International Journal of Creative and Open Research in Engineering and Management
ISSN: **3108-1754 (Online)**
Volume 02 Issue 05 May-2026 | Impact Factor: 3.5

# Comparing Branded and Generic Drug Dissolution Under Biowaiver Criteria: A Review

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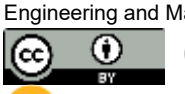
**How to Cite this Article**:
Hulawale, A., Sawant, M. & Jogdand, A. (2026). Comparing Branded and Generic Drug Dissolution Under Biowaiver Criteria: A Review. International Journal of Creative and Open Research in Engineering and Management, 02(05). https://doi.org/10.55041/ijcope.v2i5.631





https://doi.org/10.55041/ijcope.v2i5.631

## Abstract

The global pharmaceutical market increasingly depends on the interchangeability of branded and generic drug products to improve healthcare accessibility and reduce treatment costs. To ensure therapeutic consistency, generic medicines are required to demonstrate pharmaceutical and therapeutic equivalence to their branded counterparts through stringent regulatory evaluation procedures. Among these procedures, dissolution testing serves as a critical surrogate indicator of in vivo drug performance and plays a central role in assessing product quality, bioavailability, and bioequivalence. The Biopharmaceutics Classification System (BCS)-based biowaiver approach has emerged as a scientifically justified strategy that permits the waiver of costly and ethically demanding in vivo bioequivalence studies by relying primarily on in vitro dissolution data, provided specific regulatory criteria are fulfilled. This review critically evaluates published scientific evidence concerning the comparative dissolution behavior of branded and generic oral solid dosage forms, with particular emphasis on the application of BCS-based biowaiver principles under WHO, FDA, EMA, and ICH regulatory frameworks. Comparative dissolution studies indicate that although many generic products demonstrate dissolution profiles comparable to innovator products, variations may occur due to differences in excipient composition, manufacturing processes, particle size distribution, and polymorphic characteristics of the active pharmaceutical ingredient. The similarity factor (f2) remains the most widely accepted regulatory tool for dissolution profile comparison despite recognized statistical limitations. BCS Class I and III drugs continue to be the primary candidates for biowaiver approval, while selected Class II drugs may qualify under specific conditions. Overall, BCS-based biowaiver approaches represent a scientifically reliable, economically beneficial, and ethically sound alternative to in vivo bioequivalence studies when applied using validated dissolution methodologies and harmonized regulatory standards.

**Keywords:** Biowaiver; Dissolution profile; Generic drugs; Branded drugs; BCS classification; Similarity factor (f2); In vitro dissolution; Pharmaceutical equivalence; Biopharmaceutics Classification System; Therapeutic equivalence.

## 1. Introduction

### 1.1 Overview of Drug Products: Branded and Generic

Pharmaceutical products available in the global marketplace are broadly classified into two categories: innovator (branded) drugs and generic drugs. A branded drug is a novel pharmaceutical product developed and marketed by an originator company following extensive preclinical and clinical research leading to regulatory approval. These products are protected by patents and data exclusivity provisions, conferring commercial exclusivity for a defined period. In contrast, a generic drug is defined by the United States Food and Drug Administration (FDA) as a drug product that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use [1].

Therapeutic equivalence implies that two drug products, when administered in the same dosage under the same conditions, will produce the same therapeutic effect. Regulatory frameworks distinguish between pharmaceutical equivalence identical active ingredient, strength, and dosage form — and therapeutic equivalence, which additionally requires demonstrated bioequivalence. The underlying assumption governing generic substitution is that pharmaceutical equivalence combined with bioequivalence constitutes sufficient evidence for therapeutic interchangeability [2].

The global pharmaceutical market was valued at approximately USD 1.48 trillion in 2022 and is projected to exceed USD 2.0 trillion by 2030. Generic drugs constitute approximately 89% of prescriptions dispensed in the United States and represent a similarly dominant share in major European markets and across the developing world [3]. This remarkable penetration reflects both patent expiry of blockbuster molecules and sustained policy commitment to generic promotion as a healthcare cost-reduction strategy.

### 1.2 Need for Generic Drug Evaluation

The rationale for rigorous generic drug evaluation is multifaceted. From an economic perspective, generic drug prescribing generates substantial healthcare cost savings the FDA estimates that generic drugs save U.S. patients and healthcare systems over USD 300 billion annually [4]. From a public health perspective, access to affordable medicines of documented quality is a fundamental pillar of universal healthcare coverage, as articulated in the WHO Model List of Essential Medicines and the Sustainable Development Goals (SDGs).

Critical appraisal of the published literature suggests that many concerns regarding generic drug performance are not supported by systematic evidence and may reflect prescriber bias or inadequate understanding of bioequivalence standards. Nevertheless, isolated but well-documented failures often attributable to poor manufacturing quality rather than fundamental generic-innovator differences underscore the importance of robust quality assurance systems and post-market surveillance [7]. Dissolution testing, as an integral component of both pre-approval evaluation and post-approval quality control, is central to ensuring ongoing therapeutic equivalence.

### 1.3 Importance of Dissolution Testing

Dissolution testing characterizes the rate and extent to which an active pharmaceutical ingredient (API) is released from its dosage form into an aqueous medium under controlled conditions. For oral solid dosage forms tablets and capsules dissolution is the first and often rate-limiting step in the absorption cascade, preceding drug transport across the gastrointestinal mucosa. Consequently, the dissolution profile of a drug product is a critical quality attribute (CQA) with direct implications for bioavailability, onset of action, and therapeutic performance [8].

From a quality control perspective, dissolution testing serves as both a release test and a tool for detecting formulation changes that may alter in vivo performance. Regulatory agencies worldwide mandate dissolution testing at defined time points, using pharmacopoeial or product-specific methods, as part of the marketing authorization dossier and routine batch release testing. The United States Pharmacopeia (USP), European Pharmacopoeia (EP), Indian Pharmacopoeia (IP), British Pharmacopoeia (BP), and Japanese Pharmacopoeia (JP) all include dissolution testing specifications for immediate-release and modified-release products [9].

### 1.4 Concept of Biowaiver

A biowaiver is a regulatory mechanism that permits waiving the requirement for an in vivo bioequivalence study, allowing approval of a drug product based primarily on in vitro data. The term was formally introduced in the context of generic drug approval but has since been extended to post-approval change scenarios, formulation scale-up, and international regulatory submissions [11].

Historically, all generic drug applications required demonstration of bioequivalence through pharmacokinetic studies in human volunteers a time-consuming, expensive, and ethically complex undertaking. Amidon and colleagues' seminal 1995 publication proposing the BCS provided the theoretical framework for predicting in vivo performance from drug solubility and permeability characteristics, thereby establishing a scientifically rational basis for selective waiver of in vivo studies [12].

## 2. Drug Dissolution: Fundamental Concepts

### 2.1 Definition and Physicochemical Basis of Dissolution

Dissolution is defined as the process by which a solid substance enters the solvent to yield a solution. In the pharmaceutical context, dissolution encompasses the dynamic process by which an API is released from its solid dosage form matrix, disaggregated (if applicable), and solubilized in the gastrointestinal fluid, forming a solution available for absorption [14].

The classical mathematical description of dissolution rate was formulated by Noyes and Whitney in 1897, subsequently refined by Nernst and Brunner [15]:

$$dC/dt = (D \times A) / (h \times V) \times (Cs - C)$$

Where dC/dt is the dissolution rate, D is the diffusion coefficient, A is the surface area of the dissolving solid, h is the thickness of the diffusion layer, V is the volume of dissolution medium, Cs is the saturation solubility, and C is the concentration of drug in the bulk solution at time t. This equation reveals the fundamental variables governing dissolution rate: drug surface area (influenced by particle size and wettability), solubility, and diffusion layer thickness. Modifications to any of these parameters through pharmaceutical formulation strategies micronization, co-crystallization, salt formation, amorphous solid dispersion aim to enhance the dissolution rate of poorly soluble drugs [16]

### 2.2 Mechanisms of Drug Dissolution

Three primary theoretical models describe the mechanism of dissolution from solid surfaces:

Diffusion Layer (Film) Theory: Proposed by Nernst and Brunner (1904), this model postulates the existence of a static diffusion layer of thickness h adjacent to the dissolving solid surface. Drug molecules dissolve at the solid-liquid interface (achieving concentration Cs), then diffuse through this layer into the bulk solution (concentration C). This model is the most widely applied in pharmaceutical science and forms the theoretical basis of the Noyes-Whitney equation [17].

Interfacial Barrier Model: This model proposes that the rate-limiting step is not diffusion through a static layer but rather the surface reaction at the solid-liquid interface. It is particularly relevant for drugs whose dissolution is controlled by a chemical reaction for example, pH-dependent dissolution where protonation state governs solubility. The model is applicable to basic drugs dissolving in acidic media and to certain polymorphic forms [18].

### 2.3 Factors Affecting Drug Dissolution

Drug dissolution in vitro and in vivo is governed by a complex interplay of physicochemical, formulation, and environmental factors. Each factor must be critically considered in the context of generic-branded comparisons.

#### 2.3.1 Particle Size and Surface Area

Particle size reduction (micronization) dramatically increases drug surface area (A in Noyes-Whitney), thereby enhancing dissolution rate for drugs exhibiting dissolution-rate-limited absorption (BCS Class II). Nanosizing reducing particle diameter below 1 μm further increases surface area and may additionally enhance solubility through the Ostwald-Freundlich effect [20]. Generic formulations may employ different particle size

specifications than the innovator, which can translate into measurable differences in dissolution profiles even when both products are within pharmacopoeial acceptance criteria. Kulkarni et al. (2020) demonstrated that generic ibuprofen tablets with median particle size of 45 μm exhibited significantly faster dissolution at pH 7.4 compared to branded products with median particle size of 80 μm, though both met the >75% dissolution at 45 minutes USP specification [21].

2.3.2 Polymorphism

Many APIs exist in multiple crystalline forms (polymorphs) or as amorphous solids, each with distinct physicochemical properties including solubility and intrinsic dissolution rate. The metastable polymorph typically exhibits higher apparent solubility and faster dissolution but may convert to the stable (lower solubility) form during processing or storage a phenomenon of critical regulatory concern. The most infamous example is ritonavir (Norvir), where emergence of a new, less soluble polymorph (Form II) in 1998 necessitated temporary market withdrawal of the semi-solid formulation [22]. Generic manufacturers are obligated to demonstrate polymorphic form equivalence to the reference listed drug (RLD), though the analytical sensitivity of commonly employed methods (XRPD, DSC) may not detect minor polymorphic impurities [23].

2.3.3 pH of Dissolution Medium

The dissolution of ionizable drugs is profoundly dependent on the pH of the surrounding medium. Weakly acidic drugs (e.g., ibuprofen, naproxen) exhibit higher solubility in alkaline media, whereas weakly basic drugs (e.g., ketoconazole, itraconazole) dissolve preferentially in acidic environments. The pH progression along the gastrointestinal tract from gastric pH 1-2 to duodenal pH 4-6 to jejunal/ileal pH 6.5-7.5 creates a dynamic dissolution environment that must be adequately replicated in vitro. Regulatory guidelines mandate dissolution testing at pH 1.2, 4.5, and 6.8 for biowaiver evaluation, representing the physiological range of the gastrointestinal tract [24].

2.3.4 Excipients

Pharmaceutical excipients, while defined as pharmacologically inert components, exert profound effects on drug dissolution through multiple mechanisms. Disintegrants (e.g., croscarmellose sodium, sodium starch glycolate) facilitate tablet/capsule disintegration, exposing drug particles to the dissolution medium. Solubilizers (e.g., poloxamers, SDS) enhance drug wettability and can dramatically increase dissolution rates of hydrophobic APIs. Binders, diluents, and lubricants influence tablet hardness, porosity, and wetting characteristics [25]. Critically, generic manufacturers are not obligated to use identical excipients to the innovator product; they must only demonstrate that their excipients do not adversely affect bioequivalence. This creates significant latitude for dissolution-altering formulation differences that may not be adequately captured by single-point dissolution specifications [26].

2.3.5 Manufacturing Process Variables

The manufacturing process exerts substantial influence on drug dissolution through its effects on tablet physical properties. Compression force during tableting determines tablet hardness, porosity, and internal structure, all of which govern dissolution medium penetration. Wet granulation may affect drug crystallinity and particle morphology; spray drying may create amorphous API, significantly altering dissolution kinetics. Coating processes particularly for enteric-coated and modified-release products are critical determinants of dissolution behavior and must be rigorously characterized in both branded and generic products [27].

2.3.6 Agitation Speed and Hydrodynamics

Agitation speed in dissolution testing apparatus influences the thickness of the diffusion layer (h) and hence the dissolution rate. For USP Apparatus II (Paddle), rotation at 50 rpm versus 75 rpm can produce markedly different dissolution profiles, particularly for hydrophobic or slow-dissolving formulations. Similarly, sinkers used to prevent tablet flotation in Apparatus I/II may influence drug release kinetics. Consistent apparatus conditions are critical for reproducible inter-laboratory and inter-study comparisons [28].

2.4 Dissolution Testing Apparatus

Table 1. Comparative Overview of USP Dissolution Apparatus

| Apparatus | Type | Principle | Advantages | Limitations |
|---|---|---|---|---|
| USP I | Rotating Basket | Drug placed in mesh basket; rotated at 50-100 rpm in dissolution medium | Suitable for capsules, floating tablets; reduces coning | Not ideal for poorly soluble drugs; basket clogging possible |
| USP II | Paddle | Paddle rotates at 25-100 rpm above tablet resting on vessel floor | Most widely used; robust; reproducible | Coning artefact; tablet sticking to vessel |
| USP III | Reciprocating Cylinder | Tablet in cylinder oscillated through dissolution medium | Simulates GI transit; multi-pH testing | Less common; complex; limited standardization |
| USP IV | Flow-Through Cell | Continuous flow of medium past drug in cell | Sink conditions maintained; ideal for poorly soluble drugs | Expensive; complex setup; less routine use |

The choice of dissolution apparatus is dictated by the dosage form, drug properties, and regulatory requirements. USP Apparatus II (Paddle) is the most frequently employed for immediate-release tablets, while USP Apparatus I (Basket) find utility for capsules and certain tablet types. USP Apparatus IV (Flow-Through Cell) is increasingly preferred for poorly soluble BCS Class II and IV drugs where maintenance of sink conditions is critical to generating physiologically relevant dissolution data [29]. WHO Guidelines (TRS 992) and FDA guidance documents specify acceptable apparatus types for biowaiver dissolution studies.

3. Biopharmaceutics Classification System (BCS)

3.1 Historical Development and Purpose

The Biopharmaceutics Classification System (BCS) was conceptualized and formally proposed by Gordon Amidon and colleagues in a landmark 1995 publication in Pharmaceutical Research [12]. The BCS provides a scientific framework for classifying drug substances according to their aqueous solubility and intestinal permeability the two primary determinants of oral drug absorption. The system's fundamental premise is that dissolution, solubility, and intestinal permeability are the key parameters governing the rate and extent of drug absorption from oral solid dosage forms.

The primary regulatory significance of BCS lies in its ability to predict when in vitro dissolution data may serve as a reliable surrogate for in vivo pharmacokinetic data, thereby supporting biowaivers. Since its original proposal, the BCS framework has been adopted by WHO (TRS 937, 992, 1003), FDA (2000, 2015 Guidance documents), EMA (2010 Guideline on BCS), and most recently incorporated into ICH M9 guideline (2019/2021), achieving unprecedented international regulatory harmonization [30].

3.2 BCS Classification

Table 2. BCS Classification System: Comparative Characteristics and Biowaiver Eligibility

| BCS Class | Solubility | Permeability | Rate-Limiting Step | Example Drugs | Biowaiver Eligibility |
|---|---|---|---|---|---|
| Class I | High | High | Gastric emptying | Metoprolol, Verapamil, Diltiazem | Eligible (rapid dissolution) |
| Class II | Low | High | Dissolution rate | Ibuprofen, Piroxicam, Carbamazepine | Eligible for some (BCS II acids; very rapid dissolution) |
| Class III | High | Low | Permeability | Cimetidine, Acyclovir, Ranitidine | Eligible (very rapid dissolution + excipient criteria) |
| Class IV | Low | Low | Both | Hydrochlorothiazide, Furosemide | Not eligible |

## 4. Regulatory Framework for Biowaiver

4.1 WHO Guidelines

The World Health Organization has published several landmark guidance documents governing biowaiver applications, most notably Technical Report Series (TRS) 937 (2006), TRS 992 (2016), and TRS 1003 (2017). These guidelines are particularly influential in low- and middle-income countries where WHO prequalification standards drive generic medicine quality assurance.

WHO TRS 992 Annex 7 (2016) represents the most comprehensive WHO biowaiver guidance. It specifies eligibility for BCS Class I and Class III drugs and introduces provisions for select BCS Class II weak acids (notably ibuprofen, metronidazole). The WHO definition of high solubility employs pH 1.2 to 6.8 (versus FDA's extended range to pH 7.5), a distinction with practical implications for basic drugs with pH-dependent solubility. WHO guidelines emphasize that excipients in the test product should not be qualitatively or quantitatively different from those of the reference product in a way that would affect drug absorption, particularly for Class III drugs where GI fluid composition may influence permeability [39].

4.2 FDA Guidelines

The FDA's Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2000) was the first regulatory implementation of BCS-based biowaivers in a major regulatory jurisdiction. This guidance covered BCS Class I drugs and introduced the standards for rapid dissolution (>85% in 30 minutes) and very rapid dissolution (>85% in 15 minutes) [40].

The 2015 FDA Draft Guidance Update expanded biowaiver eligibility to include BCS Class III drugs meeting very rapid dissolution criteria, aligning more closely with WHO and EMA positions. Importantly, FDA's definition of high solubility extends to pH 7.5, encompassing more ionized acid forms that may exhibit reduced solubility at the higher pH. The FDA also maintains that the solubility pH range of 1.2 to 7.5 better represents the range of gastric and intestinal pH values encountered in the gastrointestinal tract [41]. The recent ICH M9 harmonization effort (implemented by FDA in 2021) further refined FDA biowaiver criteria.

4.3 EMA Guidelines

The European Medicines Agency published its Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) in 2010, with specific provisions for BCS-based biowaivers. EMA's approach closely aligns with WHO TRS 937/992, recognizing BCS Class I and III drugs as biowaiver candidates. EMA defines high permeability as >85% absorbed, slightly lower than the FDA/WHO threshold of 90%, reflecting differences in the pharmacokinetic data available for qualifying reference compounds [42].

A distinctive feature of EMA guidance is its relatively more prescriptive treatment of excipient considerations for Class III drugs, recognizing that excipients such as surfactants and absorption enhancers can modulate intestinal permeability. EMA requires that Class III biowaiver applications demonstrate not only rapid dissolution of the test product but also qualitative sameness and quantitative similarity of formulation excipients relative to the reference [43].

4.4 ICH M9 Guideline

The ICH M9 Biopharmaceutics Classification System-Based Biowaivers guideline, finalized in 2021, represents a milestone achievement in international regulatory harmonization. Developed through the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), M9 was adopted by FDA, EMA, and regulatory agencies in Japan, Canada, and other ICH member countries [44].

ICH M9 harmonizes pH ranges for solubility testing (1.2 to 6.8), dissolytion criteria, and BCS class eligibility across major markets. It also provides guidance on acceptable permeability methods and introduces provisions for in silico permeability prediction as supplementary evidence. A critical advancement in ICH M9 is the explicit risk-based framework for BCS Class II weak acids and the recognition that PBPK modeling may supplement dissolution data in borderline cases. However, ICH M9 does not achieve full international harmonization — several major pharmaceutical markets, including India (CDSCO) and China (NMPA), maintain independent biowaiver guidelines that may diverge from ICH M9 in specific provisions [45].

Table 3. Comparative Overview of International Biowaiver Regulatory Guidelines

| Parameter | WHO (2006/2016) | FDA (2000/2015) | EMA (2010) |
|---|---|---|---|
| **BCS Classes Eligible** | I and III (with conditions) | I only (originally); III with conditions (2015 update) | I and III |
| **Solubility Definition** | Highest dose soluble in 250 mL pH 1-6.8 | Highest dose soluble in 250 mL pH 1-7.5 | Highest dose soluble in 250 mL pH 1-6.8 |
| **Rapid Dissolution Criterion** | >85% in 30 min at pH 1.2, 4.5, 6.8 | >85% in 30 min at pH 1.2, 4.0, 6.8 | >85% in 30 min at pH 1.2, 4.5, 6.8 |
| **Very Rapid Dissolution** | >85% in 15 min | >85% in 15 min | >85% in 15 min |
| **Similarity Factor (f2)** | Required when <85% in 15 min | Required when <85% in 15 min | Required when <85% in 15 min |
| **Excipient Consideration** | Known excipients at standard levels | Generally recognized as safe (GRAS) | Well-established use and known safety |
| **Permeability Criterion** | >90% absorbed | >90% absorbed (mass balance) | >85% absorbed |

4.5 Requirements for Granting a Biowaiver

Across regulatory jurisdictions, the following core criteria must be satisfied for biowaiver approval of immediate-release oral solid dosage forms:

(1) BCS Classification: The drug substance must be classified as BCS Class I, III, or select Class II (weak acids, under WHO provisions). The classification must be supported by documented, validated solubility and permeability data.

(2) Dissolution Criteria  Rapid and Very Rapid Dissolution: The test product must demonstrate rapid dissolution (>85% in 30 minutes) at all three pH values (1.2, 4.5, 6.8) using specified dissolution apparatus and conditions. If both test and reference demonstrate >85% dissolution in 15 minutes (very rapid dissolution), profile comparison using f2 is not required. When either product fails the 15-minute criterion, an f2 value of ≥50 across all three pH media is required to demonstrate similarity.
(3) Excipient Qualification: Excipients in the test product must be generally recognized as safe (GRAS) or have established pharmaceutical use. For Class III biowaivers, excipient composition must not qualitatively differ from the reference, and any quantitative differences must be scientifically justified as unlikely to affect drug absorption.
(4) Same Dosage Form and Route: Test and reference must share the same solid oral dosage form intended for oral administration.

## 5. Comparative Evaluation of Branded and Generic Drug Products

5.1 Bioequivalence Versus Therapeutic Equivalence

Bioequivalence is established when two drug products, formulated as pharmaceutical equivalents, exhibit similar bioavailability profiles rate and extent of drug absorption such that they are expected to produce the same therapeutic effect. Regulatory standards define bioequivalence using the 90% confidence interval (CI) for the ratio of pharmacokinetic parameters (Cmax, AUC) falling within 80–125% for the test/reference product [50].
Davit et al. (2009) conducted a landmark analysis of FDA bioequivalence studies and demonstrated that the average difference in Cmax and AUC between approved generic and innovator products was approximately 3.5% far within the 80-125% acceptance limits and clinically inconsequential for most drugs. This finding effectively countered the widespread perception of substantial pharmacokinetic differences between generic and branded products [52].
In contrast, studies focusing on specific drug categories and dissolution behavior reveal greater nuance. A systematic review by Kesselheim et al. (2016) examining clinical evidence for antiepileptic drug generics found that while most studies showed equivalent outcomes, isolated cases of breakthrough seizures following generic substitution were documented, particularly for carbamazepine and valproic acid. These observations, while not establishing pharmacokinetic non-equivalence per se, highlight the clinical context within which dissolution similarity data must be interpreted [53].

## 6. Dissolution Profile Comparison Methods

6.1 Model-Dependent Methods

Mathematical modeling of dissolution data provides mechanistic insight into drug release kinetics and complements model-independent profile comparison. Several pharmacokinetic models are commonly employed:

Table 4. Dissolution Kinetic Models: Equations, Mechanisms, and Applications

| Model | Equation | Rate-Limiting Mechanism | Application | Interpretation |
|---|---|---|---|---|
| Zero-Order | $Qt = Q0 + K0t$ | Constant release independent of concentration | Controlled-release, osmotic systems | Linear cumulative release vs time |
| First-Order | $\ln Qt = \ln Q0 + K1t$ | Concentration-dependent release | Immediate-release of water-soluble drugs | Log of cumulative remaining drug vs time is linear |
| Higuchi | $Qt = KH \sqrt{t}$ | Diffusion from matrix | Matrix tablets, patches | Cumulative drug release proportional |

| | | | | |
|---|---|---|---|---|
| | | | | to square root of time |
| Korsmeyer-Peppas | $M_t/M_\infty = Kt^n$ | Diffusion ($n \leq 0.45$) or anomalous transport | Polymer-based controlled release | $n<0.45$: Fickian; $0.45<n<0.89$: anomalous; $n>0.89$: Case II |

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