SLAS Technology 38 (2026) 100406

Contents lists available at ScienceDirect

SLAS Technology

journal homepage: www.elsevier.com/locate/slast

Full Length Article

A method for the evaluation of automated solid dosing technologies for mid-scale dosing tasks in laboratory automation

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ARTICLE INFO

Keywords:
Solid dosing
Powders
Laboratory automation
Biotechnological laboratories
Mid-scale
High-throughput

ABSTRACT

Solid dosing is a tedious and time-consuming task in everyday laboratory work. Manual solid dosing can cause several health issues due to handling of toxic materials or posture errors. Automated solid dosing technologies intend to overcome these issues and increase efficiency. However, these technologies are predominantly developed for miniaturized high-throughput use cases and dosing in the milligram-range. Although solid dosing in the lower gram-range is frequently performed in biotechnological laboratories, there is a lack of evaluated automated dosing technologies in this range. The aim of this study is to investigate the requirements for automated solid dosing in biotechnological laboratories and to introduce a method for the evaluation of existing of-the-shelf dosing technologies. Based on that, one system, the *Mettler Toledo XPR Automatic Balance*, is tested for application in biotechnological laboratories according to these requirements.

1. Introduction

Solid dosing accompanies major laboratory processes, independent, whether it is a chemical synthesis or the preparation of a biochemical assay. The manual dosing of solids typically occurs by using a spatula and disposable weighing dishes. Solids tempt to have individual physical and chemical properties leading to diverse morphologies. The various morphologies of solids complicate their handling. Sticky and lumpy solids often require mechanical impact for dosing while fluffy and porous solids are difficult to pick up with the spatula [1–6]. Combined with the high frequency of solid handling tasks, this basic laboratory operation appears to be increasingly time consuming and tedious [6]. Furthermore, manual solid dosing bears many health issues due to the handling of toxic chemicals. In addition, physical strains such as posture errors are caused by ergonomically unfavourable movements during dosing [4,6,7]. As part of ever-increasing laboratory automation approaches [6,8–15], technologies for the automated dosing of solids are also constantly evolving. Diverse automated solid dosing technologies exist utilizing volumetric or gravimetric techniques [6,16–20]. Both technologies are usually based on funnel-shaped dosing heads that exploit gravity. Volumetric dosing technologies are based on dispensing multiple predefined volumes to reach a desired solid amount [6,8,16,20]. In contrast gravimetric solid dosing technologies are based on a screw or pin that transports the solid to the opening of a funnel-shaped dosing head through vibration or rotation. This happens in combination with a scale and by continuous dispensing until a desired amount is reached [1,6,8,20,21]. Both technologies are already well established in the life science sector and are used for small-scale solid dosing in the milligram-range in miniaturized high-throughput laboratory workflows [6,8]. Comparing the two technologies the volumetric technology is suiy for fast dispensing whereas gravimetric dispensing is better suited for accurate and precise dosing of variable dosing amounts. Nevertheless, both technologies still lack robustness considering the diverse morphologies of solids [6,8,20]. Commercially available systems are for example the *Zinsser REDI-Tool* [22] from *Zinsser Analytic* for volumetric solid dosing and the *Mettler Toledo XPR Automatic Balance* [23] as well as

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https://doi.org/10.1016/j.slast.2026.100406
Received 15 December 2025; Received in revised form 16 February 2026; Accepted 5 March 2026
Available online 6 March 2026

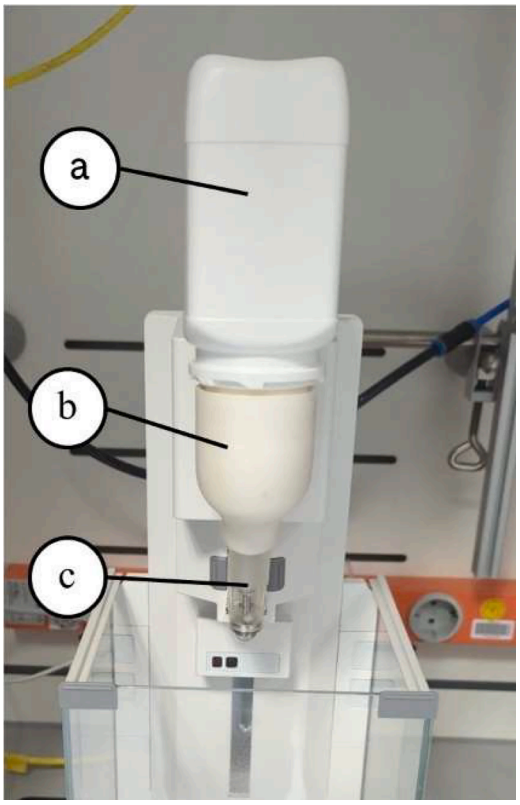

Fig. 1. Mettler Toledo dosing head adapted to 250 mL solid reservoirs. a) 250 mL solid reservoir. b) adapter. c) Mettler Toledo dosing head.

the *Chemspeed Crystal Powderdose* [24] for gravimetric solid dosing [6]. The*Zinsser REDI-Tool* has a dosing range of up to 1 g, the *Chemspeed Crystal Powderdose* of up to 20 g and the *Mettler Toledo XPR Automatic Balance* of up to 8 g. The *Mettler Toledo XPR Automatic Balance* system in particular features a modular design that facilitates customization for diverse experimental configurations. It comprises the so called *Q3* dosing module in combination with diverse balances of the *XPR* series. The system enables robotic handling and operation by robotic arms, allowing for streamlined operation within larger automated laboratory systems. In addition, flexible solid handling of various solids without adjustment effort is realizable by the use of changeable dosing heads [23]. The *Mettler Toledo XPR Automatic Balance* [23] (formerly known as the *Mettler Toledo Quantos*) has been used and tested in several publications [17,18,25] and in an industrial setting. The focus of most of the studies exploring the system was small-scale dosing in the milligram-range [17,21,25,26]. Research articles by Bahr et al. [17,25] tested similar chemicals representative for diverse morphologies up to a maximum of 50 mg dispensing amount. Also, Jiang et al. [18] tested the *Mettler Toledo Quantos* in a range between 20 mg and 1000 mg.

However, solid dosing is a highly tedious and time-consuming task that appears in many further processes that are not miniaturized as typically the case in life science high-throughput processes [6,19]. Accordingly, higher dosing amounts need to be dosed automatically. In biotechnological laboratories liquid preparations in multiple dimensions up to one litre of liquid and under atmospheric environment are prepared for sample preparation and analysis. In this case usually higher solid amounts in the gram-range need to be dosed. Accordingly, there is a lack of research data testing existing cost-effective systems beyond the milligram-range, which is often required in biotechnological laboratories, for example when it comes to the production of buffers.

The aim of this study is to define the major requirements for automated solid dosing in biotechnological laboratories. The investigated requirements are then used for the elaboration of existing automated solid dosing technologies, in this case the *Mettler Toledo XPR Automatic Balance*. We explore the dosing requirements based on the needs of biotechnological laboratories.

2. Automated solid dosing requirements for biotechnological laboratories

Biotechnological laboratories in industry comprise quality control laboratories and small-scale production laboratories among others. Especially, quality control laboratories but also production laboratories perform sample preparation and analysis using High-Performance Liquid Chromatography (HPLC) devices or Photometers. For this liquid or solid samples are handled and buffer solutions are prepared. In case of production laboratories buffers are required not only for analytical testing but also for production itself. Based on that solid dosing is a routine task. For analytical testing and small-scale production, buffers in the range of 1 L volumes are handled. As a result, solid chemicals with diverse morphologies, in the mid-scale range between 5 g and 100 g are handled in high accuracy. In addition, cross contaminations need to be avoided, and dosing times are kept low. Based on that, the following requirements for an automated solid dosing device for biotechnological laboratories need to be fulfilled:

- a mid-scale dosing quantity ability between 5 g and 100 g,
- dosing ability of diverse morphologies in regards of flowability, particle size and dispersity,
- dosability with an accuracy of 1 to 5%,
- avoidance of cross-contamination through cleaning or separated equipment per solid,
- a discrete dosing time of less than 300 s per solid and
- functional in atmospheric environment with moderate humidity.

3. Materials and methods

According to the automated solid dosing requirements introduced in Section 2 a method for the evaluation of existing of-the-shelf dosing technologies is introduced.

The test set up was performed accordingly:

- Five solid amounts between 5 g and 100 g are tested comprising 5 g, 25 g, 50 g, 75 g and 100 g.
- Each test amount is tested in three replicates.
- A minimum of 13 solids with different morphologies comprising flowability and particle size are tested.
- The time spent per solid dosage is measured.
- Measurements are performed under atmospheric environment.
- The recorded target weight and the dosing time is measured and visualized for each solid and evaluated by linear regression.

Based on this test setup the fulfilment of the above-mentioned requirements is evaluated. With this, existing of-the-shelf systems become assessable according to their applicability in biotechnological laboratories. As an example, we evaluated the *Mettler Toledo* dosing system.

We tested the *Mettler Toledo* Q3 dosing module in combination with a *XPR205DR* balance (Mettler-Toledo GmbH, Germany) [23]. The various dosing heads available by the supplier are intended for dosing of a range between 0.1 mg and 8 g. In addition to the dosing reservoirs with a volume of 125 mL, this is in line with the intended goal of the supplier of dosing small amounts in the milligram range. Two types of dosing heads, with the ability to dose particle diameter d_p bigger than 1 mm and poorly flowing solids, comprising the QH012-LNLW [27] and the QH012-LNCT [28] were selected. Both heads include a stirrer and a pin to loosen the solid in the dosing head. The LNLW dosing head does only stir whereas the LNCT pulsates the stirrer in the dosing chamber vertically in addition to the stirring motion. According to the supplier the LNLW is recommended for dosing between 200 mg and 1 g and the LNCT

Table 1
Comparison of dosing error and dosing time with error for LNCT and LNLW for dosing of 5 g.

Solid	LNCT		LNLW	
	[%]	[s]	[%]	[s]
Tris	0.32 ± 0.25	26.67 ± 4.62	0.92 ± 0.28	78.67 ± 24.44
MES	0.42 ± 0.43	47.33 ± 23.86	1.15 ± 0.35	79.67 ± 26.01
NaCl	0.48 ± 0.21	44.33 ± 11.85	0.48 ± 0.05	62.67 ± 25.15
$CaCl_2$	0.20 ± 0.06	46.00 ± 22.65	0.21 ± 0.09	47.00 ± 2.00
$C_6H_8O_7$	0.21 ± 0.12	48.33 ± 4.04	0.48 ± 0.28	74.67 ± 25.42
KH_2PO_4	0.40 ± 0.27	161.33 ± 121.62	-	-
KCl	0.41 ± 0.31	183.67 ± 136.35	0.42 ± 0.16	121.50 ± 76.88

Table 2
Qualitative analysis of the tested solids and dosable amounts.

Solids	Dosing amount [g]	Qualitative Analysis
2-Amino-2-(hydroxymethyl)propane-1,3-diol (Tris), $C_4H_{11}NO_3$	5, 25, 50, 75, 100	free-flowing
2-morpholin-4-ylethanesulfonic acid (MES), $C_6H_{13}NO_4S$	5, 25, 50, 75, 100	free-flowing
Sodium chloride, NaCl	5, 25, 50, 75, 100	free-flowing
Calcium chloride, $CaCl_2$	5, 25, 50, 75, 100	free-flowing
Citric acid, $C_6H_8O_7$	5, 25, 50, 75	free-flowing
Potassium dihydrogen phosphate, KH_2PO_4	5, 25, 50	sticky-lumpy
Potassium chloride, KCl	5, 25	sticky-lumpy
Potassium hydrogen phosphate, $K_2HPO_4 \times 3H_2O$	-	sticky-lumpy
Magnesium chloride, $MgCl_2 \times 6H_2O$	-	sticky-lumpy
2-[4-(2-Hydroxyethyl)piperazin-1-yl]ethane-1-sulfonic acid (HEPES), $C_8H_{18}N_2O_4S$	-	sticky-lumpy
Ammonium acetate, $C_2H_7NO_2$	-	sticky-lumpy
Tris HCl, $C_4H_{11}NO_3$ HCl,	-	sticky-lumpy
Ammonium sulfate, $N_2H_8SO_4$	-	sticky-lumpy

is recommended for dosing 1 g to 8 g. The two different dosing heads are tested for each solid at a weight of 5 g to decide the better suited dosing head according to the solid behaviour. The dosing capability was tested starting with 5 g and then progressing to 25 g, 50 g, 75 g, and finally 100 g. If a solid could no longer be dosed in a certain quantity, the dosing scale issued an error message.

Based on the limited capacity of the original solid reservoirs we 3D-printed an adapter from the thread of the dosing heads to use larger reservoirs and to handle the solids in original containers with a size of 250 ml (Fig. 1).

To increase the reliability of the execution and data collection of the test series, a Python script was used to interact with the interface of the dosing scale. *Mettler Toledo* provides commands which were triggered through the SOAP (Simple Object Access Protocol) communication protocol. The implemented script takes user input for the target weight and substance name, forwards the dosing command to the scale, and sets the dosing tolerance to 1% for every dosing command. After completion of the dosing process, the program receives the results from the dosing scale and centrally stores them in a CSV (Comma-separated Values) file with a timestamp.

To understand the variability in the dosing performance of the solids, the materials were analysed for water content, angle of repose, morphology and particle size distribution. The angle of repose was measured using the fixed funnel method. The solids were poured through a funnel from a fixed height onto a level surface. The resulting cone height and radius were used to calculate the angle. Water content was determined by Karl Fischer Titration using a Metrohm titration system (Metrohm Deutschland GmbH & Co. KG, Germany) and calculated automatically by the system software per manufacturer instructions. The morphology and size distribution of the bulk solids were

Table 3
Dosing time and dosing error for Tris, MES, NaCl, $CaCl_2$, $C_6H_8O_7$, KH_2PO_4 and KCl using the LNCT and LNLW dosing heads. Empty fields mark that measurements were not continued and n<3 marks the solids that were tested but were not dosable in three replicates.

Solid	5.0 g	25.0 g	50.0 g	75.0 g	100.0 g
LNCT_Tris	26.67 ± 4.62 s 0.32 ± 0.25 %	110.00 ± 13.89 s 1.18 ± 0.19 %	192.33 ± 11.15 s 0.52 ± 0.04 %	281.67 ± 22.74 s 0.36 ± 0.03 %	377.33 ± 29.37 s 0.31 ± 0.04 %
LNLW_Tris	78.67 ± 24.44 s 0.92 ± 0.28 %				
LNCT_MES	47.33 ± 23.86 s 0.42 ± 0.43 %	98.33 ± 16.07 s 1.40 ± 0.13 %	164.00 ± 20.42 s 0.67 ± 0.14 %	225.33 ± 10.97 s 0.48 ± 0.03 %	341.00 ± 17.09 s 0.42 ± 0.08 %
LNLW_MES	79.67 ± 26.01 s 1.15 ± 0.35 %				
LNCT_NaCl	44.33 ± 11.85 s 0.48 ± 0.21 %	89.67 ± 73.91 s 0.19 ± 0.15 %	93.67 ± 11.15 s 1.63 ± 0.24 %	134.00 ± 3.00 s 1.13 ± 0.15 %	151.67 ± 12.22 s 0.74 ± 0.05 %
LNLW_NaCl	62.67 ± 25.15 s 0.48 ± 0.05 %	121.33 ± 1.53 s 0.59 ± 0.04 %	241.67 ± 9.50 s 0.29 ± 0.03 %	365.00 ± 12.77 s 0.21 ± 0.02 %	472.33 ± 19.86 s 0.14 ± 0.00 %
LNCT_$CaCl_2$	46.00 ± 22.65 s 0.20 ± 0.06 %	111.33 ± 15.04 s 1.09 ± 0.10 %	185.00 ± 6.00 s 0.53 ± 0.03 %	274.33 ± 24.09 s 0.44 ± 0.08 %	352.00 ± 57.42 s 0.35 ± 0.11 %
LNLW_$CaCl_2$	47.00 ± 2.00 s 0.21 ± 0.09 %	170.67 ± 5.69 s 0.59 ± 0.08 %	349.67 ± 22.94 s 0.28 ± 0.03 %	n < 3	
LNCT_$C_6H_8O_7$	48.33 ± 4.04 s 0.21 ± 0.12 %	151.00 ± 11.00 s 0.52 ± 0.04 %	307.33 ± 14.01 s 0.27 ± 0.03 %	476.67 ± 30.92 s 0.17 ± 0.05 %	n < 3
LNLW_$C_6H_8O_7$	74.67 ± 25.42 s 0.48 ± 0.28 %	n < 3			
LNCT_KH_2PO_4	161.33 ± 121.62 s 0.40 ± 0.27 %	238.67 ± 17.67 s 0.18 ± 0.02 %	478.33 ± 72.60 s 0.10 ± 0.01 %	n < 3	
LNLW_KH_2PO_4	n < 3				
LNCT_KCl	183.67 ± 136.35 s 0.41 ± 0.31 %	139.00 ± 24.27 s 0.32 ± 0.11 %	n < 3		
LNLW_KCl	121.50 ± 76.88 s 0.42 ± 0.16 %	n < 3			

analysed by dynamic image analysis using a Microtrac Camsizer X2+ (Microtrac Retsch GmbH, Germany) equipped with an X-Jet air pressure dispersion module. Key parameters including the median particle size (d_{50}), sphericity, span, and aspect ratio were calculated based on volume-weighted distribution (Q3) by the system software in accordance with the manufacturer's instructions. Solids were tested as received without further pretreatment.

4. Results and discussion

Prior to quantitative analysis, the thirteen selected compounds were qualitatively divided into two main groups based on a preliminary visual assessment of their macro-morphological properties, comprising:

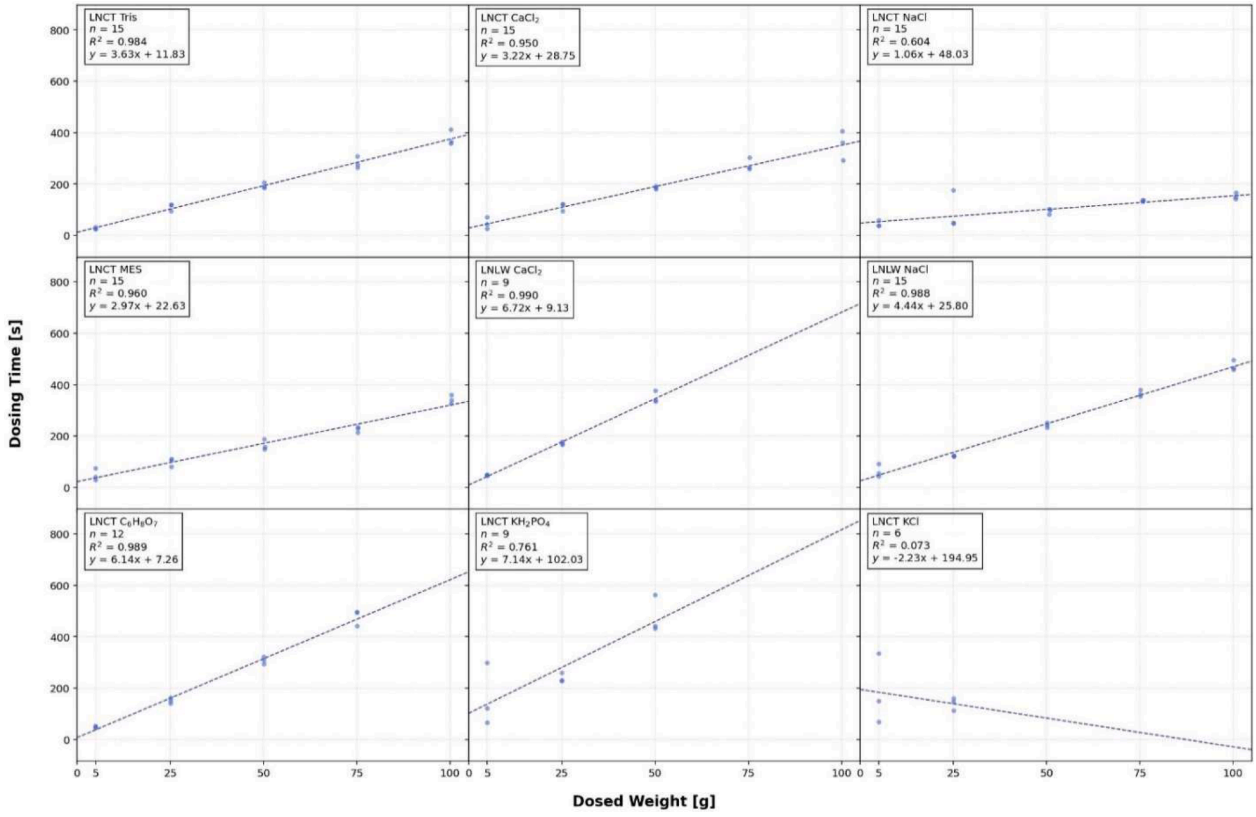

Fig. 2. Graphical visualization of target weight against dosing time for Tris, MES, NaCl, $CaCl_2$, $C_6H_8O_7$, KH_2PO_4 and KCl. Tris and MES were dosed with the LNCT up to a range of 100 g. NaCl and $CaCl_2$ are depicted for dosing with the LNCT and LNLW. $C_6H_8O_7$, KH_2PO_4 and KCl are dosed with the LNCT.

Table 4
Measured values for water content, angle of repose and particle size distribution comprising median particle size (d_{50}), sphericity, span, and aspect ratio for the tested solids. Critical values are marked in red. Empty fields mark that the value was not measurable.

Solid	Water Content [%]	Angle of Repose	d_{50} [mm]	Span	Sphericity	Aspect Ratio
Tris	0.1	38	0.4487	1.001	0.778	0.623
MES	4.5	37	0.1335	1.339	0.833	0.668
NaCl	0	29	0.5144	0.442	0.951	0.857
$CaCl_2$	24.6	43	0.2846	1.120	0.829	0.692
$C_6H_8O_7$	8.3	30	0.6993	1.293	0.847	0.686
KH_2PO_4	0	36	0.2994	1.278	0.864	0.755
KCl	0.2	32	0.3344	0.584	0.858	0.780
$K_2HPO_4 \times 3H_2O$	23.6	51				
$MgCl_2 \times 6H_2O$	52.3	42				
HEPES	0.1	45	0.0322	46.423	0.713	0.659
$C_2H_7NO_2$	0.8	50				
Tris HCl	0.5	38	0.4724	1.294	0.872	0.746
$N_2H_8SO_4$	0.3	25	1.1775	0.813	0.823	0.684

- free-flowing bulks comprising Tris, MES, NaCl, $CaCl_2$ as well as $C_6H_8O_7$ and
- sticky-lumpy bulks comprising KH_2PO_4, KCl, K_2HPO_4, $MgCl_2$, HEPES, $C_2H_7NO_2$, Tris HCl as well as $N_2H_8SO_4$.

In a first test setup the dosability of the solids was tested at 5 g comparing the LNLW and the LNCT dosing heads (Table 1).

First dosing tests show that predominantly the free-flowing solids were dosable in the range of 5 g. Only KCl and KH_2PO_4 from the sticky-lumpy solids were able to be dosed in this mid-scale dosing range. Comparing the two dosing heads there is no significant difference in dosing accuracy, which was below 1% for every solid except for the dosing of MES with the LNLW. Primarily deviations are observed when comparing the dosing time. For Tris and MES dosing with the LNCT

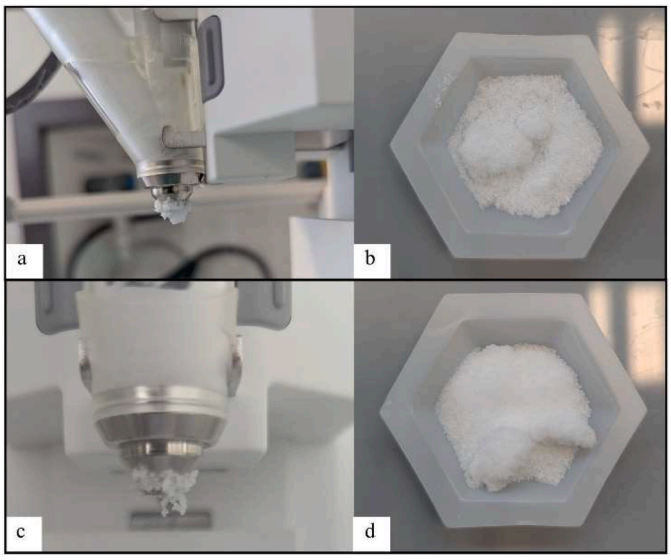

Fig. 3. Depicted is the solid structure of KH_2PO_4 (a & b) and NaCl (c & d). a) and c) show agglomeration effects at the opening of the dosing head. b) and d) show the solid structure.

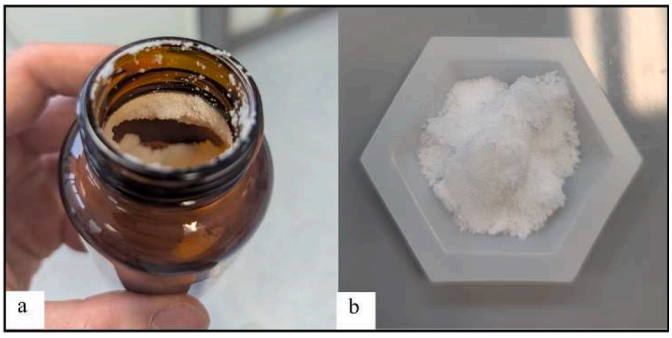

Fig. 4. Solid structure of KCl. (a) shows the adherence of the solid to the surface and (b) shows the sticky and lumpy morphology of the solid.

occurred to be minimally more accurate and, above all, much faster. Based on that the LNCT was used for further dosing experiments. For NaCl dosing with the LNCT compared to dosing with the LNLW occurred slightly faster. However, since the difference is not significant, dosing of NaCl was tested with both heads over the range of up to 100 g. The LNLW was also used for dosing of $CaCl_2$, because dosing of the 5 g bulk showed a consistent dosing time with a lower error than with the LNCT. However, when performing further dosing tests, it showed that only with the LNCT $CaCl_2$ was dosable to an amount of 100 g whereas with the LNLW dosing was only possible up to 50 g. For $C_6H_8O_7$ dosing with the LNCT was faster than with the LNLW. But when continuing dosing, the LNCT was not able to dose more than 75 g. Otherwise, when testing the LNLW for its dosing ability greater than 5 g it appeared that dosing of 25 g was not possible (Table 2). KH_2PO_4 was only dosable with the LNCT. For KCl on the one side dosing with the LNLW was faster than dosing with the LNCT but on the other side dosing of 25 g was not possible. Therefore, the LNCT was used for further dosing tests. In conclusion, vertical pulsating of the stirrer in the dosing chamber as it is the case for the LNCT in addition to the stirring motion shows better applicability for mid-scale dosing of at least free-flowing solids.

The test results show that even though the LNCT was mostly better suited for dosing of 5 g, dosing with the LNLW, albeit somewhat slower, designed for dosing of a maximum of 1 g was also possible. With the LNCT 4 solids comprising Tris, MES, NaCl and $CaCl_2$, out of the 13 tested solids were able to be dosed up to a quantity of 100 g. Citric acid was dosed up to a quantity of 75 g and KH_2PO_4 up to a quantity of 50 g. KCl was dosable up to 25 g. These results are particularly remarkable considering that the LNCT was originally designed for a maximum dose of only 8 g. The other solids including K_2HPO_4, $MgCl_2$, HEPES, $C_2H_7NO_2$, Tris HCl and $N_2H_8SO_4$ were not dosable in the range of 5 to100 g (Table 2).

Considering the dosing times, when dosing in the milligram-range, Bahr et al. [17] measured a mean dispensing time of less than 50 s. When dosing in the lower gram-range the dosing time is higher. A linear time profile is measured for all dosable solids apart from KCl. This linear time profile indicates that the two dosing heads, comprising the LNCT and the LNLW, ensure a uniform dosing over time. For the practical application this makes it possible to calculate the time required for a proportionally increasing dosage of each solid within a workflow of weighing multiple solids (Fig. 2).

For the solids which where dosable over the complete dosing range between 5 g and 100 g a dosing time starting at around 30 s for 5 g up to around 400 s for 100 g was measured. Only the dosing of NaCl with the LNCT dosing head occurred to be very fast with an increasing dosing time for 100 g of up to 152 s compared to dosing with the LNLW dosing head. Dosing times of 400 s are slightly higher than the target 300 s defined in Section 2 but are traced back to the predefined accuracy of 1%. The dosing accuracy for dosing in the mid-scale range with the *Mettler-Toledo* dosing module appears to be very high. Except for a few minimal deviations, the accuracy for most doses in the range of 5-100 g is below the specified limit of 1% (Table 3).

Citric acid was only dosable up to 75 g which is traced back to the high water content of 8.3% (Table 4) [3]. A steadily decreasing dosage capability was observed for KH_2PO_4 and KCl. This is attributed to the sticky-lumpy structure of the powders. For KH_2PO_4 agglomeration at the opening of the dosing head appeared to be the limiting factor causing the decreased dosability of the solid until 50 g. Strongly varying dosing times caused by lacking free-flowability of the solid lead to a low coefficient of determination R^2 of 0.8. However, similar agglomeration was observed for NaCl (Fig. 3) and did not influence the dosability of the solid that showed a high coefficient of determination of 0.988 (Fig. 2).

The restricted dosability of KCl of up to 25 g appears to be due to the strong adherence of the solid to the surface of the container and the dosing head. This prevents the solid from flowing into the dosing chamber of the dosing head, so that when dosing larger amounts, no more solid moves into the dosing chamber (Fig. 4). This also affects the dosing robustness as can be seen in the coefficient of determination and the variable dosing times for 5 g and 25 g.

A quantitative analysis of the physical morphology parameters of the solids was performed to examine the free-flowing and sticky-lumpy macro-morphological properties of the solids (Fig. 5).

The quantitative analysis of the solids according to water content, angle of repose, particle size distribution, and morphology allows for a differentiated understanding of their physical properties, however, no universal pattern for predicting dosing performance is identifiable for the entire data set. While a general correlation is absent, individual parameters offer reasonable explanations for the failure of specific compounds (Table 4). For instance, for $K_2HPO_4 \times 3H_2O$ and $MgCl_2 \times 6H_2O$ the increased water content causes the sticky-lumpy morphology of the solids and the lacking dosability [3,5]. Together with $C_2H_7NO_2$, characterization of the three solids with dynamic image analysis was not possible due to the stickiness of the solids. Regarding $C_2H_7NO_2$ the increased angle of repose indicates the limited flowability and thus dosability of the solid which also applies to $K_2HPO_4 \times 3H_2O$ [29]. While the cohesive nature of $C_2H_7NO_2$ suggests limited dosability in the tested gram-range, it has been successfully dispensed at a 1000 mg scale by Jang et al. [18] using the Mettler Toledo System. These observations indicate that the dosability of a solid is not only dependant on morphology but is also influenced by the scale of operation and the target mass. In the case of $N_2H_8SO_4$ and HEPES the particle size appears to majorly influence their macroscopic sticky-lumpy morphology and

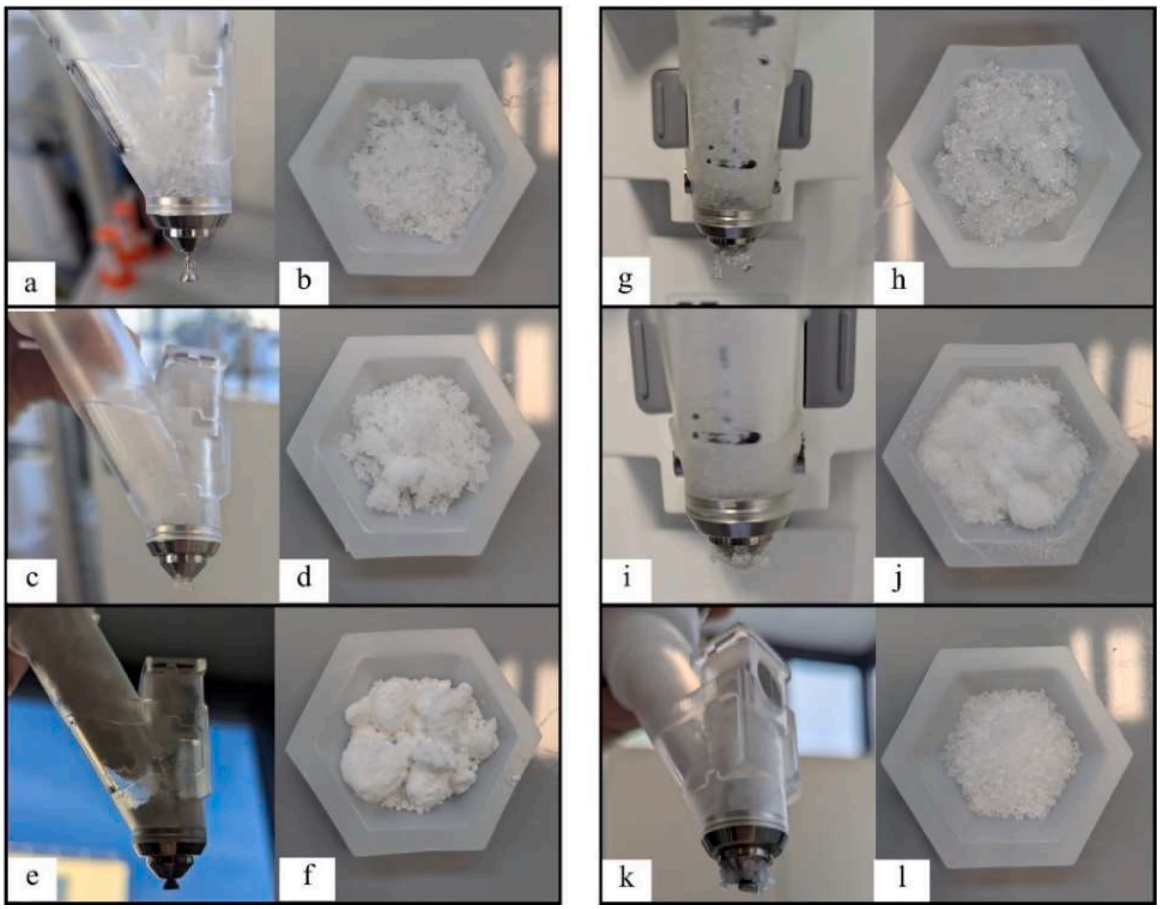

Fig. 5. Depicted are the solid structures of K_2HPO_4, MgC_{l2}, HEPES, $C_2H_7NO_2$, Tris HCl and $N_2H_8SO_4$. (a) and (b) K_2HPO_4, (c) and (d) MgC_{l2}, (e) and (f) HEPES, (g) and (h) C2H7NO2, (i) and (j) Tris HCl and (k) and (l) $N_2H_8SO_4$.

flowability. On the one side the increased particle diameter of $N_2H_8SO_4$ seems to lead to mechanical interlocking of the particles, preventing them from flowing downwards into the dosing chamber [30]. On the other side, for HEPES the small particle diameter leads to a compaction of the powder caused by cohesive behaviour due to adhesive forces, resulting in clumping and a lack of flowability [29–31]. This is also evident in the broad span of the particle size distribution of HEPES, indicating a high degree of polydispersity and potentially causing segregation effects [30]. A comparison between Tris and Tris HCl reveals no significant difference in their quantitative physical parameters. However, the experimental results (Table 2) indicated that the sticky-lumpy morphology of Tris HCl compared to Tris caused the poor dosability. In contrast, MES, $CaCl_2$ and $C_6H_8O_7$ demonstrated successful dosing performance despite increased water contents. This was particularly evident in the case of $CaCl_2$. The reduced dosing performance of KH_2PO_4 and KCl occurred despite any unremarkable values across all quantitatively measured physical parameters (Table 4).

These observations demonstrate that dosing failure is often multicausal and cannot be attributed to a single parameter. While established quantitative analytical parameters provide an essential explanatory foundation, they do not fully capture the complex material behaviour encountered during automated dosing to allow for a definitive predictive model on dosing performance. Furthermore, the results show that dosability is not a static material parameter but is significantly influenced by the scale of operation. Therefore, empirical evaluation remains an indispensable requirement to accurately determine dosing performance, as practical validation is necessary to bridge the gap between quantitative analysis and hardware-specific behaviour.

Finally, the results show that even though the *Mettler Toledo XPR Automatic Balance* is designed for dosing in the small-scale range dosing in the mid-scale range is also possible. This is especially the case for free-flowing solids. In addition, sticky-lumpy solids are also dosable, albeit only to a limited extent. Free-flowing solids were dosable in a range of 5 g to 100 g comprising Tris, MES, NaCl and $CaCl_2$. Especially, vertical pulsating of the stirrer in the dosing chamber as it is the case for the LNCT in addition to the stirring motion shows better applicability for mid-scale dosing. The dosing time of 400 s is slightly longer than the target 300 s, but can be traced back to the stated accuracy of 1%. However, this was achieved in almost all cases and confirms the dosing accuracy of the dosing system. In addition, the linear time profile during dosing shows that when a solid is dosable, there is no blocking or delay by the dosing head enabling calculation of the time required for a proportionally in-creasing dosage of each solid within a workflow of weighing multiple solids. Cross-contamination is avoided by using one dosing head for each solid. The option of using an adapter to screw a larger reservoir or the original container onto the dosing heads is also advantageous.

5. Conclusion

As laboratory process automation approaches become increasingly prevalent, the automation of solid dosing represents a bottleneck, particularly in the field of biotechnological laboratories. The method introduced for the evaluation of automated solid dosing technologies enables to assess the systems regarding their ability and functionality for dosing in the mid-scale range to close the gap between manual and miniaturized high-throughput dosing. For this, automated solid dosing requirements for sample preparation and analysis in biotechnological

laboratories comprising amount, solid morphology, accuracy, purity, time and atmospheric conditions are considered. The *Mettler Toledo* system primarily meets the requirements for accuracy and avoidance of cross-contamination. In addition, free-flowing solids are dosable in a dosing range up to 100 g, although the system is designed only for a maximum of 8 g according to the dosing heads specification. Besides, partially sticky-lumpy solids were also dosable with the dosing module. The linear time profile during the dosing also shows a delay-free and block-free dosing with the system. The free-flowing solids are dosable under atmospheric conditions, as well as some sticky-lumpy solids. Furthermore, this study highlights that while quantitative scientific indicators are essential for identifying specific material constraints, they do not allow for a definitive predictive model. This emphasizes the need of empirical, device-specific testing at the intended scale of operation to address the complexity of the interactions between solids and hardware as a necessary complement to quantitative analysis.

6. Future perspectives

Further evaluations of more existing off-the-shelf automated systems according to the introduced method enable a comprehensive assessment of the state-of-the-art technologies and their suitability for mid-scale dosing applications in biotechnological laboratories. Based on this evaluation, it is possible to develop future lab technologies specifically designed for the mid-scale dosing range capable of handling sticky-lumpy solids in atmospheric conditions.

CRediT authorship contribution statement

Aziza El Hariry: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alexander Hirvell:** Writing – review & editing, Writing – original draft, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Philipp Nöcker:** Writing – review & editing, Validation, Software, Investigation, Formal analysis, Data curation, Conceptualization. **Felix Heinrich-Zellner:** Writing – review & editing, Validation, Software, Investigation, Formal analysis, Data curation, Conceptualization. **Cornelia Conover:** Writing – review & editing, Validation, Software, Investigation, Formal analysis, Data curation, Conceptualization. **Rüdiger Bauer:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Markus Reischl:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This work was supported by the Program Material Systems Engineering of the Helmholtz Association, Institute for Automation and Applied Informatics, Karlsruhe Institute of Technology, Eggenstein-Leopoldshafen, Germany; and the Global Engineering and Technology Department, the Process Technology Department and the Manufacturing Science & Technology Department, Roche Diagnostics GmbH, Penzberg, Germany. Open access funding is enabled and organized by the Global Engineering and Technology Department, Roche Diagnostics GmbH, Penzberg, Germany.

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