Effect of Surface Anisotropy of Crystal Habits on Dissolution Performance

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Flow of Presentation

- Effect of solid form on solubility and dissolution
- Role of crystal habit on solubility and dissolution
- Case Study – Celecoxib
  Unmilled and Milled API, Drug Product

Effect of Solid Form on Solubility and Dissolution

Parameters	Salt	Polymorphs	Amorphous	Co-crystal
Solubility	2 - 1000 ↑	2 - 3 ↑	4 - 14 ↑	4- 20 ↑
Dissolution rate	↑	↑	↑	↑

Quality, safety and efficacy of BCS class II and IV drugs can be sensitive to their solid forms

ICH HARMONISED TRIPARTITE GUIDELINE

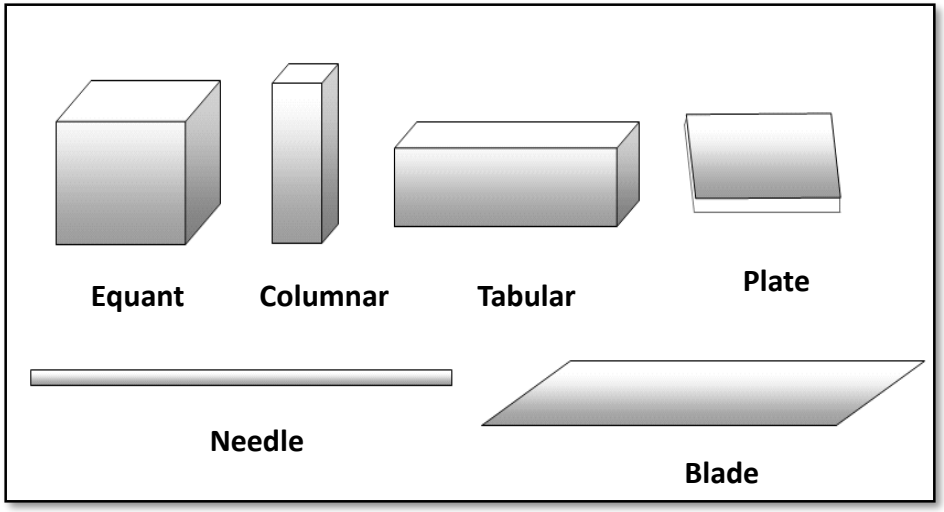
SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES

Q6A

Solid forms (Polymorph, Pseudo-polymorph and Amorphous form) should be monitored and controlled

Crystal Habit: External Appearance of Crystal

Description of crystal habits (USP)



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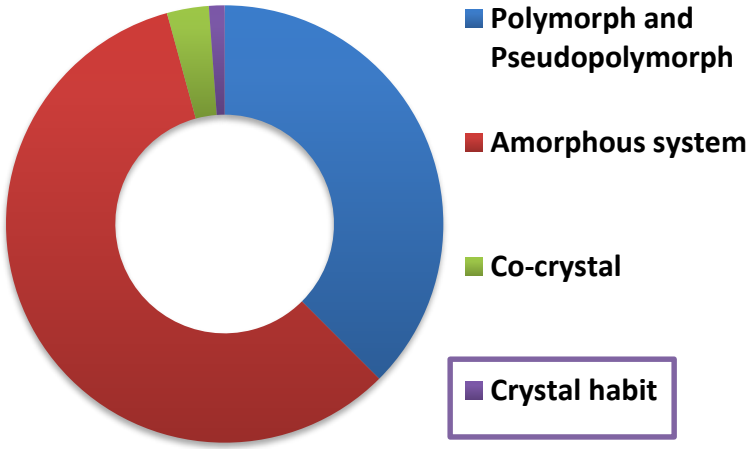
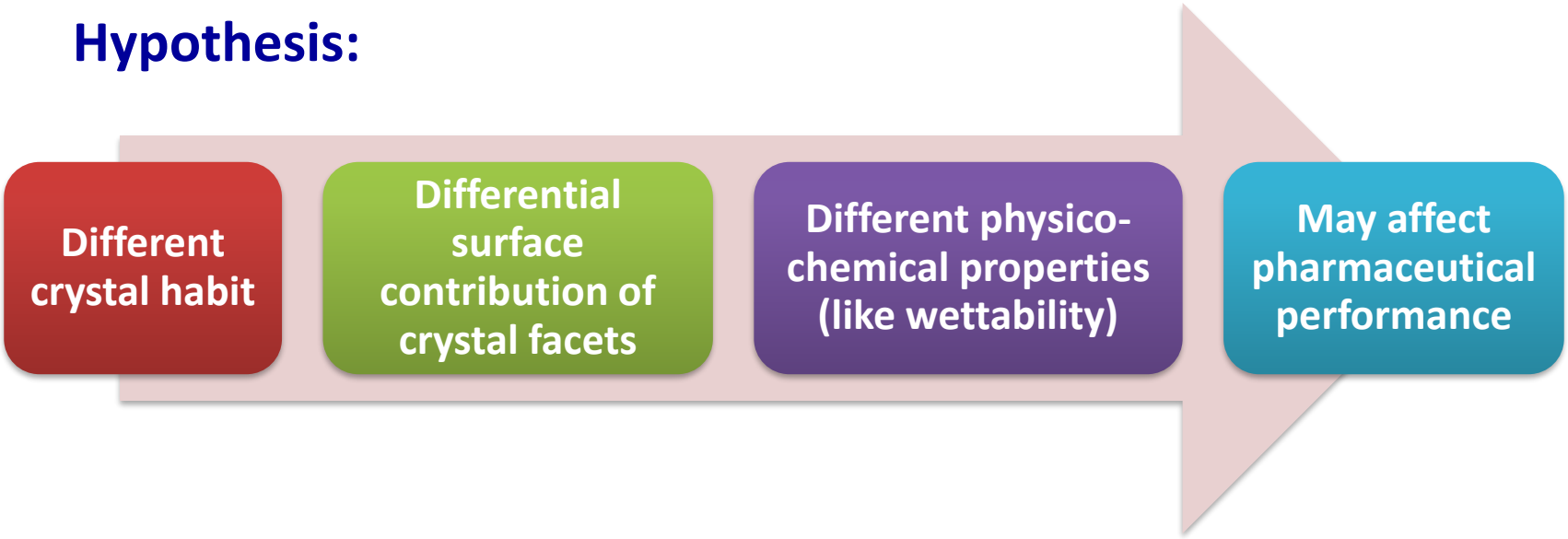


Crystal Habit

Can two different crystal habits of the same polymorph of an API show different dissolution behavior?

Hypothesis:



Crystal Habit: Literature References

2958 Vol. 30 (1982)

Chem. Pharm. Bull. 30(8)2958—2963(1982)

Crystal Habits and Dissolution Behavior of Aspirin[1)]

Atsushi Watanabe,*,[a] Yumiko Yamaoka,[a] and Kozo Takada[b]

Faculty of Pharmaceutical Sciences, Kobe-Gakuin University,[a] Arise, Ikawadani-cho, Tarumi-ku, Kobe 673, Japan and Pharmacy of Kyoto National Hospital,[b] 1-1 Mukohata-cho, Fukakusa, Fushimi-ku, Kyoto 612, Japan

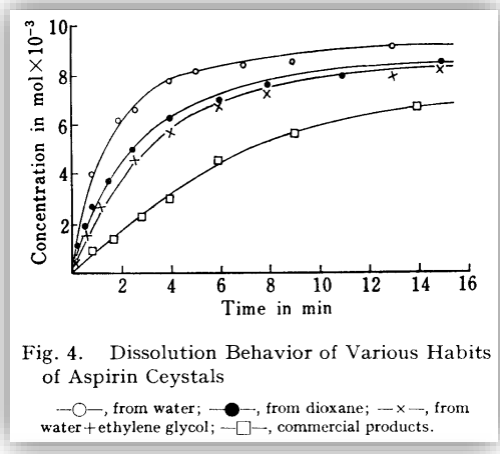


Fig. 4. Dissolution Behavior of Various Habits of Aspirin Ceystals

—○—, from water; —●—, from dioxane; —×—, from water+ethylene glycol; —□—, commercial products.

Anisotropic Surface Chemistry of Aspirin Crystals

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Hydrophilicity order for aspirin facets is:
(0 1 1) > (1 0 0) > (0 0 1)

Pharmaceutical Research, Vol. 18, No. 3, 2001

An *In Situ* Dissolution Study of Aspirin Crystal Planes (100) and (001) by Atomic Force Microscopy

Ardeshir Danesh,[1] Simon D. Connell,[1] Martyn C. Davies,[1] Clive J. Roberts,[1,3] Saul J. B. Tendler,[1] Phillip M. Williams,[1] and M. J. Wilkins[2]

Received August 14, 2000; accepted December 8, 2000

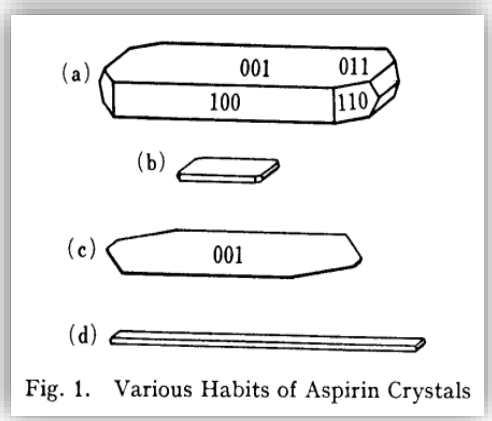
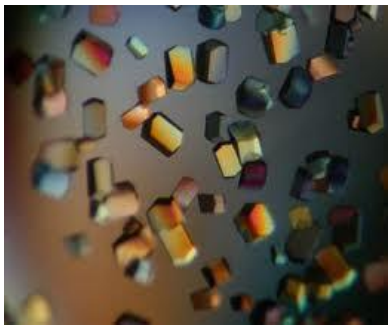
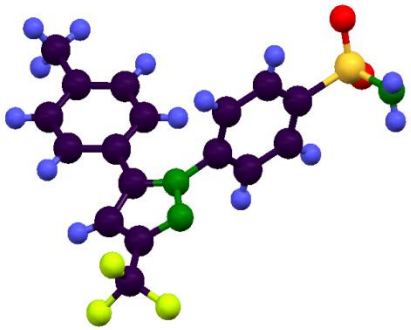


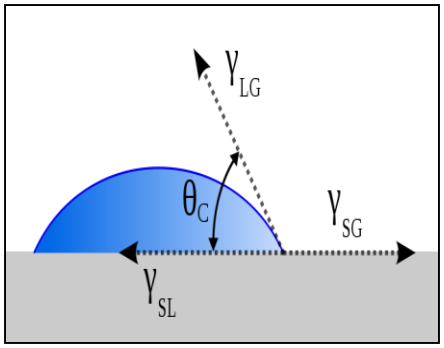
Fig. 1. Various Habits of Aspirin Crystals

It was postulated that the differences in dissolution behavior of different crystal habits of Aspirin could be due to (1) differences in dissolution velocity of different crystallographic facets and (2) their relative exposure on crystal surface

A Case study - Celecoxib



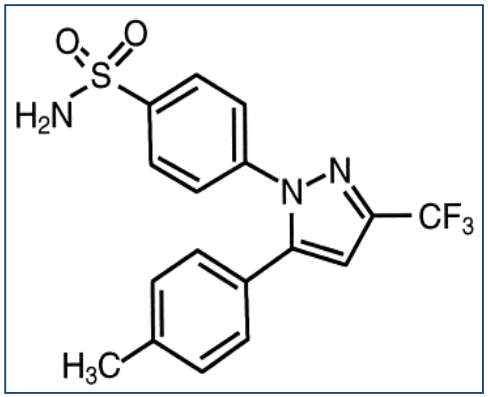




Physico-chemical properties of Celecoxib

- BCS class II drug, first COX-2 selective inhibitor (375-fold selectivity)
- Crystalline form III used in Celebrex® (Pfizer)

Properties	CEL
Description	White to off-white crystalline powder
Melting point (°C)	Form III: 159-162
pK_a	11.1 (weak acid)
Log *P*	3.5
Solubility	Practically insoluble in water (~ 3.7 µg/mL)
Dissolution Time (T_{disso})	7238.1 min
Absorbable Dose (D_{abs})	7.4 mg
Strength (mg)	100, 200 and 400



Celecoxib (CEL) has solubility and dissolution rate limited oral bioavailability

Kasim et. al., *Mol. Pharm.* **1:** 85-96 (2003).

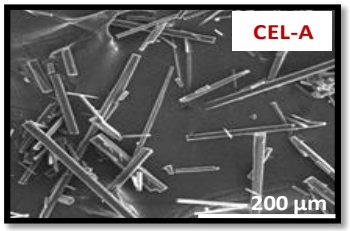
Role of crystal habits on solubility and dissolution performance

Generation and Characterization of CEL Crystal Habits

Saturated solution of CEL in Toluene → Cooled at 25 °C → Acicular crystals

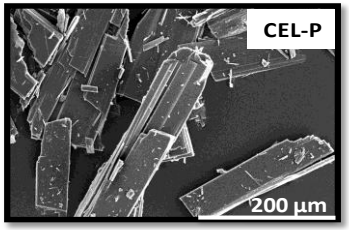
Degree of supersaturation: 190%

Aspect ratio: 12-20

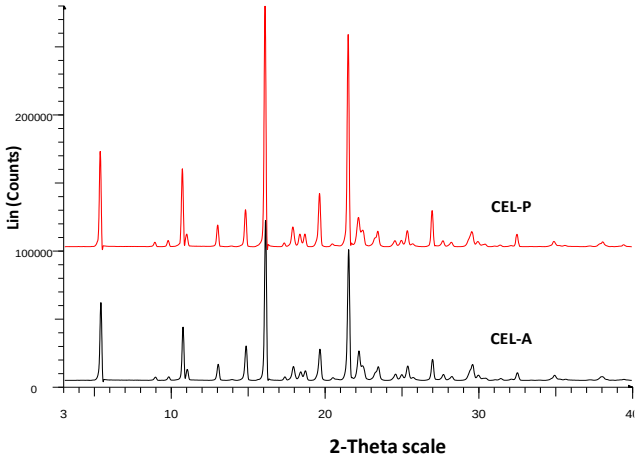


Saturated solution of CEL in Toluene → Evaporate the solvent at 60 °C → Plate shaped crystals

Degree of supersaturation: 102%



Aspect ratio: 4-8



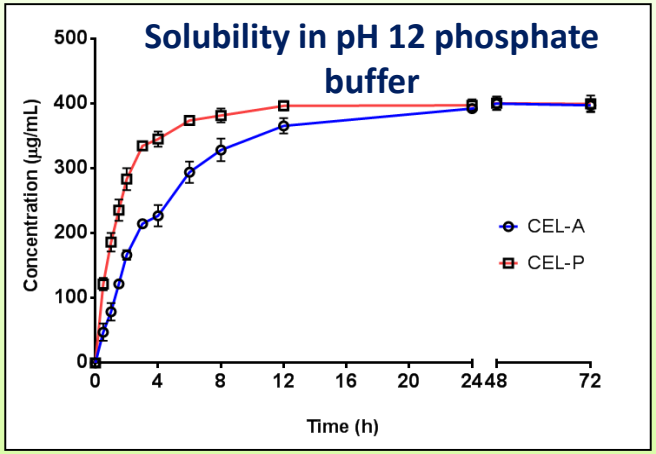
Sample	Melting point (°C) (n = 3)	Heat of fusion (J/g) (n = 3)	True density (g/mL) (n = 3)
CEL-A	162.01 ± 1.82	90.19 ± 0.59	1.521 ± 0.03
CEL-P	161.13 ± 1.13	91.03 ± 2.08	1.522 ± 0.04

DSC and PXRD analysis revealed same polymorph (Form III) for both CEL samples

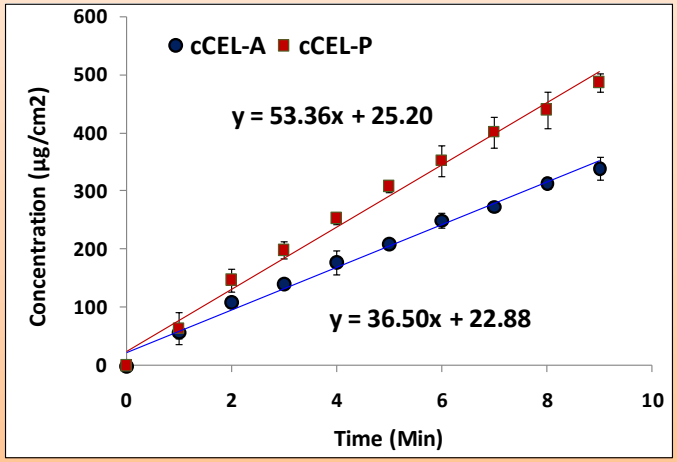
Solubility and Dissolution Behavior

Sample	D_{10} (µm)	D_{50} (µm)	D_{90} (µm)	Specific surface area (m^2/g) (n = 3)
CEL-A	158.5	200.4	251.3	0.93 ± 0.01
CEL-P	162.8	198.5	256.4	0.87 ± 0.04

Solubility Study Parameters	
Apparatus	Shaker water bath
Media	pH 12 phosphate buffer
RPM	100
Temperature	37 ± 0.5 °C



Intrinsic Dissolution Rate (IDR) pH 12 phosphate buffer



Significantly different IDR ($p < 0.05$)

CEL-P exhibited significantly faster dissolution kinetics and higher IDR in aqueous media as compared to CEL-A

Wettability and Surface Free Energy

Sessile Drop Contact Angle Technique

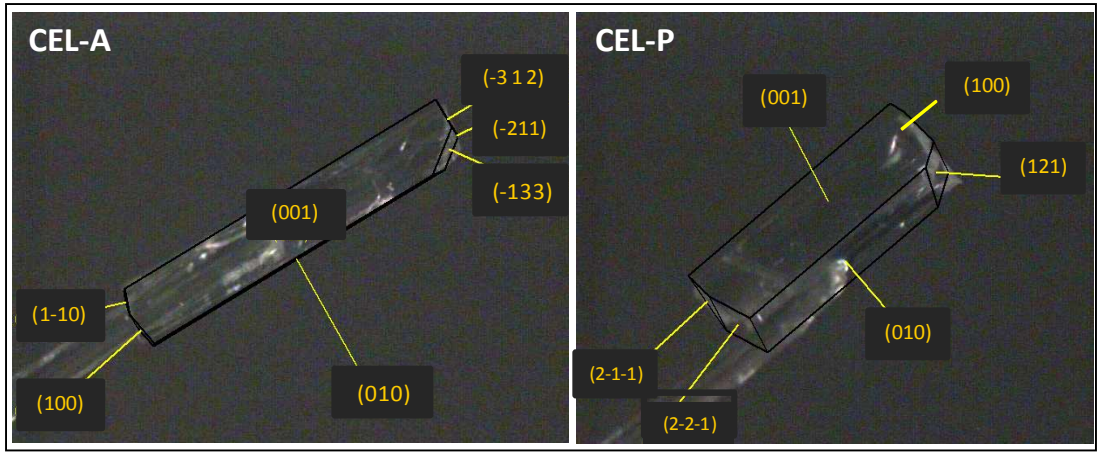
Sample	Contact Angle (°)				Surface free energy (mJ/m^2)		
	Water	pH 12 phosphate buffer	EG	DIM	Total	Dispersive	Polar
CEL-A	102.0° ± 0.7°	94.5° ± 1.2°	72.1° ± 0.8°	20.8° ± 2.0°	47.93	47.54	0.81
CEL-P	91.5° ± 1.3°	85.3° ± 1.8°	66.4° ± 2.2°	27.8° ± 0.6°	47.10	45.10	2.65

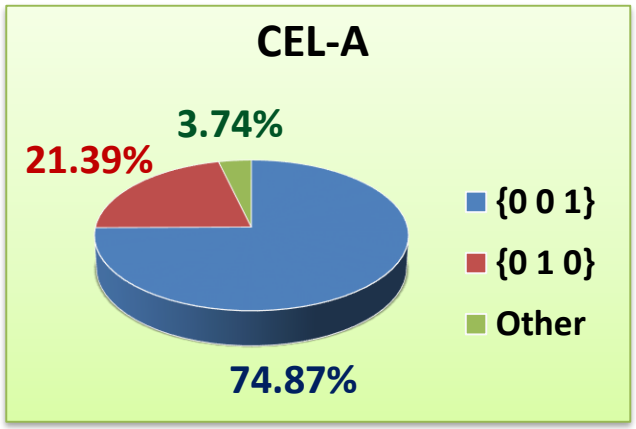
CEL-P exhibited better wettability with aqueous media and higher polar component of surface free energy. This could be due to higher exposure of hydrophilic elements on its surface

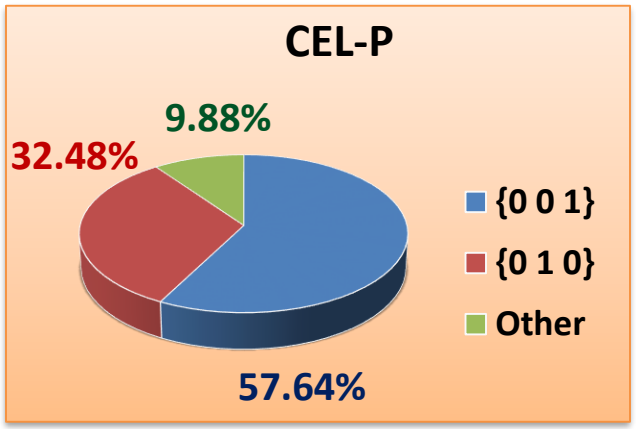
EG: Ethylene glycol, DIM: Di-iodomethane

Face Indexation Study

- The term **facet** refers to the **flat surface** of a crystal
- Chemical environment of each facet of a crystal is different

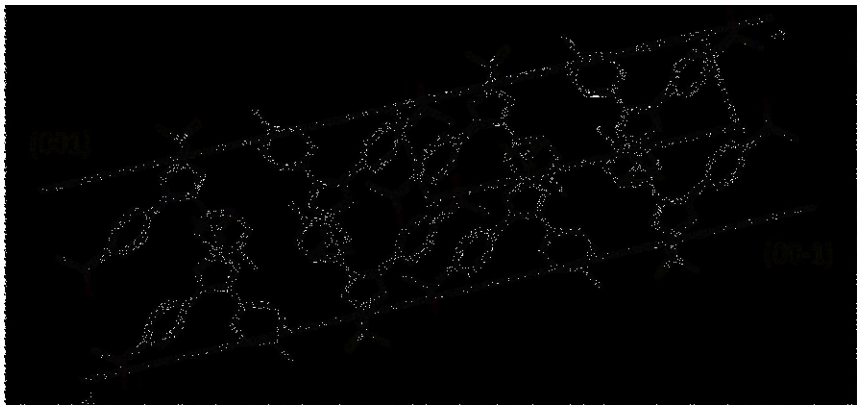


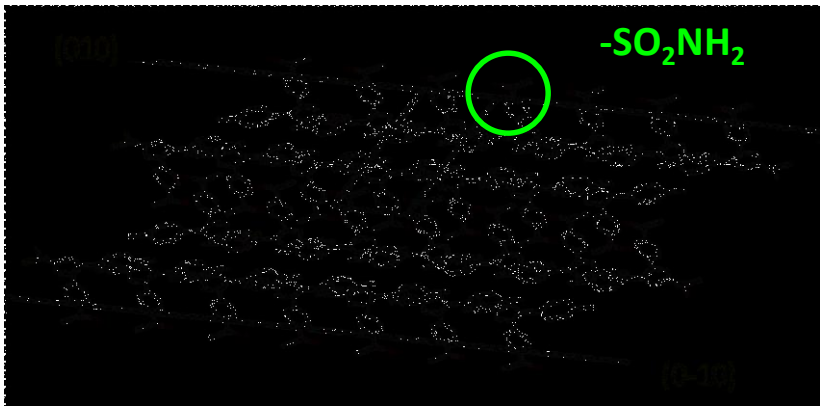




The work was carried out at University of Minnesota (USA), in collaboration with Dr Calvin Sun

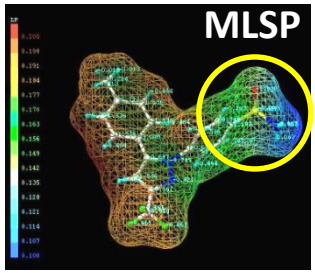
Molecular Modeling Study





Presence of methyl phenyl and –CF_3 groups made this facet more hydrophobic

Bed of sulphonamide group made this facet more hydrophilic



This made CEL-A more hydrophobic

This made CEL-P more hydrophilic

Differential dissolution performance

MLSP: Molecular lipophilic surface potential

Surface Characterization

X-Ray Photoelectron Spectroscopy

Sample	% Atomic composition				
	O 1s	N 1s	S 2p	F 1s	C 1s
CEL-A	8.48	10.51	10.70	10.12	60.17
CEL-P	9.25	13.13	11.72	10.47	55.41

Hydrophilic elements

Hydrophobic elements

CEL-P exhibited higher surface exposure of hydrophilic elements like oxygen, nitrogen and sulphur while CEL-A exhibited higher surface exposure of hydrophobic elements like carbon and fluorine

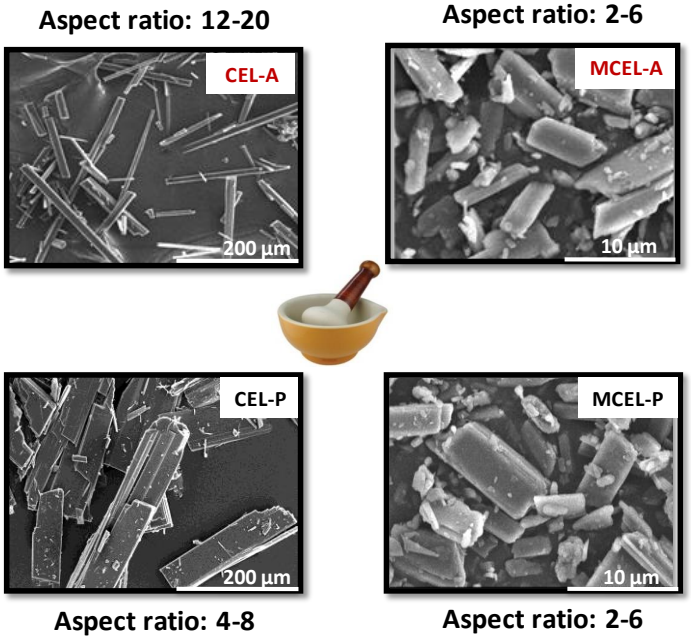
EG: Ethylene glycol, DIM: Di-iodomethane

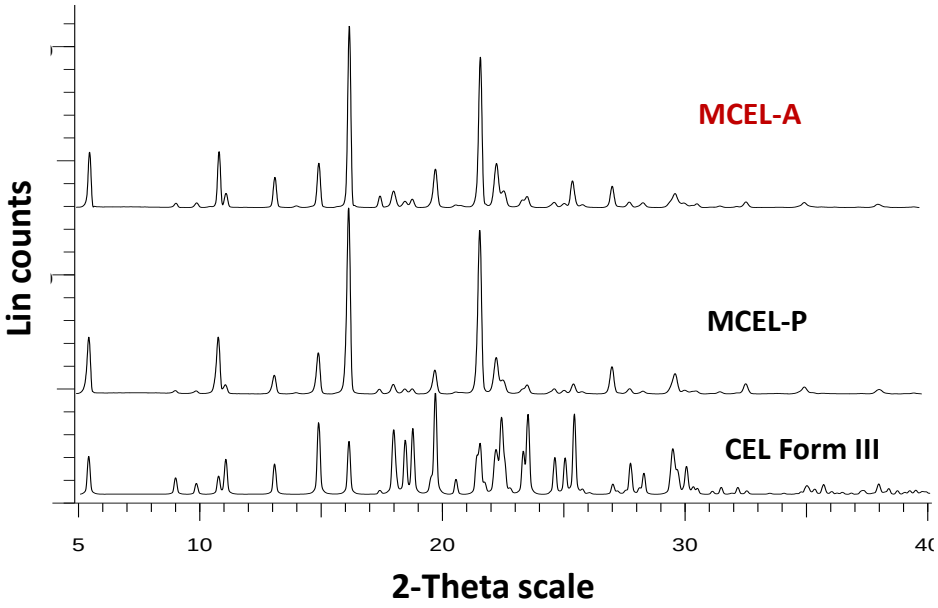
Summarizing…

Despite of having **similar polymorphic form** and **powder surface area**, **CEL-P** exhibited **significantly faster dissolution kinetics than CEL-A** in aqueous media due to **higher exposure of relatively hydrophilic facet (0 1 0) as against relatively hydrophobic facet (0 0 1)**

Solubility and dissolution performance of milled Crystal Habits

Reduction of Particle Size - Milling





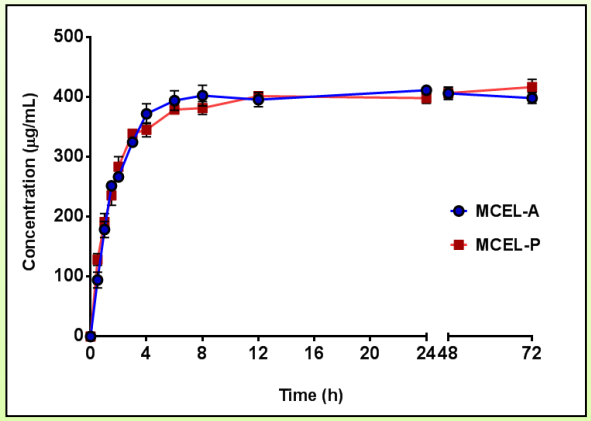
Sample	Melting point (°C) (n = 3)	Heat of fusion (J/g) (n = 3)	True density (g/mL) (n = 3)
MCEL-A	161.75 ± 1.32	90.89 ± 1.66	1.518 ± 0.02
MCEL-P	162.09 ± 1.02	90.63 ± 1.58	1.520 ± 0.03

1. There is no alteration in solid form of both CEL crystal habits even after milling
2. DSC and PXRD analysis revealed same polymorph (Form III) for both the milled CEL samples

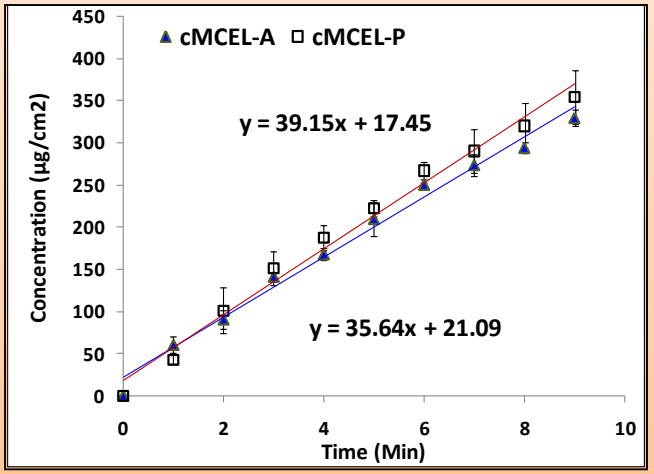
Solubility and Dissolution Behavior

Sample	D_{10} (µm)	D_{50} (µm)	D_{90} (µm)	Specific surface area (m^2/g) (n = 3)
MCEL-A	2.7	5.0	8.9	1.98 ± 0.03
MCEL-P	2.8	5.2	9.2	1.97 ± 0.02

Solubility study in pH 12 phosphate buffer



Intrinsic Dissolution Rate (IDR) pH 12 phosphate buffer



IDR ($p > 0.05$)

Milled fractions of both the crystal habits did not show significant differences in dissolution kinetics and had similar IDR

Surface Characterization

Sessile Drop Contact Angle Technique

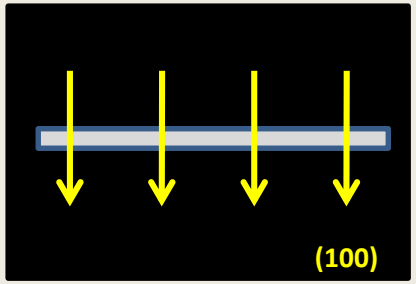
Sample	Contact Angle (°)				Surface free energy (mJ/m²)		
	Water	pH 12 phosphate buffer	EG	DIM	Total	Dispersive	Polar
CEL-A	102.0° ± 0.7°	94.5° ± 1.2°	72.1° ± 0.8°	20.8° ± 2.0°	47.93	47.54	0.81
MCEL-A	96.6° ± 0.8°	93.4° ± 1.7°	70.4° ± 1.6°	27.8° ± 1.0°	46.64	45.10	1.56
CEL-P	**91.5° ± 1.3°**	**85.3° ± 1.8°**	**66.4° ± 2.2°**	**27.8° ± 0.6°**	**47.10**	**45.10**	**2.65**
MCEL-P	101.0° ± 1.2°	97.1° ± 2.3°	74.2° ± 1.4°	18.2° ± 0.4°	49.44	48.29	1.48

MCEL-A and MCEL-P exhibited similar wetting properties with aqueous media and similar polar component, though different dispersive component of surface free energy

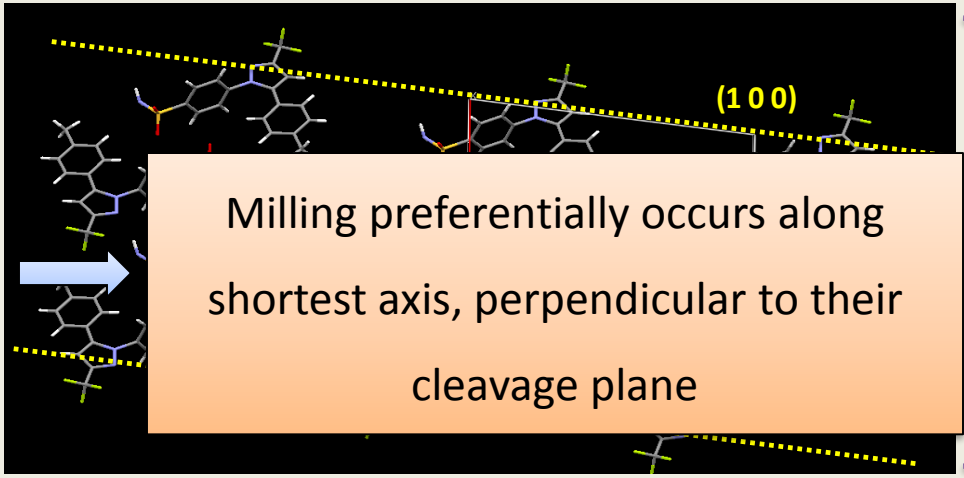
X-Ray Photoelectron Spectroscopy

Sample	% Atomic composition				
	O 1s	N 1s	S 2p	F 1s	C 1s
CEL-A	8.48	10.51	10.70	10.12	60.17
MCEL-A	9.09	10.92	8.40	10.89	60.70
CEL-P	**9.25**	**13.13**	**11.72**	**10.47**	**55.41**
MCEL-P	8.54	10.13	7.48	12.72	61.13

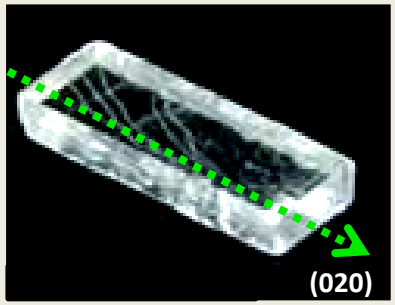
EG: Ethylene glycol, DIM: Di-iodomethane



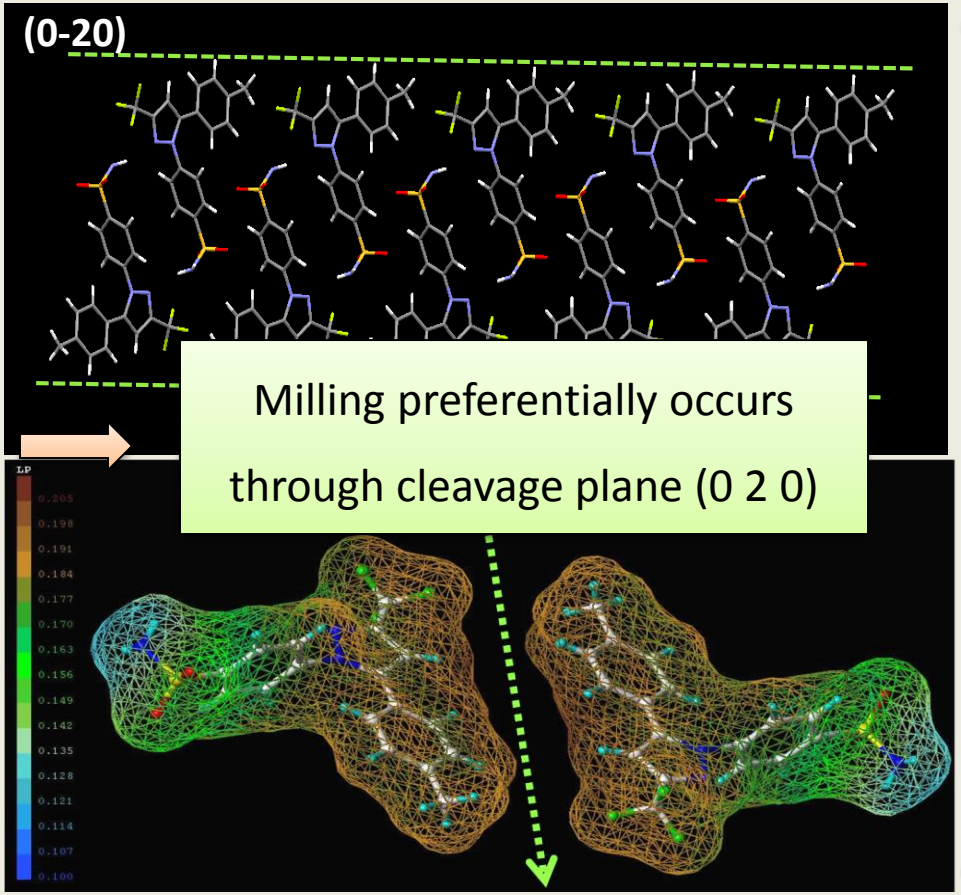
CEL-A



Milling of acicular crystals : **exposure of hydrophilic and hydrophobic moieties** remained largely unaltered



CEL-P



Milling of plate shaped crystals: **increases exposure of hydrophobic moieties** on the surface

Summarizing…

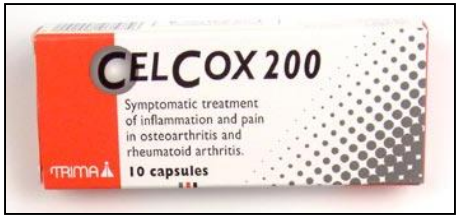
Despite of having differences in unmilled form, **milled fractions** of both the crystal habits did **not show significant difference in their dissolution profiles** in aqueous media. This is attributed to **differential cleavage behavior of CEL-A and CEL-P during milling** that modified the exposure of surface facets

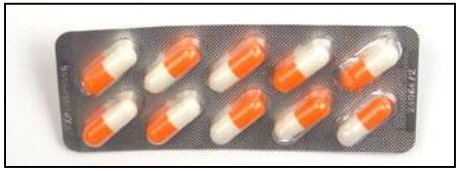
Drug product performance containing milled Crystal Habits

Celecoxib Capsules

Qualitative and Quantitative Composition

Component	Function	Quantity (mg)
Celecoxib	Active ingredient	200
Lactose monohydrate	Diluent	45
Povidone	Binder	1.5
Sodiun lauryl sulfate	Wetting agent	15
Cross carmellose	Disintegrant	10
Magnesium stearate	Lubricant	3.5

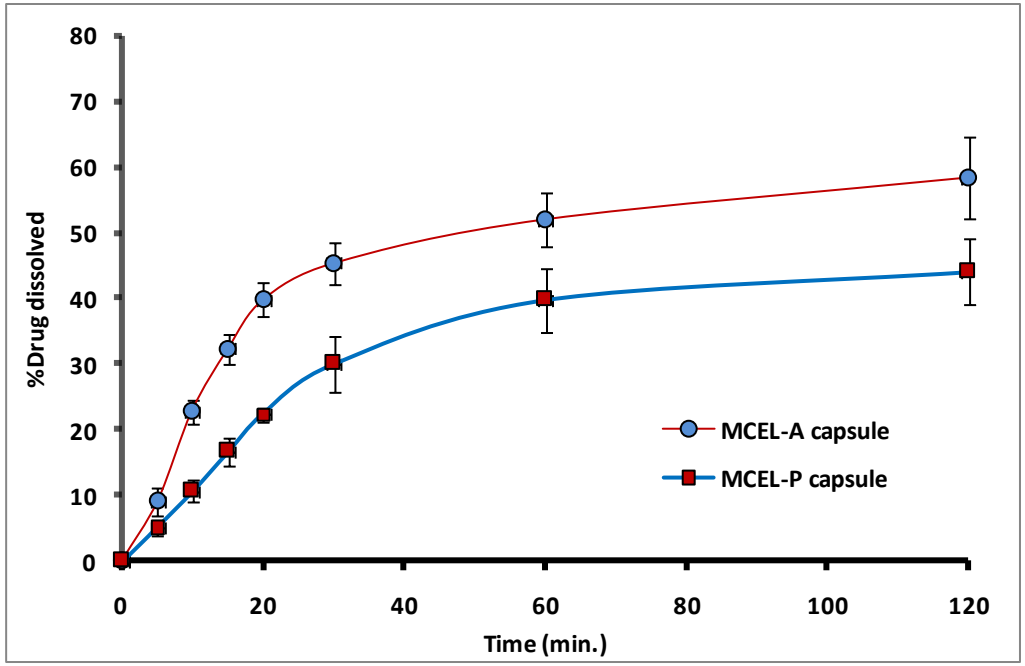




Weighing → **Blending** (15 min) → **Lubricant addition and mixing** → **Capsule filling** (Direct filling)

In Vitro Dissolution Study

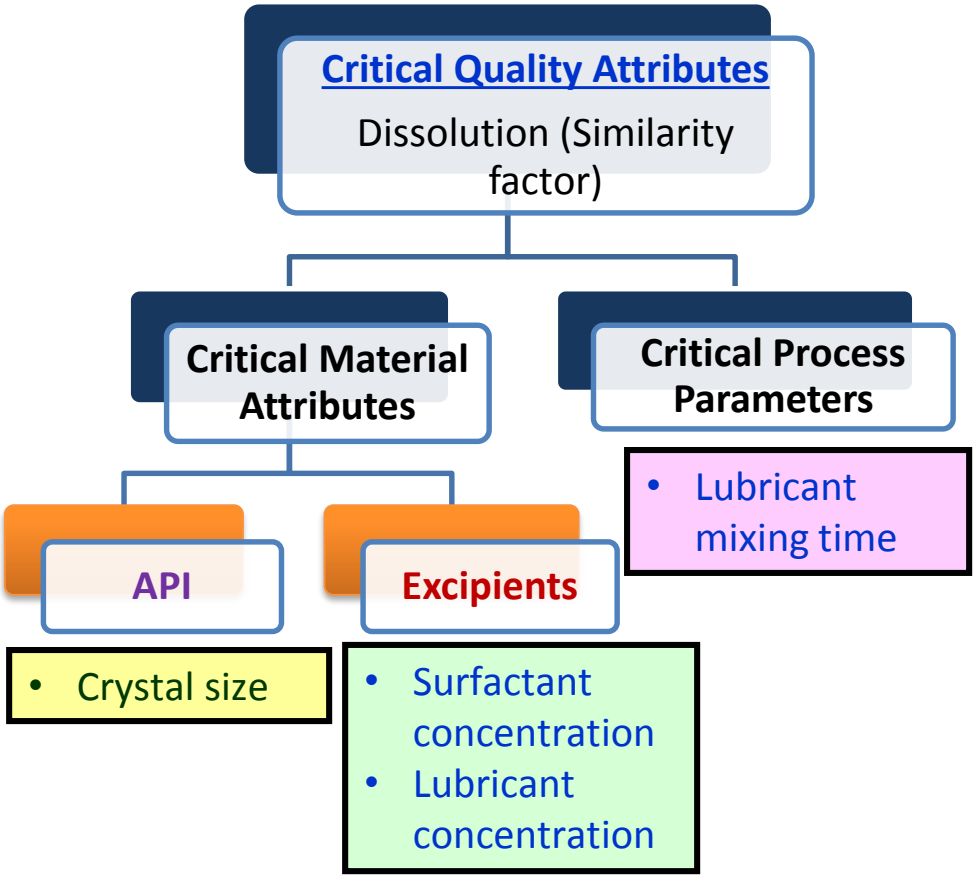
Dissolution Parameters	
Apparatus	USP II (Paddle type)
Media	pH 12 phosphate buffer
Volume	500 mL (@ 37 ± 0.5 °C)
RPM	100
Volume withdrawn	2 mL
Analytical method	HPLC



1. Significant differences were observed in dissolution profiles of CEL capsules of milled fractions of two different crystal habits
2. Surprisingly, milled fraction of CEL-P showed decreased dissolution kinetics when compared with milled CEL-A in capsule dosage form

Quality by Design - Risk Assessment

Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs)



Full factorial augmented to Face Centred CCD design
Design Expert version 9.0, Stat Ease Inc. MN, USA

Input variable	Unit	Low level	High level
Crystal size (D_{90})	µm	10	250
Surfactant concentration	%	0	5
Lubricant concentration	%	0.25	5
Lubricant mixing time	min	2	10

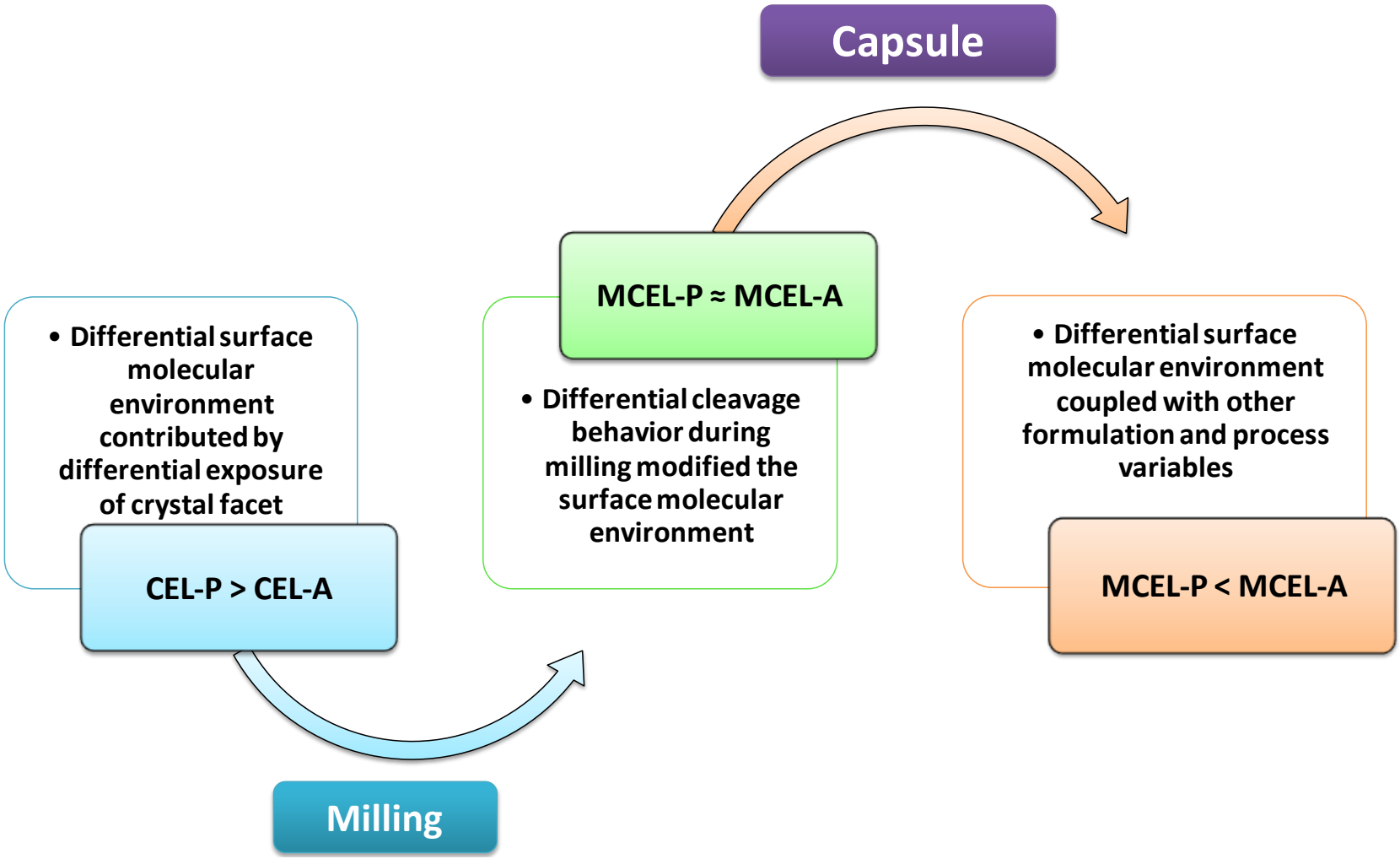
Factor Effects and Interactions

Final Equation in Terms of Coded Factors
Similarity factor = 47.03 – (1.57* A)- (3.83* B) + (0.24* C) – (5.77*D) + (0.50* AB) + (0.31* AC) + (2.26* AD) – (1.68* BC) + (0.49* BD) + (0.31* CD) – (5.39* A^2) – (1.39* B^2) + (3.11* C^2) + (1.11* D^2)

Code	Factor/Factor interactions	p-value Prob > F	Effect on similarity factor
A	**Particle size**	**0.0027**	**Negative**
B	**Surfactant concentration**	**< 0.0001**	**Negative**
C	**Lubricant concentration**	0.6171	No significant effect
D	**Lubricant mixing time**	**< 0.0001**	**Negative**
AB	**Particle size + Surfactant concentration**	0.3213	No significant effect
AC	**Particle size + Lubricant concentration**	0.5311	No significant effect
AD	**Particle size + Lubricant mixing time**	**0.0001**	**Positive**
BC	**Surfactant concentration + Lubricant concentration**	**0.0025**	**Negative**
BD	**Surfactant concentration + Lubricant mixing time**	0.3323	No significant effect
CD	**Lubricant concentration + Lubricant mixing time**	0.5323	No significant effect

1. **Particle surface interaction with excipients like surfactant and / or lubricant (because both of them act on surface of particle) can be possible and**
2. **Lubricant mixing time plays significant role in interaction between particle surface and lubricant**

Performance of Unmilled and milled Crystal Habits

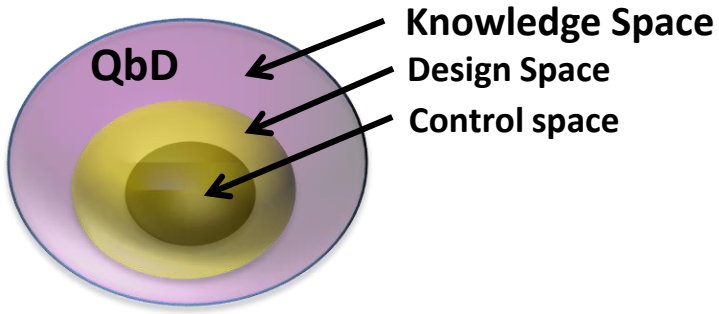


Learnings and Recommendations

- This study demonstrated contribution of crystal habits on differential surface anisotropy leading to differences in pharmaceutical behavior

- **Crystal habit** can be an important material property and shall **encourage the pharmaceutical industry to go beyond** conventional material properties like **polymorphism** and **understand contribution of crystal habits** on product performance of BCS class II drugs

- This structure property relationship is a step forward towards expanding the **knowledge space** and thus helps in rationalizing development of a **'Control Strategy'** for solid oral dosage forms to ensure the product quality



Acknowledgement

Dr Sameer Modi
Graduated in 2016

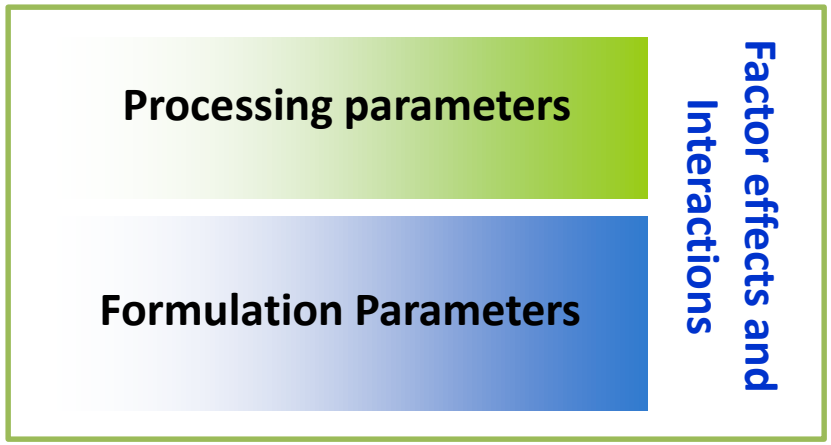
Thank You…

akbansal@niper.ac.in

Conclusions So Far…

- Milled fraction of CEL-P showed decreased dissolution performance when compared with milled fraction of CEL-A in capsule dosage form, though their powder dissolution profile and IDR did not show significant differences
- This counterintuitive dissolution behavior could be attributed to differential dispersive (nonpolar) component of surface free energy of milled fractions of different crystal habits along with
  1. Particle surface interaction with excipients like surfactant and / or lubricant (because both of them act on surface of particle) and
  2. Variable processing parameters like lubricant mixing time

Quality by Design (QbD)



Quality Target Product Profile (QTPP)

↓

Identify Critical Quality Attributes (CQAs)

↓

Perform Risk Assessment

↓

Establish Design Space

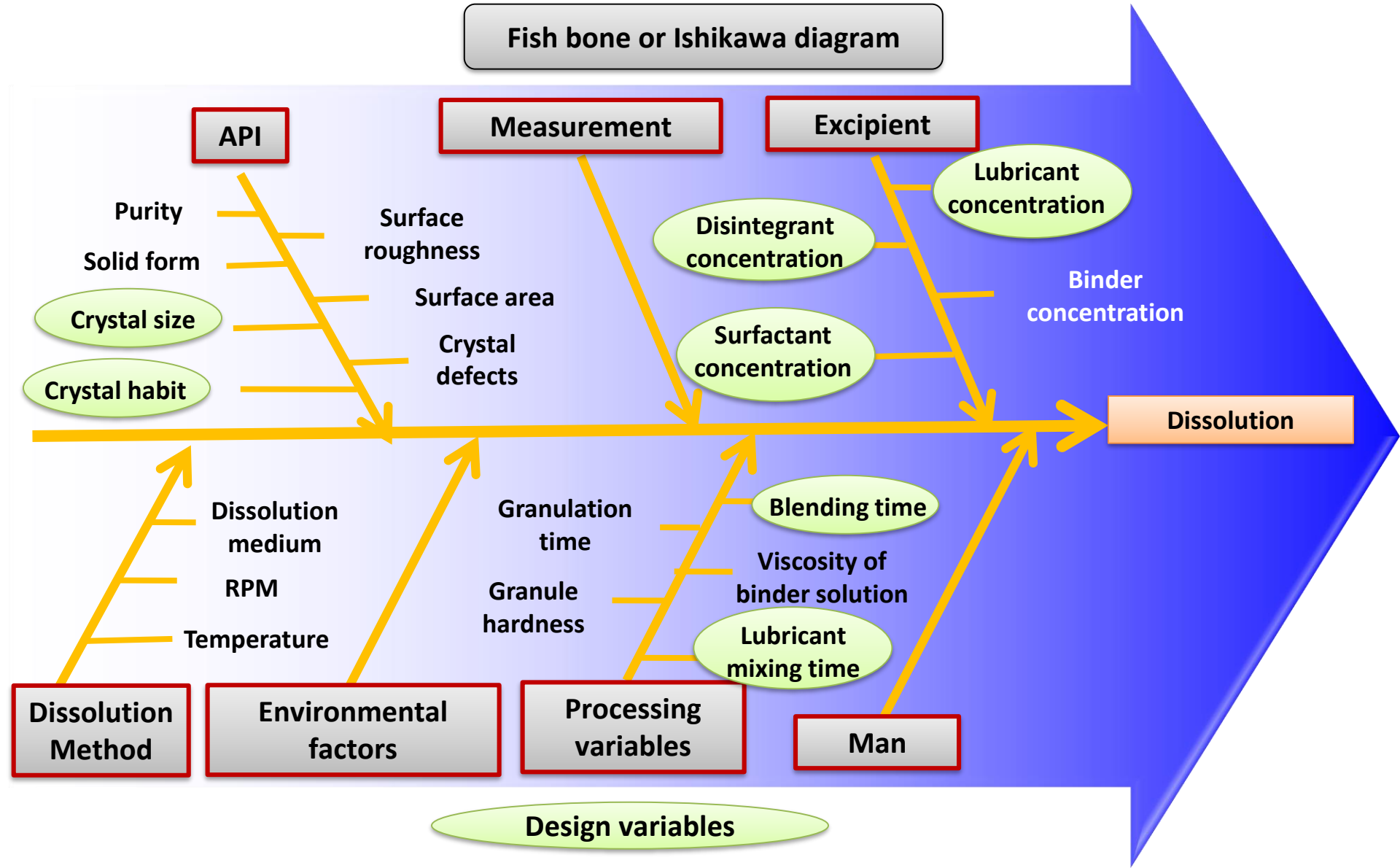
↓

Define Control Strategy

↓

Life Cycle Management, Continuous Improvement

Risk Assessment – Risk Identification



Risk Assessment – Risk Analysis

Failure Mode Effect Analysis (FMEA)

Risk Priority Number (RPN) = Severity X Occurrence X Detectability

Sr. No.	Parameters	Severity	Detectability	Occurrence	RPN	Cum	% Cum	Comments
1	Crystal size	5	3	5	75	75	17.5	10-250 µm (Lower and higher limits)
2	Surfactant concentration	5	3	5	75	150	35.0	0.5-5% (Lower and higher limits)
3	Lubricant concentration	5	5	3	75	225	52.4	0.25-5% (Lower and higher limits)
4	Lubricant mixing time	5	3	5	75	300	69.9	2-10 min (Lower and higher limits)
5	Crystal habit	5	3	5	75	375	87.4	We can not control crystal habit after particle size reduction
6	Blending time	3	3	3	27	402	93.7	15 min (Fixed based on prior knowledge)
7	Disintegrant concentration	3	3	3	27	429	100.0	10 mg (Fixed based on prior knowledge)

Cum: Cumulative, 5: High, 3: Middle and 1: Low

Experimental Design – Response Surface Method

Std	Space type	Input variables				Response (Similarity factor)
		A:Particle size (µm)	B: Surfactant concentration (%)	C: Lubricant concentration (%)	D:Lubricant mixing time (min)	
1	Factorial	10	0.000	0.250	2	60
2	Factorial	250	0.000	0.250	2	46
3	Factorial	10	5.000	0.250	2	51
4	Factorial	250	5.000	0.250	2	47
5	Factorial	10	0.000	5.000	2	63
6	Factorial	250	0.000	5.000	2	52
7	Factorial	10	5.000	5.000	2	45
8	Factorial	250	5.000	5.000	2	43
9	Factorial	10	0.000	0.250	10	39
10	Factorial	250	0.000	0.250	10	41
11	Factorial	10	5.000	0.250	10	37
12	Factorial	250	5.000	0.250	10	36
13	Factorial	10	0.000	5.000	10	42
14	Factorial	250	0.000	5.000	10	46
15	Factorial	10	5.000	5.000	10	34
16	Factorial	250	5.000	5.000	10	33
17	Center	130	2.500	2.625	6	48
18	Center	130	2.500	2.625	6	45
19	Center	130	2.500	2.625	6	47
20	Center	130	2.500	2.625	6	46

Design Evaluation and Analysis

Degrees of Freedom (df) for Evaluation	
Model	14
Residuals	22
Lack of Fit	10
Pure Error	12
Corr Total	36

Source	Sequential p-value	Lack of Fit p-value	Adjusted R-Squared	Predicted R-Squared	Comment
Linear	< 0.0001	0.0018	0.7398	0.6815	
2FI	0.0070	0.0117	0.8304	0.7408	
Quadratic	0.0020	0.1310	0.9042	0.7965	Suggested
Cubic	0.0623	0.6112	0.9383	0.7238	Aliased

ANOVA Summary

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Comments
Model	1804.16	14	128.87	25.28	< 0.0001	Significant
Lack of Fit	69.83	10	6.98	1.98	0.1310	Not significant

Regression Analysis

Parameter	Value	Parameter	Value
Std. Dev.	2.26	R-Squared	0.9415
Mean	45.86	Adj R-Squared	0.9042
C.V. %	4.92	Pred R-Squared	0.7965

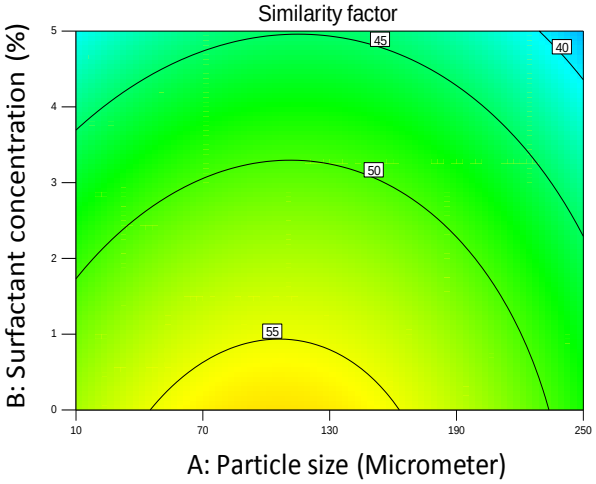
All the design evaluation parameters are within the acceptable range and/or limits

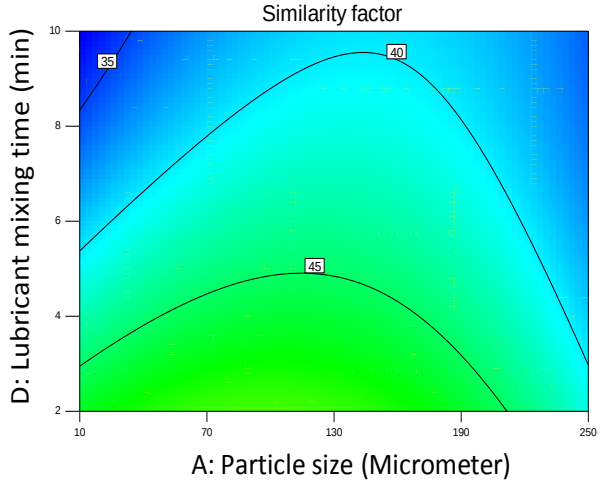
Factor Effects and Interactions – Contour Plots

A

63
33
Similarity factor

Actual Factors
C: Lubricant concentration = 5
D: Lubricant mixing time = 5





B

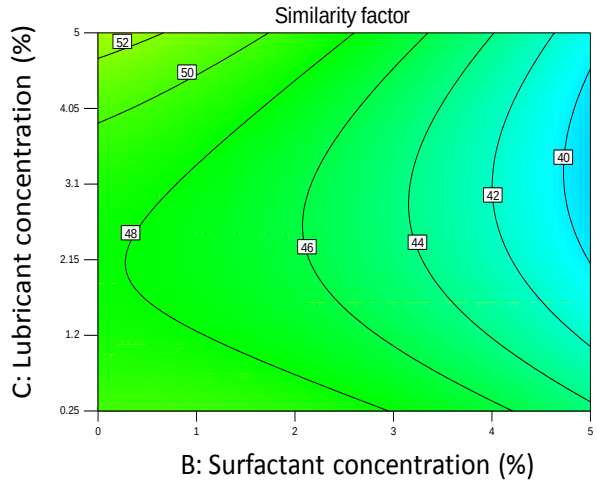
63
33
Similarity factor

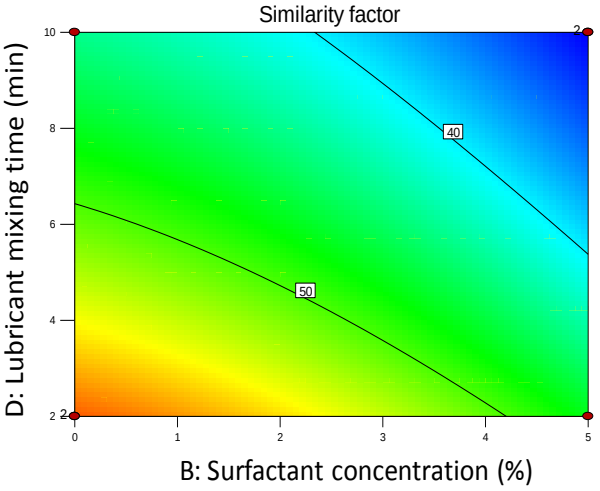
Actual Factors
B: Surfactant concentration = 5
C: Lubricant concentration = 5

C

63
33
Similarity factor

Actual Factors
A: Particle size = 10
D: Lubricant mixing time = 5





D

63
33
Similarity factor

Actual Factors
A: Particle size = 10
C: Lubricant concentration = 5

This established 'stand alone' effect of each factor and interactions between them

Quality Target Product Profile (QTPP)

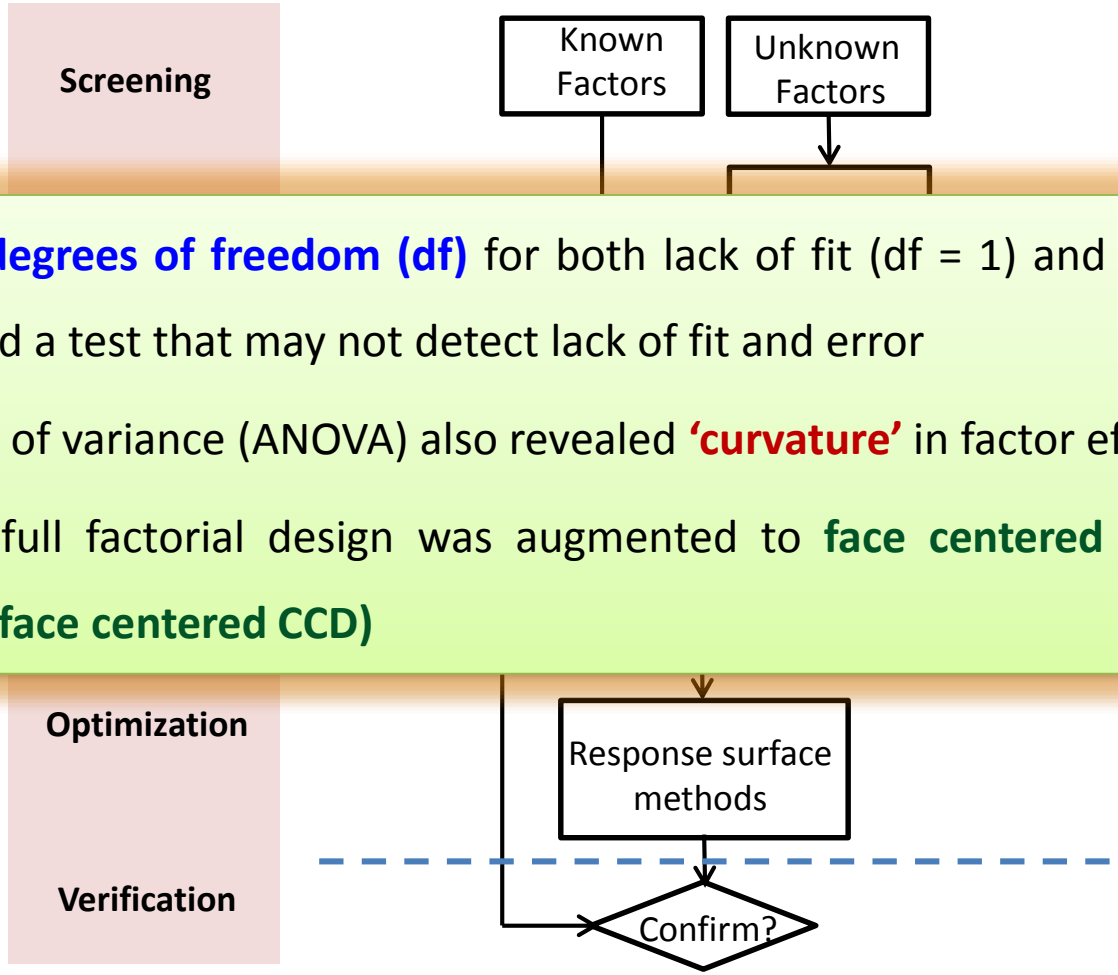
QTPP Elements		Target	Justification
Dosage form		Capsule	Pharmaceutical equivalence requirement, same dosage form
Dosage design		Immediate release	Immediate release Design needed to meet label claims
Route of administration		Oral	Pharmaceutical equivalence requirement, same route of administration
Dosage strength		200 mg	Pharmaceutical equivalence requirement, same strength
Pharmacokinetics		Immediate release Enabling Tmax in 2.5 h or less Bioequivalent to RLD	Bioequivalence requirement Needed to ensure rapid onset and efficacy
Stability		At least 24 month shelf life at room temperature	Equivalent to or better than RLD shelf-life
Drug product quality attributes	Physical attributes	Pharmacokinetics equivalence requirement: Must meet the same compendial or other applicable (quality) standards (i.e. identity, assay, purity and quality)	
	Identification		
	Assay		
	Content uniformity		
	Dissolution		
	Degradation products		
	Residual solvents		
	Water content		
	Microbial Limits		
Container closure system		Container closure system qualified as suitable for this drug product	Needed to achieve the target shelf-life and to ensure tablet integrity during shipping
Administration /concurrence with labeling		Similar food effect as RLD	RLD labeling indicates that a high fat meal increases the AUC and Cmax by 8-12%.
Alternative methods of administration		None	None are listed in the RLD label

Identify Critical Quality Attributes (CQAs)

Quality attributes of the drug product		Target	Is this a CQA	Justification
Physical attributes	Appearance	Color and shape acceptable to patient. No visual capsule defects observed.	No	Not directly linked to safety and efficacy.
	Odor	No unpleasant odor	No	Not directly linked to safety and efficacy.
	Size	Similar to RLD	No	For comparable ease of swallowing and patient acceptance, the target for capsule dimensions is set similar to the RLD
Identification		Positive for CEL	Yes*	Though identification is critical for safety and efficacy, this CQA can be effectively controlled and will be monitored at drug product release. Formulation and process variables do not impact identity. Therefore, this CQA will not be discussed during formulation and process development
Content uniformity		Conforms to USP <905> uniformity of dosage units	Yes*	Variability in content uniformity may affect safety and efficacy. However, formulation and process variables are unlikely to impacts this CQA because of high CEL content in final formulation.
Dissolution		**Should be similar as innovator product**	**Yes**	**Failure to meet dissolution specification can impact bioavailability. Both formulation and process variables impact dissolution profile. This CQA will be investigated throughout formulation and process development.**
Degradation product		Any unknown impurity: NMT 0.2% Total impurities: NMT 1.0%	Yes*	Degradation product can impact safety. However, there was no evidence of generation of any degradation products due to formulation and processing variables.
Residual solvent		USP <467> option 1	Yes*	Residual solvent can impact safety. However, no solvent is used in the drug product manufacturing process. Therefore, formulation and process variables are unlikely to impact the CQA.
Water content		NMT 4.0% w/w	NO	CEL is not sensitive to hydrolysis and moisture will not impact stability.
Microbial limit		Meets relevant pharmacopoeia criteria	Yes*	Non compliance with microbial limits will impact patient safety. However, in this case, the risk of microbial growth is very low because direct powder filling operation is utilized for this product. Therefore, this CQA will not be discussed in detail during formulation and process development

Design of Experiments (DoE) – Selection of Design

Design of experiments (DOE) is a systematic method to determine the relationship between factors affecting a process and the output of that process.



- **Lesser degrees of freedom (df)** for both lack of fit (df = 1) and pure error (df = 2) indicated a test that may not detect lack of fit and error
- Analysis of variance (ANOVA) also revealed **'curvature'** in factor effects
- Hence, full factorial design was augmented to **face centered central composite design (face centered CCD)**

Experimental Validation of Model

Batch No	Design variables				Similarity factor (Response)			CI for Mean		99% of Population	
	A (µm)	B (%)	C (%)	D (min)	Predicted Mean	Predicted Median	Observed	95% CI low	95% CI high	95% TI low	95% TI high
1	250	2.5	2.625	6	43	43	42	39	46	32	53
2	10	2.5	2.625	6	41	41	43	38	45	31	52
3	130	5.0	2.625	6	39	39	39	35	42	28	49

Interestingly, In capsule dissolution study…

Dissolution of CEL-A < Dissolution of CEL-P

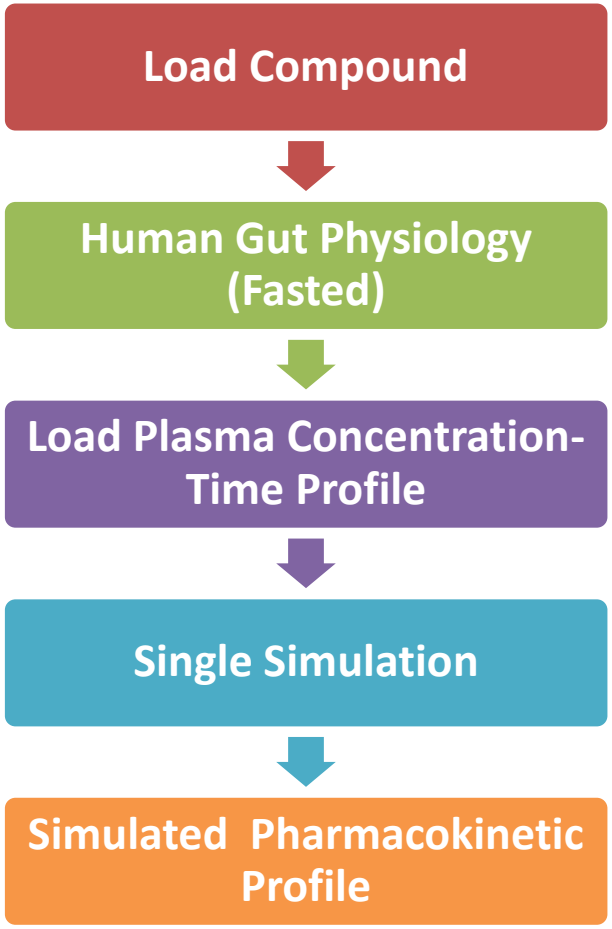
Dissolution of milled CEL-A > Dissolution of milled CEL-P

✓ The predicted (40) and experimentally observed (36) values for similarity factor were in

- Differential anisotropic surface chemistry of CEL crystal habits (Higher exposure of hydrophilic facet on CEL-P)
- Differential cleavage behavior of two CEL crystal habits (leading to hydrophobization of surface of milled CEL-P)
- Competitive particle surface interaction with surfactant and/or lubricant and
- Over lubrication due to excessive use of lubricant and/or higher lubricant mixing time

GastroPlus™ Simulation Study

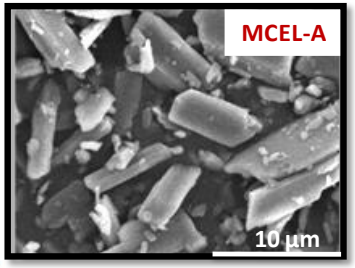
Protocol



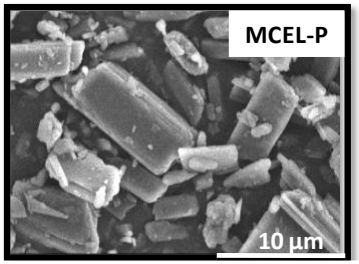
Parameter	Value
Molecular formula	$C_{17}H_{14}F_3N_3O_2S$
Molecular weight	381.373 g/mol
Log*P*	3.5
p*Ka*	11.1
Human jejunal permeability (P_{eff})	2.21 X 10^{-4} cm/s
Dose	200 mg
Dose volume	250 mL
pH of the reference solubility	12
Solubility*	0.4 mg/mL
Mean precipitation time#	900 s
Drug particle density	1.52 g/mL
Diffusion coefficient#	0.6753 X 10^5 cm^2/s
Body weight	70 kg
Simulation time	48 h
Clearance (Cl)#	8.9 L/h
Volume of distribution (Vd)#	0.035 L/kg
Compartmental rate constants#	$K_{1/2}$: 0.18753 h^{-1} $K_{2/1}$: 0.10823 h^{-1}
Solubility values in various dissolution media*	FaSSGF (pH 1.6): 0.0023 mg/mL FaSSIF-V2 (pH 6.5): 0.0153 mg/mL

*Shono *et al, Eur J Pharm and Biopharm.* **73:** 107–114 (2009), # Predicted in PKPlus® module

Aspect ratio: 2-6



Aspect ratio: 2-6



Summarizing…

- **Milled fraction of CEL-P showed decreased dissolution** performance in clinically relevant dissolution medium as compared to milled fraction of CEL-A in capsule dosage form
- Differential **surface hydrophobicity coupled with other 'CMAs' and 'CPPs'** contributed to this counterintuitive behavior
- This work has successfully established 'stand alone' effect of each factor and interactions between them on dissolution performance of milled fractions of different crystal habits in capsule dosage form, using **'Design of Experiments (DoE)'** approach
- This novel finding opens up **crystal habit as a 'Critical Material Attribute'** governing **Critical Quality Attribute (CQA)** of drug products containing BCS class II drugs

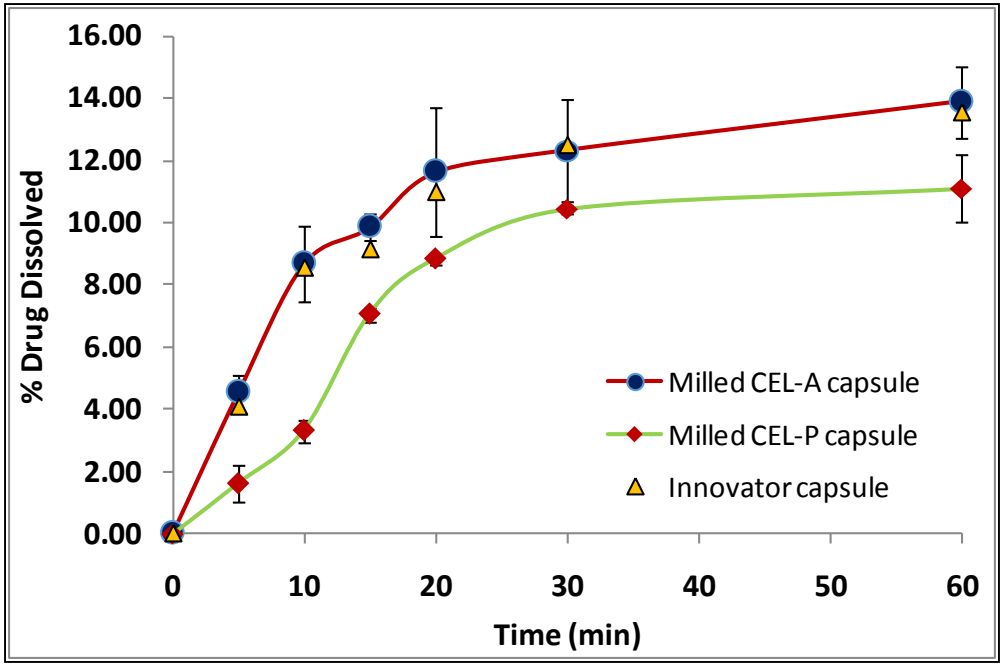
Development of PBPK Model

- PBPK model was developed for predicting pharmacokinetic parameters of Celecoxib capsule using GastroPlus® software
- It was found that **phosphate buffer having pH 11 is clinically relevant dissolution media to predict pharmacokinetic parameters of Celecoxib**
- It gives opportunity to evaluate role of milled fractions of both the crystal habits on dissolution behavior and predicting pharmacokinetic parameters in capsule dosage form

PBPK: Physiologically-based pharmacokinetic

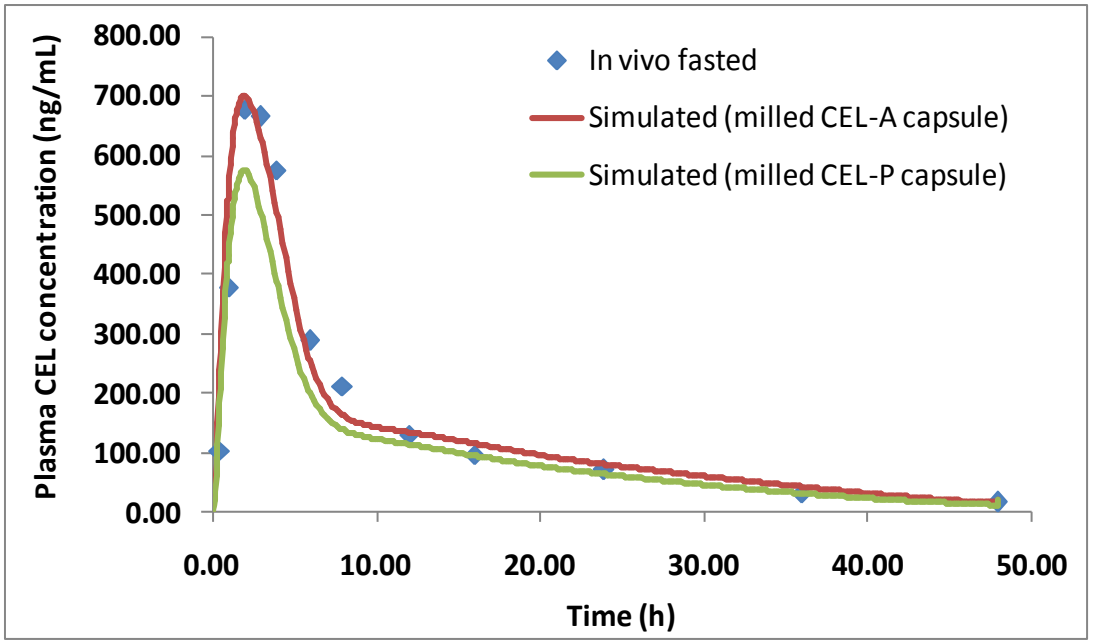
In Vitro Dissolution Study

Dissolution Parameters	
Apparatus	USP II (Paddle type)
Media	pH 11 phosphate buffer
Volume	500 mL (@ 37 ± 0.5 °C)
RPM	100
Volume withdrawn	2 mL
Analytical method used	HPLC



1. Significant differences were observed in dissolution profiles of CEL capsules of milled fractions of two different crystal habits
2. Surprisingly, milled fraction of CEL-P showed decreased dissolution kinetics when compared with milled CEL-A in capsule dosage form
3. Dissolution profile of milled CEL-A capsule matches with the dissolution profile of innovator capsule

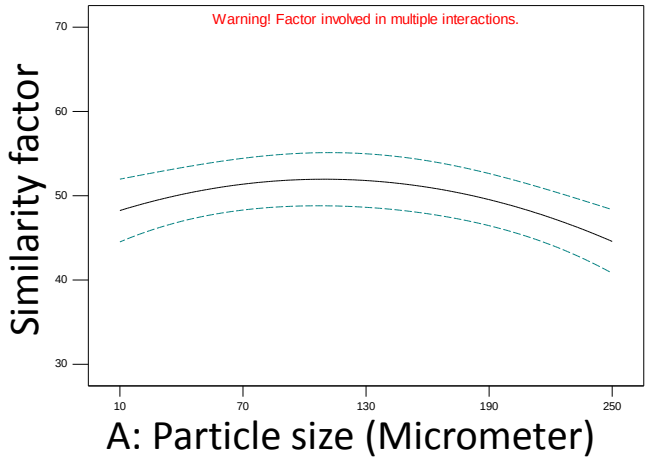
Simulated Pharmacokinetic Profile in Human

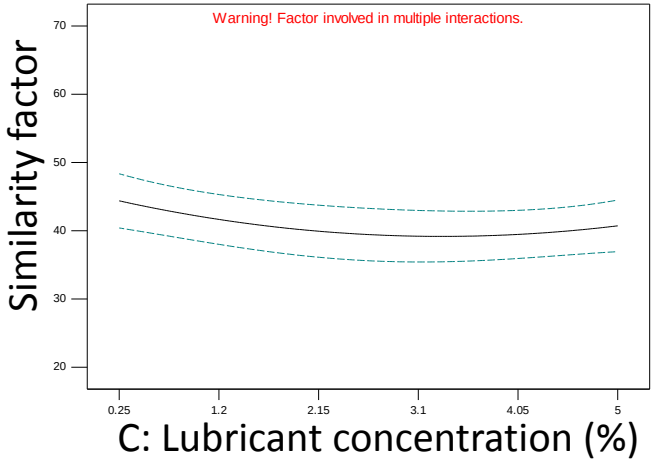


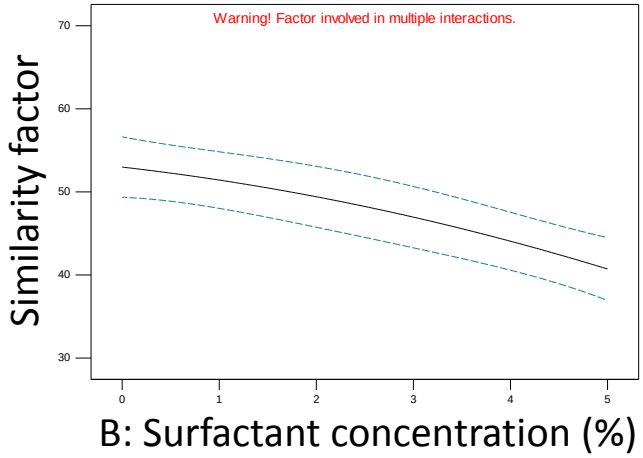
CEL Formulation	AUC $_{0\text{-}48}$ (ng.h/mL)	C_{max} (ng/mL)	T_{max} (h)
Innovator capsule	6323.1	661.51	1.92
Milled CEL-A capsule	6449.9	673.29	1.92
Milled CEL-P capsule	4799.2	512.25	1.98

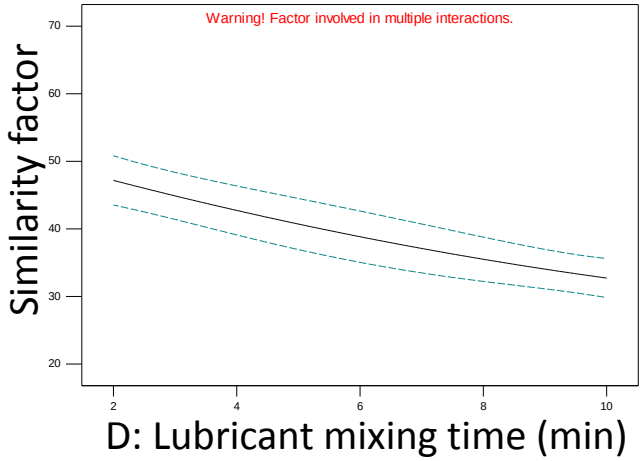
Significant differences were observed in simulated pharmacokinetic parameters of CEL capsules of two milled fractions of different crystal habits

Individual Factor Effects









Significant Factor Interactions