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Evaluation of PAT Methods for Potential Application in Small-Scale, Multipurpose Pharmaceutical Manufacturing Platforms

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Supporting Information

ABSTRACT: Small-scale (refrigerator-sized, 1.0 (width) × 0.7 (length) × 1.8 m (height)), multipurpose pharmaceutical manufacturing platforms (PMP) necessitate unique high demands on process analytical technologies (PAT), for instance, in in situ, real-time monitoring of liquid formulations (solution and suspension) to determine the strength prior to the release from PMPs that are not comparable to lab-scale or industrial-scale needs. Commercially available plug-and-play PATs were evaluated for their potential application in PMPs regarding versatility, flexibility, reliability, and physical size (including the control box). The results presented here indicate that single-frequency ultrasounds currently surpass commercially available plug-and-play PATs in ways such as focused beam reflectance measurements, conductivity, and turbidity as well as UV−vis, Fourier transform infrared, near-infrared, and Raman spectroscopy for the purpose of in situ, real-time concentration monitoring of aqueous and alcohol-based solutions and suspension-formulated drugs in one single PAT device, as it is preferred in PMPs to maintain a small footprint.

1. INTRODUCTION

Active pharmaceutical ingredients (APIs) are produced traditionally through several iterative, time- and cost-intensive batch manufacturing steps that can require moving materials between facilities around the world and lengthy final product testing.[1−3] Typically, numerous chemical synthesis steps are required, followed by intensive purification steps conducted in one plant and the final formulation in another facility.[1,4] As a result, the production of a finished formulation can require up to a total of 12 months.[2]

The United States Food and Drug Administration (FDA) has thoroughly reviewed that the limitations of batch manufacturing are root causes of drug shortages,[5] a threatening global problem.[6−9] A potential solution to overcome this threat could be decentralized, small-scale (table-top), multipurpose pharmaceutical manufacturing platforms (PMP) combining the synthesis of APIs, purification, and drug formulations in one device.[10] Such portable, end-to-end PMPs,[10] as shown in Figure 1, can (1) be configured to produce multiple drug products, (2) be located at locations where drug products are required, (3) be put into immediate production of drugs based on demand rather than drugs being stockpiled (e.g., for humanitarian needs), (4) reduces formulation complexity relative to products needing yearlong stability, and (5) be advantageous for drugs with a short shelf life.

The realization of these PMPs requires innovation in chemical synthesis,[11] separation processes,[12,13] automation, and process control via process analytical technologies (PATs).[10] Therefore, the objective of this comparative study is to evaluate multiple commercially available plug-and-play PATs as potential tools for quantitative, in situ, real-time monitoring of API concentrations in liquid formulations (solution and suspension) to determine the strength prior to the release from PMPs.[10]

Generally, the pharmaceutical industry follows the quality-by-design (QbD) approach, initially advocated by the FDA and adopted by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).[14] QbD includes the application of PAT to guarantee the required product quality of drug formulations, and among other things, the concentration of the API.[14] Therefore, a variety of methods for the quantification of APIs in pharmaceutical formulations have been intensively discussed in recent years.[15−18] These studies have addressed the application of PATs, such as in near-infrared (NIR), Raman, and ultrasound attenuation spectroscopy. Other studies have assessed the application of Fourier transform infrared (FTIR) spectroscopy, focused beam reflectance measurements (FBRM), ultraviolet (UV) spectroscopy, turbidity, or conductivity to measure solution/suspension properties.[19−22] All of these PATs provide the possibility to monitor process parameters in situ and in real time, which leads to more constant product quality by real-time process decision making and process adjustments through feedback and feedforward control systems. However, to be applied for monitoring of liquid formulations[23] in multipurpose PMPs,[10] four key challenges regarding PATs need to be overcome. Moreover, it should be achieved ideally with one single PAT to maintain a small footprint,[10] which is unlike typical manufacturing in the pharmaceutical industry, where generally multiple PATs are utilized to cover the analytical tasks and challenges listed below (Figure 2):[23]

1. Versatility: to measure all processed APIs (multipurpose) with different properties (conductive, dilute, dense, opaque, etc.);

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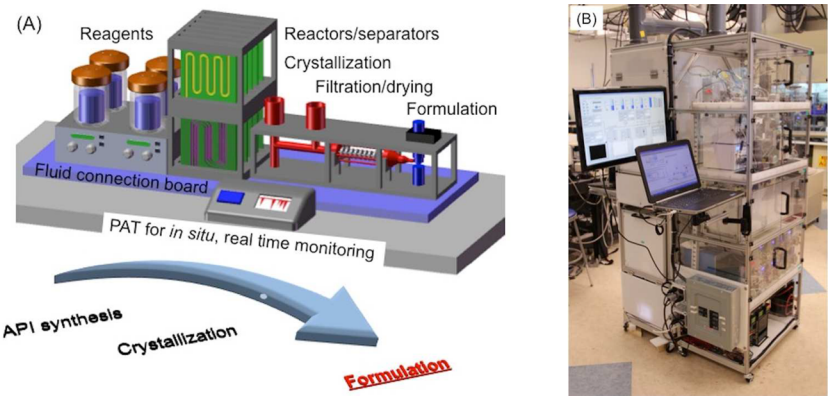

Figure 1. Portable, end-to-end, small-scale, multipurpose pharmaceutical manufacturing platform (PMP). (A) Concept design and (B) laboratory prototype.[10]

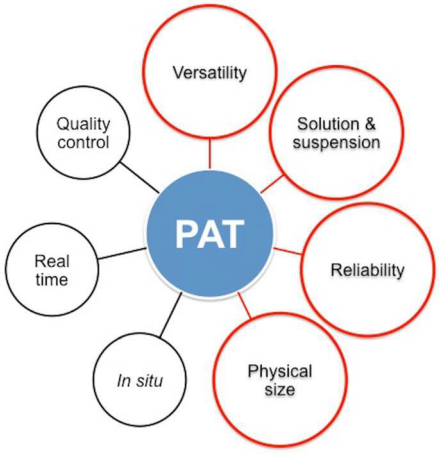

Figure 2. Requirements and key challenges (big red circles) of PAT applied in small-scale PMPs.

2. Flexibility: to measure the concentration of different types of liquid formulations (solution and suspension);
3. Reliability: to measure consistently and reproducibly without drifting even after disassembling and reassembling for maintenance and cleaning of the equipment as well as after the transportation of the PMPs from location A to location B as needed for the on-demand character of PMPs;[10] and
4. Physical size: all individual PAT units need to be compact to maintain a small footprint that fit into the space constraints (including control box) of the refrigerator-sized PMP [1.0 (width) × 0.7 (length) × 1.8 m (height)] that are packed with reactors, pumps, valves, motors, electronics, etc.[10]

For instance, commercially available plug-and-play spectroscopic techniques commonly used in the pharmaceutical industry, such as FTIR, NIR, Raman, ultrasound attenuation, etc., do not fit into the space constraints of PMPs (key challenge: physical size) because generally the control boxes of these devices are too big to maintain the concept of a small-footprint manufacturing device.[10] For the aforementioned PATs, small-scale (miniaturized) spectroscopic instruments are available, but after preliminary testing (data not shown), it was found that these optical fiber-based devices lack robustness and reliability. The optical fibers are too sensitive for vibrations and necessary cleaning/maintenance activities in PMPs that would require additional recalibration efforts once a PMP has been cleaned and prepared for manufacturing (key challenge: reliability). Here, hand-held devices without optical fibers, which have already been adopted in the pharmaceutical industry for raw material verification and cleanliness checking, could be a solution in the future.[20,23−25] However, to the best of our knowledge, the commercially available hand-held PATs are currently lacking adaptors to be used as plug-and-play devices in reactor setups.[26] Therefore, these techniques have been excluded from the list of potential PATs for PMPs. The list contains spectroscopic and low-cost PATs such as conductivity, density, or single-frequency ultrasound (SFUS) (Figure 3). Unlike spectroscopic techniques, low-cost PATs are

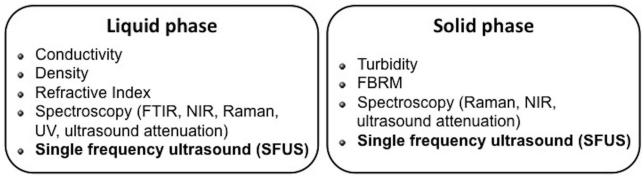

Figure 3. Commercially available plug-and-play PATs for liquid and solid phase measurements.

limited to single-component systems[22] as needed for the liquid formulations in a proof of principle PMP.[10] Consistent with the on-demand format of PMPs, which must be ready when needed and stable for at least 31 days, aqueous or alcohol-based formulations have been studied in this work which justifies the evaluation of low-cost PATs.[10]

Most of the PATs shown in Figure 3 are limited to measure either the solid or liquid phase. Moreover, the application of the individual PATs might by accompanied by obstacles regarding electrically nonconducting (e.g., for conductivity measurement), dense, concentrated, or optically opaque solutions.[22,27,28] Comparatively, the ultrasound-based technologies have advantages because most materials are ultrasonically transparent and hence allow the analysis of a broad variety of sample types (solution, suspension, lotion, emulsion, etc.).[16,18,27−29] In the past decade, several studies have pioneered the use of ultrasound spectroscopy in the quantification of drug concentration in different types of formulations.[15,16,18] Contrary to ultrasound spectroscopy, SFUS, an ultrasound-based PAT operating at only one single frequency and smaller in physical size, has been studied intensively as a fast, reliable, and cost-effective PAT in

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crystallization processes to measure liquid concentration and suspension density.[22,27,28,30−32] However, to the best of our knowledge, in situ, real-time monitoring of drug concentration in liquid pharmaceutical formulations (solution/suspension) has not been assessed by means of SFUS.

The aim of this study is to evaluate the application of SFUS as a versatile, reliable, cost-effective, and small-scale PAT to measure the concentration of liquid pharmaceutical formulations (solution/suspension). The quality and versatility of SFUS were assessed by comparing the results with the outcome of established PATs (available for this study), which are able to measure suspension concentration (FBRM and turbidity) as well as solution concentration (conductivity, attenuated total reflection FTIR system (FlowIR), and UV−vis) that are relatively small in size (including the control box). The latter is particularly important if the PAT should be utilized in small-scale applications with critical space limitations (e.g., PMPs).[10]

2. EXPERIMENTAL SECTION

Materials. For this comparative study, seven APIs were selected, differing in molecular weight as well as type and dosage of aqueous formulation. Atropine sulfate (ATR), doxycycline monohydrate (DOX), fluoxetine hydrochloride (FLU), ibuprofen (IBU), and lidocaine hydrochloride (LID) were purchased from Shunyi Bio-Chemical Technology Co, Ltd. (China). Diazepam (DIA) was obtained from Sigma-Aldrich (United States), and diphenhydramine hydrochloride (DPH) was procured from Alfa Aesar (United States). Polysorbate 80 as a surfactant, sodium carboxymethyl cellulose (NaCMC) as a viscosity modifier, and sodium hydroxide (NaOH) as a pH modifier were purchased from Sigma-Aldrich. Ethanol (200 proof) was acquired from VWR International (United States). Distilled water (Milli-Q, Millipore) was used for all aqueous formulations.

Preparation of Formulations. All APIs were formulated without further purification in their commercial aqueous oral forms as solutions or suspensions, except ATR, which is only available as an injection, and DIA, which is formulated in a 19% (v/v) ethanol/water solution.[33] To formulate DIA, the API was predissolved in pure ethanol, and the concentration was adjusted to 5.3 mg/mL. Then, water was added to dilute the solution to the final concentration of 1 mg/mL. Within this study, all DIA experiments were conducted in pure ethanol. All APIs were formulated in aqueous or alcohol-based formulation matrixes as applied in a proof of principle PMP.[10] Moreover, the purpose of PMPs is to deliver an on-site, on-time, and on-demand pharmacy, which means the drugs are supposed to be consumed immediately or few days after the formulation to justify the applied approach to study simplified formulation matrixes.

The formulation details of all seven APIs[33] and their specifications regarding the United States Pharmacopeia (USP)[34] are summarized in Table 1.

Experimental Setup. A jacketed reactor (V = 400 mL) for temperature control with a seven-necked lid and a marine impeller was used to evaluate the PAT methods for their suitability to be applied in PMPs. Multiple PAT probes, including ultrasound (unprotected, LiquiSonic 30, SensoTech GmbH),[27,28,32] conductivity (Fogale Nanotech), turbidity (FSC402, Mettler Toledo) and UV−vis (Varian) were inserted into the reactor. The attenuated total reflection Fourier transform infrared system (FlowIR, Mettler Toledo) was connected via a circulation system that included a pump to transport the solutions/suspensions through the flow cell of the device. Apart from this setup, the experiments with FBRM (G400, Mettler Toledo) were conducted utilizing the EasyMax system (Mettler Toledo) with a temperature-controlled (T = 25 °C) 50 mL reactor. For a deeper understanding of the principle mechanism of each of the established PATs applied in this study, readers can refer to references 20, 22, 27, 28, and 35.

Table 1. Formulation Details for APIs Utilized in this Study

formulation	API	excipients	dosage[33] (mg/mL)	USP limits[34] (%)
solution	LID	4% NaCMC in water + NaOH (adjust pH 5.0−7.0)	20	±5
	FLU	water	2.5	±10
	DPH	water	2.5	±10
	ATR	water	1	±7
	DIA	19% (v/v) ethanol in water[a]	1	±5
suspension	IBU	5% (v/v) polysorbate 80 in water	20	±10
	DOX	5% (v/v) polysorbate 80 in water	5	−10 to +25

[a]Within this study, all DIA experiments were conducted in pure ethanol.

Procedures. To evaluate the accuracy and sensitivity of the PATs in measuring the concentration of all of the liquid formulations listed in Table 1, two independent sets of calibration and validation experiments were conducted. The calibration experiments started with the blank liquid excipient solutions. Once the recorded signals from all involved PATs were stabilized, defined amounts of the APIs were incrementally added into the reactor, resulting in stepwise changes in the signal detected by the PATs. The magnitudes of these signals corresponded to the total amount of API present in the liquid excipient. Basic second-order polynomial expressions (except for the conductivity of LID, Figure S8B) were used to construct the calibration curves (PAT signals vs concentrations) with the best possible fit for each PAT and API. The calibration experiment in this comparative early stage method development study consisted of a minimum of 4 different concentrations from 0 up to 10 times of the desired dosage for each API (Table 1). This represents the expected concentration range of the APIs being formulated in a proof of principle PMP.[10] The validation experiments started with measurement of the PAT signals for known API concentrations that differed from the calibration data. Subsequently, the signals were used to calculate the API concentrations for each PAT based on the respective calibration models. To evaluate the accuracy of the PATs and the calibration models, the root-mean-square errors of the predicted values (RMSEP) were calculated:

$$\mathrm{RMSEP} = \sqrt{\frac{1}{N}\sum_{N}^{i=1}(\hat{x}_i - x_i)^2} \quad (1)$$

where $\hat{x}_i$ is the model-estimated concentration for sample i, x_i is the measured concentration of sample i, and N is the number of test samples. Hence, RMSEP has the concentration unit mg/mL and can therefore be utilized to compare the predicted value with the measured value under consideration of the USP limits[34] given in Table 1.

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Table 2. Summary of Calibration and Validation Experiments for all PATs and APIs Utilized in this Study[a]

		SFUS		conductivity		FBRM		turbidity	
formulation	API	R^2	RMSEP	R^2	RMSEP	R^2	RMSEP	R^2	RMSEP
solution	LID	1	0.23	1	0.47				
	FLU	0.9999	0.04	0.9997	0.06				
	DPH	1	0.02	1	0.04				
	ATR	1	0.06	0.9991	0.06				
	DIA	0.9994	0.03						
suspension	IBU	1	0.6			0.9995	0.2	1	1.06
	DOX	0.9998	0.39					0.9995	0.21

[a] R^2 indicates coefficient of determination for calibration experiments, RMSEP indicates root-mean-square error of prediction for validation experiments, and a blank indicates no result or measurement.

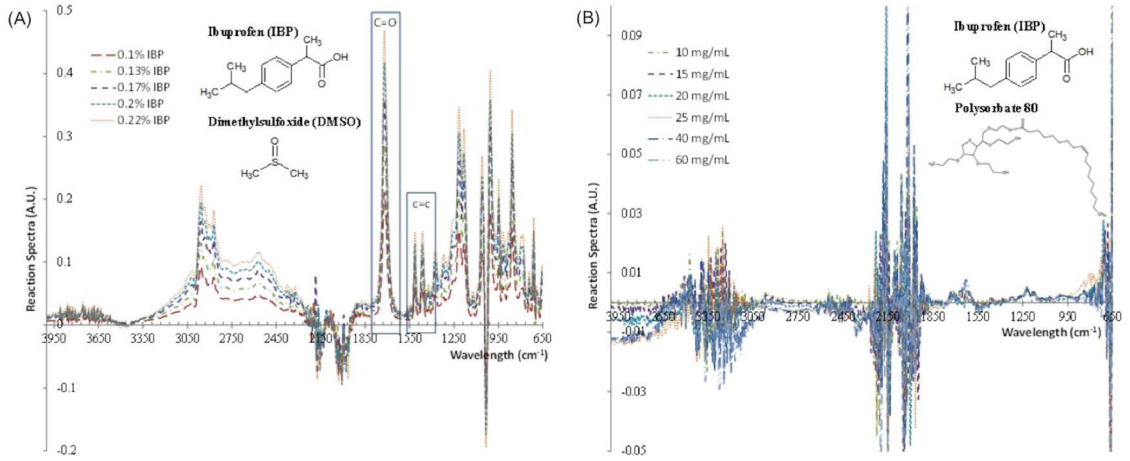

Figure 4. FTIR spectra for different IBU concentrations (blank dispersant spectrum subtracted). (A) Solution concentration of IBU in DMSO. (B) Particle concentration suspended in 5% polysorbate 80.

3. RESULTS AND DISCUSSION

3.1. Evaluation. The results from all of the calibration and evaluation experiments are summarized in Table 2 (for plots, see Figures S1–S15). All PATs demonstrate a relatively good coefficient of determination (R^2) with at least $R^2 > 0.98$ for the seven investigated API formulations. This indicates a suitable correlation between the variable concentration and the measured parameter of each PAT with the chosen model to fit the data. However, of all considered PATs and for all types of formulations (solution/suspension), SFUS demonstrates the highest R^2 of >0.999. Moreover, the SFUS calibration models show the smallest RMSEP of all PATs with an average of <0.2 for all studied APIs and types of formulation.

While conductivity generally shows a good performance (R^2 and RMSEP) in measuring the concentration of all solution formulations (except DIA) this technique does not provide information regarding suspension density (Figure 3). Moreover, the conductivity technique is limited by the conductivity of the solvent and the dissolved material (electrolyte). Ethanol is used as a solvent to formulate DIA, which has a much lower conductivity (1.4×10^{-9} S/cm) compared to that of water (0.5 S/cm), which is used for all other formulations.[36] Furthermore, DIA is a weak electrolyte (base) with a pK_a value of 3.4.[37] This example of DIA/ethanol formulation demonstrates the limits of the conductivity technique as a versatile PAT (for plots, see Figures S5 and S12).

The turbidity measuring technique provides very good R^2 with an average >0.999 (for plots, see Figures S13 and S14). The correlation between the FBRM signal and the suspension density looks promising with $R^2 > 0.999$ as well. However, FBRM, a count-based technique,[35] seems to be limited to the low concentration range because it was difficult to obtain stabilized FBRM signals at concentrations >24 mg/mL (data not shown) for IBU, which is a high-dosage drug (20 mg/mL, Table 1).[33] Specifically, to measure the suspension density, it was assumed that the number of particles counted with FBRM increases as suspension density increases. However, this assumption is true for only the low concentration range because higher suspension densities cause less total particle counts.[38] As the suspension density increases, there is a higher probability that the laser beam will immediately hit another small particle after passing across one particle and will reflect with similar intensity. This makes the differentiation of individual chord lengths difficult. The phenomenon is mentioned as "masking effect" or "snowstorm effect" in the literature because of its similarity to the visual limitations during a snowstorm when objects are difficult to observe or are completely invisible due to a dense layer of snow particles.[39,40] In PMPs, the final product would need to be diluted to the desired dosage from high suspension concentrations (much higher than 24 mg/mL). Consequently, FBRM does not fulfill the monitoring purposes during the formulation process of IBU, and no further experiments with DOX were conducted. Moreover, although FBRM and turbidity show similar RMSEP values compared to SFUS (Table 2), both techniques were not able to measure solution concentrations, which reveals the boundaries of these two techniques as versatile and flexible PATs ideally suited for PMPs (Figure 2).

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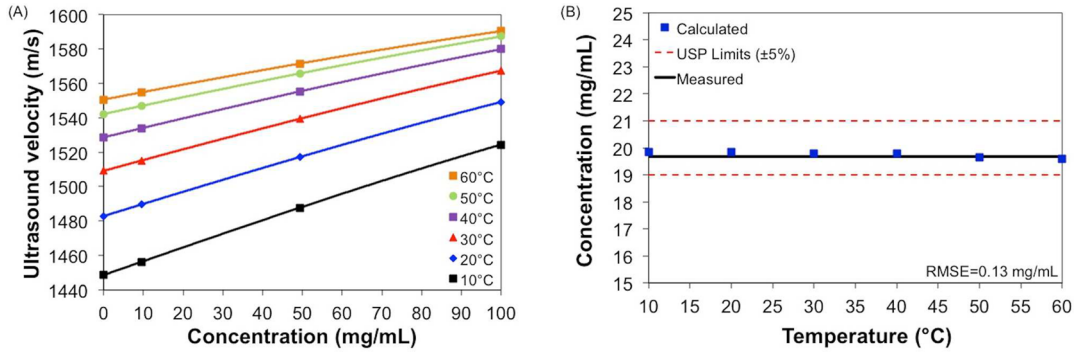

Figure 5. Results of nonisothermal SFUS calibration and validation experiments of LID. (A) Calibration results. (B) Validation results for the target dosage of 20 mg/mL.

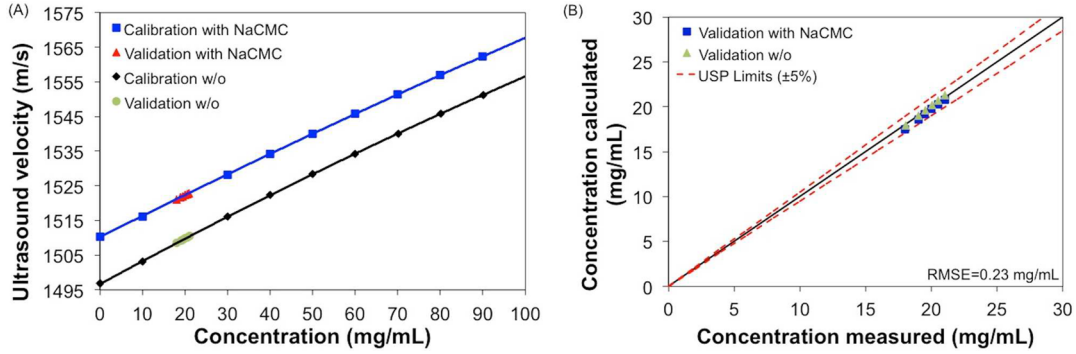

Figure 6. Impact of inactive pharmaceutical ingredient NaCMC (viscosity modifier) within the formulation matrix of the LID solution under isothermal conditions (T = 20 °C). (A) Ultrasound velocity versus concentration and (B) calculated versus measured concentration.

The FlowIR provides high quantitative and qualitative data about the solution concentration as it could be shown for IBU in DMSO (Figure 4A). However, the FlowIR was also unable to measure the solid concentration in suspensions as demonstrated for IBU formulated in water (Figure 4B). Additionally, the application of FlowIR was accompanied by partial clogging in the sensor head if there were particles that were undissolved and/or too big to be pumped through the circulation system. Although, this issue could be overcome easily by using proper filters and will not hamper the successful application of FlowIR in PMPs.[10] Thus, despite its limits in suspension handling and suspension measurement, FlowIR should be the small-scale PAT of choice for in situ, real-time reaction monitoring of APIs formed in flow synthesis processes[10,41] and for formulation if PMPs are exclusively designed for solution formulated drugs. However, because the objective of this comparative study was to evaluate PATs able to measure solution and suspension formulations, ideally in one device, no further tests in terms of liquid formulations were conducted with FlowIR.

The application of UV−vis (wavelengths 209, 210, and 211 nm with a flow cell path length of 10 mm) was accompanied by signal overload in the considered concentration range from 25 to 180 mg/g, which represents about 10 times the target concentration (Table 1). However, the installation of an automated predilution system raised concerns regarding additional space consumption in the PMP and sampling issues. Therefore, no further experiments were performed. The examples of FlowIR and UV−vis highlight the sensitivity of both techniques as PATs regarding robustness and versatility for in situ real-time liquid formulation monitoring in PMPs.

As an interim conclusion, it can be noted that all PATs evaluated in this study demonstrate their capability to measure accurately and reliably either the liquid or the solid phase of liquid formulations. Consequently, those PATs should certainly be considered for in situ, real-time monitoring of liquid formulations in future PMPs. However, considering the objective of this comparative study, only SFUS provides the most promising results regarding the key prerequisites of PATs for multipurpose PMPs (Figure 2), which includes versatility (aqueous and alcohol-based formulation matrixes), flexibility (measurement of solution and suspension formulation), reliability, and physical size (small control box). SFUS was the only PAT able to overcome these prerequisites in one single PAT device, which helps to maintain a small footprint of PMPs.[10] To further assess the capabilities of SFUS, a low-cost PAT, additional evaluation tests were conducted to provide valuable insight in the early stage of method development for a PMP.[10]

3.2. Single Frequency Ultrasound. All calibration and validation experiments discussed in the previous section were conducted under the isothermal conditions with simplified formulation matrixes, as utilized in the formulation processes of the previously published proof of concept.[10] Therefore, additional tests were conducted to stress the accuracy of SFUS under more complex formulation boundaries. The ultrasound velocity is temperature dependent[27,28] and needs to be considered carefully to measure reliably and accurately even under slight temperature fluctuation in the manufacturing process. Figure 5 depicts the results of these nonisothermal studies for LID.

Figure 5B shows a trend of the calculated versus measured values from slightly overpredicted to slightly underpredicted

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with increasing temperature in the expected temperature range, indicating that a different mathematical fit should be plotted to better represent the calibration data.[42] However, considering that only four calibration points per temperature were used in this early stage of PAT evaluation, SFUS can accurately measure the target dosage of LID even under nonisothermal conditions (Figure 5). Effects such as temperature, liquid concentration, and scattering caused by crystals are taken into account in the ultrasound velocity and the attenuation measured by SFUS.[27,28] Only the possible effect of viscosity[43,44] has not yet been considered in SFUS independently.[27,28]

Therefore, the effect of viscosity was investigated by analyzing the influence of more complex formulation matrixes of LID on the accuracy of SFUS. In these tests, the inactive pharmaceutical ingredient NaCMC, a commonly used viscosity modifier, was added to the formulation matrix of the LID solution (Table 1).

Figure 6A emphasizes that the addition of 4% NaCMC to the formulation matrix of LID causes a parallel shift in the ultimate ultrasound velocity, but the trend and accuracy of the measurements (Figure 6B) are not negatively affected. This result can be derived from the Wood equation for a fluid:[45]

$$\nu_{US} = \frac{1}{\sqrt{\kappa\rho}} \tag{2}$$

where ν_{US} is the ultrasound velocity, κ is the adiabatic compressibility, and ρ is the density of the fluid. The ultrasound velocity is affected by a change in the adiabatic compressibility and density due to the addition of another compound (Figure 6A), which can lead to a positive or negative shift.[32] Consequently, future studies have to evaluate this aspect with the consideration that the variability of incoming raw materials might impact the composition of the resulting liquid formulations, causing a shift in the ultrasound velocity.

The last point that must be stressed is the level of accuracy of SFUS. As can be extracted from Table 2, even low-dosage formulations like FLU (4 mg/mL), DPH (2.5 mg/mL), and ATR (1 mg/mL) can be precisely measured within the required USP limits[34] (Table 1 and Figures S2−S4). Although it has to be noted that, for this early stage comparative study, the validation experiments were conducted over a relatively limited concentration range of the calibration experiments to focus on the target dosage of the APIs. Consequently, the RMSEP values are not fully representative for the entire concentration range. This aspect needs to be addressed in future evaluation studies.

Generally, the accuracy of SFUS does not depend on the dosage of the formulation but rather on the change of the ultrasound velocity as a function of the API concentration, which is a material property.[32] In other words, the larger the change in the ultrasound velocity caused by a change in the liquid concentration of a particular API, the more precise SFUS can measure. The key limit here is the resolution of 0.01 m/s of the SFUS device. Whether an API is suitable to be monitored with SFUS for in situ monitoring of real-time drug release of liquid dosage formulation can be determined in one easy dilution experiment by evaluating the change of the ultrasound velocity and attenuation with decreasing concentration at a constant temperature. For a suitable API of interest, the concentration resolved by a change in the ultrasound velocity or attenuation should be within the limits given by the USP.[34]

4. CONCLUSION

This comparative study indicates that SFUS, with its versatility, flexibility, reliability, and physical size, which are all prerequisites that ideally need to be fulfilled by a single PAT to be applied for in situ real-time concentration monitoring of liquid formulations in a proof of principle PMP,[10] is a cost effective and accurate PAT. Here, SFUS currently surpasses commercially available plug-and-play PATs such as FBRM, conductivity, turbidity, UV−vis, FlowIR, NIR, and Raman spectroscopy for the purpose of concentration monitoring. With the necessary further studies and regulatory approvals,[46] SFUS has potential as an in situ monitoring PAT for the real-time quantification of drug concentrations in liquid formulations manufactured in tomorrow's PMPs.[10]

However, the choice of a PAT always depends on the process requirements and the needs of the user. For instance, industrial large-scale[23] or innovative small-scale applications,[46] process development, or in situ real-time monitoring of liquid formulations of complex or simplified (aqueous or alcohol-based) liquid formulation matrices demand different PAT requirements and have to be considered carefully for each individual application. Therefore, this study might be used as a rational tool for the selection of the right PAT and as an advocate to emphasize the need to develop miniaturized PATs that are ready to be used as plug-and-play in future PMPs.[10]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.6b00129.

Details regarding calibration models and validation experiments for atropine sulfate, diazepam, diphenhydramine hydrochloride, doxycycline monohydrate, fluoxetine hydrochloride, ibuprofen, and lidocaine hydrochloride for the PAT methods of single frequency ultrasound, conductivity, turbidity, and FBRM (PDF)

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Notes

The authors declare no competing financial interest.

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