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Perspective

Drugs need to be formulated with scale-up in mind

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A B S T R A C T

Formulation scale-up remains a major hurdle in drug development in part because preliminary formulation research efforts rarely consider the challenges of scaling up production for commercialization. This Perspective outlines considerations around scalability that can be incorporated into formulation design work in order to increase the chances of successful translation. Both technical (unit operations, excipient selection, scaling principles) and non-technical (funding, publications, and personnel) considerations are discussed, with a focus on lab-scale work by academic researchers.

1. Introduction

Pharmaceutical scientists and engineers have a beautiful mandate: to invent, study, and develop drug products that are effective against human disease. Academic researchers in this space, who have more agility to pursue their own research interests than their industrial counterparts, typically focus on the former two goals, uncovering fundamental scientific principles relevant to pharmaceutical science that can then be leveraged into promising new lead molecules or delivery strategies.

With that said, how many times have you read a drug delivery research paper that did all of the following? (1) Showed extremely impressive preliminary in vivo results; (2) gave few details about the techniques used during formulation and/or used lab methods that are non-scalable, and (3) spent exactly one sentence toward the end of the conclusions section saying something to the effect of 'Future efforts will eventually involve someone – (implication: someone *else*) – figuring out a cost-effective way to scale up the achievement reported herein.'

But scaling up a promising formulation is not someone else's problem. Robust and reproducible production is a non-negotiable requirement in a formulation's path from discovery to commercialization (Fig. 1). There are numerous examples of formulations or delivery strategies that failed because the leap from lab-scale synthesis to pilot or commercial production was too perilous, meaning reproducibly maintaining critical quality attributes (CQAs) within acceptable limits proved to be prohibitively expensive [1,2]. Some of these formulations started as attractive leads in a high-impact journal article that, on closer examination, utilized steps that proved too costly or too difficult to control at scale. If a preliminary formulation is not well-positioned to make the jump from formulation to scale-up, one of three things can happen. One is that the reported approach is identified as impossible and ignored by industry. If a company does pick it up, or a startup is formed around it, another outcome is that a mid-air course correction can be attempted – i.e., poorly-controlled processes with low reproducibility can be replaced with reliable unit operations in the hope that whatever comes out the other end still performs as intended. There is no guarantee that it will. And if this fails, the third route is that the drug or drug delivery system has to be re-formulated. The first of these options is a far cry from the field's mandate. The latter two each carry significant risk and may divert resources from more promising technologies and products.

Research scientists and engineers who design or utilize drug formulations in our work – especially those of us in academic research – therefore have a responsibility to be mindful about how we make our formulations. We should make good-faith efforts to utilize processes, actives, excipients, and operational parameters that are representative of what can realistically be done at the industrial scale. We ought to evaluate what we make not only for biological activity, but also for viability of production, and to report on the latter alongside the efficacy data. Many academic labs do very good work illuminating fundamental *scientific* principles that inform formulation design, such as thermodynamics or biological interactions. There are likewise fundamental *engineering* principles underpinning scale-up that we should hold in mind when we design formulations. Doing so will ease the transition from formulation to scale-up and help position our formulations for translational success later (Fig. 1). The late Professor Takeru Higuchi is said to have remarked that "Drugs need to be designed with delivery in

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mind," [3] emphasizing the fundamental link between Discovery and Formulation. Likewise for Formulation and Scale-up.

The goal of this Perspective is to outline considerations for developing novel (particularly particle-based) formulations with a scale-up mindset. My intended audience is primarily academic researchers. Many companies are increasingly building integrated teams to work on Formulation and Development at the same time, sometimes even with strong lines of communication back to Discovery [4]. This integrated, interdisciplinary approach rarely occurs in university labs, where the incentive structure often relegates scale-up to an afterthought. There are also major obstacles academics face when integrating scale-up mindfulness in our work that must be contended with: material availability, unfamiliarity with process design and scaling principles, a tricky funding landscape, and a publishing landscape that sometimes dismisses the field of scale-up as lacking scientific novelty, to name a few. These and other considerations are discussed as a primer for readers to incorporate a scale-up mindset into their work.

2. Technical considerations

2.1. Critical quality attributes

CQAs are "physical, chemical, biological, or microbiological properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality." [5] In the journey from discovery to commercialization, it is essential to determine the 'design space' of a drug product, i.e.: (1) what the CQAs of a given formulation (e.g. particle size, mass ratio of active to excipient) are, (2) the acceptable limits within which each CQA must remain for satisfactory formulation performance, and (3) how unit operation choice, operational parameters, etc. affect those CQAs – holding them within or taking them outside of the acceptable range.

Often the design space is poorly defined and not well-explored during early formulation work. This happens (understandably) because the all-important readout is the in vivo evaluation step, which is the slowest and most expensive assay that an early formulation is subjected to. As such, academics and start-ups cannot explore the design space using in vivo performance as the readout. But there are usually in vitro assays – at higher throughput and lower cost – that are used to narrow down formulation candidates before the in vivo tests. These can be rationally designed to give some preliminary indication of how changes to CQAs affect performance (or don't). Designing these tests with the formulation's overall design space in mind – and reporting the results – is one way that researchers can contribute early to the effort of identifying CQAs, their limits, and even the effects that unit operations and other parameters have on them. Of course, this contribution is only possible if materials and methods sections in papers are written in a highly-detailed way that enables replication.

2.2. Scalability in unit operation selection

The introduction spoke unfavorably about "lab methods that are non-scalable." Many readers will not have a sense of what that means, and this is itself part of the situation that I want to address. This section discusses ways to think about formulation techniques in terms of scalability.

A reproducible unit operation is one that achieves acceptable consistency in spatial distribution of material and energy over time scales that are significantly shorter than what is critical to the process at hand. Operations can be scalable (a) in time, meaning they are reproducible over long time scales and large quantities of material ('long' and 'large' vary widely by modality) and/or (b) in space, meaning equivalent reproducibility can be achieved in vessels of different number and sizes.

The following case study 'zooms in' on a common lab technique to demonstrate examples of material and energy distribution considerations to think about when approaching scale-up. The same can be done for any unit operation.

Case study: consider the act of mixing two liquids – an oil containing a surfactant and an aqueous phase – to form an emulsion. Dropwise addition of the oil phase into a magnetically-stirred beaker of the water phase using a pipette is a common lab technique that is neither reproducible nor scalable:

- Even for a researcher with outstanding dexterity, pipette tip location in space inevitably varies over time, meaning the droplets neither have the same momentum (varying height above the air/water interface alters droplet velocity at impact) nor impact the same location each time.
- Even if a pipetting robot were used to finely control the tip location in space (such a robot would certainly still exhibit variability in its movement, though this may fall within an acceptable range), the rate of droplet dispensing, and the volume of droplets, the environment

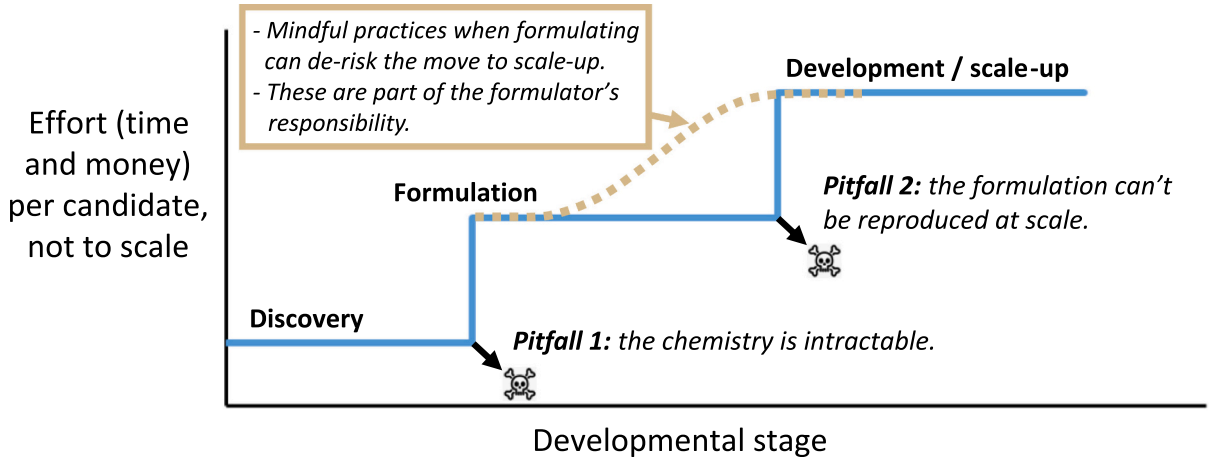

Fig. 1. A simplified view of the major steps in the developmental path for a drug product. If developmental stages are performed in isolation, the move from one to the next is a step function in difficulty (y-axis) that can be fatal to the development pipeline for a given candidate. Companies are increasingly integrating Formulation and Development teams to mitigate the risk presented in Pitfall 2. Academic researchers should likewise be mindful that their formulations will eventually need to be scaled up as a prerequisite for commercialization, and choose unit operations, excipients, and other parameters accordingly and as early in research projects as feasible.
Note: after the Discovery stage, a candidate is commonly called a 'drug substance.' Only after Development does it become a 'drug product.' The path from drug substance to drug product therefore includes both formulation and scale-up.

into which droplet $n + 1$ falls is different from the environment into which droplet n fell.
- The solvent quality changes with each subsequent droplet, becoming higher in oil volume fraction and lower in water volume fraction. This in turn affects the degree of supersaturation experienced by the oil molecules in droplet n versus $n + 1$ and introduces variability over time in the driving force for phase separation and stabilization by the surfactant molecules.
- The previous bullet assumes that the beaker is perfectly well-mixed between droplet n and $n + 1$, which is also not realistic. In reality, the top of the liquid is likely to become at least somewhat oil-rich and water-poor as oil addition continues, affecting solvent quality and phase separation, unless there is such a long time interval between droplets as to render the process totally impractical.
- The total volume of liquid in the beaker also increases as oil is added, affecting the vortex created by the magnetic stir bar; the shear force felt by droplet n vs. $n + 1$ is different as a result.

Mixing via dropwise addition into a magnetically stirring beaker may appear to be reliable and reproducible in the lab, and many studies understandably use it because of this. In practice, the inherent variability described above precludes this mixing geometry from being scalable (although the mental image of a 350 L vessel containing a colossal stir bar over a huge magnetic stir plate, a pipette suspended above it pointing down like the sword of Damocles, is usually good for a laugh). For liquid-phase mixing, processes utilizing continuous flow can therefore be considered as an alternative; this is discussed further below.

Note the qualifier "over time scales that are significantly shorter than what is critical to the process at hand" in the definition above. In polymer nanoparticle antisolvent precipitation, for example, the critical physical process – molecular diffusion leading to precipitation, self-assembly, and stabilization – is expected to take place on the time scale of tens of milliseconds [6]. Therefore, to be scalable and reproducible, the mixing must be both faster than this (<10 ms) and consistent over the course of the process. The relevant time and length scales vary by application. Mixing considered 'rapid' in one application may not be fast enough for another: 'rapid' relative to what?

Questions to ask, therefore, are: 'Is there sufficient evidence to suggest that the current lab-scale version is readily translatable to a larger scale?' More specifically, 'Is there a version of each unit operation I need to use that is scalable and reproducible on the length and time scales relevant to the critical physical and chemical processes taking place in this step in my process? If so, does it exist in a scaled-down form I can use at the bench? Could I use those methods from the very beginning of my formulation work? Or, if not, after using less-scalable operations for high throughput screening, could I try re-making my formulation using those operations, at least once, and include those results in my study?' Material limitations are often critical in academic research, so small-scale versions of materially-intensive unit operations such as spray drying and rapid liquid mixing are especially useful to have, and this is an important area of equipment development.

Brief heuristic comments on common lab techniques and unit operations used in formulation research:

Mixing and coating: for stirred vessels, overhead mixing is essential at scale. Magnetic stir bars are unreliable. Techniques that are not representative of processes at scale include hand mixing or dropwise addition of solvent into antisolvent for antisolvent precipitation or emulsification, as well as probe-tip sonication / thin film rehydration for emulsion or liposome preparation. Scalable mixing and blending operations include rotor-stator or high-pressure homogenization, powder blending, extrusion, particle milling, fluid bed coating for particles above 50 um (coating particles below this size can prove difficult to scale), and continuous flow operations such as static mixing (depending on the time scales relevant to the process) and turbulent mixing for nanoprecipitation. Continuous microfluidic laminar mixing is highly reproducible but limited in how it scales in vessel size and, depending on the application, how it scales in time. E.g. for an antisolvent precipitation application, solids deposition on channels walls over time ('fouling' or 'clogging') can impact and even occlude flow, meaning microfluidic mixers are not reproducible over long time scales [7–9]. Evaluating these processes for fouling is valuable but expensive, since the phenomenon may only emerge to a detectable degree after lengthy operation that requires significant material investment. Using these mixers to form emulsions may be acceptable, though the limitation in vessel size scaling persists. Overcoming that limit may require parallelization ('scale-out' rather than scale-up).

Separation: Tangential flow filtration is preferred over dialysis or centrifugal ultrafiltration for solvent exchange and is a standard scalable operation for liquid-phase solids concentration. Spray drying (including the formation of spray-dried dispersions, particularly if solvent recycle is possible and inlet solids concentrations are not too low), tray drying, and lyophilization are reliable drying operations. The latter is typically done in batches instead of continuous or semicontinuous operation, but this is typically justifiable from a cost standpoint for high-value products.

2.3. Stability

The formulation that is evaluated in vitro or in vivo in many papers is actually an intermediate that has not been subjected to all the operations that a final dosage form would be, particularly sterile filtration and storage. If a formulation does not survive residual solvent removal, filtration, or freezing, then perhaps in vivo results from an unfiltered, never-frozen 'primary formulation' containing residual solvent should not be reported as a promising lead until solutions to some of these obstacles are at least attempted and included in the report. Similarly, for processes involving multiple unit operations, physical and chemical stability of the intermediates over time should be evaluated and reported, since the holding time between unit operations typically increases with scale. Measuring stability of a final or semifinal dosage form in representative primary packaging and storage conditions is also valuable. Stability and scalability considerations go hand-in-hand, not least in part because stability studies require producing enough material at $t = 0$ to run the test. If reproducibly making even that much proves to be a challenge, the formulation process may need more work before being reported on.

2.4. Materials and excipients

It is prudent to use pharma-grade materials when formulating and not to use excipients for which pharmaceutical grades do not exist. The same is true for salt / free acid / free base forms of both active ingredients and excipients. For studies involving the synthesis of novel actives or excipients, the scalability and yield of the chemistries involved should be critically assessed. Particularly for excipients, synthesis pathways that are likely to be prohibitively expensive at scale – e.g. those with very many steps, unacceptably low yields, very low concentrations requiring removal or processing of huge amounts of solvent relative to solids yield, or that utilize difficult-to-scale chemistries such as atom-transfer radical polymerization – should be evaluated for alternatives if the cost-benefit balance tips too far toward costs. Those not used to performing cost-benefit analyses may be able to partner with industry contacts for support in making a first pass at evaluating a process's economic acceptability.

A final consideration here is around the expected dosage and drug loading (the mass fraction of drug) of a drug product. Taken together, these two parameters define the volume of one dose of drug product. If this volume is too high – e.g. too large to fit in a standard injection vial or too large to be administered to a patient without unacceptably high patient burden – the formulation is likely to fail in development. It is therefore prudent to estimate an approximate dose and acceptable administration volume, then use those to develop a minimum acceptable bound for drug loading during initial formulation work.

3. Non-technical considerations

3.1. The personnel landscape

In June 2018, Juan Andres, then Senior Vice President for Manufacturing, Quality, and Technical Development at Moderna, told the company's cohort of summer interns something to the effect of: "Science is making a very nice steak dinner for two, cooked-to-order and perfect, with nice sides, good presentation, everything. *Engineering* is making that *exact same* very nice steak dinner *for five hundred*, in one night, with the sides coming out at the same time as the meat, still cooked-to-order, still perfect." Designing formulations with scale-up in mind is an area where engineers – especially chemical and biological engineers, whose undergraduate training traditionally includes a focus on process design and unit operations – are particularly able to add value [10,11].

One concept commonly used in chemical, biological, and mechanical engineering but seen less frequently in other fields is the idea of characterizing a process by splitting it into its constituent dimensionless numbers, which are ratios of relevant forces (e.g. Reynolds number), times (e.g. Damköhler number), diffusivities of mass (Sherwood) or heat (Nusselt), etc., involved in the transport of matter and energy during the process. This approach can be applied to all the types of unit operations used in pharmaceutical manufacturing: mixing, separations, phase changes, reactions, fermentation, etc. Because these numbers are ratios, they can be held constant as vessel size and/or process times are increased by correspondingly increasing the relevant flows, forces, etc. in the process. This is one reliable way to begin approaching scale-up.

3.2. The funding landscape

For academics interested in developing novel scalable unit operations or designing scaled-down versions of existing scalable operations that are typically too material-intensive for academic research, the funding landscape can be difficult to navigate. In the U.S., neither the NSF nor NIH has mechanisms dedicated to process intensification or scale-up upstream of the Small Business Innovation Research and Small Business Technology Transfer opportunities, which are available only to academic researchers who have formed a startup company or partnered with an existing eligible small business. Centers such as the NIH National Center for Advancing Translational Sciences' (NCATS) Clinical and Translational Science Awards (CTSA) Program typically do not emphasize process scale-up, instead focusing on clinical research, clinical practice, disease progression, disease risk across populations, etc. Importantly, the FDA does support research efforts around process integration, intensification, and continuous manufacturing, as well as the development of novel unit operations, through its Broad Agency Announcement (BAA) mechanism. The BAA may therefore be an attractive route to pursue for academic groups or academic-industrial partnerships. Collaborative partnerships with industry can also lead to company-sponsored projects focused on this kind of work, which can be designed to be formulation-agnostic and therefore fit into pre-competitive space with the freedom to publish that is desirable for academia.

NGOs are another possible source of funds. The Gates Foundation sponsored a seven-year project in Professor Robert Prud'homme's lab at Princeton that I was involved in during my Ph.D. there and into the first year of my research group at Purdue. That effort focused extensively on taking a process design approach to drug formulation research and is the basis of much of the thinking that led to this Perspective. The project's goal was to develop an integrated process to encapsulate hydrophobic small molecule global health drugs into polymeric nanocarrier suspensions that were then dried to yield a stable dry powder, with the goal of improving oral bioavailability. We did not begin with a formulation, but with the goal of designing a scalable process to use for making all the formulations in the course of the work. As the saying goes, 'the process was the product.' Design constraints were outlined early: the process could add no more than $0.60 per dose in total costs, and the output dosage form needed to be a flowable dry powder that rapidly redispersed in water, improved oral bioavailability, and maintained physical and chemical stability against ambient sub-Saharan African heat and humidity in paper sachet storage. The three major unit operations in the final process – turbulent mixing for antisolvent precipitation, tangential flow filtration for solvent exchange and nanocarrier concentration, and spray drying – were continuous and scalable, and the excipients used were low-cost and available at pharmaceutical grade. This streamlined technology transfer to WuXi AppTec for rapid implementation and preclinical validation. WuXi quickly produced 350 L batches of the formulation with nanocarrier size, dissolution kinetics, and stability behavior identical to the 5 mL batches made at Princeton [12].

3.3. The publishing landscape

The technical section on stability above discouraged reporting on an intermediate formulation without including at least some initial evaluations of its performance through downstream unit operations that would be expected for a final dosage form. Determining where to draw that line – i.e., should a study be split across two papers, one on the primary formulation and a sequel on processing? – is a case-by-case decision. It is valuable to include at least some preliminary processing and stability considerations in a first report, as many labs are not equipped (nor should they all be) to do a deep dive into process scale-up as a second study. And even for those that are, the results from a subsequent scale-up study may be negative and therefore difficult to publish.

Including some preliminary processing considerations in a first published report that mainly focuses on biological efficacy is also a way to encourage a field-wide attitude shift toward the scale-up mindset. Some pharmaceutical journals do not include scale-up in their scope, meaning that if a follow-up article focused solely on process scale-up is written, it is likely to be relegated to an engineering journal where most pharmaceutical scientists will not encounter it. We have submitted manuscripts containing research oriented around formulation scale-up that were desk-rejected as 'technical reports rather than original research.' Consider a hypothetical paper that describes producing at the 1 L scale a formulation that could previously only be made reproducibly in 5 mL batches, and also gives mechanistic explanations for why the old way did not work and the new way does. Such research would be both novel and valuable, and should be considered for publication in pharmaceutical journals.

4. Conclusion

I want to stress that these considerations are not being outlined with an intent to discourage innovation. The attitude here is not 'never publish anything short of a final dosage form' or 'never make anything in small batches.' The advantages of using non-scalable unit operations such as magnetically-stirred beakers in initial formulation work are clear: convenience, familiarity, low capital investment, and low material requirements. The advantages of publishing a formulation with attractive in vivo results without first evaluating stability or scalability are also clear: this route is faster to yield the currency that academics are incentivized to trade in – publications, attention, and citations – and does demonstrate some degree of proof of principle for the formulation's therapeutic benefit. The disadvantage of both approaches is the same: the picture they paint about a formulation's true potential is incomplete in a way that is often fatal to future translation.

The point of this discussion is rather that translation is the ultimate mandate for our field, and we should keep our eye on that ball even in work that is far upstream of it. We can and should make good-faith efforts to approach the critical issue of scale-up early on in our work, and to build scalability into our formulations from the onset as much as we

reasonably can. Of course, even if we do, there is no guarantee that the process will work identically as it moves from the lab to pilot or production scales. This should not discourage us from trying to maximize the chance that CQAs remain acceptable across scales.

The attitude is also not 'only use unit operations that the industry already knows how to use.' Developing novel scalable unit operations or scalable versions of bench techniques is clearly a valuable area of research. Likewise for developing versions of existing large-scale operations with lower material intensity. Some of these techniques, even in their current smallest lab-scale iterations, have such high minimum material requirements that they preclude use by academic researchers working with precious APIs such as mRNA. Scaling down these operations even further for use in academic formulation research is a major unmet need. At present, substituting lower-cost materials that are analogous to the prohibitively-expensive compound when running these processes (e.g. yeast RNA for mRNA) is an imperfect solution.

Incorporating a scale-up mindset into formulation research requires a deliberate investment of time and resources: utilizing scalable and reproducible unit operations as appropriate, selecting acceptable materials and excipients, and evaluating stability throughout the formulation process. I believe we have a responsibility to keep these considerations in mind during our work, and that these costs are more than made up for by the benefits toward potential translational success.

CRediT authorship contribution statement

Kurt D. Ristroph: Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

Data availability

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