



Research Article

Concept for the Urban Production of Pharmaceuticals to Compensate for Local Shortages

Joachim Berlak* , Tobias Götz 

FOM University, Campus Munich, Arnulfstr. 30, 80335 Munich, Germany
E-mail: joachim.berlak@fom.de

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Abstract: Long and complex supply chains are one of the main reasons for drug shortages. The COVID-19 pandemic and abrupt global lockdown have highlighted how precarious the global pharmaceutical market is. This paper presents a concept for pharmaceutical production in greenfield, urban and local areas as a way to mitigate drug shortages around the world. This approach represents a paradigm shift because the production of medicine tablets still happens mostly at big brownfield sites. The concept is based on the VDI 5200 guidelines and procedures used for factory planning at general production plants. The derived methodology takes three phases into account and enables the integration of continuous tablet manufacturing into urban areas to supply the local population with medicine.

Keywords: urban production, pharmaceutical industry, continuous tablet production, factory planning

1. Introduction

Ensuring that patients have access to the drugs and active pharmaceutical ingredients (APIs) that they need is essential to maintaining a modern healthcare system [1]. However, supply disruptions in the pharmaceutical industry have been a well-known and much-discussed problem in recent years [1-4]. The ongoing COVID-19 pandemic, in particular, has raised public awareness of the supply challenge that the healthcare sector faces [4]. There are numerous causes of supply shortages, and a single or a chain of problem(s) along the value chain can lead to the shortage of a specific drug [5]. Table 1 ascribes these shortages to unforeseeable and foreseeable causes.

The factors listed in Table 1 can be traced back to three possible root causes: economy, supply chain and regulations [6]. With the outsourcing of drugs (e.g. to Asia), the medicine supply chain has become longer and more complex [7]. In addition, a concentration process among pharmaceutical manufacturers has resulted in fewer manufacturers of ingredients and drugs serving the global market despite an ever-increasing demand for different kinds of drugs [6]. Figure 1 gives a basic illustration of a pharmaceutical supply chain. The locations of primary and secondary manufacturing facilities are often geographically separated, which has a positive impact on tax and transfer prices [8]. Owing to the pressure on costs associated with the lengthy and expensive manufacturing processes in primary and secondary production, many drug manufacturers have relocated their production to countries that have low production costs, like China and India [7].

Table 1. Reasons for drug shortages [6: p.12].

Unforeseeable causes	Foreseeable causes
Natural disasters	Product discontinuation
Manufacturing problems	Industry consolidation
Raw material shortages	Limited production capacity
Non-compliance with regulation standards	Just-in-time inventories
Packaging shortages	Rationing and quotas
Unexpected demand	Deliberate shortage to manipulate prices
Epidemics, pandemics	Market shift
Parallel distribution	New formulation, patent expiry or launch of a new competitor

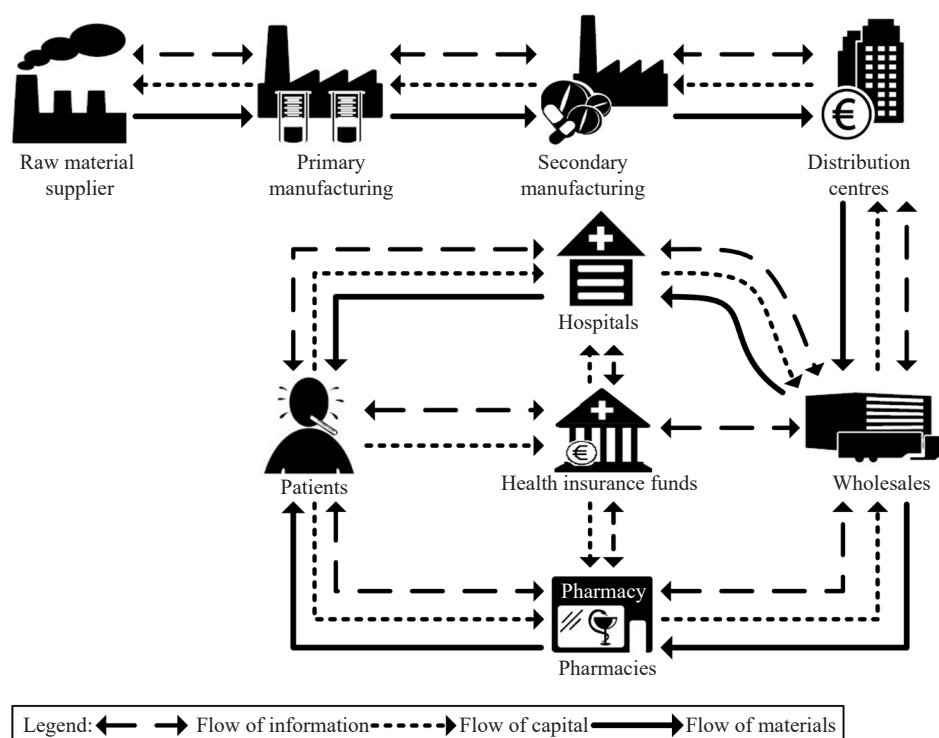


Figure 1. Fundamental pharmaceutical supply chain [8: p.931, 9: p.186]

The COVID-19 pandemic has demonstrated how much the rest of the world depends on drug-exporting countries. The abrupt global lockdown and resulting economic consequences have revealed the dependence on pharmaceutical manufacturing locations in India and China. On 3 March 2020, the Indian government imposed an export ban on 26 pharmaceuticals [10], including APIs and drugs like paracetamol and several antibiotics. India's freeze on exports came in response to China's supply disruption of APIs, which account for 70% of the production volume of pharmaceuticals required in the country [11].

In summary, there are many reasons for pharmaceutical product supply shortages. The situation is further exacerbated by the dependence on drug-exporting countries, and new ways must be developed to tackle this challenge.

One opportunity to counteract the dependence on drug-exporting countries is the local and near-patient production of pharmaceuticals in metropolitan regions.

In general, urban production of products is still a relatively young field of research. As a result, there have been few concepts and approaches for relocation from greenfield to urban areas. This is understood as a research gap, which

this paper addresses. The objective is to present a new approach that helps to successfully relocate pharmaceutical production to urban areas. The focus is on already existing production technology, which seems most suitable for the urban production of pharmaceuticals in tablet form. The new approach of urban drug production should help to supply the local population of a metropolis with enough drugs to counteract shortages in the drug supply.

2. Theoretical background

This section provides an overview of relevant research topics and is divided into two subsections: urban production and the manufacturing process of tablets.

2.1 Urban production

Urban production refers to a mixture of small and medium-sized businesses focused on customer-specific products that are locally produced and sold [12, 13]. This form of production is different from Industry 1.0 and 2.0, whose emissions (e.g. noise, smell and dirt) harm the environment and are why the plants have traditionally been located on the urban periphery [12]. Urban production is a low-emission and resource-efficient production method that can be re-integrated into densely populated areas by using new technologies such as networked production methods with the keyword Industry 4.0 and additive manufacturing processes [14]. However, attention must be paid to sustainable production concerning the economy, ecology and social issues [15]. The economic perspective demands higher profitability of production in factories [12]. From an ecological point of view, the production of goods should have a low or positive impact on the environment [16]. The factory as a social workplace serves as both a learning and a training environment [17], and the urban factory is a holistic production system that creates synergy with the environment [14]. Figure 2 shows an urban factory of the future that has a positive impact on its surroundings and the global environment.

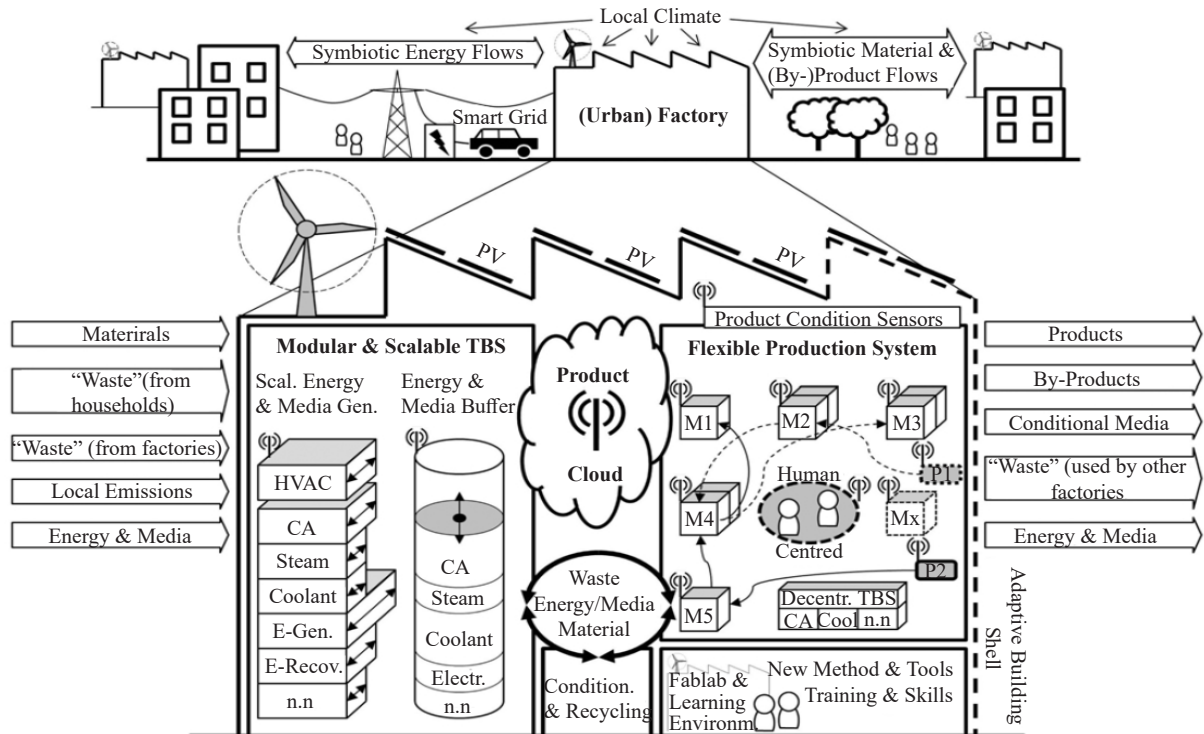


Figure 2. Urban factory of the future [14: p.287].

Relocating to an urban area creates synergy between the employees and the urban population. The proximity to potential customers makes the urban area a significant choice criterion for employees. In addition, production in urban areas offers proximity to knowledge and research institutions, a high density of workers and an existing infrastructure [12]. Thus, the factory and the city can benefit positively from each other [14, 16]. Working in the city means local employees do not have to spend a long time commuting and can be viewed as an attractive opportunity for a better work–life balance [12]. The urban factory also offers an opportunity to better respond to customer needs. Thus, with production close to the customer, identification with the product and the factory can be enhanced [12]. The other concepts are based on this idea of urban production.

2.2 Tablet manufacturing process

As a form of dosage, the tablet is of great importance - it is small and compact [18, 19], and conventional production happens in large quantities at a low cost [19, 20]. In its solid, single-dose form, a tablet consists not only of one or more active ingredients that make up the active component of the drug but also of several excipients [19]. Those active ingredients are responsible for the pharmacological effect, while the auxiliary ingredients are needed for manufacturing and meeting the requirements of being patient-friendly [21, 22]. The ingredients are packaged in a ready-to-use tablet during the manufacturing process depicted in Figure 3:

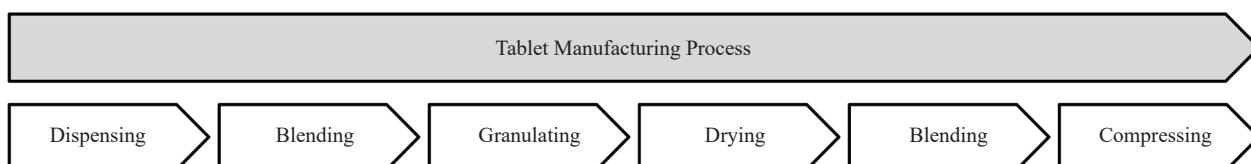


Figure 3. Tablet manufacturing process.

After the pressing process, certain tablets are coated with a fine film [19]. The aim is to delay the release of the active ingredient in certain drugs or to mask the bitter taste or unpleasant odour. [23, 24]. In addition, the coating can contain coloured pigments designating the indication of the drug. The manufacturing processes illustrated in Figure 3 can be carried out by using two different production methods, which are explained below.

2.3 Batch-based tablet production

The pharmaceutical industry’s batch production of tablets is state-of-the-art [25]. Here, a defined quantity of starting materials passes sequentially through the process steps mentioned in Figure 3. Each sub-process in the batch procedure consists of three steps: loading, processing and removal [26]. Figure 4 depicts the batch-based production of tablets.

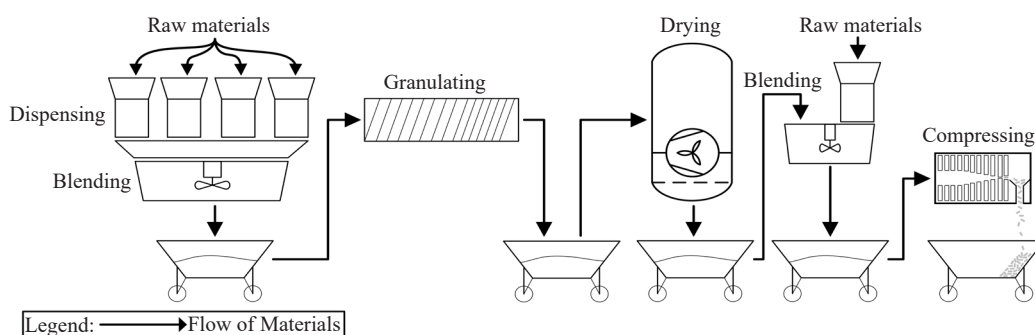


Figure 4. Batch-based production of tablets.

The processing of a sub-process has to finish before the next step in the process can start. Between process steps, the batch is subjected to an in-process control and checked for the defined quality [27]. Owing to costly sampling and throughput times during analysis, it can take up to several days for the intermediate product to be released, which can lead to delays between the individual steps [27]. If the material does not meet quality standards, the batch may be re-processed or destroyed [25]. Once the final step in the process has been taken and a final quality check has been carried out, the batch can be released in its entirety.

2.4 Continuous tablet production

Continuous tablet production is characterized by raw materials and materials being continuously supplied to and removed from the system throughout the entire manufacturing process [25]. In addition, all non-value-adding steps, such as waiting time for the next process step or the storage of intermediate products, were eliminated in the above-mentioned manufacturing process [28]. Figure 5 shows an example of continuous tablet production.

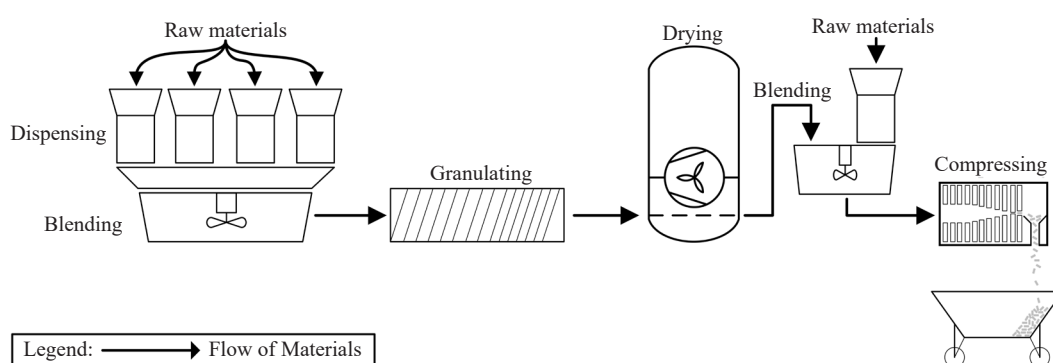


Figure 5. Continuous tablet production.

The process steps with identical objectives mentioned in Figure 3 still exist but now form a chain. Hence, the individual process steps run simultaneously [25]. Continuous production links individual operations into an integrated manufacturing process [25]. As a result, the materials are fed directly to each process step for further processing. This requires that the intermediate-produced products be of acceptable and suitable quality and the entire process be monitored by process analytical technology (PAT) to provide real-time data for process control [25]. PAT is a system that affects the drug product's quality and properties through timely measurement and targeted in-process control [27]. As a result, an increase in efficiency is achieved by continuous tablet production [25, 29].

3. Materials and methods

The approach for building urban tablet production facilities proposed below is based on VDI 5200 Part 1 [30] procedures for general factory planning. The factory planning process is divided into seven phases, which are depicted in Figure 6. These phases are processed sequentially, and only one part of this model is processed, depending on the planning content and planning depth [30].

For this prevailing concept, the first three phases are applied: setting objectives, establishing the product basis and planning the concept. All subsequent steps (e.g. detailed planning) are topics for future research.

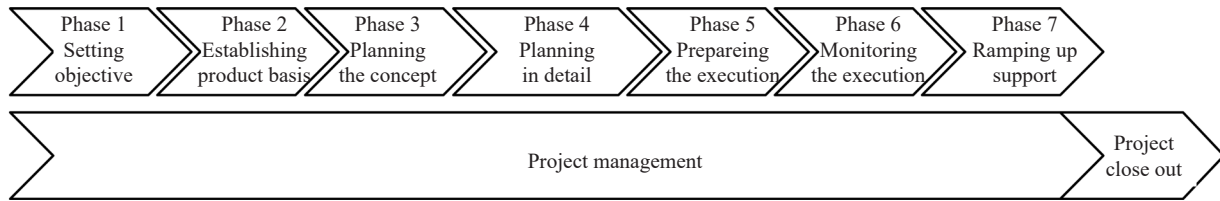


Figure 6. Phase model of the factory planning process [30: p.8].

3.1 Phase 1: Setting objectives and general constraints

Defining the objectives helps to clarify the task of planning operations at the factory. In this phase, the company’s goals and the framework conditions for the factory are determined [30]. The goal is to go from the general to the particular within the set framework. The following configuration in Table 2 is an example of an urban tablet production facility.

Table 2. Objective of the urban factory.

Objectives of the urban tablet production facility	
Mandatory	<ul style="list-style-type: none"> Compliance with legal regulations Service level 100% Integration in urban areas
Nice-to-have	<ul style="list-style-type: none"> Automation level >60% Higher variation of APIs
Non-goals	<ul style="list-style-type: none"> No integration of the urban factory in industrial areas

For the urban factory producing pharmaceuticals for people, the general conditions from a regulatory point of view relate to the product and the inner-city factory. To integrate a factory into the urban area, it is necessary to adhere to certain building regulations and specifications about the emission guide values [31, 32].

The design and operation of the urban factory must comply with the legal requirements that apply to the concept, including good manufacturing practice (GMP), relevant building regulations and emission control laws. Once this phase with objectives and constraints has been completed, the next phase can begin.

3.2 Phase 2: Establishing a basis for the project

The goal of the initial steps is to generate or collect all the data and information required for the planning of the factory [30]. Next, all the information needed for the concept phase must be collected and prepared.

3.2.1 Production type

For the urban tablet production facility, a suitable production type must be selected. Framework order manufacturing is recommended when a customer expects demand for similar products over a defined period [33]. The framework agreements can be concluded with drug wholesalers who supply the medicine to local hospitals and pharmacies. Figure 7 shows the supply chain of the urban drug factory and the interface between the drug wholesaler and the urban tablet factory.

Based on the expected shortfall of medicines, the wholesaler can call for a binding quantity contract [33] before identifying the necessary manufacturing technology to produce the tablets.

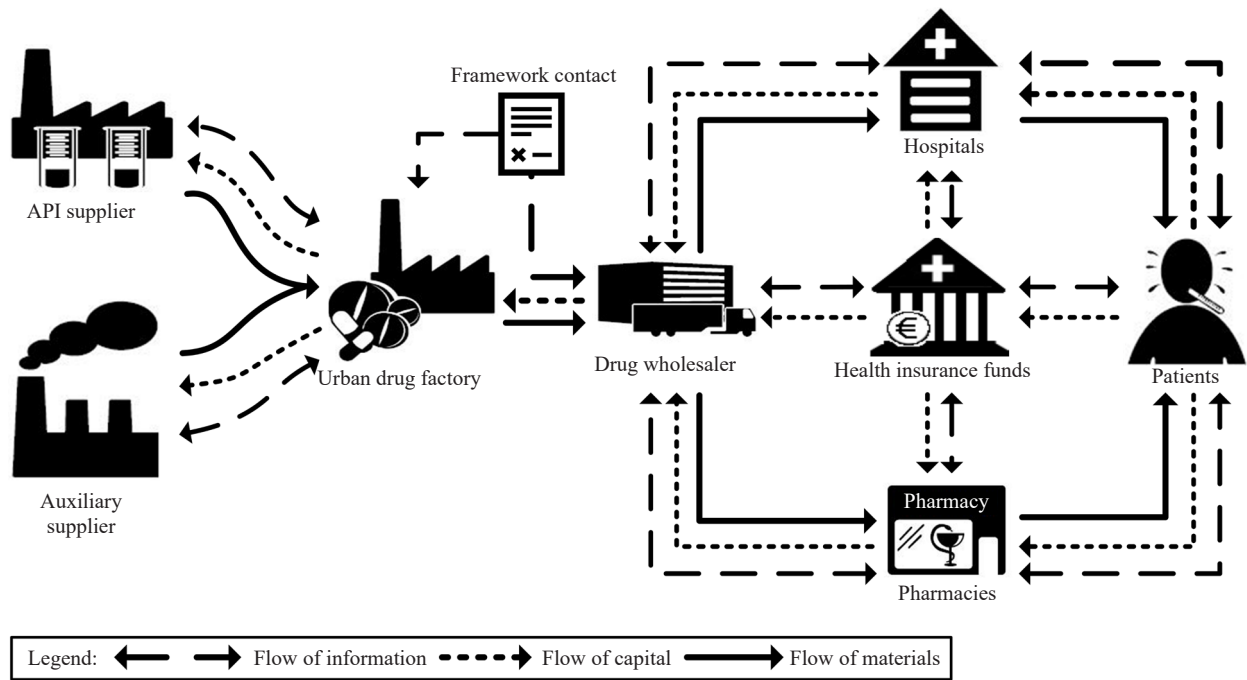


Figure 7. Supply chain of urban drug manufacturing.

3.2.2 Manufacturing technology

Two manufacturing processes can be used for tablet production: batch-based and continuous [34]. For tablet manufacturing in urban areas, the continuous tablet manufacturing process can be considered the most suitable [25] for the following reasons:

- smaller equipment
- smaller space requirement
- efficient and high throughput
- reduced safety risks
- no storage costs for intermediate products
- continuous transport of intermediate materials to the next production unit
- reduced batch-to-batch variation and
- increased operator safety

Once the production technology has been selected, the procurement strategy for the starting materials and the necessary storage is defined.

3.2.3 Procurement and storage

Procurement of raw materials according to the just-in-time (JIT) strategy avoids costly warehousing [35]. As a result, smaller storage areas and less capital are required [35]. This dovetails with space-saving production in urban areas [32]. However, Table 1 identifies the JIT strategy as one of the causes of supply shortages for medicines. This presents a dilemma between the service level of 100% set in Phase 1 and small-scale production in urban areas. Another of the urban factory's objectives is to compensate for the supply shortage of medicines by moving away from JIT procurement and towards stockpiling the active ingredients and excipients needed for production. To keep tablet production unaffected by any raw material supply shortages, the stockpiling of raw materials is recommended. Doing so makes the urban factory independent of sequential supply shortages and enables it to react quickly to an increase in demand [8]. Moreover, stockpiling has a positive effect on the urban environment as it reduces the role of inner-city transport to supply the urban factory [36].

3.2.4 Distribution

The manufactured pharmaceuticals are distributed via wholesalers based on framework agreement regulations. Given the urban environment and in order to reduce delivery traffic, green logistics concepts (which protect the environment) are applied. A green factory can be defined as a manufacturing floor that reduces waste elements like extra work, energy, time and cost by quickly responding to external uncontrollable changes (e.g. regulation, due date or supply) [37]. Based on the green factory concept [37], the delivery of pharmaceuticals in cooperation with several logistics companies can be achieved [38]. Through economies of scale, this can save delivery costs and time [39]. In addition, logistics cooperation will have a positive impact on the urban environment by reducing the number of delivery vehicles, optimizing delivery times and distances and, therefore, enabling green tablet production factories [39]. Pharmaceuticals are subject to certain requirements for storage and transport that are regulated in good distribution practices. Among other things, it is essential to ensure that temperature-sensitive medicines have not been exposed to harmful temperature fluctuations during the supply chain [40]. Furthermore, documentation relating to the cooling chain must be continuously provided [40]. When selecting a logistics partner, there has to be strict compliance with the applicable regulations to exclude product damage and, subsequently, any risk to patients.

3.3 Phase 3: Concept planning

Once the plant's objectives and basic principles have been determined, the concept planning phase can start. In Phase 3, the factory is designed by using the manufacturing technology selected in Phase 2. The objective is to make the tablet factory as compact as possible so that it can be integrated into an urban area. First, all the processes required for value creation are defined [30].

3.3.1 Process definition of the urban factory

The value-adding processes are dictated by the sequence of the tablet manufacturing process as shown in Figure 3. For continuous production, this means that the processes of dispensing, blending, granulating, drying, blending and compressing have to be completed in a timed sequence. A value-added diagram of the urban factory is shown in Figure 8.

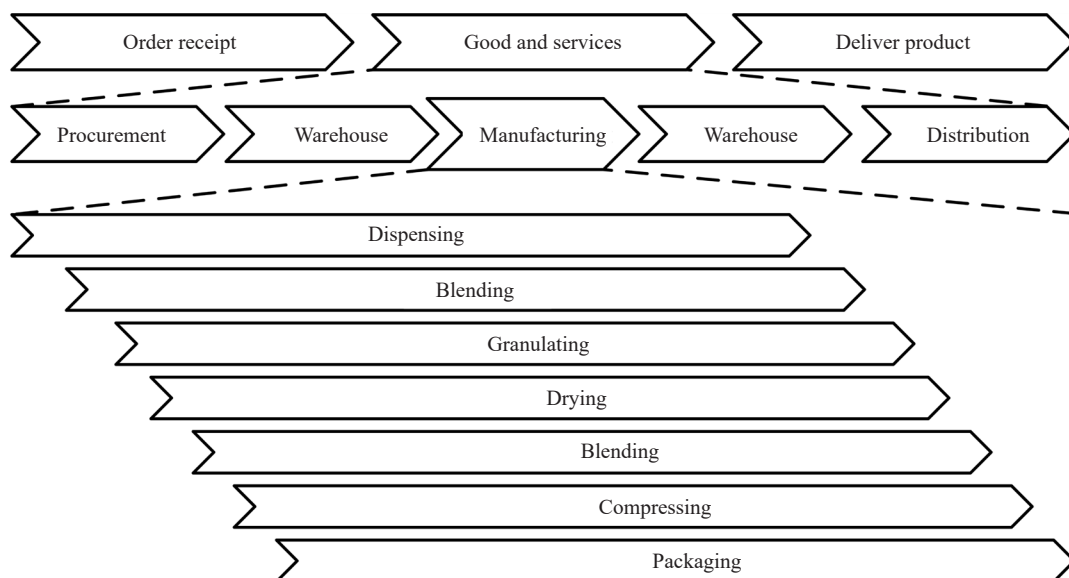


Figure 8. Batch-based production of tablets.

Production is triggered when an order is received in a made-to-order environment. A master agreement for a

quantity contract is concluded, which refers to the production type of the urban factory defined in Phase 2. Purchasing compares the actual stock with the target stock of the required raw materials.

If the re-order level falls below the defined minimum quantity, a supply order is triggered. The starting materials (i.e. the active and the auxiliary materials) are taken from the warehouse for a day's production and made available to the production line in properly labelled containers under item 5.32 of the GMP guidelines [41]. If all the required raw materials are available for production, continuous tablet production can be initiated in line with the defined sequence presented in Figure 8. The tablets are then transferred to the outgoing goods warehouse and prepared for delivery.

3.3.2 Flow of material

The internal material flow is triggered by the production order. This is followed by a continuous flow of the materials required for the order. The Sankey diagram [42] in Figure 9 shows the urban factory's directional flow scheme and the steps in the process.

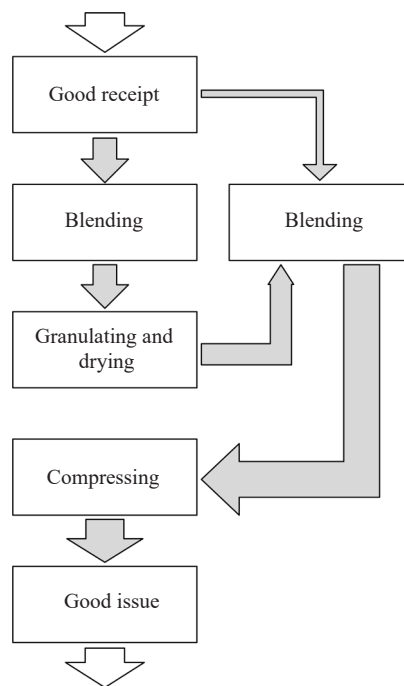


Figure 9. Sankey diagram of the internal flow of material.

The sequence of the individual steps and the flow intensity is represented by the thickness of the arrows [42]. The white arrows entering the goods receipt box and leaving the goods issue box represent the external flow of material. This diagram can be used to visualize the material flow intensity between each process step. Thus, the most frequented areas can be identified and taken into account when planning a material flow-oriented layout. Next, a room concept for the urban factory is sketched out.

3.3.3 Room concept

The operating rooms must be suitable for the production of pharmaceuticals with regard to their type, size and equipment [43] and designed to avoid possible errors and negative impacts. Furthermore, operations have to follow a logical sequence, and the equipment should be arranged appropriately [41]. To prevent contamination, which would lower the quality, structural separation between the pharmaceutical production area (i.e. the so-called GMP area) and

the non-GMP area is recommended [43]. These two zones can be connected – for example, by a personnel and material gate [44]. Through the personnel gate, production employees reach the manufacturing area via a changing room. The material gate is used to supply the production area with raw materials, machines and consumables. A close demarcation between the GMP and non-GMP areas can minimize equipment costs for the cleanroom. The requirements of emission control laws can be met more easily since only the area in which production takes place needs to be soundproofed.

3.3.4 Determination of area requirements

To determine the required production area, the bottom-up principle is applied [45]. The area required per module is calculated by multiplying object-related machine footprints by factors. The footprints can be taken from the manufacturers’ datasheets. Next, the required production area is calculated based on the sum of the individual module requirement areas. Factors include transport area (40%) and additional area (20%). For continuous tablet production, the factor for an intermediate storage area is not included in the calculation. Table 3 shows how individual module areas and the total production area are calculated.

Table 3. Example of calculating the production area in the urban tablet factory.

Module	Footprint	Transport area 40%	Additional area 20%	Module area	Sizing
Dispensing-blending module I	6.25 m ²	2.5 m ²	1.25 m ²	10 m ²	Capacities 1-25 kg/hr
Wet granulate, dry module	1.94 m ²	0.78 m ²	0.39 m ²	3.11 m ²	Nominal throughput 0.5-2.5 kg/hr
Dispensing-blending module II	6.25 m ²	2.5 m ²	1.25 m ²	10 m ²	Capacities 1-25 kg/hr
Tablet press	0.98 m ²	0.4 m ²	0.2 m ²	1.58 m ²	Max. 86,400 tablets/hr
Total production area				24.69 m ²	

4. Results

Figure 10 gives an example of a continuous production line. Two dispensing-blending modules, a module for continuous wet granulation and drying, and a tablet press are shown. All process steps - from raw material feed to tablet compression - are chained together. And on the right-hand side, there is a module that coats the finished tablets.



Figure 10. Example of a continuous tablet production line in an urban factory (photo reproduced with permission from © L.B. Bohle Maschinen und Verfahren GmbH).

The individual modules are arranged in the process sequence, which corresponds to the material flow-oriented scheme for continuous tablet production. Figure 10 shows that the dispensing-blending modules can be arranged in the second level above the remaining modules if the ceiling is high enough. This manufacturing process with the above-mentioned layout is ideally suited to urban areas as it enables small-scale tablet production, which saves space. However, to make production compatible with urban areas, the emission guide values for the protection of residents must be complied with. This can be achieved with sufficient sound insulation in the production area.

5. Discussion and conclusion

In metropolitan areas, the availability of usable and residential space is scarce. To accommodate a drug manufacturing factory in a dense urban environment, the main usable space must be utilized as economically as possible with a focus on the production area. Continuous tablet production makes the manufacturing process very efficient in terms of space. A continuous flow of materials between the individual process steps eliminates the need for additional storage space. Furthermore, with sufficient corner height, certain modules can be arranged on a second level, which contributes to positive space efficiency.

By utilizing already existing pharmaceutical production technologies, such as the area-efficient continuous tablet production process, the integration of tablet production in urban areas can be successful. Furthermore, this paradigm shift can help to supply the local population with medicines and thus contribute to the prevention of drug shortages. In addition, it is possible to react quickly to fluctuations in demand if the active ingredients and excipients are available in sufficient quantities. However, there is still a dependence on the suppliers of active ingredients and excipients, as well as pharmaceutical companies.

Concerning urban production, the COVID-19 pandemic also offers new opportunities. Working from home, which is becoming a trend, will likely take different forms in a wide variety of areas [46]. Many employees will continue to work from home even after the pandemic [47, 48]. We can assume that the supply of office and commercial real estate will undergo a structural change in the long term [46, 49, 50]. Thus, reduced demand for inner-city office buildings could have a positive impact on the shift of production back to the city [51]. As explained, the production of tablets in urban areas requires a relatively small amount of space. Therefore, production could easily be integrated into the office space that would no longer be needed. The lack of available space in metropolitan areas is still viewed negatively today [32], but this could be reversed in the future, at least regarding office properties [52]. Thus, from both an economic and a socio-political perspective, relocating drug production to vacant inner-city commercial real estate would be a win-win situation for all parties involved.

Future research should focus on how this method is applied to greenfield and brownfield tablet manufacturing plant projects in order to further evaluate usability and profitability.

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