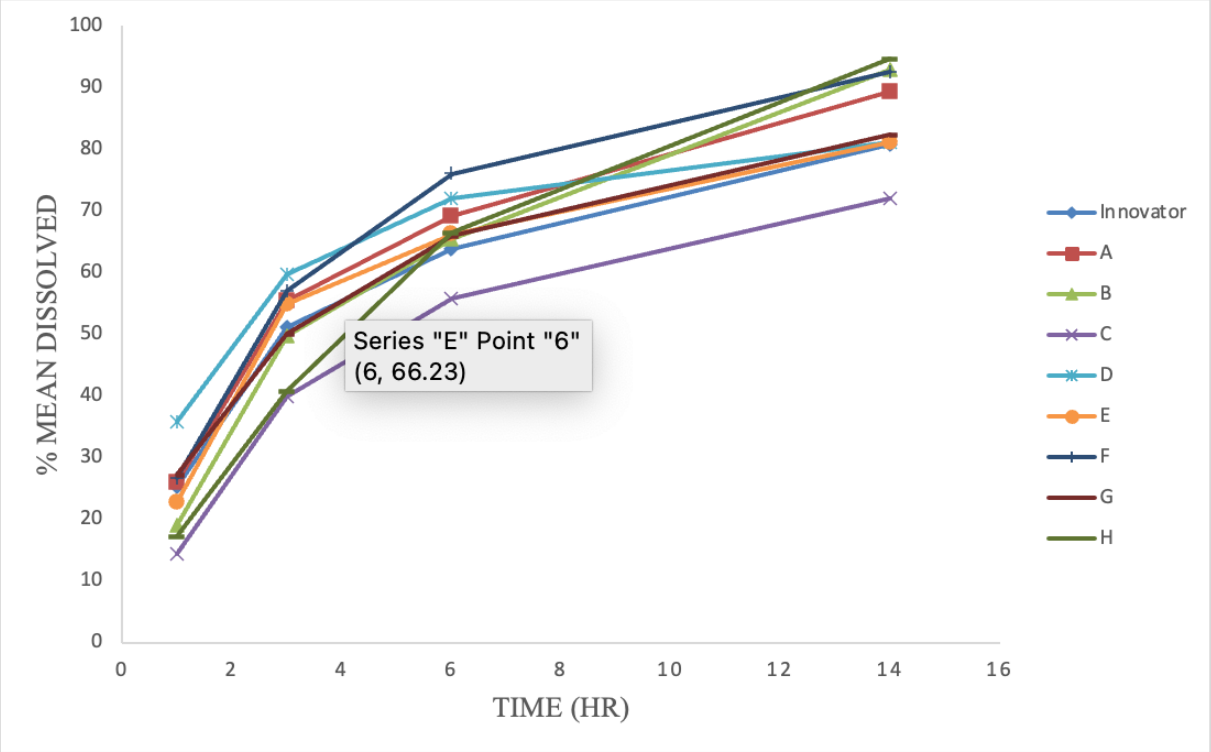

Fig.1: Comparative graphical representation of mean dissolution profiles of eight generic brands of Itopride PR / SR Capsules

Table 2 summarises the mean percent dissolved at each time point, the relative standard deviation (RSD), and the upper and lower limits.

Table 2: Dissolution data and descriptive statistics of nine meloxicam tablet brands

Time (Hrs)	Brand	Mean%	RSD	Lower limit	Upper limit
1	Ganaton	25.34	12.15	19.79	27.85
	A	26.03	2.94	25.38	27.38
	B	19	6.85	16.92	20.57
	C	14.41	10.65	12.73	16.33
	D	35.8	12.19	31.77	41.62
	E	22.79	5.28	20.61	24.02
	F	26.7	4.24	25.12	28.35
	G	27.24	11.73	23.28	31.15
	H	17.23	2.77	16.83	18.11
3	Ganaton	51.24	2.71	49.25	53.6
	A	55.46	2.45	53.32	56.82
	B	49.72	6.38	45.35	52.94
	C	39.98	6.26	37.43	43.87
	D	59.74	10.34	54.83	67.82

	E	54.12	13.72	45.29	67.55
	F	57.08	2.72	55.15	59.45
	G	50.05	6.79	45.26	54.85
	H	40.76	3.12	39.04	42.55
6	Ganaton	63.86	8.37	53.13	66.8
	A	69.25	2.98	66.99	72.66
	B	65.4	8.04	57.31	71.33
	C	55.74	3.68	53.03	59.38
	D	72.1	8.76	66.79	81.16
	E	66.94	4.49	63.86	72.64
	F	76.04	3.13	73.07	78.82
	G	65.96	5.87	60.25	71.42
	H	66.52	3.05	63.89	69.17
14	Ganaton	80.68	10.28	64.56	86.21
	A	89.39	2.9	86.29	92.88
	B	92.87	4.28	87.84	96.66
	C	71.95	5.97	65.42	77.25
	D	81.2	8.45	75.29	90.37
	E	81.04	1.67	79.96	83.69
	F	92.61	3.29	89.11	97.2
	G	82.37	5.58	75.68	87.83
	H	94.70	1.88	91.91	96.63

Fit Factors

Table 1 shows the f1, f2 and of Itopride sustained release capsules. The reference product employed for the calculation of f1 and f2 was Ganaton OD (the Innovator Product). The drug release from the test products closely resembled that of the reference brand, as indicated by f2 values exceeding 50 and f1 values falling below 15.

Table 3: Calculated difference factor (f1) and similarity factor (f2) of all generic samples

Marketer	*Difference Factor (f1)*	*Similarity Factor (f2)*
A	8.6	62.44
B	9.76	57.66
C	17.66	50.21
D	12.54	54.94
E	4.02	78.39
F	14.16	52.07
G	3.11	84.75
H	15.95	50.46

As per the available literature, when comparing dissolution profiles of two products, if the f2 value is equal to or greater than 50%, it suggests that the dissimilarity in dissolution profiles between two products is less than 10%. F2 values equal to or greater than 65% indicate a reduction to 5% in the differences. Furthermore, when the f2 value reaches or exceeds 83%, it signifies differences smaller than 2% [35,40,45]. Additionally, f1 values equal to or less than 15 indicate the absence of significant cumulative distinctions between the profiles, as outlined by the FDA in 1997.

Dissolution Efficiency

The dissolution efficiency for each brand included in the study is shown in table 4. For only four brands the difference between dissolution efficiency of generic and innovator was within limits.

Table 4 Dissolution efficiencies (D.E) of the eight generics brands with innovator brand

Brand	DE	Difference with Reference
Ganaton	76.97	0.00
A	84.01	-7.04
B	81.35	2.66
C	65.93	15.42
D	84.33	-18.40
E	79.11	5.22
F	89.12	-10.01
G	78.57	10.55
H	80.35	-1.78

Mean Dissolution Time

The mean dissolution time for each brand included in the study is shown in table 5. Brand H had the highest MDT while brand D had the lowest MDT, respectively.

Table 5: MDT of the eight generics brands with innovator brand

Brand	MDT
Ganaton	3.59
A	3.75
B	4.48
C	4.05
D	2.62
E	3.37
F	3.51
G	3.58
H	4.79

Model Dependant Methods

The model-dependent approach showed that all of tested Itopride Hydrochloride sustained release capsules were best explained by Weibull curve with highest determination coefficient (R^2) and lower AIC as shown in the table 6.

Table 6: Parameters of the mathematical models and descriptive statistics for the dissolution data

		BRANDS								
Model	Statistics	Ganaton	A	B	C	D	E	G	F	H
Zero order	Rsqr	-0.2434	-0.0609	0.4997	0.3970	-1.9988	-0.2158	-0.2482	-0.0858	0.7042
	AIC	32.4605	32.8806	31.0556	29.9622	34.6245	32.8797	32.5366	33.4612	29.5795
	MSC	-0.7179	-0.5592	0.1926	0.0058	-1.5982	-0.6954	-0.7217	-0.5823	0.7182
First Order	Rsqr	0.8195	0.9357	0.9849	0.8861	0.5664	0.8509	0.8456	0.9776	0.9975
	AIC	24.7410	21.6669	17.0485	23.2961	26.8887	24.4864	24.1778	17.9424	10.4785
	MSC	1.2120	2.2443	3.6943	1.6724	0.3357	1.4029	1.3680	3.2974	5.4934
Higuchi	Rsqr	0.8752	0.9050	0.9691	0.9390	0.4484	0.8383	0.8874	0.8871	0.9716
	AIC	23.2661	23.2285	19.9162	20.7999	27.8522	24.8111	22.9158	24.4073	20.2137
	MSC	1.5807	1.8539	2.9774	2.2964	0.0949	1.3218	1.6835	1.6812	3.0596
Korsemeyer	Rsqr	0.9577	0.9583	0.9694	0.9421	0.9292	0.9136	0.9709	0.9426	0.9799
	AIC	20.9400	21.9306	21.8769	22.5918	21.6409	24.3051	19.4961	23.6992	20.8324
	MSC	2.1623	2.1784	2.4872	1.8484	1.6477	1.4483	2.5384	1.8582	2.9050
Hixson	Rsqr	0.6639	0.8618	0.9548	0.7790	0.3611	0.7243	0.7068	0.9353	0.9946
	AIC	27.2282	24.7288	21.4413	25.9478	28.4397	26.9443	26.7421	22.1782	13.5711
	MSC	0.5902	1.4788	2.5961	1.0094	-0.0520	0.7884	0.7269	2.2384	4.7203
Weibull	Rsqr	0.9881	0.9919	0.9908	0.9743	0.9762	0.9648	0.9972	0.9971	0.9983
	AIC	15.8676	15.3621	17.0907	19.3432	17.2837	20.7116	10.1361	11.8172	10.8713
	MSC	3.4304	3.8205	3.6838	2.6606	2.7370	2.3466	4.8784	4.8287	5.3952

Conclusion

It's important to note that not all generic products, even if they contain the same active ingredient in similar dosage forms and strengths, are necessarily equivalent. Class I drugs according to the Biopharmaceutics Classification System (BCS) with rapid dissolution characteristics may share the same active ingredient and quantity but can still exhibit noteworthy distinctions in meeting in-vitro equivalence criteria [46]. The current research was performed with the goal to assess Itopride sustained release capsules to determine whether medications produced by various brands can be substituted interchangeably.

The variations in release patterns observed among Itopride sustained release capsules raise concerns about the potential impact on the bioavailability of the active ingredient. This raises questions about whether these products can be considered interchangeable. However, it's important to note that additional guidance and investigation are required to ascertain whether the observed in vitro differences hold any clinical significance.

The conducted in vitro release studies can be viewed as initial assessments that precede in vivo studies, especially in the context of bioequivalence testing. This type of assessment demands relatively minimal resources in terms of cost and time and can be extensively applied during the developmental phases of both the composition and manufacturing technology of the product. In situations where there are alterations in the composition of excipients or changes in the production facilities (manufacturing site) for a previously manufactured product, it becomes imperative to employ this test as a mandatory quality control measure to confirm the consistency of release dynamics.

The effectiveness of extended-release formulations is heavily influenced by the quality of the excipients used in manufacturing and the precision of the manufacturing process itself. Due to their inherent characteristics, distinct brands of sustained release products are generally less likely to be equivalent when compared to various brands of immediate, conventional release products. As a result, some Drug Regulatory Authorities (DRAs) adopt the stance that such products should never be considered interchangeable. In contrast, other authorities outline a range of assessments that need to be carried out, which might include comparative clinical trials under certain conditions [47].

In summary, it is advisable to strengthen and enhance the capabilities of drug regulatory authorities, particularly for the oversight of sensitive medicines, through robust post-marketing surveillance. All regulatory bodies should adhere to the necessity of bioequivalence studies as part of market authorization requirements. Additional research should also be conducted on the tested products to arrive at a more definitive conclusion regarding the interchangeability of generic products with the innovator. Furthermore, the consideration of in-vivo bioequivalence studies for generic products is of utmost importance.

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