Ten Years of the Manufacturing Classification System: A review of literature applications and an extension of the framework to continuous manufacture

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Abstract

The MCS initiative was first introduced in 2013. Since then, two MCS papers have been published: the first proposing a structured approach to consider the impact of drug substance physical properties on manufacturability and the second outlining real world examples of MCS principles. By 2023, both publications had been extensively cited by over 240 publications. This article firstly reviews this citing work and consider how the MCS concepts have been received and are being applied. Secondly, we will extend the MCS framework to continuous manufacture.

The review structure follows the flow of drug product development focussing first on optimisation of API properties. The exploitation of links between API particle properties and manufacturability using large datasets seems particularly promising. Subsequently, applications of the MCS for formulation design include a detailed look at the impact of percolation threshold, the role of excipients and how other classification systems can be of assistance. The final review section focusses on manufacturing process development, covering the impact of strain rate sensitivity and modelling applications.

The second part of the paper focuses on continuous processing proposing a parallel MCS framework alongside the existing batch manufacturing guidance. Specifically, we propose that continuous direct compression can accommodate a wider range of API properties compared to its batch equivalent.

Introduction

The Manufacturing Classification System (MCS) grew out of an Academy of Pharmaceutical Sciences (APS) conference in 2013 aiming to link the properties of Active Pharmaceutical Ingredients (API) to manufacturing process selection. Two peer-reviewed papers followed: the first paper outlined the concept of an MCS based on processing route[1]. These routes were Direct Compression (DC) *MCS Class 1*, Dry Granulation (DG) *MCS Class 2,* Wet Granulation (WG) *MCS Class 3,* and Other Technologies (OT) *MCS Class 4*. The MCS preference is to choose the lowest Class that will deliver a robust final manufacturing process.

Whilst more complex routes can allow the formulator to process a wider range of API properties, they can have their downsides in increasing process complexity, cost of goods and introducing stability risk. The second paper analysed commercial formulation data from regulatory filings and concluded that a simple model using API solubility and dose was linked to drug product process choice[2]. More specifically, poorly water-soluble APIs and higher doses are associated with higher MCS Class numbers. This paper also gave some initial consideration to continuous manufacturing (CM) and how its MCS considerations could vary compared to batch manufacture but did not propose a detailed MCS structure for continuous.

This paper has two aims. Firstly, to carry out a literature review to establish if we can build on our existing knowledge through publicly available research and secondly, to carry out an in-depth analysis of the API properties that are suitable for CM for incorporation into the MCS framework and to determine its relationship to batch manufacture.

Literature Review Introduction

The structure of the review will adhere to the drug product development process. The MCS working group believes that the API is the starting point for drug product manufacture, and therefore, we have started with a Materials Science section focussing on API properties and their optimization. The next section examines how the MCS can be applied to the design of formulations, including a detailed examination of the impact of percolation threshold, the role of excipients, and how other classification systems can be helpful. The final section of the review concentrates on manufacturing process development, encompassing the role of strain rate sensitivity and the application of modelling techniques.

There has been a steady increase in the number of papers citing the MCS since the initial publication in 2015, followed by a relatively consistent number in the last few years. Although the original 2015 paper was authored from the United Kingdom, an analysis of the geographic location of citing papers shows that awareness of the concepts has spread globally. The United Kingdom, United States and Germany have generated the highest number of citing papers comprising over half of the total. There are contributing citations across a broad range of European countries as well as in Asia with China, Japan and India demonstrating the greatest awareness of the MCS and there are also several citing papers from Brazil and Australia. A standalone MCS working group of the Japan Pharmaceutical Manufacturers Association conducted two surveys in Japan and is preparing to publish the results.

The MCS was developed and presented from an industrial context, outlining principles and properties to facilitate selection of robust oral solid dose manufacturing processes. In Table 1, an analysis of the author affiliation of citing papers shows an increased awareness and usage by academic researchers, as well as a significant proportion of citing papers that have been developed through academic and industrial collaboration. These mixed collaborations show the relevance of the MCS to the industrial environment based upon sound science and enables more information to be extracted from scale-down characterisation or miniaturisation techniques.

Before we start the literature review proper, it is important to note that, of the papers reviewed, there is a substantial number that use the MCS as a reference source for desirable or undesirable particle properties e.g., when carrying out crystal engineering. Although the MCS may be most often referred to in passing, it does illustrate that it is increasingly being used as a source for such standards by both industrial and academic groups. A summary of the references used can be found in Table 2.

Materials Science Summary

Studies that used the MCS as a starting point for investigating the influence of material properties on manufacturability were classified into three main categories:

1. Relationship between molecular properties and manufacturability.
2. Relationship between particle properties of single materials and manufacturability.
3. Relationship between particle properties of multiple materials and manufacturability.

Relationship between molecular properties and manufacturability

The approach of using digital tools to enable understanding of manufacturability using the chemical structure as an input is an intriguing one and an extension of the MCS concept which relies on particle properties. A study published as part of the Advanced Digital Design of Pharmaceutical Therapeutics (ADDoPT) project made use of digital techniques to propose a means to establish a chain of properties from molecular structure (based on single crystal data) to powder properties[3]. The authors suggested that *in silico* models could be used to estimate properties which in turn could be used to assess the feasibility of different processing routes via the MCS concept. The authors specifically concluded that through a combination of computational and topological methods, the particle properties of the drug lamotrigine could be better understood, thus providing a means to rationalize formulation and manufacturing issues encountered for the material. Such approaches propose an engaging mechanism to work from a chemical structure through to particle properties and thereby some understanding of powder properties. It must be noted that such approaches rely on an assumption that 'perfect' single crystal particles can be used as a surrogate for real-world particle behaviours. In practice, a range of morphologies is often observed within a single API, many of which contain imperfections. Even perfect particles will undergo attrition and chipping during processing. It can be argued that such defects may predominate when defining bulk and powder properties, thus meaning that a link between molecular properties and manufacturability may be challenging. We are still some way off from linking the molecular properties of individual API and their manufacturability requirements.

Relationship between particle properties and manufacturability (single material):

The MCS provided a framework that explained what formulators need to look for in their API to successfully manufacture drug product, thus enabling assessment of the impact

of particle properties such as size, shape and crystal habit on processability. This allowed researchers to move on from merely demonstrating that particle engineering approaches could be used to change crystal morphologies to a space where specific properties/habits could be targeted to enable improved processability. An increased focus on particle shape to enable improvements in powder processability was also observed.

Morrisson *et al*[4] agreed with the MCS view that single API parameters were not sufficient to explain API properties such as dissolution and cohesivity. Only by studying a number of important properties together, the so-called "API camera", could a holistic view of API properties be realised. Useful case studies identified how changes in API properties were the root cause behind poor flow and slow dissolution.

In an example of the increased focus on particle shape, Wilson *et al*[5] utilised the principles of the MCS, linking the shape of particles to bulk properties such as flow and processability. The authors adapted the crystal habit of a needle-like API, by means of wet milling and/or temperature cycling, to change the length and width of the particles. The work demonstrated that the shape of the particles had a notable impact on both powder handling metrics (e.g., cohesion, flow) and roller compaction (RC) processability. The authors reported that reductions in elongation of the particles typically lead to improved flow, reduced cohesion and improved processability, in this case demonstrated through reduced variability during RC of formulated blends containing the engineered APIs. Similarly, Ghazi *et al*[6] investigated the effect of particle shape and size on processability. In this work, the effect of acetaminophen particle shape and size on tablet characteristics was investigated for a range of high API loaded formulations manufactured by direct compression (DC). Three different classes of acetaminophen were selected, and tablets were produced using both single tablet and rotary tablet press processes. A comprehensive series of blend (e.g., content uniformity and segregation potential) and tablet (e.g., compaction profile, hardness, disintegration, dissolution and friability) characterization tests were then applied to show that tablet hardness, disintegration and friability were very sensitive to the shape and size of the API particles with needle-like particle habits observed to have a negative impact of processability and performance similar to the Wilson *et al* findings[5].

Another study on particle shape[7] used X-ray microtomography (XRMT) to visualise consolidation in powder beds predicting bulk and tap density behaviour for two different morphologies (prismatic and needle like) of L-glutamic acid. The use of XRMT enabled the authors to image blend components 3-dimensionally thus providing greater insight into the particle characteristics. The XRMT data gave an insight into why the prismatic material was more efficient in packing than the needles and why bimodal particles facilitate packing and tabletting. The study demonstrated that whilst the prismatic morphology enabled stacking of particles, with smaller particles filled the remaining voids, the needles formed stacks with the particle axis broadly perpendicular to the powder bed axial coordinate forming a "web" of interlocked particles thereby reducing the bed's ability to reorientate the particles. XRMT was able to visualise the structure of both the powder bed and compacts of material. This gives valuable information linking particle properties to bulk behaviour such as flow and

compactibility. The technique could visualise the poor geometric packing of needle-like particles.

In two other studies[8, 9] X-ray microscopy (XRM) was applied with an artificial intelligence image analysis algorithm to assess and understand the impact of API and excipients particle size[8] and particle morphology[9] during solid dosage manufacturing. In the first study the API and excipients particle size evolution was followed during blending, dry granulation and compression; The XRM data showed that attrition of the API agglomerates occurred during dry granulation resulting in an increase in fines and which was also observed in the tablet. Applying XRM to spray dried particles[9] demonstrated the usability of XRM to give insight in the impact of different particle morphology created by variation in spray drying conditions resulting in two different batches of spray dried powders with different properties for the same API. The dissolution behaviour of the two corresponding tablets based on the spray dried powders could be explained by the differences in tablet microstructure including porosity, surface area and pore connectivity. The two studies and the previous one demonstrate that X-ray techniques can be a highly useful tool for further quantitative insights and impact of the different unit operations in oral solids manufacturing.

Another very relevant study[10] examined API particle size distributions frequently encountered in industry: jet-milled and wet milled particles. Flowability of the pure API lots was similarly poor regardless of how they were milled. However, when blends with excipients were prepared, the flowability was significantly improved for the wet milled API mixtures (having bigger API particle size) compared to the jet milled API. It is likely that these observations could relate to percolation threshold effects[2]: the wet-milled API may not show improved flow by itself but will require a lower amount of excipient added to make it processible. The finding that similarly poor flowing APIs could result in significantly different blends is important in early phase development during API selection.

Two papers by a University of Copenhagen-led group told a holistic story about how altering crystal morphology can lead to improved powder flow properties. In their first study, the authors succeeded in altering the morphology of 5-aminosalicylic acid (5-ASA) from acicular to a range of different particle shapes (e.g., prisms, columnar, tabular and lath) using a series of crystallization solvents to inhibit growth of selected crystal facets thereby delivering changes in particle morphology[11]. A follow-up paper focussed on how different morphologies affected bulk powder properties such as flow and bulk density, and processability (e.g., tensile strength of pure API compacts)[12]. They found that morphologies such as needles and plates resulted in poor flow, low bulk density but acceptable tensile strength whereas spheroids, elongated hexagons and rhombohedrons resulted in more free-flowing powders with higher bulk densities but lower tensile strengths, once again demonstrating the importance of particle shape/habit on the processability of powders.

Researchers from Ghent University[13] investigated how variations in particle properties can change the bulk behaviour and processability of an API and the associated high API loaded formulations. In this case the impact of changes in the process route (crystallisation conditions and post-crystallisation process steps) on the particle characteristics (particle size and shape, agglomerate size and surface properties) and associated processability

characteristics for the formulated material (feeding, blending, granulation and compressibility) were assessed. The work demonstrated that the flow of the API was dominated by the agglomerate size / fraction and the crystal length; the latter characteristic was also suggested to correlate to the propensity for agglomerate formation and their relative strength. It should be noted that the authors of this study took a stepwise approach to narrow down the important parameters by means of multivariate analysis, an approach that assumes that all important factors are included in the initial screening.

In the above studies, the effect of the input particle properties of a single species on the bulk powder properties and/or processability was addressed with the underlying assumption that those properties do not change during subsequent processing. A short focus paper[14] addressed an important question of changes in API properties during processing due to mechanical, thermal or other stresses. The authors demonstrated how changes in size and shape of API particles within multi-component systems (e.g., blends) could be determined and this approach was then utilised to enable an understanding of how the API properties change at various stages of a process train. This work, an extension of the MCS, poses some interesting challenges with regard to the ability to understand (model) the influence of input API particle properties on processing behaviour when those characteristics are changed during manufacturing and the requirement, in such cases, to track the nature of the particles at each stage. The behaviour of a particle that sticks, for example, is governed by its size when it reaches the tablet punch, not its size prior to processing. Could understanding the propensity for morphological change be a future topic of interest?

Relationship between particle properties and manufacturability (multiple materials)

In the previous section, several research teams addressed the influence of the particle properties of a single species on the bulk powder properties and/or processability. However, looking at a single material has its limitations. Several studies attempted to address this effect by means of larger populations of API/excipient species to investigate a wider range of characteristics and behaviours. These approaches often utilised complied databases of materials, both generic and proprietary. The Ghent University group for example utilised databases on excipient and API properties, but these are not open databases[13].

Ferreira *et al*[15] looked at moving beyond the external, high-level MCS to an internal company MCS. The paper highlighted the strategy which targeted only analytical techniques relevant to the problems in hand, gathering high quality data on appropriate instrumentation, conducting data analysis on the data obtained with an aim to put the data in an overall context (e.g., understand how new materials fit into the spectrum and history of materials) and then use this to compose Target Material Profiles (i.e., instruction to chemists on the material parameters needed to make the desired drug product). The authors highlighted the risk of using percentile descriptors (statistical descriptors of log-normal distributions e.g., D[v,0.5]) for particle size and shape data where distributions are not perfectly log-normal as the descriptors may not completely describe the true nature of the materials. An example of PCA modelling of samples with three distinct classes of bimodality using both percentiles (D[v,0.1],

D[v,0.5] and D[v,0.9]) and whole distributions showed that differentiation of the classes could not be achieved using the percentiles as the descriptors did not adequately describe the nature of the distributions.

Barjat *et al*[16] used a library in a comprehensive experimental study to predict powder flowability in continuous direct compression (CDC) based on a range of powder and bulk measurements. In this case, the library was built using data collected from the ADDoPT consortium of several UK based companies and academic groups. The dataset constituted a wide range of properties for 58 APIs and 48 excipients with the characterisation data selected prior to the study based on an understanding of the most likely particle attributes to have an influence on the output parameter. As such, the paper picks up many ideas of MCS and even extends the application, e.g., by applying the statistical model to *in silico* particles to optimize the performance. The results of the study demonstrated that the flowability of the particles could be predicted using the measured particle characteristics with particle size and shape in general the best predictors of flow. Echoing the findings from Ferreira *et al*[17], the authors used whole size and shape distributions rather than percentile descriptors and made a first attempt to describe shape and size in a single plot. Some additional interesting findings of the study were that the use of number weighted size and shape data precluded the need for surface area data in the model whilst surface energy data were observed to provide no relationship to powder flowability.

The benefits of the utilisation of whole particle size distributions, especially when combining both size and shape distributions was further developed in a paper describing the utilisation of image analysis characterisation data spanning well over a decade's worth of powders[18]. The authors described how whole distributions (volume and number weighted) for particle size and particle shape for over 1000 materials enabled the development of a morphological landscape enabling a better means to compare the behaviour of historical materials and suggested the approach could lead to improved understanding of the inter-relationship between particle and bulk powder behaviours such as flow. The authors provided an example of three commercial successful DC APIs in the landscape showing that their properties were very similar and generally match the requirements set out in the original MCS paper albeit all materials had bimodal size distributions leading the authors to suggest this distribution shape as a possible additional 'characteristic' for DC materials.

A complementary but distinct study from AstraZeneca linked a bulk property (flow) along with drug loading to see its influence on process choice utilising an extensive industrial database of materials[19]. Historical data (3909 experiments) from a shear cell apparatus were extracted and analysed. These data were composed of different material types, including APIs, excipients, blends and granules constituting almost a decade worth of development project data. The study demonstrated that the API flow properties were a good indicator of handling challenges and the complexity of the processing route required for eventual product success. This paper provides a great example of how historical data can be utilised to generate understanding. An obvious next step would be to examine material particle properties and how they link to the bulk property of flow. This would complete the chain linking particle properties to process choice.

A University of Toyama-led group utilised a library of 81 API materials to model the relationship between physicochemical properties of the APIs and the tensile strength of tablets[20]. Each of the APIs were evaluated for characteristics such as particle size distribution, bulk density, tapped density, Hausner ratio, moisture content, elastic recovery, molecular weight, and partition coefficient. Tablets containing 50% API, 49% MCC and 1% Mg stearate were then prepared, and their tensile strength measured. The results of the study revealed that diameter of powder particles at the 10th percentile of the cumulative percentage size distribution was the most crucial factor for tensile strength. A second paper used the same library to model the influence of 20 API properties at three levels of tableting pressure on the corresponding tablet properties: i.e. tensile strength, disintegration time[21]. As with the previous study, the APIs were incorporated in a standard formulation and directly tableted; other manufacturing routes were not addressed. In this study, the diameter of powder particles at the 10th percentile of the cumulative percentage size distribution and the specific surface energy were the most crucial factors for tensile strength and disintegration time. It should be noted that in both cases, the conclusions of the modelling were not verified in practice. One possible limitation of this type of approach is the assumption that all relevant characteristics are captured in the library. Careful consideration of the variable selections and their possible relationship to the output properties is required to ensure results of models are truly indicative of the particles and not an artifact related to deficiencies in the dataset and/or modelling i.e. there is a risk the model simply "overtrained" on a small dataset with resulting limited predictive power.

In a study reported by Van Snick *et al*[22], an extensive raw material property database was developed including a wide variety of APIs and excipients with different functionalities. In total 55 different materials were characterized and described by over 100 raw material descriptors related to particle size and shape distribution, specific surface area, bulk, tapped and true density, compressibility, electrostatic charge, moisture content, hygroscopicity, permeability, flowability and wall friction. The purpose was to aid the development of *in silico* systems for the prediction of material properties to shorten product development time and improve process control by rationalizing the number of critical techniques for routine characterization of materials. The application of this database is discussed further in the CM section later in this paper.

MCS in Formulation Design Papers

In this section we will move into the territory of traditional drug product development where the API is combined with excipients. This introduces increased complexity with the need to consider these new materials as well as the impact of drug loading and the importance of percolation threshold. Complexity increases further in the case of dosage forms such as minitablets, fixed dose combination products and multiple unit systems. An overarching approach taken in the literature was to use MCS as a guidance to select the optimal robust manufacturing process based on scientific rationale. Some authors[23] have also included MCS as part of a larger decision tree where a structured approach was taken to obtain a suitable formulation design, as well as a robust manufacturing process. We will also

discuss different classification systems such as the Sistema Experto para Desarrollo de Medicamentos (SeDeM) Expert System and the Compression Behaviour Classification System (CBCS) and outline how they might be complementary to the MCS.

Percolation threshold

The concept of percolation threshold and its impact on properties were previously described in the MCS papers. Percolation theory is part of statistical physics and the application of such fractal concepts has been recently reviewed for the field of oral dosage forms[24]. A percolation threshold corresponds to a critical concentration of a formulation component (i.e., API or excipient concentration or alternatively, a corresponding solid fraction or porosity) above which an abrupt change in drug product properties occurs, due to the formation of a continuous network of contact points[25]. Drug product properties can be described in a critical range by a power law with a characteristic exponent[26]. However, a complication is that the percolation threshold itself is not universal but depends, for example, on API properties such as particle size and shape. A threshold drug concentration was proposed in contrast to a gradual change in blend properties with increasing drug concentration[27]. As excipients can be generally regarded as helpful for manufacturability, and API as generally unhelpful, it was proposed that issues can be expected to occur in manufacturability and drug product quality above the percolation threshold concentration of API. For example, increased bulk flow variability was observed in blends above the API threshold that subsequently resulted in an increased fill weight variability in capsule manufacturing[28]. In terms of a quality by design (QbD) approach to pharmaceutical development, the percolation threshold model can aid identification of a threshold level of drug above which critical quality attributes of the formulation become highly variable and hence outside of robust manufacturing ranges. Therefore, knowledge of the percolation threshold of drug and/or excipient level can aid robust formulation development.

Queiroz *et al*[29] used tablet envelope density and tablet tensile strength to predict percolation thresholds mathematically. The authors studied mixtures of ibuprofen and microcrystalline cellulose and the values obtained were consistent with earlier reported threshold values for similar drug/excipient combinations. Dilution capacities of 19% (w/w) and 17% (w/w) ibuprofen were calculated for both Vivapur® and Emcocel® blends, respectively. A change in blend behaviour above the threshold value was confirmed by experimental flow data with weight variability due to poor flow noted. Also, Raman imaging confirmed the presence of coherent clusters of drug on the tablet surface above the threshold value. The minor differences in physical properties between MCC grades did not result in significantly different dilution capacities. The modelling approach used in this study can be applied to early formulation development studies to identify optimal drug loading for robust pharmaceutical blend processing.

Wenzel *et al*[30] confirmed the critical importance of drug load by studying formulations containing different concentrations of the poorly soluble API mefenamic acid. Manufacturing involved RC and tableting followed by dissolution testing of the final dosage form using a

biorelevant medium. It was observed that the increasing intragranular mefenamic acid concentrations influenced granule and tablet characteristics (such as granule size distribution, compression pressure during tableting and tablet disintegration), and at the same time negatively impacted the dissolution rate. A percolation threshold of approximately 20% (w/w) was determined for both micronized API and sieve fraction, while the impact of drug load on the dissolution kinetics was more pronounced for micronized API, which is in agreement with MCS observations[2]. Hirschberg *et al*[31] confirmed the finding that smaller API particle sizes had lower percolation thresholds in this case influencing flow properties. They found that the critical drug loading was lower for blend flow than tabletability meaning that flow was the limiting property for these APIs. In our later section on CM, we will outline how this technology could aid manufacturability for such APIs.

It can be concluded that percolation theory provides a useful theoretical framework to approach the complex and non-linear behavior of pharmaceutical dosage forms. It was outlined previously that part of a structured formulation development should early on consider the MCS[23] and in a phase of limited API availability, any guidance based on percolation theory is highly beneficial.

MCS and excipients

The basic idea of the MCS was to select a manufacturing technology based on defined material properties of the API. This was because the API was considered as the most troublesome material for processing, with excipients assumed to be designed to be good at making oral solid dosage forms. However, some authors have disagreed with this approach and have proposed extending the concept of the MCS to the selection of excipients either as a separate system or one that is integrated with API selection. There is a particular need to establish a scientific justification for the definitions used by excipient manufacturers to classify different excipient grades as being suitable for particular processes. There are currently differing approaches as to how such companies classify whether materials are suitable for DC, for example.

Orubu and Tuleu[32] examined the challenges during product development of flexible pediatric solid oral formulations for low-income countries. A preferred route of manufacturing in these countries is the comparatively low-cost DC approach. Intriguingly, they proposed that combining the MCS with a complementary excipient guide could lead to a "single expert system". The excipient guide may help to select excipients to compensate for undesired API properties. Regarding the excipient guide they refer to Suñé-Negre *et al*[33] who used the SEDEM Diagram Expert System to classify DC excipients. This suggestion is just an initial proposal with no examples presented or detail on how it could work in practice.

Arndt and Kleinebudde[27] emphasized that the MCS is based on the properties of all the raw materials employed in tableting. Hence the properties of excipients, as well as of the API, should be considered when proposing an extension of MCS. The paper looked at RC of dry binders, followed by tableting at different compression speeds, with the aim of understanding the binder functionality for dry binders of chemically different types.

Viscoelasticity, plasticity or abrasiveness were derived from force-displacement curves of tablets, on which bonding energy and out-of-die Heckel analysis were performed in order to get a comprehensive understanding of the mechanical properties of dry binder for tableting.

The group at Heinrich Heine University further built on this philosophy of understanding the relationship between properties of all starting materials and the feasibility of a certain production route. They proposed to expand knowledge of how excipients can be further modified by particle design beyond the traditional considerations of size and shape. Instead of selecting the suitable excipients for an intended route, the excipients should be designed to improve the overall performance of the intermediate granules and the derived tablets, targeted to a certain manufacturing technology. Excipients can serve as surrogates for APIs to study the relations between particle properties and route of manufacturing. Lessons learned from excipients regarding particle design and morphology may be transferred to APIs.

This was exemplified by the use of functionalized calcium carbonate in a RC / DG (RCDG) process[34]. Another excipient which was examined was anhydrous calcium phosphate[35]. There were substantial differences in blend suitability for RCDG based on the structure of excipient particles. Compact crystals behaved differently from agglomerates of small primary particles. A special functionalized type with large porous agglomerates of extremely small primary particles showed a unique performance in RCDG. The authors proposed that "the morphology of the raw material should be taken into account for the evaluation of the loss in tabletability of dry granules and described particle properties of an agglomerated raw material should be implemented in a potential manufacturing classification system". The same group studied a third excipient, examining the effect of lactose particle size and morphology (agglomerates and primary particles) on the properties of the dry granules and tablets produced [36]. They found that lactose morphology affected the strength of DC compacts. In this case, the morphology of the particles was more qualitative in nature than previous studies, reporting a general overarching description of the shape of the materials rather than providing measured characterisations, with minimal variations in particle morphology. These studies are not necessarily an extension of the MCS to excipients, but the insights derived from studying different types of an excipient may be transferred to APIs which can be designed in such a manner that manufacturing is facilitated.

Berkenkemper *et al*[37] supported this, explaining that excipient attributes play an important role during drug product manufacturing, as well as having an impact on product performance. A manufacturing process based on API characteristics matched with the right excipient and with the manufacturing process could support formulation design. The authors used a formulation with 20% ibuprofen in DC and DG. Based on the findings MCC would be preferred as filler in DC, and mannitol in DG. Regarding the disintegrant performance, crospovidone showed a high sensitivity to DG while croscarmellose was less affected. The results shown were more a selection of excipients for different manufacturing routes and less a selection of excipients based on API properties. A systematic approach to select excipients based on API properties rather than a case-by-case approach is not made. However, excipient attributes are generally well known relative to novel APIs. The authors' view was that the

purpose of the MCS was to predict whether simple addition of excipients can aid DC processability. If not, MCS determines the degree of additional processing, such as granulation, which in turn further influences excipient selection. Characterization of API properties dictates choice of process, which, in turn dictates choice of excipients. However, by contrast, excipient properties may support multiple processes.

Putting it all together: Applying the MCS to formulation development and comparison to other classification systems

Oishi *et al*[38] explored the creation of a novel large dataset for ibuprofen tablets comprising several granulation methods. They used normalized linear regression including interaction terms to predict the tablet critical quality attributes from critical material attributes such as API particle size and bulk density and critical process parameters. Their aim was to understand better the causal relationships between material attributes, process parameters, and critical quality attributes. They discussed that the created dataset would be important in terms of the MCS because it helps in understanding the relationship between production methodology and the products in the dataset.

Kuentz *et al*[23] reviewed different methods to select oral formulation strategies for small-molecule drugs. Various flow-charts were presented for decision making based on the specific drug properties towards a more tailored approach to formulation design. Once a promising formulation strategy has been selected, the paper emphasizes the importance of a structured approach to obtain a suitable formulation design as well as a robust manufacturing process. In this context, MCS is mentioned as it guides formulators in the selection of adequate process technology based on individual drug properties rather than relying on general knowledge and assumptions in the field of solid dosage forms. They speculated that the MCS could have merit in a risk assessment of given manufacturing processes by Artificial Intelligence (AI). However, Barjat *et al*[16] showed that large data sets containing a broad range of values were needed to enable the development of predictive systems.

Lavra *et al*[39] developed and scaled-up a fixed dose combination for HIV treatment containing three APIs. The selected process was WG due to the properties of one of the APIs not being amenable to DC. This illustrates that for combination products the process will be determined by the API with the poorest properties.

Elezaj *et al*[40] extended the concept of the MCS to develop minitablets for paediatric use. They used the MCS only in a high-level way, first utilising DC and when this did not work moved to DG which was shown to be suitable. These researchers did not make formulation selection on the basis of API particle properties or percolation threshold.

Vasiljevic *et al*[41] compared the applicability of three powder compression behaviour assessment approaches to the tableting of pellets, made by either extrusion/spheronization or kneading/granulation:

- MCS
- SeDeM

- CBCS

SeDeM evaluates material properties affecting powder processability, particularly compression behaviour. Relevant parameters were divided into 5 groups denoted as "incidence factors". In CBCS, powders are classified by compressibility, compactibility and tabletability. Compressibility is based on Heckel equations, brittle vs ductile by the Shapiro equation, and particle rearrangement by the Kawakita equation. Compactibility is assessed using the Ryshkewitch-Duckworth equation and tabletability from the Power equation. Powders with excellent tabletability even at extremely low-pressures (20–30 MPa) are classified into Category 1. Category 2 powders give increasingly acceptable tensile strengths with increasing pressure (2-3 MPa at 50-200 MPa) and Category 3 powders do not give acceptable tensile strengths even at higher pressures. Experimentally obtained parameters were mathematically transformed into the relevant radius parameters to allow visual comparisons of SeDeM and MCS. SeDeM and MCS parameters showed linear correlation. Experimental results were as expected, pellets flowed better than granules (MCS, SeDeM) but were less compactible (MCS, SeDeM, CBCS).

The authors concluded that MCS required more experiments and included more complex parameters, such as indentation hardness and dwell time sensitivity. However, this was based on the authors' interpretation that all Hancock DC criteria needed to be tested which is not necessarily the case. SeDeM was less demanding but did not give information on compactability. CBCS is compression only, whereas MCS and SeDeM also address density, flowability and particle size/shape. SeDeM limit values focus on an ideally compressible powder whereas MCS DC limit values appear more as a guideline, based on satisfying broader acceptable values rather than achieving an ideal case. Vasiljević *et al*[42] extended this comparison of the different descriptive approaches to powders. They examined both compressibility, compactability and tabletability descriptors as well as fundamental compression equations. They concluded similarly that the MCS had the optimal balance of complexity and coverage of key manufacturability attributes.

Fridgeirsdottir *et al*[43] reviewed applying different approaches to obtain an optimized formulation and manufacturing route for a poorly soluble drug. MCS was mentioned alongside other classification schemes such as the BCS and DCS as supportive tools helping formulators to select an optimized processing route. The four MCS classes were described and the opinion stated that MCS is not fully developed yet but is promising as an aid in formulation development. Other tools such as decision trees and guidance maps were summarised to give a holistic tool to the formulator.

Dai *et al*[44] evaluated the SeDeM expert system for tablet formulation design in relation to the MCS. They concluded that data in the SeDeM complemented the MCS allowing for better classification between DC and other processing routes. 12-sided radar charts applied by the SeDeM could provide a quick overview of risk levels and help identify poor physical characteristics and possible failure modes of the compression process.

In summary, all three systems are complementary: the MCS focuses on linking API properties to manufacturability, SeDeM focuses on matching excipients to the process (and API), whereas the CBCS is specialized in its focus on compactability.

Manufacturing Process Development

Introduction

In this section, a review of papers with a focus on manufacturing process development that were found to have cited the MCS will be presented. The discussion is grouped into several sections. Firstly, a summary of the different process technologies represented in the citations is discussed. Then, papers that discuss strain rate sensitivity in the context of scale-up of tablet compaction processes are analysed. This is followed by papers describing modelling approaches to predicting manufacturing performance are discussed. With the increased importance of digital approaches to accelerate pharmaceutical development, this is an important area for enhancing the predictive capability of the MCS approach. In the final section, a more in-depth discussion of CM is made. This is an important evolution of the MCS concept as, in addition to review, the section presents new proposals for the use of MCS in CM.

Process Technologies

Figure 3 shows a summary of the technologies covered by manufacturing process development focussed papers. Research based on DG and WG (MCS classes 2 and 3, respectively) most frequently cite the MCS publications. The next most frequent technology focus is feeders relating to their use in continuous processes[45, 46]. There are also a number that focus on DC, and CDC in particular[47-50]. These two categories of feeder and DC technology are essentially associated with MCS Class 1. Overall, the majority of papers citing the MCS focus on manufacturing technologies that cover classes 1-3. There are potentially several reasons for this. Firstly, these technologies are most frequently used for solid oral dosage manufacture[2]. Secondly, more detail was presented around associated physical property criteria and performance criteria for classes 1-3 in the MCS publications and therefore there it is of greater relevance to other researchers. Out of all the citing papers, only two deal directly with/reference the MCS class 4 of 'Other Technologies'.

Tran *et al* [51] reviewed the formulations and processing techniques used to produce freeze dried tablets. This review makes reference to the first MCS paper, specifically identifying DC as a straightforward way to produce tablets and explaining that tablet properties depend on excipients. Importantly, the paper then states that DC is not suitable for low bulk density powders and powders with poor flow. Freeze drying of liquids in blisters is offered as an alternative tablet production technology for powders with these properties.

Sauer *et al* [52] discussed formulation of a high drug load amorphous solid dispersion tablet using spray drying followed by dry granulation. The spray drying process resulting in a

powder with low bulk density and poor flowability. Process development requires material attributes outlined by the MCS to be considered in conjunction with process parameters to achieve the required critical quality attributes of the product. The MCS and its principles have also been referenced to inform process parameters.

Hwang *et al*[53] used the MCS to optimise a RC process. It was noted that the formulation contained fines in excess of the MCS specification and API content 37% exceeded the MCS recommendation for the percolation threshold of 20% for micronised API. The authors acknowledge these deviations could lead to a risk of sticking and picking and therefore introduced a fines reprocessing step to the process.

Compaction Speed (Strain rate sensitivity)

One often ignored factor is the influence of compaction speed on manufacturability: development studies may be biased towards lower speeds. Strain rate sensitivity (SRS) is a term used in pharmaceutical science to define compact properties dependent on the rate of compaction. The term can be used for both the differences in deformation yield pressure in-die due to the rate of compaction and the effects on strength properties of the resulting compact due to rate and dwell time effects on bond strength. Detailed definitions and methodologies for SRS calculation are beyond the scope of this paper.

The SRS of high drug load compression mixes should be assessed before scale-up (faster press speeds). Because SRS is dependent on the compression profile of a given tablet press (pre-compression, dwell time/punch velocity), early evaluation on a compaction simulator is recommended. Although SRS values have long been used for describing the time-dependent behavior of specific materials[1, 53, 54], most have used yield stress which can be challenging to relate back to tablet critical quality attributes such as tensile strength and dissolution. There is still no standard for selecting the range of compaction rates for the calculation when focusing on compact strength properties[55]. The range over which the strength speed sensitivity is calculated is very much dependent upon the test equipment available which makes robust comparisons problematic[56]. Kalaria *et al*[57] developed a useful methodology for assessing strain rate sensitivity by comparing tablet properties compressed at tablet press speeds of 50 and 90rpm. High SRS (30% or more in tensile strength) was considered a major risk for scale up, with the target for any tensile strength reduction being less than 0.5MPa.

Modelling

Modelling approaches using the MCS philosophy describing and predicting the relationship between material properties, process parameters and product attributes have been developed to increase process understanding, inform process route selection and scale-up. While statistical models are widely employed, the prediction capability of these models across products, processes and scales, is limited due to variability in material and equipment characteristics. Tahir *et al* [58] addressed some of these limitations with their PLS modelling

approach. The feed factor of common excipient materials through a loss-in-weight feeder was predicted using a generic model for excipients grouped based on their powder properties by PCA. Statistical models were developed for prediction of DC tablet properties upon scale-up by including blend flow and compaction behaviour, and tablet press model as categorical variables[47, 59]. In contrast to statistical models, mechanistic models provide first principle understanding and thereby reduce the requirement for extensive experimentation. Other researchers [60] developed a mechanistic model to predict the rate of discharge from an IBC based on powder average particle size and IBC opening diameter. Reynolds *et al*[61], presented a range of mechanistic models to develop and scale-up unit operations in an RC system. Pohl and Kleinebudde [62] reviewed the application of regime maps as a semi-empirical tool to aid the scale-up of processes, specifically granulation processes. Regime maps are an alternative modelling approach to statistical models to predict formulation behaviour during scale-up and inform process understanding.

An illustrative example of how the MCS principles can be utilised for mechanistic modelling of a tablet production system is provided by White *et al*[63]. MCS material attribute specifications were employed in a comprehensive manner to inform the development of a system model for tablet production via two process pathways: DC and a RC step. The system modelling approach connected individual unit operations and material models to create a single model which could account for the interdependency between individual unit operations and interactions between material properties, processing parameters and product attributes. The material constraints for design space responses generated from the system model were set with reference to MCS material attribute specifications. Additionally, the ability of the system model to inform process selection based on API properties and tablet critical quality attributes was illustrated through the generation of process classification maps. This paper is an excellent example of how the MCS criteria can be utilised for *in-silico* selection of process routes and process parameters based on API, intermediate and finished product properties.

Continuous Manufacturing Considerations for an MCS

Although the first MCS paper[1] primarily referenced traditional batch pharmaceutical manufacturing platforms, the second[2] discussed the relevance of the concepts for CM and that inclusion of CM into the MCS would require further consideration. During the literature review of MCS citing papers, some themes were identified which are intrinsically linked to the discussion on incorporating CM into the MCS. The impact of the API attributes on the blend flow and tablet compression are the key areas of focus when considering CM. Furthermore, the percolation threshold for API manufacturability (e.g. blend flow) increases, relative to the percolation threshold impacting product quality (e.g. dissolution rate).

Amongst the manufacturing process development papers citing the MCS papers, 22 are related to CM and the integration of continuous processes as defined by ASTM standards[64]. Several citing papers make general reference to MCS concepts. For example, continuous DG focussed papers refer to its selection if DC is not feasible[65, 66]. Continuous WG

focussed papers point out the selection of this technology is appropriate where drug load is particularly high or low or where API properties are particularly cohesive[67, 68]. Meena *et al*[69] present an example where continuous WG was selected for manufacture of a high (95%) loading of a poorly compacting API (acetaminophen). To meet MCS criteria for sufficient tensile strength, WG was required because this was not possible with DC or DG. Further details of these papers will be discussed in the subsequent context of how the current MCS can be extended to CM.

Beyond references to the MCS, there have been a handful of attempts to simplify the choice of batch or CM processes by developing regime maps to aid in the selection process. The second MCS paper[2] presented a regime map of drug loading vs API flowability showing the manufacturing processing route for a range of products in batch manufacturing where decreasing flowability and increasing drug loading resulted in shift from DC → DG → WG (i.e., an increase in process complexity)[19]. White *et al*[63] took this a step further and developed a system-based model to aid in the selection of CDC vs batch RC which incorporated material properties with the mechanistic unit operation models. However, the primary criteria were based on tablet compression performance, which leaves out two key features that have a direct impact on tablet performance (i.e., the blends entering the tablet press may not be equivalently mixed and, do not share the same consolidation risk). From the model, two process classification maps were generated to aid in understanding the risk for selecting from classes I, II, or III based on API mass fraction *vs* API flowability *vs* blend bulk density respectively[63]. They further explored two different tablet masses with the same drug loading and showed that larger tablets improved the likelihood of manufacturing CDC and RC process. This was mainly due to the combination of the API flowability influence from the higher drug loading on the smaller tablets and resulted in a regime map where API flowability had a narrower band for DC & RC processes. While the maps presented were admittedly simplified, they are based on the assumption that blends produced *via* batch are equivalent to blends produced in CM and therefore the compression step to form a tablet assumes that the compression performance is independent to this fact.

It is an open question if the decision between batch or CM is as simple as comparing performance between stand-alone unit operations, without considering the interdependency and assumptions made between upstream and downstream transformation steps from raw material to final dosage form. The forthcoming discussion will review and discuss the key technical considerations which would drive the selection of one mode of manufacturing over the other. We will first review the relevant considerations when choosing a batch or CM process, followed by a declaration of principles for incorporating it into the MCS.

A perspective often provided when deciding to use batch or CM processes is "*that not all API properties are suitable for CDC, that are suitable for DC*", where Wahlich[70] referenced data presented from the second MCS paper[2] on API properties GSK had investigated as suitable for CDC. The current version of the MCS does not provide guidance for choosing batch or CM routes, or whether the decision should be influenced by formulation or process specific requirements. The choice of DC versus granulation is presented broadly on the basis of favourable API properties, intended dosing regime, and manufacturing route based on batch

manufacturing, and verified by the study from AstraZeneca which demonstrated API flow properties were a good indicator of handling challenges and the complexity of the processing route required for eventual success and referenced in the section above on the relationship between particle properties and manufacturability (multiple materials).

To the contrary perspective, CM processes (particularly CDC) have been shown to be quite robust to variation of API properties since the referenced data was presented. Multiple case studies have been investigated in literature which demonstrate that CDC is a viable alternative manufacturing route to access a DC process, whereas the current MCS would recommend a batch granulation processes[71, 72]. CM has shown it can overcome the risk for segregation and the performance issues associated with poor blend flow of batch DC. However, this can only be true when the CM process train is properly designed at the interfaces between unit operations. The suitability of API properties for CM primarily lies in the ability to transport the bulk material to the feeder. Special attention needs to be given to the upstream bulk material handling design, but if this can be overcome, the ingredients are then actively fed into a continuous blender[73] and the API physical properties are less influential on process performance when under the appropriate feeding control scheme and associated design space. The forthcoming subsections will discuss these concepts in the context of choosing batch or CM to facilitate informed decision-making regarding risk management and impact of ownership.

Bulk Powder Supply and Feeding

The primary material handing risk that needs to be managed for batch or CM is the ability to supply the individual raw materials to the process and the transfer of the blend to the tablet press. These are challenges that need to be considered whether the raw materials are transferred to downstream equipment through IBCs, containment bags or even plastic containers. This requirement means that for CM, the bulk material handling upstream of feeding may be more sensitive to the inherent flow properties for a given raw ingredient than in batch manufacturing where raw materials are manually added to a container and then blended. The material handling in batch is focused on the flow of the blend out of its container for subsequent processing. With the appropriate control strategy in CM, there can be no impact to CQAs because this is mainly bulk transport to the feeder, rather than metered feeding of the correct ingredient proportions into the blender through time. Bulk material flow issues (raw material or blend) can typically be solved through mechanical flow aids [74] and optimizing the formulation components where possible. For CM, APIs are particularly the focus, as their flow properties have the potential to be quite variable, especially in earlier phases of development. A number of cited papers presented a range of powder characterisation techniques to improve insight and prediction of the relationship between material properties and the subsequent feeder performance.

Allenspach *et al*[45] presented some of these techniques, including angle of repose, bulk/tap density, dynamic flow angle, cohesive index and triboelectric charging. In particular, materials with large charge accumulation resulted in electrostatic build up during feeder

operation that caused an increased number of mass flow excursions during the run. As part of the UK-based collaborative research project called REMEDIES (RE-configuring MEDIcines End-to-end Supply) to evaluate the CDC operating space with respect to input material attributes, Yadav *et al*[46] also characterized a range of excipients and grades of acetaminophen alongside performance on a continuous powder feeder and confirmed a wide operating space of feeder performance over a range of divergent properties. Building on Yadav's work and through REMEDIES, Tahir *et al*[58] (2020) used these results to build a predictive model of feeder performance. The most significant material properties that were predictive of feeder performance were found to be the shear cell flow function coefficient (ffc), tap density and Carr's index. The most challenging powder that was run on the feeder was micronized acetaminophen. This powder has a bulk density of 0.19 g/cm^3, a d10 of 3 µm and a d90 of 33 µm. These properties are well outside of an ideal DC material[1], indicating that loss in weight continuous feeders have significant capability to deliver powders that are typically suboptimal for batch DC and potentially can widen the criteria for MCS class 1. The reason for this is that once the raw ingredient is delivered into the feeder, the feeders actively convey the powder from the hopper into the blender with the assistance of optimised screw options and mechanical configurations to aid powder flow[75-78].

Every unit operation in batch or continuous processes significantly benefits from risk-based development to assure that the long-term process is robust to incoming variation of the raw ingredients, and feeding is no different. Ensuring consistent feeding often comes down to the correct mechanical configuration combined with the optimal feedback control algorithm, which is a standard part of feeding development. The feeder operates by controlling a mass flow rate signal via loss in weight over a duration period of microseconds. However, the signal is increasingly difficult to detect over the ambient noise as the mass flow rate is reduced to levels where the signal to noise ratio becomes low for control. If it is feasible, the more obvious solution may be to increase the mass flow rate of the system, while keeping the feeding ratios the same to improve the signal to noise ratio. In cases where that may not be possible due to a limited supply of API or need for extremely small batch sizes, advanced algorithms[79, 80] or mini-batch feeding/blending[81] systems might be employed to supply the blend continuously to the tablet press. Another method that is routinely employed to mitigate feeding challenges due to low mass flow rates and cohesive powder is to pre-blend[75] with an excipient such as a glidant[77], effectively to have a batch blending step before dispensing to the feeder.

Continuous Blending

If the feeding has been established, the next key consideration is the blend homogeneity over time, whereas batch processes require homogeneity over space[82]. CM processes achieve homogeneity by actively blending the material *via* convective force imparted by the speed of the mixing paddles and their relative configuration to achieve a desired hold-up mass (control volume multiplied by the blend density)[83] rather than passive diffusion as in a typical batch bin blender. After the powder enters the blender in the right proportions, the powder is actively being further mixed down to the desired sale of scrutiny

(e.g. a unit dose) for the majority of the time. The blended material is then continuously supplied by gravity directly to a tablet press for compression[71, 73, 84, 85]. The combination of the active transport of the powder and short distance between unit operations in CM processes provides little opportunity for blended powder to segregate before tableting.

Jaspers *et al*[86] performed an in-depth study showing that the resulting materials properties of batch *vs* continuous blends were not necessarily equivalent. In CM of oral solids, blending performance is less sensitive to the selection of flow properties and particles sizes compared to batch, leading to reduced segregation risk and improved homogeneity. There was one observation however which saw that spray dried lactose had a lower degree of blend uniformity over batch, likely due to segregation during sampling from the extreme differences in particle morphology between lactose and API. In addition, they found that higher drug loading (up to 30%) showed improved homogeneity over batch blending. Lower drug loading (down to 2%) did show larger deviations in percent label claim, but this was a feeding issue at low flow rates rather than a blending performance issue. The results of this study highlight that batch manufacturing comprised a different risk profile compared to continuous when considering material properties. More importantly, excipient material properties had a limited effect on blend uniformity relative to the batch processes.

The most obvious benefit of blending powders via a continuous process is that the risk for segregation downstream, normally present in batch DC, is significantly reduced or even removed. This is because continuous blending allows for wider ratios of material particle sizes and morphologies relative batch DC. The first MCS paper[1] highlighted that successful DC requires consistent API properties typically over a narrower range than granulation in classes 2 and 3. The second MCS paper[2] then evaluated company specific case studies and found that failure modes due to drug loading and particle size ratios between the excipient and the API can be explained by the percolation threshold theory and that increasing the drug loading of poor flowing APIs leads to a higher risk of tableting for DC processes. When considering that an effective way to successfully increase drug loading for DC processes may be to increase the particle size ratio between the excipient and the API, segregation of the API becomes increasingly likely during powder transfers between unit operations. The different segregation mechanisms of pharmaceutical blends tied to batch manufacturing, are well known: for sifting segregation to occur the ratio of particle sizes must be at least 1.3:1 for binary mixtures[87]. Therefore, to increase drug loading while reducing segregation risk, granulation processes are typically favoured over batch DC processes. However, it has been consistently shown in literature that a CDC process is segregation resistant[71, 88, 89].

A less obvious benefit of CM over batch processing is that CM is more tolerant to poor powder blend flow. Karttunen *et al*[50] presented a comparison of a batch DC and a CDC process. They investigated low (2%) and high (22%) drug loadings of a formulation with a cohesive and a free-flowing API. The process performance was characterised using tablet content uniformity. The continuous process was found to have performed better for the high drug loading. The low dose using a batch process exhibited slightly improved content uniformity than the continuous process, however this was found to be due to the inadequate interface between the feeders and the blender combined with a very low mass flow rate.

They concluded that the CDC process was not sensitive to the poor flow of the powder blend and therefore, 1) higher drug loadings were possible compared with batch process, and 2) the performance of the low drug loading formulation could match the batch performance with an improvement to the interface and further optimization of the line rate. The ability to process low dose formulations via CM was further demonstrated by Van Snick *et al*[49] who investigated the performance of a CDC process for a low dose (2.5%), cohesive API. Through optimisation of the blender configuration, they demonstrated that suitable uniformity of content could be achieved.

Impact of Removing Intermediate Bulk Containers Via Application of CM

In a CM process, all the unit operations are processing simultaneously, and this logically leads to the removal of IBCs to transfer between unit operations. However, this also means that the flow properties of the blend are critical at transitions between the unit operations to prevent powder arches during gravity transfers, or stagnant zones within the blender. In CM processes, there will not be an opportunity as in batch to investigate and manually assist obstructed powder flow. Therefore, it will be important to determine the proper transition geometries, surface roughness, and automated mechanical assistance that are appropriate for the given blend flow properties. The benefit here is that once the CM process is adequately designed and commissioned, there will not need to be scale up to different equipment as in batch, where many of the flow and segregation issues arise at larger scale.

In batch manufacturing, even in the absence of segregation, there is still a potential for powder consolidation which can lead to interrupted flow patterns during discharge of the IBC to the tablet press and variable fill level in the feed frame. Leung *et al*[90] found that the active stress state of the blend at the onset of discharge is more critical than the passive state following discharge in predicting powder flow obstruction exiting an IBC because the major principal stress is significantly higher in the active state than the passive state. This can lead to arching and extremely stable ratholes upon discharge into the tablet press which require mechanical intervention to promote consistent flow [90]. While funnel flow discharge from an IBC is not fundamentally an issue, it is still an added risk to manage, therefore mass flow discharge is often the desired flow pattern and the gold standard for engineering consistent powder flow from an IBC. Nauke *et al*[81] *examined* 260 flow pattern estimations, based on 20 real-life IBCs and 13 investigational powder blends, and observed that only 5% of the time mass flow was achieved. This was attributed to the geometry of the IBCs and the shallow hopper angle. The methodologies to design bins to ensure mass flow are mature[91], but this is not often practical or economical in a multiproduct manufacturing facility because the optimal IBC design is a function of material properties and batch size, both of which are highly variable and would require a customized IBC design for each product formulation.

A major reason for choosing granulation is that granulation promotes mass flow discharge patterns due to their denser and larger particle sizes and this allows for standardization of IBC geometries in a production facility. For the CM line, since there is no

longer an IBC feeding the press, this risk is also practically negligible as it is common for less than 1 kg of powder to sit above the tablet press in a vertical chute (i.e. zero hopper half angle to promote maximum chance for mass flow), and therefore the competing stresses acting against gravity on the powder are less critical to ensure consistent flow into the tablet press. This means that discharge risk resulting from the mismatch of a product's blend material properties with IBC design in batch processes can be virtually eliminated if employing CM and ultimately have an impact on improving consistent flow into feed frame of the tablet press. It is known that variable powder fill level in the feed frame has been shown to directly result in variable die fill [92]. Leaving then only routine tablet press setup of calibrating tablet parameters (e.g. fill depth, compression force) to provide the desired tablet attributes (e.g., weight, tensile strength, porosity, etc). Therefore, if a specific batch process possesses this risk of variable powder flow into the feed frame, the formulator should immediately consider if a continuous process can mitigate it.

If the continuous blend can be uniformly transferred into the tablet press, then it is only a matter of consistent flow into the die as with any tabletting process. Bekaert *et al*[83] sought to identify quantitative relationships between blend properties, critical quality attributes (CQA) and critical process parameters (CPP) related to blending and tabletting for a CDC line. Thirty ternary blends were selected (based on a 9.9% API, 89.3% filler, and 0.75% lubricant) to cover a wide range of blend properties to develop a predictive PLS model using material properties. They found a clear correlation between blender responses and blender configuration, but very limited impact from blend properties other than bulk density. The compression step exhibited standard die filling consistency issues for cohesive and adhesive blends as would be seen in a batch process influenced by the blend properties flowability, density, compressibility, and permeability. An additional investigation comparing a discrepancy between blend uniformity and content uniformity found that a broad variation in blend properties and larger CU variabilities were due to inconsistent flow into the die rather than demixing. This is not to say that segregation risk does not exist in the feed frame of the tablet press for CM processes, but any risk for segregation in the feed frame is agnostic to the choice of batch or CM and likely an issue to be resolved during formulation development.

Additional Considerations: Residence Time Distribution and Material Traceability

A key consideration for any CM process however, is the need to develop an understanding of the residence time distribution (RTD), which defines the probability distribution of time that a unit of material spends within the process. The RTD is used to infer and characterize the amount of back mixing provided by the blender and provides knowledge of how much feeding variation will be acceptable for the CM process to achieve the desired CQAs. Thus, the RTD can be tuned to provide the appropriate amount of dampening to the residual feeder variability, which may be influenced by material properties. This means that there is an inextricable link between feeding and blending performance which is governed by the RTD. There may be a practical limit though, to how much process dampening is desired. A highly damped process is also a very sluggish process to manage control of process disturbances and this can have a significant impact on yields, especially for small batch sizes.

In either batch or CM, assurance of adequate homogeneity is a prerequisite to assure that the lot will be "uniform in character and quality and within specified limits"[81] . As Wahlich referenced[70], "*homogeneity of a batch-based manufacturing route is achieved through space*", therefore there is typically not a driver to develop knowledge of the RTD for batch-based unit operations, with an exception for continuous unit operations managed in batch mode (i.e. twin screw granulation). Even for RC, which is continuous, the process is generally assumed to be plug flow, where there is no back mixing. For batch, homogeneity is dependent on the working volume, blender rotation speed, time for a given IBC geometry [93] and the state of mixedness of 1) the final blend prior to granulation or 2) compression if using MCS class 1 processes. That is, the state of the final blend in batch depends on the number of revolutions and speed, but in continuous the state of the blend is dependent on the degree of back mixing; a function of the number of blade passes the powder experiences within the control volume of the blender[94] and the RTD.

The RTD is also required for material traceability[95], determining the real time risk for process disturbances[96], and precise isolation of non-conforming material from said disturbances or other CPPs or IPCs which influence the state-of-control[97, 98]. Karttunen *et al*[99] present an RTD analysis of three continuous technologies, hot-melt extrusion (HME), DG and WG. They investigated different methodologies for obtaining the RTD and found that using in-line NIR or optical monitoring of a colour tracer were suitable means to measure the response to an impulse of tracer (i.e. the RTD). However, the type of CM process employed may dictate the complexity of the RTD model required to accurately model the system. Regardless, they found that "*the difficulties and benefits were more related to the measurement techniques than the process in question*." When considering a CM process, it will be a priority to ensure there are means for understanding the RTD impact on the process and how to characterize it.

MCS Guided Selection of Batch or CM

Based on the papers that have referenced the MCS and the prior discussion on considerations for implementing CM processes, the choice of CM *vs* batch should be strongly influenced by the ability to consistently feed the raw ingredients into the process before subsequent downstream compression and possibly a film coating step – the end of most batch or CM processes. With that in mind, any choice of CM process needs to assure a blend which satisfies the requirements for powder to always flow into the die and to have adequate tensile strength. This means that to choose continuous is to choose homogeneity through time vs space and the material characteristics which have the greatest risk on time-based homogeneity will be the most critical. For the continuous versions of classes 1, 2 and 3 manufacturing processes, feeding and blending will be critical, such that low concentrations of API with variable properties may be suitable for compression, but may challenge the equipment capability to accurately feed the material. A balance between acceptable feeder variability and blender dampening by the RTD will heavily weight the risk for developing a continuous over a batch process. However, the application of feeding and blending has demonstrated a benefit to reduce the risk for segregation, a risk that typically drives the batch

process towards granulation technologies and away from batch DC processes. The choice may then be batch granulation vs CDC. However, formulations which require extremely high drug loading, may result in low bulk density at the time of compression and require granulation regardless of a low segregation risk, and this may drive the desire for a granulation process. The choice of batch vs CM in this case may be more business driven or culturally motivated (e.g. company preference or to increase utilisation of legacy batch manufacturing equipment).

Batch or Continuous Process Selection

To understand when to choose batch or CM process routes, we have to go back to understanding why we granulate in the first place. As described by the first MCS paper[1], the main reason is "*to overcome poor API properties… by forming denser larger particles which are more amenable to processing*". It was also identified in the first MCS paper, that many powder processing risks are a consequence of post drug substance manufacture modifications as in the case of poorly soluble APIs. In these cases, modifications to the APIs can negatively impact the flow and likely require granulation. This was further discussed in the second MCS paper[2], when reviewing the dataset on manufacturing processes utilized by Cordon Pharma where wet granulation was preferred in early stages of development due to the variable properties of the drug compound, and the unsuitability of the API physical properties for the given drug loading rendered the formulation inadequate to achieve DC. While granulation is a viable solution for managing necessary changes to the modified API, it also leads to a more complex process, greater costs of manufacture, and is more challenging to identify root causes for investigations.

It is clear that CM provides advantages for robust and routine commercial manufacturing over batch manufacturing. However, due to the different priorities during earlier stage development, the process is often developed for an equally robust (but typically more complex) batch granulation process which becomes locked-in due to the additional risk of impacting the results of costly clinical trials. There may be significant late-stage processing advantages which could be realized if CM was adopted earlier in the product development cycle. There is currently limited guidance at best facilitating how to make that decision. Considering the discussion thus far, it is proposed that the selection of CM or batch may be best suited as a 2-stage decision; 1) what resulting blend properties enable robust tablet compression, and 2) what material properties are amenable to feeding and blending. The Figure 4 decision tree is suggested as a starting point for determining the risk of selecting batch or CM processes.

Developing a CDC process can be achieved for both high and low drug loadings. In either case, the first stage focuses on the tabletting risk as it relates to the performance of the final blend and the second stage on the feeding and blending risk as a dependence on API properties. It is the opinion of this group that it is more fundamental to determine the risk for making a tablet before considering the risk for metering the material into the process.

1. When the drug loading is high, it is likely that the tablet compactability and blend flowability will be influenced by the percolation threshold, and the blend properties will be dominated by the neat or modified API; defining two check points influencing the decision of whether to directly compress, or to granulate.
    a. The first check is on tablet compactability and weight variability, i.e. whether there is enough volume in the die to compress the blend into a tablet and if the powder blend flows into the die consistently. If this is not possible or the risk is sufficiently high, it may be possible to reformulate to produce a denser more flowable blend; if not, the choice is likely to reformulate for a granulation process. For simplicity, we assume the high drug load blend is robust to the risk for segregation and therefore it is not a checkpoint here. Considering CM processes, segregation would likely not be a risk either.
    b. The second checkpoint is on API and material flowability. The question here is whether the raw components and the blend can successfully flow into and through the feeders resulting in a final blend that consistently flows into the tablet press. If the flowability is poor, there may be an additional opportunity to improve the flow by pre-blending the poor flowing materials or with flow enhancing excipients such as silicon dioxide. If this is successful, there is a path toward CDC, otherwise granulation may be the less risky option.
2. If the drug loading is low, the blend properties are more likely to be weighted towards the resulting average flowability of the excipient blend. The key assumption here is that the blend can be engineered for a low tableting risk, given the additional formulation flexibility provided when the API load is low. This leaves segregation as the primarily risk to manage. Again, this results in 2 checkpoints.
    a. For the first checkpoint, as discussed at length already, CM essentially removes the risk for blend segregation prior to tableting, so a blend at risk for segregation may be capable for CDC where it would fail with DC. Finally, if there is no segregation risk to begin with, there could be the option to manufacture in batch or CDC.
    b. The second checkpoint is the same as that for high drug load. The materials need to flow into the process, and at low drug loading this means the feeders may be compromised by the noise when operating at low mass flow rates. If the mass flow rate signal to noise cannot be improved via advanced control algorithms or pre-blending with a carrier, then it may be best to granulate.

Certainly, there is also the situation where a high drug loading can encounter segregation issues, or a low drug loading may have compactability concerns, but for the sake of simplicity and given these scenarios are less probable, they were not included in the decision flow. Indeed, each product would likely traverse this decision tree on a case-by-case basis and in the context of the manufacturer's strengths and culture. If the end result is to granulate, this can be done via batch or continuous against the unique considerations for granulation. However, post granulation processing is typically a DC process and therefore it would again traverse the decision tree to determine if it should be done so via batch or CM.

High level MCS risk matrix

To summarise the key manufacturability risks associated with batch and continuous process selection, the following qualitative figures are presented. For batch manufacturing processes, primarily described by the initial MCS paper[1], we refer to MCS classes 1 through 4. Following the qualitative figure, MCS class 1 is suitable for more favourable API properties (such as flowability and bulk density) at low to medium drug loadings (up to a percolation limit, where API properties will begin to dominate). Very low drug loadings less than 2% are subject to uniformity and segregation risks that will need to be mitigated, such as using a granulation process (MCS 2 and 3). MCS class 2 will typically be suitable at higher drug loadings for favourable API properties and at lower drug loadings for unfavourable API properties. MCS class 3 can also be suitable in these regions, but class 3 and class 4 (other technologies) will typically be required for unfavourable API properties at high drug loadings, where those properties will dominate.

In the case of CM, we can see that the space for DC is expanded to cover a broader range of API properties, including unfavourable API properties at lower drug loadings. At very low drug loadings, generally defined for CM as less than 3%[49, 71, 87, 89], segregation is no longer a major risk; however, CM can be more challenging due to difficulties in controlling dosing due to reduced signal to noise ratios in feeders, especially when operating at low throughputs. Continuous granulation technologies are typically more suited to unfavourable API properties at high drug load.

In summary these qualitative plots can help identify the simplest manufacturing process suitable for processing a given API and formulation drug load, although product lifecycle strategy should also be considered. In early development, when the API is limited and variable, it may be more efficient to develop batch DC or even granulation processes, but as the product matures and transfers into commercial manufacturing where larger volumes are needed, it will be important to have considered if a CM process may be more suitable for the long-term needs.

Conclusions and Future Work

Whilst the second MCS paper discussed the primary material properties which impact manufacturability, this review has shown the value of large datasets allowing a multivariate approach. The ADDoPT (Advance Digital Design of Pharmaceutical Therapeutics) programme showed that reaching agreement on techniques that were important was possible and that a moderately large dataset could yield a lot of knowledge. This work also illustrated that we should aim for richer datasets rather than merely larger datasets. This could, for example, include the use of whole particle size distributions rather than just D10, D50, D90 descriptors. Truly Big Data will be hard to achieve within individual institutions as there are only a relatively limited number of new APIs. It would be beneficial to have a common database with comparable, standardised data that all the industry could access. This working group puts out a call for an academic or professional institution to host such a database which would allow for pre-competitive collaboration. The database needs to be sufficiently large and

varied to encompass the complexities of the system we are looking at and include negative data related to things that were considered not to be a success.

Other areas which were identified as in need of further investigation include:

- What link, if any, exists between API molecular properties and processability?
- The relationship between different milling and drying techniques and API processability
- Revised techniques to measure important particle characteristics that we currently know we cannot measure properly e.g. surface energy.
- The propensity for attrition and morphological change during processing as this may explain apparent outliers whose measure particle properties do not correspond to manufacturability.

Overall, the last ten years has witnessed progress in explaining why formulators take the decisions that they do. An immediate goal of linking API properties to bulk properties and onward to manufacturability via percolation threshold seems in reach. The work of the MCS is more relevant than ever as we move forward. With the rise in CM, the manufacturability space is seen to generally increase relative to batch and this results in a more direct linkage between the formulation design and the intended product quality. That is, the percolation threshold for an API when formulated more likely has a direct the impact on CQAs in commercial production and is less convoluted by the manufacturability risk associated with technology transfers.

1. Leane M, Pitt K, Reynolds G, Group MCSW. A proposal for a drug product Manufacturing Classification System (MCS) for oral solid dosage forms. Pharmaceutical development and technology. 2015;20(1):12-21.
2. Leane M, Pitt K, Reynolds GK, Dawson N, Ziegler I, Szepes A, Crean AM, Agnol RD, Broegmann B, Charlton ST, Davies C, Gamble J, Gamlen M, Hsiao WK, Khimyak YZ, Khinast J, Kleinebudde P, Moreton C, Oswald M, Page S, Paudel A, Sahoo R, Sheehan S, Stamato H, Stone E, Grp MCSW. Manufacturing classification system in the real world: factors influencing manufacturing process choices for filed commercial oral solid dosage formulations, case studies from industry and considerations for continuous processing. Pharmaceutical Development and Technology. 2018;23(10):964-77.
3. Bryant MJ, Rosbottom I, Bruno IJ, Docherty R, Edge CM, Hammond RB, Peeling R, Pickering J, Roberts KJ, Maloney AGP. "Particle Informatics": Advancing Our Understanding of Particle Properties through Digital Design. Crystal Growth & Design. 2019;19(9):5258-66.
4. Morrison H, Osan R, Horstman E, Lee E, Ritchie S, Payne P, Scott ME, Geier MJ, Wang XT. Correlation of Drug Substance Bulk Properties to Predict and Troubleshoot the Formulation of Drug Products: The API Camera. Organic Process Research & Development. 2021;25(4):1036-46.
5. Wilson D, Bunker M, Milne D, Jawor-Baczynska A, Powell A, Blyth J, Streather D. Particle engineering of needle shaped crystals by wet milling and temperature cycling: Optimisation for roller compaction. Powder Technology. 2018;339:641-50.
6. Ghazi N, Liu Z, Bhatt C, Kiang S, Cuitino A. Investigating the Effect of APAP Crystals on Tablet Behavior Manufactured by Direct Compression. Aaps Pharmscitech. 2019;20(5):1-14.
7. Turner TD, Gajjar P, Fragkopoulos IS, Carr J, Nguyen TTH, Hooper D, Clarke F, Dawson N, Withers PJ, Roberts KJ. Measuring the Particle Packing of L-Glutamic Acid Crystals through X-ray Computed Tomography for Understanding Powder Flow and Consolidation Behavior. Crystal Growth & Design. 2020;20(7):4252-63.
8. Zhu A, Mao C, Luner PE, Lomeo J, So C, Marchal S, Zhang S. Investigation of Quantitative X-ray Microscopy for Assessment of API and Excipient Microstructure Evolution in Solid Dosage Processing. AAPS PharmSciTech. 2022;23(5):117.
9. Zhang S, Stroud PA, Zhu A, Johnson MJ, Lomeo J, Burcham CL, Hinds J, Blakely KA-F, Walworth MJ. Characterizing the impact of spray dried particle morphology on tablet dissolution using quantitative X-ray microscopy. European Journal of Pharmaceutical Sciences. 2021;165:105921.
10. Trementozzi AN, Leung CY, Osei-Yeboah F, Irdam E, Lin YQ, MacPhee JM, Boulas P, Karki SB, Zawaneh PN. Engineered particles demonstrate improved flow properties at elevated drug loadings for direct compression manufacturing. International Journal of Pharmaceutics. 2017;523(1):133-41.
11. Pudasaini N, Parker CR, Hagen SU, Bond AD, Rantanen J. Role of Solvent Selection on Crystal Habit of 5-Aminosalicylic Acid-Combined Experimental and Computational Approach. Journal of Pharmaceutical Sciences. 2018;107(4):1112-21.
12. Pudasaini N, Upadhyay PP, Parker CR, Hagen SU, Bond AD, Rantanen J. Downstream Processability of Crystal Habit-Modified Active Pharmaceutical Ingredient. Organic Process Research & Development. 2017;21(4):571-7.
13. Stauffer F, Vanhoorne V, Pilcer G, Chavez PF, Rome S, Schubert MA, Aerts L, De Beer T. Raw material variability of an active pharmaceutical ingredient and its relevance for processability in secondary continuous pharmaceutical manufacturing. European Journal of Pharmaceutics and Biopharmaceutics. 2018;127:92-103.
14. Gamble JF, Dennis AB, Hutchins P, Jones JW, Musembi P, Tobyn M. Determination of process variables affecting drug particle attrition withinmulti-component blends during powder feed transmission. Pharmaceutical Development and Technology. 2017;22(7):904-9.

15. Ferreira AP, Gamble JF, Leane MM, Park H, Olusanmi D, Tobyn M. Enhanced Understanding of Pharmaceutical Materials Through Advanced Characterisation and Analysis. Aaps Pharmscitech. 2018;19(8):3462-80.
16. Barjat H, Checkley S, Chitu T, Dawson N, Farshchi A, Ferreira A, Gamble J, Leane M, Mitchell A, Morris C, Pitt K, Storey R, Tahir F, Tobyn M. Demonstration of the Feasibility of Predicting the Flow of Pharmaceutically Relevant Powders from Particle and Bulk Physical Properties. Journal of Pharmaceutical Innovation. 2021;16(1):181-96.
17. Ferreira AP, Rawlinson-Malone CF, Gamble J, Nicholson S, Tobyn M. Applications of Multivariate Analysis to Monitor and Predict Pharmaceutical Materials Properties. In: Ferreira AP, Menezes JC, Tobyn M, editors. Multivariate Analysis in the Pharmaceutical Industry2018. p. 235-67.
18. Gamble JF, Akseli I, Ferreira AP, Leane M, Thomas S, Tobyn M, Wadams RC. Morphological distribution mapping: Utilisation of modelling to integrate particle size and shape distributions. International Journal of Pharmaceutics. 2023;635:122743.
19. Megarry AJ, Swainson SME, Roberts RJ, Reynolds GK. A big data approach to pharmaceutical flow properties. International Journal of Pharmaceutics. 2019;555:337-45.
20. Hayashi Y, Oishi T, Shirotori K, Marumo Y, Kosugi A, Kumada S, Hirai D, Takayama K, Onuki Y. Modeling of quantitative relationships between physicochemical properties of active pharmaceutical ingredients and tensile strength of tablets using a boosted tree. Drug Development and Industrial Pharmacy. 2018;44(7):1090-8.
21. Hayashi Y, Nakano Y, Marumo Y, Kumada S, Okada K, Onuki Y. Application of machine learning to a material library for modeling of relationships between material properties and tablet properties. International Journal of Pharmaceutics. 2021;609:121158.
22. Van Snick B, Dhondt J, Pandelaere K, Bertels J, Mertens R, Klingeleers D, Di Pretoro G, Remon JP, Vervaet C, De Beer T, Vanhoorne V. A multivariate raw material property database to facilitate drug product development and enable in-silico design of pharmaceutical dry powder processes. International Journal of Pharmaceutics. 2018;549(1-2):415-35.
23. Kuentz M, Holm R, Elder DP. Methodology of oral formulation selection in the pharmaceutical industry. European Journal of Pharmaceutical Sciences. 2016;87:136-63.
24. Abreu-Villela R, Kuentz M, Caraballo I. Benefits of fractal approaches in solid dosage form development. Pharmaceutical research. 2019;36:1-13.
25. Stauffer D, Aharony A. Introduction to percolation theory: Taylor & Francis; 2018.
26. Pippa N, Dokoumetzidis A, Demetzos C, Macheras P. On the ubiquitous presence of fractals and fractal concepts in pharmaceutical sciences: a review. International journal of pharmaceutics. 2013;456(2):340-52.
27. Arndt OR, Kleinebudde P. Towards a better understanding of dry binder functionality. International Journal of Pharmaceutics. 2018;552(1-2):258-64.
28. Nalluri VR, Puchkov M, Kuentz M. Toward better understanding of powder avalanching and shear cell parameters of drug–excipient blends to design minimal weight variability into pharmaceutical capsules. International journal of pharmaceutics. 2013;442(1-2):49-56.
29. Queiroz ALP, Faisal W, Devine K, Garvie-Cook H, Vucen S, Crean AM. The application of percolation threshold theory to predict compaction behaviour of pharmaceutical powder blends. Powder Technology. 2019;354:188-98.
30. Wenzel T, Stillhart C, Kleinebudde P, Szepes A. Influence of drug load on dissolution behavior of tablets containing a poorly water-soluble drug: estimation of the percolation threshold. Drug Development and Industrial Pharmacy. 2017;43(8):1265-75.
31. Hirschberg C, Sun CC, Rantanen J. Analytical method development for powder characterization: Visualization of the critical drug loading affecting the processability of a formulation for direct compression. Journal of Pharmaceutical and Biomedical Analysis. 2016;128:462-8.
32. Orubu ESF, Tuleu C. Medicines for children: flexible solid oral formulations. Bulletin of the World Health Organization. 2017;95(3):238-40.

33. Suñé-Negre JM, Roig M, Fuster R, Hernández C, Ruhí R, García-Montoya E, Pérez-Lozano P, Miñarro M, Ticó JR. New classification of directly compressible (DC) excipients in function of the SeDeM Diagarm Expert System. International Journal of Pharmaceutics. 2014;470(1-2):15-27.
34. Grote S, Kleinebudde P. Impact of functionalized particle structure on roll compaction/dry granulation and tableting of calcium carbonate. International Journal of Pharmaceutics. 2018;544(1):235-41.
35. Grote S, Kleinebudde P. Roll Compaction/Dry Granulation of Dibasic Calcium Phosphate Anhydrous-Does the Morphology of the Raw Material Influence the Tabletability of Dry Granules? Journal of Pharmaceutical Sciences. 2018;107(4):1104-11.
36. Grote S, Kleinebudde P. A comparative study of the influence of alpha-lactose monohydrate particle morphology on granule and tablet properties after roll compaction/dry granulation. Pharmaceutical Development and Technology. 2019;24(3):314-22.
37. Berkenkemper S, Keizer HL, Lindenberg M, Szepes A, Kleinebudde P. Functionality of disintegrants with different mechanisms after roll compaction. International Journal of Pharmaceutics. 2020;584:119434.
38. Oishi T, Hayashi Y, Noguchi M, Yano F, Kumada S, Takayama K, Okada K, Onuki Y. Creation of novel large dataset comprising several granulation methods and the prediction of tablet properties from critical material attributes and critical process parameters using regularized linear regression models including interaction terms. International Journal of Pharmaceutics. 2020;577:119083.
39. Lavra ZMM, de Medeiros FPM, da Silva RMF, Rosa TA, Sales VDW, Silva L, de Sousa A, de Lima LG, Rolim LA, Neto PJR. Formulation, Development and Scale-Up of Fixed-Dose Combination Tablets Containing Zidovudine, Lamivudine and Nevirapine. Current Hiv Research. 2019;17(5):360-7.
40. Elezaj V, Lura A, Canha L, Breitkreutz J. Pharmaceutical Development of Film-Coated Mini-Tablets with Losartan Potassium for Epidermolysis Bullosa. Pharmaceutics. 2022;14(3):570.
41. Vasiljevic I, Turkovic E, Piller M, Zimmer A, Parojcic J. An investigation into applicability of different compression behaviour assessment approaches for multiparticulate units characterization. Powder Technology. 2021;379:526-36.
42. Vasiljević I, Turković E, Aleksić I, Parojčić J. Mathematical approaches for powders and multiparticulate units processability characterization in pharmaceutical development. Archives of Pharmacy. 2022;72(Notebook 6):637-60.
43. Fridgeirsdottir GA, Harris R, Fischer PM, Roberts CJ. Support tools in formulation development for poorly soluble drugs. Journal of Pharmaceutical Sciences. 2016;105(8):2260-9.
44. Dai S, Xu B, Shi G, Liu J, Zhang Z, Shi X, Qiao Y. SeDeM expert system for directly compressed tablet formulation: A review and new perspectives. Powder Technology. 2019;342:517-27.
45. Allenspach C, Timmins P, Lumay G, Holman J, Minko T. Loss-in-weight feeding, powder flow and electrostatic evaluation for direct compression hydroxypropyl methylcellulose (HPMC) to support continuous manufacturing. International Journal of Pharmaceutics. 2021;596:120259.
46. Yadav IK, Holman J, Meehan E, Tahir F, Khoo J, Taylor J, Benedetti A, Aderinto O, Bajwa G. Influence of material properties and equipment configuration on loss-in-weight feeder performance for drug product continuous manufacture. Powder Technology. 2019;348:126-37.
47. Peddapatla RVG, Sheridan G, Slevin C, Swaminathan S, Browning I, O'Reilly C, Worku ZA, Egan D, Sheehan S, Crean AM. Process Model Approach to Predict Tablet Weight Variability for Direct Compression Formulations at Pilot and Production Scale. Pharmaceutics. 2021;13(7):1033.
48. Peddapatla RVG, Slevin C, Sheridan G, Beirne C, Swaminathan S, Browning I, O'Reilly C, Worku ZA, Egan D, Sheehan S, Crean AM. Modelling the Compaction Step of a Platform Direct Compression Process. Pharmaceutics. 2022;14(4):695.
49. Van Snick B, Holman J, Vanhoorne V, Kumar A, De Beer T, Remon JP, Vervaet C. Development of a continuous direct compression platform for low-dose drug products. International Journal of Pharmaceutics. 2017;529(1-2):329-46.
50. Karttunen AP, Wikstrom H, Tajarobi P, Fransson M, Sparen A, Marucci M, Ketolainen J, Folestad S, Korhonen O, Abrahmsen-Alami S. Comparison between integrated continuous direct

compression line and batch processing - The effect of raw material properties. European Journal of Pharmaceutical Sciences. 2019;133:40-53.
51. Tran PHL, Lee BJ, Tran TTD. Strategies and formulations of freeze-dried tablets for controlled drug delivery. International Journal of Pharmaceutics. 2021;597.
52. Sauer A, Warashina S, Mishra SM, Lesser I, Kirchhofer K. Downstream processing of spray-dried ASD with hypromellose acetate succinate - Roller compaction and subsequent compression into high ASD load tablets. International Journal of Pharmaceutics-X. 2021;3:100099.
53. Hwang KM, Kim SY, Nguyen TT, Cho CH, Park ES. Use of roller compaction and fines recycling process in the preparation of erlotinib hydrochloride tablets. European Journal of Pharmaceutical Sciences. 2019;131:99-110.
54. Tarlier N, Soulairol I, Bataille B, Baylac G, Ravel P, Nofrerias I, Lefevre P, Sharkawi T. Compaction behavior and deformation mechanism of directly compressible textured mannitol in a rotary tablet press simulator. International journal of pharmaceutics. 2015;495(1):410-9.
55. Cho CH, Kim JY, Park ES. Systematic approach to elucidate compaction behavior of acyclovir using a compaction simulator. International Journal of Pharmaceutics. 2020;575:118904.
56. Doktorovova S, Stone EH, Henriques J. A Fundamental Study on Compression Properties and Strain Rate Sensitivity of Spray-Dried Amorphous Solid Dispersions. Aaps Pharmscitech. 2022;23(4):96.
57. Kalaria DR, Parker K, Reynolds GK, Laru J. An industrial approach towards solid dosage development for first-in-human studies: Application of predictive science and lean principles. Drug Discovery Today. 2020;25(3):505-18.
58. Tahir F, Palmer J, Khoo J, Holman J, Yadav IK, Reynolds G, Meehan E, Mitchell A, Bajwa G. Development of feed factor prediction models for loss-in-weight powder feeders. Powder Technology. 2020;364:1025-38.
59. Peddapatla RVG, Slevin C, Sheridan G, Beirne C, Swaminathan S, Browning I, O'Reilly C, Worku ZA, Egan D, Sheehan S, Crean AM. Modelling the Compaction Step of a Platform Direct Compression Process. PHARMACEUTICS. 2022;14(4):695.
60. Wikstrom H, Remmelgas J, Solin S, Marucci M, Sandler N, Boissier C, Tajarobi P. Powder flow from an intermediate bulk container - Discharge predictions and experimental evaluation. International Journal of Pharmaceutics. 2021;597:120309.
61. Reynolds G. MODEL-BASED DEVELOPMENT OF ROLLER COMPACTION PROCESSES. Chemical Engineering in the Pharmaceutical Industry: Active Pharmaceutical Ingredients, Second Edition; 2019. p. 119-45.
62. Pohl S, Kleinebudde P. A review of regime maps for granulation. International Journal of Pharmaceutics. 2020;587:119660.
63. White LR, Molloy M, Shaw RJ, Reynolds GK. System model driven selection of robust tablet manufacturing processes based on drug loading and formulation physical attributes. European Journal of Pharmaceutical Sciences. 2022;172:106140.
64. ASTM. Standard E55, E29648–14 Standard Guide for Application of Continuous Pro- cessing in the Pharmaceutical Industry. West Conshohocken, PA: ASTM International; 2014.
65. Wilms A, Teske A, Meier R, Wiedey R, Kleinebudde P. Implementing Feedback Granule Size Control in a Continuous Dry Granulation Line Using Controlled Impeller Speed of the Granulation Unit, Compaction Force and Gap Width. Journal of Pharmaceutical Innovation. 2022;17(2):449-59.
66. Wilms A, Kleinebudde P. Optimization of residence time distribution in RCDG and an assessment of its applicability in continuous manufacturing. Particuology. 2021;56:43-9.
67. Vanhoorne V, Vervaet C. Recent progress in continuous manufacturing of oral solid dosage forms. International Journal of Pharmaceutics. 2020;579:119194.
68. Monaco D, Omar C, Reynolds GK, Tajarobi P, Litster JD, Salman AD. Drying in a continuous wet granulation line: Investigation of different end of drying control methods. Powder Technology. 2021;392:157-66.

69. Meena AK, Desai D, Serajuddin A. Development and Optimization of a Wet Granulation Process at Elevated Temperature for a Poorly Compactible Drug Using Twin Screw Extruder for Continuous Manufacturing. Journal of Pharmaceutical Sciences. 2017;106(2):589-600.
70. Wahlich J. Review: Continuous Manufacturing of Small Molecule Solid Oral Dosage Forms. Pharmaceutics. 2021;13(8):1311.
71. Ervasti T, Niinikoski H, Mäki-Lohiluoma E, Leppinen H, Ketolainen J, Korhonen O, Lakio S. The comparison of two challenging low dose APIs in a continuous direct compression process. Pharmaceutics. 2020;12(3):279.
72. Schaller BE, Moroney KM, Castro-Dominguez B, Cronin P, Belen-Girona J, Ruane P, Croker DM, Walker GM. Systematic development of a high dosage formulation to enable direct compression of a poorly flowing API: A case study. International journal of pharmaceutics. 2019;566:615-30.
73. Roth WJ, Almaya A, Kramer TT, Hofer JD. A demonstration of mixing robustness in a direct compression continuous manufacturing process. Journal of Pharmaceutical Sciences. 2017;106(5):1339-46.
74. ISPE. Good Practice Guide: Continuous Manufacturing of Oral Solid Dosage Forms. Chapter 2: Material Handling https://ispe.org/publications/guidance-documents/good-practice-guide-continuous-manufacturing-oral-solid-dosage-forms2022 [21-Dec-2023].
75. Hörmann-Kincses TR, Beretta M, Kruisz J, Stauffer F, Birk G, Piccione PM, Holman J, Khinast JG. Predicting powder feedability: a workflow for assessing the risk of flow stagnation and defining the operating space for different powder-feeder combinations. International Journal of Pharmaceutics. 2022;629:122364.
76. Wang Y, Li T, Muzzio FJ, Glasser BJ. Predicting feeder performance based on material flow properties. Powder technology. 2017;308:135-48.
77. Engisch WE, Muzzio FJ. Loss-in-weight feeding trials case study: pharmaceutical formulation. Journal of Pharmaceutical Innovation. 2015;10:56-75.
78. Bautista M, Maurer R, Rolinger L, Gavi E, Piccione PM. Mini-Batch Continuous Direct Compression: Overview and Control Strategy Insights. American Pharmaceutical Review. 2022(October):46-53.
79. Destro F, Muñoz SG, Bezzo F, Barolo M. Powder composition monitoring in continuous pharmaceutical solid-dosage form manufacturing using state estimation–Proof of concept. International Journal of Pharmaceutics. 2021;605:120808.
80. Hanson J. Control of a system of loss-in-weight feeders for drug product continuous manufacturing. Powder Technology. 2018;331:236-43.
81. Bautista M, Maurer R, Rolinger L, Gavi E, Piccione PM. Mini-Batch Continuous Direct Compression: Overview and Control Strategy Insights. American Pharmaceutical Review. 2022:46-53.
82. Nasr MM, Krumme M, Matsuda Y, Trout BL, Badman C, Mascia S, Cooney CL, Jensen KD, Florence A, Johnston C. Regulatory perspectives on continuous pharmaceutical manufacturing: moving from theory to practice: September 26-27, 2016, international symposium on the continuous manufacturing of pharmaceuticals. Journal of pharmaceutical sciences. 2017;106(11):3199-206.
83. Bekaert B, Van Snick B, Pandelaere K, Dhondt J, Di Pretoro G, De Beer T, Vervaet C, Vanhoorne V. Continuous direct compression: Development of an empirical predictive model and challenges regarding PAT implementation. International Journal of Pharmaceutics: X. 2022;4:100110.
84. Holman J, Tantuccio A, Palmer J, van Doninck T, Meyer R. A very boring 120 h: 15 million tablets under a continuous state of control. Powder Technology. 2021;382:208-31.
85. Simonaho S-P, Ketolainen J, Ervasti T, Toiviainen M, Korhonen O. Continuous manufacturing of tablets with PROMIS-line—Introduction and case studies from continuous feeding, blending and tableting. European Journal of Pharmaceutical Sciences. 2016;90:38-46.
86. Jaspers M, Kulkarni SS, Tegel F, Roelofs TP, de Wit MT, Janssen PH, Meir B, Weinekötter R, Dickhoff BH. Batch versus continuous blending of binary and ternary pharmaceutical powder mixtures. International Journal of Pharmaceutics: X. 2022;4:100111.

87. Jakubowska E, Ciepluch N. Blend segregation in tablets manufacturing and its effect on drug content uniformity—a review. Pharmaceutics. 2021;13(11):1909.
88. Oka S, Sahay A, Meng W, Muzzio F. Diminished segregation in continuous powder mixing. Powder Technology. 2017;309:79-88.
89. Lakio S, Ervasti T, Tajarobi P, Wikström H, Fransson M, Karttunen A-P, Ketolainen J, Folestad S, Abrahmsén-Alami S, Korhonen O. Provoking an end-to-end continuous direct compression line with raw materials prone to segregation. European Journal of Pharmaceutical Sciences. 2017;109:514-24.
90. Leung LY, Mao C, Pieters SR, Yang C-Y. A proposed complete methodology to predict gravity flow obstruction of pharmaceutical powders in drug product manufacturing. Journal of pharmaceutical sciences. 2019;108(1):464-75.
91. Jenike AW. Storage and flow of solids. Bulletin No 123, Utah State University. 1964.
92. Sierra-Vega NO, Romañach RJ, Méndez R. Feed frame: The last processing step before the tablet compaction in pharmaceutical manufacturing. International journal of pharmaceutics. 2019;572:118728.
93. Yeom SB, Choi DH. Scale-up strategy in quality by design approach for pharmaceutical blending process with discrete element method simulation. Pharmaceutics. 2019;11(6):264.
94. Gao Y, Vanarase A, Muzzio F, Ierapetritou M. Characterizing continuous powder mixing using residence time distribution. Chemical Engineering Science. 2011;66(3):417-25.
95. Engisch W, Muzzio F. Using residence time distributions (RTDs) to address the traceability of raw materials in continuous pharmaceutical manufacturing. Journal of pharmaceutical innovation. 2016;11:64-81.
96. Bhalode P, Razavi SM, Roman-Ospino A, Scicolone J, Callegari G, Tian G, Koolivand A, Krull S, Ierapetritou MG, Muzzio FJ. Optimal quantification of residence time distribution profiles from a quality assurance perspective. International Journal of Pharmaceutics. 2023;634:122653.
97. Hurley S, Tantuccio A, Escotet-Espinoza MS, Flamm M, Metzger M. Development and Use of a Residence Time Distribution (RTD) Model Control Strategy for a Continuous Manufacturing Drug Product Pharmaceutical Process. Pharmaceutics. 2022;14(2):355.
98. ICH. International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. Continuous manufacturing of drug substances and drug products Q13 https://database.ich.org/sites/default/files/ICH_Q13_Step4_Guideline_2022_1116.pdf: ICH; 2022 [06-Jan-2024].
99. Karttunen AP, Hormann TR, De Leersnyder F, Ketolainen J, De Beer T, Hsiao WK, Korhonen O. Measurement of residence time distributions and material tracking on three continuous manufacturing lines. International Journal of Pharmaceutics. 2019;563:184-97.
100. Batra A, Desai D, Serajuddin ATM. Investigating the Use of Polymeric Binders in Twin Screw Melt Granulation Process for Improving Compactibility of Drugs. Journal of Pharmaceutical Sciences. 2017;106(1):140-50.
101. Batra A, Desai D, Serajuddin AM. Conversion of alpha-lactose monohydrate to anhydrous form with superior tabletability by twin-screw extrusion at elevated temperature. International Journal of Pharmaceutics. 2020;588:119790.
102. Batra A, Thongsukmak A, Desai D, Serajuddin AT. The effect of process variables and binder concentration on tabletability of metformin hydrochloride and acetaminophen granules produced by twin screw melt granulation with different polymeric binders. AAPS PharmSciTech. 2021;22(4):154.
103. Bano G, Dhenge RM, Diab S, Goodwin DJ, Gorringe L, Ahmed M, Elkes R, Zomer S. Streamlining the development of an industrial dry granulation process for an immediate release tablet with systems modelling. CHEMICAL ENGINEERING RESEARCH & DESIGN. 2022;178:421-37.
104. Conceicao J, Adeoye O, Cabral-Marques HM, Lobo JMS. Hydroxypropyl-beta-Cyclodextrin and beta-Cyclodextrin as Tablet Fillers for Direct Compression. Aaps Pharmscitech. 2018;19(6):2710-8.

105. Erdemir D, Daftary V, Lindrud M, Buckley D, Lane G, Malsbury A, Tao J, Kopp N, Hsieh DS, Nikitczuk W, Engstrom JD. Design and Scale-up of a Co-processing Technology to Improve Powder Properties of Drug Substances. Organic Process Research & Development. 2019;23(12):2685-98.
106. Hamidi FWA, Anuar MS, Baharuddin AS, Mohamed MAP, Naim MN, Tahir SM. Compaction behaviour and mechanical characteristics of chewable binary tablet mixture containing lactose and date powders. International Journal of Research in Pharmaceutical Sciences. 2019;10:3385-91.
107. Junnila A, Wikstrom H, Megarry A, Gholami A, Papathanasiou F, Blomberg A, Ketolainen J, Tajarobi P. Faster to First-time-in-Human: Prediction of the liquid solid ratio for continuous wet granulation. European Journal of Pharmaceutical Sciences. 2022;172:106151.
108. Kleinebudde P. Improving Process Understanding in Roll Compaction. Journal of Pharmaceutical Sciences. 2022;111(2):552-8.
109. Liu SB, Wang CG, Chen HB, Sun CQC. Sweet Sulfamethazine Acesulfamate Crystals with Improved Compaction Property. Crystal Growth & Design. 2021;21(2):1077-85.
110. Liang ZX, Chen HB, Wang CG, Sun CC. Discovery, Characterization, and Pharmaceutical Applications of Two Loratadine-Oxalic Acid Cocrystals. Crystals. 2020;10(11):996.
111. Lura A, Breitkreutz J. Manufacturing of mini-tablets. Focus and impact of the tooling systems. Journal of Drug Delivery Science and Technology. 2022;72:103357.
112. Mangal H, Kirsolak M, Kleinebudde P. Roll compaction/dry granulation: Suitability of different binders. International Journal of Pharmaceutics. 2016;503(1-2):213-9.
113. Mangal S, Meiser F, Tan G, Gengenbach T, Morton DAV, Larson I. Applying surface energy derived cohesive-adhesive balance model in predicting the mixing, flow and compaction behaviour of interactive mixtures. European Journal of Pharmaceutics and Biopharmaceutics. 2016;104:110-6.
114. Markl D, Zeitler JA. A Review of Disintegration Mechanisms and Measurement Techniques. Pharmaceutical Research. 2017;34(5):890-917.
115. Moseson DE, Eren A, Altman KJ, Corum ID, Li MY, Su YC, Nagy ZK, Taylor LS. Optimization of Amorphization Kinetics during Hot Melt Extrusion by Particle Engineering: An Experimental and Computational Study. Crystal Growth & Design. 2022;22(1):821-41.
116. Persson AS, Pazesh S, Alderborn G. Tabletability and compactibility of alpha-lactose monohydrate powders of different particle size. I. Experimental comparison. Pharmaceutical Development and Technology. 2022;27(3):319-30.
117. Rowe JM, Charlton ST, McCann RJ. Development, Scale-Up, and Optimization of Process Parameters: Roller Compaction Theory and Practice. Qiu Y, Chen Y, Zhang GGZ, Yu L, Mantri RV, editors2017. 869-915 p.
118. Steenweg C, Habicht J, Wohlgemuth K. Continuous Isolation of Particles with Varying Aspect Ratios up to Thin Needles Achieving Free-Flowing Products. Crystals. 2022;12(2):137.
119. Tanner T, Antikainen O, Pollet A, Raikkonen H, Ehlers H, Juppo A, Yliruusi J. Predicting tablet tensile strength with a model derived from the gravitation-based high-velocity compaction analysis data. International Journal of Pharmaceutics. 2019;566:194-202.
120. Tofiq M, Nordstrom J, Persson AS, Alderborn G. Effect of excipient properties and blend ratio on the compression properties of dry granulated particles prepared from microcrystalline cellulose and lactose. Powder Technology. 2022;399:117207.
121. van den Ban S, Goodwin DJ. The impact of granule density on tabletting and pharmaceutical product performance. Pharmaceutical research. 2017;34:1002-11.
122. Wade JB, Miesle JE, Auiles SL, Sen M. Exploring the wet granulation growth regime map - validating the boundary between nucleation and induction. Chemical Engineering Research & Design. 2020;156:469-77.
123. Wang Z, Cao J, Li W, Wang Y, Luo G, Qiao Y, Zhang Y, Xu B. Using a material database and data fusion method to accelerate the process model development of high shear wet granulation. Scientific Reports. 2021;11(1):16514.

124. Zieschang L, Klein M, Jung N, Kramer J, Windbergs M. Formulation development of medicated chewing gum tablets by direct compression using the SeDeM-Diagram-Expert-System. European Journal of Pharmaceutics and Biopharmaceutics. 2019;144:68-78.

Table 1 Sector distribution of citations

Author affiliation	Number of citing papers
Academic	56
Industrial	17
Academic/Industry Collaboration	89

Table 2: References which utilize the MCS as a reference source

Reference	Ref in paper	MCS Property
[100]	A tablet tensile strength of 1.7 MPa was considered to be the minimum limit when the RC process was used.	Tablet properties
[101]	A tablet formulation is recommended to have a tensile strength >1.7 MPa to withstand stresses during coating, packaging, shipping and handling.	Tablet properties
[102]	Tablets produced by twin screw melt granulation were considered to have sufficient strength for downstream processing if they met a tensile strength > 1.7 MPa.	Tensile Strength
[103]	Target strength for tablets manufactured by RC.	Tensile Strength
[104]	The three main processing routes for pharmaceutical oral solid dosage forms.	Processing routes for OSDs.
[105]	Bulk density>0.5 g/mL, PSD with D10 > 30 µm and D90 < 1000 µm, and aspect ratio of < 1.5.	Criteria for successful DC material
[106]	The preferred target value of tablet tensile strength in pharmaceutical manufacturing lies within the range of 1-2 MPa	Tensile Strength
[107]	Manufacturing Classification System (MCS) Working Group suggested that as much as 40% of all tablet formulations are manufactured with a WG step.	Processing routes for OSDs.
[108]	Compared with WG, roll compaction/ DG (RCDG) is less complicated saving time and costs.	Processing routes for OSDs.
[109]	Their API had “good thermal stability required for tabletting as indicated by negligible weight loss below 150C.”	Moisture uptake
[110]	“The TGA profile of Lor-Oxa CAB showed negligible weight loss below 150 C, suggesting acceptable thermal stability.”	Moisture uptake

111	The quality of the tabletability of a powder or formulation can be described by the slope after a linear regression or by evaluating the tableting pressure, which is needed to get a tensile strength in a range between 1-2 MPa	Tensile Strength
112	RCDG is considered first, when DC is not recommended	Processing routes for OSDs.
113	Typically, a Carr's index between 21 and 25 and Hausner's ratio between 1.26 and 1.34 are considered suitable for industrial scale tablet manufacturing.	Flow
114	Processing limitations when it comes to DC due to properties of API, like small particle size and needle-like morphology.	Process route choice
69	Tablet tensile strength criteria to establish a target tensile strength for tablets produced from granules manufactured using a twin-screw extruder WG process.	Tensile Strength
115	Particles <30 µm tend to have low bulk density, high compressibility, and high cohesivity, yielding poor flow properties and additional challenges for material feeding	Particle size
47	DC is a relatively simple method to manufacture pharmaceutical tablets. It involves two primary processing steps, viz., blending and compaction and is less complicated compared to tablet production involving a DG or WG step.	Processing route
59	DC tablet production is considered the simplest process for tablet production by the MCS class 1. Despite its simplicity, tablet production via the DC process is less commonly employed compared to the more complex process of tabletting via a granulation step. DC is more commonly employed for class 1/3 drugs categorised by the biopharmaceutical classification system compared to class 2/4.	Processing Route
116	The target tensile strength for a tablet is 2MPa.	Tensile Strength
61	Referenced the MCS particle D[v,0.5] of 50–500 µm recommendation for tableting in relation to the impact of granule particle size on powder flow.	Particle Size

[117]	Discusses RC of high drug load formulations in the context of ideal RC material properties.	Tablet Properties
[52]	For tablets, a tensile strength of >1.7 MPa at SF < 0.85 is considered acceptable for further processing	Tensile Strength
[118]	However, for pharmaceutical crystals, smaller particle sizes between 50–500 µm and a mean particle size of around 80 µm is targeted to enable DC while still enabling dissolution in the human body	Particle Size
[119]	Sufficient tensile strength of approximately at least 2 MPa was an important property of a tablet so that it can withstand stress from further manufacturing unit operations after compaction.	Tensile strength
[120]	Two of the major manufacturing routes in current use are based on wet and DG technologies.	Processing Route
[10]	Compaction of both wet and jet milled powder blends resulted in robust tablets with tensile strength above 2 MPa.	Tensile Strength
[121]	Manufacturability criteria for 40% drug load tablets manufactured using high shear WG.	Tensile Strength
[122]	Granules produced by a WG induction growth regime had reduced porosity and were less compactible compared to granules produced by a nucleation growth regime.	Tensile Strength
[123]	WG was the most popular process choice compared with DC, DG, OT during the pharmaceutical development of over 80% of early-stage compounds.	Processing Route
[124]	In general, the particle size ratio of the gum base to the active substance shows a great influence on the blend behaviour during the tableting process.	Percolation Threshold

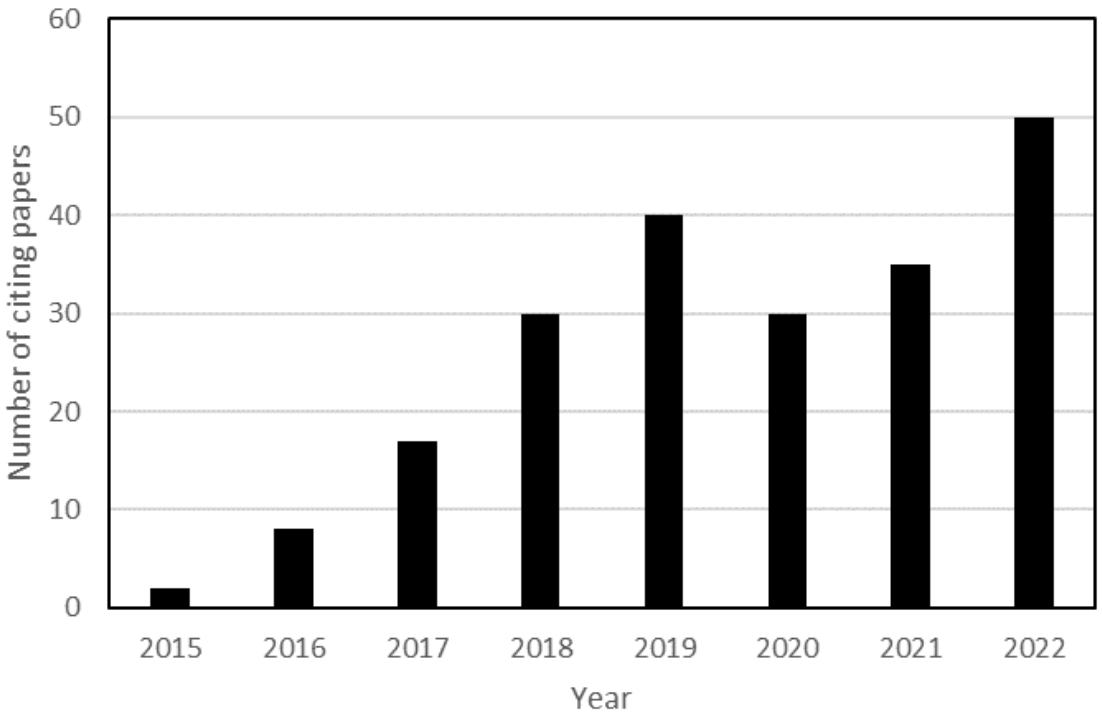

Figure 1: Number of citations of MCS

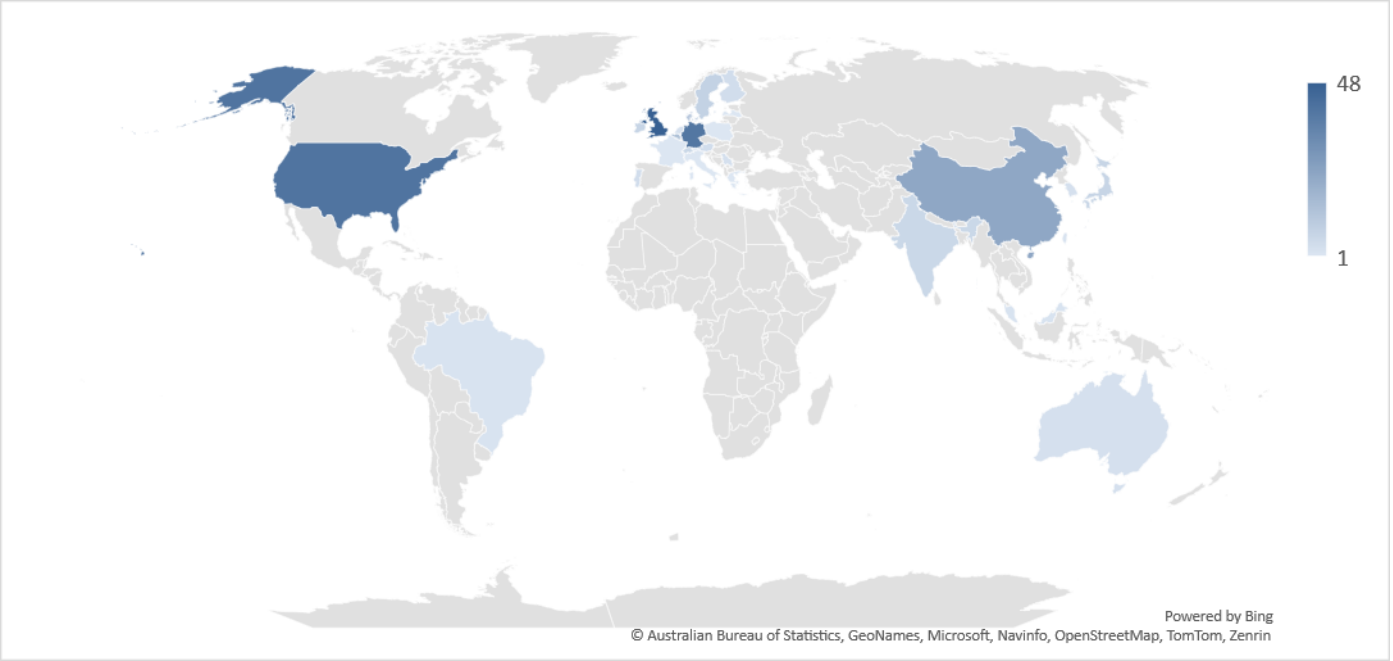

Figure 2: Geographic distribution of MCS citing papers

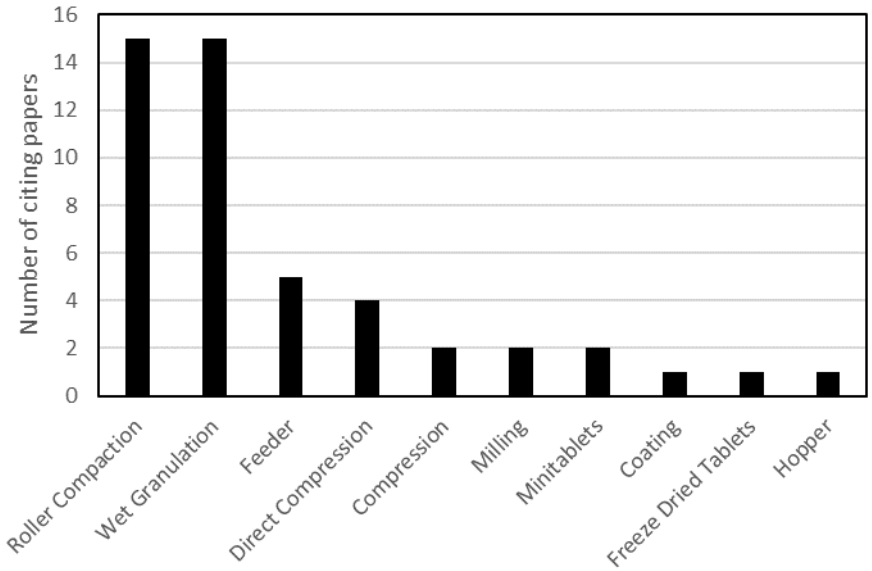

Figure 3: Summary of the technologies covered by manufacturing process development focussed papers

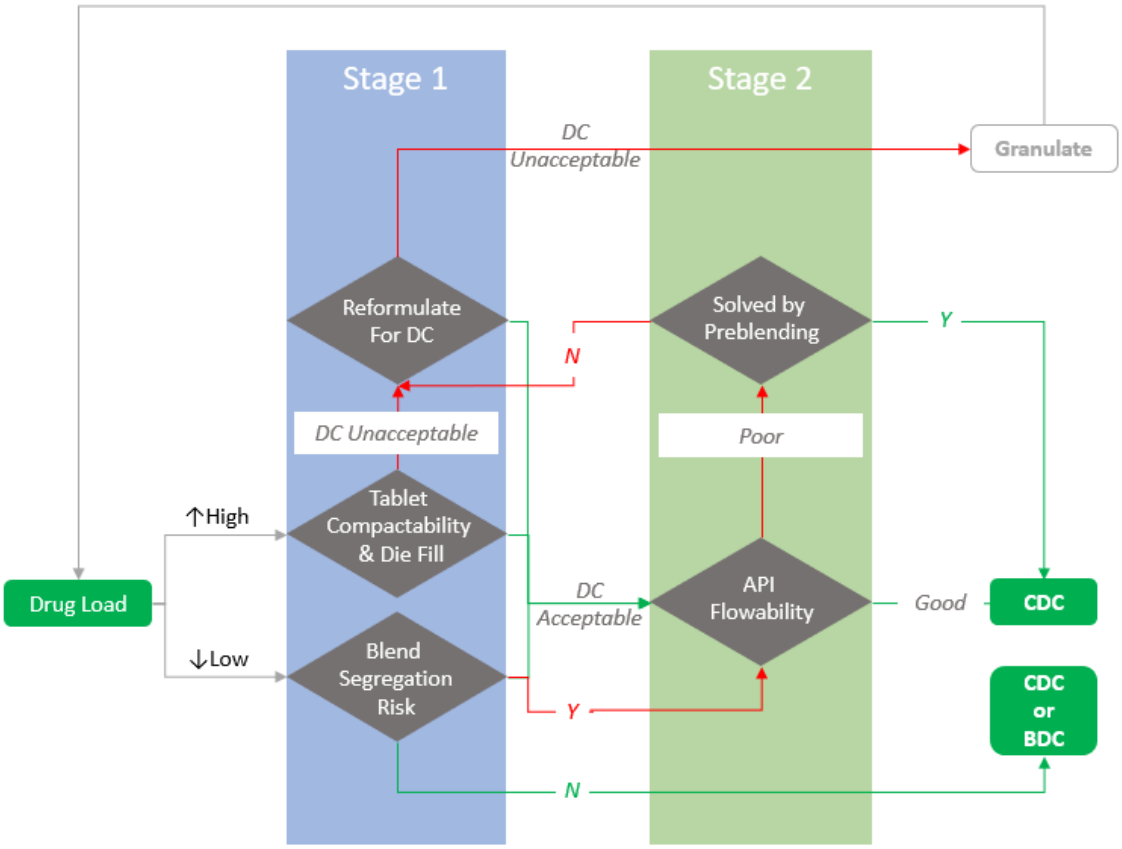

Figure 4: Proposal for deciding for choosing batch or continuous manufacturing processes

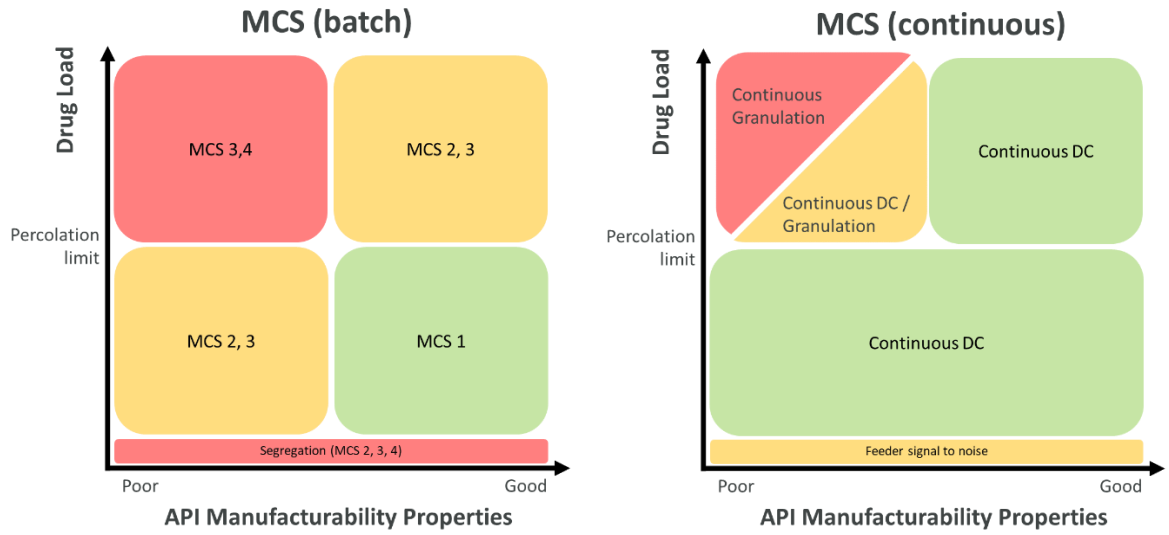

Figure 5: MCS Matrix for Batch and Continuous Manufacturing