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Direct Compression of High-Dose BCS Class II NSAID Tablets: Formulation Challenges, Excipient Functionality, Dissolution Enhancement and Emerging Manufacturing Strategies

M. Alagusundaram [1*] G.Santhanam[1] V.S.Sagar[2] Neelaveni Thangavel[2] Karthik Baskar[2] P.Ashwini[2]

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Abstract
Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the management of pain and inflammation, but formulation of immediate-release tablets can be challenging when the active pharmaceutical ingredient (API) is present at a high dose and exhibits poor aqueous solubility and unfavorable powder-flow properties. These challenges become particularly important for BCS Class II drugs, for which dissolution can be a rate-limiting step in oral absorption. Direct compression is an attractive manufacturing approach because it reduces the number of unit operations and can provide a simple, economical and robust process; however, successful implementation depends strongly on powder flow, compressibility, compactibility, segregation control, lubrication and rapid tablet disintegration. This review discusses the major formulation challenges associated with high-dose BCS Class II NSAID tablets, the principles and advantages of direct compression, the functionality of commonly used excipients, the role of particle engineering and co-processed excipients, and strategies for improving dissolution and immediate-release performance. The influence of lubrication, compression and disintegration on tablet quality is also considered. Quality by Design (QbD), continuous direct compression and emerging manufacturing technologies are discussed as approaches for improving process understanding and product robustness. Overall, rational selection and optimization of API–excipient combinations, together with control of critical material attributes and critical process parameters, are essential for developing high-dose directly compressed NSAID tablets with consistent mechanical strength, rapid disintegration and reproducible drug release.

Keywords
NSAIDs; BCS Class II; direct compression; high drug loading; tablet formulation; excipients; dissolution enhancement; disintegration; co-processed excipients; continuous manufacturing; Quality by Design.

I. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) constitute an important class of medicines used for the relief of pain, inflammation and fever. Their clinical use extends across acute and chronic conditions, including musculoskeletal disorders and osteoarthritis. Although NSAIDs are effective pharmacological agents, their use is associated with gastrointestinal, renal and cardiovascular safety considerations, making appropriate drug selection and dosing important [1–9].

From a pharmaceutical-development perspective, formulation of NSAIDs can present additional challenges. Several compounds have limited aqueous solubility, while some exhibit poor flow, inadequate compressibility or high dose requirements. These properties can complicate manufacture of robust immediate-release tablets and may result in slow or variable drug dissolution. For a high-dose BCS Class II drug, the formulation must accommodate a substantial quantity of API while still maintaining adequate powder flow, blend uniformity, tabletability, rapid disintegration and efficient dissolution.

Direct compression is one of the simplest approaches for tablet manufacturing because the powder blend can be compressed without a separate granulation step. Nevertheless, direct compression places stringent requirements on the physical properties of the formulation components. The performance of the final tablet depends on the interplay between API properties, excipient functionality, particle-size distribution, lubrication, compression conditions and post-compression disintegration and dissolution [10–15].

This review summarizes the principal considerations involved in developing high-dose BCS Class II NSAID tablets by direct compression and examines formulation strategies that can

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improve manufacturability and drug-release performance.

1. NSAIDs: Therapeutic Importance and Pharmaceutical Challenges

NSAIDs exert their therapeutic effects primarily through inhibition of cyclooxygenase (COX) enzymes and consequent reduction in prostaglandin synthesis. The selectivity of individual NSAIDs toward COX-1 and COX-2 varies and contributes to differences in pharmacological and safety profiles [2–7]. NSAID-associated adverse effects include gastrointestinal injury and renal complications, while cardiovascular risk is also an important consideration for some agents [8,9,17–19].

In addition to pharmacological considerations, the physicochemical properties of an NSAID strongly influence formulation design. A drug with low aqueous solubility may show dissolution-limited absorption, while poor powder flow can adversely affect feeding, blending and die filling. High dose loading further reduces the amount of excipient available to provide binding, flow enhancement or disintegration. Consequently, high-dose NSAID tablet development requires a balance between drug loading and the functional contribution of excipients.

2. BCS Class II Drugs and Dissolution-Limited Absorption

The Biopharmaceutics Classification System (BCS) categorizes drugs according to aqueous solubility and intestinal permeability. BCS Class II compounds are characterized by high permeability and low solubility. For such compounds, dissolution can become a critical determinant of the amount and rate of drug available for absorption.

For an immediate-release tablet, the sequence of events after administration generally involves wetting of the tablet, penetration of gastrointestinal fluid, disintegration into granules and primary particles, dissolution of the API and subsequent absorption. Any factor that slows these steps can reduce the rate of drug release. Therefore, formulation strategies for BCS Class II NSAIDs frequently focus on improving wetting, increasing effective surface area, reducing particle-size limitations and facilitating rapid tablet disintegration [20–23].

Dissolution enhancement approaches may include particle engineering, use of suitable surfactant or wetting functionality, amorphous or solid-state approaches, inclusion complexes and other formulation technologies. Cyclodextrin inclusion complexes, for example, have been investigated as a strategy for improving the dissolution behavior of poorly soluble NSAIDs [23].

3. High-Dose NSAID Tablet Formulation

High drug loading presents a particular challenge in immediate-release tablet development. When the API constitutes a large proportion of the tablet, relatively little space remains for functional excipients. The formulation must therefore obtain multiple functions—flow improvement, binding, lubrication and disintegration—from a limited excipient fraction.

3.1 High Drug Loading

High-dose formulations can show poor flow and reduced compressibility because the API may dominate the physical behavior of the blend. Increasing excipient concentration is not always possible because it increases tablet size. Selection of high-functionality excipients is therefore important.

3.2 Poor Powder Flow

Flowability influences hopper discharge, feeder performance, die filling and tablet-weight uniformity. Powder flow is affected by particle size, shape, surface roughness, density, cohesion and moisture. Flow indicators should be interpreted together with the underlying powder properties rather than used in isolation [24].

3.3 Compressibility and Compactibility

Successful compression requires the powder to consolidate into a mechanically sound tablet. Compression physics depends on particle deformation, fragmentation, bonding and the applied compression force [25]. API properties and excipient grade can strongly influence tensile strength and tablet defects.

3.4 Blend Uniformity and Segregation

Differences in particle size and density between API and excipients can promote segregation during handling. Blender size and particle-size differences can influence mixing performance [26]. This is particularly important in high-dose direct compression, where formulation uniformity must be maintained throughout processing.

4. Direct Compression as a Tablet Manufacturing Technology

Direct compression involves blending the API and

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excipients followed by compression into tablets without an intermediate granulation operation. Its principal advantages include a reduced number of processing steps, lower processing time, reduced exposure to heat and moisture and comparatively simple scale-up. These benefits can make direct compression attractive for immediate-release products [11–15].

However, direct compression transfers much of the responsibility for process robustness to the starting powders. Materials must possess adequate flow and compression characteristics, and the formulation must remain homogeneous during transfer and feeding. Consequently, direct compression should not be considered simply as the omission of granulation; it is a formulation strategy that requires deliberate control of powder properties.

5. Direct Compression Compared with Granulation

Granulation can improve flow, reduce segregation and enhance compressibility by converting fine powders into larger agglomerates. Both wet and dry granulation can alter granule structure and tablet properties, and comparative studies have demonstrated that the chosen granulation route can significantly affect final product performance [27].

Direct compression may nevertheless be preferred when the formulation possesses sufficient flow and tableting functionality or when the advantages of a simpler process outweigh the benefits of granulation. For high-dose BCS Class II NSAIDs, the choice should be based on a systematic assessment of material attributes, formulation functionality and target product quality attributes.

6. Role of Excipients in Direct Compression

Excipients are central to the success of direct compression. The formulation may require a combination of filler/binder, disintegrant, glidant and lubricant functionality.

6.1 Microcrystalline Cellulose

Microcrystalline cellulose (MCC) is widely used as a direct-compression filler/binder because of its favorable compaction behavior. Its deformation characteristics allow strong interparticle bonding and can contribute to tablet mechanical strength [29].

6.2 Pregelatinized Starch

Pregelatinized starch can provide binding and contribute to disintegration. Its functionality can be useful in formulations where both compactibility and tablet breakup are required.

6.3 Sodium Starch Glycolate

Sodium starch glycolate (SSG) is a superdisintegrant that promotes rapid tablet disintegration primarily through swelling and water uptake. The choice and concentration of a disintegrant should be optimized because excessive quantities may not necessarily improve overall dissolution [30,34].

6.4 Colloidal Silicon Dioxide

Colloidal silicon dioxide is commonly employed as a glidant to improve powder flow and reduce interparticle cohesion. In high-drug-loading formulations, small quantities can have a substantial effect on handling characteristics.

6.5 Talc

Talc can contribute to glidant and anti-adherent functionality and may assist in reducing sticking during compression.

6.6 Magnesium Stearate

Magnesium stearate is one of the most widely used tablet lubricants. It reduces friction between powder and tooling, but excessive lubrication or prolonged blending can modify powder bonding and tablet properties [31].

7. Co-Processed Excipients

Co-processed excipients are engineered combinations of two or more established excipients designed to provide improved functionality compared with individual components. They can enhance flow, compressibility, compactibility and tablet robustness and are particularly useful where formulation space is limited by high drug loading [12,13,32,33].

The development of high-functionality excipients is relevant to direct compression because the formulation must achieve acceptable performance without relying on granulation to correct poor powder properties. Spray-drying and other particle-engineering approaches have also been explored to produce powders suitable for direct compression [35].

8. Particle Engineering and Powder Properties

Particle size and particle-size distribution influence flow, mixing, packing, compaction and dissolution. Fine particles may provide a greater surface area for dissolution but can exhibit increased cohesion and poor flow. Conversely, larger particles may improve flow while reducing the surface area available for

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dissolution. Therefore, optimization requires balancing powder handling with drug-release requirements.

Powder characterization should include relevant material attributes such as particle-size distribution, bulk density, tapped density, flow indicators, moisture and morphology. Understanding these properties supports rational selection of manufacturing conditions and helps identify potential risks of segregation and feeding variability [24–26].

9. Lubrication and Its Influence on Tablet Performance

Lubrication is essential for reducing die-wall friction and facilitating tablet ejection. Magnesium stearate is highly effective, but its hydrophobic nature and coating of particle surfaces can influence interparticle bonding and wetting. The duration and intensity of lubrication should therefore be controlled as critical process parameters.

Alternative lubricants have also been investigated for direct compression because lubricant selection can influence both process performance and tablet quality [31]. Lubrication should be optimized rather than maximized, particularly when rapid dissolution is a key target.

10. Tablet Disintegration and Dissolution

Immediate-release tablets should disintegrate promptly after contact with gastrointestinal fluid, allowing the API to become available for dissolution. Disintegration depends on tablet porosity, compression pressure, excipient type, disintegrant concentration, wetting and storage conditions [30,36].

Compression force can increase mechanical strength but may also reduce porosity and liquid penetration. Consequently, an optimum balance is required between hardness and rapid disintegration. Surface liquid absorption and swelling kinetics are among the factors that help explain how tablets break apart after wetting [36].

For BCS Class II NSAIDs, rapid disintegration alone is not sufficient if the API remains poorly soluble. Dissolution enhancement must therefore address both tablet breakup and the intrinsic dissolution behavior of the drug.

11. Dissolution Enhancement Strategies for NSAIDs

Dissolution enhancement can be approached through formulation and material-engineering strategies. Particle-size reduction increases surface area and may accelerate dissolution, although excessively fine powders can impair flow. Solid-state modification, amorphous systems, inclusion complexes and other technologies can also improve apparent solubility or dissolution rate [22,23,37].

For ibuprofen and other NSAIDs, formulation and delivery strategies have been studied extensively, demonstrating that formulation can influence the rate at which drug becomes available for absorption [20,21]. The selection of a strategy should consider manufacturability, physical stability, dose loading and compatibility with the intended dosage form.

12. Immediate-Release NSAID Tablets

Immediate-release NSAID tablets are designed to release drug rapidly after administration. Formulation performance is determined by the combined effects of API properties, excipient selection, particle characteristics, compression conditions and disintegration.

Studies of directly compressed NSAID formulations illustrate the importance of excipient grade and manufacturing approach. Comparative evaluation of diclofenac sodium tablets prepared with direct-compression excipients versus wet granulation has highlighted the impact of formulation and process selection on tablet quality [28]. Direct compression optimization has also been reported for ibuprofen tablets [40].

13. Continuous Direct Compression

Continuous direct compression is an emerging manufacturing platform in which material feeding, blending and compression occur continuously rather than as discrete batch operations. It offers potential advantages in process control, reduced hold times and improved manufacturing efficiency. Recent reviews have summarized the development and process considerations of continuous direct compression [38]. Continuous manufacturing has also been investigated for sustained-release tablets, demonstrating the broader potential of continuous powder-processing platforms [39].

For high-dose immediate-release NSAID products, continuous direct compression may offer opportunities for tighter control of material residence time and process consistency, provided that powder feeding, blend uniformity and process monitoring are adequately addressed.

14. Quality by Design Approach

Quality by Design (QbD) provides a systematic

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framework for linking material attributes and process parameters to critical quality attributes (CQAs). In direct compression, relevant CQAs can include assay, content uniformity, tablet weight, hardness or tensile strength, friability, disintegration and dissolution.

Potential critical material attributes include API particle size, morphology, bulk density, flow properties and moisture, while critical process parameters may include blending time, lubrication time, feeder settings, compression force and turret speed. A risk-based approach can identify the variables most likely to affect product performance and guide experimental design and control-strategy development [25,29].

15. Evaluation of Directly Compressed NSAID Tablets

A comprehensive evaluation program should include both pre-compression and post-compression tests. Pre-compression characterization may include bulk density, tapped density, angle of repose or other flowability indicators, particle-size distribution and moisture assessment.

Post-compression testing generally includes appearance, weight variation, thickness, hardness or tensile strength, friability, disintegration and dissolution. Drug assay and content uniformity are important for confirming dose accuracy. Dissolution testing is particularly critical for BCS Class II drugs because release from the dosage form can have a direct impact on drug availability.

The interpretation of these tests should be integrated rather than considered independently. For example, increasing compression force may improve mechanical strength while delaying disintegration and dissolution. Similarly, increasing lubricant concentration may improve ejection while adversely affecting wetting and tablet bonding.

16. Evidence from NSAID Direct-Compression Studies

Published work supports the feasibility of direct compression for selected NSAID formulations. Direct-compression development of ibuprofen tablets has demonstrated that appropriate formulation and optimization can produce satisfactory tablet performance [40]. Comparative work with diclofenac sodium has further emphasized the role of direct-compression excipients and the influence of manufacturing route on tablet characteristics [28].

More broadly, reviews of direct-compression excipients establish that successful tableting depends on matching excipient functionality to the physical and mechanical requirements of the API [11–15,29]. These findings support a formulation strategy in which high-functionality excipients are selected to address poor flow, compactibility and disintegration simultaneously.

17. Emerging Strategies

Current development trends include engineered excipients, spray-dried materials, co-processing, continuous manufacturing and increasingly data-driven process control. Spray drying has been investigated as a method for generating pharmaceutical powders with properties suitable for direct compression [35]. Co-processed excipients provide another route to improving functionality without increasing the number of processing steps [12,13,32,33].

Future development is likely to emphasize integrated control of powder properties, process monitoring and dissolution performance. For BCS Class II drugs, formulation design should increasingly combine manufacturability with strategies that improve the rate and reproducibility of drug dissolution.

18. Critical Analysis and Research Gaps

Although direct compression offers substantial manufacturing advantages, it is not universally suitable for high-dose BCS Class II NSAIDs. The dominant limitation may shift between poor flow, inadequate compactibility, segregation, lubrication sensitivity and dissolution depending on the API and excipient combination.

Important research gaps include better prediction of direct-compression performance from API material attributes, improved understanding of high-drug-loading blend segregation, optimization of lubrication without compromising dissolution, and systematic integration of particle engineering with continuous manufacturing. More comparative studies are also needed to establish when direct compression provides a meaningful advantage over wet or dry granulation for specific high-dose NSAID products.

19. Future Perspectives

Future formulation development should focus on multifunctional excipient systems, engineered API particles, robust QbD-based control strategies and continuous processing. Advanced characterization tools and process analytical technologies may further improve understanding of powder behavior and enable real-time monitoring.

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For high-dose BCS Class II NSAIDs, the ideal formulation would combine high drug loading with reliable flow, minimal segregation, efficient compaction, rapid disintegration and enhanced dissolution. Achieving this combination will require simultaneous optimization of formulation composition and process conditions rather than isolated optimization of individual excipients.

II. Conclusion

Direct compression is a promising manufacturing approach for high-dose immediate-release BCS Class II NSAID tablets when the formulation can be engineered to overcome the intrinsic limitations of the API. The major challenges include poor flow, high drug loading, compressibility and compactibility limitations, segregation risk, lubrication sensitivity and dissolution constraints. MCC, pregelatinized starch, superdisintegrants, glidants and lubricants can provide complementary functionality, while co-processed excipients and particle-engineering approaches can further expand the formulation design space.

For poorly soluble NSAIDs, successful product development must ultimately connect powder properties and tablet manufacturing behavior with rapid and reproducible drug dissolution. QbD and continuous manufacturing approaches offer opportunities to improve process understanding and robustness. Overall, rational material selection, controlled processing and integrated evaluation remain essential for developing high-quality directly compressed NSAID tablets.

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