doi:10.2533/chimia.2023.616 Chimia 77 (2023) 616–619

How Technical Innovations May Help to Prevent Drug Shortages in Switzerland

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Abstract: In this work, we investigated the technical feasibility of 'on-demand' production of selected drugs to cover their demand for a time window of 90 days. We focused on two sub-processes 'automated chemical synthesis' and 'formulation in micropellets' to enable personalized dosing. The production of drugs 'on-demand' is challenging, important, but also attractive. Switzerland could thus gain access to an additional instrument for increasing resilience for supply-critical drugs. The biggest challenge in the case study presented here is the scalability of automated chemical synthesis and the application range of micropellet formulations.

Keywords: Automation of chemical synthesis · Drug shortage · Micropellet formulation · On-demand production · Personalized healthcare

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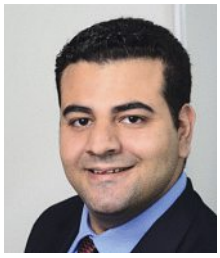

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Introduction

Due to the increasing medicine shortages[1–3] in recent years, the question arises whether there are technical innovations that can prevent or at least shorten supply bottlenecks quickly and at short notice. We investigated within the framework of a SATW project the 'on-demand' production of four drugs for sales volumes prescribed to patients in Switzerland for 90 days, based on an innovative technology for chemical production and formula-

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tion that allows highly automated production of drugs at individual dosages.

This report is a case study based on information and data from publications and patents. It provides guidance on the feasibility of on-demand manufacturing.

We selected four drugs considering the current supply shortages: Formoterol (FLUTIFORM®; OXIS®; FORADIL®; FOSTER®), L-thyroxine (ELTROXIN®; EUTHYROX®; TIROSINT®), levetiracetam (LEVETIRACETAM®; KEPPRA®), and acetaminophen (paracetamol and many others). We did not investigate regulatory aspects for the approval of such 'on-demand' dosage forms, *e.g.* bio-equivalence studies that may be required.

What Quantities of Drugs Are Needed?

Supply shortages of active pharmaceutical ingredients (API) are volatile and can last several weeks. We therefore asked ourselves whether, with a lead time in the order of 90 days, drug substances can be manufactured 'on-demand' with the inclusion of compulsory stocks for relevant raw materials.

The volumes sold in 90 days in Switzerland are small for formoterol and L-thyroxine, but high to very high for levetiracetam and paracetamol.

Table 1 summarizes the sales volumes in 90 days, the number of synthesis steps and starting materials, and the market prices. The market prices listed are data from a European supplier of products and services in the pharmaceutical sector and from internet suppliers in Asia. They are approximate values that can vary greatly and even at short notice.

Table 1. Key data for four selected drugs (API) 'on-demand' in Switzerland (kg /90 d), synthesis steps (Steps), starting materials needed (React), drug price in EUR/kg and API price for 90-days production (API in EUR)

API	kg / 90d	Steps	React	EUR / kg	Price EUR / 90d
Formoterol	0.14	5	3	35,000	4,900
L-Thyroxine	2.50	5	2	5,000	11,500
Levetiracetam	2,250	2	1	110	247,500
Paracetamol	47,500	1	1	17	807,500

How the Production of Drugs 'On-demand' Could Be Designed

The conventional route to the production of a finished dosage form involves the synthesis of complex organic molecules and their formulation.

A manufacturing paradigm developed in recent years based on modular platforms requires only a few manual interventions for the recombination of modules along the entire manufacturing process. Automation *via* robotics and AI support (*e.g.* retrosynthetic process optimization) will be key elements to increase the application diversity in terms of performing different reaction types[4–6] or formulations and their scalability.

In the field of dosage form manufacturing, there are several modern approaches aimed at improving the efficacy and safety of drugs and facilitating their patient-tailored use.[7] In this work, we focused on fluid bed processes that can precisely produce shape, size, stability, and homogeneity of dosage forms in single or multiple layers with one or different active ingredients.

Our approach to 'on-demand' drug substance manufacturing is threefold. (1) design of chemical synthesis of active ingredients, (2) software-assisted automated synthesis of active ingredients, and (3) formulation of active ingredients using micropellets.

The companies Chemspeed Technologies AG with their software-controlled automated platforms as core technology for small-scale production and/or process optimization and Glatt Pharmaceuticals Services GmbH with their formulation technologies based on micropellets helped to plausibilize and concretize the 'on-demand' production of the selected drugs.

Chemical Synthetic Production of the Selected Active Ingredients

The syntheses of the active pharmaceutical ingredients L-thyroxine (levothyroxine sodium), formoterol, levetiracetam and paracetamol are described in the literature.

Our study covers the synthesis of the four agents. The 'on-demand' synthesis of L-thyroxine is described in detail.[8–10] For the remaining three active ingredients, we report only the results, which are summarized in Table 3 further below.

The method chosen for preparation is shown in Fig. 1. It starts from a common tyrosine derivative (**1**) and leads to levothyroxine sodium (**7**) *via* five synthesis steps (**1**–**5**). Since it is not possible to predict which intermediate will be unavailable in case of shortages, we assume here the worst case, and start with tyrosine derivative **1**.

The selected procedures were carried out on a gram scale. The yields of the synthesis steps are in the range of about 70–95%. The overall yield over all reaction steps is 35–40%.

According to our estimates, the conventional batch production of 2.3 kg of levothyroxine sodium salt requires reactors with volumes between 10 L and 100 L and the whole preparation takes about 15 days (Table 2).

If intermediates **5** or **6** are available, the synthesis of the L-thyroxine active **7** ingredient is considerably shortened, since the iodination and the synthesis of the sodium salt of L-thyroxine are not very problematic reaction steps and proceed with good yields.

Transfer of Chemical Synthesis to the Chemspeed Automated Workstation

The Chemspeed AUTOPLANT workstation is designed for high-throughput experiments in the development and optimization of pharmaceuticals, agrochemicals, polymers, specialty chemicals, catalysts, and many other products. The automation of a chemical process to produce active pharmaceutical ingredients requires versatile and accurate handling of substances. In particular solids, liquids, pastes and waxes must be dispensed reliably and robustly. The Chemspeed AUTOPLANT workstation allows gravimetric dosing overhead directly into the reactor.[11,12]

The synthesis protocol for L-thyroxine developed in the laboratory is implemented in the automated workflows of the workstation. The robot performs all synthesis steps analogously to the synthesis steps in the laboratory. In our case study, only the programming of the synthesis steps was performed.

To produce 2.3 kg of L-thyroxine sodium, an AUTOPLANT workstation is required. The automated chemical synthesis is performed in 6 1L reactors. The yields of the individual synthesis steps determine the number of runs or repetitions needed, and the time required to produce the required product quantities. In total, the 2.3 kg of levothyroxine sodium requires about 44 days, with synthesis steps I and II being the most time-consuming with 29.2 and 10.8 days, respectively. If synthesis stages I and II are omitted, the production time is reduced to about 5 days.

It is worthy of note that in both automated synthesis and batch production of L-thyroxine, the individual reaction steps must be verified and, if necessary, optimized. The time required for purification of the intermediates and the final product is not yet included in these 44.5 days. If each step proceeds with 98% yield, which corresponds to a good yield for an optimized synthesis,

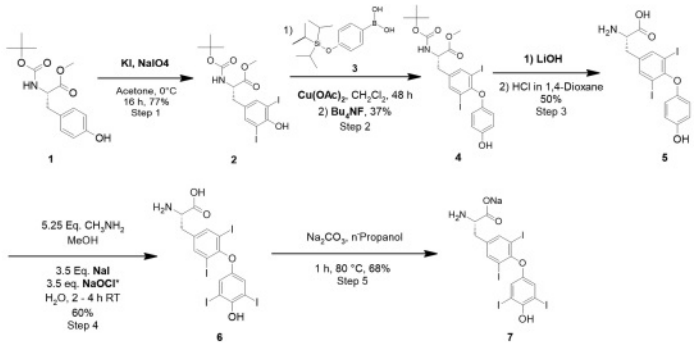

Fig. 1. Synthesis of levothyroxine sodium in five steps. 1: Starting material; 2,4,5,6: Intermediates; 3: Precursor; 7: Product: levothyroxine sodium.

the total yield over 5 steps would be 90%. This would reduce the production time to only about 26 days. If two AUTOPLANT platforms are used in parallel, the manufacturing time is reduced to about 23 days, or to about 12 days at 90% yield.

Results for all Four Drugs

For the chemical syntheses of formoterol, levetiracetam and paracetamol, synthesis routes have been developed in an analogous manner and their transferability to the AUTOPLANT platform has been investigated. The results for all four drugs are summarized in Table 3. Not unexpectedly, it turns out that 'on-demand' production of drugs with low sales volumes is quite feasible, but the costs will be considerably higher compared to conventional synthesis. The target volumes for levetiracetam and even more so for paracetamol are not achievable.

Micropellets for the Production of Personalized Dosage Forms 'On-demand'

Another technical innovation in pharmaceutical technology is a continuous fluidized bed agglomeration process for the production of pellets and micropellets. Such micropellets allow precision dosing for personalized medicine. Micropellets have a size range of 100 to 400 micrometers with a very narrow particle size distribution and an active ingredient content of up to 95 percent. They allow seamless scale-up from very small batches of a few grams to batch sizes of several 100 kilograms.

L-thyroxine is currently offered on the market in dosages of 25–200 µg tablets. Individual dosing is now made possible here by the production of L-thyroxine pellets with 25 µg and 50 µg of active ingredient, which can be individually combined in capsules or a sachet. The L-thyroxine pellets consist of a layer of active ingredient and a protective layer applied on top.

The highly effective active ingredient L-thyroxine is diluted approx. 1:3000 with neutral cellulose to be safely processed with a standard technology in a normal pharmaceutical environment. The powdered substances, which are suspended or dissolved in water, for example, are applied with a suitable binder as an active substance layer to the starter pellets presented.

Both the active ingredient layer and the protective layer are processed using the bottom spray fluid bed technique (Wurster fluid bed technique) in a batch process. The manufacturing process for L-thyroxine pellets is schematically shown in Fig. 2.

With 2.3 kg of L-thyroxine as API, about 7,750 kg micropellets in a total of 3 million capsules of the different dose strengths can be produced. With a lead time of 2 weeks, the pellets could be produced within 4 weeks, for example, 1 × per month or 1 × per quarter in corresponding production campaigns.

Levetiracetam is formulated into high-dose pellets (active ingredient content: *e.g.* 60% w/w) for use in children and adults. Thus, dosages of 250, 500, 750 and 1000 mg are feasible. The pellets can be filled into capsules, which only serve as primary packaging material and have to be emptied for use, but do not have to be swallowed (*e.g.* sprinkle caps, capsules size 000). For example, the highest dosages of 750 and 1000 mg can be filled in 2 capsules.

Paracetamol is granulated and formulated into 500 mg tablets; pellet production is not economical for bulk paracetamol (Table 4).

Formoterol was not specifically assessed in terms of its formulation, as it still needs to be formulated as a dry powder for inhalation. This is quite feasible given the low volume requirements but is relatively expensive 'on-demand'.

Conclusions

Innovative technologies for drug manufacturing are emerging and may become central for 'on-demand', patient-centric and decentralized drug supply. High automation levels in synthesis and formulation allow on one side production and on the other side online QC and GAMP-compliant manufacturing.

The production of drugs 'on-demand' is demanding, important, but also attractive. Switzerland could thus access an additional tool to increase resilience for supply-critical drugs. Switzerland can play a leading role here as one of the world's most innovative countries with a high share of pharmaceutical and automation knowledge. However, improved procurement resilience in chemistry does not come for free and requires a strategic reorientation. The biggest challenge in the case study presented here is the scalability of automated chemical synthesis. The case study presented suggests the following:

'Automated chemical synthesis' is suitable for low-dose APIs. The maximum reactor size is 1L total volume. In principle, scalability is achieved by multiplying the number of reactors and platforms. Production costs are relatively independent of location

Step	Reactants[a]	kg / 90d	Yield %	Product per run (g)[b]	Runs[c]	Product per step (kg)	Time (d)
	1	1.9					
1	**2**	2.9	77	84	35	2.9	29.2
2	**3**						
	4	2.9	81	237	13	3.1	10.8
3	**5**	2.3	95	1'494	2	3.0	0.6
4	**6**	3.3	95	432	8	3.5	1.7
5	**7**	**2.3**	68	210	11	**2.3**	2.3
						Total	**44.5**

Table 2. Key figures for synthesis of 2.3 kg L-thyroxine sodium salt with AUTOPLANT platform: Synthesis steps, number of required reactants and their amount in kg for 90 days, yield of synthesis, amount of product per run and required number of runs, product per step and required time in days (d)

[a]**1** and **3** are reactants; [b]calculated based on literature data; [c]one run works on six reactors with V = 1 liter

Table 3. Summary table of 'on-demand' synthesis evaluation for four APIs showing the required steps and reactants (React), feasibility to adapt to the AUTOPLANT platform, their need in CH for 90 days compared with the synthesis capacity in 90 days (C/N)

API	Steps (React)	AUTO-PLANT	Need kg / 90d	Capacity kg / 90d	C / N /%
Formoterol	5 (1)	OK	0.14	0.2	143
L-Thyroxine	5 (2)	OK	2.5	2.3	92
Levetiracetam	2 (1)	OK	2,250	0.05	0.0001
Paracetamol	1 (1)	OK	47,500	1.0	0.002

(high-wage or low-wage environment), as little personnel costs are involved. Depending on the complexity and yield of the synthesis steps, a capacity limit is reached where a conventional production method is more suitable. At what level this limit is reached must be clarified in each individual case.

The ***'micropellet method'*** for formulation is possible in the entire quantity range investigated. For drugs that are sold in large quantities at low prices, such as paracetamol, classical tablet formulations are possible and more cost-effective for production 'on-demand'.

We assume that, compared to the present considerations, there is still considerable ***potential for optimization*** in the synthesis route and yields, which must be explored in individual cases.

Both 'automated chemical synthesis' and formulation by the 'micropellet method' can be carried out in apparatus that can basically be used for different products (***multipurpose plants***). If such plants are available for emergency use, they can be used to cover a certain spectrum of drug substances.

Beyond controlling drug shortages 'on-demand' drug manufacturing may in future also play an important role in the current trend of pharmacotherapy towards patient-centric, personalized medicine.

In summary our case study shows ***that the 'on-demand' manufacturing is technically feasible***. The biggest challenge in the case study presented here is the scalability of automated chemical synthesis and the application range of micropellet formulations. Nevertheless, we expect that the process designed here could easily be improved by several optimization steps. Whether 'on-demand' drug substance manufacturing will be used primarily for small volume and personalized medicines will depend on the scalability of the manufacturing techniques described above.

Acknowledgements

We would like to thank Esther Koller, Hans-Peter Meyer and Janine Hosp from SATW for enabling and supporting our drug shortage project. We thank the industry partners, Michael Schneider from Chemspeed Technologies AG and Mirko Nowak, Annette Grave and Philippe Tschopp from Glatt Pharmaceutical Services GmbH & Co. KG for supporting the project and Adrian Rüegsegger for his help editing the manuscript.

Received: July 14, 2023

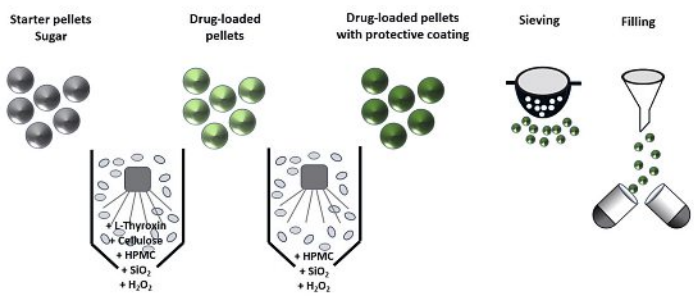

Fig. 2. Manufacturing scheme for L-thyroxine micropellets.

Table 4. Key parameters for drug formulations 'on-demand', showing the amount of formulated drug needed in 90 days, the preferred formulation (DPI: dry powder inhaler; MP: micropellet), and assessment if the formulated drugs are ready for Personalized Medicine (PM), feasibility for 'on-demand' production and cost estimates (medium: ca. 2x / high: > 5x costs of current formulation).

Drug	Formulations	PM ready	Feasibility	Cost est.
Formoterol	DPI	+[a]	n.a.	n.a.
L-Thyroxine	MP coated, 0.1% w/w	++	very good	medium
Levetiracetam	MP coated, 60% w/w	++	very good	medium
Paracetamol	Tablets, granulated	o	feasible	high

[a]Formoterol spray is already now considered PM ready.

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