International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Direct Compression Development of Celecoxib Tablet Through Solid State in Dimethyl Sulfoxide

Deovrat Kumar[1], Shalini Sharma[2], Aryavrat[3]

[1,2,3]Haridwar University, Roorkee

Abstract:

Tablets are the most desirable solid oral dosage form for patients. Direct compression (DC) tablet formulation is the most economical, robust and efficient way of tablet manufacture. Being sensitive to properties of the Active Pharmaceutical Ingredient (API), direct compression tablet formulation is not available for the high dose non-steroidal anti-inflammatory drug, celecoxib (CEL) due to the undesirable properties of the commercial solid form of celecoxib, including low bulk density, poor flowability and tablet lamination issues.

The solid form used in commercially available celecoxib capsules is a polymorph of celecoxib, Form III. Form III celecoxib is a needle shaped crystal, which is exceptionally elastic. This high elasticity, verified by nano indentation and three-point bending tests, is unfavorable for good tablet quality and performance during high speed tableting. Through understanding the molecular interactions by analyzing the celecoxib crystal structure, a structural model for high elasticity is built and validated by Raman spectroscopy. Interlocked molecular packing without slip plane and the presence of isotropic hydrogen bond network are major structural features responsible for both the exceptional elastic flexibility and high stiffness of the celecoxib crystal.

celecoxib Form III exhibits unsatisfactory flowability and tablet lamination issues for DC tablet manufacturing. Pharmaceutically acceptable solvates of celecoxib offer better flow, compaction and dissolution properties than celecoxib Form III. Two stoichiometric solvates of celecoxib and *N*-methyl-2-pyrrolidone (NMP) are extensively characterized and examined, which establishes a clear crystal structure-property relationship essential for crystal vi engineering of celecoxib. Through crystal engineering, a DC tablet formulation of celecoxib is successfully developed using the dimethyl sulfoxide (DMSO) solvate of celecoxib. This pharmaceutically acceptable solvate is highly stable and also exhibited much improved manufacturability compared to celecoxib Form III, including better flowability, lower elasticity and bulk density (superior tablet quality) as well as better dissolution performance.

As a Class II drug in the biopharmaceutics classification system with low solubility and high permeability, the high dose of celecoxib is partially attributed to its limited solubility. Amorphous celecoxib, although providing solubility advantages as the thermodynamically high energy state, is unstable and prone to crystallization. The study of crystal growth of amorphous celecoxib reveals a fast glass-to-crystal growth mode at room temperature with a surface-enhanced mechanism. This paves the way for future development of a stable amorphous solid dispersion tablet product of celecoxib with improved dissolution performance and tablet manufacturability.

In summary, by understanding the structural origin of undesired properties of celecoxib, successful development of the most patient-compliant tablet dosage form by direct compression can be achieved. This sets an excellent example of utilizing a solid state engineering approach to effectively overcome challenges encountered in direct compression tablet development.

Keywords: CEL – Celecoxib, API (Active Pharmaceutical Limited),Raman Spectroscopy dimethyl sulfoxide (DMSO),etc

1. Introduction

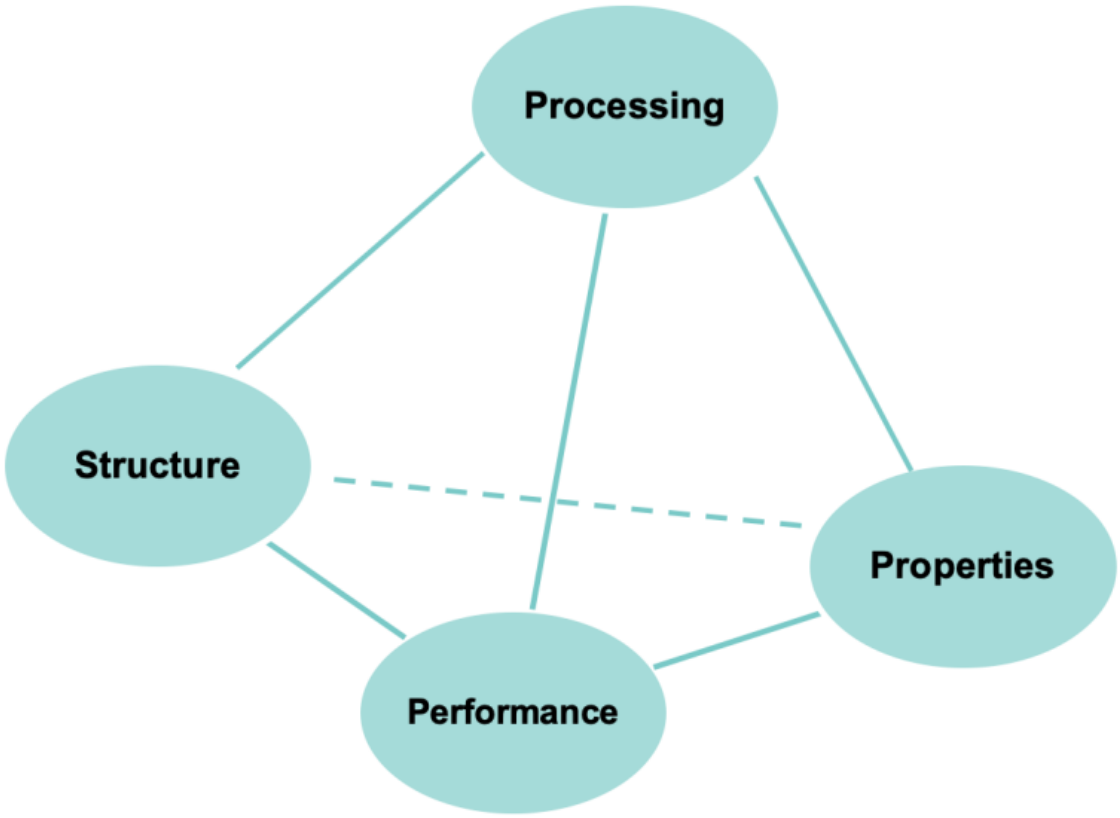
Among all dosage forms, tablets are the most widely produced dosage form and are more advantageous than other forms in many ways: 1) elegancy in terms of different shapes/sizes and high patient compliance; 2) precisely controlled dosing for patients; 3) good physical and chemical stability; 4) faster and easier production and transportation and 5) more straightforward and economical manufacturing processes. 1 Although tablet formulation is most desirable for both patients and pharmaceutical companies, it is not always easy to successfully develop a tablet formulation. A balance among aspects of preformulation and formulation, including physical and chemical stability, solubility, powder flow properties, tablet friability and tensile strength, must be achieved during tablet formulation design.

To attain the desired characteristics of the optimal formulation, multiple approaches can be employed. Solid-state properties of active pharmaceutical ingredients (APIs) can be engineered by screening for different solid forms, such as amorphous solid, polymorph/cocrystal/salt/solvate and hydrate. For a given API solid form, particle and powder properties can be engineered by particle size reduction, dry and wet granulation. Lastly, fine-tuning tablet performance can be achieved by altering the formulation compositions. For drugs that are less potent or of low solubility, high doses are usually required for the tablet to demonstrate the desired therapeutic effect. For these types of drugs, the final property of the formulation is highly dependent on the API properties, and the space for manipulating drug product performance through formulation design is limited. In this case, although high drug loading can be achieved by wet granulation and dry 3 granulation to uniformly disperse the API and densify the powder blend, 2 the granulation process is often costly and requires extra steps and more strict process controls. In comparison, direct compression is the more desirable way for tablet manufacturing. Out of all these possible solid-state engineering methods, API engineering to improve the properties is the most effective.

In this work, a non-steroidal anti-inflammatory drug for treating pain and arthritis, celecoxib celecoxib is used as an example of high dose drug that is challenging for direct compression (DC) tablet formulation development. The marketed celecoxib product is in form of capsules, Celebrex®, which are usually prescribed in high doses of 200 mg or 400 mg. The marketed product contains the most stable polymorph, Form III of celecoxib, which has undesired properties for DC tablets. 3, 4 Wet granulation was employed in the original Celebrex® capsules to improve the poor flow properties of API for capsule filling. 4 However, this process is complex, costly and possess risks of overgranulation and chemical and physical stability. 5 In addition, these capsules are of relatively large sizes and thus lower patient compliance than tablets. In addition, the lag time before releasing the drug from capsules is unfavorable for pain medications like celecoxib, which is preferred to have faster action. To develop a DC tablet formulation of celecoxib, the unwanted properties of Form III celecoxib needs to be overcome. This

includes poor flow properties, low bulk density and tablet lamination issue during high speed direct compression. 4

Here we aim to improve celecoxib properties through solid-state engineering to enable the development of a suitable DC tablet. This is achieved using a combined crystal engineering and Quality by Design (*QbD*) approach. The guiding principles behind this 4



Celecoxib (**Figure-1**) is a widely prescribed nonsteroidal anti-inflammatory drug (NSAID) developed by Pfizer to treat arthritis, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and acute pain, with also analgesic and antipyretic characteristics. Celecoxib (CEL) is a cyclo-oxygenase (COX) inhibitor that selectively inhibits COX-2 over COX-1 both *in vitro* and *ex vivo*. CEL is commercially available as capsules, with available doses of 100 mg, 200 mg and 400 mg. celecoxib is a class II compound in the Biopharmaceutics Classification System (BCS), having high permeability and low solubility. The absolute oral bioavailability of celecoxib in dogs was 64-88 % if given as solution and 22-40 % if given as capsule. The absolute bioavailability of celecoxib in human was not studied due to its low water solubility.

Molecular structure of celecoxib, MW=381.373 g/mol

Celecoxib was developed as a first-in-class COX-2 inhibitor, approved for its role in treating osteoarthritis and rheumatoid arthritis, with potential in treating acute pain. 118 It soon became a blockbuster drug and widely prescribed by doctors. All dosages (100 to 200mg)

400 mg twice daily) has clinically shown similar efficacy to conventional NSAIDs (e.g. 500 mg naproxen) in pain relief and improvement in functionality. Meanwhile, celecoxib has a much safer gastrointestinal profile and is well tolerated by patients. 118 The recommended dose of CEL is 200 mg/day for osteoarthritis, and 100 to 200 mg twice daily for rheumatoid arthritis in adults. No significant food effect was observed in healthy human subjects

2. Objectives:

The main goal of this work is to use solid state engineering methods to solve the issues associated with the existing commercial Form III of celecoxib that hinder the development of a direct compression tablet formulation. The guiding hypothesis of this work is that solid-state engineering is effective in overcoming deficient properties of celecoxib and enables the successful development of a direct compression tablet formulation. In testing this hypothesis, it is necessary to characterize the solid-state properties of various drugs.

Single Crystal Preparation of Elastic Crystals of CEL Form III

200 mg of Form III as-received Celecoxib was dissolved in 10 mL methanol. The methanol solution of celecoxib was allowed to slowly evaporate in the chemical hood until dryness. Very long needles were crystallized from the solution and used in looping, bending and single crystal X-ray diffraction experiments. 30

3. Methods

3.1 Single Crystal X-ray Diffraction Experiment

Single crystal X-ray diffraction (SCXRD) of form III celecoxib was performed on a Bruker D8 Venture diffractometer (Bruker AXS Inc., Madison, Wisconsin) equipped with a Bruker PHOTON-II CMOS detector. The data collection was done at 100 (2) K with a Mo$K\alpha$ radiation source (IμS 3.0 microfocus tube). Data integration was performed with the SAINT program, the SADABS program was used for scaling and absorption correction purposes and XPREP was used for space group determination and data merging. The crystal structure was solved and refined using the ShelXle program (a graphical user interface for SHELXL174). The crystal structure was solved using SHELXT (Intrinsic Phasing) methods. The hydrogen atoms were either placed geometrically from the difference Fourier map or allowed to ride on their parent atoms in the refinement cycles. All non-hydrogen atoms were refined with anisotropic displacement parameters. CCDC 1875184 contains the supplementary crystallographic data for CEL form III for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

3.2 Face Index of CEL Form III

Face indexing of needle–shaped CEL form III crystals was done on a Bruker D8 Venture diffractometer (Bruker AXS Inc., Madison, Wisconsin) equipped with a Bruker PHOTON-II CMOS detector. The major face is (001) along the *c* axis; the minor faces along *c* axis are $(01\bar{1})$ or $(0\bar{1}1)$ face. Another minor face is (100). 31 forms of CEL, including the crystal growth mechanism and kinetics of amorphous CEL and structure-property relationships of new crystal forms of CEL.

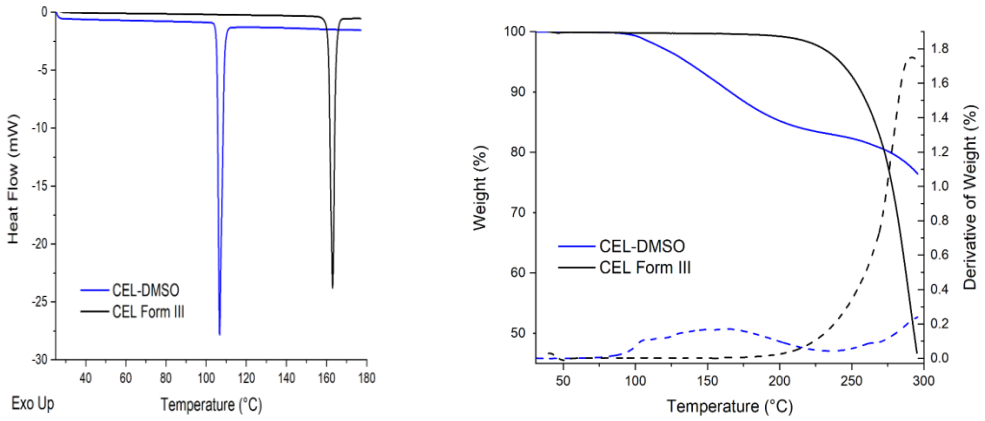
4. Preparation of Tablet Formulations

All formulation components, except MgSt, were first mixed roughly in an amber glass bottle with spatula, and then using a Turbula mixer (Glen Mills Inc., Clifton, NJ) at 49 rpm for 10 minutes. MgSt, the lubricant, was added only after this for another 5-minute mixing by Turbula at 49 rpm to avoid over-lubrication.

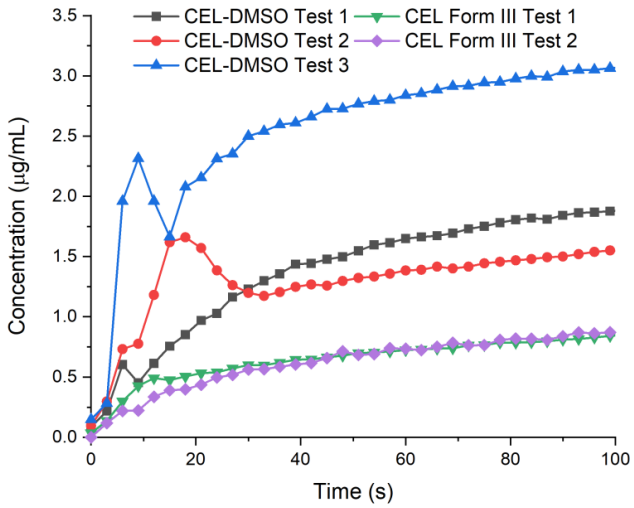
5. Tabletability Profiling

Tablets of each formulation were made on a compaction simulator (Styl' One Evolution, MedelPharm, Beynost, France), simulating a Korsch XL100 press. To attain the same dose of 200 mg per tablet, tablet weights were 600 mg for celecoxib -DMSO formulations, and 500 mg for celecoxib formulations, made using 11.28 mm and 9.53 mm flat face tooling, respectively. Different tooling sizes were used to maintain a suitable diameter to thickness ratio of 2 - 2.32. A dwell time of 30 ms (16,320 tablets/hour) was used to make tablets for expedited friability, disintegration time, and dissolution tests for formulations containing CEL-DMSO. For comparing tabletability profiling, flat face round tooling (8 mm diameter) was used to compress 200 mg tablets using a dwell time of 100 ms, since tablets from the celecoxib Form III formulation severely laminated at shorter dwell times.

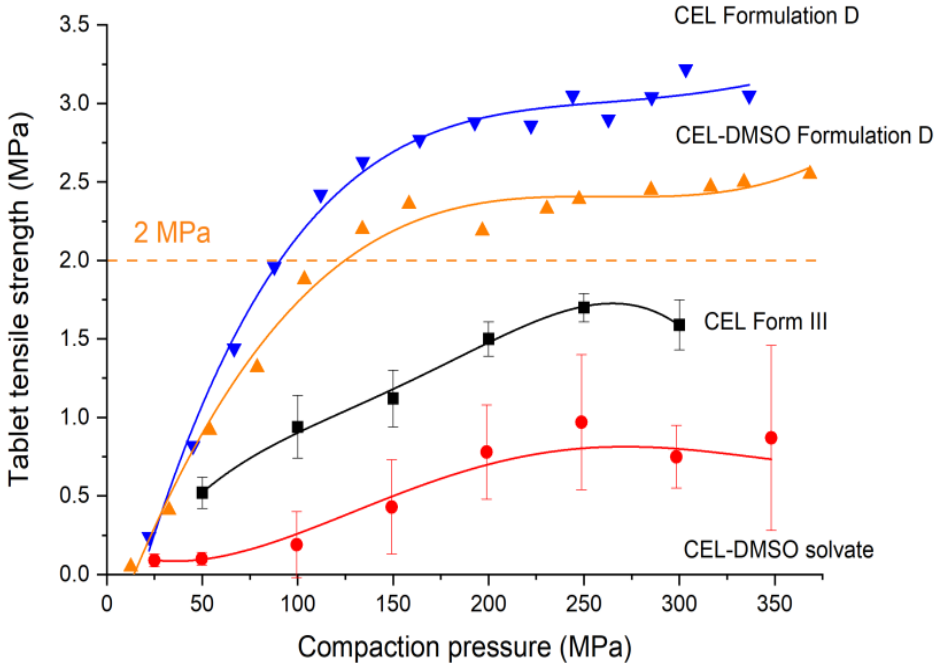
The tabletabilities of the pure celecoxib Form III and CEL-DMSO were characterized using 8 mm flat face round tooling with external lubrication on a Materials Testing Machine (ZwickRoell 1485, Ulm, Germany). The compaction pressures for tabletability profiles ranged 12 - 370 MPa. 85



a) DSC and b) TGA thermographs of Celecoxib-Dimethylsulfoxide solvate crystals. The dashed lines in represents the first derivative of weight signals.



(Figure -2) IDR data showing Celecoxib -Dimethylsilfoxide tests and Celecoxib Form III tests at 25°C. Three Celecoxib-Dimethylsulfoxide curves showed different extents of supersaturation followed by rapid precipitation and phase conversion to Form III.



Tabletability profiles

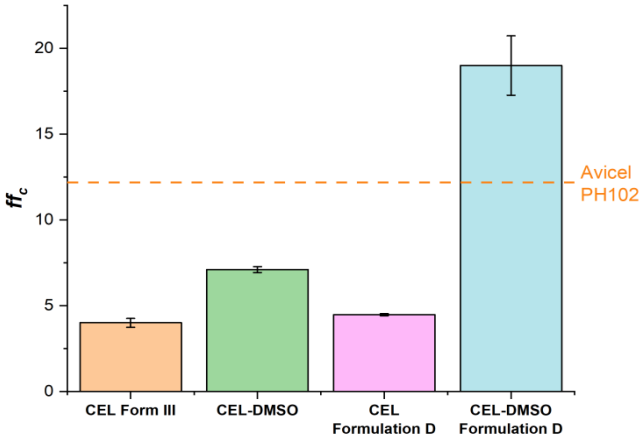


Figure-(3and 4) flowability of Celecoxib-Dimethylsulfoxide solvate, Celecoxib Form III and Their Formulations

Components (%)	Formulation A	Formulation B	Formulation C	Formulation D
API (CEL or CEL-DMSO)	50	40	40	40
Avicel PH102	23	41.5	-	-
Mannitol Pearlitol 100SD	20	11	-	-
Nanocoated Avicel PH102	-	-	52.5	52.25
Crospovidone	4.75	4.75	4.75	4.75
SLS	2	2	2	2
MgSt	0.25	0.75	0.75	1
Tablet weight (CEL)	400 mg	500 mg	500 mg	500 mg
Tablet weight (CEL-DMSO)	500 mg	600 mg	600 mg	600 mg

Table: 1-Summary of tablet formulation compositions and weights. The total amount of Celecoxib in each 200 mg.

Conclusion:

We have developed a direct compression tablet formulation of Celcoxib using Dimethyl sulfoxide solvate of Celecoxib, which exhibits improved flowability, manufacturability, tablet quality, and faster dissolution over those of Celecoxib. The formulation development process was efficient because of the employment of predictive techniques for assessing powder flowability and tableting performance. This study is another example that shows the benefits of combining crystal engineering and materials science to enable the development of high quality tablet products efficiently.

Reference:

1. Gibson, M., *Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form*. 2nd ed.; CRC Press: 2016.
2. Sun, C. C.; Hou, H.; Gao, P.; Ma, C.; Medina, C.; Alvarez, F. J., Development of a high drug load tablet formulation based on assessment of powder manufacturability: moving towards quality by design. *J. Pharm. Sci.* **2009,** *98* (1), 239-47.
3. Ferro, L. J.; Miyake, P. S. Polymorphic crystalline forms of celecoxib. US 7476744 B2, Jan. 13, **2009**.
4. Gao, D.; Hlinak, A. J.; Mazhary, A. M.; Truelove, J. E.; Vaughn, M. B. Celecoxib Compositions. Jan.8, **2015**.
5. Suresh, P.; Sreedhar, I.; Vaidhiswaran, R.; Venugopal, A., A comprehensive review on process and engineering aspects of pharmaceutical wet granulation. *Chemical Engineering Journal* **2017,** *328*, 785-815.
6. Sun, C. C., Materials science tetrahedron--a useful tool for pharmaceutical research and development. *J. Pharm. Sci.* **2009,** *98* (5), 1671-87.

7. Kottke, M. J.; Rudnic, E. M., Modern Pharmaceutics. In *Modern Pharmaceutics*, Banker, G. S.; Siepmann, J.; Rhodes, C., Eds. CRC Press: Boca Raton, **2002**.
8. Li, Z.; Zhao, L.; Lin, X.; Shen, L.; Feng, Y., Direct compaction: An update of materials, trouble-shooting, and application. *Int. J. Pharm.* **2017,** *529* (1-2), 543-556.