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Life Cycle Assessment of Pharmaceutical Tablet Manufacturing: A Comparative Analysis and Systems Model Integration Framework

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Abstract

Pharmaceutical drug products in the form of tablets are produced via a series of manufacturing steps, transforming powder blends to compacted granules with carefully selected properties such as tensile strength and dissolution time. Typical oral solid dosage form (OSD) manufacturing processes include direct compression (DC), roller compaction (RC), high shear granulation (HSG) and continuous direct compression (CDC). Design of each process step is required to achieve end-product quality for the specific material properties and available equipment, although design decisions are typically made without a quantitative understanding of the impact on product environmental footprint. Using a 'cradle to gate' life cycle assessment (LCA) methodology, a quantitative sustainability comparison has been made between standard OSD manufacturing platforms across different production scales. The results demonstrate that for small batch sizes, DC produces tablets with the lowest carbon footprint, however at larger batch sizes, CDC is the most carbon efficient manufacturing platform. Due to the high carbon footprint of the active pharmaceutical ingredient (API), formulation process yields had the greatest impact on overall carbon footprint, although emissions from equipment energy, cleaning and facility overheads were also analysed. Data from these LCA models has been combined with systems models of the CDC manufacturing processes. These combined models are used to demonstrate the optimisation of processes to meet robust product quality attribute targets whilst identify opportunities to minimise the drug product carbon footprint.

Key words

Sustainability, life cycle assessment, systems modelling, optimisation, continuous direct compression

1. Introduction

Due to the complex nature of pharmaceuticals, their production presents a significant environmental burden (Debaveye et al., 2016). Active pharmaceutical ingredient (API) synthesis often demands complex chemistry and multiple-step reaction pathways which can be highly resource intensive, leading to a global warming potential (GWP) 25 times larger than that of a basic chemical (Chen et al., 2024; Wernet et al., 2010). Specialised excipients are often then required to formulate the drug product resulting in the pharmaceutical industry's large carbon footprint, which is shown to have greater emissions than the automotive industry (Belkhir & Elmeligi, 2019; van der Merwe et al., 2020). The pharmaceutical industry is facing increasing pressure to improve sustainability, and in particular, reducing carbon emissions is becoming a growing challenge. The manufacture of pharmaceuticals contributed close to a third of the overall carbon footprint for Britain's National Health Service (NHS) in 2019 (Tennison et al., 2021). With health systems beginning to implement targets for greenhouse gas emissions, pharmaceutical companies are focusing on reducing their carbon footprints (Booth et al., 2023).

Oral solid dosage forms (OSD), most commonly tablets and capsules, are typically the most popular pharmaceutical dosage form, owing to their convenient administration, safety and stability (Shaikh et al., 2018). This paper concerns selection and optimisation of OSD manufacturing platforms to reduce environmental impacts, primarily focusing on tablet manufacturing. Broadly speaking, the manufacturing process for tablets can be split into two key routes; direct compression (DC), and granulation followed by compression (Leane et al., 2015). DC consists of blending active pharmaceutical ingredient (API) with excipients such as fillers, binders and lubricants, and compacting the powder into a tablet. DC is predominantly carried out as a batch process, although continuous direct compression (CDC) is an emerging technology, with recent FDA approvals including Prezista® (Lyytikäinen et al., 2024). Granulation can generally be split into wet granulation and dry granulation techniques and although several granulation methods exist, this paper focuses on high shear granulation (HSG) and roller compaction (RC). HSG involves a dry mixing step of powders, followed by addition of a liquid binder and a wet massing stage where particles aggregate, forming granules (Liu et al., 2021). A subsequent drying step is required after the granulation process, and a milling step is commonly used to reduce oversized granules. RC involves feeding a powder blend through counter-rotating rolls. The rolls exert mechanical force on the powder, producing a compacted ribbon which is then milled to form granules (Freeman et al., 2016).

Life cycle assessment (LCA) evaluates the environmental impacts a product has over its lifetime, producing a quantitative measure which can be used to identify sources of environmental impacts and drive sustainable development. LCA has been used to quantify environmental impacts in the pharmaceutical industry for both API synthesis and drug product manufacture, such as in (Parvatker et al., 2019), (Siegert et al., 2020) and (Wang et al., 2021). One recent publication by (Hadinoto et al., 2022) assesses environmental impacts of ibuprofen tablets produced by wet granulation and DC, including the influence of production scale. Sustainability comparisons have also been made between different granulation methods by (Karunanayake et al., 2024), focusing on energy consumption, material use and time. Additionally, comparisons between batch and continuous processing have been made for drug substance manufacturing and wet granulation (De Soete et al., 2013; Lee et al., 2016). There is however a lack of holistic LCA comparisons between process technologies used in OSD manufacturing, and at present there are no LCAs covering CDC available in literature.

Although approaches to LCA have been standardised within ISO 14040, the methodology of current LCAs in literature varies with differences in scope and impact assessment categories. One consistent finding in most work reviewed is the challenges encountered with data availability (Chen et al., 2024), (Cespi et al., 2015). There are several methods in literature for estimating missing life cycle inventory (LCI) data, and a hierarchy of these methods has been presented by (Parvatker & Eckelman, 2019). While there are a few examples of excipient material LCAs available in literature, such as microcrystalline cellulose, (Katakajwala & Mohan, 2020), LCI data is particularly difficult to find for pharmaceutical grade excipients. As such, it is often necessary to use a proxy value or rely on process calculations to estimate these values (Huber et al., 2022).

Pharmaceutical process design and optimisation is increasingly guided by digital activities such as systems modelling. System models, sometimes referred to as 'digital twins', are created by the connection of process models for multiple unit operations, connected as in the physical system. This enables simulation of the relationship between material properties and process settings across different process stages, and end-product qualities. A number of system models of the CDC process have been described in the recent literature, for example by (García-Muñoz et al., 2018), (Tian et al., 2021), and (Moreno-Benito et al., 2022). Inclusion of LCA models in system models is a natural extension, allowing a more holistic assessment that includes the impact of material and process choices on both the product quality attributes and the sustainability of the overall process, facilitating the identification and selection of more sustainable manufacturing processes and settings.

In this study, a 'cradle-to-gate' LCA methodology was used to perform a quantitative sustainability comparison between standard OSD manufacturing platforms: RC, DC, HSG and CDC. Since carbon footprint data was more readily available for materials used in the formulation, global warming potential (GWP) was selected as the impact category for the study. An LCA was performed for each manufacturing platform across different manufacturing scales. The LCA examined impacts relating to materials, energy consumption from equipment and facility overheads, as well as cleaning and waste impacts. Additionally, the LCA models were coupled with a system model for a CDC process to assess sustainability impacts relating to process parameters in a framework that would allow for process design and optimisation to consider carbon cost alongside product quality and productivity metrics. This paper is structured as follows: section 2 presents an overview of the key steps and material flows in different OSD manufacturing processes, followed by a description of modelling choices and process settings used here; sections 3 and 4 present the LCA and system modelling methodologies; section 5 presents results for each (stand-alone LCA calculations and system model with embedded LCA calculations); and section 6 presents the conclusions.

2. Drug product manufacture

The OSD manufacturing processes analysed within this work are DC, CDC, RC and HSG. The key unit operations and associated materials for each manufacturing process are illustrated in Figure 1. The DC process consists of a blending step, followed by compression, and pan coating unit operations. CDC is a single, continuous unit operation featuring blending and compression, followed by a separate pan coating unit operation. The manufacturing process for RC comprises an initial blend, which is roller compacted, then an additional lubrication blend, compression and pan coating. For HSG, the unit operations used are high shear granulation, wet milling, fluid bed drying (FBD), dry milling, compression and pan coating. The following subsections provide details about modelling choices and process settings for the OSD manufacturing processes considered in this work.

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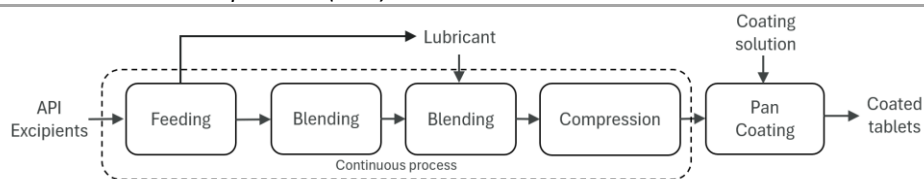
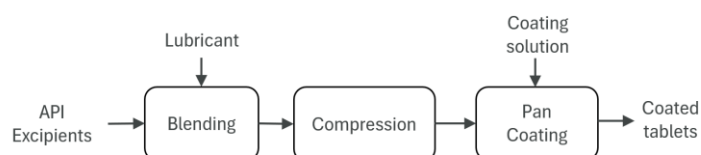
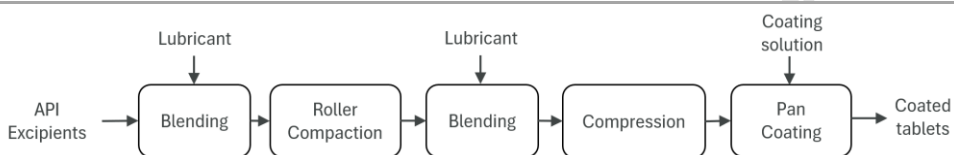
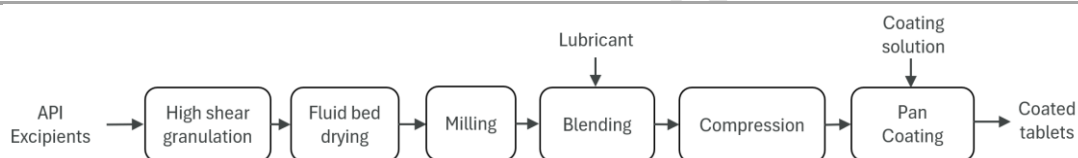
Continuous direct compression (CDC)*Direct compression (DC)**Roller compaction (RC)**High shear granulation (HSG)*

Figure 1 Process flow diagrams for different OSD manufacturing processes illustrating key unit operations and flow of materials

2.1. Batch blending

Batch blending was modelled using an intermediate bulk container (IBC) blender operating at a constant rotational speed of 15 rpm. The number of blending revolutions was set to 750 for the main blend, and 120 for the lubricated blend. The batch blending unit operation was used for the direct compression, high shear granulation and roller compaction platform comparisons.

2.2. High shear granulation

HSG was modelled based on an 800L bottom drive mixer. The batch size for granulation was assumed to be 0.25 of the granulator's volume. The HSG model assumed five minutes of dry mixing, followed by six minutes of liquid binder addition, and two minutes of granulation. The main drive operating speed was assumed to be a constant 75 rpm for dry mixing, liquid addition and granulation stages, while the chopper ran at 2000 rpm for liquid addition and granulation stages only. Water was added at 25% w/w.

2.3. Fluid bed drying

The FBD model assumed that for a batch size of 100 kg, there is a typical drying time of 45 minutes, using a constant air flow of 3000 cubic meters per hour. The inlet and outlet temperatures for heating the drying air were assumed to be 5°C and 65°C, respectively.

2.4. Roller compaction

The roller compactor was modelled using 10 cm width, 25 cm diameter rollers at a roll speed of 10 rpm, with a 2 mm separation between rollers. The true density of the material was assumed to be 1400 kg/m³, producing a ribbon with a relative density of 0.7.

2.5. Milling

Milling was modelled using a conical screen mill and assuming an impeller tip speed of 12 m/s. The milling process had an operational time of 15 minutes, for a batch size of 100 kg.

2.6. Batch compression

A rotary tablet press was used to model batch compression, with 49 stations operating at a constant rotation speed of 70 rpm. The batch compression unit operation is common to all platform comparisons except from continuous direct compression.

2.7. Continuous direct compression

The continuous direct compression unit operation consists of two continuous blenders and six feeders, with one feeder for each component of the formulation, and an integrated tablet press. The CDC process was taken to require three residence time distributions to reach steady state, operating at a constant throughput of 50 kg/hr.

2.8. Pan coating

Tablet coating was modelled based on a pan coater operating with a coat weight gain of 3%. Drying air was assumed to be heated from 5 to 65°C using an electric heater with 100% efficiency.

2.9. Formulation

A generic formulation was used for consistency, so that baseline formulation contributions could be excluded from the platform comparison analysis. As a result, the differences in manufacturing impacts could then be highlighted between platforms. A generic API was used, with a 20% drug loading within the formulation, reflecting a typical oral solid formulation. The tablet core formulation, common to all manufacturing platforms, is shown in Table 1.

Table 1 Tablet core formulation for a generic API to be used in all platform comparisons

Component	Composition (% w/w)
API	20.0
Microcrystalline cellulose	47.7
Lactose	21.8
Crospovidone	5.0
Magnesium stearate	1.5
Hydroxypropyl cellulose	4.0

An aqueous film coating formulation was sourced from literature (Roy et al., 2009). An adjustment was made to discount the minor, coloured pigments within the formulation since the concentration is so low that the environmental contribution from these pigments is assumed to be negligible. The resulting formulation is shown in Table 2.

Table 2 Coating formulation to be used in all platform comparisons

Component	Composition (% w/w)
Hypromellose	7.5

Propylene glycol	2.0
Titanium dioxide	3.0
Purified water	87.5

3. Life cycle assessment methodology

3.1. Functional unit and system boundary

A 'cradle-to-gate' approach was used to define the system boundary for the LCA, with a functional unit comprising the production of 1 kg of coated tablets (with core and coating compositions as in Table 1 and Table 2). The scope of the LCA is demonstrated in Figure 2, showing the key components. The input materials to the formulation process are considered, including their associated extraction and transformation impacts. Energy required for processing equipment and the manufacturing facility is considered, along with cleaning contributions, yield losses and waste disposal incurred during the production of coated tablets. The gate for the assessment is the coated tablet production, as such, impacts from packaging, distribution and patient use are not considered in this assessment.

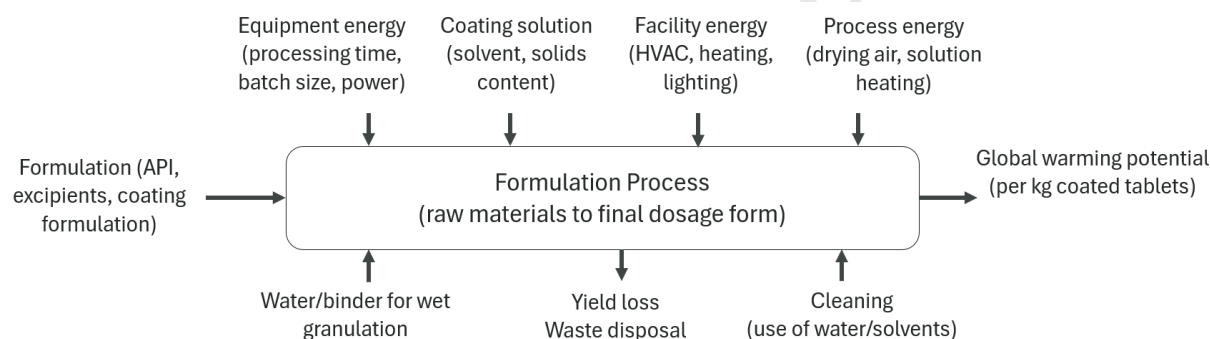


Figure 2 Scope of life cycle assessment

3.2. Materials

During the life cycle inventory (LCI) development stage, we followed a hierarchical approach for estimation of missing data as presented by (Parvatker & Eckelman, 2019). Where possible, the Ecoinvent LCI database was used to obtain values for excipients and auxiliary materials (Wernet et al., 2016). All electricity requirements were modelled using a low fossil fuel electricity source from the Ecoinvent database (medium voltage Europe without Switzerland electricity mix). For excipients not available within the Ecoinvent database, a value from literature was sourced, or a similar material with readily available LCI data, was used as a proxy. This proxy material was typically a precursor to the unavailable component, similar to the methodology for estimating missing LCI data used in other pharmaceutical LCAs, such as (Parvatker et al., 2019). API contribution was modelled using a proxy value of 1500 kgCO₂e/kg, based on medium emission API data obtained from the Association of the British Pharmaceutical Industry Blister Pack Carbon Evaluation Tool (ABPI & Carbon Trust, 2023).

An LCA value for microcrystalline cellulose (MCC) was sourced from literature, however this value used an electricity source from a high percentage fossil fuel electricity mix. Within this LCA, (Katakajwala & Mohan, 2020) concluded that over 95% of this carbon footprint from the MCC production was associated with the electricity consumption. To align with other materials, the LCA value was modified to change the electricity source to a low percentage fossil fuel electricity mix, resulting in a carbon footprint of 71.7 kgCO₂e/kg.

Proxy information and data sources for the formulation materials are summarised in Table 3. While proxy materials were used for some components of the formulation, these components each consisted less than 5% of the overall formulation. Additionally, to focus on the process related contributions of different manufacturing platforms, a consistent formulation was used across all platforms. As such, the selection of proxy materials will not impact the conclusions of the platform comparison. For dry processes, including direct compression, CDC and roller compaction, it is often necessary to use a specialist grade of excipient to improve the properties of the blend, for example with improved flowability (Leane et al., 2024). These specialised excipients may require additional processing, such as spray drying, and therefore have an elevated environmental impact. For dry processes, the impact of excipient grade was investigated by modelling an additional spray drying step for each excipient. Spray drying impacts were calculated based on the energy consumption of industrial spray dryers (Baker & McKenzie, 2005), with a 15% w/w solids loading assumed for an aqueous spray drying process (Chiou et al., 2008).

Typical process yields were incorporated into each unit operation, with the impact of yield loss material disposal assessed through a hazardous waste incineration step, sourced from the EcoInvent database and modified to account for molecular carbon release being calculated separately.

Table 3 LCA data sources for formulation materials

Material in formulation	LCA data source
API	(ABPI & Carbon Trust, 2023)
Microcrystalline cellulose	Modified from (Katakojwala & Mohan, 2020)
Lactose	(Flysjö, 2012)
Crospovidone	N-methyl-2-pyrrolidone (EcoInvent database)
Magnesium stearate	Stearic acid (EcoInvent database)
Hydroxypropyl cellulose	Carboxymethyl cellulose (EcoInvent database)
Hypromellose	Carboxymethyl cellulose (EcoInvent database)
Propylene glycol	Propylene glycol (EcoInvent database)
Titanium dioxide	Titanium dioxide (EcoInvent database)
Purified water	Purified water (EcoInvent database)

3.3. Equipment

Energy consumption was assessed both on a unit operation basis, considering unit operation energy requirements, in addition to a facility basis, considering the energy requirement of heating, lighting and air handling within the production facility.

Unit operation energy use was calculated using three key methods. The first method relates to equipment where the motor component is the main contribution to power consumption, for example in screw feeders. Assuming that the maximum equipment power is reached at the maximum motor speed, a linear correlation is used to estimate equipment power at given operating parameters. For equipment typically operated at fixed speeds and for a set duration where the major power contributor is torque, such as blenders, a similar method was applied, although maximum power is correlated with maximum load. Finally, for equipment with a heating or drying element, such as coaters, it is assumed that primary energy contribution is required to heat the incoming air. Power use is therefore calculated based on an enthalpy balance of the air, and the subsequent electricity requirement assuming a heater with 100% efficiency.

3.3.1. Batch blending

The power correlation for batch blending was established based on a Müller FTMF 200 MG10 blender (Müller AG Processing, Switzerland), with a maximum capacity of 100 kg and a power rating of 3.1 kW. Power was then scaled linearly based on mass within the blender.

3.3.2. High shear granulation

Two power correlations were calculated for the high shear granulator chopper and main drive, using values obtained from a Diosna P800 (DIOSNA Dierks & Sohne GmbH, Germany). The correlations for the chopper were based on power ratings of 10 kW and 12 kW for corresponding motor speeds of 1460 rpm and 2935 rpm. Similarly, correlations for the main drive were linearly constructed between power ratings of 35 kW and 53 kW for speeds of 49 rpm and 98 rpm, respectively.

3.3.3. Fluid bed drying

Energy consumption for the FBD unit operation was calculated based on the enthalpy balance of the drying air, shown below in equation 1, where Q is the duty (kW), \dot{m} is the air mass flowrate (kg/s), C_p is the heat capacity (kJ/kg/°C), and $T_{\text{air,outlet}}$ and $T_{\text{air,inlet}}$ are the outlet and inlet air temperatures respectively (°C).

$$Q = \dot{m}C_p(T_{\text{air,outlet}} - T_{\text{air,inlet}}) \quad (1)$$

It was assumed that the majority of the energy requirement for the unit operation comes from the drying air, as such other energy expenditures for this equipment were not considered. Electricity consumption to heat the air was then estimated assuming an electric heater with 100% efficiency.

3.3.4. Roller compaction

Power consumption for the RC unit operation was estimated based on a Gerteis MACRO-PACTOR roller compactor (Gerteis, Switzerland). A correlation between an active line power rating of 16 kW and a maximum operating speed of 30 rpm for the rollers. Operating time for a given batch size was determined based on the mass flow rate of material through the rollers, calculated from equations 2 and 3 by (Reynolds et al., 2010).

$$\bar{v} = \pi D N_R \quad (2)$$

Here, \bar{v} is the roller tip speed (m/s), D is the roller diameter (m), and N_R is the roller speed (rpm).

$$\dot{m}_R = \rho_{\text{true}} \gamma_R \bar{v} W S \quad (3)$$

Here, ρ_{true} is the material true density (kg/m³), γ_R the ribbon relative density, and W and S are the roller width (m) and separation (m), respectively.

3.3.5. Milling

Milling was modelled based on a Quadro 194 Overdriven Comil® (Quadro, Canada), with a maximum power of 4 kW. A linear correlation was constructed between the maximum power, and a maximum impeller tip speed of 15 m/s based on impeller speeds reported by (Reynolds, 2010).

3.3.6. Batch compression

A Fette 3090i tablet press (Fette Compacting, Germany) was used to estimate power consumption for the batch compression unit operation. The unit has a maximum power consumption on 17 kW, and a maximum turret rotation speed of 120 rpm, power consumption was linearly correlated with turret rotation speed using these maximum values.

3.3.7. Continuous direct compression

The CDC process is modelled with two blenders, six feeders, a tablet press, control panel and tablet tester. For the blenders and feeders, linear correlations were constructed between motor speed and nominal power. For the blenders, this used a maximum motor speed of 450 rpm and nominal power of 1.16 kW, while the feeders each had a nominal power of 0.5 kW and maximum motor speed of 10,000 rpm. The tablet press power consumption was estimated using a relationship between turret speed and power, using a nominal power of 6 kW and maximum speed of 110 rpm to create a linear correlation. Additional auxiliary equipment consisting of a control panel and tablet tester, with power ratings of 2 and 0.08 kW, respectively, were assumed to be on for the duration of processing.

3.3.8. Pan coating

Similarly to the fluid bed drying unit operation, it was assumed that the heat requirement for drying air was the main contributor to energy consumption in the pan coater. Energy use was then calculated through an enthalpy balance of the drying air, and the associated electricity requirement assuming an electric heater with 100% efficiency. Spray rate was estimated based on the batch size and air flow rate was then estimated based on the estimated spray rate value. Both values were estimated based on experiential parameter selection across a range of production scales.

3.4. Processing facility overheads

Energy consumption for the processing facility overheads was calculated in addition to individual equipment items. The facility energy contribution captures the overheads for the processing rooms, including heating, air handling and lighting. A 'building energy intensity' value (kWh/m²) was calculated using annual electricity meter (consumption in kWh) and building footprint data (area in m²) from a representative OSD manufacturing facility as shown in equation 4.

$$\text{building energy intensity} = \frac{\text{annual electricity consumption}}{\text{building area}} \quad (4)$$

Space requirements for each unit operation were estimated based on an assumed fixed size 'dirty room' area, plus a 'clean room' area which was scaled for relative equipment size and complexity. Facility energy contribution was then calculated using the building energy intensity and room size, multiplied by processing or cleaning durations, to account for overheads during both stages.

Cleaning contribution was built into the models using LCA data from a representative commercial cleaning process for a pan coater. Cleaning impacts were scaled on a kilogram basis and the carbon emissions were then estimated for other equipment by using water consumption data from cleaning procedures. The cleaning emissions consider the use of cold, hot and purified water in addition to cleaning agents, and associated power requirements. A comparison of the cleaning impacts for each piece of equipment is shown in Figure 3.

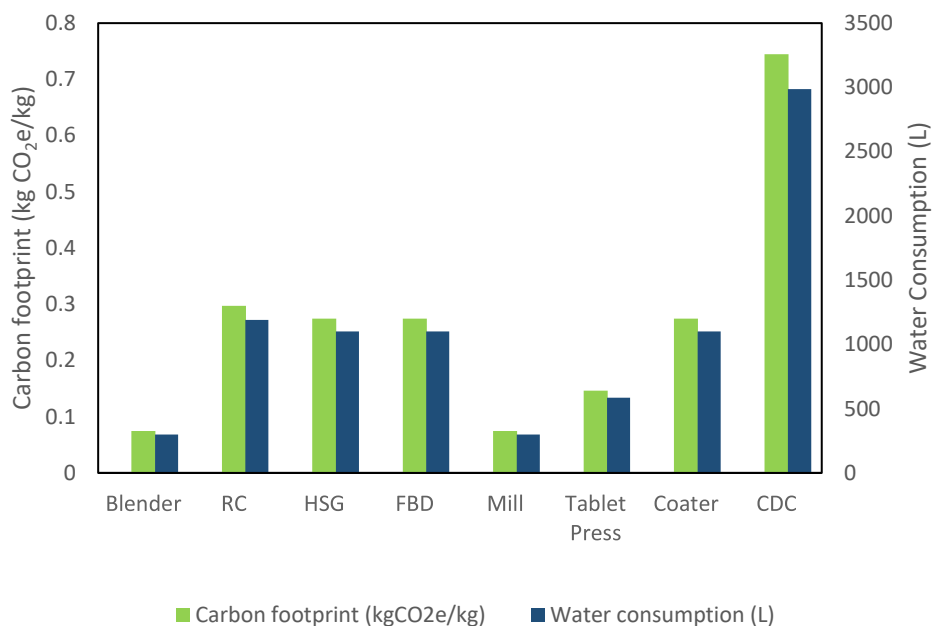


Figure 3 Cleaning contributions to LCA models for each unit operation

3.5. Process yields and waste considerations

For batch unit operations, average yield data from over 7000 commercial product batches was used. Using data from such a large range of batches and products provides a general baseline for the platform comparison. Specific API properties that impact manufacturability may lead to scenarios with lower or higher values. Since yield data from an optimised, commercial CDC process was not available, CDC yield was predicted based on assumed losses. For CDC, the yield losses were assumed to be from the start up and shut down procedures when running the continuous line. Assuming three residence times to reach steady state, the start up process was estimated to consume 3.6 kg of material at a given throughput of 50 kg. The shut down losses result from the holdup mass within the system, corresponding to 1.2 kg of loss. It was assumed that during the steady state running period, the CDC process operates at 100% yield.

Table 4 Summary of process yields across different manufacturing platforms

Manufacturing stage	Average yield (%)	Number of batches assessed
Dry granulation (powder blending + roller compaction)	99.8	1990
Wet granulation (powder blending + HSG + FBD)	97.3	497
Tablet compression	96.6	2609
Tablet coating	99.6	2559

Yields were accounted for within the LCA models through an overage required to reach the final functional unit and assumed that all material losses from low yield were treated as waste. Molecular carbon release of yield loss waste was calculated on a stoichiometric basis, assuming complete combustion. Waste disposal used the hazardous waste incineration process, sourced from the Ecoinvent database, adjusted to account for molecular carbon release being calculated separately.

3.6. Life cycle impact assessment

Models for each manufacturing platform were constructed within SimaPro 9.4 LCA software (Pré Sustainability B.V.). The ReCiPe 2016 Midpoint (H) V1.05 / World (2010) H calculation method was used, with global warming selected as the key impact category for this assessment. While inclusion of additional impact categories would provide a more holistic sustainability assessment, lack of data availability meant that a proxy value for carbon footprint was used to model the API impacts, and since data for other impact categories was not available, the focus of this study is on carbon footprint. To understand the impacts of scale, different batch sizes were assessed for each platform, with results normalised to one kilogram of coated tablets to enable comparison.

4. Systems modelling methodology

This work demonstrates the integration of LCA models with system models for OSD manufacture, a step towards enabling process design and optimisation which considers sustainability in addition to conventional metrics. A CDC system model was constructed for manufacture of the 100 mg tablets defined in Table 1. The system model was developed in gPROMS Formulated Products (v2023.1.0, Siemens), using the standard model libraries without customisation.

The CDC system model, shown in Figure 4, comprises individual material feeders for each component, with API, fillers and disintegrant fed into blender 1, and the ensuing powder blend combined with lubricant in blender 2. The feeders were modelled as continuously stirred tank reactors with gravimetric screw control and a fixed feed factor of 2 g/rev. The two horizontal blenders were modelled using the tanks in series model, with two tanks for each, and with the mean residence time in blender 1 calculated based on its throughput (49.2 kg/h) and residence mass (0.4 kg or 1.2 kg), and the same for blender 2 (50 kg/h, 0.28 kg). Tablet compression in the tablet press was modelled using the Reynolds (Reynolds et al., 2017) model to calculate tablet porosity and tensile strength, based on generic compressibility properties for the blend. The API content of the tablets was monitored, and the time spent out of specification (defined as > 2% deviation in API content) was recorded to determine the quantity of acceptable material produced during operation.

The operating window was defined by excluding the first three blender 1 mean residence times to approximate onset of steady state operation (as described in section 2.7) and calculating the end time needed to achieve a fixed mass of material (100 kg, 200 kg, 500 kg powder) with a throughput of 50 kg/h.

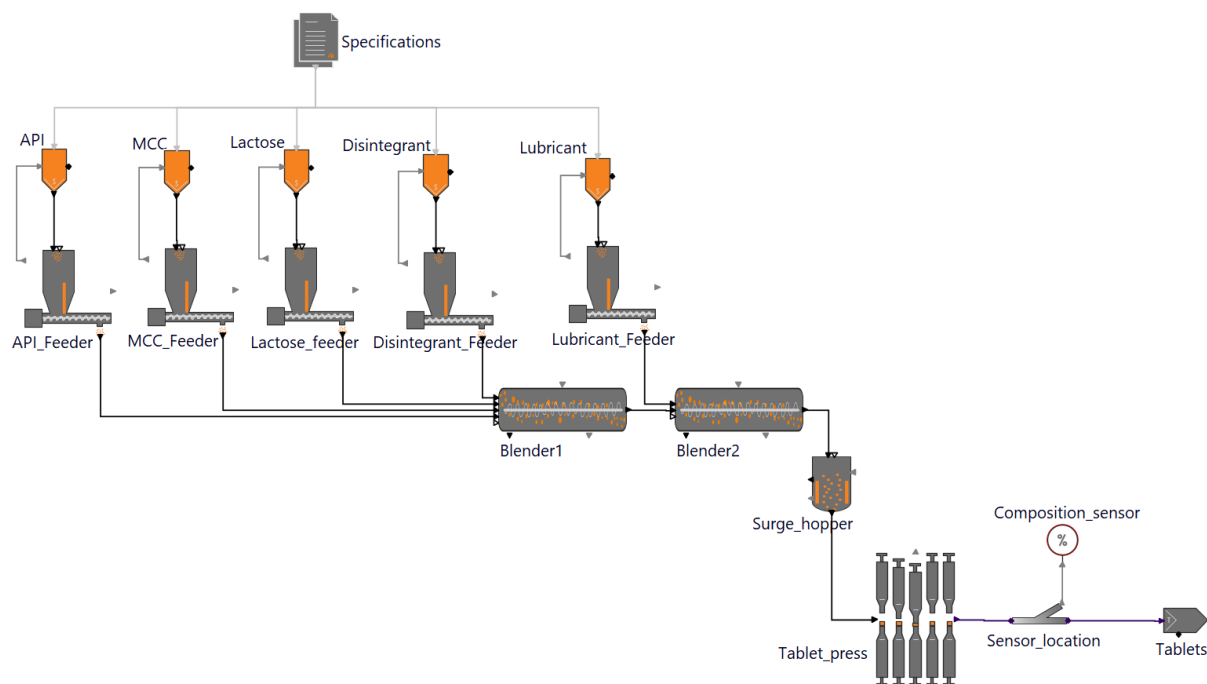


Figure 4 Overview of CDC system model

LCA calculations using methodologies outlined in sections 3.2 and 3.3 were integrated with the systems model using custom modelling in gPROMS including material contributions (emissions per kilogram of formulation) and the process/equipment contributions (emissions due to feeder, blender, and tablet press power demand during operation).

To demonstrate the utility of embedded LCA calculations in the system model, API feeder disturbances were simulated and the resulting impact on out of specification material was assessed from a carbon cost perspective. An API pulse was simulated every 50 kg of powder processed, and the magnitude and duration of the pulse were varied to assess its impact on the quantity of out of specification material produced and corresponding emissions per kilogram of in specification tablets obtained. A relatively large magnitude and duration was used to provide a clear comparison between cases for illustration purposes, and is comparable with the methodology used to generate “funnel plots” (García-Muñoz et al., 2018). In practice, disturbances would be smaller.

5. Results and discussion

5.1. Life cycle assessment

The LCA methodology described in section 3 was applied to the OSD manufacturing processes defined in section 2. In this section, we compare the selected OSD manufacturing platforms (CDC, DC, RC and HSG) in terms of overall impact on carbon footprint to manufacture one kilogram of the same tablets (Table 1), and break this down further to explore the impact of material qualities and processing stages. Finally, we present results from sensitivity studies around process scale, processing time and electricity source.

5.1.1. Breakdown of API contribution to baseline formulation

An LCA performed on one kilogram of coated tablets provides the baseline formulation contribution of 325 kgCO₂e. Most of this carbon footprint originates from the API production, with the API footprint contributing 89.5%, compared to 10.5% of impacts from all other excipients and coat formulation. Within the results of the platform comparison, the baseline formulation contribution is

subtracted to illustrate the impact of the manufacturing process and yield losses from each platform on the overall formulation carbon footprint.

5.1.2. Platform comparison

Life cycle impact assessments of each processing platform were conducted across different production scales between 50 kg and 500 kg. A holistic comparison was made across the different manufacturing methods, and included an excipient impact adjustment for dry processes, to account for additional pre-processing required for the specialised grades of excipients required for improved flowability. When performing the LCA, all impacts were normalised per kg coated tablets, to allow for comparison to be made across batch sizes. Since the carbon footprint is dominated by API production, the baseline formulation contribution of 325 kgCO₂e per kg was subtracted from the overall impact to show the carbon footprint impacts resulting from the OSD manufacturing processes only.

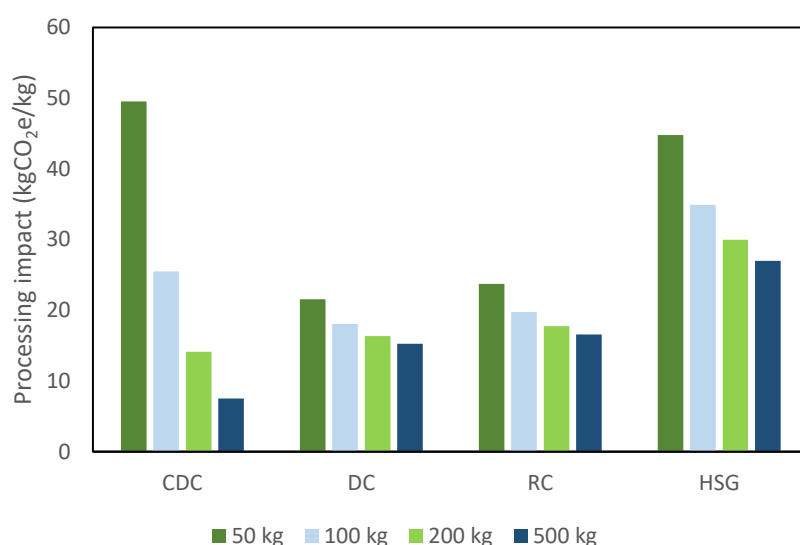


Figure 5 Comparison of carbon footprint impacts associated with the production of 1 kg coated tablets across different manufacturing platforms and batch sizes. The baseline formulation contribution of 325 kgCO₂e is excluded from results

Figure 5 shows the carbon footprint impact that each OSD manufacturing platform adds to the baseline formulation contribution of one kg of coated tablets across different batch sizes. All manufacturing platforms show a relationship between batch size and processing impact, with reduced impacts at larger batch sizes, however for CDC this difference is much more significant. For CDC the relationship between batch size and impact is mostly driven by process yield, since API has a very large carbon footprint. The assumption of fixed start up and shut down losses means that the process yield is derived from these losses relative to the overall batch size, and subsequently, at larger batch sizes both yield and carbon footprint are improved. On the other hand, at small batch sizes CDC is the most carbon intensive manufacturing process. Additionally, for all platforms increases in batch sizes are favourable for carbon emission reduction as fixed contributions such as cleaning become relatively lower per kg at larger batch sizes.

Across the batch processes assessed, DC has the lowest carbon footprint impact when compared to granulation processes such as RC and HSG. This is largely due to the cumulative effect of additional unit operations on the overall process yield, and overhead contributions such as cleaning requirements. The batch size above which CDC has a lower processing impact than other OSD platforms is estimated to be approximately 170 kg.

5.1.3. Impact of material pre-processing/grade

Specialised grades of excipients may be required to facilitate flowability and compression in dry processes, whereas HSG may be able to use less processed material to attain the same product quality. For example, spray-dried mannitol grades such as Partek M200 and Pearlitol 200SD were found to be suitable for direct compression due to their superior flowability and tableability (Paul et al., 2018). To understand the influence of excipient pre-processing on overall process sustainability, specialised grades of excipients were modelled with additional impacts, calculated based on a spray drying process, incorporated into the life cycle inventory for dry processes. For HSG, this excipient pre-processing was not considered. While the impacts for some excipients were increased by as much as 25%, the total excipient impact, when excluding API impacts, was only increased by 1% for the specialist grade material. Due to the magnitude of the API contribution compared with excipients, the baseline formulation impact of the dry processes was only 0.1% higher than the respective wet granulation process. The results in Figure 5 already include the considerations of excipient grade, with the baseline formulation impact taken as the standard material.

5.1.4. Breakdown of process contributions

To understand the key factors affecting the carbon footprint, the contributions of raw materials, equipment energy, facility overheads during processing and cleaning, cleaning and yield loss including waste processing were examined for a 100 kg batch size. The baseline formulation contribution, to the overall formulation process carbon footprint varies between 90 and 95% across the manufacturing platforms, contributing the least to high shear granulation, and most to direct compression, in agreement with their overall processing impacts as demonstrated in Figure 5. To allow comparison, the baseline formulation contribution is subtracted from this assessment, however, impacts from overage material required due to yield losses are still included. Figure 6 shows a breakdown of the carbon footprint sources.

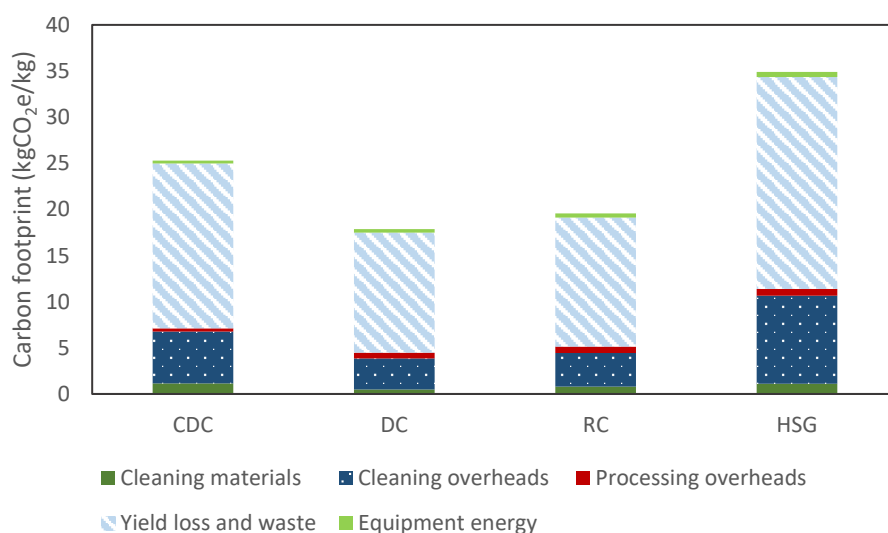


Figure 6 Breakdown of contribution to formulation process impacts, excluding baseline formulation contribution

For all manufacturing platforms, yield loss and waste have the largest contribution to the formulation process carbon footprint, greater than the combined impacts of the other categories. This is due to the high carbon footprint of the additional API needed to produce 1 kg of material at a lower yield. The yield loss and waste impacts reflect the relative differences in yield for each manufacturing

platform, with CDC having a slightly lower yield than DC and RC at the 100 kg scale. Since process yield was shown to have the largest influence on carbon footprint, a sensitivity analysis was conducted on the waste assumptions for the CDC process. The total losses assumed represent an optimised CDC process, therefore Monte Carlo simulations were performed to understand the impact of a 10% increase in the CDC waste. The results of the sensitivity analysis on waste shows that for a 95% confidence interval CDC remains the most carbon efficient manufacturing process for batch sizes of 200 kg and above. Full results of the Monte Carlo simulations are presented in the Appendices (7.1).

Following the yield losses, the next biggest contributor to carbon footprint was the energy consumption resulting from facility overheads during the cleaning process. The CDC cleaning procedure is more complex and time consuming than DC and RC unit operations, resulting in a higher contribution of materials and facility overheads during cleaning for CDC. On the other hand, HSG has a significantly higher impact from facility overheads during cleaning, owing to the number of unit operations and cumulative effect of heating, lighting and air handling throughout the cleaning duration of each piece of equipment. Equipment processing energy contributes a minimal amount to the overall impact across all manufacturing platforms, but particularly CDC. This is due to the high throughput and efficiency of the CDC line. HSG has the highest equipment energy contribution, which is predominantly impacted by the additional unit operations required for the process, but also the energy intensive drying step following granulation.

5.1.5. Sensitivity to batch size and equipment scale

During the life cycle inventory development phase, both large- and small-scale unit operation models were constructed using typical manufacturing equipment used between pilot scale to commercial scale. For example, equipment energy models for both a Gerteis MINI-PACTOR and MACRO-PACTOR were constructed for small- and large-scale RC, respectively. While the equipment had slightly different power ratings and therefore energy consumptions, this accounted to less than 0.5% of the overall formulation process impacts, and therefore large-scale unit operation energy models were used for all comparisons. Further detail on equipment scales is available in the Appendices (7.2).

To enable comparison across batch sizes, all results were standardised as impacts per kilogram of coated tablets. To test the robustness of the batch size parameter across non-continuous unit operations within the LCA equipment models, assessments were made between the operation of a single, large batch compared with multiple smaller batches. Since the batch equipment energy models are scaled linearly based on processing time and load, the resulting energy impacts per kilogram of material are identical across different batch sizes.

5.1.6. Sensitivity to waiting time between unit operations for batch processes

For batch processes, there are typically intermediate waiting periods where material is held between unit operations. To understand the influence of these waiting times on the non-material carbon footprint impacts for each platform, a sensitivity analysis was performed to vary the waiting times between manufacturing steps. Figure 7 demonstrates a clear relationship between waiting time and the associated carbon footprint, excluding material contributions, which results from the increased processing time and resultant facility overheads. For HSG, this impact is greater, mainly due to the additional unit operations compared with RC and DC. The CDC line is assumed to be fully continuous and therefore has no waiting time impact.

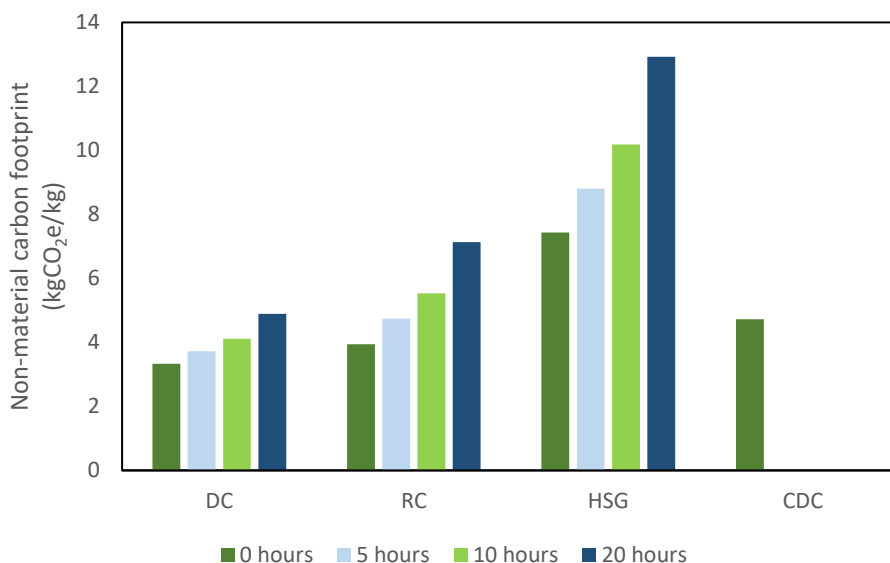


Figure 7 Impact of waiting time between unit operations on overhead carbon footprint contribution. Formulation material contributions excluded from analysis

5.1.7. Cleaning process sensitivity analyses

Since the facility overheads during cleaning is the highest contributor to the processing carbon footprint when excluding material impacts, the assumptions relating its calculation were examined as part of a sensitivity analysis. For a batch size of 100 kg, the room area and cleaning duration were independently varied between 50% less and 50% more than the nominal values to verify the impact on non-material related carbon footprint. The room area increase resulted in a percentage increase in non-material carbon footprint between 33% and 38%, with HSG having the largest increase, which is due to this platform having the most unit operations. An increase in cleaning duration raised the non-material carbon footprint by 23% to 32% and followed the same trend between platforms. Full results of the sensitivity analyses are available in the Appendices (7.3). Room area has a more significant impact on non-material carbon footprint when compared with cleaning duration, which is to be expected since this increases the facility overhead contribution during processing as well as during cleaning. However, a change in cleaning time does not affect the facility overhead contribution during processing and therefore is slightly less influential than room area.

5.1.8. Sensitivity to source of electricity for processing

During the life cycle inventory development, LCA data for microcrystalline cellulose was sourced from literature and modified to adjust the electricity contribution from a high fossil fuel percentage to a low fossil fuel percentage electricity mix. For the platform comparison and associated analyses, electricity was sourced from the EcolInvent database using a low fossil fuel electricity mix (Europe without Switzerland – medium voltage). To understand the impact of energy sources on the overall results, a sensitivity analysis was performed using a comparison between energy mixes with high and low percentages of fossil fuels. The platform comparison was repeated for a batch size of 100 kg, instead using a high fossil fuel electricity mix (Indian Southern grid – medium voltage). The results in Figure 8, which exclude the baseline formulation contribution, demonstrate that the formulation process impacts are increased significantly for the high fossil fuel electricity mix due to its higher carbon footprint. For CDC, DC and RC, this corresponds to approximately a 60% increase in carbon

footprint, while HSG increases by nearly 77%, largely due to its energy intensive manufacturing process and cleaning requirement.

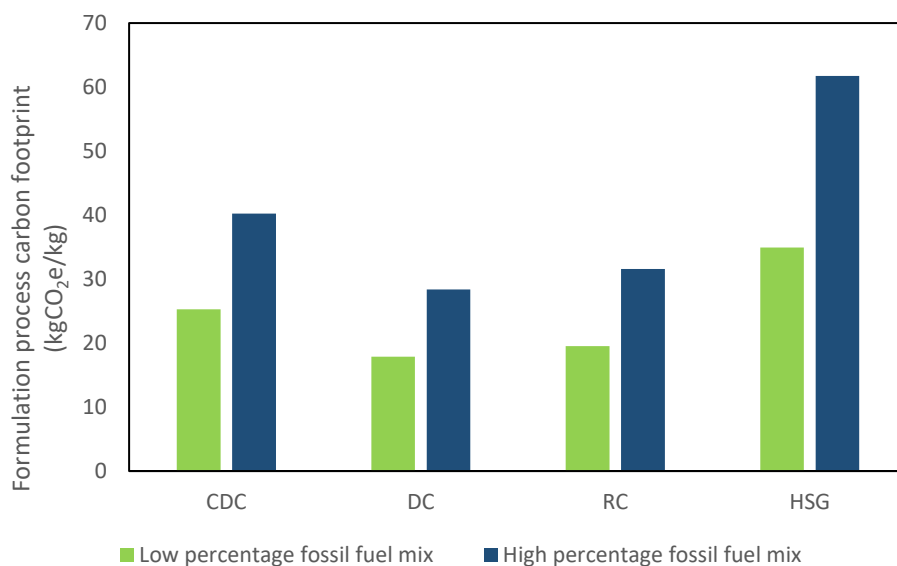


Figure 8 Results of sensitivity analysis on electricity source. Baseline formulation contribution excluded from comparison

5.1.9. Packaging and distribution

The cradle-to-gate boundary with the focus of the functional unit as the final, coated tablet excludes the impact of subsequent packaging and distribution. In particular, blister packs, often including aluminium for protection, can generate substantial waste (Raju et al., 2016). The focus of this study was on the global warming potential impact of tablet manufacturing technologies and therefore these contributions were excluded. However, there can be some level of dependency between formulation, process and packaging. High shear wet granulation may enable higher drug loadings in a formulation (Leane et al., 2018). In some high-dose circumstances, achieving a higher drug loading could reduce the number of tablets per dose and therefore result in a reduction in packaging material.

5.2. Systems modelling

To illustrate the coupling of the system model with the LCA equations, the impact of feeder disturbances and blender residence mass was investigated. A key design objective in developing a CDC process is to mitigate the impact of mass flow variability from the feeders on the composition of the final tablets. Feeder variability may be influenced by poor physical properties of the raw materials, in particular the API (Leane et al., 2024). The propagation of feeder variability through the process is influenced by the overall residence time distribution (RTD). The primary blender in this simulation contributes a large proportion of the residence mass and therefore controls the overall system RTD. For a given RTD, it is important to understand the magnitude and duration of a feeder mass flowrate deviation in order to establish a robust process and control strategy. This relationship is often visualised by a funnel plot, which maps contours of tablet concentration as a function of feeder disturbance magnitude and duration (García-Muñoz et al., 2018). The addition of LCA calculations that depend on operating conditions and material consumption provides insight into the effect of this system design on the overall carbon footprint of the manufacturing process.

5.2.1. Impact of API feeder deviation duration and magnitude

Two CDC systems were compared, differing in the residence mass in blender 1. System 1 had a smaller residence mass of 0.4 kg while system 2 had a larger residence mass of 1.2 kg. The duration of the API feeder deviation was increased from 0–100 seconds and the magnitude was increased from 0–100% of the API flow rate. In practise, controls should be in place to prevent large and extended disturbances, but this analysis provides a methodology to visualise the environmental impact across the funnel plot space. API feeder deviations were generated at 50 kg processing intervals to scale for larger batch sizes. Figure 9 shows the total kgCO₂e per kg of in specification tablets for each case, based on a batch size of 500 kg. To simplify presentation of results, the total mass of the feeder disturbance is calculated from the magnitude and duration. Neither system was impacted by the smallest or shortest API disturbances. As the API disturbance magnitude and duration were increased, the system with the larger residence mass was observed to be better able to smooth out the impact and reduce the peak concentration deviation in the tablet, resulting in fewer out of specification tablets. For a large and long enough deviation, this mixing behaviour was not able to prevent out of specification waste and then it was worse in the case of the larger residence mass because the excess material can build up and create a deviation for a longer period. Figure 10 shows tablet concentration over a period of the run time two deviations, highlighting that the larger residence mass reduces the peak concentration, but extends the period during which the concentration remains out of specification.

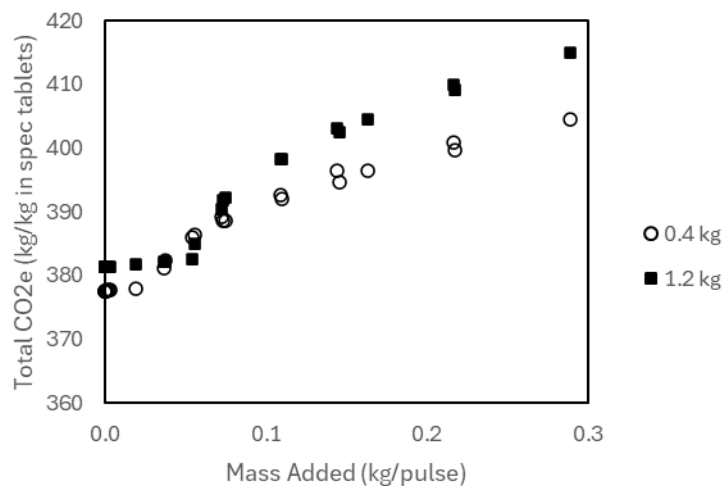


Figure 9 Total kgCO₂e per kg of in specification tablets between two CDC systems with 0.4 kg and 1.2 kg blender 1 residence mass, after processing 500 kg of powder

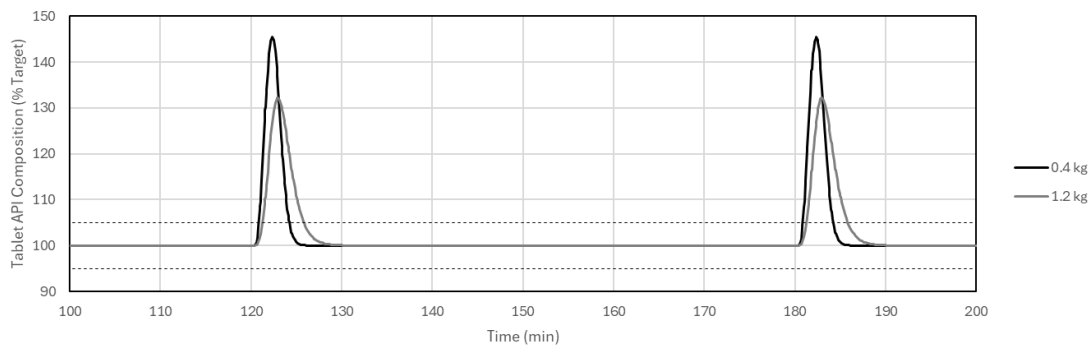


Figure 10 Tablet API composition change during two feeder deviation pulses for two CDC systems with 0.4 kg and 1.2 kg blender 1 residence mass

5.2.2. Impact of powder mass processed

Simulations were performed for different durations to produce overall batch sizes of 100, 200 and 500 kg. Figure 11 shows the difference in carbon footprint between the larger and smaller residence mass systems. At the smallest batch size of 100 kg, the larger residence mass system has a significantly higher carbon footprint due to the larger process start up waste as a proportion of the overall production (ca 6 kg compared with 2 kg). As the batch size increases, this relative shift in carbon footprint between the two systems becomes less important as the startup becomes a smaller proportion of the overall production.

As the amount of API introduced to the system by disturbances is increased, there is initially a smaller number of tablets rejected by the higher residence mass system due to the reduction in the peak concentration. This leads to a reduction in the disparity between the carbon footprint of the two residence mass systems. In the case of a batch size of 500 kg, there is even a period where the higher residence mass system has a smaller carbon footprint than the lower residence mass system. This is seen to occur with a disturbance mass of approximately 50 g. As the disturbance mass is increased further, the suppression in the peak concentration becomes insufficient to avoid rejection of tablets from the higher residence mass system. As shown in Figure 10, the higher residence mass system then leads to greater tablet rejection due to the longer period of time the concentration remains out of specification.

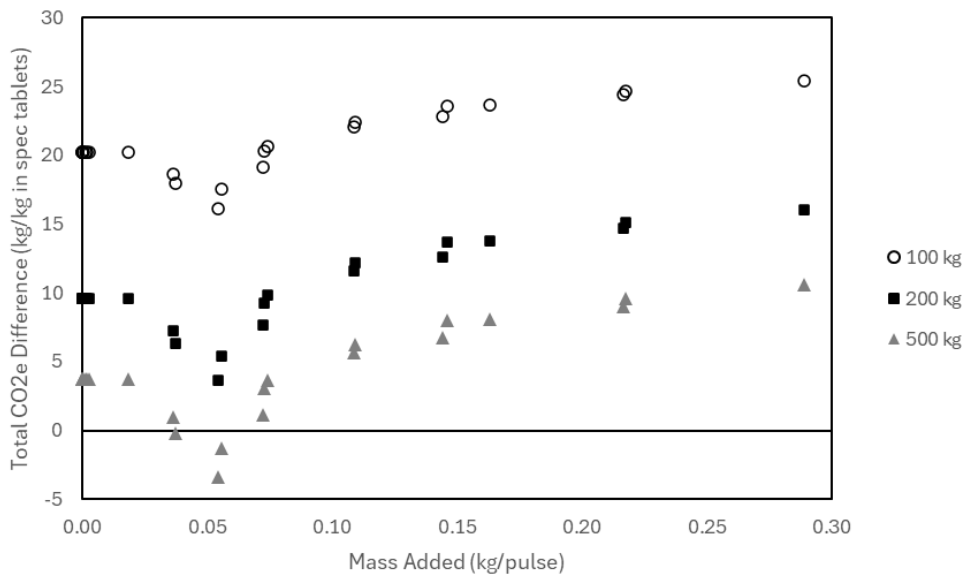


Figure 11 Difference between the total carbon footprint of the CDC systems with blender 1 residence mass of 1.2 kg and 0.4 kg, respectively. A positive value indicates that the system with residence mass of 1.2 kg has a higher carbon footprint than the system with residence mass of 0.4 kg

Overall, the coupling of the systems model along with the LCA equations enables a more holistic study of the relative impact of process design decisions on both the robustness of the process and the global warming potential. In this example, the general observations show that a larger batch size leads to a reduced carbon footprint per tablet as shown by the previous LCA analysis. In more detail, the dynamics of the process related to residence mass and therefore residence time distribution can be taken into account. In the scenarios studied, the lower residence mass system results in a more favourable carbon footprint. In practice, the process should be designed such that the expected level of variability in the feed rate will not trigger rejection of out of specification tablets – i.e. this process should operate below a disturbance mass of 50 g as shown in Figure 9 In this case, depending on the

batch size and expected level of variability a higher residence mass may in fact yield an improved carbon footprint.

6. Conclusion

A holistic approach was employed using LCA to compare environmental impacts associated with the production of one kilogram of coated tablets using common OSD manufacturing platforms across a range of scales. The results of the platform comparison demonstrated that CDC has the potential to produce tablets with the lowest processing impacts, although this requires a sufficiently large batch size due to the impacts on yield from the start up and shut down processes. At small batch sizes, direct compression has the lowest impact followed by roller compaction, whereas high shear granulation typically has higher impacts due to the additional processing steps, including the energy intensive drying stage.

Analysis of the overall OSD manufacturing impacts demonstrate that the overall product impact is largely driven by the high carbon footprint of the API, and as such, process yields at the formulation stage have the largest overall environmental impact. Impacts associated with energy use are relatively small compared to raw material impacts, although these can be affected by the source of electricity. Cleaning processes had a significant contribution to non-material carbon footprint impacts, through use of solvents and water, as well as the facility operational impacts during the cleaning process.

Due to limited availability of LCA data for excipients, proxies were used for a number of materials within the formulation. The impact of additional processing steps for specialised grades of excipients was assessed and found to have a limited effect on the overall carbon footprint.

A proof of concept for integration of LCA methodology within systems modelling of formulation processes was presented. The analysis investigated the operation of a CDC process to understand the influence of process parameters such as residence mass and manufacturing scale on product carbon footprint. For the continuous process, start up and out of specification (e.g. due to API disturbances) losses increase the carbon cost per acceptable tablet illustrating how the coupling of LCA with systems modelling enables more holistic process design and optimisation, including sustainability metrics.

7. Appendices

7.1. Monte Carlo simulations on CDC waste uncertainty

Monte Carlo simulations (n=1000 with 95% confidence) were performed using a triangle distribution with a mean of 4.8 kg and a maximum of +10% for the CDC waste value. Since the value of 4.8 kg assumes an optimised process, a minimum of 4.7 kg was used. Results of Monte Carlo simulations are presented in Table 5, where the baseline formulation contribution of 325 kgCO₂e/kg is excluded.

Table 5 Results of CDC process carbon footprints from Monte Carlo simulations performed on CDC waste uncertainty

Batch size (kg)	Mean (kgCO ₂ e/kg)	2.50% (kgCO ₂ e/kg)	97.5% (kgCO ₂ e/kg)
50	50.3	48.8	52.5
100	25.7	25.1	26.7
200	14.1	13.8	14.6
500	7.4	7.2	7.6

7.2. Small- and large-scale unit operation LCA models

During the development of the unit operation LCA models, equipment energy correlations were initially established for both pilot scale and commercial scale processing equipment. For example, equipment energy consumption for roller compaction was modelled based on both the Gerteis MINI-PACTOR and MACRO-PACTOR. A similar approach was followed for the direct compression and high shear granulation process models. Table 6 shows results of a comparison between the carbon footprint results for small- and large-scale models. Since the results agree within 0.5%, it was decided that the large-scale unit operation model is representative across the different scales investigated as part of the platform comparison, and therefore these large-scale models were used for all analyses.

Table 6 Comparison between small- and large-scale unit operation models, results for 100 kg batch size

Platform	Small-scale model (kgCO ₂ e/kg)	Large-scale model (kgCO ₂ e/kg)	Percentage difference (%)
Direct Compression	354.2	353.8	-0.1
Roller Compaction	358.2	357.0	-0.3
High shear granulation	385.1	387.2	0.5

7.3. Sensitivity analyses on room area and cleaning time

Sensitivity analyses were performed on the assumptions for room area and cleaning time, by varying each of these parameters by +/- 50%. Results are shown in Table 7 and Table 8.

Table 7 Sensitivity analysis of room area on non-material carbon footprint (100 kg batch size)

Manufacturing platform	Room area impact (kgCO ₂ e/kg, % change)		
	Smaller room (-50%)	Nominal room area	Larger room (+50%)
CDC	3.5 (- 25%)	4.7	6.3 (+ 34%)
DC	2.4 (- 27%)	3.3	4.5 (+ 35%)
RC	3.0 (- 25%)	3.9	5.2 (+ 33%)
HSG	5.2 (- 30%)	7.4	10.2 (+ 38%)

Table 8 Sensitivity analysis of cleaning time on non-material carbon footprint (100 kg batch size)

Manufacturing platform	Cleaning time impact (kgCO ₂ e/kg, % change)
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	Shorter time (-50%)	Nominal time	Longer time (+50%)
CDC	3.3 (- 30%)	4.7	6.1 (+ 30%)
DC	2.5 (- 25%)	3.3	4.2 (+ 25%)
RC	3.0 (- 23%)	3.9	4.9 (+ 23%)
HSG	5.0 (- 32%)	7.4	9.8 (+ 23%)

Data availability

The data in this work is confidential to AstraZeneca and consequently has not been shared.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Flora Bouchier reports a relationship with AstraZeneca that includes: employment and equity or stocks. Astrid Boje reports a relationship with AstraZeneca that includes: employment and equity or stocks. Gavin Reynolds reports a relationship with AstraZeneca that includes: employment and equity or stocks. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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