



INFLUENCE OF API CRYSTAL HABIT ON THE IN VITRO-IN VIVO PERFORMANCE AND BIOEQUIVALENCE OF CELECOXIB CAPSULES

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ABSTRACT

Celecoxib is a Biopharmaceutics Classification System (BCS) Class II drug whose oral absorption is predominantly governed by dissolution and solubilization processes. Consequently, active pharmaceutical ingredient (API) physical attributes may significantly influence pharmaceutical performance and bioavailability. The present investigation evaluated the impact of API crystal habit on the manufacturability, dissolution behavior, stability, and bioequivalence performance of celecoxib capsules. Comparative characterization was performed using microscopic examination, scanning electron microscopy (SEM), particle size distribution analysis, powder flow assessment, dissolution testing in OGD-recommended and multimedia conditions, biorelevant dissolution studies in FaSSIF and FeSSIF media, accelerated stability studies, and fasting-state bioequivalence evaluation. Microscopic and SEM observations revealed distinct differences in crystal habit between the reference listed drug (RLD) API and the test formulation API. The RLD predominantly exhibited rounded or pin-milled particles, whereas the test API consisted primarily of plate-shaped crystals with a greater tendency toward aggregation. Despite these morphological differences, particle size distributions were broadly comparable. The test formulation demonstrated dissolution similarity to the RLD across all evaluated media, including OGD-recommended dissolution conditions, multimedia dissolution testing, and biorelevant FaSSIF and FeSSIF media. Accelerated stability studies conducted at 40°C/75% RH for six months confirmed acceptable assay, dissolution, moisture content, and impurity profiles throughout storage. However, fasting-state bioequivalence evaluation demonstrated supra-bioavailability of the test formulation relative to the RLD. The findings indicate that crystal habit-related API attributes may influence in vivo performance despite comparable dissolution behavior and stability characteristics. The study highlights the limitations of conventional dissolution methodologies in predicting bioequivalence outcomes for celecoxib and emphasizes the importance of comprehensive API morphology assessment during supplier qualification, formulation development, and bioequivalence risk evaluation.

KEYWORDS: Celecoxib, Bioequivalence, API Source, Dissolution, BCS Class II, Physical Characteristics, FaSSIF, FeSSIF, Stability, Powder Flow.

1. INTRODUCTION

Celecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor belonging to the non-steroidal anti-inflammatory drug (NSAID) class and is widely prescribed for the treatment of chronic and acute inflammatory conditions, including osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute pain, and primary dysmenorrhea.^[1,2] The clinical introduction of Celecoxib represented a significant therapeutic

advancement, as selective COX-2 inhibition provides potent anti-inflammatory and analgesic efficacy while substantially reducing the gastrointestinal adverse effects associated with non-selective cyclooxygenase-1 (COX-1) inhibition.^[3,4]

From a physicochemical standpoint, Celecoxib is a highly lipophilic diaryl pyrazole compound characterized by extremely low aqueous solubility across the

physiological pH range.^[5] Owing to this intrinsic solubility limitation and its high intestinal permeability, Celecoxib is classified as a Biopharmaceutics Classification System (BCS) Class II drug.^[6,7] For BCS Class II compounds, oral absorption is predominantly dissolution-rate limited rather than permeability-limited, making *in vivo* drug exposure highly sensitive to formulation attributes and intrinsic active pharmaceutical ingredient (API) properties.^[8,9]

The development of generic formulations of poorly soluble drugs remains challenging because subtle differences in active pharmaceutical ingredient (API) properties may influence product performance. Traditionally, particle size distribution (PSD) and polymorphic form have been regarded as critical material attributes affecting dissolution behavior and bioavailability. However, increasing evidence suggests that crystal habit may also play an important role in determining pharmaceutical and biopharmaceutical performance.

Clinically, Celecoxib is predominantly marketed as hard gelatin capsules, a dosage form selected to enhance dispersion of the poorly soluble API and to facilitate dissolution through carefully optimized excipient systems and controlled particle size distribution.^[10]

Crystal habit refers to the external morphology of a crystal and is influenced by crystallization conditions, solvent systems, cooling rates, and process parameters employed during API manufacture. Even when particle size distribution and polymorphic form remain unchanged, differences in crystal habit may alter powder flow, packing behavior, wettability, aggregation tendencies, dissolution kinetics, and oral bioavailability.^[11,12]

The reference listed drug (RLD), Celebrex®, has consistently demonstrated robust and reproducible *in vivo* performance across clinical studies.^[13] This reliability is widely attributed to a tightly controlled API design, encompassing a well-defined particle size range, controlled crystal habit, and optimized surface properties, in conjunction with a formulation strategy tailored to mitigate dissolution-rate limitations.^[14,15] Replicating this *in vivo* performance in generic formulations has proven difficult, and several bioequivalence studies have reported cases where *in vitro* dissolution similarity failed to translate into *in vivo* equivalence.^[16] These findings challenge the conventional assumption that comparable dissolution profiles alone are sufficient to ensure bioequivalence for BCS Class II drugs.^[17]

Recent material-science-driven investigations have further highlighted the critical role of crystal habit and anisotropic surface chemistry in governing the biopharmaceutical performance of celecoxib.^[18] Distinct crystal facets exhibit different surface energies,

molecular packing densities, and wettability characteristics, all of which directly influence drug–medium interactions during the dissolution process.^[19] Experimental comparisons between acicular (needle-shaped), plate-like, and lath-shaped celecoxib crystals have demonstrated that crystal habit modification—achieved through controlled crystallization conditions—can significantly alter dissolution kinetics and oral bioavailability.^[20]

Beyond biopharmaceutical performance, crystal habit also exerts a profound influence on downstream manufacturability, including powder flow, compressibility, interparticle friction, and surface roughness. Acicular celecoxib crystals are frequently associated with poor flowability and encapsulation challenges, whereas plate-like or lath-shaped isomorphs generally demonstrate improved manufacturability and robustness. Collectively, celecoxib represents a paradigmatic example of a BCS Class II drug for which API solid-state properties—particularly particle size, crystal habit, and surface chemistry—play a decisive role in dissolution behavior, oral bioavailability, and bioequivalence outcomes. A comprehensive understanding and rigorous control of these attributes are therefore essential for the successful development of generic celecoxib formulations capable of consistently matching the *in vivo* performance of the RLD.

2. Problem Statement and Study Rationale

Despite meeting pharmacopeial specifications and demonstrating similarity in conventional *in vitro* dissolution testing, multiple generic celecoxib formulations have exhibited bioinequivalence or suprabioavailability relative to the reference listed drug (RLD).^[3,8] These inconsistent outcomes indicate that routine quality control parameters and standard dissolution methodologies may be insufficient to capture the true critical quality attributes governing *in vivo* performance for celecoxib.^[14,15]

A key but often under-addressed contributor to this variability is API crystal habit and particle morphology. Although particle size distribution is routinely controlled during API manufacture, increasing evidence suggests that crystal habit may independently influence dissolution behavior, wettability, particle aggregation, manufacturability, and oral absorption. Celecoxib APIs obtained from different manufacturers may exhibit distinct crystal morphologies despite comparable particle size distributions and identical polymorphic form. Such differences may influence pharmaceutical performance and contribute to unexpected bioequivalence outcomes.^[4,9,16]

These attributes directly influence powder flow, blend homogeneity, capsule fill performance, wetting behavior in gastrointestinal fluids, and—most critically—the kinetics of dissolution.^[4,6,14] Plate-shaped or highly anisotropic particles may alter crystal facet exposure,

wettability, aggregation behavior and dissolution kinetics, potentially resulting in altered *in vivo* absorption and systemic exposure.^[4,7,11] Conversely, coarser, agglomerated, or poorly wettable particles may dissolve incompletely or slowly, leading to reduced systemic exposure and biofailure.^[8,16]

The central problem addressed in this study is the disconnect between *in vitro* dissolution similarity and *in vivo* bioequivalence for celecoxib capsules when APIs differing crystal morphology are employed.^[3,8,14] The rationale of the present work is to systematically elucidate the relationship between API crystal habit, and *in vivo* pharmacokinetic behavior, even under conditions where conventional dissolution profiles appear comparable.^[4,7,15] Such understanding is critical for the rational design of bioequivalent celecoxib formulations and for the development of more predictive and discriminative *in vitro* evaluation strategies.^[14–16]

3. Bioequivalence Challenges Specific to Celebrex

Achieving bioequivalence with Celebrex® poses unique and well-documented challenges, primarily due to the dissolution-limited absorption and formulation sensitivity of celecoxib.^[4,8,16] Unlike highly soluble compounds, celecoxib exhibits non-linear and formulation-dependent absorption, wherein relatively small variations in API or formulation characteristics can result in disproportionately large changes in systemic exposure, including C_{max} and AUC.^[7,11,12]

3.1 Dissolution-Limited Absorption

For BCS Class II drugs such as celecoxib, dissolution is the rate-limiting step in oral absorption.^[1,12,16] Standard compendial dissolution tests are often optimized for quality control rather than biorelevance and may lack sufficient discriminatory power to detect subtle yet clinically meaningful differences in early-stage dissolution, particle wetting, and deaggregation behaviour.^[14,15] As a result, formulations that appear equivalent *in vitro* may diverge significantly *in vivo*.^[3,8]

3.2 Sensitivity to API Particle Size and Shape

Celebrex® employs a narrowly controlled API particle size range and crystal morphology that collectively promote optimal wetting and dissolution under physiological conditions.^[5,6] Generic formulations utilizing APIs with finer particles or acicular crystal habits may dissolve more rapidly *in vivo*, leading to suprabioavailability.^[4,7,11] In contrast, formulations containing coarser, irregular, or poorly wettable particles may exhibit delayed or incomplete dissolution, resulting in sub-therapeutic systemic exposure.^[8,16]

3.3 Role of Wettability and Surface Energy

Wettability refers to the ability of gastrointestinal fluids or dissolution media to spread over the API surface and is commonly quantified by contact angle (θ) measurements.^[18] A low contact angle corresponds to good wetting and rapid dissolution, whereas a high contact angle indicates poor wetting and delayed or variable dissolution.^[14,18]

Surface energy represents the excess energy associated with unsatisfied molecular bonds at the particle surface.^[4,9] High surface energy can promote particle aggregation, poor flowability, and dissolution variability.^[6,16] In anisotropic crystals—particularly needle-shaped particles—surface energy is not uniformly distributed across crystal facets, resulting in facet-dependent wetting behaviour.^[4,18] For BCS Class II drugs such as celecoxib, these surface phenomena directly modulate dissolution kinetics and, consequently, oral bioavailability.^[7,11,12]

4. MATERIALS AND METHODS

4.1 Materials

Active pharmaceutical ingredient (API): Celecoxib

Excipients: lactose monohydrate, PVP K29/32, sodium Lauryl sulfate, Croscarmellose sodium, and magnesium stearate.

COMPOSITION

S. No	Material name	Brand name	Purpose	Specifications	Manufacturer	Qty/Unit (mg)			
						400mg	200mg	100mg	50mg
Intra Granular portion									
1	Celecoxib	Not applicable	Active	-	-	400.00	200.00	100.00	50.00
2	Lactose monohydrate	Pharmatose 200M	Diluent	USP-NF	DFE Pharma	101.90	50.95	25.48	12.74
3	Croscarmellose sodium	Ac-Di-Sol® SD-711	Disintegrant	USP-NF	FMC Biopolymer	8.00	4.00	2.00	1.00
4	Povidone K29/32	Plasdone K-29/32	Binder	USP-NF	Ashland	8.40	4.20	2.10	1.05
5	Sodium lauryl sulphate	Kolliphor SLS fine	Solubilizer	USP-NF	BASF	16.20	8.10	4.05	2.03
6	Purified water	Not applicable	Granulation liquid	USP	Not applicable	Qs	Qs	Qs	Qs
Extra granular portion									
7	Magnesium stearate	Ligamed MF-2V	Lubricant	USP-NF	Peter Greven	5.50	2.75	1.38	0.69
Total weight of net content(mg)						540.0	270.0	135.0	67.5
8	Empty hard gelatin capsules of Size '0'		NA	IH	ACG	96.00	-	-	-
9	Empty hard gelatin capsules of Size '2'		NA	IH	ACG	-	63.00	-	-
10	Empty hard gelatin capsules of Size '4'		NA	IH	ACG	-	-	39.00	39.00
Total weight of net content(mg)						636.0	333.0	174.0	106.5

4.2 Manufacturing Process

The formulation was manufactured using a wet granulation process consisting of:

Sifting → High Shear Granulation → Fluid Bed Drying → Blending → Lubrication → Capsule Filling

		Sifting		
		↓		
High shear mixer granulator	→	Granulation		
		↓		
Fluid bed dryer	→	Drying		
		↓		
Conta blender	→	Blending		
		↓		
Conta blender	→	Lubrication	→	IPQA sampling for analysis as per in-process specification
Capsule filling machine	→	Capsule filling	→	IPQA sampling for analysis as per finished product specification
		↓		
Packing and Induction sealing Machine	→	Packing and Sealing	→	Packing will be done based on the requirement

4.3 Particle Size and Morphological Evaluation

Particle size distribution was evaluated using laser diffraction techniques. Microscopic examination was performed to compare particle appearance among the API sources.

4.4 Dissolution Studies

The following dissolution methods were employed:

OGD Dissolution Medium

- 0.04 M Tribasic Sodium Phosphate Buffer (pH 12), 1% SLS, USP Apparatus II, 75 rpm, 1000 mL

Multimedia Dissolution

- 0.1 N HCl + 1% SLS
- pH 4.5 Acetate Buffer + 1% SLS
- pH 6.8 Phosphate Buffer + 1% SLS

Biorelevant Dissolution

- FaSSIF
- FeSSIF

4.5 Stability Studies

Accelerated stability studies were performed at: 40°C ± 2°C / 75% RH ± 5% RH-6 months

4.6 Bioequivalence Study

A randomized fasting-state crossover study was performed comparing the test formulation with the RLD. Primary pharmacokinetic parameters:

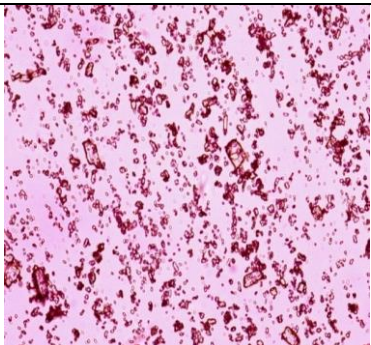
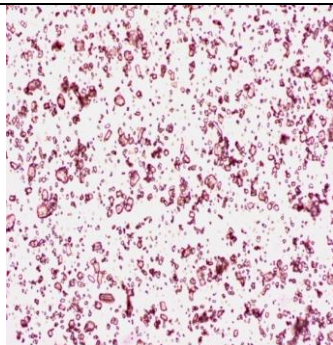
- C_{max}
- AUC_{0-t}
- AUC_{0-inf}

4.7 Statistical Analysis

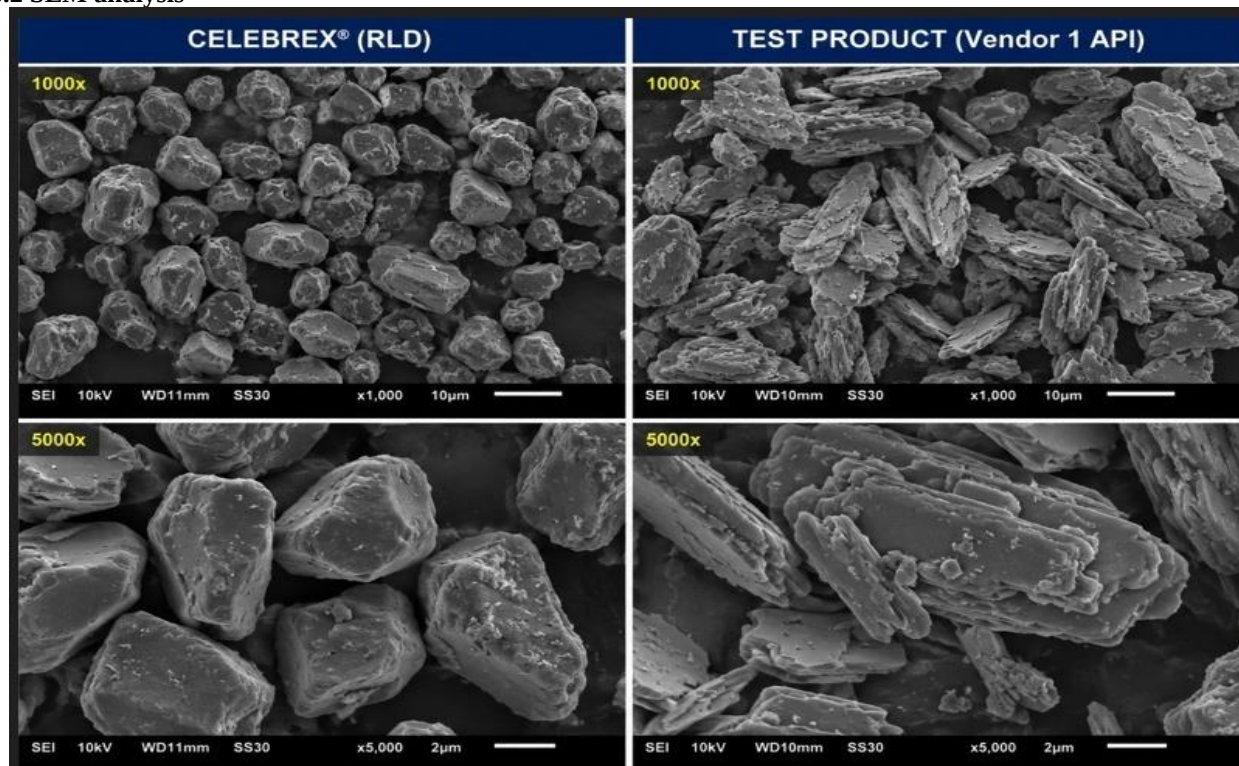
Pharmacokinetic parameters (C_{max}, AUC_{0-t}, and AUC_{0-inf}) were log-transformed prior to statistical evaluation. Bioequivalence assessment was performed using analysis of variance (ANOVA) appropriate for a two-treatment, two-period crossover design. Geometric mean ratios and corresponding 90% confidence intervals were calculated. Bioequivalence was concluded when confidence intervals were within the regulatory acceptance range of 80.00–125.00%.

5. RESULTS

5.1 PSD Comparison

Parameter		RLD	Test
PSD	d(50)	3-4 microns	4-6 microns
	d(90)	7-8 microns	8-9 microns
Microscopic images			
Shape		Predominantly Round/Pin Milled shape, occasionally needles	Plate shaped with aggregates

5.2 SEM analysis



Attribute	RLD	Test
Morphology	Rounded/pin-milled particles	Plate-shaped particles
Aspect Ratio	Lower	Higher
Aggregation Tendency	Observed lower	Observed higher
Bioequivalence Outcome	Reference	Supra-bioavailability

OBSERVATION

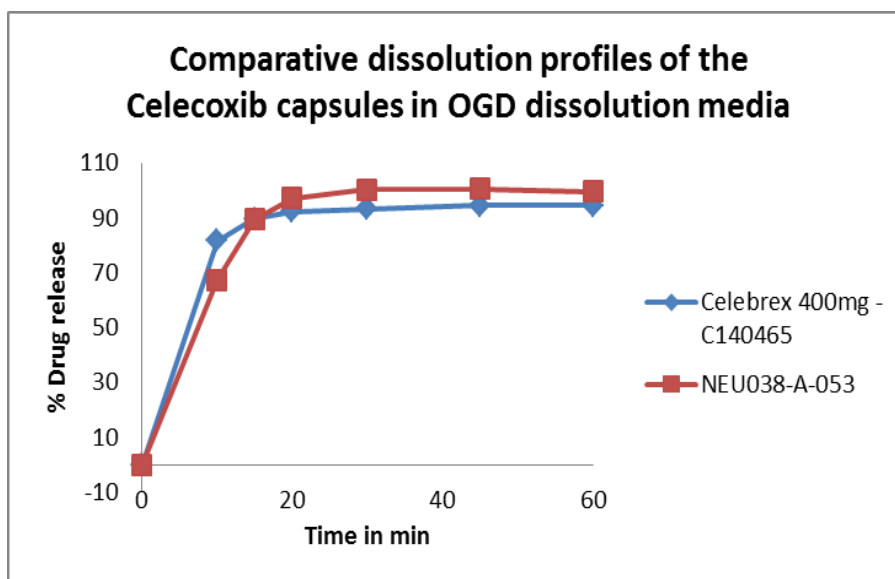
Microscopic and SEM evaluations demonstrated clear differences in particle morphology between the evaluated API sources. The reference API predominantly exhibited rounded or pin-milled particles with relatively uniform morphology, whereas Test product API consisted primarily of plate-shaped crystals with a greater tendency

toward particle stacking and aggregation. Although particle size distributions were broadly comparable, substantial differences in crystal habit were observed. These findings suggest that crystal morphology rather than particle size distribution represented the primary distinguishing characteristic among the evaluated API sources.

5.3 OGD dissolution media

OGD media	Dissolution	Batch no.	RLD-Celebrex capsules 400mg C140465		Test product -Celecoxib capsules 400mg NEU038-A-053	
			% Release	%RSD	% Release	%RSD
		Time in min				
0.04M tri basic sodium phosphate (pH 12) with 1% SLS, 75rpm, paddle, 1000mL		10	81.7	6.7	67.4	11.4
		15	89.5	4.2	89.3	6.1
		20	92.3	4.9	97.1	3.6
		30	93.1	4	100.2	3.3
		45	94.4	2.8	100.4	1.8
		60	94.4	2.8	99.5	1.9
F2 value		--	--		Similar*	

*More than 85% of the drug is dissolved within 15 minutes, dissolution profiles may be accepted as similar based on a single time point



5.4 Multimedia Dissolution Studies

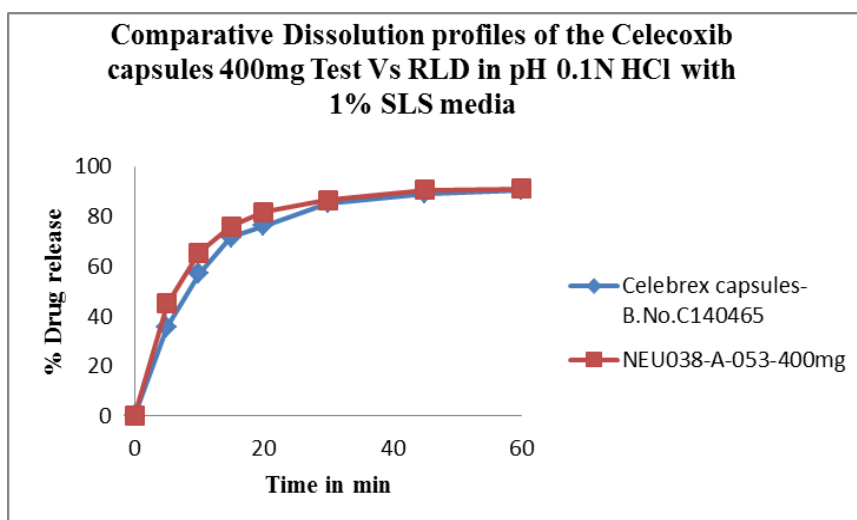
Multimedia -1: 0.1 N HCL with 1% SLS

The Comparative dissolution of Celecoxib test product

Vs Reference product in 0.1 N HCL with 1% SLS was compiled in below Tabel.

Table: Multimedia dissolution in 0.1 N HCL with 1% SLS.

Name of the product→		Celebrex capsules 400mg		Celecoxib capsules 400mg	
Dissolution media	Batch no.→	B.No.C140465		NEU038-A-053	
	Time in min	% Release	%RSD	% Release	%RSD
0.1N HCl (pH 1.2) +1.0% SLS, Volume – 1000 ml, Apparatus – USP II, 75 RPM with sinkers	5	35.7	24.1	45.0	22.5
	10	57.0	18.9	65.4	12.2
	15	71.6	8.5	76.1	6.3
	20	76.2	11.1	81.7	5.9
	30	85.4	6.6	86.6	5.4
	45	89.1	3.6	90.5	3.7
	60	90.5	3.4	91.0	3.2
F2 value				59	

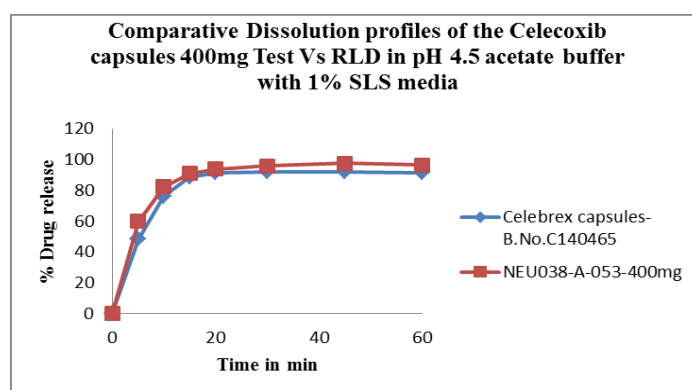


Multi media -2: pH 4.5 acetate buffer with 1% SLS
below Table contains comparative dissolution of Celecoxib test product Vs Reference product in pH 4.5 acetate buffer with 1% SLS.

Multimedia dissolution in 4.5 acetate buffer with 1% SLS.

Name of the product→		Celebrex capsules 400mg		Celecoxib capsules 400mg	
Dissolution media	Batch no.	Celebrex capsules B.No.C140465		NEU038-A-053	
	Time in min	% Release	%RSD	% Release	%RSD
PH 4.5 Acetate buffer+1.0% SLS, Volume – 1000 ml, Apparatus – USP II, 75 RPM with sinkers	5	48.4	15.6	59.8	8.5
	10	76.1	6.3	82.2	3
	15	88.7	3.1	90.9	2.2
	20	91.6	3.2	93.9	3.5
	30	92.0	3.2	95.7	3.4
	45	92.0	2.8	97.6	2.9
	60	91.6	2.7	96.5	1.6
F2 value				NA	

*F2 is not considered because more than 85% release found in 15mins



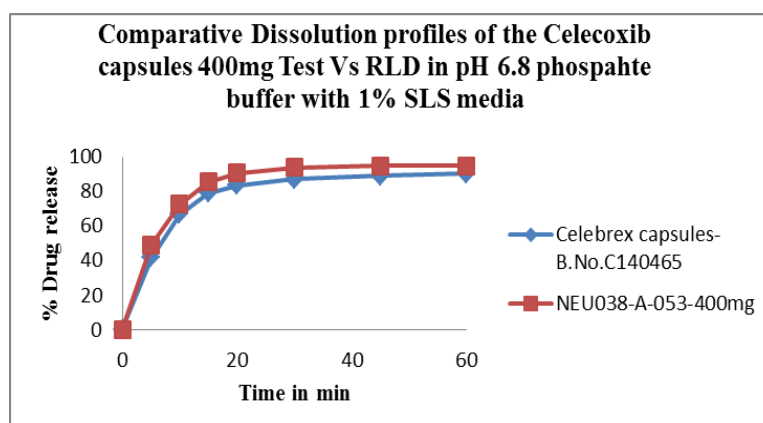
Multi media -3: pH 6.8 phosphate buffer with 1% SLS.

Vs Reference product in pH 6.8 acetate buffer with 1% SLS were captured in below Table.

The Comparative dissolution of Celecoxib test product

Table: Multimedia dissolution in 6.8 phosphate buffer with 1% SLS.

Name of the product→		Celebrex capsules 400mg		Celecoxib capsules 400mg	
Dissolution media	Batch no.	Celebrex capsules B.No.C140465		NEU038-A-053	
	Time in min	% Release	%RSD	% Release	%RSD
PH 6.8 Phosphate buffer+1.0% SLS, Volume – 1000 ml, Apparatus – USP II, 75 RPM with sinkers	5	41.8	22.7	48.9	22.3
	10	66.7	10	72.7	17.1
	15	78.9	7.1	85.5	6.1
	20	83.4	4.6	90.5	2.1
	30	87.0	2.7	93.7	2.2
	45	88.9	2.3	94.8	2.1
	60	90.3	2.2	94.8	1.7
F2 value				58	



5.5 Biorelevant Dissolution Studies Dissolution in FaSSIF Media

Batch no.	Celebrex capsules B.No. N99016		Celecoxib capsules 400mg	
Time in min	% Release	%RSD	% Release	%RSD
3	1.4	84.2	1.1	83.2
6	1.3	80.0	1.2	79.2
9	1.5	60.5	0.9	97.9
15	1.5	66.2	1.1	93.5
30	1.1	67.8	1.3	76.5
45	1.1	78.6	1.1	86.6
60	1.7	66.6	1.4	78.5

Dissolution in FeSSIF Media

Batch no.	Celebrex capsules B.No. N99016		Celecoxib capsules 400mg	
Time in min	% Release	%RSD	% Release	%RSD
3	6.2	50.0	7.1	43.4
6	9.4	35.8	10.5	37.2
9	12.5	29.4	12.6	29.6
15	13.0	29.9	15.5	33.9
30	13.8	23.7	13.8	30.0
45	13.8	31.9	14.5	33.2
60	14.0	29.0	14.9	31.8

OBSERVATION

Across all dissolution conditions evaluated, including OGD-recommended media, multimedia dissolution

testing, and biorelevant FaSSIF and FeSSIF media, the test formulation demonstrated dissolution behavior comparable to that of the RLD.

5.6 Stability data

Name of product		Celecoxib Capsules 400mg						
Pack details		HDPE bottle 120cc (Shriji polymers)/38mm (Shriji polymers), 60's count						
Condition				RT	40°C/75%RH			
		Specifications		Initial	1M	3M	6M	
Description		White to off-white powder filled hard gelatine capsules of white opaque cap and body		Complies	Complies	Complies	Complies	
Assay (%)		95.0-105.0%		100.4	98.1	98.0	98.0	
Dissolution	Tier1: 0.04M tri basic sodium phosphate (pH 12) with 1% SLS, 1000mL, 75 rpm, USP II	Time point 45min	NLT 75 (Q) in 45min	Min: 98.0 Max: 102.0 Avg:100.0% % RSD:1.6%	Min: 99.3 Max: 100.7 Avg:100.2% %RSD:0.5%	Min: 97.4 Max: 99.0 Avg:98.5% %RSD:0.7%	Min: 98.4 Max: 101.0 Avg:98.5% %RSD:0.8%	
Water content (%w/w)		NMT 4.0%		1.40	1.30	1.60	1.80	
Related substances				%Impurity	%Impurity	%Impurity	%Impurity	
Related compound A		NMT 0.2%		0.00	0.02	0.00	0.00	
Related compound B		NMT 0.2%		0.00	0.01	0.00	0.00	
Any individual impurity		NMT 0.2%		0.00	0.00	0.00	0.00	
Total % of impurities		NMT 1.0%		0.00	0.02	0.077	0.097	

OBSERVATION

The formulation remained physically and chemically stable throughout six months of accelerated storage at 40°C/75% RH. No significant changes were observed in

assay, dissolution performance, moisture content, or impurity levels. Therefore, formulation instability is unlikely to have contributed to the observed differences

in pharmacokinetic performance between the test formulation and the RLD.

5.7 Bioequivalence Study Results (Test vs. RLD)

PK Data Summary (n=18 per treatment)

Parameter	Test	Reference (RLD)
C _{max} (ng/mL)	1612.73	1241.89
AUC _{0-t} (hr·ng/mL)	15904.28	13865.09
AUC _{0-inf} (hr·ng/mL)	16426.54	14499.24
T _{max} (hr)	3.0	2.67

BE Statistics

PK Parameter	T/R Ratio (%)	90% CI (%)	BE Range	Outcome
C _{max}	132.42	111.35–157.47	80–125%	Fail
AUC _{0-t}	119.73	109.07–131.43	80–125%	Fail
AUC _{0-inf}	119.48	108.50–131.57	80–125%	Fail

6. DISCUSSION

Celecoxib is a poorly water-soluble BCS Class II drug for which oral absorption is predominantly governed by dissolution and solubilization processes. Consequently, API physical characteristics may exert a substantial influence on pharmaceutical performance and systemic exposure. While particle size distribution has traditionally been regarded as the primary material attribute influencing dissolution and bioavailability, increasing evidence suggests that crystal habit may independently affect wettability, aggregation behavior, crystal facet exposure, and drug absorption.

In the present study, particle size distributions of the evaluated APIs were broadly comparable. However, microscopic and SEM evaluations revealed substantial differences in crystal habit. The RLD API predominantly exhibited rounded or pin-milled particles with relatively isotropic morphology, whereas the API used in the test formulation consisted mainly of plate-shaped crystals with higher aspect ratio and greater aggregation tendency. These morphological differences were further reflected in powder flow characteristics.

Despite these differences, the formulations demonstrated comparable dissolution performance across OGD-recommended media, multimedia dissolution conditions, and biorelevant FaSSIF and FeSSIF media. Particularly noteworthy was the excellent similarity observed in FaSSIF and FeSSIF, which are generally considered more physiologically relevant dissolution systems. These findings suggest that conventional dissolution methodologies, including biorelevant dissolution approaches, were unable to adequately differentiate the formulations.

Accelerated stability studies demonstrated acceptable physical and chemical stability throughout the study period. Assay, dissolution, moisture content, and impurity levels remained within predefined acceptance criteria. Therefore, neither formulation instability nor changes in product quality during storage could explain the observed pharmacokinetic differences.

The most significant finding of the study was the occurrence of supra-bioavailability despite dissolution similarity. The test formulation exhibited significantly higher C_{max}, AUC_{0-t}, and AUC_{0-inf} values compared with the RLD, resulting in failure of bioequivalence acceptance criteria. Since formulation composition, manufacturing process, dissolution performance, and stability characteristics were comparable, crystal habit emerged as the most plausible differentiating factor contributing to the observed pharmacokinetic outcome.

Published investigations have demonstrated that crystal habit can influence celecoxib biopharmaceutical performance independent of particle size distribution and polymorphic form. Variations in crystal morphology may alter crystal facet exposure, surface energy distribution, wettability, aggregation behavior, and intrinsic dissolution characteristics. The plate-shaped crystals observed in the test API may have promoted more favorable particle-fluid interactions under physiological conditions, resulting in enhanced absorption and increased systemic exposure relative to the RLD.

Although advanced characterization techniques such as intrinsic dissolution rate measurement, contact-angle analysis, surface energy determination, and quantitative image analysis were not performed, the collective evidence suggests that crystal habit represented the primary distinguishing attribute between the evaluated APIs. The results therefore support the hypothesis that crystal habit may function as a critical material attribute capable of influencing bioequivalence outcomes for celecoxib formulations.

These findings emphasize the importance of comprehensive API characterization beyond routine particle size distribution and dissolution testing. For poorly soluble compounds such as celecoxib, crystal morphology should be considered during API supplier qualification, formulation development, and bioequivalence risk assessment to minimize the likelihood of unexpected in vivo performance differences.

7. CONCLUSIONS

The present investigation evaluated the influence of API crystal habit on the pharmaceutical performance and bioequivalence of celecoxib capsules. The developed formulation demonstrated acceptable manufacturability, dissolution similarity, and stability throughout the study period. Comparable dissolution profiles were observed in OGD-recommended media, multimedia dissolution conditions, and biorelevant FaSSIF and FeSSIF media, indicating that conventional *in vitro* testing methodologies were unable to differentiate the formulations.

Despite comparable particle size distribution, formulation composition, dissolution behavior, and stability characteristics, the test formulation exhibited supra-bioavailability during fasting-state bioequivalence evaluation. Microscopic and SEM analyses demonstrated that the API used in the test formulation possessed a predominantly plate-shaped crystal habit with greater aggregation tendency, whereas the RLD API exhibited rounded or pin-milled particles with comparatively isotropic morphology.

Crystal habit represented the most significant distinguishing attribute between the evaluated APIs and is therefore considered the most likely contributor to the observed pharmacokinetic differences. These findings demonstrate that crystal morphology may influence oral absorption independently of conventional dissolution performance and highlight the limitations of relying solely on dissolution similarity to predict bioequivalence outcomes for celecoxib formulations.

The study underscores the importance of considering crystal habit as a critical material attribute during API supplier qualification, formulation development, and risk assessment activities for generic celecoxib products and other poorly soluble drug substances. Future investigations involving advanced surface characterization and intrinsic dissolution studies may further elucidate the mechanistic relationship between crystal habit and *in vivo* performance.

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