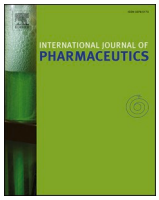
International Journal of Pharmaceutics 647 (2023) 123509

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm



Challenges encountered in the transfer of atorvastatin tablet manufacturing - commercial batch-based production as a basis for small-scale continuous tablet manufacturing tests

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ARTICLE INFO

Keywords:
Pharmaceutical continuous manufacturing
Tableting
Dry granulation
Twin screw feeding
Oral solid dosage form

ABSTRACT

As is the case with batch-based tableting processes, continuous tablet manufacturing can be conducted by direct compression or with a granulation step such as dry or wet granulation included in the production procedure. In this work, continuous manufacturing tests were performed with a commercial tablet formulation, while maintaining its original material composition. Challenges were encountered with the feeding performance of the API during initial tests which required designing different powder pre-blend compositions. After the pre-blend optimization phase, granules were prepared with a roller compactor. Tableting was conducted with the granules and an additional brief continuous direct compression run was completed with some ungranulated mixture. The tablets were assessed with off-line tests, applying the quality requirements demanded for the batch-manufactured product. Chemical maps were obtained by Raman mapping and elemental maps by scanning electron microscopy with energy-dispersive X-ray spectroscopy. Large variations in both tablet weights and breaking forces were observed in all tested samples, resulting in significant quality complications. It was suspected that the API tended to adhere to the process equipment, accounting for the low API content in the powder mixture and tablets. These results suggest that this API or the tablet composition was unsuitable for manufacturing in a continuous line; further testing could be continued with different materials and changes in the process.

1. Introduction

In continuous manufacturing, the process units are connected and they are operated in a continuous manner (Pauli et al., 2020). This means that the addition of starting materials at the beginning of the manufacturing line and the collection of the final product at the end of the line occur simultaneously. In a continuous process, the batch size is the result of the run time and the material throughput. Despite the many benefits of continuous manufacturing, unlike most other fields of industry, the pharmaceutical industry still relies predominantly on inefficient batch processes (Hu, 2021; Plumb, 2005; Rogers et al., 2020; Srai et al., 2015). This gives rise to quality defects and long lead times which can even cause drug shortages. However, significant progress has been achieved lately in the implementation of continuous manufacturing of pharmaceutical products (Allenspach et al., 2021; Billups and Singh, 2020). This stems from numerous studies investigating its different aspects i.e. the optimal types of equipment and materials as well as a deeper understanding of the entire process. Continuously manufactured pharmaceuticals representing high and low volumes of production have already been introduced to the market. Examples of continuously manufactured products are Orkambi®, Symdeko®, Trikafta®, Prezista®, Verzenio® and Daurismo® (Hu, 2021). These represent both

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https://doi.org/10.1016/j.ijpharm.2023.123509
Received 21 September 2023; Received in revised form 7 October 2023; Accepted 10 October 2023
Available online 11 October 2023

new compounds and process conversions of previously batch-manufactured products.

Continuous tablet manufacturing encompasses multiple possible process routes such as direct compression, wet granulation, dry granulation or hot melt extrusion (Allenspach et al., 2021; Malevez and Copot, 2021; Maniruzzaman and Nokhodchi, 2017; Metta et al., 2018). Owing to its simplicity, continuous direct compression (CDC) is a manufacturing approach with many benefits. Some of the recognized challenges with CDC processing are the poor flow and unsatisfactory compactability properties of many APIs. To avoid these problems, it is recommended to choose excipients that are designed for direct compression. Other available possibilities are coprocessing the API with excipients, adding glidants and utilizing vibration to improve flowability (Allenspach et al., 2021; Huang et al., 2015). However, there are materials that require granulation to obtain better flowability to ensure their manufacture into high-quality tablets (Bacher et al., 2007; Perez-Gandarillas et al., 2016). Another benefit of granulation is that it often reduces the amounts of dusting and segregation (Mansa et al., 2008). Roller compaction is a dry granulation method that can be operated in a continuous manner (Herting and Kleinebudde, 2007; Reynolds et al., 2010). This granulation method is suitable for moisture or heat-sensitive materials as no liquid addition or drying phases are required in the process. The drawbacks of roller compaction include the reduction of tablet tensile strength and the presence of fines among the granules (Herting and Kleinebudde, 2008; Souihi et al., 2013). Because of its high tensile strength, microcrystalline cellulose is often chosen as a filler for roller compaction.

In addition to traditional analytical tests, tablets can be analyzed with complementary research methods to improve process understanding. Scanning electron microscopy (SEM) with energy-dispersive X-ray spectroscopy (EDS) and Raman spectroscopy are methods that can provide elemental or molecular information about samples (Hayes et al., 2019). The API distribution in tablets can be assessed non-destructively with chemical mapping based on these mentioned techniques (Scoutaris et al., 2014). In SEM imaging, an electron beam with a constant kinetic energy is focused on the sample. Different detectors can be used to collect various types of data from the samples after the beam has interacted with the material under study (Brodusch et al., 2018). While secondary electrons are often valence electrons that are ejected from the sample due to atomic ionization, primary electrons can be used to detect electron backscatter diffraction. These electrons from the beam are backscattered from the sample after a limited degree of absorption. In the EDS method, the electron beam of SEM stimulates the atoms of the sample, generating X-rays that are observed with detectors (Goldstein et al., 2003). The released X-ray quanta are formed when the atoms are ionized by the electron beam, causing empty spaces in electron shells which are filled with electrons from outer shells. This results in an energy emission in the form of characteristic X-rays with energies that depend on which atom is involved in analyzed areas, enabling the identification of its presence in the study material.

Atorvastatin is a globally consumed antilipemic drug (Oliveira et al., 2013), making it an interesting candidate for research on continuous tablet manufacturing. However, like many other APIs, it has poor flow and bioavailability properties (Chen et al., 2022; Megarry et al., 2019; Pingali et al., 2009; Shamsuddin et al., 2016). Particle size reduction is one way to improve oral bioavailability, but this can exert detrimental effects on flow properties. As APIs are the only materials that cannot be substituted in a product, a balance needs to be obtained between the material's pharmaceutical properties. Serious technological challenges may result from the poor flowability of a material blend, for example, uneven filling of dies causes significant differences in tablet weights and breaking forces (Mendez et al., 2010; Nachajski et al., 2019). Obviously, this leads to the situation that different tablets contain varying amounts of the API (Murase et al., 2022). The challenges regarding variations in the die filling in the production of small tablets (≤6 mm) have been recognized in earlier studies (Goh et al., 2019, 2017). However, small tablets such as the formulation chosen for this study are widely available on the market.

The aim of this study was to test the manufacturing of a commercial batch-manufactured tablet product with a continuous manufacturing line. This approach with a real product has not received much attention in academic research on continuous tablet manufacturing. Here, the original materials and their proportions of the batch-manufactured product were used in every continuous test run. This provided the possibility to compare the test results to the actual product's specification and to assess if a process conversion without changes in materials would be feasible. In our earlier publication, process optimization led to a successful process conversion with another commercial tablet product (Lyytikäinen et al., 2022). However, prior to embarking on this project, it was hypothesized that the production of these tablets would be challenging due to the physical characteristics of atorvastatin. Since the pharmaceutical industry has shown interest in adopting continuous manufacturing, tests with products currently manufactured in batch processes and already marketed can provide important information on the equipment and process differences to be taken into consideration when switching from batch to continuous manufacturing.

2. Materials and methods

The production technology conversion tests were performed with atorvastatin 10 mg tablets of Zentiva. The tablet composition is described in Table 1. The batch-manufactured tablets are coated, but in this study, only the tablet cores were inspected as the coating step was not within the scope of this research project. The batch manufacturing process includes a dry granulation step with roller compaction and this process step was included in all of the continuous manufacturing tests, except in a short direct compression run. No conveyors were used in this study, meaning that the materials were transferred manually into feeders in the pre-blending process and in the first mixing step. Manual transportation of materials occurred also when the mixture was filled into the roller compactor and ultimately in the filling of feeders prior to tableting. Details of the manufacturing line can be found in earlier publications (Ervasti et al., 2015; Simonaho et al., 2016).

During preliminary feeding studies, it became clear that separate feeding of atorvastatin was not feasible due to observed bridging in the feeder hopper and the poor stability of the feed rate. The following parts of the text explain the process optimization steps of this study.

2.1. Pre-blending and roller compaction

The first attempt to improve the API feeding properties was to mix it with silica using a V-blender (non-commercial equipment constructed at the University of Eastern Finland) which slightly improved the feed rate stability (Supplementary data, Fig S1). The tests proceeded to granulation and tableting. When assessing granule flowability, tests assessing angle of repose and Carr compressibility index (Ph. Eur. 2.9.36) were performed for granules that were compressed for the first tableting runs. The angle of repose was measured with a PT-X Powder tester (Hosokawa Micron Corporation, Japan) and the bulk and tapped densities (Ph. Eur. 2.9.34) were determined with an Erweka SVM tapping device (Germany).

After the whole tableting process was completed for the first time, it was evident that there were too large variations in both tablet weights and breaking forces (data not shown). Other pre-blend approaches were investigated to see if they could overcome these issues. Due to the many ingredients present in this product and the maximum number of feeders (four per feeding station), each processing option consisted of two pre-blends: one with excipients and the API and the other consisting of only excipients (Table 2). The pre-blends were formed in multiple sub-batches with the V-blender which was rotated at a 20-rpm speed for 12 min for each sub-batch. All pre-blend sub-batches with different compositions weighed approximately 3 kg. In order to ensure adequate

Table 1
Ingredients of the specified 10 mg atorvastatin tablets.

Material	Abbreviation	Trade name	Manufacturer	Function	% (m/m) in the formulation
Atorvastatin calcium	Atorvastatin		MSN Pharmachem Pvt. Ltd.	Active substance	10.34
Calcium carbonate		Scoralite	Scora	pH-adjusting agent	32.00
Microcrystalline cellulose	MCC	Comprecel M102D+	Mingtai Chemical Co. Ltd	Diluent, disintegrant	30.00
Lactose monohydrate	Lactose	Tablettose 80	MEGGLE GmbH & Co.	Diluent	11.66
Low-substituted hydroxypropyl cellulose	LS-HPC		Shin-Etsu Chemical Co. Ltd.	Binder, disintegrant	10.00
Povidone		Kollidon 12 PF	BASF	Binder, dissolution enhancer	4.00
Colloidal anhydrous silicon dioxide	Silica	Aerosil 200	Evonik	Glidant	1.00
Magnesium stearate	MgSt		Peter Greven Nederland C.V.	Lubricant	1.00

Table 2
Designed pre-blend compositions.

Name of the pre-blend pair	API containing pre-blend	Excipient pre-blend
A	Atorvastatin	Calcium carbonate
	MCC (1/3 of total)	LS-HPC
.		Povidone
		Silica
B	Atorvastatin	Calcium carbonate (2/3 of total)
	Silica (1/2 of total)	LS-HPC
	Calcium carbonate (1/3 of total)	Povidone
		Silica (1/2 of total)
C	Atorvastatin	Calcium carbonate
	Silica	LS-HPC
	MCC (1/3 of total)	Povidone

mixing, the pre-blends were additionally mixed with the continuous mixer (Modulomix, Hosokawa Micron B.V., Netherlands) at 900 rpm.

When forming the mixture for roller compaction, these pre-blend combinations were mixed with MgSt (1/2 of the total amount in the final product) and the remaining MCC. The two pre-blends and these additional excipients were fed with feeders mentioned in Table 3 into the continuous mixer. Three mixer speeds were tested (700, 900 and 1100 rpm) for each mixture. Powder samples were collected at 0, 5 and 10 min after the start with each mixer speed. The produced mixtures for granulation were later called mixtures A, B and C corresponding to the pre-blends from which they were manufactured. Another pre-blend composition containing the API (atorvastatin and lactose blend) was prepared but it was observed to adhere to many parts of the equipment such as feeder screws and thus further tests with this blend were discontinued.

The mixtures for roller compaction were compared with a UV–Vis spectrophotometer (preliminary tests, data not shown) and final testing was conducted with UPLC measurements (internal procedure of Zentiva). These measurements were aimed to select the most suitable mixture based on its API content. Detailed data from these measurements are not shown. According to these tests, mixture A was excluded from further studies due to the extensive variation in the API content. Mixtures B and C had relatively similar API contents, however both were low (slightly over 90% of the label claim). Eventually, mixture B was chosen for the preparation of granules by roller compaction.

Mixture B was granulated with a roller compactor (Pharmapaktor L200/30P with a flake crusher FC 200, Hosokawa Bepex, Germany). The feeding screw speed was 14–15 rpm, the roll speed was 3.5 rpm and the roll pressure was approximately 27 kN. The flake crusher speed was 32 rpm.

Table 3
The feeders and materials used to form the mixtures.

Feeder type (Coperion K-Tron, Switzerland)	Material
K-ML-D5-KT20	Excipient pre-blend
K-ML-D5-KT20	MCC
K-CL-SFS-KT20	API containing pre-blend
K-CL-SFS-MT12	MgSt

2.2. Continuous tableting

After the granules were prepared, tableting was conducted with three feeders in the process setup. The total material feed rate was 14.4 kg/h. Lactose was fed with K-ML-D5-KT20, the remaining ½ of MgSt with K-CL-SFS-MT12 and the granules with K-CL-SFS-KT20. Initially, 15 kg of granules were placed in the feeder and manual refilling with 10 kg occurred twice. MgSt was refilled once during the process. Granules and lactose were directed to the mixer from the first inlet port and MgSt from the second one. The continuous mixer speed was 900 rpm. The tablet press (PR1000, PTK, South Korea) was operated with the settings described in Table 4. The tablet press was instrumented with 16 round and concave 6 mm three-tip punches that had embossed marks and a score line.

The target tablet weight was 100 mg and the lowest acceptable breaking force values were 40 N. These values were monitored during the compression with an analytical scale (202A, Precisa, Switzerland) and a breaking force tester (CT5, Engineering Systems, UK). The tableting run with granules lasted for 2 h. A direct compression run where the granules were replaced with an ungranulated mixture lasted for 15 min. No material refills occurred in this run. Tablet samples were taken every 5 min in the tableting run with granules and at 2-minute intervals in the direct compression run.

2.3. Intermediate material and tablet tests

2.3.1. Tablet weight, breaking force, friability and disintegration

Tablet weights were measured with an analytical scale AG245 (Mettler Toledo, Germany) with the same breaking force tester being used as applied in process monitoring. Friability testing was performed according to Ph. Eur. 2.9.7. with a TA3 (Erweka, Germany). A disintegration test was done for six tablets from each of the selected time points with a DT3 (Sotax, Switzerland) apparatus following test A of Ph. Eur. 2.9.1. Purified water was used as a solvent and discs were used in the test. The acceptability limit for the disintegration time was 15 min.

2.3.2. API content assay and content uniformity

Mixture B and granules prepared with the same mixture were analyzed with the assay of API content (internal procedure of Zentiva). Tablet samples from the direct compression run and the tableting run

Table 4
Tablet compression settings.

	Tableting with granules	Direct compression
Turret speed (rpm)	45 ± 3	36
Force feeder paddle wheel speed (rpm)	80	58
Filling depth (mm)	3.70 ± 0.20	4.65 ± 0.03
Punch displacement / minimum tablet thickness	1.13	1.02 ± 0.07
Average compression force (kN)	21 ± 2	23 ± 3

with granules were assessed with the API content assay and content uniformity measurements.

2.3.3. SEM-EDS and Raman mapping

When evaluating especially the distribution of atorvastatin in tablets, spectroscopical methods were applied. Mixture, granule and tablet samples were inspected with a scanning electron microscope (Carl Zeiss Sigma HD VP, Carl Zeiss NTS, UK) with a secondary electron detector (SE2), backscattered electron detector (HDBSD) and two energy-dispersive X-ray spectroscopy (EDS) detectors (60 mm2 silicon drift detectors, Thermo Scientific, USA). The electron acceleration voltage was 20 kV and a nitrogen gas environment of 20 Pa was used in the vacuum chamber during low vacuum conditions. As the samples were electrically non-conductive, this low-pressure gas medium was utilized to eliminate electron charge exposure. The samples were attached to aluminum stubs with double-sided carbon tape. No other sample processing such as sample coating was conducted prior to imaging to ensure sufficient material contrast. The analyzed tablets were dedusted and their surfaces were screened. Elemental mapping was based on the identification of certain elements of the raw materials. Some of the materials were tracked with the following elements found in their structures: atorvastatin ($C_{66}H_{68}CaF_2N_4O_{10}$; F), calcium carbonate ($CaCO_3$; Ca), MgSt ($C_{36}H_{70}MgO_4$; Mg) and silica (SiO_2; Si). The mapping was performed from each sample for 1000 s acquisition time using Thermo Scientific Pathfinder v1.4 software. Quantitative map type with atomic % data were the mapping processing settings. They displayed the atomic concentrations of the elements in the sample. Mean and gated rank filters were applied to enhance the contrast and sharpen the images.

Raman mapping was performed as an additional mapping technique in the tablet assessment. Representative smooth tablet cross-sections were prepared by fixing them into paraffin blocks and cutting them lengthwise with a microtome (Leica RM2255, Leica Microsystems, Germany) after the blocks had solidified at room temperature. Commercial Paraplast bulk (Leica Biosystems, Germany) was used to prepare paraffin blocks with tablets. Two tablets were analyzed for each process type (direct compression at the 11 min time point and tableting with granules at 1 h 50 min). Tablets prepared in this way were placed on an aluminum slide which was inserted into the sample compartment equipped with a software-controlled motorized xyz stage and subjected to Raman analysis.

A dispersive Raman microscope (inVia Reflex, Renishaw, UK) was operated with the Peltier–cooled CCD detector (Renishaw RenCam, 1040 × 256 pixels) and controlled by Wire 5.5 (Renishaw, UK) software. Raman spectra were collected using an NIR laser with an excitation wavelength of 785 nm in a line arrangement with the objective 50x (numerical aperture 0.75). Raman mapping was performed in high-resolution (HR) mode with spectra being acquired in the range 1800 – 730 cm − 1. The size of the map was approximately 215 × 137 pixels with ×, y-step size 4 μm. The exposure time was 0.1 s and the laser power was set to 100%. Data sets of Raman spectra were processed to chemical maps. The maps were created using the chemometric method Direct Classical Least Squares (DCLS) in the Wire program (5.5, Renishaw, UK). The principle of creating Raman maps by DCLS has been described in another article (Čapková-Helešicová et al., 2019).

3. Results and discussion

3.1. Pre-blending and granulation

The angle of repose results of the granules from the preliminary tableting runs indicated passable flow properties (45 degrees) according to Ph. Eur. 2.9.36. However, the variabilities in the weights and breaking forces of the prepared tablets seemed inadequate for this kind of flowability value. For example, a Carr compressibility index value of 25 is associated with passable flowability according to the same section of Ph. Eur.

3.2. Tablet tests

3.2.1. Tablet weight, breaking force, friability and disintegration

Regardless of process optimization attempts, the tablet weight and breaking force results revealed extensive variation in both tableting runs (Fig. 1). The results were unacceptable due to the lack of uniformity between tablets despite the average results being maintained at target levels at many time points.

The friability and disintegration results showed no consistency between the measured time points (Fig. 2). In the case of disintegration time, some samples did not comply with the 15-minute limit. Additionally, the disintegration times varied noticeably between the tablets within a time point. The variations in these values were not surprising when one considers the tablet weight and breaking force results.

3.2.2. API content assay and content uniformity

The results of the API assay of mixture B were 92.9% and 94.2% of the declared amount. The granule samples showed values of 93.3% and 93.4%. The API assay results of tablets varied significantly (Fig. 3). This was not unexpected based on the observed tablet weight results. It can be suspected that inconsistent test results throughout the process were caused by flowability issues (Sun, 2010).

The content uniformity target (acceptance value $\leq$ 15%) was narrowly met only at one time point in the direct compression run whereas all of the results from the tableting with granules were non-complying (Table 5). Interestingly, the values were closer to the target with direct compression.

3.2.3. SEM-EDS and Raman mapping

As Fig. 4 reveals, calcium carbonate and atorvastatin can be seen throughout the analyzed samples. Despite the fact that there was a lower concentration of MgSt in comparison to most of the other ingredients in the product, it seemed to be present in separate clusters in these samples. All the materials could not be distinguished, e.g. MCC did not contain a trackable atom in its structure because carbon, oxygen and hydrogen are present also in other materials of the formulation. In this analysis, it should be kept in mind that it is not possible to draw any firm conclusions regarding material quantities from these elemental maps.

As can be seen from the Raman maps (Fig. 5), atorvastatin was scattered more evenly than lactose despite their contents in the product being fairly similar. However, atorvastatin was mixed into the pre-blend which may explain its better dispersion. Interestingly, lactose is seen in separate regions in both tablet samples. In the compression runs with granules, lactose was added after the granulation. This could have led to differences between the tablet types. When the sizes of these regions with lactose are compared to the areas that are occupied by other materials, it is unlikely that they would cause issues related to poor API content uniformity in tablets. The API seems to be found near MCC even though they were not present in the same pre-blend. More materials could be tracked in these Raman measurements than in the SEM-EDS method in the case of this product. As an example, the distinct areas consisting of lactose could not be observed with SEM-EDS. Overall, both map types provide information about a small sample area and different regions may be present in the studied and other compressed tablets. No evidence was found in the mapping images of large API clusters that would be indicative of very poor mixing. It seemed that the materials were evenly distributed in the samples that were analyzed with these methods. SEM images without EDS mapping are available in the Supplementary data (Fig. S2 and Fig. S3).

Despite multiple attempts to modify the pre-blending of the materials in this formulation, no quality-complying tablets could be produced with the original product's composition on the described continuous manufacturing setup. The reason for the low content of atorvastatin could not be resolved. It could be speculated that this API tended to

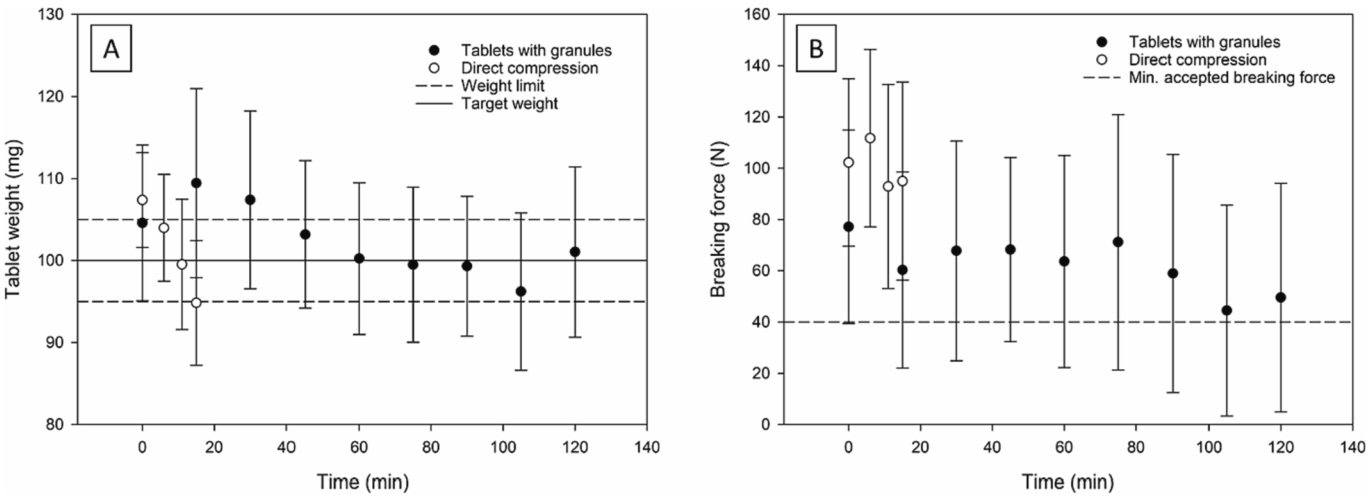

Fig. 1. Tablet weight (A) and breaking force (B) results of the tableting runs with and without roller compaction.

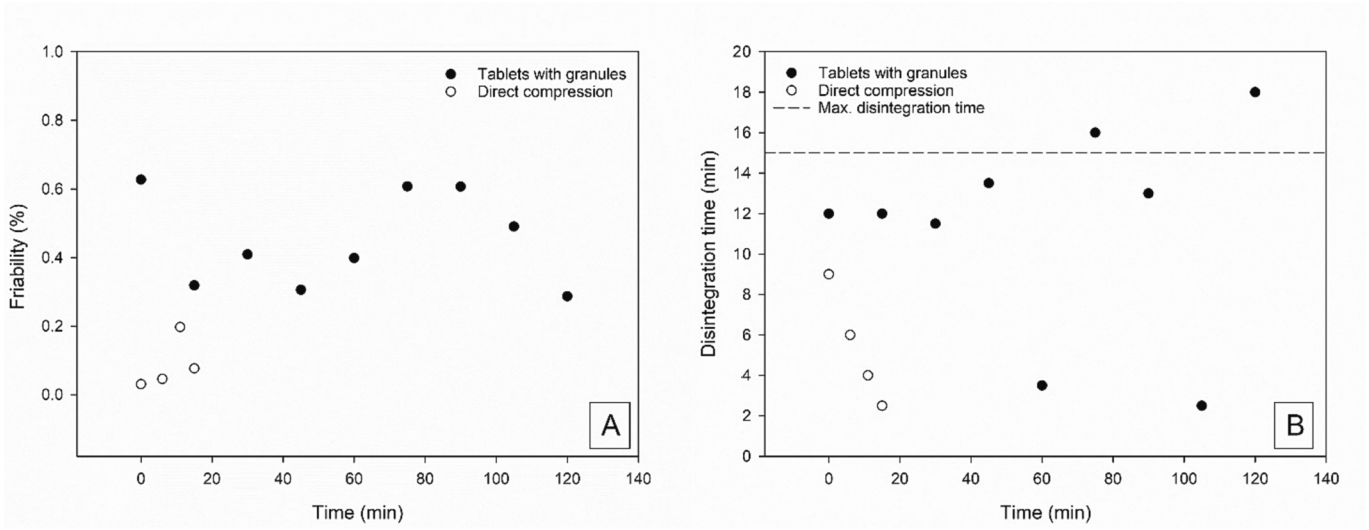

Fig. 2. Friability (A) and disintegration (B) values of the tableting runs with and without a granulation step.

adhere to the walls of our equipment; this is supported by the visible and difficult-to-clean residue detected at the end of the tests. However, the content remained low even after the mixing and feeding had been continued for a moderate amount of time. Component adhesion to surfaces on continuous manufacturing lines has been recognized in the literature (Moghtadernejad et al., 2018). The effect might be related to the tendency of a material to gain an electrostatic charge during its processing. The phenomenon stems from friction and the transfer of electrons and can cause particles to attract each other. (Domike and Cooney, 2015). Surface adhesion of materials could lead to the production of subpotent tablets until the stuck material becomes displaced from the equipment's walls. Should this occur, the outcome could cause a deviation in the material concentration and ultimately superpotent tablets. Powder adhesion can also be a cause for concern if it occurs at a PAT interface. Due to the risks associated with the high adherence tendency of the API, no further process optimization was continued with this product.

In this study, the API had been acquired for these tests and the stability of the raw API material was not suspected to be the reason for the low content values. The performance of the feeders (K-ML-D5-KT20 and K-CL-SFS-KT20) had been tested with an external scale and the target amounts of the fed materials were met. Thus, the reason for the encountered challenges was probably attributable to the unsuitable material or mixture composition for this type of manufacturing line. For this reason, some modifications to the product composition would be justified after these initial technology transfer tests. It is unlikely that this product could be manufactured on the described manufacturing line without making alterations to the formulation. Considering process parameter changes, turret speed is known to affect die filling (Peeters et al., 2015). However, reduction of tableting speed would not be a possible solution to the issues that emerged during this work because the tests were designed to be conducted with the lowest possible feed rates with the utilized equipment. In this case, the lubricant feeder was operated near to the lower limit of its range.

If tests were to be continued with these same materials, one putative modification would be diluting the API with a larger quantity of excipients than in the presented pre-blends as this could perhaps improve the flowability of the mixture. It is possible that after this change, the die and punch sizes could be increased. This could reduce the observed tablet weight variation as has been reported in the literature (Gopireddy et al., 2016). Another approach that could help to obtain a more uniform filling of the dies would be to change the punch type from a multi-tip punch unit to one with a single tip. Experiments could be conducted to determine if this change would exert any effect on the tablet weight

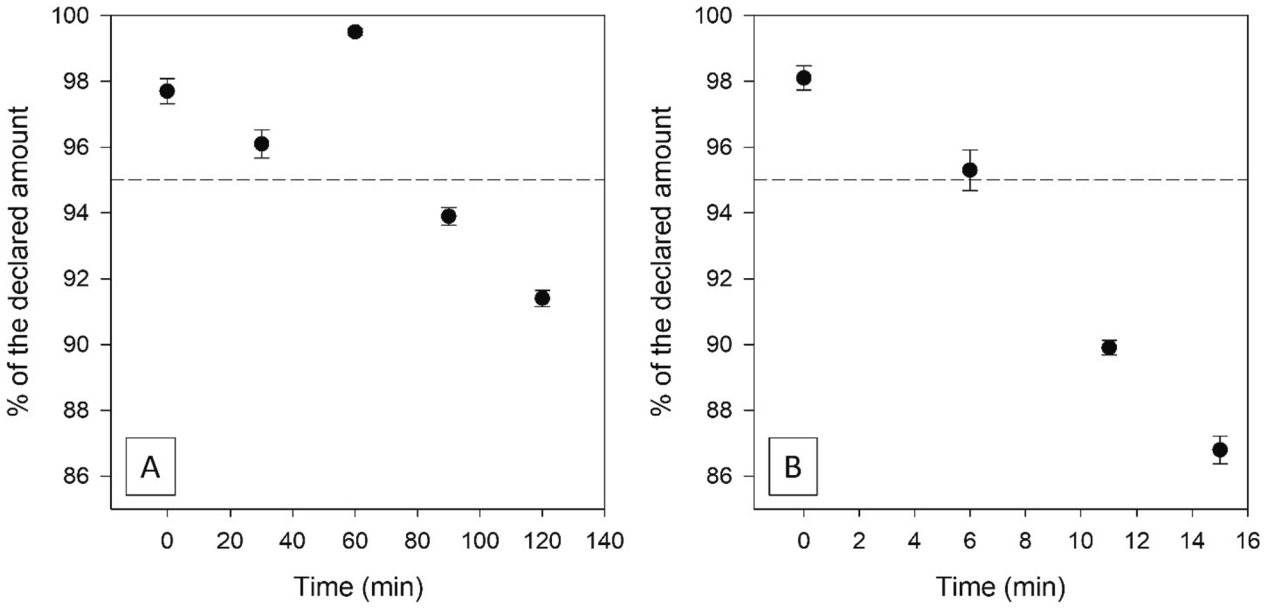

Fig. 3. Atorvastatin assay results of tableting run with granules (A) and direct compression run (B). The error bars illustrate relative standard deviations.

Table 5
Content uniformity results.

Tableting run and time point	Acceptance value %
Tablets with granules	
0 min	24.9
60 min	27.5
120 min	25.7
Direct compression	
0 min	14.8
6 min	18.4

variation with this product. However, these approaches would still not be optimal because they would resemble the original batch manufacturing process since a pre-blending step would be required in order to obtain adequate flowability. It has to be remembered that the batch manufacturing method has already been proven to produce quality-complying tablets since the studied product has been on the market for years. This dilution approach was not tested because of the size limitation of the utilized V-blender. A possible addition to the continuous manufacturing process would be to sieve or mill the materials, perhaps during multiple points of the process. Conical mills have been integrated into continuous manufacturing lines as a way to eliminate material lumps (Singh et al., 2015). Sieving process steps are also included in the batch-manufacturing process of this product.

The most significant challenges encountered in these tableting tests were related to the poor processability of atorvastatin. One possibility to improve the flow properties could be to test a differently manufactured API form because it is known that the material's crystal characteristics affect its physical–chemical properties (Besenhard et al., 2017; Chen et al., 2011). By undertaking crystal engineering, it may also be possible to modify the compression properties, possibly enabling direct compression (Chattoraj and Sun, 2018). A recent study proposed that co-processing an API with excipients could be an option for conventional particle engineering as a way of overcoming difficulties caused by powder properties (Erdemir et al., 2022). Overall, along with flow properties, it will be necessary to take into account the well-recognized dissolution challenges of atorvastatin when changing the formulation's

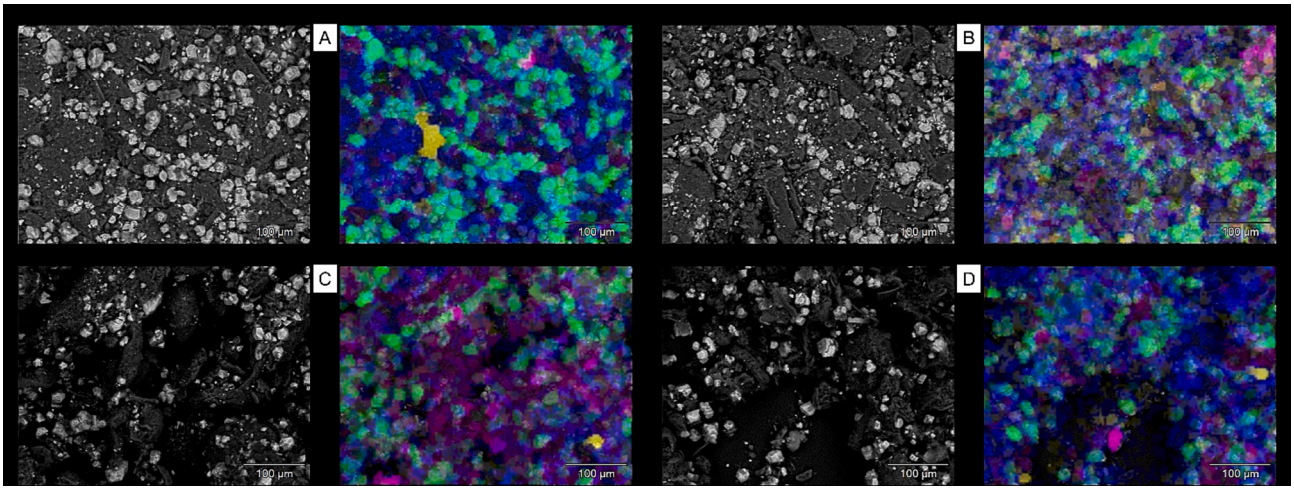

Fig. 4. SEM-EDS elemental maps indicating calcium carbonate (green), atorvastatin (blue), magnesium stearate (yellow) and silica (magenta) in tablets of the direct compression run (A), tablets with granules (B), granules (C) and the mixture for granulation (D). The SEM (backscattered electron) images are on the left side and the elemental maps obtained from the same images are on their right side.

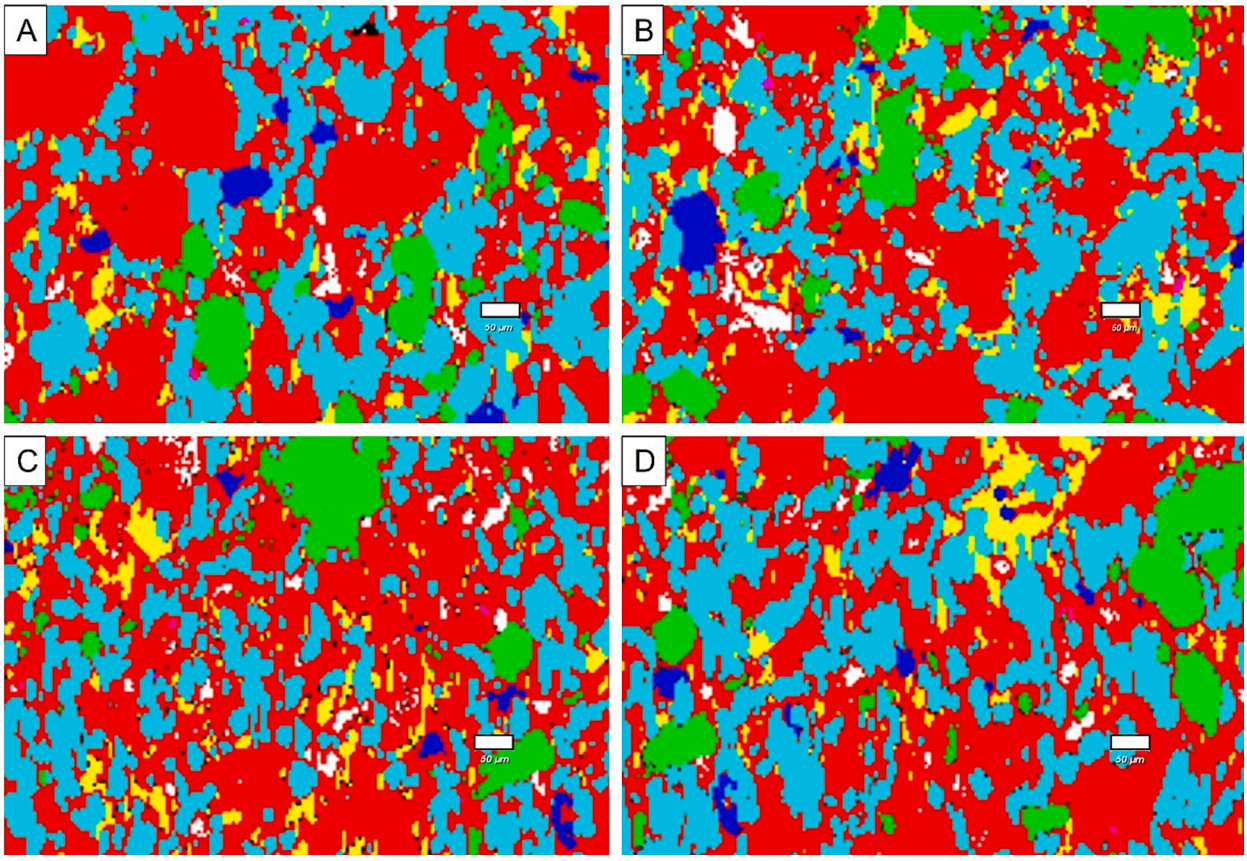

Fig. 5. Raman maps of tablet cross-sections. The maps represent the material distributions of tablets from direct compression (A, B) and the tablets that contain granules (C, D). The colors mark the following materials: atorvastatin (yellow), MCC (red), calcium carbonate (cyan), lactose (green), HPC (grey), MgSt (magenta) and povidone (blue). The white blocks show a 50 μm reference scale.

composition (Zhang et al., 2009). An improvement in the dissolution rate of atorvastatin has been achieved with amorphous atorvastatin with a round particle morphology being observed after spray-drying of the amorphous form. (Kim et al., 2008). It could be assumed that this particle shape could improve the flowability of atorvastatin. Ultimately, once a suitably flowing API form or a pre-blend has been found, these trials could be continued in a more truly continuous manner, linking the unit operations together by utilizing conveyors and implementing PAT in the tests. Perhaps after these steps, the total material throughput could be increased to evaluate how a scaling-up would work with this material combination.

The CDC run produced surprisingly little differences compared to the process with a granulation step. However, the run was short which limits the extent of the conclusions. Other options for further process development could include wet granulation methods. Nonetheless, the results of this work revealed some challenges that can emerge in the process development phase. To the best of our knowledge, this was the first published case study where a batch-based formulation did not perform according to set quality requirements on a pharmaceutical continuous manufacturing line. However, by changing the material composition of the product and redesigning it with continuous manufacturing in mind, it may well be that continuous tablet production could be achieved with this API. As could be expected, success in these process conversions seems to depend on the product's composition. A continued exploration of optimal ways to undertake continuous manufacturing of atorvastatin tablets could be worthwhile because this API has major medical significance and considerable commercial importance (Rádl et al., 2002).

4. Conclusions

The objective of this study was to test whether it would be possible to achieve a process conversion from commercial batch manufacturing to continuous manufacturing while maintaining the original product's composition. Unfortunately, the aim of producing quality-complying atorvastatin 10 mg tablets on continuous manufacturing line was not achieved in these trials. Atorvastatin was found to be very poorly flowing, and it tended to adhere to the walls of our equipment. Differences in processabilities were found with the different pre-blend designs. The API content was lower than the target in the mixture, granules and in some of the tablet samples. The content uniformities of the tablets showed unacceptably high values which is likely related to the extensive variabilities in the tablet weights. However, poor flowabilities of APIs and tablet weight variation in the production of low-weight tablets are well-known problems encountered in pharmaceutical development. The emerging initial challenges are considered as resolvable, since the target quality properties were based on a product that is available on the market. In the end, the API did seem to be uniformly distributed in the continuously manufactured tablets according to both the outcomes of the SEM-EDS and Raman mapping. The next approaches could involve a change in the composition of the formulation or undertaking some other modifications to the process protocol.

Uncited reference.

Goh et al. (2017).

CRediT authorship contribution statement

Jenna Lyytikäinen: Methodology, Investigation, Visualization, Writing – original draft. **Saini Kyllönen:** Investigation, Writing –

original draft. **Tuomas Ervasti:** Investigation, Writing – original draft. **Eelis Komulainen:** Methodology, Investigation, Writing – original draft. **Tomáš Pekarek:** Methodology, Investigation, Writing – original draft. **Jitka Slunečková:** Methodology, Investigation, Writing – original draft. **Jari Leskinen:** Methodology, Investigation, Writing – original draft. **Jarkko Ketolainen:** Supervision, Writing – review & editing. **Tomáš Kubelka:** Project administration, Conceptualization, Resources, Writing – review & editing. **Pawel Stasiak:** Project administration, Conceptualization, Resources, Writing – review & editing. **Ossi Korhonen:** Project administration, Methodology, Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

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.

Data availability

The data that has been used is confidential.

Acknowledgments

This work was supported by the Pharmaceutical Applied Research Center (The Parc). Zentiva and the Finnish Cultural Foundation are acknowledged for supporting this study financially. Zentiva is thanked for providing the raw materials, tablet press punches and dies. Oskari Saarimäki is warmly thanked for participating in the pre-blending studies.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2023.123509.

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