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Review

Organ-on-a-Chip for Drug Screening: A Bright Future for Sustainability? A Critical Review

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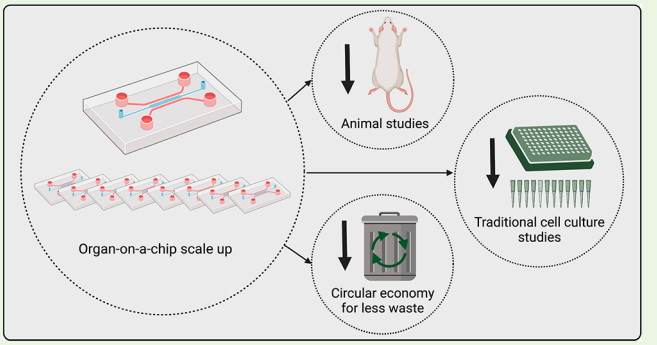
ABSTRACT: Globalization has raised concerns about spreading diseases and emphasized the need for quick and efficient methods for drug screening. Established drug efficacy and toxicity approaches have proven obsolete, with a high failure rate in clinical trials. Organ-on-a-chip has emerged as an essential alternative to outdated techniques, precisely simulating important characteristics of organs and predicting drug pharmacokinetics more ethically and efficiently. Although promising, most organ-on-a-chip devices are still manufactured using principles and materials from the micromachining industry. The abusive use of plastic for traditional drug screening methods and device production should be considered when substituting technologies so that the compensation for the generation of plastic waste can be projected. This critical review outlines recent advances for organ-on-a-chip in the industry and estimates the possibility of scaling up its production. Moreover, it analyzes trends in organ-on-a-chip publications and provides suggestions for a more sustainable future for organ-on-a-chip research and production.



KEYWORDS: *Organ-on-a-chip, drug screening, plastic abuse, sustainability*

INTRODUCTION

Drug screening and testing are highly debated topics in science, as it is critical to keep methods up-to-date to achieve more efficient results. However, the pharmaceutical industry has faced failures in clinical trials due to the poor efficacy of the current methods used for drug screening.[1,2] Although advances have been made in this field, the analytical methods used for drug testing have remained the same since the beginning of the past century.[3]

Animal testing was the first method broadly used, and it brought advances to the medical and pharmaceutical fields despite the ethical issues and poor efficacy and predictability involved.[4,5] It is important to note that *in vivo* experiments include multiple unmanageable variables and conditions, leading to very complex interpretations. With the advent of cell culture, a range of new techniques have started to be explored, bringing the possibility of more ethical and efficient drug testing approaches. One of the most recent advances in cell culture is 3D culture, which provides an environment that more closely resembles the physiology of human tissues through the use of extracellular matrices that allow the growth of multiple layers of cells.[6,7] Despite evidencing incredible advances, 2D and 3D cell culture still fail to predict organ responses to new drugs in clinical trials, are time-consuming, and account for extensive costs. Although 2D cell culture generates large amounts of data with relatively short investments, these results are far from those observed *in vivo* and require computational modeling for drug response evaluation.[7,8] Biomimetic 3D tissue, instead, nearly mimics drug delivery and penetration *in vivo* and has the advantage of allowing observation of cell−cell interaction. However, 3D culture fails to represent a crucial characteristic, the dynamicity of drug delivery, failing to simulate shear and drag forces, which are essential for a more reliable result.[8] Furthermore, the absence of other factors present in biological scenarios, such as the repositioning of nutrients, the gradients of substances, and mechanical stress, distances the individual cell responses from the ones obtained in organs.

With the advancement of new technologies and capabilities, organ-on-a-chip (OoC) has become an essential target of recent developments. These devices may accurately mimic the

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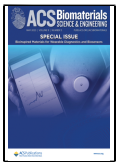

features of organs by the inoculation of cell lines and continuous perfusion of nutrients. As a result, these devices can now access cell−cell interactions, physiological microenvironments, tissue communication, and vascular infusion in ways that no previous technology could.[9,10] As a result, these devices may be used to predict organ behavior and even pharmacokinetics in a more ethical and efficient manner.[11]

Organs-on-chips are being extensively developed today to address industry needs, and a variety of new materials and methods are being introduced to this technology. Still, most devices are manufactured using the same old-fashioned plastics used by the micromachine industry. An alternative that might become popular in the field of OoCs is biodegradable materials, as long as they provide the expected features for this purpose, such as biocompatibility, transparency, and moldability, among others. Moreover, a range of methods have already been established to fabricate durable and efficient devices, although it is not common to find references that suggest the possible reuse of such devices.[12,13]

Despite considerable efforts to make OoC devices the future of pharmaceutical research, as scientists in the twenty-first century, we must take sustainability into account and assess whether or not this technology may be harmful or advantageous to the environment. In this situation, it is important to examine an array of aspects, such as the usage of chemicals, costs, the quantity and type of materials employed, their biodegradability, and production processes.[14,15] In addition, the disposability of devices is a reality that is already changing with a few efforts to create reusable chips.[16] This critical review recapitulates the advances in organ-on-a-chip and discusses whether this technology can replace current in-use techniques for drug development in a more sustainable way. Furthermore, it stipulates cost-effective relationships, exploring possibilities for a practical and ecofriendly future for the pharmaceutical industry.

IN VITRO MODELING PROGRESSION

Animal testing has long been a standard for drug development and disease behavior studies. This method can give insights into body functions and physiological processes by using animals to predict the behavior of humans.[17] However, this approach is in constant conflict with bioethical values and has proven to be incompatible with the behavior observed in human candidates in many cases, in addition to the low throughput observed.[2,18] In fact, neither efficacy nor toxicity are well predicted in animal models, as evidenced by the 80% failure rate of new drugs during clinical trials due to enormous differences between organisms.[19] The search for new methods of exploring drug development and disease modeling became necessary. Therefore, *in vitro* assays became a reality with the constant enhancement of 2D culture.

Conventional 2D culture is well established and standardized for drug screening. These systems are generally made of rigid, transparent plastic or glass material, and the methodologies involved in this technique are adaptable, comparable, and reproducible. Cells in 2D assays are easily accessed for analysis, and their manipulation is simple, making this method very popular among drug/disease researchers.[20] The cost involved in the research for new drug candidates is very obscure, and the data are hidden from public access. However, a study[14] estimates that the current investment for *in vitro*/*in vivo* screening ranges from US$660 to US$2,760 million per new drug. This cost is a rough estimate since the actual values are unknown, and it is used as a base for estimating the impact of organ-on-a-chip in the industry. In addition, the previous estimated cost involved all phases of testing, research, personnel, and material consumption for launching a new drug candidate. However, it does not consider the cost effectiveness and the waste generated by the traditional screening methods.[14]

Research laboratories worldwide are estimated to generate 5.5 million tons of plastic waste, raising an environmental concern considering that the materials used for *in vitro* testing are primarily disposable.[21,22] In addition, 2D traditional culture assays are established as high reagent consumers, making them environmentally and financially not the best option for medical and pharmaceutical applications.[23] Therefore, considering the lack of efficacy in 2D *in vitro* testing, the limited scope, and the extensive waste generated by this approach, the upcoming drug screening methods must evolve in all these senses.

3D cell culture and organs-on-a-chip have begun to be explored in the past decades. With the popularization of extracellular matrix (ECM) gel for cell culture and the exploration of the micromachining field for biomedical applications, organ-on-a-chip technology became an important field of study.[11] The possibility of combining multiple types of cells in the same device and creating an environment that more closely resembles human tissues is desirable for studying new drugs and pathologies. Although 3D cell modeling has been used for this matter and has shown significant advances, this technique presents drawbacks, such as low reproducibility, sampling obstacles, and lack of comparative human functions.[11,24,25]

Organs-on-chips (OoCs) instead attempt to overcome almost all the restrictions offered by the latter techniques. Inspired by the semiconductor and micromachining industries, OoCs are generally made of plastic polymers, such as poly(dimethyl siloxane) (PDMS), polyester, or glass, using microscale mold techniques for their fabrication.[11] Due to their architecture, OoCs allow for a more specific microenvironment, being more comparable to the physiological state of a human tissue. Characteristics such as flow rate, fluid exchange, and mechanical and electrical stimuli make OoCs the most acceptable option for substituting the former drug screening approaches. In addition, it is possible to directly measure analytical responses by coupling microsensors into those devices.[26−28] OoCs are recognized by their reduced size; generally, channels are in the micro- to millimeter scale, lowering the consumption of reagents and culture media to nano- and picoliters. This characteristic is essential to reducing costs and the waste generated by studies involving new drug candidates. The use of culture media, expensive cell reagents, and toxic solvents is considerably reduced with OoC since the volumes in this approach are much lower.[29] Additionally, OoC technology is estimated to reduce 10−26% of R&D costs per new drug, which is equivalent to US$169 to US$706 million.[14]

On the other hand, OoCs have limitations like any other technique, for example, because of the complexity of those systems, the biological output, and compatibility with analytical instruments. Furthermore, the materials widely used in OoC manufacturing are still disposable plastic, and this technology is still dependent on traditional 2D and 3D cell culture for the generation and expansion of cells.[13] Regarding this dependency, a realistic scenario for generating less plastic waste would be substituting disposable and long-lasting materials, for recyclable and biodegradable ones instead.

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Also, it is expected that the use of OoC reduces the use of traditional cell culture screening methods in the overall scenario. Finally, as a new science with great perspectives for replacing the current methods for drug screening, it would be favorable to reconsider the material disposability of OoC and traditional cell culture in the early stages and evaluate not only the possibility but also the fostering of biodegradable components in OoC and cell culture materials production.

OoC FABRICATION AND ITS IMPACT

As discussed in previous sections, the mass manufacture and use of disposable OoCs may result in future environmental problems, with the primary causes being (1) the materials utilized in their fabrication and (2) the fabrication techniques used. Next, we will review each topic in detail, comparing the potential environmental damage caused by mass-producing OoCs with the methods currently applied in cell culture.

MATERIALS FOR OoC FABRICATION

The literature on OoCs reports a wide variety of organs or structures, including, among others, lung-,[30−32] gut-,[33,34] liver-,[35,36] brain-,[37,38] heart-,[39,40] and kidney-on-a-chip.[41,42] Each OoC presents key characteristics to achieve high fidelity of *in vivo* biological behavior, which presents unique challenges for its production. In such a scenario, one of the main points of a good design for an OoC is the choice of the right materials. Lung-on-a-chip devices, for example, may require mimicking the expansion and contraction of the lungs, while a heart-on-a-chip might require mimicking heartbeats. In such cases, robust, flexible, and stretchable materials are ideally required, with poly(dimethyl siloxane) (PDMS) being a frequent choice. In its turn, the presence of an exchange barrier (i.e., the blood−brain barrier, air/blood in the lungs, the blood−excretion route in the kidneys, etc.) is commonly simulated by porous membranes with different cell cultures on both sides of the membrane. The membranes are usually composed of polymers such as poly(ethylene terephthalate) (PET),[43] poly(carbonate) (PC),[44] poly(ester),[45,46] or PDMS[30,47] and have pore sizes in the micrometer range. When the design of the OoC does not require moving structures, rigid chips are a great option, as their manufacturing can be more straightforward. These are based on glass and thermoplastics such as poly(methyl methacrylate) (PMMA, acrylic). Lastly, synthetic or natural hydrogels are an excellent choice when the OoCs involve the interface between cells and the extracellular matrix. They consist of a three-dimensional network of polymer chains that can hold significant amounts of water.[48] As solutes can diffuse across the aqueous solution within the fibers,[49] hydrogels are highly suitable for reproducing the extracellular matrix while maintaining the mechanical support required by cell cultures.

Following that, we will cover the main characteristics of the three most applied materials in OoC manufacturing (PDMS, glass, and thermoplastics) and their possible impact on the environment when mass-producing microchips.

PDMS. PDMS presents a range of other desirable characteristics for producing OoC devices in addition to being flexible and stretchable, including being transparent, being easily cast into different shapes, providing tight sealing to glass or other PDMS pieces, being relatively low-cost ($0.30/g),[50,51] being gas-permeable, and being biocompatible. It also has some critical downsides, including its hydrophobicity, absorbability, and fluorescence, which can hamper optical measurements.[52] Currently, the recycling of silicon elastomers is highly challenging, and researchers have been studying new cross-linking strategies to allow this process to be performed.[53] Furthermore, although there is evidence that liquid PDMS is rapidly degraded (in a few months) in certain environmental conditions, solid PDMS is known for its stability over a wide range of temperatures and for resisting UV and O_3 exposure, essential characteristics for efficient sterilization of OoC devices.[54,55] Solid PDMS is non-biodegradable, and data shows that silicon-based pieces can take up to 500 years to degrade,[56] making them a potential environmental hazard. Finally, PDMS-based OoCs can be autoclaved, increasing the reusability potential of OoCs based on them. However, because the polymer may absorb molecules into its structure, the use of devices might be limited to specific applications.

Glass. Glass, in its turn, is hydrophilic, biocompatible, transparent, low cost ($ 0.017/g),[57] resistant to mechanical stress and temperature fluctuations, and highly inert, making it ideal for building OoCs for tests of absorption rates.[52] The material, however, is inflexible and requires more time-consuming fabrication techniques compared to commonly applied polymers. It is estimated that the production of glass-based OoCs can be up to 10 times more expensive than PDMS.[58] Furthermore, it is gas impermeable, which can cause problems with bubble trapping but can also be helpful for studies under anaerobic conditions.[52] Although glass is one of the longest-lasting manufactured materials, taking up to 1 million years to degrade, it is easily recyclable.[59,60] Furthermore, glass can be autoclaved and is highly inert, increasing the potential to develop reusable OoC devices. It should be noted that glass−glass bonding requires chemical procedures to be performed at high temperatures, the use of corrosive acids,[61] or the use of adhesives, possibly hampering recycling processes.

Thermoplastics. Thermoplastic-based chips can be easily mass-produced, have low costs ($0.015/g for clear acrylic),[62] and are biocompatible but also are inflexible, may present autofluorescence, have poor gas permeability, and are not always transparent, hampering the visibility of cells under microscopes. Furthermore, these devices are inadequate for performing studies at high temperatures, as these materials present relatively low melting points (160 °C for acrylic, for example).[52] Regarding environmental aspects, thermoplastics are commonly durable and non-biodegradable.[63] Although this material is known to be inert, reusing thermoplastic-based OoCs must proceed with caution, as these are incompatible with using many solvents or autoclaves for sterilization.

It is safe to say that the majority of OoCs currently produced rely on the critical characteristics of PDMS or thermoplastics, making the construction of devices with materials that are biodegradable or easily recyclable an excellent challenge for researchers. Using glass to fabricate microchips makes recycling easier but hampers mass production. On the other hand, OoCs partially composed of biodegradable materials have been described in the literature,[64] but to the best of our knowledge, few fully biodegradable chips have been produced to date.[65] Recently, poly(lactic acid) (PLA) has been suggested as a sustainable material for the production of OoCs, as it is derived from renewable organic sources (i.e., corn starch or sugar cane) and is compatible with mass production techniques such as injection molding.[65] The polymer is biodegradable, biocompatible, transparent, and inert and presents low autofluorescence, making it a promising material

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for the production of OoCs.[65,66] When hydrolytically degraded, PLA is converted back to its monomer (lactic acid) or carbon dioxide and water, an ecofriendly material.[66,67] The typical half-life of the polymer is 30 weeks, which might be adjusted as needed but can be a problem if extremely long experiments are required.[66]

A different aspect directly involved in the environmental impact is the reusability of devices. As discussed in previous sections, the great majority of publications related to OoCs rely on single use devices. Producing a reusable chip might be challenging, as the device must be suitable for multiple sterilization cycles, be highly inert, and allow extensive cleaning. However, research on reusable chips has been recently reported. Sakolish et al.[65] have produced a reusable microfluidic model of the human proximal tubule and glomerulus, while Sun et al.[66] have developed a reusable, standardized universal interface module for OoC applications.

The discussion of the environmental impact of mass-producing OoCs for cell culture assays is not complete if we do not consider the impact that current techniques possess in this field. In traditional assays, cells are cultured in flasks, and tests are carried out on well plates. OoC devices still require cells to be cultured in flasks, mainly replacing well plates for the tests. Microplates are commonly composed of poly(styrene), poly(propylene), poly(carbonate), or glass, and it is estimated that approximately 63 g of plastic is used to produce a 96-well plate.[69] As a means of comparison, a two-layer 3 × 4 cm^2 OoC produced with PMMA (3 mm thickness) uses around 8.5 g of the polymer. If we consider that each microchip will be used for a single test, about 815 g of PMMA would be required to perform 96 tests, an increase of almost 13 times the amount of material compared to the traditional 96-well plate. It is essential to note that, depending on the protocols and the cell lines cultivated on the chip, multiple tests can be performed in a single device, but these numbers are commonly limited to low values. Therefore, significant waste is expected if the same tests are performed using OoCs. Last, typical 96-well culture plates cost approximately $4.88 per unit ($0.05 per test).[14] Commercial OoC kits, in turn, range from $75 to over $1300.[43,70] The price of lab-made devices varies with the materials and techniques used but is estimated to be around $5 for a typical PDMS-based chip.[71] It is important to note, however, that a reduction of 10−26% in costs in research and development is expected with the use of OoCs due to their increased efficiency in predicting human body behavior, as we mentioned above.[72]

FABRICATION METHODS FOR OoCs

Similar to the materials used in the fabrication of OoCs, the techniques chosen to build each chip depend on its required features. The most common approach to fabricating PDMS-based devices is to construct a mold using photolithography and produce OoCs through soft lithography. Glass-based OoCs, in turn, are usually produced by wet etching, laser scribing, or photolithography.[73,74] Last, thermoplastic-based devices can be quickly produced through photolithography followed by hot embossing or injection molding.[52] It is interesting to notice that the production of OoCs using such approaches usually generates chemical residues. Photolithography, for example, uses solvents in many stages, including development and lift-off. Solvents are usually produced by distillation and are energy-demanding, with separations accounting for 10−15% of worldwide energy use.[70] Therefore, scaling up the use of solvents could bring direct environmental harm not only due to their disposal but also due to their production methods. In such a scenario, the recovery and reuse of solvents in these production techniques are critical aspects of the sustainability of the chemical industry.[71] It is important to note that traditional microplates are mass produced by injection molding, allowing many plates to be produced in a single metallic mold, not generating a significant amount of chemical residues. However, the energy consumption for processing the polymers is still a concern and is currently estimated to be around 3 kWh/kg.[72]

MODIFICATION OF OoC PLATFORMS

OoC platforms can be modified with different surface treatments or materials to provide additional features or desired characteristics. For example, oxygen plasma has been commonly used to temporarily provide hydrophilic properties to PDMS due to the introduction of polar functional groups (mainly SiOH) and for providing strong bonding.[75] Polydopamine (PDA) coatings, on the other hand, are a simple and versatile option for providing a biocompatible surface with improved cell adhesion and proliferation properties. The sterilization of devices using heating, UV, or chemicals might influence the properties of the treated surfaces. For example, a study by Davidsen and colleagues showed increased hydrophobicity of PDA coatings after thermal treatment (121 °C, 24 h), which was accompanied by increased cell proliferation. The coating has shown a greater amount of superficial quinone groups and a decrease in the number of primary amine groups.[76] Therefore, successive sterilization cycles might influence the functioning of the device, with the adequate strategy being defined by studying the device composition and end use. The effect of these common surface modifications should also be carefully studied in new and unconventional materials, ensuring higher versatility and tunability in the developed OoCs.

Structures can also be added to the chips to provide additional features. For example, electrodes can be added to or built into the OoC platforms to serve as the basis for sensors or biosensors.[77,78] Commonly, electrodes are composed of Au, Pt, Ag, or different forms of carbon and can be added to the microfluidic platforms through photolithography, for example.[79] These electrodes might be modified with chemicals (i.e., polymers, nanomaterials) or biomolecules (i.e., antibodies, aptamers, enzymes, etc.) in order to precisely and adequately detect the desired targets.[80,81] Especially if biomolecules are used, adequate sterilization of the OoCs becomes extremely challenging. In this scenario, measurement systems that can be decoupled for sterilization (for example, no-contact optical-based measurements and capacitively coupled contactless conductivity detection (C^4D)) might be interesting options. This increases the complexity of the process and, depending on the technique and materials used, might make sterilization unfeasible.

OoC FOR PHARMACEUTICS

Implementing OoC in research and development of new pharmaceutical drugs can increase efficacy, reduce costs, and substitute for animal research.[14] However, implementing new technologies is challenging, burdened by regulatory concerns and mismatches in priorities among developers in scientific contexts. Furthermore, the demands of the industry for

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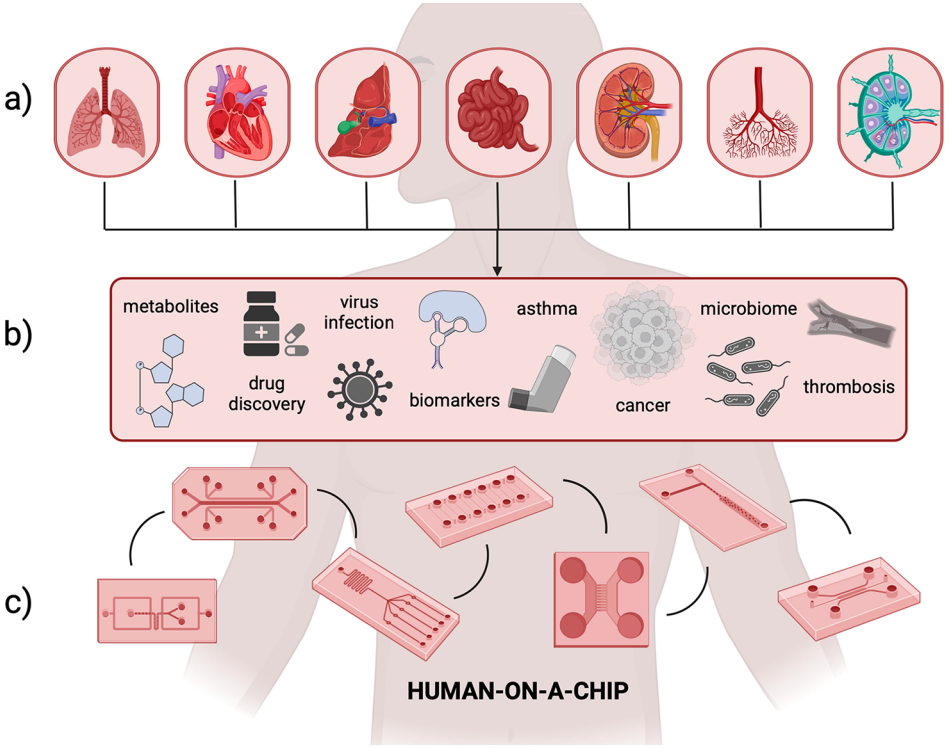

Figure 1. Main organs on chips, their application in the pharmaceutical industry, and their connection to creating a human-on-a-chip. (A) The main organs applied to OoC implementation, in order: lung, heart, liver, intestine, kidney, blood vessel, and lymph node. (B) Most typical applications of OoC for the pharmaceutical industry. (C) Multiple OoC designs representing different organs connected, leading to the development of a Human-on-a-chip or a Body-on-a-chip. Made with Biorender.com.

manufacturability, compatibility, and robustness are other factors to be considered.[82,83] Understanding the complexity involved in this subject, funding agencies have made efforts to facilitate the implementation of OoC. Some examples are the Tissue Chip Program, launched in the US in 2012, and ORCHID in Europe from 2017 to 2019. Such programs were created to promote collaboration between OoC-developing researchers and startups, the pharmaceutical industry, and regulatory agencies to develop products to solve specific market problems. Specific activities of the Tissue Chip Program included investigating stem cells as potential sources to populate OoCs and enabling the study of biological systems in space.[84,85] ORCHID activities included investing in OoC technology platforms (including high-throughput data analysis) and multiple organ models.[85] These efforts have started to yield results in government policies recently. In December 2022, the Food and Drug Administration (FDA) determined that animal testing would no longer be required for the approval of new drugs.[86] This decision was taken after the agency committed a 5-million-dollar budget to explore alternative testing methods earlier that year.[87]

Although there are intense efforts to make OoC progress, there are also limitations. Probst et al. identified three main challenges for OoC technology to meet industry benchmarks for high-throughput screening. Among them are material limitations in fabrication and scale-up, which can only be overcome through a significant increase in cost; the lack of integration with online analytics and sensors, which are currently limited to only a few parameters; and the low-throughput of essential processes, such as perfusion, sampling, and cell injection, since sterility and stress control are crucial for cell culture.[84]

However, since the mid-2000s, a few companies have commercialized OoC platforms and managed to implement OoC technology in the pharmaceutical industry.[85] Their primary applications are identifying and validating new targets, drug discovery, pharmacokinetics and dynamics, preclinical safety, and clinical development.[82] Also, the most widely investigated single organ models are the liver, heart, lung, intestine/gut, kidney, and blood vessel.[88] Among the noteworthy multicellular platforms are OrganoPlates from Mimetas, which present microfluidic tridimensional cell cultures in a pump-free perfusion system; and HUMIMIC from TissUse, a multiorgan platform with an on-chip micropump. Both allow increased throughput and multiple applications, which are currently implemented by companies such as Roche, Bayer, and AstraZeneca, among others.[88]

MAIN ORGAN CHIPS AND THEIR PHARMACEUTICAL RELEVANCE

Liver. The liver is the central organ for drug and toxin metabolism. OoCs that reproduce the bile duct,[89] hepatic lobules,[90] and hepatic sinusoids[91] were developed for metabolite formation,[92] drug toxicity assessment,[93] virus infection,[94] and alcohol studies.[9,16,95] Recent advances include using 3D cell culture for multiparameter and high-content analysis in future works.[9,16]

Heart. Heart disease is the leading cause of human mortality.[16] It is recognized that the contractility of cardiomyocytes is closely related to various factors, including flow rate, calcium concentration, substrate, and electrical stimulation,[9] all of which can be closely controlled using OoC. Recent advances include improving substrates,[96] monitoring important biomarkers,[97] and studying cell contraction.[9,98]

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Lung. The primary role of the lungs is to transfer oxygen to the blood. Currently, most lung chips focus on the effects of mechanical airway pressure, shear forces, and the blood−air barrier[16,68] using a two-channel chip with mechanical motion.[30] Recent advances include improved gas exchange for oxygenators,[99] simulation of the lung microenvironment for cancer,[100] and assessment of asthma treatment assessments.[101]

Intestine. Essential for digestion and absorption of nutrients, intestinal chips are built in a two-hollow microchannel, including a substrate for the intestine and blood cells to interact with each other and an airstream for peristaltic-like stimuli.[102,103] Recent advances include the culture of biopsy-derived cells closely resembling small intestine characteristics[103] for drug development and studies featuring the intestine microbiome[102] and its morphology.[104]

Kidney. Important for toxicity studies, kidney chips are composed of two layers: with a medium pool on the base and a porous membrane with cell culture and continuous medium perfusion on top.[105] The latest advances include simulation of responses often observed in humans under viral infection and prediction of host−parasite mechanisms.[105,106] Several devices have been developed to assess drug transport and nephrotoxicity.[46,65,107]

Blood Vessel. Necessary for mass and nutrient transfer among organs, vessel chips are challenging and diverse because of their complexity. They are used mainly to evaluate vascular diseases such as atherosclerosis, thrombosis, inflammations, and tumor metastasis.[108−110] Recent advances include the use of 3D cell culture to study angiogenesis, cell interactions,[9,111] inflammatory responses,[112] and tumor adhesion and migration.[113,114] Figure 1 shows the mentioned OoCs and their main functionalities.

Lymph Node. Responsible for initiating the immune response and key to determining the immunotoxicity of new drugs,[115] lymph node OoCs are often multicompartmental to mimic the complex, specialized architecture of this organ.[116,117] They enable the investigation of tumor−immune interactions, T cell−dendritic cell interactions, immunological quantifications, and real-time imaging of cell movement.[116,118−120]

PERSPECTIVES FOR INDUSTRY SCALE

A microdevice such as an OoC is likely to have a low environmental impact compared to mass production. For this reason, it is vital to predict the likelihood of OoC scaling up and the substitution of the traditional methods currently used for drug development. In this topic, we will discuss the numbers of the current OoC market and predict the future scaling up of this technology, considering environmental aspects.

Invariably, new technologies and innovations follow new business opportunities. OoC can decrease the productivity gap in the entire pharmaceutical sector, saving time, effort, and money for the research and development of new drug candidates (R&D).[121] Therefore, the market for this technology has significant business potential.[122] An initial perspective of this potential is determined from the perspective of R&D savings in pharmaceutical companies, which can reach 10 to 26% of the entire R&D costs within 5 years.[14,123] Considering R&D spending ranging around 83 billion dollars,[124,125] the saving potential of OoC is certainly multimillion scale,[122] with surveys estimating the market size of US$350 million up to 2030.[126]

Regardless of the potential for OoC, the pharmaceutical industry hesitates to adopt this technology as a standard. This hesitation is most likely due to the need for an initial investment in a standardized and highly reliable OoC production system,[14,127] which is crucial to provide the necessary reproducibility and accuracy for drug discovery and development. As a nonstandardized new technology, OoC platforms still need to accurately predict every new drug's *in vivo* behavior, yet recent research and OoC industry efforts are in development to cross this barrier.[128] Ewart and Roth[123] stated that OoC developers and the end-users must cooperate to achieve good acceptance in pharmaceutical companies. This acceptance would allow for a faster proof of concept, adapting and substituting the traditional tests. Therefore, new companies and start-ups are rising to fill gaps in OoC technology, mainly by standardizing several aspects of the chips. This includes research involving substrates, cells, device materials and protocols, interfaces with analytical instruments, and assay protocols.[128,129]

Currently, the leaders in the OoC market are still relatively small companies, such as Emulate (USA), Mimetas (NL), Hesperos (USA), Aim Biotech (SG), AxoSim (USA), InSphero (CH), Nortis (USA), Micronit (NL), BEOnChip (ES), Mesobiotech (FR), and TissUse GmbH (DE).[126,128−132] The fabricants compete for OoC implementation and the development of high-throughput systems and work closely with major pharmaceutical companies to develop targeted solutions.[129] Emulate, for example, has Roche, Takeda Pharmaceuticals, Merck, and Janssen as partners,[133−135] while TissUse develops OoC for AstraZeneca and Roche.[129,136,137]

As the OoC business is still in the early stages of development and does not present much data, we may look at similar consolidated technology markets, such as those for microfluidics, to get a broad idea. Although microfluidics involves a larger market than OoC, both are considered similar in the manufacturing methods and aggregated value of the devices.[11,138,139] Except for companies operating in different branches, such as Thermo Fischer Scientific, Danaher Corporation, and Illumina, Fluidigm Corporation is the foremost company in the microfluidics business, with a revenue of US$130.8 million.[140] Emulate is the second, currently presenting a revenue of US$1.92 million revenue,[141] only a tiny fraction, although the investments in this company are among the highest in the field.[133,141] On the other hand, the OoC business is still expanding, with total venture funding of US$224.3 million, according to CrunchBase.[133] Extrapolating the potential profit for this business (US$350 million in 2030),[126] it is possible to assume that the market for OoC is in its embryonic stage, with its current production representing a small portion of its future scale.

It is only a matter of time before OoC devices become massive, which leads us to think about the environmental impact they may cause. There are several OoC producers; however, the materials and techniques employed for fabrication are mostly the same for all, mainly due to the cost-effectiveness of those protocols.[133] Considering that 858,000 OoC units are expected to be produced in 2022,[129] and an estimate of 8.5 g of PMMA used per device, it is expected that approximately 7.3 tons of waste will be generated by the OoC industry in 2022. However, as the market for OoC grows, the number of devices produced will also increase, intensifying waste production. To account for this waste generation caused by the OoC market, the market size can be

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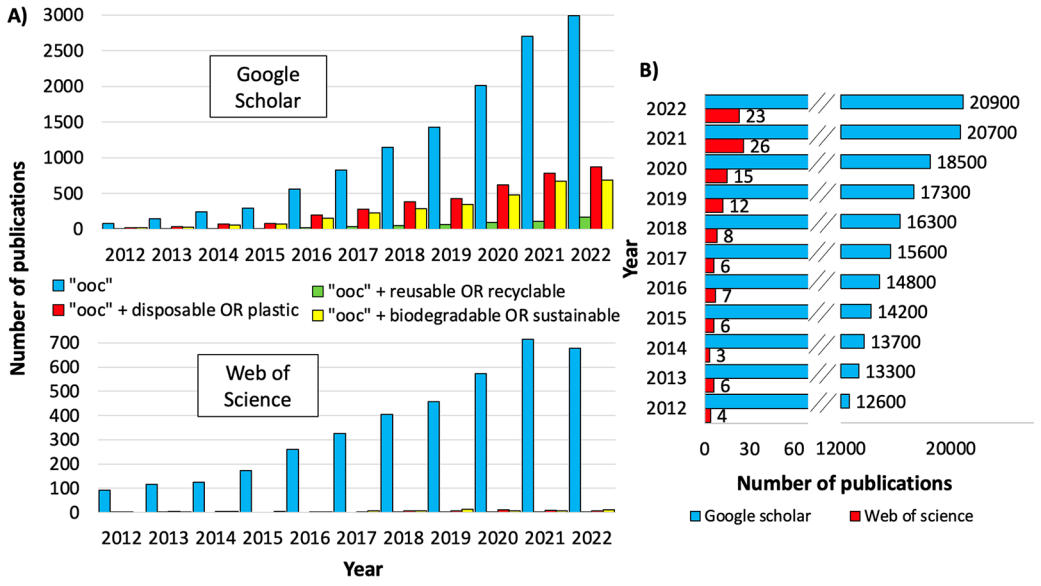

Figure 2. (A) Yearly evolution in number of publications in OoC research, with the bar charts representing the trends in organ-on-a-chip publications for the last ten years in two databases, Google Scholar and Web of Science. The colors indicate the terms used for each additional research for both databases. (B) Database search for "Cell culture and plastic waste", showing the bar chart with the tendency in publications in both databases over 10 years.

correlated with the number of OoC manufactured, which is used to calculate the total plastic waste. Considering the market size projections for 2022 and 2030 of US$117[129] and US$350.8 million,[126] respectively, we can project the number of OoC to be produced in 2030 at about 2.575 million devices, equivalent to approximately 21.9 tons of PMMA waste, roughly three times the amount projected for 2022. For comparison purposes, in 2017, it was estimated that 348 million tons of plastic had been produced,[142] of which 6 million tons were generated by research laboratories worldwide.[21,22] From these 6 million tons, we can estimate 1.3 million tons of plastic waste being generated specifically from biochemistry, genetics, and molecular biology laboratories worldwide, according to the number of programs and institutes in those fields around the world.[21,22,143] It is important to point out that the specific amount of plastic waste generated by cell culture laboratories is not explored by the literature, indicating a lack of interest in the impact that this could cause.

Finally, by the previous projections, OoC plastic waste currently represents a small portion of total laboratory waste, even when considering the waste generated specifically from biotech laboratories. Considering the high potential of OoC to substitute several experiments of the currently used methodologies and the ability to reduce costs, energy, time, and resources in drug development, we estimate a lower environmental impact than the in-use techniques. For example, we anticipate the use of fewer well plates, cell culture flasks, and Petri dishes for specific experiments once OoC devices can sometimes substitute for an entire well plate. This, of course, requires more in deep analysis since OoC is still being improved to provide efficient and reliable results. Moreover, the predictions for waste generation from OoC devices in the future are still lower than those for plastic residue produced today by biotech research laboratories. However, maintaining the current numbers of plastic waste production should not be the ultimate goal, but rather the mass reduction of waste and the replacement of primitive habits. For such purposes, we envision the use of biodegradable and/or reusable materials for the development of OoCs, in parallel with the implementation of a circular economy model for OoCs and cell culture materials. Noteworthy, the proper savings from the OoC impact on drug discovery could be used to research greener materials and protocols for OoC devices, cell culture flasks, and reagents.

IS OoC A SUSTAINABLE OPTION?

The OoC is already a reality in scientific laboratories, and scaling it for industrial purposes is becoming tangible. Cost-effectiveness research had already proven a 25% improvement in effectiveness and a US$700 million reduction in costs.[14] Also, OoC systems drastically reduce reagent consumption, which is significantly better for the environment and reduces costs.

The fabrication of OoCs is inspired by concepts of the micromachining industry, which is based on plastic and non-biodegradable materials.[52] Current efforts in OoC research are focused on enhancing reproducibility and human similarity and expanding the use of OoCs for a whole range of possibilities in the medical, pharmaceutical, and chemical industries.[52] It is poorly reported in the literature, though, on efforts to substitute plastic materials in the OoC fabrication process and in traditional cell culture. In addition, research on reusable, sterilizable materials for cell culture and microchips is scarce.

To elucidate this scenario, we have collected data from two search databases, Google Scholar and Web of Science. The research was based on two factors: reusable/disposable OoC and the use of biodegradable/sustainable materials in OoC fabrication. Data from 10 years (2012−2022) was collected and compared in the graphs shown in Figure 2A. For the evaluation, the terms used for the search were "organ on chip", "organ on chip + reusable OR recyclable," "organ on chip + disposable OR plastic", and "organ on chip + biodegradable OR sustainable." The results were organized and compared in two bar charts, one for each database platform. In addition, we have made a search on the trending publications based on the plastic waste generated by traditional cell culture, finding an

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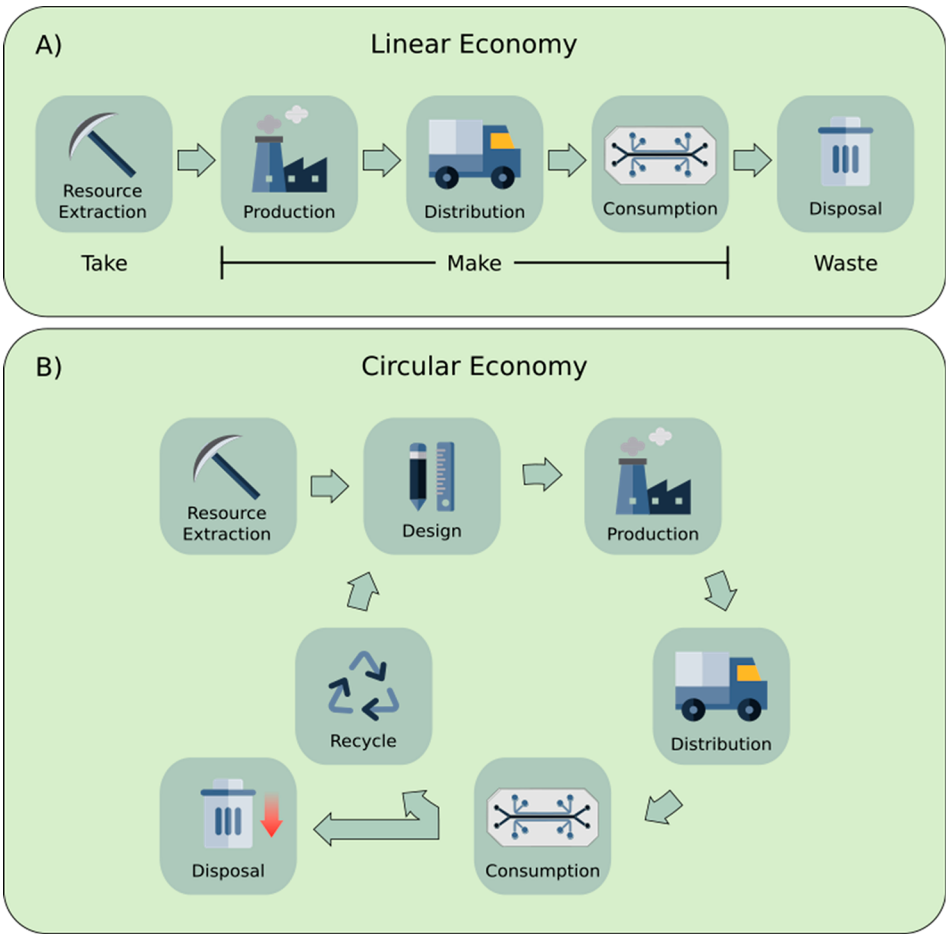

Figure 3. Different economic models for Organ-on-a-chip technology and cell culture. (A) Linear economy model, indicating the steps from extracting materials for manufacturing OoCs to the disposal following a finite process. (B) Circular economy model from resource extraction to the recycling process, with a possibility for reuse or recycling. In this model, the waste generated is considerably lower.

increasing concern on the topic over the years. For the search, we have used "Cell culture + plastic waste" as the input, and the bar chart with the number of publications over the years for the two databases is displayed in Figure 2B.

The search results showed an increasing tendency in OoC research over the years for both platforms until 2022, and even though the amount of reusable and biodegradable OoC research is low compared to the overall number, they are all increasing over time. For Google Scholar, it is possible to notice a higher accumulated number of publications with disposable OoC (3796) compared to reusable OoC (581) and biodegradable OoC (3089) over ten years. For Web of Science, instead, the accumulated number of publications with biodegradable OOC (63) is greater than that with disposable OoC (55) and reusable OoC (11). It is worth mentioning that not all disposable OoCs are referenced as such in publications because of the adverse claims anchored to them. However, nearly all publications involving reusable and biodegradable OoC use these terms as a substantial appeal. Publications involving reusable OoC are remarkably low compared to the other searches, indicating that this approach might include implementation obstacles and may even generate a lack of interest. The implementation of reusable OoCs can be challenging because of the whole process of fabrication and sterilization. As mentioned in this review, developing an OoC involves a diligent procedure, including stages that require glues and tapes, making a second use very problematic and sometimes impracticable. In addition, the sterility of the OoC is a crucial factor; eventually, this can be an obstacle to reusing the chip, which is later discussed in more depth in this review. Evaluating the number of publications involving the term "Biodegradable OoC", we see a considerably higher number compared to reusable chips over the years. This trend is probably due to the increasing interest in working with biodegradable materials such as PLA and the consequent financial impact caused by the use of such materials, as mentioned above. Finally, it is also possible to observe in both database searches an increasing number of papers involving cell culture and plastic waste, showing the growing concern for this topic. Despite the rise and scale of OoCs, their reliance on traditional cell culture for cell generation and expansion is unavoidable. Thus, it is important to highlight the role of plastic in traditional cell culture and the possibilities to overcome the continuous generation of plastic waste with effective solutions.

Considering the evaluated number of publications and what this review covers, it is possible to infer that OoC is undeniably becoming a recognized technology and soon will be scaled to large productions. However, new technologies must take into account their environmental impact to be successfully established. Financially, OoC has proven beneficial,[14] and considering reagent consumption and the waste generated by such, OoC is considered an enormous advance.[144] However, the materials broadly used in its fabrication are the same old-

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fashioned, poorly recyclable plastic from the biochemistry industry. We can observe from the graphs in Figure 2 that there is interest in exploring biodegradable materials for the fabrication of OoC, although this subject needs more attention in order to prosper. Upon evaluating the graphs, we can see that biodegradable materials are the best option for more sustainable OoC production. Therefore, if those materials are not neglected, it is possible to build innovative and green technology to replace and enhance in-use methods. Moreover, those solutions must include traditional cell culture, given that OoC is remarkably dependent on it.

Finally, according to our research, not much is explored about reusable OoC, and considering all the fabrication processes, this is a much more complex system. However, reusable and recyclable prototypes are the most desirable when implementing ecofriendly technologies. Therefore, considering the principles of a circular economy,[145] we propose a greener point of view for the fabrication and scaling up of OoC, also considering possibilities for a more ecofriendly cell culture course of action.

CIRCULAR ECONOMY APPLIED TO OoC AND CELL CULTURE

Currently, most industrial and economic processes are based on a linear model, which takes finite resources from natural sources, transforms them into products, and eventually returns them to nature as a pollutant, considerably harming the environment (Figure 3A).[145] The economy is also not benefitted by the linear model because most finite extracted resources do not reach their maximum use.[145,146] Cell culture laboratories apply this linear model to perform biological assays using sterile plastic materials. These are not sterilizable under safe conditions, so they are discarded after a single use. In addition, the research prospect presented earlier in this work also demonstrates that most OoC devices reported in the literature are disposable, a few works have introduced the use of biodegradable materials, and only a tiny portion includes reusable devices.

Furthermore, to discuss human activities that impact the environment, it is imperative to mention the United Nations Conference on the Environment (Stockholm), in which the term sustainable development was first coined.[147−149] The term refers to a change in lifestyle carried out in a way that conserves the resources of the terrestrial ecosystem by applying the 3R (Recycle, Reuse and Reduce) premise.[150] Sustainability has broad and flexible objectives related to using resources to benefit the economic, social, and environmental sectors in a balanced way.[151]

The circular economy, instead, has a different environmental model and a new perspective on resource use and is becoming an attractive business model, since it mainly aims to benefit companies and/or economic government systems while reducing its environmental impact.[150,151] The most accepted concept of a circular economy was formulated by the Ellen MacArthur Foundation: "a circular economy is an industrial system that is restorative or regenerative by intention and design".[137] The circular economy suggests that, within a business model, energy and materials must be reused efficiently, achieving a green chain. It is possible to implement this idea by idealizing a durable and reusable project that minimizes the input and waste of resources/energy by slowing production, diminishing steps within production, and designating the final waste.[150−152] In this system, resource use must be optimized in a closed cycle, in which the waste must be destined for reuse or at least for reuse steps such as disassembly and recycling processes (Figure 3B).[151]

Therefore, applying the sustainability model and the circular economy not only to OoC production but also to traditional cell culture models may be a viable solution to minimize the environmental impact that this new technology might cause in the future of drug development. The number of technology companies and start-ups[153] in the world has been substantially growing, and the need for innovative solutions in the pharmaceutical field is proving to be a driving factor for the appearance of new companies in the field.[1] As explored before in this review, today we have 58 OoC-based companies worldwide, which primarily display OoC as disposable products.[154] In this context, using disposable plastic for preclinical analysis could be minimized by establishing a circular economy model from the beginning. In this model, conventional 2D cell culture screening models, such as well plates and transwells, could be replaced by nondisposable or more ecofriendly OoC devices. In this critical review, we envision prospective ideas for the use of the circular economy applied to this innovative concept of OoC, including its application for reusable and recyclable OoC. Moreover, we address the challenges faced in the implementation of each sustainable model, recognizing the role of traditional cell culture as the most important plastic waste generator.

Reusable Options. As mentioned above, a second use of an OoC or even cell culture materials is not as appealing as the use of biodegradable materials by researchers. Reusing materials involves high precision steps of sterilization, which might concern the user as to whether the sterilization process is effective or not and how much this could cost. However, the research on the robustness of biodegradable materials for bioengineering is also expensive, leading to a debate on what is the best option from a green perspective. A combination of the use of biodegradable materials and the reuse of the supplies for cell culture and OoC could be a wise choice. That could be possible by using sterilizable materials that resist high temperatures, UV irradiation, decontamination solutions, and a high sterilization cycle. Materials such as PDMS, elastomers, glass, and thermoplastics already show these characteristics, although a perfect solution would be introducing ecofriendly materials such as PLA for this purpose.[52,69] The reuse should involve the exclusive development of open-top devices and a sterilization process performed by the user by disassembling, cleaning, and disinfecting the chip using the traditional methods of decontamination. This concept must be evaluated and deeply studied to be implemented, but investments and efforts are required for it to become real. The simple reuse of a device would certainly reduce costs and, more importantly, waste, but the combination of reuse and recyclable or biodegradable materials would create a new environmental cycle for this business.

Biodegradable/Recyclable Options. Using recyclable materials for OoC production and for cell culture could introduce a circular economy model in which the producer, recycler, and end-user would work collectively more efficiently in a business model. In this scenario, materials such as PDMS could be subjected to disruption, exposed to high temperatures, filtered, and polymerized to form silicone oil.[155] This oil could be applied as an additive in the cosmetic, automotive, and surface treatment industries.[53] Furthermore, the use of biodegradable materials for the production of OoC and cell

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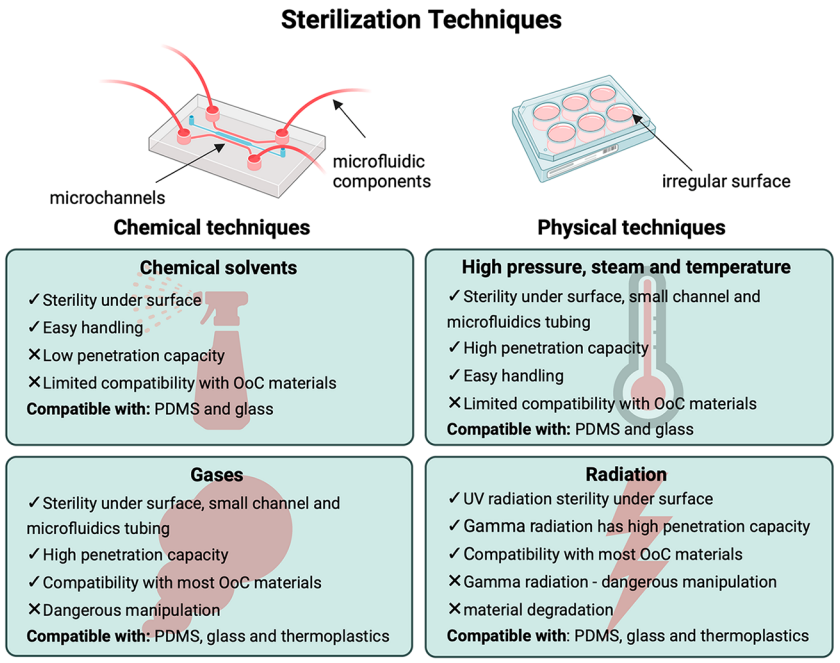

Figure 4. Diagram of advantages and disadvantages of different sterilization methods and their susceptibility to the different materials.

culture consumables is increasing, as evaluated by this review, showing a compelling interest among researchers in the field. The use of these materials is desirable and nonaggressive and could also be part of environmental cycles. Food industry waste could also be used to produce such polymers for OoC and cell culture flasks fabrication, improving two processes at once.[156−158] Finally, an ideal solution would be to optimize all these suggestions to find a sustainable and financially balanced way to use plastic materials for pharmaceutical research.

STERILIZATION PROCESSES

Sterilization is a process that removes or kills undesirable microorganisms from materials so that cells can be safely cultured.[159] OoC and cell culture flasks, sterilization processes include chemical and physical techniques, and the best methods are chosen according to the material usage (see Figure 4).

Physical methods include autoclaving and dry heat for temperature-resistant materials such as PDMS and glass, which achieve temperatures up to 180 °C and are ecofriendly and effective.[160] γ Radiation is another example, ideal for thermoplastics such as PMMA, PET, and poly(ethylene), although it is a high-cost, toxic, and unfavorable option for low-scale production.[160] Finally, UV sterilization is another validated technique for surface disinfection by applying UV light radiation in the germicide range (200−280 nm).[161] This technique affects nucleic acids by causing adenine−thymine collapse followed by thymine dimerization[161] and has no thermal restrictions. Both gamma and UV radiation are incompatible with a few plastic materials due to the constant material degradation over a few cycles of sterilization.

Chemical methods include disinfection, sterilization, and gas sterilization. Several chemicals (alcohols, aldehydes, halogens, phenols, surfactants, and heavy metals) are sterile under surface contact for up to 12 h.[160] However, they are not as efficient as thermal treatment due to their limited penetration capacity, which is limited for microchannels such as OoC.[160] Ethylene oxide (45−63 °C) and formaldehyde (70−75 °C) streams are used as sterilizing gases.[162] They are broadly used to sterilize heat-sensitive medical equipment and allow sterilization of many materials,[160,162] including thermally unstable polymers. However, these gases are considered mutagenic and carcinogenic.[160]

The experimental performance of the cells depends on the efficiency of the sterilization process for either the microfluidic components in OoC systems or plastic components in traditional cell culture. Considering that, inefficient sterilization, mainly in the tiny microfluidic channels, might add risks and disadvantages to the analysis routine of a cell culture laboratory. Moreover, this could raise concerns about cross-contamination, delays in the delivery of results, time-wasting, and an increasing risk of accidents involving the autoclave, gases, and radiation.

From all the methodologies mentioned above and considering what was covered in this article, ethylene oxide and γ radiation are considered the best methods for large-scale sterilization.[163] This includes the production of OoCs on industrial scale and their reuse for clinical studies, as well as the sterilization of plastic materials for cell culture. These techniques are considered efficient for disinfection due to their susceptibility to most materials used for OoC and cell culture, such as PMMA, glass, PDMS, and PC. Finally, ethylene oxide and γ radiation can be reliably used for sterilization of microfluidic channels and irregular surfaces due to their high penetration capacity.[163]

CONCLUSION

The necessity for new and more reliable methods for drug screening has led us to the most recent advance in the area, OoCs, which are still in development. OoC is becoming an essential possibility to replace old standard methods for the pharmaceutical industry, showing cost reduction estimates of 10−26%[14] and a roughly estimated waste reduction of over 3 million tons of plastic compared to the waste generated by research laboratories. Moreover, OoC displays a fair decline in reagent and supply consumption.[29] However, there are

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concerns about the materials and methods used for OoC fabrication since they still represent non-recyclable and unsustainable ideas inherited from the micromachining industry. In addition, OoC still relies on traditional 2D and 3D cell culture for cell growth and expansion, evidencing the need for better and more sustainable approaches to cell culture. Although there have been efforts to change this scenario, only a tiny fraction (29.5% for Google Scholar and 1.9% for Web of Science over the past ten years) of publications in the area are eager to discuss the environmental impact this technology might cause and suggest greener solutions. However, it is possible to observe a rising concern in publications relating to cell culture and plastic waste over the years, which greatly affects the waste generated for OoC research. As a perspective for this new science, we can envision OoC substituting old methodologies as it develops because of its advantages. However, unlike the former approaches for drug screening, as 21st-century researchers, we must reflect on the environmental impact of OoC technology and invest in cleaner, cleverer, and more complete solutions.

This work discussed estimates for OoC to become a standard test for drug screening and its implications. We have concluded that the environmental impact would be lower if compared to in-place methodologies, but OoC is still attached to the use of traditional plasticware. We have suggested a few possibilities for a greener introduction of OoC to the industry based on concepts of a circular economy and ecofriendly possibilities for the continuous use of traditional cell culture for OoC. The data survey we collected showed a greater interest in using biodegradable materials for OoC production than reuse or recycling. However, combining recycling, reuse, and using biodegradable materials would create a new concept of the use of technology in the pharmaceutical industry. Finally, considering the complexity involved in implementing such ideas, investments and interests must be put into this field to succeed.

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Notes

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