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ARTIFICIAL INTELLIGENCE AND DIGITAL TWIN TECHNOLOGY IN POLYMERIC NANOSPONGES: CONVERGENCE, APPLICATIONS, AND FUTURE DIRECTIONS

Dr. A. Dinesh Raja*, Kaviyarasu R., Raghuram K., Subasri S., Subica S., Veerabalaji M.

Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore – 641048.

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***Corresponding Author: Dr. A. Dinesh Raja**
Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore – 641048.
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ABSTRACT

The polymeric nanosponges, which are hyper-cross-linked three-dimensional nanostructures, have progressed from a laboratory curiosity to a platform for delivering drugs, decontaminating environments and formulating cosmetics in the last 20 years. It's their porous, cage-like structure that can be precisely engineered and fine-tuned virtually endlessly by changing the parent polymer, the cross-linking compound, and the reaction conditions, providing formulators with control over the particle size, the amount of drug loaded and the drug release rate. The same tunability has been the stumbling block in nanosponge synthesis, however, because researchers have to test dozens of different ratios of polymers to cross-linkers before they find a combination that works. This review explores how these two computational technologies, artificial intelligence (AI) and digital twins, are starting to shift that equation. We illustrate the evolution of nanosponge chemistry, highlight the use of machine learning models for predicting nanosponge yield, particle size, encapsulation efficiency, and release behavior from formulation parameters, and discuss how digital twin concepts, initially developed for pharmaceutical production lines, are now being applied to model nanosponge production lines in real time. We also discuss the practical challenges that make it difficult to use these tools in the laboratory, such as the small and fragmented datasets, the high costs of constructing a twin and validating it, and the regulatory framework that wasn't designed for a self-updating model; and we provide a glimpse at where the field is likely to go in the next five to 10 years.

KEYWORDS: Polymeric Nanosponges, AI, Digital Twin, Machine Learning, Drug delivery.

1. INTRODUCTION

Nanotechnology first made its debut into the field of pharmaceutical science with a simple promise: if a delivery vehicle was made smaller, nanometres smaller, then a host of problems — such as the inability to dissolve a drug in water, its too fast degradation, and toxicity to off-target cells — would become more manageable. That is the root of the clinical relevance of liposomes, dendrimers and polymeric nanoparticles. Nanosponges are a same family but they got it to their good by a different path. A nanosponge is designed by hyper-cross-linking a polymer structure filled with nanoscale cavities, in contrast to the mechanism of a single vesicle or matrix containing a drug.[14]

It was first described in the early 2000s at the University of Turin where cyclodextrin-based cross-linked particles in the shape of spheres were prepared by reacting β-cyclodextrin with a polyfunctional cross-linker (such as diphenyl carbonate or carbonyldiimidazole). The hydrophobicity of the cavity formed by the toroidal structure of cyclodextrins was known to have a beneficial effect as a solubilizing agent in pharmaceutical science, so that the combined effect of a large number of cyclodextrin units was simply to have a much larger surface area pulling a poorly soluble drug into the aqueous solution. In the years since then, the nanosponge class has expanded far beyond the bounds of cyclodextrins to include ethylcellulose nanosponge, hyper-cross-linked polystyrenes, Eudragit-based nanosponge, inorganic nanosponge based on a silicone or titanium, and even DNAzyme-based nanosponges, all of which have different applications with different types of drugs and different administration routes.[14,9]

The same development problem remains: The efficacy and release characteristics of a nanosponge are a complex network of factors that includes molar ratio of polymer to cross linker, reaction temperature, stirring rate, choice of solvent, choice of drying method, etc. Usually, a controlled series of dozens of batches has been conducted to this space for a particular system using a design-of-experiments approach such as a central composite design, Box–Behnken design, or factorial design, and a response-surface model has been fit to the data. These statistical tools are still useful but are essentially reactive in nature: they describe relationships that are found in the data collected, but are not very useful when the number of variables increases, or when relationships between variables become nonlinear.[4,5,7]

There are two computational trends that are moving towards it. The first is the growing application of machine learning and, more recently, deep learning to predict formulation outcomes directly from the data relating to the formulation composition and process, rather than conducting many physical tests to arrive at an optimum formulation. The second, the digital twin, is a virtual representation of a physical process that is always current and constantly monitored during the manufacturing of it, which has already been used in the pharmaceutical industry for tablet compression, bioreactor control and quality-by-design monitoring. The concept of nanosponge production is a newer idea, but it has also been thought of in other components of the pharmaceutical digital ecosystem, and it is this review that outlines the current state of nanosponge research compared to the other technologies.[22,26]

2. Polymeric Nanosponges. Structure, Synthesis, and Applications

2.1 Structural classes and materials

In general, nanosponges are solid, porous, cross-linked polymeric materials in the nanometre-to-micrometre size range, and according to some definitions include hydrogels and metal-organic frameworks. The most widely studied variant of cyclodextrins are the cyclodextrin based nanosponges, which are made by cross-linking cyclodextrins with chemicals like diphenyl carbonate, carbonyldiimidazole or pyromellitic dianhydride, which hardens the cavities into an insoluble network without sacrificing the ability to engage in host–guest inclusion chemistry. In addition to cyclodextrins, the

release of drugs like carboplatin has been explored with the use of ethylcellulose nanosponges, buffering of acidic tumour microenvironments has been attempted using calcium carbonate nanosponges, and metallic or inorganic versions containing carbon nanotubes, silver nanowires or titanium dioxide have been studied when a nanosponge is required to serve as a surface for sensing or catalysis as well as a drug reservoir.[14,9,10]

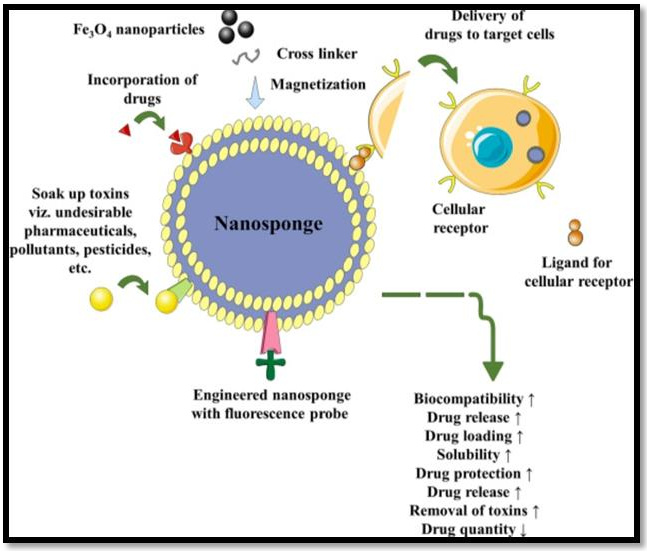

Figure 1: Schematic representation of a hyper-cross-linked polymeric nanosponge, showing drug incorporation, magnetization with Fe_3O_4 nanoparticles, ligand-mediated delivery to a target-cell receptor, and adsorption ("soaking up") of undesirable pharmaceuticals, pollutants, and pesticides — with associated gains in biocompatibility, drug loading, solubility, drug protection, and controlled release.[10]

Structural and compositional variants of nanosponges are increasingly characterised at the nanoscale using electron microscopy, which confirms the spherical, core–shell morphology and narrow size distribution that formulators aim to control through the choice of polymer and cross-linker chemistry.[14]

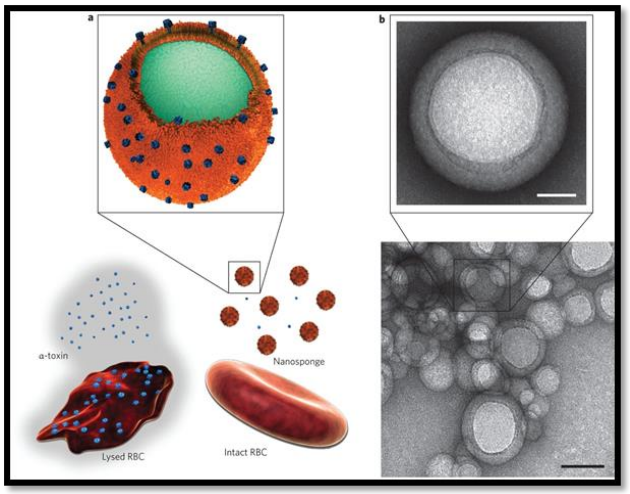

Figure 2: (a) Structural illustration of a red-blood-cell-membrane-functionalised nanosponge, showing surface-bound α-toxin neutralised on intact nanosponge particles versus lysed red blood cells (RBCs) exposed to free α-toxin — an example of biomimetic nanosponge engineering for toxin sequestration. (b) Transmission electron microscopy (TEM) images confirming the spherical core–shell morphology and size distribution of the

nanosponge particles, the type of characterisation data that ultimately feeds formulation-to-property datasets used to train machine learning models.[16]

2.2 Synthesis & The variables that matter

There are a few basic methods by which the most common cyclodextrin nanosponges are still prepared, these include: solvent based cross linking under reflux, melting or fusion, ultrasound-assisted synthesis and microwave-assisted synthesis, where microwave synthesis has emerged as a more convenient and time-saving method as it minimizes the need of organic solvents and fits better within the green-chemistry paradigm. Regardless of which pathway is followed, the following few levers apply to the behaviour of the particle produced: the polymer/molar ratio of cross-linker, reaction temperature and time, stirring or microwave power, and drying/purification step post reaction. Many such studies have been conducted to optimize these parameters with response-surface methodology (RSM) and have shown, for example, that particle size and yield in the cyclodextrin nanosponge synthesis is a non-obvious coupled response to the reaction temperature, time and stirring speed, which is just the sort of multi-parameter interaction that would make manual optimization a slow process.[4,5,6]

2.3 Application in other non-pharmaceutical areas

The most compelling pharmaceutical argument for nanosponges is the potential to improve the solubility of poorly soluble drugs (BCS Class II and IV) and the ability to control release. Several reported examples, all demonstrating improvements in either solubility, sustained release or bioavailability compared to the free drug, include nanosponge formulations of piroxicam for the purpose of enhancing oral solubility, domperidone via a greener microwave assisted route, naftifine hydrochloride for topical antifungal therapy and antimalarial combinations for dry suspensions in the paediatric population. In oncology, cyclodextrin nanosponges have been applied to trap drugs like camptothecin, curcumin, and others, taking advantage of the hydrophobic cavity to shield labile drug molecules and adjust the release rates; also, cholesterol-functionalized nanosponges have been demonstrated to enhance the cellular uptake and increase the cytotoxicity against breast cancer cell lines without toxicity to the normal fibroblasts.[3,2,8,1,15,17,16]

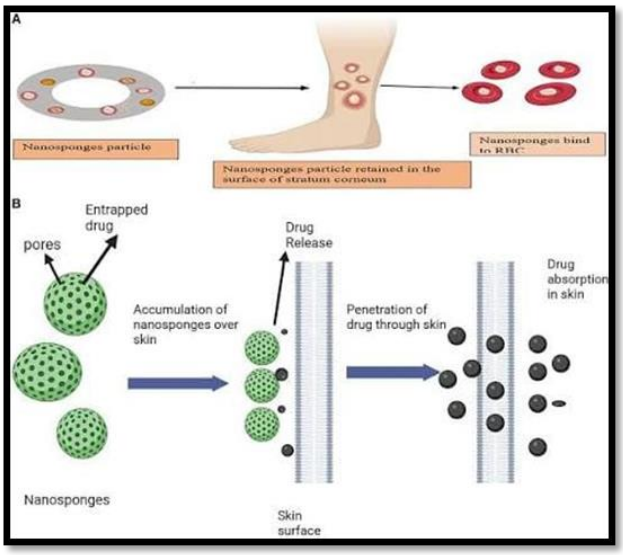

Figure 3: (A) Nanosponge particles retained on the surface of the stratum corneum and interacting with red blood cells (RBCs), illustrating the type of topical delivery route relevant to nanosponge formulations such as naftifine hydrochloride for antifungal therapy. (B) Proposed mechanism of drug release from nanosponges at

the skin surface: accumulation of nanosponges over the skin, release of entrapped drug from surface pores, penetration of the released drug through the skin, and subsequent drug absorption within the skin.[8]

Nanosponges have also made an impact beyond the realm of traditional drug delivery. Host–guest cavity chemistry is the key to the use of cyclodextrins as nanosponges for drugs and is also being explored for soil and aquifer bioremediation and for removal of heavy metals, dyes, pharmaceutical residues, and per- and polyfluoroalkyl substances (PFAS) from contaminated water. They are biodegradable and are not as harmful to non-target organisms as some conventional remediation chemistries.[12,18]

The solubility enhancement technology has found its way into ever more diverse applications, including cosmetic use, agriculture and crop protection, chemical sensing and as a protein or gene carrier.[13,10]

3. Artificial Intelligence in the Design of Nanosponge and Nanocarrier for Drug Delivery

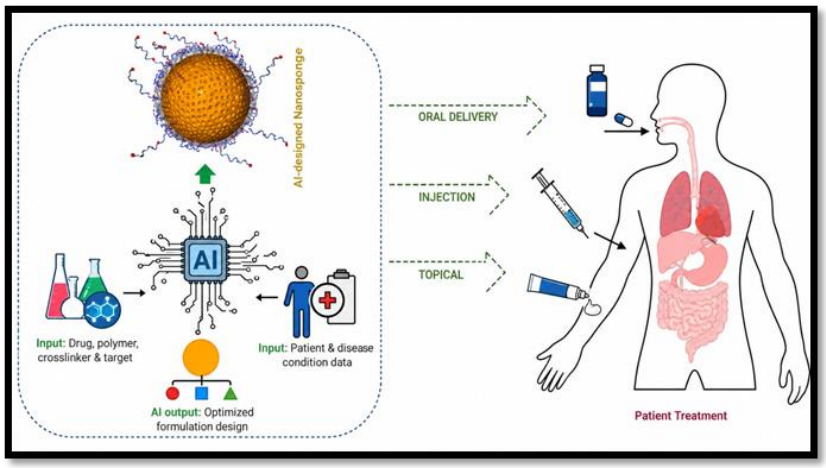

Figure 4: AI-assisted design of a nanosponge carrier, integrating drug, polymer, crosslinker, and target inputs together with patient- and disease-condition data to generate an optimized formulation design suitable for oral, injectable, or topical delivery — illustrating the type of formulation-to-property prediction pipeline discussed in this section.[22,24]

3.1 From design of experiments to machine learning

For years, the workhorse methods for optimizing nanosponge production have been design of experiments (DoE) techniques like central composite and Box–Behnken designs, which are statistically transparent and involve relatively few experimental runs. The problem with them is that the response surfaces they produce are generally low order polynomial models that are not very good at handling the threshold or sharply non-linear behaviour that can occur in cross-linking chemistry, for instance, a reaction that cannot form solid nanosponges at all until a certain ratio of the cross linker is reached, but then behaves smoothly after that. Machine learning models in particular and artificial neural networks in general do not need to be formulated ahead of time and hence have been applied in the broader nanomedicine context to predict drug-loading efficiency and release characteristics of lipid and polymeric nanoparticles, for example, by compositional descriptors without having to conduct an extensive experimental matrix.[7,21]

One such example from the nanosponge literature, but more specific and directly apposable, is the modeling of doxorubicin release from pH- and temperature-responsive polymer hydrogels using artificial neural networks, which were able to learn the release parameters from a limited number of experiments at a select few pH/temperature points instead of conducting a full series of experiments at all combinations of pH and temperature. The same concept can be extended to nanosponges: if a formulator has a series of formulation(s) with known polymer to cross-linker ratio, reaction temperature, and stirring speed, then a supervised model can be developed to predict the resulting particle size, polydispersity index, percent yield or drug entrapment efficiency for formulations that have never been physically tested, thereby reducing the number of experiments the formulator must conduct before confirmatory trials.[19]

3.2 What AI is being asked to predict

In the wider field of nanomedicine, there are four prediction tasks that appear so frequently that they can be classified as the current "use cases" for nanosponge properties, with each mapping relatively directly onto one of these tasks.[20,21,23,24,25] Formulation to property prediction: predicting polymer type, cross linker ratio, process parameters, particle size, zeta potential, polydispersity and yield, and so on, minimizing the number of physical batches required to find an optimum.[20,24]

Release-kinetics modelling: prediction of the shape of a drug-release curve (burst release, sustained release or stimuli triggered) from the formulation composition without having to measure it empirically for all the candidates.[19]

Biodistribution and interaction prediction: prediction of behaviour of a nanocarrier after introduction into a biological system, including tissue distribution and efficiency of delivery to a target site; an area of active research using machine learning models trained on data from the pharmacokinetics (PK) of nanoparticles.[21]

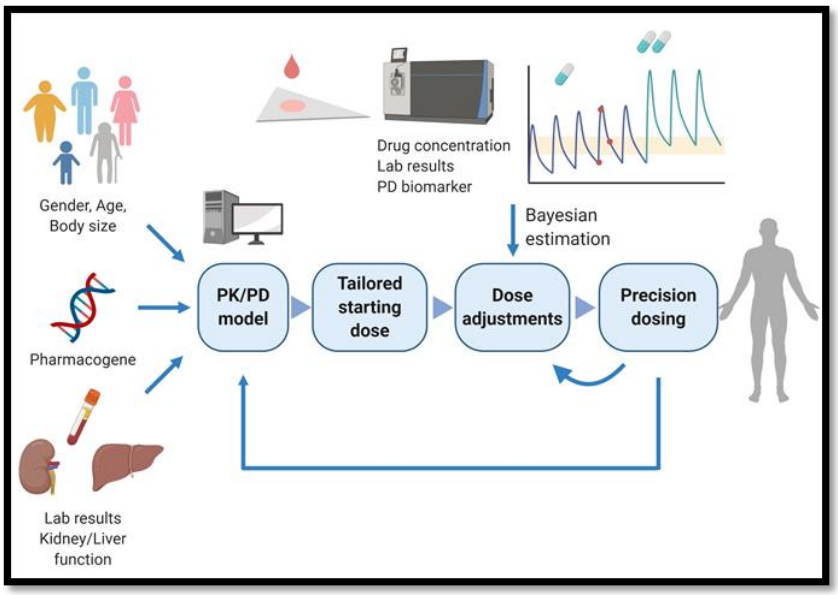

Figure 5: Workflow of a pharmacokinetic/pharmacodynamic (PK/PD)-based precision dosing model, integrating patient demographic data (gender, age, body size), pharmacogenetic profile, kidney/liver function, and measured drug concentration or pharmacodynamic biomarkers. Bayesian estimation is used to refine dose adjustments and achieve individualized precision dosing — the type of PK-informed machine learning framework referenced for biodistribution and interaction prediction of nanocarriers.[21]

Manufacturing quality control: Process data pattern-recognition models identify batches that may not meet specification before a complete batch of release testing.[26]

Some precision about the literature on nanosponge is in order in relation to this list. The published studies using a direct computational optimization approach for nanosponges are still largely based on classical response surface and factorial design statistics, with only a handful of examples in the broader literature on polymeric nanoparticles, liposomes and micelles employing deep learning. It is an important nuance for a new field such as nanosponge: The tools are clearly transferable and the underlying chemical processes are more similar but a narrow literature search for machine-learning models specifically on nanosponge data yields a much narrower selection of publications than a broad search on nanocarriers. Much of the AI-nanosponges connection, as a whole, should be viewed as an extrapolation from related and more well-studied systems of nanocarriers, and not as a fully developed sub-field.[22,25]

3.3 Data limitation & the trial-error legacy

The third factor, data limitations, is the trial-and-error legacy. The third is data limitations — the legacy of trial and error.[25]

Data is the largest practical limitation in this area of machine learning. Nanosponge formulation studies are usually single laboratory studies that result in a handful of batches (typically 10-20) that are run in accordance with a single design of experiments (DOE), which is sufficient to design a response surface but insufficient to fit a powerful neural network without overfitting. The difficulty of cross-study data collections stems from the fact that the laboratories rarely report the results in a standardized form, employ different cross-linkers, characterization tools, and rarely publish a raw data set in a shared repository. Like the materials-genome and nanoinformatics projects for nanoparticles more generally, AI models in this niche will likely continue to be trained on relatively small datasets, datasets that are formulation specific, until the nanosponge-specific data becomes more standardized and, in turn, more abundant.[22,25]

4. Digital Twin Technology & Nanosponge's extension in manufacturing.

4.1 What a digital twin is?

A digital twin is not just a simulation. The distinguishing feature is the ability to make predictions or recommendations within the virtual model which are fed back into the physical system, and to update the virtual system’s internal state to match the real operating state of the physical system. The distinguishing feature is the ability to make predictions/recommendations within a virtual model which are fed back to alter the physical system, and to update the virtual system’s internal state in response to the real operating state of the physical system. So, a complete digital twin has three elements — the physical asset, the virtual model and the data-communication layers that link them — and it is the closed loop between those elements that make a digital twin different to an offline simulation with the fidelity of the model.[26,28]

4.2 Digital twins in pharmaceutical manufacturing

Digital twins have come to the pharmaceutical industry, in large part, with the Industry 4.0 and quality-by-design (QBD) themes, and perhaps the most developed application has been in tablet compression; in this case, a series of process analytical technology (PAT) sensors feeds real-time composition and particle-size data into a virtual model that predicts the quality of the tablets downstream before the batch is finished. Field reviews report that this PAT-related strategy has been shown to decrease the number of out-of-specification batches in manufacturing of small molecule and

biologics, and mention the increasing focus on digital twins that span the entire pharmaceutical lifecycle, from virtual screening of candidate molecules or nanocarrier formulations in the early stages of drug discovery to control of biopharmaceutical bioreactors and, increasingly, in personalized medicine applications where a patient's own data is fed into a virtual model to forecast their potential treatment response.[26,27,29]

Yet, with this progress, the same reviews note that no pharmaceutical manufacturing operation has yet come close to the true digital twin of a continuously updated, bi-direction connected virtual copy; most existing digital twins are more like advanced and data-rich process models that have some real-time feedback. They are commonly referenced in the literature; these barriers include: Integration of data from different legacy instruments and control systems, the computational cost of maintaining model accuracy over time as the process drifts, and the regulatory framework are based on validated static manufacturing processes, which only now must be assessed on how a self-updating virtual model would be qualified and audited.[28,29]

4.3. Production of nanosponge and nanomedicine – extending the concept

In the case of nanomedicine, the digital twin is being suggested as an adjunct to the quality-by-design approach, a digital infrastructure that would parallel molecular simulation tools powered by artificial intelligence and in silico screening of candidate nanoparticle formulations with real-time monitoring and digital twins of the physical nanoparticle synthesis process, thus making nanoparticle synthesis more reproducible and less reliant on labour-intensive trial batches. When applied to nanosponges, this would involve connecting sensors that measure the temperature of the reaction, its stirring rate and the power of the microwaves directly to a virtual model, trained on the same formulation-to-property relationships described in Section 3, so that a formulator could alter the amount of cross-linker during the course of the reaction and immediately see the particle size and yield predicted by the virtual model, without having to wait for the batch to be processed to the end and then characterized off line.[30,31]

It is worth emphasizing, however, that the integration is only conceptually demonstrated, not for nanosponges in particular. While both sides of the picture are well documented in published literature, with machine learning applied to the formulation of nanosponge and digital twins in pharmaceutical manufacturing, the published literature does not yet contain a working and documented digital twin that is based on a production line for an actual nanosponge formulation. There is a good technical argument, taken from neighbouring application areas in biologics and small-molecule manufacturing, for the ability of such an integration; and, early digital-nanomedicine framework papers that list nanosponges as one of the types of nanocarriers that an infrastructure would eventually have to accommodate.[30,31]

5. Where the two technologies Meet?

The usefulness of pairing AI with a digital twin, as opposed to using one or the other, is that they are each a complementary half of the problem. A machine learning model trained with historical data on the formulation, is excellent at suggesting where in a large parameter space, an interesting or promising nanosponge formulation might be located, but it has no idea how to check if the suggestion is correct or not in the current state of a reactor at a particular time. A digital twin provides just that missing feedback loop: It compares the model's prediction with the sensor data from the physical batch in real time and can make the necessary correction: for example, changing the stirring speed or reaction time — before the batch goes "out of specification." In this perspective, the AI model is the twin's predictive model, and the twin is the data flow that ensures that the model's predictions remain grounded on what is happening in reality rather than during the period the model was trained.[27,30]

Current Digital-Twin reviews of pharmaceutical continuous manufacturing are focused on the direction of travel, which is closed loop, and there is no obvious chemical reason why the process of making nanosponge products couldn't follow this path too, as it involves a set of well-defined process variables — temperature, time and stirring or microwave power — that are monitored. The distance is not one of principle but one of engineering and validation work: somebody must develop the sensor integration and put together a sufficiently large database of formulations to train a model that will be accurate, and somebody must convince a regulator that the system, which is a composite of the different sensors, will behave reliably. This section is inevitably predicated on the convergence as it would look, as opposed to a specific case of a convergence that is already working, since nothing of that sort has yet occurred in a published, documented way, for nanosponges.[26,31]

6. Challenges and Limitations

6.1 Scarcity and standardization of data

As with all machine learning models, the quality and quantity of data used for training is essential: nanosponge research has yet to yield the very large, standardized, multi-laboratory datasets that make deep learning truly powerful elsewhere. Characterization methods, reporting conventions and even the type of cross-linkers and polymers the laboratory uses to make its own, are not the same across studies so, no easy pooling of data to create a bigger 'training set'.[22,25]

6.2 Interpretability of models and regulatory trust

Complex machine learning models and neural networks are often criticised for being "black boxes" — predicting an outcome correctly, but without a formulation scientist or regulator being able to easily interrogate the model and confirm the predictions. This is more important for the pharmaceutical industry than for any other industry, as regulators must know why a formulation was accepted or rejected, and not only because a model indicated this. To fill this gap, the development of explainable AI techniques is growing, but it is not yet common practice in the optimization studies on nanocarriers.[24,25]

6.3. Regulatory qualification and validation of digital twins

By definition, a digital twin that constantly evolves with live process data is a moving target and current pharmaceutical validation frameworks were developed around the premise that a manufacturing process remains constant after validation. The tension between continuous model updating and the requirement for a documented, auditable, unchanging process definition is also not fully resolved, and is highlighted as one of the key 'open questions' in general pharmaceutical manufacturing reviews for the adoption of digital twins, and not just for nanomedicine.[26,28]

6.4. Cost, Infrastructure and Scale

Most nanosponge development to date has been done in university labs that are optimizing small batches and are not in the post-Lab 5.0 setting, where the different sensors, the data infrastructure, and the computational modelling skills necessary to build even a partial digital twin are present. If that is to be achieved, it will probably require industry collaborations or shared research facilities to create twins and not academic groups developing twins from the ground up.[27,30]

6.5 Nanotoxicity & translational barriers unrelated to computation

It's important to note that not all barriers to nanosponge translation are computational. While AI and digital twins don't address nanotoxicity, batch-to-batch reproducibility at manufacturing scale and uncertainty in the regulatory landscape regarding novel excipients are ongoing challenges for the broader nanosponge field that don't have to be solved by any means by AI or digital twins, but could be addressed by improved predictive modelling to detect problematic formulations earlier in development and minimize the number of batches that would need to undergo toxicity testing before failing.[11,10]

7. Future Directions

A few trends appear poised to influence the future of the development of AI and digital twins in nanosponge research in the years ahead.[22]

Nanosponge datasets shared and standardized: Community effort similar to materials-genome and nanoinformatics projects could provide machine learning models with the bulk and consistency of data which is now lacking, leading to a more generalizable prediction of properties from formulation.[22,25]

Hybrid mechanistic-machine learning models: Whilst physics-based models of cross-linking chemistry exist, there is potential to reduce training data requirements whilst still maintaining some level of interpretability, as explored in the broader literature of pharmaceutical process-modelling.[7,19]

Assembling pilot scale digital twins of nanosponge manufacturing — the most likely near-term step would not be a digital twin of a patient but a digital twin of a single manufacturing line for nanosponge production that is equipped with sensors measuring temperature, stirring, and yield, a strategy that has already been adopted for continuous tablet manufacture.[27,30]

Explainable AI as a requirement for regulatory acceptance: As regulators gain better understanding of the use of AI in formulation development, a model that makes sense, or can be understood by a human, will likely be preferred over black-box models, especially for any nanosponge product that is intended for parenteral or inhaled use where the safety margins are tighter.[24,25]

The convergence with personalized medicine: Digital twin platforms that are currently under discussion for individualized treatment planning in oncology may, in principle, be applied for nanosponge-based carriers that are tailored to the microenvironment of a given tumour or metabolic profile of a patient; however, this is a significantly more distant prospect than manufacturing applications.[31,20]

8. CONCLUSION

What started out as a curiosity in cyclodextrin chemistry has now become a true platform technology for the delivery and processing of small molecule drugs in the oral, topical, and parenteral spaces, as well as in oncology and environmental cleanup. Both the computational tools being added atop that chemistry, first machine learning for formulation prediction and next digital twins for real-time process monitoring, are proven in other parts of pharmaceutical science and have a viable technical justification for application to nanosponge development in particular. Yet, the honest truth is that this integration is more "promise" than "practice": machine learning has been successfully used to integrate into the general nanocarriers field, and to a lesser extent directly into the field of

nanosponges; digital twins are a reality in the broader context of pharmaceutical manufacturing, but a working, published digital twin of an actual nanosponge production line has yet to be proven. It's not going to be solved through the development of new algorithms, it's going to be solved through less sexy groundwork: larger and more standardized data, sensor-instrumented pilot lines, and a regulatory discussion of how to validate a learning model. As the corners of the surrounding pharmaceutical production have progressed in this direction in the last few years, nanosponge research is poised to do the same as well, though it is a few steps behind.[27,32]

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