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EDITORIAL

Can 3D printing of oral drugs help fight the current COVID-19 pandemic (and similar crisis in the future)?

Wen-Kai Hsiao[a], Barbara Lorber[b] and Amrit Paudel[a,b]

[a]Research Center Pharmaceutical Engineering GmbH, Graz, Austria; [b]Faculty of Technical Chemistry, Chemical and Process Engineering and Biotechnology, Graz University of Technology, Graz, Austria

ABSTRACT

The ongoing COVID-19 crisis has highlighted the importance of a robust drug supply chain which can be quickly and flexibly ramped up to produce life-saving drug treatments. 3D printing (3DP) of oral solid dosage forms (OSDF) could be a viable part of the emergency drug production response to support vulnerable patients in rural regions and other isolated locations. In the context of the current pandemic, the suitability of different 3DP technologies will depend on the physicochemical properties, unit dose strength and BCS classification of the repurposed drug compounds currently being trialed for COVID-19. Furthermore, the deployment strategy should focus on simplifying dosage forms and formulations, scaling down the size and complexity of the printing systems and real-time quality assurance via process analytical technologies (PAT).

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1. COVID-19: an expanding health crisis

The novel coronavirus (SARS-CoV-2) and the associated disease (COVID-19) were first detected in China in December 2019, and has since caused an ever expanding and accelerating health crisis around the world. As of 5th of May 2020 there are over 250,000 deaths, linking to more than 3.6 million confirmed cases in 212 countries and territories. The crisis has put an enormous strain on the global healthcare system and caused severe social-economic disruptions worldwide.

In addition to the quarantine/social distancing measures used to limit the spread of COVID-19, the race is also on to search for effective therapeutic solutions. As most experts agree that an effective vaccine is minimally 12 to 18 months away, the current focus is on repurposing existing drug treatments for patients affected by COVID-19. In March this year, the Innovative Medicines Initiative (IMI) of the European Union announced a fast-track, €45 million call for relevant therapeutic and diagnostic solutions, and the World Health Organization (WHO) launched an unprecedented global trial to test the effectiveness of several potential antiviral compounds against SARS-CoV-2 [1,2]. There are also on-going efforts to adapt a systematic approach to quickly identify additional compounds suitable for repurposing [3,4]. Table 1 summarizes the key small molecule therapeutics that are being repurposed for the COVID-19 crisis, including their basic physicochemical properties, doses being tested for COVID-19 and clinical status.

However, once an effective drug treatment option has been identified, a crucial question remains: How can we quickly ramp up the drug production and, more importantly, make the drug available to all patients in need even in remote, under-developed parts of the world? The latter is a particularly relevant point as managing an epidemic can severely affect the global manufacturing supply chain, as vividly highlighted in the current crisis. We will hereby evaluate the potential and challenges of leveraging three-dimensional (3D) printing technologies to tackle this issue.

2. Recent advances in 3D-drug printing and its feasibility to tackle the crisis

A key benefit of 3D printing (3DP) technology has always been its ability to support distributed manufacturing. As a largely single-step construction process, i.e. with minimal interim- and post-processing steps, it can deliver finished products without extensive logistic infrastructure and matured supply chains. In the current crisis, it has already been used to produce respirator valves for the ventilators used in the badly affected Lombardy region in Italy [5]. However, can 3DP be effectively leveraged to address drug product supply issues in a similar manner?

In our 2018 review, we have reviewed and identified the promises and challenges of applying 3DP technology to oral solid dosage forms (OSDF) production [6]. In the interim years we have observed a notable maturity in the investigation and development direction. Although most studies still focused on either dosage form innovations, such as multicomponent controlled-release polypills and custom capsular devices for pulsed drug release, or repurposing other 3DP technologies, such as selective laser sintering (SLS), direct powder extrusion and electrohydrodynamic printing [7–11], many researchers are now recognizing the need to develop platform knowledge to facilitate the uptake of 3DP for this application [12,13].

Whereas these reported advances certainly expand the horizon of 3DP as an alternative drug production method, the same conclusion from our previous review still applies: implementation of any novel production technology should

CONTACT Wen-Kai Hsiao wen-kai.hsiao@rcpe.at Research Center Pharmaceutical Engineering GmbH, Graz, Austria

Table 1. Summary of the current COVID-19 drug repurposing effort.

Drug candidates[a]	logP[b]	Solubility (mg/ml)[b]	MP (°C)[c]	COVID unit dose (mg)	BCS	Development status for COVID[d]
Azvudine	−0.86	0.94	–	–	–	Clinical (Chinese CT[§])
Baloxavir marboxil	2.09	0.04	–	–	–	Clinical (Roche)
Brilacidin	2.88	0.15	–	–	–	Pre-clinical
Chloroquine[†]	5.11	0.03	88	500	1	Clinical (WHO global CT plus others)
Camostat Mesilate	−0.78	–	194	–	1	Pre-clinical
Cobicistat	4.28	0.00	87–105	–	–	Clinical (Janssen)
Danoprevir	3.06	0.15	–	–	–	Clinical (Ascletis)
Darunavir	1.93	0.10	91–95	–	–	Clinical
Ebastine	6.56	0.01	80–82	–	–	Clinical (Chinese CT with Lopinavir and IF-α)
Emtricitabine	−0.77	3.72	138	–	–	Clinical (Gilead, with Tenofovir)
Favipiravir	−0.74	4.46	187–193	–	–	Clinical (Fujifilm, Chinese CT)
Fingolimod	3.72	0.49	–	–	–	Clinical (Novartis, Chinese CT)
Galidesivir	−1.47	3.06	–	–	–	Pre-clinical
Hydroxychloroquine[†]	3.94	0.13	90	400	1	Clinical (WHO global CT plus others; some with azithromycin)
Ifenprodil	3.55	0.29	114	–	–	Pre-clinical
Lopinavir[†]	3.53	0.02	120	100–50	4	Clinical (Kaletra); WHO global CT
Losartan	3.59	0.15	184	–	–	Clinical (Uni Minnesota)
Nafamostat	1.92	0.62	178–180	–	–	Pre-clinical
Remdesivir[†]	1.6	0.00	–	200	–	Clinical (Phase III); WHO global CT
Ritonavir[†]	3.53	0.02	120–122	400–200	4	Clinical (Kaletra); WHO global CT
Ruxolitinib	1.97	0.09	84–89	–	–	Clinical (Chinese CT)
Thalidomide	−0.69	0.05	269–275	–	2	Pre-clinical
Tenofovir	−1.34	19.88	278	–	–	Clinical (Gilead, with Emtricitabin)
Umifenovir	4.69	0.0231	–	–	–	Clinical (Chinese CT)

[a]Properties of non-salt forms; [†] WHO Solidarity global trial candidates
[b]Calculated using ADMET Predictor (Simulation Plus, CA, USA) in pH 6.5 (fasted state simulated intestinal fluid or FaSIF)
[c]From www.chemspider.com
[d]From https://milkeninstitute.org/covid-19-tracker as of 5 April 2020; [§] CT: Clinical trial

be driven by drug product and patient requirements. In the context of the current crisis, we need to harmonize the formulation requirements of the repurposed drug compounds with the attributes of the potential 3DP technologies.

Many of repurposing candidates for COVID-19 are known to pose poor aqueous solubility, thus belonging to biopharmaceutics classification system (BCS) II and IV. Oral administration of these drugs will require bioavailability enabling formulations such as amorphous solid dispersion (ASD) for their clinical success. This is especially valid if they show lower anti-viral potencies as compared to their indicated therapies and thus require higher doses. In this context FDM-printed ASD using hydrophilic polymeric excipients could be suitable. One of the limitations of this approach, however, will be the high drug melting point which will require amorphization prior to filament generation or printing.

High dose requirement, on the other hand, presents a different challenge. For example, chloroquine is an antimalarial/amebicide drug with a well-known biopharmaceutics profile. Although its applicable therapeutic window for COVID-19 is unknown, it is generally administered using a high dose (up to 1000 mg per administration). Therefore, integrating such a large drug load into an FDM-printed dose while maintaining required patient acceptance factors, e.g. dose size for swallowing, may be challenging. As an alternative, the inkjet powder bed printing approach has been well-established to produce highly loaded drug doses effectively and could be more appropriate for this compound [6].

Furthermore, several repurposing approaches have combined therapeutic treatments in clinical testing, as shown in Table 1. This is necessary to avoid saturation of one treatment mechanism which can lead to drug resistance especially in the case of anti-viral drugs. In such instances, multi-compartment and multi-layer 3D printing can be leveraged for developing variable or fixed dose combination of two or more anti-viral therapeutics. Yet another crucial dimension of repurposed therapeutics in health emergencies is the risk of misuse and dose dumping. In this case, embedding drugs in 3D printed dosage forms could provide physical and chemical barriers against tampering.

3. Expert opinion on perspectives & challenges

Once effective drug treatments have been identified for repurposing, we believe that the most efficient way to quickly ramp up the production of these life-saving drugs will be by other mass production innovations, such as continuous manufacturing (CM) technologies. However, we also believe that 3DP has the potential to allow flexible and decentralized drug production in disease hot spots where there are insufficient supply chains and logistical infrastructure. Potential scenarios include a rural health clinic in a remote location or a community isolated by extensive quarantine measures, e.g. a cruise ship. This could be an effective way to strengthen our response to the current and future health crisis.

The key challenge, as described in the previous section, will be the synergy between the formulation requirements and selected 3DP technologies. For high drug loading, inkjet-powder bed printing remains the most flexible 3DP technology for dose production. The quick-dissolving nature of the inkjet-powder bed printed doses could ease the administration burden for critically ill patients in the current pandemic. Poorly soluble compounds, on the other hand, may benefit from the solubility enhancement potential of dose printing using FDM filaments created with ASD formulations. Furthermore, locking the active drug compounds into

a formulated filament could reduce the potential misuse of drug treatment during the panic of an ongoing crisis [14].

A key issue raised in our previous review on 3DP of OSDF relates to production throughput and scalability, particularly in regards to the FDM technology. Although its slow production rate could be offset by the low-cost and simple nature of a FDM 3D printer which allows it to be deployed quickly and broadly, we may wish to re-consider the utility of printing complex dosage forms in a time of crisis. Alternatively, the approach of FDM printing of rapid-dissolving, drug containing oral films may be more appropriate [15]. Regarding process scalability, the development focus should be on scaling *down* instead of up to facilitate distributed manufacturing in a crisis. For example, the current implementation focus of the inkjet-powder bed technology appears to be on establishing a commercial-scale, mass-production facility. We believe that the current crisis demonstrates the value of developing a simpler, small-scale inkjet-powder bed system. Such a system could be, in theory, be coupled with drug synthesis innovations such as flow chemistry and continuous crystallization/separation/drying technologies to create a mobile, end-to-end drug production line for crisis response.

Finally, quality control (QC) requirements for drug production cannot be ignored even in crisis time. The rapid, small batch production nature of 3DP OSDF means that traditional QC and product release approaches based on statistical sampling and wet chemistry analytical methods, e.g. dissolution testing and high-performance liquid chromatography (HPLC), may no longer be appropriate. On that front, progress has been made not only to demonstrate the feasibility of various process analytical technology (PAT) solutions to confirm, for example, printed dose assay and content uniformity, but to develop a quantitative QC approach using tools recognized in FDA and EMA guidelines [16]. Therefore, such an approach will likely be acceptable in a crisis response scenario.

Due to the fast-moving nature of the current COVID-19 crisis, the role of most 3DP technologies in the coming weeks and months is likely to be limited to enhancing the availability of crucial and life-saving apparatuses such as ventilators. However, a dynamic and robust drug supply will be the key to manage future crises and we believe that further development of 3DP for OSDF should be aligned with that goal.

Abbreviations

Three dimensional (3D); 3D printing (3DP); fused deposition modelling (FDM); selective laser sintering (SLS); oral solid dosage forms (OSDF); biopharmaceutics classification system (BCS); amorphous solid dispersion (ASD); continuous manufacturing (CM); quality control (QC); high-performance liquid chromatography (HPLC); process analytical technology (PAT)

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Declaration of interest

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