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Review paper

Current status and future directions of high-throughput ADME screening in drug discovery

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ABSTRACT

During the last decade high-throughput in vitro absorption, distribution, metabolism and excretion (HT-ADME) screening has become an essential part of any drug discovery effort of synthetic molecules. The conduct of HT-ADME screening has been "industrialized" due to the extensive development of software and automation tools in cell culture, assay incubation, sample analysis and data analysis. The HT-ADME assay portfolio continues to expand in emerging areas such as drug-transporter interactions, early soft spot identification, and ADME screening of peptide drug candidates. Additionally, thanks to the very large and high-quality HT-ADME data sets available in many biopharma companies, in silico prediction of ADME properties using machine learning has also gained much momentum in recent years. In this review, we discuss the current state-of-the-art practices in HT-ADME screening including assay portfolio, assay automation, sample analysis, data processing, and prediction model building. In addition, we also offer perspectives in future development of this exciting field.

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1. Introduction

High-throughput in vitro ADME (absorption, distribution, metabolism and excretion) screening (HT-ADME) has been widely adopted as an essential part of lead optimization for synthetic molecules (small molecules and more recently peptides) since around the year 2000 [1–3]. HT-ADME screening usually consists of in vitro assay suites that assess compound properties (or liabilities) such as metabolism [4,5], permeability [6–8], drug-drug-interactions [9–11], physicochemical properties [12,13] and also toxicities [14,15]. Several key technologies, including automated liquid handling [16], high speed liquid chromatography—tandem mass spectrometry (LC-MS/MS) for sample analysis [17,18], and software and automation tools [19–21], have together enabled these in vitro assays to be performed in high-density plate format (96, 384 or even 1536-well plates [22]) with the throughput and capacity required for early phases of drug discovery. It has been proven with industry-wide data that addressing ADME properties early in the discovery process helps significantly reduce attrition rates of drug candidates due to pharmacokinetic properties later in development [23]. There have been a number of comprehensive reviews covering the history

and common practices of HT-ADME screening and sample analysis [17,24—28].

Due to its critical role in drug discovery, the last decade (2010—2019) saw a number of significant developments in HT-ADME screening. First of all, the conduct of ADME screening has been "industrialized" through the development of software and automation that has facilitated assay incubation, sample analysis, data review and reporting. While in vitro ADME screening used to be conducted almost exclusively at big pharmaceutical companies, these mostly off-the-shelf tools have really "industrialized" ADME screening, empowering labs of different sizes, operating models (centralized, distributed, outsourced, etc.) and geographic locations to perform these screening assays with high efficiency. Secondly, cutting edge liquid handling and analysis technologies continued to be incorporated into ADME screening to further improve speed, quality and cost-effectiveness. Thirdly, the ADME screening assay portfolio continued to expand, especially in areas such as drug-transporter interactions, early soft spot identification, and ADME screening of peptide drug candidates. And lastly, the data generated by ADME screening assays have been widely used to develop in silico models with machine learning approaches to predict ADME properties. In this review we cover the recent developments and the state-of-the-art in these aforementioned areas; in addition we also offer a perspective on emerging sciences and technologies for next decade in the field of ADME screening.

2. The "industrialization" of ADME screening

At the time of its inception in the late 1990's, in vitro ADME screening was almost exclusively performed at large pharmaceutical companies, where the significant size of the discovery portfolio ensured enough assay demand, therefore justifying the substantial investment required in infrastructure and expertise development [24,29–31]. There were no existing commercially-available solutions to HT-ADME automation and sample analysis at the time; therefore, many companies developed their own customized solutions. The assay automation of that era tended to be stand-alone, workstation-based, with limited integration of various components [29,32]. Similarly, various custom solutions were developed for automated LC-MS/MS method development, sample analysis and data review [33–36]. While these highly innovative solutions laid the foundation for the field of HT-ADME screening as we know today, they required a high level of expertise in automation and bioanalysis to develop and maintain. The proprietary nature of these solutions also prevented them from being used in any other companies. As a result, HT-ADME screening was very much a "luxury" enjoyed by drug discovery organizations in only a handful of the largest pharmaceutical companies at the time.

From 2010 to 2019, with the importance of ADME screening in drug discovery well understood, and also thanks to the maturation of the underlying technologies, vendors started to commercialize products based on these previously proprietary tools specifically designed for HT-ADME screening.

2.1. Assay automation

In assay automation, multiple vendors including Tecan, Hamilton, PerkinElmer and many others, now offer complete, off-the-shelf solutions for ADME screening assays [4,16,37]. These solutions are typically based on a core platform of liquid handling, with additional accessories such as plate stores, shakers, incubators, filtration devices, centrifuges and sealers to perform tasks necessary for various HT-ADME assays. Several other vendors, including HighRes Biosolutions [38] and Agilent [39], offer fully integrated automation systems consisting of all of the aforementioned components, as well as one (or more) robotic arm(s) and corresponding software schedulers, for fully automated, truly walk-away assay operation. Multiple plates and multiple assays can be scheduled and conducted on the same system, thus realizing the most operation efficiency.

2.2. LC-MS/MS bioanalysis

LC-MS/MS with step or ballistic gradient LC, coupled with selected reaction monitoring (SRM) on triple-quadrupole mass spectrometers, has been the method of choice for HT-ADME sample analysis [40]. As pointed out by our previous review, the key challenges there are the large number of compounds requiring MS/MS optimization, the large sample number requiring analysis, and the large amount of data to process and review [17]. To address the requirement of SRM MS/MS conditions, automated optimization through flow injection analysis (FIA) is usually the solution [41]. To speed up the LC-MS/MS sample analysis, several approaches have been developed. The first is multiplexed LC-MS/MS, where multiple independent LC systems (channels) are connected through a switching valve to a single mass spectrometer; staggered injections are then made in synchronization with the switching valve, so that at any given time only the elution window from a single channel goes into the mass spectrometer. Either a 2x (for a 2-channel system) or a 4x (for a 4-channel system) speed improvement is possible with the multiplexing approach [13,42]. Another

commonly used approach is direct online solid phase extraction – mass spectrometry (online SPE-MS), often also called "trap and elute", where small SPE cartridges packed with quite large particles (~50 μm) are used to perform essentially a desalting step for the sample first, and the analytes are then eluted with 100% organic solvent directly into the mass spectrometer [9,43,44]. The online SPE-MS approach offers a higher speed (5–10 s/sample) than the multiplexed LC-MS approach (30–60 s/sample), but obviously affords less chromatographic separation. Therefore, online SPE-MS is typically used for probe-based assays (i.e., Cytochrome P450 inhibition), where a single analyte and its stable isotopically labeled internal standard are analyzed for a large number of samples. On the other hand, multiplexed LC-MS/MS is commonly used in assays where many different compounds, all with different physico-chemical properties, need to be analyzed from a single assay batch (i.e., from metabolic stability or permeability assays).

Recently, similar to automation solutions, several vendors now offer complete hardware and software packages for the LC-MS/MS sample analysis of HT-ADME assay samples using these afore-mentioned approaches. For example, Thermo offers the Quick-Quan™ package where MS/MS optimization, method generation and sample analysis can be fully automated on their triple-quadrupole instruments [5,45,46]. Optionally, QuickQuan can be further integrated with the Thermo multiplexed frontend LC system (Aria) to achieve an analysis time as fast as 15 s/sample with gradient elution, which is desirable for the large number of samples encountered in HT-ADME screening [42,47].

Another vendor, Sciex, offers a highly integrated solution for HT-ADME analysis named DiscoveryQuant™. Originally based on a proprietary solution developed at Pfizer [48], DiscoveryQuant™ underwent multiple iterations of development as a collaboration project between Sciex and multiple partners in the biopharma industry, and has now evolved into the most widely adopted software tool for HT-ADME bioanalysis [21,49,50]. The automated SRM MS/MS optimization routine in DiscoveryQuant™ has two unique and very useful features. First, it uses only a single loop injection (~1 min) with nested MS(/MS) scans to perform optimization of precursor ion, product ion, de-clustering voltage and collision energy, which has greatly simplified the optimization process and increased the optimization speed. Secondly, DiscoveryQuant™ has a powerful database feature where all optimized conditions from one instrument can be uploaded to a centralized database that allows sharing among many different Sciex instruments across the hall, or even across the globe, as illustrated in Fig. 1. A closely-related product, LeadScape™, not only incorporates all DiscoveryQuant™ features, but also controls the Apricot Designs Dual Arm (ADDA) [51] or LeadScape-1 (LS-1) [52] multiplexed auto-sampler for high-speed online-SPE or gradient LC separation in front of Sciex mass spectrometers. The online SPE-MS approach can achieve an analysis speed as fast as 5 s/sample, whereas the gradient LC mode can have a speed of approximately 15 s on the ADDA/LS-1 platform. Once the data are acquired, DiscoveryQuant™/LeadScape™ also has a data review module to perform automatic peak integration. Additional data review tools, including MultiQuant™ by Sciex and Gubbs Mass Spec Utility (GMSU) by Gubbs Inc, have also been widely used to process LC-MS/MS data from HT-ADME samples.

Taken together, these off-the-shelf and scalable solutions greatly enabled HT-ADME workflows in labs in biopharmaceutical companies of various sizes [9,43,53–55], in contract research organizations (CRO's) [56] and in academic research centers [57,58]. Therefore, HT-ADME screening has evolved from a workflow done by only a few large pharmaceutical companies in the 2000's to a standard practice anywhere where drug discovery research is conducted during the last decade.
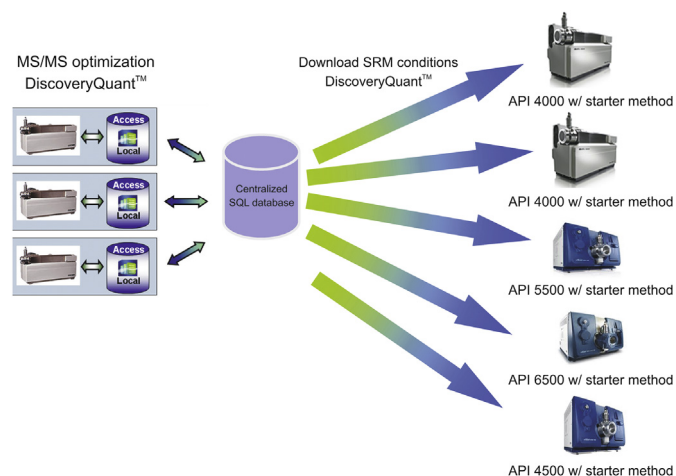
Fig. 1. Centralized SRM database allows sharing of MS/MS conditions across multiple sites and instrument platforms using DiscoveryQuant™. SRM: selected reaction monitoring. Instrument pictures are used with permission from Sciex.

3. Cutting-edge technologies in HT-ADME screening

In parallel to the industrialization of routine HT-ADME screening, novel and cutting-edge technologies have also continued to be tested and implemented in the field during the last decade thanks to the innovative culture of the existing HT-ADME community of practitioners. In this section, we review some of the technologies that have been adopted or are currently being evaluated in the HT-ADME screening laboratory.

3.1. Liquid handling

Liquid handling of sub-μL volumes has become a truly enabling technology for all screening communities (lead discovery, HT-ADME, etc.) in drug discovery. Low volume dispensing is critical in limiting the percentage of organic solvent (0.5% or lower) in the assay mixture, and the ability to accurately and reproducibly dispense nanoliter volumes can pave the way to assay miniaturization by reducing total incubation volume (and therefore reagent consumption). There are many technologies capable of nanoliter dispensing, with two enjoying the most success to date.

The mosquito® line of liquid handlers by SPT Labtech uses disposable, miniaturized positive displacement pipette tips to accurately transfer volumes as low as 25–50 nL. Since it uses a positive displacement approach for pipetting, a mosquito® liquid handler can easily transfer different liquid types, without resorting to re-calibration based on viscosity. Successful applications of mosquito® liquid handlers for low volume dispensing in HT-ADME assays have been reported [59].

Another highly successful nanoliter transfer approach uses sound waves to acoustically separate nanoliter-sized droplets from liquid meniscus in the source plate and eject them to the destination plate. Highly accurate, reproducible and rapid transfer of liquid volumes as low as 2.5 nL can be achieved in only several minutes for a 384-well plate [60]. First adopted in the high-throughput screening [61] and compound management [62] environment, acoustic transfer technologies have now been applied extensively in HT-ADME screening assays, especially those requiring serial dilutions for IC_{50} determination [25]. One caveat of the acoustic transfer approach is the need for calibration for each liquid type since different sound energy levels need to be applied for liquids with different properties (surface tension, viscosity, etc.). Two vendors currently offer acoustic dispensers: Echo by Labcyte®, and

ATS® by EDC Biosystems. A comparison of the two low-volume transfer approaches is presented in Table 1.

### 3.2. High-throughput sample analysis approaches

Sample analysis is another area where emerging technologies have been continuously evaluated and implemented. As mentioned previously, LC-MS/MS is still the workhorse in HT-ADME bioanalysis. However, it has been very difficult to break the 1 s/sample barrier for any chromatography and autosampler-based systems, despite the development of online SPE [44,63] and multiplexed LC systems [46]. To achieve even higher throughput, direct MS analysis from samples deposited onto solid support using various ionization methods has been attempted. These ionization methods include matrix assisted laser desorption ionization (MALDI) [64], laser diode thermal desorption (LDTD) [65], direct analysis in real time (DART) [66], coated blade spray [67], and dip-and-go inductive nanoelectrospray [68] amongst others. As pointed out in a previous review [17], although many of these ionization methods can achieve (or potentially achieve) a very high speed of analysis (several samples per second), they require an additional liquid handling step to transfer liquid assay samples into a solid support, which adds cost and complexity in automation. This disadvantage can be mitigated by using the aforementioned nanoliter transfer technologies for sample transfer [69], with several examples of HT-ADME applications reported in the literature [70]. Another disadvantage of these direct ionization approaches is the moderate to severe ionization suppression effect observed [71] (since there is no chromatographic separation), and the resulting generally lower data quality when compared to LC-MS-based approach.

A very innovative approach combining acoustic ejection and direct ionization for high-throughput mass spectrometry (HTMS) analysis has been recently developed by a group from AstraZeneca [72,73]. Dubbed acoustic mist ionization mass spectrometry, this approach uses a modified Echo acoustic dispenser to eject a "mist" of picoliter-sized droplets through a heated transfer tube directly into the mass spectrometer. Ionization is accomplished by a high voltage applied to the well top. The direct, contactless and high-speed (<1s/sample) features of this technology make it a highly attractive HTMS option for various screening areas and the group has published several papers describing its use in lead discovery. The biggest challenge of the acoustic mist ionization methodology is its data quality. This is due to (1) the difficulty in maintaining reproducibility in the mist generation (since regular acoustic dispensers operate by ejecting discrete, well-controlled nL droplets); and (2) the suppression effect exerted by the sample matrix. As a result, a CV of ~30% has been reported for repeated analysis, which is considered somewhat to be high for ADME applications.

A more recent development in direct acoustic mass spectrometry has made significant progress in addressing these challenges. Developed by Sciex, their acoustic ejection mass spectrometer (AEMS) uses a simple yet elegant interface called open port

Table 1
Comparison of the two low-volume liquid handlers.

Parameters	Positive displacement	Acoustic transfer
Transfer range	25 nL to 1.2 μL	2.5 nL to 5 μL
Sample contact	Contact	Contactless
Transfer speed	Minutes per 384-well plate	Minutes per 384-well plate
Consumables	Special tips	Special plates
Sample type	Any liquids	Aqueous, DMSO
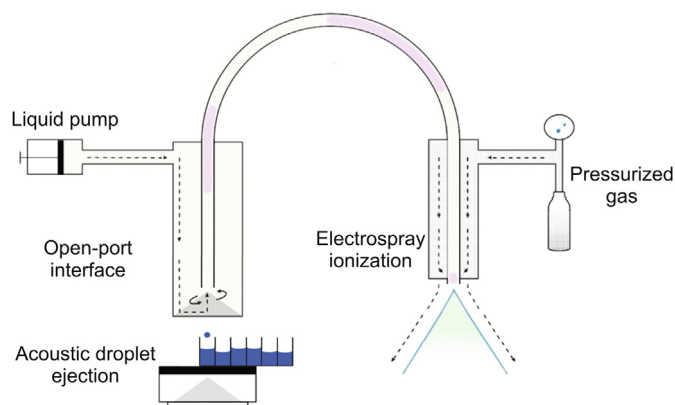
Fig. 2. Schematic of the acoustic ejection mass spectrometer (AEMS) system. Reprinted with permission from Refs. [76], Copyright (2020) American Chemical Society.

interface (OPI) to capture the droplets and transport them with a stream of carrier solvent (typically methanol) into a conventional electrospray ionization source [74–76]. Fig. 2 shows the schematic of an AEMS system [76]. AEMS with OPI enjoys the similar sub-second/sample speed and direct analysis features to those of the AMI-MS approach. In addition, it has been demonstrated that AEMS can generate highly reproducible results from assay samples thanks to the low variability of acoustic ejection of nL-sized droplets and, more importantly, the mitigation of ionization suppression by the significant dilution (~1000x) of the droplets by the carrier solvent. As a result, a typical CV of 3%–5% without the use of internal standards has been reported using AEMS for HTS and HT-ADME assay samples [74]. Obviously, the dilution effect does negatively affect the detection limit of the analytes. However, the low nM lower limit of quantitation (LLOQ) typically reported with AEMS should be sufficient to meet the requirements of most in vitro assays. Therefore, with its balance of high speed and high data quality, AEMS is poised to become the detection method of choice for label-free, biochemical or cell-based assays including those used in HT-ADME screening. A comparison of the several high-throughput MS-based readout methods for HT-ADME assays is presented in Table 2.

3.3. High resolution mass spectrometry

In addition to the speed increase on the triple-quadrupole MS platform mentioned above, another emerging trend in HT-ADME bioanalysis is the use of high-resolution accurate mass (HRAM) capability of time-of-flight or Orbitrap mass spectrometers for sample analysis. Quantitative sample analysis of HT-ADME samples has been demonstrated with HRAM, typically by using the sample pooling approach to reduce sample numbers and take full advantage of the high resolving power of the mass spectrometer [77]. More importantly, a number of quantitative/qualitative workflows have been introduced to perform metabolic soft spot analysis

concurrently with metabolic stability sample analysis [78,79].

4. Expansion of HT-ADME screening assay portfolio

4.1. Transporter assays

The assay portfolio of in vitro HT-ADME screening has continued to expand during the last decade and here we highlight some of the recently deployed assays in the field. Drug-drug-interactions and toxicity due to transporter involvement have been increasingly recognized as an important potential liability of drug candidates. As a result, inhibition assays for hepatobiliary and renal transporters (in addition to the existing intestinal transporters) have become an integral part of the drug-drug interaction (DDI) portfolio of many HT-ADME screening labs [10,11]. Some of the most commonly studied transporters in HT-ADME include hepatobiliary transporters such as organic anion-transporting polypeptide 1B1 (OATP1B1), organic anion-transporting polypeptide 1B3 (OATP1B3), sodium (Na$^+$) taurocholate cotransporting polypeptide (NTCP), bile salt export pump (BSEP) [80], renal transporters such as organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3), organic cation transporter 1 (OCT1), organic cation transporter 2 (OCT2), multidrug and toxin extrusion protein 1 transporter (MATE1), multidrug and toxin extrusion protein 2K transporter (MATE2K) [10], and intestinal transporters such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) [81]. Most of the transporter screening assays are conducted in inhibition mode by assessing the potential of a drug candidate to act as a "perpetrator" by inhibiting the activity of a given transporter. If necessary, substrate assays can be used to assess whether a drug candidate is likely to become a "victim" of a transporter-mediated DDI [82].

4.2. HT-ADME assays for peptide drug candidates

Another growing area in HT-ADME screening is the characterization of peptide drug candidates. Since its inception, HT-ADME has been mostly used to assess the properties and liabilities of small molecule drug candidates. Recently, peptides have emerged as an attractive drug modality since they can combine target affinities similar to those of biologics with physicochemical properties closer to those of small molecules. Most peptide drugs are dosed by injection due to their poor proteolytic stability, low membrane permeability and low oral bioavailability [83]. A number of synthetic strategies [84–86] have been attempted to address these challenges for orally-dosed peptide drug candidates and, correspondingly, new or modified HT-ADME assays have been developed to facilitate the lead optimization in oral peptide drug discovery. For example, permeability assays such as colon adenocarcinoma cell line (Caco-2) or parallel artificial membrane permeability assay (PAMPA) have both been used to assess the permeability of peptides [84,87]. However, due to the non-specific binding typically exhibited by peptides and the generally very low permeability values, they tend to generate null results in these

Table 2
Comparison of high-throughput MS analysis approaches. SPE: solid phase extraction; LDI: laser desorption ionization; AMI: acoustic mist ionization; AE: acoustic ejection.

Parameters	LC-MS/MS	SPE-MS/MS	LDI-MS	AMI-MS	AE-MS
Speed per well	60s	10 s	1 s	1 s	1 s
In situ sample clean up	Yes	Yes	No	No	Yes
Data variability	Low	Low	High	High	Low
Sample format	96/384	96/384	96/384	384	384/1536
Sample volume	>40 μL	>40 μL	<1 μL	<1 μL	<1 μL
Direct analysis	Yes	Yes	No	Yes	Yes

assays. Therefore, assay conditions have been modified to address these challenges. Also, additional assays such as chromatography-based experimental polar surface area (EPSA) have been developed specifically to assess the permeability of peptides [88].

4.3. High-throughput soft spot identification assays

The in vitro metabolic soft spot assay is another recent addition to the HT-ADME assay portfolio [89]. Unlike most HT-ADME assays with numbers as end points (IC_{50}, permeability values, percent bound, etc.), the metabolic soft spot assay provides structural information about the sites of metabolism (SOM), or "soft spots" of discovery compounds. Historically a very low throughput assay conducted only for a handful of lead compounds, metabolic soft spot assays have recently become quite common in HT-ADME. This is due to technological developments in two areas: first, the availability of high-performance, high-resolution mass spectrometers with generic data acquisition methods [90,91]; and, second, the development of software tools to perform automated structural elucidation in batch mode [92,93]. Equipped with the SOM information from the soft spot assay, discovery projects can now address metabolic instability synthetically for both small molecules and peptides in a more targeted way than before.

5. Future perspective

Thanks to the evolving sciences and enabling technologies, we anticipate more exciting developments in the field of HT-ADME in next decade. From an assay portfolio standpoint, emerging areas of ADME sciences will inevitably find their way into HT-ADME screening. Examples of these include new, more physiologically relevant in vitro microphysiological systems (MPS) such as 3D tissue cultures and organ(s)-on-a-chip [94–98], for better in vitro in vivo translation (IVIVT). Another trend in ADME is the use of endogenous probes (essentially biomarkers) for transporter DDI studies in vivo, which has the potential advantages of reducing pill burden and obtaining transporter DDI information from a regular phase I study [99–104]. Once the endogenous probes are validated, it is foreseeable that the corresponding in vitro HT assays can be implemented in a screening mode as well. Yet another example is HT-ADME screening of new drug modalities. In addition to small molecules and peptides, the field is poised to enter early ADME screening of new modalities including protein degraders [105–107], antisense oligonucleotides (ASO's) [108–110], antibody drug conjugates (ADC's) [111–114] and biologics [115–117]. Although the ADME science of these modalities is still currently developing, we expect more and more HT-ADME format assays will become online to support discovery efforts along with the evolving science.

With the long history of HT-ADME operation in many companies and the resulting wealth of ADME data that can be "mined", developing in silico models to predict ADME properties has long been recognized as the logical next step for HT-ADME screening [118,119]. While many ADME predictive models reported in the literature use a training set of only several hundred compounds, a large pharmaceutical company's HT-ADME dataset could contain assay results from several hundred thousand compounds. These datasets can serve as the ideal training sets for model development due to its large size, and also the fact that they are a much better representation of the chemical space occupied by the compound collection of the particular company. Computational chemistry approaches aimed at developing quantitative structure-activity relationship (QSAR) models have long been applied to ADME

properties [120,121]. More recently, various machine learning (ML) methods have been applied to develop models for clearance, permeability and DDI potentials [122–126]. With the recent rapid development in machine learning methodologies, and the large size of the HT-ADME datasets available to use as training sets, it is expected that even better predictive ADME models can be developed in the future to guide efforts such as hit triaging from lead discovery screens and in the design-make-test cycles of lead optimization in drug discovery [127].

Conflicts of interest

The author declares that there are no conflicts of interest.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpha.2020.05.004.

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