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Comparative dissolution profiling of generic and standard drug under BCS Based Biowaiver conditions

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Abstract

As specified by regulatory bodies, the current study intends to investigate the dissolving characteristics of a generic medicine product and its matching standard reference medication under Biowaiver settings. Through this comprehensive analysis, we validate the suitability of the generic drug for Biowaiver considerations. Consequently, it may potentially serve as a cost-effective alternative with therapeutic equivalence to the standard reference drug. These findings emphasize the significance of dissolution profiling in supporting the assessment of pharmaceutical quality and regulatory decision-making. This review paper also provides an overview of methodologies and statistical techniques used to compare dissolution profiles, which is a critical aspect of pharmaceutical quality assessment. The study investigates various approaches, including model-independent and model-dependent methods, in line with regulatory guidelines for evaluating whether the dissolution profiles are equivalent or comparable. We discuss the significance of choosing suitable metrics and acceptability criteria, and the effects of process and formulation modifications on dissolving profiles. The study's findings show that dissolving profiles are similar, suggesting that the generic drug's formulation satisfies the requirements to be eligible for Biowaiver. Therefore, it possesses potential for substitution with the standard drug under appropriate circumstances.

Keywords: Biowaiver; Dissolution Profiles; Regulatory guidelines; *In vitro* testing; IVIVC; Dissolution methods

1. Introduction

Generic drugs are a smarter alternative to expensive brands; it is a bioequivalent formula of any branded drug. The rapid expansion of the generic pharmaceutical industry has risen concerns about bioequivalence of generic drug in comparison to their standard counterparts, especially in cases where bio waivers are granted. Biowaiver allows for the approval of generic drug, without conducting Full scale clinical studies, relying instead on dissolution profiling as a surrogate marker for *in-vivo* performance. *In vitro* bioequivalence testing under bio waiver condition can predict bioequivalence in a safe, fast & less expensive method.

In order to release the medication from gastrointestinal absorption and make it accessible for future drug absorption, dissolution is an essential procedure. This article's goal is to give a succinct summary of the ways in which the US FDA, WHO, and EMA use dissolution testing to determine if generic medicine products are safe and effective. Dissolution testing can be developed and implemented according to a number of guidelines.

A generic drug is a smarter alternative to those expensive brands as they possess a bioequivalent formula of any branded drugs. The rapid expansion of the generic pharmaceutical industry has arisen concerns about the bioequivalence of generic drugs when compared to their standard counterparts, especially in cases where bio waivers

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have been granted. Biowaiver allows the approval of generic drugs, without conducting full scale clinical studies, relying instead on dissolution profiling as a surrogate marker for in-vivo performance. Under bio waiver conditions, *In vitro* bioequivalence testing can predict bioequivalence in a safe, fast & less expensive manner. The release of the medication from gastrointestinal absorption and its subsequent availability are largely dependent on the dissolving process. This article's goal is to give a brief summary of the ways that the US FDA, WHO, and EMA use dissolution testing to verify the safety and efficacy of generic medicine products throughout the approval process. Various guidelines are present to guide the development and implementation of dissolution testing ^[1] ^[2].

2. Biowaiver

Clinical bioequivalence investigations are thought to be waived under a Biowaiver scenario. The WHO defines a "bioequivalence waiver" as the procedure of approving a file (application) for a regulated medicine where equivalency other than *In vitro* bioequivalence testing is the foundation for approval ^[3].

2.1. Types of Biowaiver: ^[4]

- Specific dosage form
- Additional strength
- Other strength
- SUPAC
- BCS Based Biowaiver
- Same product
- Bridging

Drug products are considered bioequivalent if, after administration of the identical molar amount, the pace and extent of drug ingestion (also termed as bioavailability) into blood from two drug products containing similar pharmacological component or substances falls under commonly accepted norms. These limits are meant to ensure that a live body will operate in a same manner—specifically, it is safe and effective. Two key pharmacokinetic parameters that are often employed for assessing bioequivalence within a living organism include area under concentration time curve (AUC) and maximum concentration (C-max). These measures help assess the speed and extent of drug absorption ^[5].

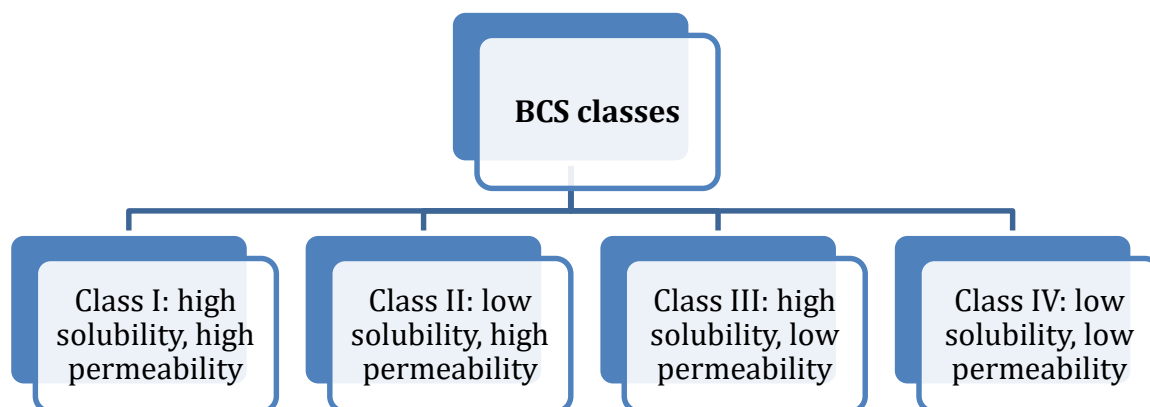


Figure 1 BCS categorizes drug substances into one of four

2.2. BCS Based Biowaiver

BCS-based Biowaiver – They are only appropriate for use in oral medication administration and solid dosage forms or suspensions for instant release. Products with limited therapeutic indices are not included. Fixed-dose combination formulations can only be used if they meet a number of requirements, included adhering to excipient and dissolving requirements, using the same dosage form and strength ^[6].

Table 1 Comparison of different BCS Based Bio waiver approaches by different regulatory authorities “[7]”, “[8]”, “[9]”

SR. NO.	PARAMETERS	USA	EU	WHO	INDIA
	Solubility	Highest dose strength is soluble in ≤ 250 ml of buffers	Highest dose strength is soluble in ≤ 250 ml of buffers	Highest dose strength is. Soluble in ≤ 250 ml of buffers	Highest dose strength is soluble in <250 ml of buffer
	pH range	1 - 7.5	1 - 6.8	1- 6.8	1 - 7.5
	Permeability	<u>Highly permeable:</u> Extent of absorption in humans is ≥ 90 %.	<u>Highly Permeable:</u> Extent of absorption in humans is ≥ 85 %	<u>Highly permeable:</u> Extent of absorption in humans is ≥ 85 %.	<u>Highly permeable:</u> Extent of absorption in human is >90 %.
	BCS based bio waiver	Class-I	Class-I, Class-3	Class-I, Class-III and Class-II weak acid	Class-I
	In-vitro Dissolution similarity of Test Ref. product	Rapidly Dissolving: ≥ 85 % of the labelled amounts the drug substance dissolve within 30 min. Apparatus: USP Type-I at 100 rpm or Type-II at 50 rpm. Dissolution Media: 0.1 N HCl or Simulated Gastric Fluid USP without enzyme pH 4.5 buffer pH 6.8 buffer N=12	<u>Class-I</u> <u>Rapidly Dissolving:</u> ≥ 85 % of the labelled amount of the drug substance dissolves within 30 minutes. <u>Class-3</u> <u>Very rapidly dissolving</u> ≥ 85 % of the labelled amount of the drug substance dissolves within 15 minutes. <u>Apparatus:</u> USP Type I at 100 rpm or Type II at 50 rpm <u>Dissolution Media:</u> 0.1 N HCl or Simulated Gastric Fluid USP Without enzyme	<u>Rapidly Dissolving:</u> <u>Class I:</u> ≥ 85 % of the labelled amount of the drug substance dissolves within 30 minutes. <u>Class III:</u> ≥ 85 % of the labelled amount of the drug substance dissolves within 15 minutes. <u>ClassII(Weak Acid):</u> ≥ 85 % of the labelled amount of the drug substance dissolves within 30 minutes at pH 6.8 <u>Apparatus:</u> USP Type I at 100 rpm or Type II at 75 rpm <u>Dissolution Media:</u> 900 ml of following media	Rapidly Dissolving: ≥ 85 % of the labeled amount of the drug substance dissolves within 30 minutes. Apparatus: USP Type I at 100 rpm or Type II at 50 rpm Dissolution Media: 900 ml of following media (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) pH 4.5 buffer; (3) pH 6.8 buffer or Simulated Intestinal Fluid USP Without enzyme N=12

			<p>pH 4.5 buffer pH 6.8 buffer N=12</p>	<p>(1) 0.1 N HCl or Simulated Gastric Fluid USP withoutenzymes; (2) pH 4.5 buffer: (3) pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. N=12</p>	
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3. *In vitro*- *In vivo* correlation (IVIVC)

3.1. United State Pharmacopoeia (USP) definition

The dosage form has a physicochemical character, and it generates a biological property that gives rise to a logical relationship between them "[10]".

3.2. Food and Drug Administration (FDA) definition

IVIVC is a mathematical model, which relates *In vivo* response to *In vitro* characteristics of dosage forms. The most typical *In vitro* features are the rate or extent of drug release/dissolution while an *In vivo* response is the plasma drug concentration or amount absorbed. This would not predict the therapeutic effect of a drug substance with a simple test for dissolution. To ensure repeatability of biologic responses, it is necessary to have a strong experimental correlation between dissolution profiles of drugs *In vitro* and their bioavailability *In vivo* as well. *In vitro*-*In vivo* correlation is the predictive mathematic model explaining this relationship between an *In vitro* property (such as rate and extent of dissolution) and an *in-vivo* characteristic such as bioavailability "[11]".

The task was primarily aimed at performing bioavailability studies on humans and thus, it is imperative to consider whether dissolution testing might be used as an alternative method instead of conducting live animals study.

- Using these measurements made under laboratory conditions to maintain consistency from batch to batch that affect its performance within the human body.
- To act like a tool during designing new dosage form that can act appropriately after being taken into our bodies.
- For checking or establishing standards for dissolutions.

Table 2 *In vitro* and *In vivo* correlations

SR. NO.	<i>IN VITRO</i>	<i>IN VIVO</i>
1	Dissolution rate	Absorption rate (or absorption time)
2	Percent of drug dissolved	Percent of drug absorbed
3	Percent of drug dissolved	Max. plasma concentration, C_{max}
4	Percent of drug dissolved	Serum drug concentration, C_1

4. Surrogate of bioequivalence study at post approval changes of drug product (SUPAC)

The SUPAC-IR guideline outlines the testing, supporting documentation, and post- approval change levels (1, 2, and 3) that are required to guarantee the drug's efficacy, safety, and quality. It is crucial to compare the resolution test profile of the change batch (reference) to the after-change batch (test) in order to accept scale-up and post-approval modifications (SUPAC). Dissolve testing may be enough in lieu of bioequivalency testing in order to receive SUPAC clearance for Level 1 or 2 alterations, as per USFDA guidelines for immediate-release oral medicinal products. The main distinction is that multi-point dissolution profiles were carried out both before and after changes for the majority of stage 2 alterations in a variety of acceptable dissolving media (water, 0.1 N HCl, pH 4.5, and pH 6.8 pH USP buffers). Dissolution test comparison (replacement). Product is required. An *In vivo* bioequivalence research is not necessary if the similarity factor (f_2) shows that the products' dissolving profiles before and after the alteration are comparable "[14]".

A bioequivalency study and bioequivalency testing are necessary, with the exception of Level 3 "change of position" alterations, when dissolution testing may be sufficient and a bioequivalence study is not needed. Supplied *In vivo* solubility to facilitate SUPAC approval for most Level 3 modifications. Additionally, the creation of a validated and appropriate IVIVC may facilitate Level 3 alterations leading to waiver *In vivo* bioequivalence studies and comparative dissolution tests between the product before and after the modification may be sufficient. As a result, the SUPAC approval procedure involves fewer *In vivo* bioequivalence studies and is more time and money-effective, particularly when IVIVC is created early in the drug development phase "[15]".

4.1. Dissolution

Dissolution is defined as the amount of material that dissolves in a particular length of time under specific parameters such as the liquid-solid interface, solvent concentration, and temperature. A dosage form, such as a pill, capsule, ointment, or other material, can be tested to see how quickly and how much of it dissolves in solution. Dissolving a drug is required for it to be bioavailable and effective. Both drug release and dissolution are used in the same phrase "[16]".

4.2. Dissolution profiling

A quality assurance test known as "dissolution profiling" determines how much of a medication tablet dissolves at different periods. It is an essential test for developing stable oral dosage forms, tablets, and capsules.

Dissolution profiling can help identify the efficacy and safety of a pharmaceutical medication. Furthermore, it can reduce the need for *In vivo* testing, especially when modest changes are made to manufacturing and medicine formulation.

The pace at which a pharmaceutical tablet dissolves is an important quality parameter. The most frequent approach to investigating tablet dissolution is to examine the dissolution profile, which reveals how much of the tablet has been broken down over time "[17]".

The US FDA has established the following standards for dissolving profiles: "[18]" "[19]", "[20]"

- The dissolution profiles can only be compared when a total of twelve or more units are used. F2 should be calculated using the average mean dissolution data from 12 units.
- The use of intervals in determining similarity factor is one way of boosting self-assurance through statistical analysis, whether or not the test and reference are statistically significant.
- For both the reference and test products, dissolving conditions including dosage form strength, time points, temperature, Rpm and entire testing time have to be similar.
- Most published literature identifies f2 value as a function of the number of dissolution time points with some authors suggesting that only once it reaches at least 85% product dissolution may it be meaningful.
- If a compound has rapid dissolution ability such that 85% is dissolved within fifteen minutes or less, there is no need for comparison of its release patterns.
- A value between 50-100 guarantees sameness for any pair of things
- Difference factors may fluctuate between zero and fifteen while still ensuring some level of variation between two items

Table 3 Dissolution Apparatus and detail as per USP "[21]", "[22]"

Sr. no.	USP Apparatus	Description	Rotational speed	Dosage form
1	USP Apparatus-I	Basket	50-120 rpm	Tablet, Capsules, Floating dosage forms (IR, DR, ER)
2	USP Apparatus – II	Paddle	25-50 rpm	Tablet, Capsules, Enteric forms (IR, DR, ER)
3	USP Apparatus – III	Reciprocating Cylinder	6-35 rpm	Extended release drug product
4	USP Apparatus – IV	Flow through cell	N/A	Implants, Powders, Suspension
5	USP Apparatus –V	Paddle over disk	25-50 rpm	Transdermal drug delivery system.
6	USP Apparatus – VI	Cylinder 6	N/A	Transdermal drug delivery system.
7	USP Apparatus – VII	Reciprocating disk	30 rpm	Extended release drug product

4.3. Methods for comparing resolution profiles

The study examined various strategies for comparing dissolution profiles, which included both model-independent and model-dependent methodologies. The model-independent approaches consisted of pairwise procedures, ratio test procedures, and ANOVA-based procedures. On the other hand, the model-specific methods utilized in the study encompassed the zero-order, first-order, Hixson-Crowell, Higuchi, quadratic, Weibull, Gompertz, and logistic models. These findings were documented in references "[23]", "[24]", "[25]"

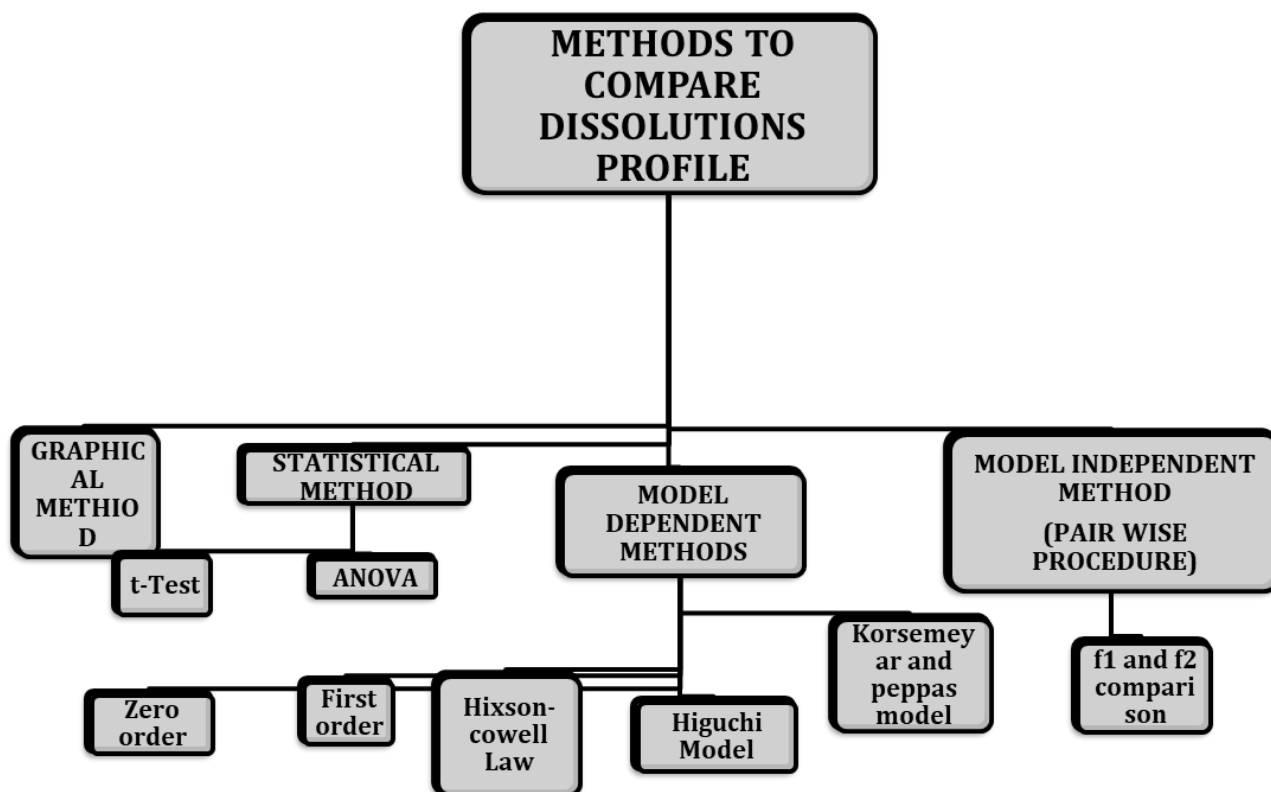


Figure 2 Methods for comparing resolution profiles

4.4. Statistical methods

4.4.1. Exploratory data analysis methods

Although the FDA does not currently support the use of exploratory data analysis tools, their use is recommended because it aids in the understanding of dissolution data.

Initially, this method can be employed to visually and quantitatively compare dissolution profile data. The average dissolution profile data for each formulation is graphically represented, with error bars indicating two standard errors for each dissolution time point. Following a quantitative analysis of the dissolution profile data, the 95% confidence intervals for variances in the mean dissolution profiles at each dissolution step are assessed "[26]".

4.4.2. Multivariate approach (Manova)

The strategies were based on designs for conducting multiple measurements. Time was considered as the recurring factor, while the concentration of dissolved water was identified as the variable that depended on other factors. In order to analyze the data, the statistical software SPSS 10.0 for Windows was utilized. Through this software, various statistical tests such as Roy's Largest Root, Hotelling's Trace, Wilks' Lambda, and Pillai's Trace were performed to derive meaningful insights from the collected data. Using a repeated measures strategy, many measurements were carried out on the same experimental unit in order to acquire information. Improved accuracy is the primary benefit of this design

over Student's t and paired t tests 13. When using repeated measures ANOVA with variables having more than two levels, two additional specific assumptions are made: compound symmetry and sphericity. The MANOVA method for repeated measurements has gained popularity since these assumptions "[28]".

4.5. Model dependent methods

4.5.1. Zero order

In the pharmaceutical sciences, the dissolution of a drug from a solid dosage form, like a tablet or capsule, is mathematically modeled using the zero-order method of dissolution profiling. This technique makes the assumption that the rate of drug breakdown is constant across time. This means that regardless of how much medicine is still needed to dissolve, a fixed amount is released per unit of time.

The zero-order dissolution profile can be mathematically defined as follows:

$$M_t = -k_0 t + M_0$$

M_t = Amount of drug dissolved at time t K_0 = Zero-order dissolution rate constant M_0 = Initial amount of drug in dosage form

4.5.2. First order

This approach is predicated on the idea that the amount of medicine that has yet to dissolve and the rate at which it dissolves are directly proportional. This implies that the proportion of the drug that dissolves over time is a constant proportion of the drug that is still dissolved.

Mathematically, the first-order dissolution profile can be described as:

$$M_t = M_0 (1 - e^{-k_1 t})$$

M_t is the amount of drug dissolved at time t
 M_0 is the initial amount of drug in dosage form
 K_1 is the first order dissolution rate constant
 e is the base of natural logarithm

When the rate of dissolution slows when the amount of drug that hasn't yet broken down is reduced, this model—which is more adaptable than the zero-order model—is frequently used. Depending on the characteristics of the medication and dosage form being studied, choosing the appropriate dissolution model is essential to accurately characterizing the dissolution kinetics.

4.6. Hixson-crowell law

In pharmaceutical research, the Hixson-Crowell Cube Root Law describes mathematically the disintegration of a solid, non-spherical dosage form, such as a tablet or pellet. This law relates the change in size or dimensions of a solid to its rate of dissolution.

The Hixson-Crowell Cube Root Law is expressed as:

$$W_t^{1/3} - W_0^{1/3} = -k (t - t_0)$$

Where:

W_t is the solid's residual weight at time t .
 W_0 is the solid's starting weight.

The rate constant unique to this rule is denoted by k_H .

t_0 is the initial time.

4.6.1. Higuchi model

The Higuchi equation is a mathematical model that is frequently used in pharmaceutical sciences to describe how pharmaceuticals dissolve from solid dosage forms, especially when diffusion is the main mode of drug release. Hiroshi Higuchi, a Japanese physicist, is honored with the name of this model. This model applies primarily to systems where the drug is disseminated in a matrix, such as in controlled-release or extended-release formulations, and it operates under the presumption that Fickian diffusion controls drug release from a solid dose form.

$$M_t = k_H \cdot t^{1/2}$$

Where

k_H is the Higuchi dissolving rate constant

M_t is the quantity of medication dissolved at time t .

4.6.2. Korsmeyer and Peppas model

It is an empirical model that is frequently used to examine and forecast drug release and dissolution behaviour. The power-law kinetics of drug release serves as the basis for this model. The Korsmeyer-Peppas model may describe a variety of drug release profiles, including those involving anomalous, non-Fickian diffusion, due to its adaptability. By fitting experimental data to this equation, researchers can get additional insight into the release mechanism and parameters that govern drug release from pharmaceutical dosage forms.

$$M_t/M_\infty = k \cdot t^n$$

Where:

M_t is the dosage of the medication released at time t .

M_∞ is the maximum amount of medication that can be discharged.

k is a constant associated with the dose form's geometric and structural properties.

n is the release exponent, which provides information on the drug release process. The releasing mechanism may be understood by looking at the value of n ; for example, when $n = 0.5$ indicates Fickian diffusion, while non-Fickian diffusion or other mechanisms may have different

Table 4 Mathematical models used to describe drug dissolution curve "[27]"

	MODEL	EQUATION	UNIT
1)	Zero order	$M_t = k_0 t + b$	Amount of drug time ⁻¹
2)	First order	$M_t = M_a(1 - e^{-k t})$	Time ⁻¹
3)	Hixson-Crowell	$W t^{1/3} - W_0^{1/3} = -KH(t - t_0)$	Drug amount ^{1/3} time ⁻¹
4)	Higuchi model	$M_t = K_H \cdot T^{1/2}$	Time ^{-1/2}
5)	Korsmeyer Peppas model	$M_t/M_\infty = k \cdot t^n$	Time ⁻ⁿ

4.7. Model Independent Method - "[29]"

Model independent methods paired wise procedure

4.7.1. DIFFERENCE FACTOR (f_1) & SIMILARITY FACTOR (f_2)

The difference factor (f_1) calculates the percentage difference between two curves at each time point and assesses the relative inaccuracy between them, following FDA criteria.

$$f_1 = \left\{ \frac{\sum_{i=1}^n |R_i - T_i|}{\sum_{i=1}^n R_i} \right\} \times 100$$

Where, n = number of time points

Rt = % dissolved at time t of reference product (pre change)

T1 = % dissolved at time t of test product (post change)

The FDA states that the similarity factor (f2) is a gauge of how comparable the two curves' percentage (%) dissolution is. It is the total of squared error transformed using the logarithmic reciprocal square root method.

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum (R_t - T_t)^2 \right)^{-0.5} \times 100 \right\}$$

Table 5 Limits for similarity and different factors

Different factor	Similarity factor	Inference
0	100	Dissolutions profile are similar
<15	>50	Similarity or equivalence of two profiles.

4.7.2. Advantages

- They are easy to create.
- To illustrate the comparability of the dissolution profile data, they provide a single figure.

4.7.3. Disadvantages

- The amount of dissolving time points used has an impact on f1 and f2 values.
- If the test and reference formulations are swapped, the difference between the two mean profiles remains constant, but f2 does not.
- It's unclear what criteria are used to determine how dissolution profiles differ or are comparable.

5. Application of dissolution profiling: “[30]”, “[31]”, “[32]” “[33]”

5.1. Regulatory Approval

Manufacturers of generic drugs are required by regulatory bodies, including the FDA in the US and the EMA in Europe, to provide proof that their product is bioequivalent to the standard/reference medication.. Comparative dissolution studies are a crucial part of this demonstration.

5.2. Ensuring Therapeutic Equivalence

Comparative dissolution studies help ensure that generic drugs perform similarly to the standard/reference drug. This is important for patient safety and efficacy.

5.3. Quality Control

Generic drug manufacturers use dissolution testing to maintain quality control during production. It ensures that each batch of the generic drug meets the standards set by the reference product.

5.4. Batch-to-Batch Consistency

These studies are used to confirm that the generic drug maintains consistency in dissolution profiles from batch to batch. Variability could indicate manufacturing issues.

5.5. Formulation Optimization

For generic drug development, dissolution studies can aid in optimizing the formulation to match the reference drug's release profile.

5.6. Switching Between Brands

Healthcare providers may use dissolution data to help patients switch from a standard/reference drug to a generic with confidence in its therapeutic equivalence.

5.7. Post-Marketing Surveillance

Comparative dissolution profiling is used to monitor generic drugs in the market to ensure that they continue to meet bioequivalence standards and maintain their quality and efficacy.

5.8. Biowaiver

Sometimes a generic medication qualifies for a Biowaiver, which can speed up regulatory clearance, if it can show faster and more thorough dissolution than the reference product.

These investigations are essential to guaranteeing that generic medications are safe, efficient, and comparable to brand-name medications, giving patients more cost-effective treatment choices while upholding strict quality and efficacy requirements.

5.9. Bioavailability Assessment

The pace and scope of a drug's absorption throughout the body can be understood through dissolution studies. The pharmacokinetics and bioavailability of a medicine may be understood with the use of this information.

6. Conclusion

The comparative dissolution profiling of generic and standard drugs under Biowaiver conditions is a pivotal aspect of pharmaceutical research and regulation. This review has demonstrated the importance of assessing the dissolution behaviour of generic drugs to ensure their equivalence with standard reference products. When conducted rigorously and in compliance with regulatory guidelines, this approach can serve as a cost-effective means of granting Biowaiver, reducing the need for full-scale bioequivalence studies. However, it is essential to emphasize the need for strict adherence to established protocols and continuous monitoring to guarantee the safety and efficacy of generic drugs. This comparative dissolution profiling is a vital tool in promoting accessibility to affordable medications while maintaining the highest standards of quality and patient welfare. It plays a crucial role in the pharmaceutical industry's on-going efforts to balance innovation, cost-Effectiveness and public health.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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