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Versatile Methods to Dispense Sub-Milligram Quantities of Solids using Chemical Coated Beads for High-Throughput Experimentation

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ABSTRACT: High-throughput experimentation (HTE) is a technique for screening multiple reaction conditions in parallel at micro- or nanoscale without depleting precious starting material. However, assembling a comprehensive screening set often involves the distribution of large number of solid reagents with diverse physical properties in small quantities. Automated solid dispensing, especially at sub-milligram scale, has long been a challenge with no practical and reliable solutions. This paper describes the use of our newly developed chemical coated beads (ChemBeads) technology to provide a universal approach to the solid handling problem. This technology, when combined with an automated solid dispensing platform, or calibrated scoops, can dispense sub-milligram quantities of a variety of solids with efficiency and adequate accuracy.

KEYWORDS: *high throughput experimentation, chemical coated beads, sub-milligram solid dispensing, automation, microscale research, ChemBeads*

INTRODUCTION

In early drug discovery, one of the primary goals is the development and optimization of synthetic reaction conditions for rapid generation of a new single compound or a collection of diverse compounds via parallel library synthesis.[1] The traditional iterative process of experimentation can be tedious, time-consuming and costly for the following reasons: (1) it requires time and manual labor to investigate a viable synthetic route to targeted compounds and carry out the solid handling for a large array of small scale reactions, (2) there is a limited supply of advanced intermediates needed for the synthesis of targeted compounds, and, (3) there is a lack of automation for quick compilation of the screening sets and to set up reactions at microscale.[2] To remedy this situation, the art of high-throughput experimentation (HTE) is progressively being employed across the pharmaceutical industry[3] and academic laboratories.[4]

Microscale HTE is a technique that aims at screening multiple reaction conditions in parallel with minimal use of precious starting material (1 mg or less per reaction).[5] Ideally, a microscale HTE approach should survey reaction conditions broadly as a starting point for chemists to further investigate and optimize the transformation. However, assembling a comprehensive screening set often involves the distribution of large number of reagents in small quantities. Previously the dispensing of materials, as stock solutions, was carried out by a liquid handler followed by evaporation of solvent, rendering it time-consuming, labor intensive and limited to only soluble reagents.[3,5] Automated solid dispensing, especially in sub-milligram scale, has long been a challenge with no practical and reliable solutions.

During our quest for a practical solution to the solid dispensing challenge, we realized that it is extremely difficult for a single robotic platform to dispense a large variety of solid

reagents with diverse physical properties. The difficulties compounded when the targeted weight is in the low to sub-milligram range, which is most desirable for setting up microscale HTE. The Enabling Technologies Consortium High Throughput Experimentation Working Group (HTE WG) described their collaborative studies on solid dispensing technologies on multiple platforms using solids with diverse physical properties commonly encountered in a pharmaceutical research and development laboratory.[6] They reported that while there were strengths and weaknesses of each robotic platform studied, there was a major limitation for these systems to accurately dispense low target masses (2 mg or less). To the best of our knowledge, there is no suitable technology that can effectively dispense sub-milligram quantities of solid reagents with various physical properties commonly used in pharmaceutical and academic laboratories. This industry-wide challenge prompted us to tackle the root cause of the problem towards a universal solution. One approach is to unify the diverse physical properties of solids into one uniform and favorable form, hence simplifying the solid dispensing process to enable a single platform to dispense a variety of solid reagents.

We recently reported a novel technology whereby solid reagents (guest particle) are coated on glass beads (host particle) to enable dispensing of various solid reagents at sub-milligram scale for high throughput experimentation (ChemBeads).[7] Herein we report the extension of the technology to include polystyrene beads as the host material and detailed studies of this technology in dispensing diverse solid reagents. ChemBeads technology utilized a dry powder coating technique to improve powder flowability, content uniformity, and dissolution properties of native solid reagents.[8] During this dry powder coating process, solid reagent adheres to the surface of the host material (glass or polystyrene

beads) via Van der Waals forces, resulting in ChemBeads that retained the high flowability of the host material.[9] In essence, the "transformed" physical properties and the low mass loading (1-20% loadings) of various solid reagents to that of the host materials can: (1) render ChemBeads of different solid reagents to have similar physical properties and enable the development of a single solid dispensing protocol for diverse solids in ChemBeads form and, (2) deliver sub-milligram amount of native reagents using milligram target mass of ChemBeads. In addition, the low variations in densities of the glass and polystyrene beads (regardless of the solid reagent coated) enabled the use of a volume to "weigh" out ChemBeads. Using a suite of 3D printed scoops with calibrated scoop volume (see Supporting Information Figure S7), ChemBeads can be dispensed manually without the need of an analytical balance.[7]

To further evaluate the effectiveness of the ChemBead approach, we set up experiments to dispense the seven test solids as chosen by the HTE WG.

MATERIALS AND METHODS

In this study, Solid Dispense Unit (SDU) and Gravimetric Dispensing Unit for Powder fine dosing (GDU-Pfd), both of which are commercially available automated powder dispensing tools from Chemspeed Technologies, were examined.[10] These tools have been used for solid dispensing in pharmaceutical laboratories. Both tools utilized gravity to deliver ChemBeads from the dispensing bottle to the receiving vial. The SDU used rotary action via an auger to dispense ChemBeads, whereas the GDU-Pfd controls the dispense of ChemBeads via rapid open/close actions of an opening at the bottom of the solid dispensing bottle.

To ensure broad adoption of the ChemBead technology, manual distribution of ChemBeads using calibrated scoops was also examined. A suite of 3D printed scoops with calibrated scoop volume (calibrated to 5, 10 and 50 mg ChemBeads) were used to distribute various solid reagents by simply scooping out Chembeads followed by lightly tapping the scoop to remove any materials that were accumulated over the rim of the scoop.[7]

The inflated mass also enabled the delivery of sub-milligram quantity of native reagents with milligram amount of ChemBeads (at 1% loading, 5 mg ChemBeads contain 0.05 mg of native solid reagent). This greatly simplified the solid dispensing process for both automated and manual methods, i.e., handling milligrams quantity of ChemBeads *vs* micrograms of native solid reagents.

Automated Solid Dispensing Platform and Calibrated Scoop Experiments.

The mass dispensed (mg) and dispense time (second) data were extracted from the log files of the automated solid dispensing systems. Dispense time refers to the time required for a given type of ChemBeads to dispense completely to a vial at the targeted mass, but excluding the time required to move the dispense head into position prior to the actual dispense. For the manual solid dispensing experiments using calibrated scoops, an automated weighing Tecan EVO robot equipped with a calibrated balance was used to determine the tare masses of a set of empty 4mL vials. ChemBeads were then dispensed into the 4 mL vial using the calibrated scoops. The set of 4 mL vials were re-weighed on the Tecan EVO to determine the net mass of ChemBeads in each vial. The average dispense time (second) per manual dispense using the calibrated scoops was defined as the difference between the start and end time needed to dispense all 3 target masses in the vials, divided

by the total number of vials. The mean, median, standard deviation, % RSD calculations on mass dispensed, and dispense time data were determined. The % error of each mass dispensed was defined as the difference between the mass dispensed and the target mass, divided by the target mass, and multiplying the result by 100 as shown below:

$$\% \text{ error } = \frac{(\text{mass dispensed} - \text{target mass})}{\text{target mass}} \text{ x } 100$$

ChemBeads Preparation.

Seven test solids were coated on commercially available glass or polystyrene beads. These host materials are easily accessible, highly flowable, have automation friendly particle sizes (200-500 micron) and have a round smooth surface for uniform coating. All seven solids and glass beads were obtained from Millipore Sigma and the polystyrene beads were purchased from Advanced ChemTech (Table 1).

Table 1. The seven solids and the host materials investigated in this study.

Material	Grade	Lot number
D-mannitol	ACS	SLBK4566V
fumed silica	Aggregate powder 0.2 – 0.3 µm	SLBW6877
L-proline	BioUltra	BCBP4505V
calcium carbonate	BioUltra	BCBM9216V
polyvinylpolypyrrolidone (PVPP)	Average mol wt 40,000	WXBC6499V
sodium chloride	BioXtra	SLBV9983
thiamine HCl	BioReagent	SLBW7025
glass beads	PN: G1277, 212-300 µm	SLBS1081V
polystyrene beads	PN: SP5070 35-45 mesh	33344

D-mannitol, L-proline and sodium chloride appeared crystalline and chunky. They were first milled down to a fine powder prior to the coating process on both glass and polystyrene beads.[7] The dry powder coating process was carried out using a Resonance

Acoustic Mixer (RAM).[11] The RAM is a mixing instrument that relies upon the application of a low-frequency, high-intensity acoustic field to facilitate mixing. A certain loading of the solid reagent was added to a vial containing either glass or polystyrene beads and then mixed using the RAM at 70% intensity for 5 to 15 minutes. For each solid material, we investigated different percent loadings of the solid to the two host materials. ChemBeads with maximum coating performance were used in this study (Table 2A and 2B). The maximum loading was defined as the maximum amount of solid reagent that can be coated on the glass and polystyrene beads evenly with no excess and loose chemical solids present.

Table 2A. Maximum loadings of solids coated on glass beads.

Solids	Loading on glass beads	ChemBead Mass Dispensed/(mg)				
		50	10	2	1	0.5
		Estimated* Mass of Native Solid Dispensed (mg)				
D-mannitol	4.70%	2.35	0.47	0.094	0.047	0.0235
fumed silica	1.70%	0.85	0.17	0.034	0.017	0.0085
L-proline	1.80%	0.90	0.18	0.036	0.018	0.009
sodium chloride	4.90%	2.45	0.49	0.098	0.049	0.0245
thiamine HCl	3.40%	1.70	0.34	0.068	0.034	0.017

*Amount calculated based on the % loading of the solids

Table 2B. Maximum loadings of solids coated on polystyrene beads.

Solids	Loading on polystyrene beads	ChemBead Mass Dispensed/(mg)				
		50	10	2	1	0.5
		Estimated* Mass of Native Solid Dispensed (mg)				
D-mannitol	1.80%	0.90	0.18	0.036	0.018	0.009
L-proline	4.00%	2.00	0.40	0.08	0.04	0.02
calcium carbonate	2.50%	1.25	0.25	0.05	0.025	0.0125
PVPP	20.0%	10.0	2.00	0.40	0.20	0.10
sodium chloride	7.00%	3.50	0.70	0.14	0.07	0.35
thiamine HCl	1.80%	0.90	0.18	0.036	0.018	0.009

*Amount calculated based on the % loading of the solids

Study Scope, Design, and Workflow

The study included the dispensing of ChemBeads to one vial as well as multiple vials using the automated platforms and the calibrated scoops and, was designed to test practical situations encountered mostly in HTE workflows by scientists in pharmaceutical laboratories. The experiment was standardized and included the following aspects:

Target mass: 0.5, 1.0, 2.0, 10.0, and 50.0 mg were used for the automated solid dispensing platforms. The 5, 10 and 50 mg calibrated scoops were used for manual dispensing of solid reagents coated on glass beads; 5 mg scoop was the smallest size designed using a 3D printer in our lab.[12] The calibrated scoops for polystyrene beads are currently in development.

Number of runs: 5 runs for each type of ChemBeads (5 coated on glass and 6 coated on polystyrene beads) at a given target mass into a 20 mL vial for the automated solid dispensing platform. 5 runs (5, 10, and 50 mg target mass) using the calibrated scoops into 20 separate 4 mL vials, for a total of 25 runs for all the ChemBeads using the automated platforms and 15 runs for all the ChemBeads using the calibrated scoops.

Number of dispenses: 1 run = 20 dispenses of the ChemBeads, for a total of 500 dispenses for each type of ChemBeads on the automated solid dispensing platforms and 300 dispenses using the calibrated scoops. A total of 7000 dispenses were made in the study.

Run order: The run involved 5 types of ChemBeads (glass beads) and 6 types of ChemBeads (polystyrene beads) aligned consecutively with varied target masses (50.0, 10.0, 2.0, 1.0, and 0.5 mg) on the automated solid dispensing platforms. For the calibrated scoops, the run involved scooping one type of ChemBeads at the different target masses (5, 10, and 50 mg consecutively) in the 20 separate 4 mL vials for each target mass.

RESULTS AND DISCUSSION

The dry powder coating process of the seven solids on the beads resulted in maximum loading of D-mannitol, L-proline, sodium chloride and thiamine HCl on both glass and polystyrene beads, fumed silica on glass beads and calcium carbonate and PVPP on polystyrene beads. The low effective mass of solid reagents (1-20 %) on beads was maximized for each individual solid (Table 2). For instance, dispensing 10 mg of thiamine HCl ChemBeads at 3.4% loading will deliver 0.34 mg of native thiamine HCl. Purities and quantities assessment of D-mannitol, thiamine HCl and L-proline ChemBeads were confirmed using quantitative NMR. In addition, a HPLC based quantification method was used to validate the amount of thiamine HCl coated on glass beads. In all cases examined, loading accuracy was determined to be within ±10% of the calculated values. (see Supporting Information for both quantitative NMR and HPLC based quantification results). For NaCl, PVPP, $CaCO_3$ and fumed silica, where NMR or HPLC quantification methods are not applicable, we used mass difference of ChemBeads (before and after coating) to estimate the loading of solids on beads.

Solid properties of each ChemBead were characterized by a variety of methods commonly used in the pharmaceutical industry to evaluate their flow properties, density and hygroscopicity (see Supporting Information for details). Results indicated that ChemBeads have low variability of density, regardless of the solid reagent coated on the beads and retained favorable flowability of the host material.

We verified the weighing data collected for any outliers and recurring patterns from the 7000 dispenses. A total of 90 dispenses were discounted and 6910 dispenses were used for the analysis. The discounted dispenses were mostly due to user error in defining the

parameters on the GDU-Pfd control software. There was no machine stall, machine time out, or zero value observed in this study. The calibrated scoops were designed for coated reagents on glass beads only and therefore they were only used to dispense D-mannitol, fumed silica, L-proline, sodium chloride and thiamine HCl ChemBeads.

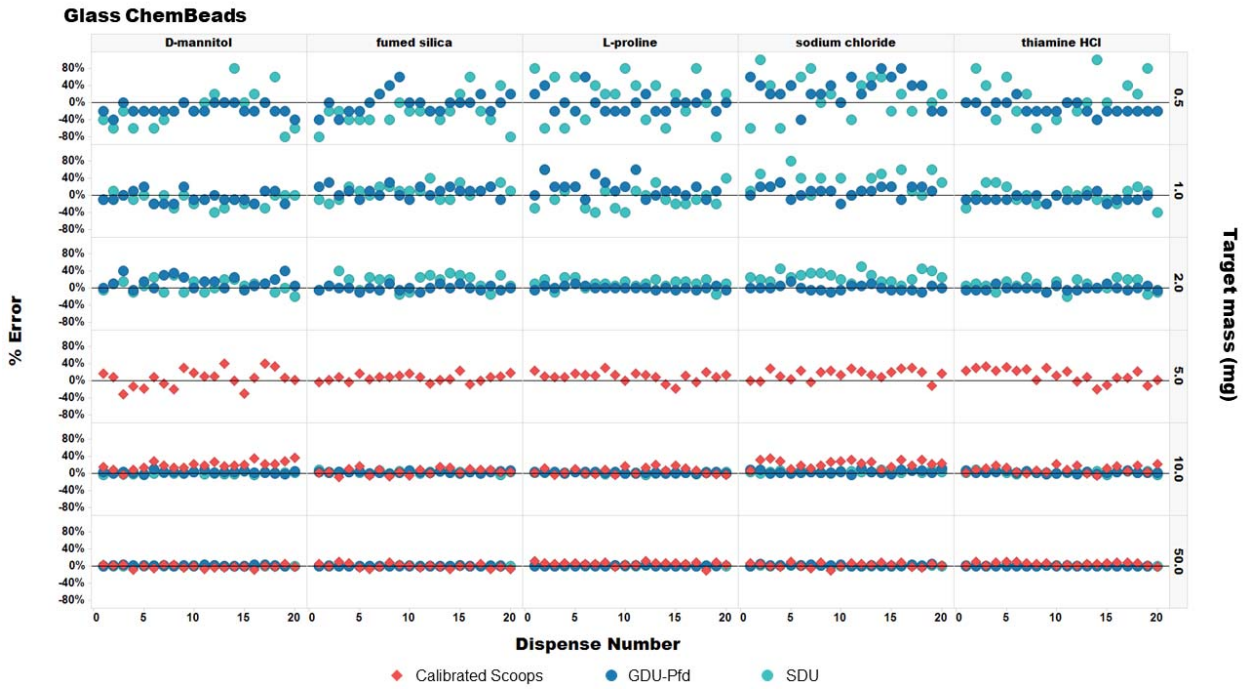


Figure 1. Scatterplot of % error values (-80% to 80%) vs. dispense number (1 – 20), broken down by reagents on glass beads (columns), target mass in mg (rows), and instrument (colors).

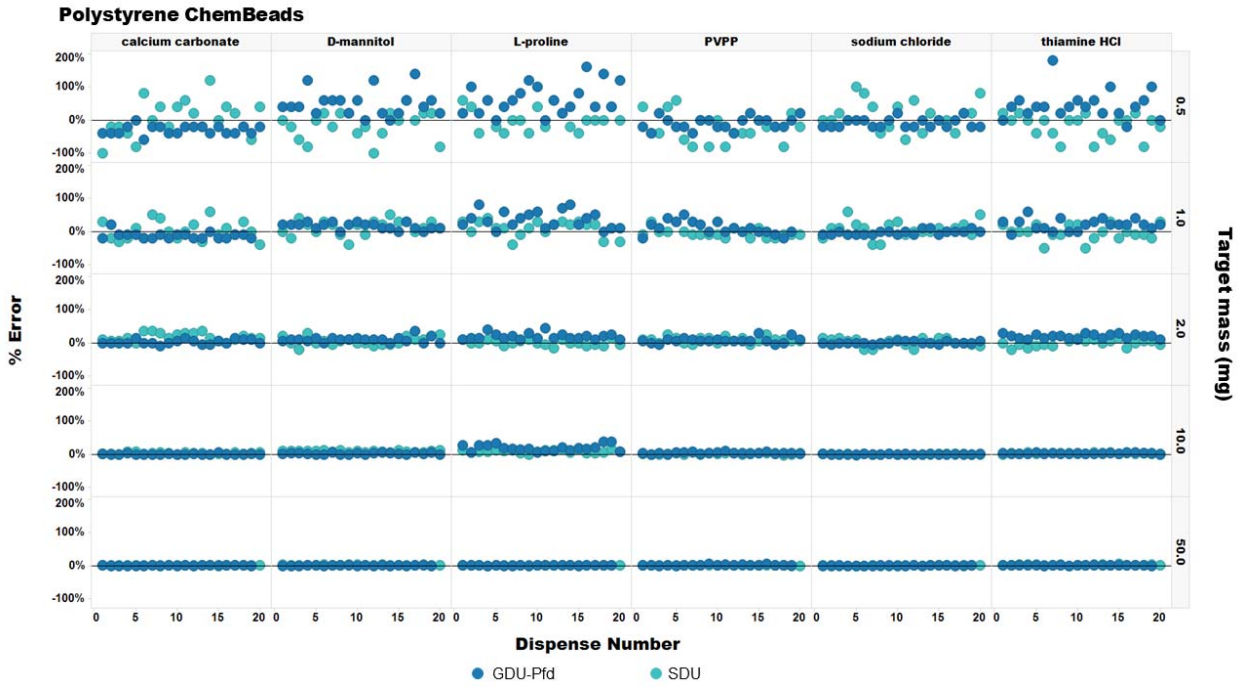


Figure 2. Scatterplot of % error values (-100% to 200%) vs. dispense number (1 – 20), broken down by reagents on polystyrene beads (columns), target mass in mg (rows), and instrument (colors).

Automated Solid Dispensing (SDU and GDU-Pfd platforms)

All eleven ChemBeads were dispensed on both SDU and GDU-Pfd equipped platforms. The data retained for analysis is shown as a scatterplot of % error versus dispense number through a run, broken down by the target mass, the type of techniques and the coated material on glass beads (Figure 1) and on polystyrene beads (Figure 2).[13] Solid dispensing protocols for coated glass and polystyrene beads were developed separately on both SDU and GDU-Pfd equipped platforms. It is important to note that once the dispense protocols were defined, the same solid dispensing protocol was used throughout the entire study, regardless of the test subject, and without any additional optimization.

The % error values decreased for all seven ChemBeads as the targeted mass increased from 0.5 mg to 50.0 mg (20 - 80% for 0.5 mg to less than 5% for 50.0 mg). For the 50.0 mg

target mass, which translated to 0.5 mg solid reagent at 1% loading, and for 10.0 mg target mass which translated to 0.1 mg solid reagent at 1% loading, the % errors were within 5% across all eleven ChemBeads. A comprehensive statistical analysis (see Supporting Information) of the 6910 dispenses also confirmed the accuracy at the 50 mg and 10 mg level with a % RSD of less than 2% and 6% respectively. The dispensing at the 0.5 mg level was performed to test the limitation of the technique. From Figures 1 and 2, some variation in the behavior of the ChemBeads based on the solid loaded and a wider % error was observed at the 0.5 mg level. The glass beads (diameter 212 – 300 μm) and polystyrene beads (diameter 350 – 500 μm) used in this study were not uniform in diameters. Dispensing at 0.5 mg and 1.0 mg represented a small number of beads (~40 glass beads/mg and ~80 polystryene beads/mg) and therefore the variation in sizes became significant and thus explaining the variation in behavior. When a higher mass of beads was dispensed (≥ 2 mg), the number of beads became high enough that the variation in diameter of individual bead played a less significant role in the dispense accuracy. We have included the 0.5 mg and 1.0 mg dispenses data to test the limitation of this technique.

HTE WG found that native fumed silica has a very low bulk density, which made it difficult to dispense using SDU.[6] We demonstrated that fumed silica at 1.7% loading on glass beads can be easily dispensed by both SDU and GDU-Pfd equipped platforms at various target masses with adequate accuracy (8 % error for 10.0 mg ChemBeads or 0.17 mg native solid, 2 % error for 50.0 mg ChemBeads or 0.85 mg native solid). When D-mannitol, L-proline, sodium chloride and thiamine HCl were coated on both glass and polystyrene beads, similar accuracy for all five target masses were observed. Overall, the GDU-Pfd achieved slightly better accuracy at all the target masses tested compared to the SDU. We speculated that the

improved accuracy was the result of the newly designed solid dispensing bottle and the GDU-Pfd tool, which allow more user-definable parameters (acceleration, amplitude, chunk size, etc) and therefore provided better control of the solid dispensing mechanism.

Manual Solid Dispensing (Calibrated Scoops)

Data collected from the 1500 dispenses across the five types of ChemBeads using calibrated scoops were analyzed and a scatterplot of % error versus dispense number through a run, analyzed by the coated material dispensed and the target mass is shown in Figure 1. A similar trend to the automated platforms was observed with % error values decreased as the target mass values increased from 5 mg to 50 mg. When the 50 and 10 mg calibrated scoops were used, less than 10% error was observed. The smallest scoop available was the 5 mg calibrated scoop and rendered about 0.25 mg (at 5% loading on beads) of native solid reagent at 20% error or less. Therefore, the 50 mg and 10 mg calibrated scoops could be a general and efficient method for manual dispense of ChemBeads without the need of an analytical balance or automated solid dispensing platforms.

Comparative Study of the 3 Solid Dispensing Techniques

A comparative analysis of the three solid dispensing methods was carried out by calculating % error for all the mass dispenses as shown in Figure 1. The % error values decreased significantly for all the ChemBeads as the target mass values increased from 0.5 mg to 50.0 mg. In all cases, 5-10% error was observed for target masses of 50.0 mg and 10.0 mg regardless of dispense method, and 2.0 mg target mass when using the GDU-Pfd tool. For our AbbVie internal HTE efforts, we have concluded that this level of accuracy is adequate and does not affect the outcome of our screening efforts.

All three solid dispensing platforms were under different laboratory environments. The SDU was located inside a constant nitrogen purged box and the GDU-Pfd was inside a closed environment (without nitrogen purge). The calibrated scoops were used in an open bench environment. Overall, the laboratory environment had little or no impact on the % error values observed.

Dispense Time Consideration

In a high throughput experimentation laboratory, where hundreds of solid reagents will need to be dispensed, efficiency of a platform in delivering targeted mass becomes a practical consideration. We collected dispense times from the log files of each platform and recorded the average dispense times for using the calibrated scoops. Dispense time and mass dispensed data from each automated solid dispensing platform and calibrated scoops were grouped by type of ChemBeads, target mass and different solid dispensing techniques, and then quantified by calculating mean, median, standard deviation, and % RSD for each subset (see Supporting Information).

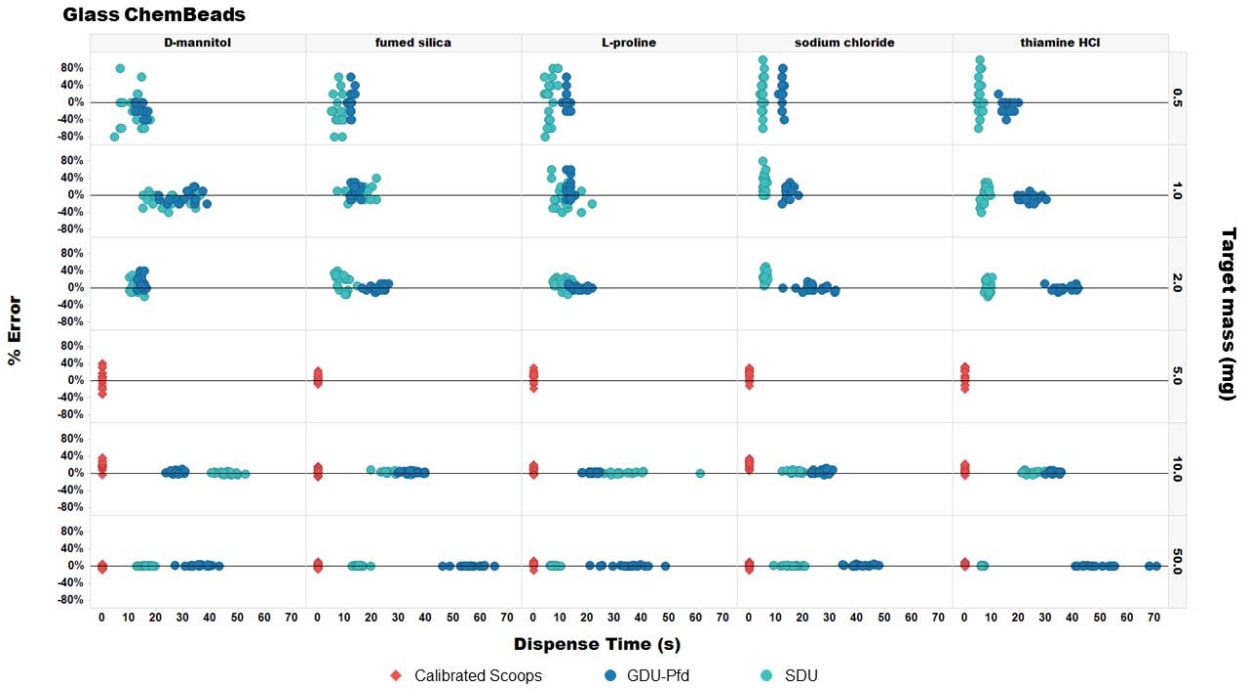


Figure 3. Scatterplot of % error values (-80% to 80%) vs. dispense time (0 – 70 s), broken down by reagents on glass beads (columns), target mass in mg (rows), and instrument (colors).

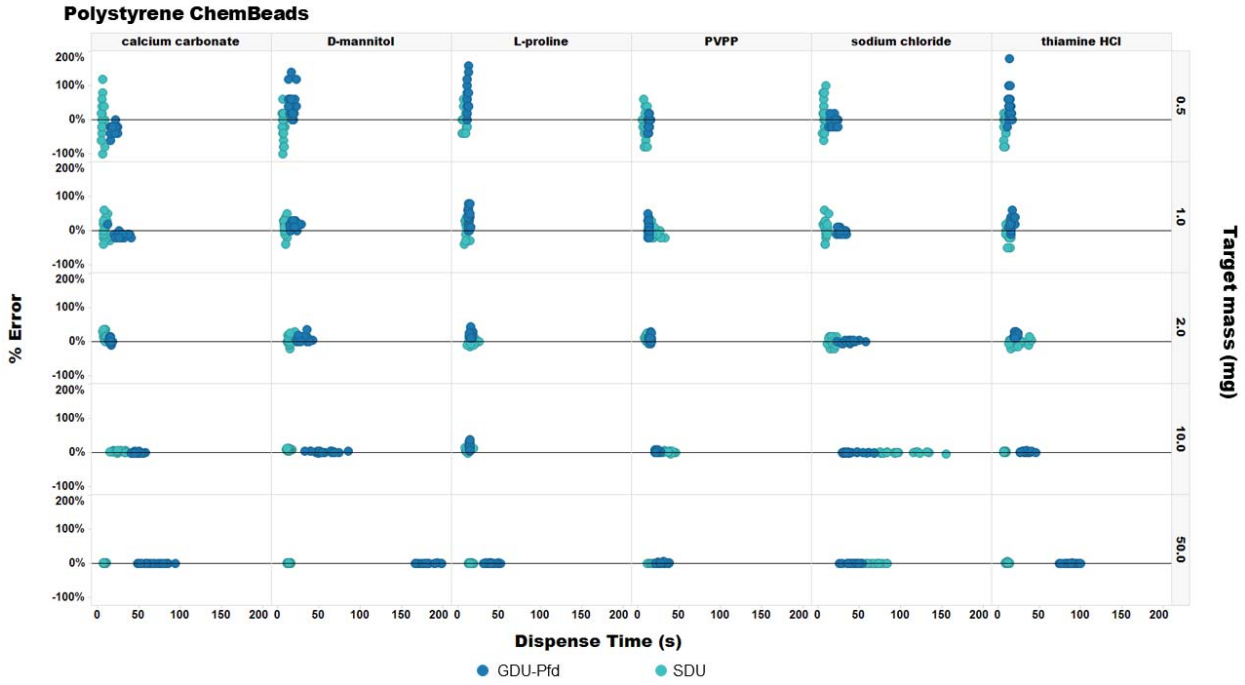


Figure 4. Scatterplot of % error values (-100% to 200%) vs. dispense time (0 – 200 s), broken down by reagents on polystyrene beads (columns), target mass in mg (rows), and instrument (colors).

A scatterplot comparing the % error vs. dispense time values, analyzed by the target masses, the type of dispensing techniques and the coated material on glass beads is shown in Figure 3 and on polystyrene beads in Figure 4. Dispense time increased as the target mass increased from 0.5 mg to 50.0 mg. A consistent trend in dispense time difference was observed when comparing the two automated platforms for all ChemBeads (both glass and polystyrene beads) across the different target masses with longer dispense time observed on the GDU-Pfd. For example, it took an average of 5 to 10 seconds on the SDU and 10 to 15 seconds on the GDU-Pfd platform for each dispensing at the 0.5 mg level for solids coated on glass beads. At the 50 mg target mass, it took an average of 10 to 15 seconds on the SDU and 35 to 45 seconds on the GDU-Pfd for each dispensing. The dispense time was also longer ($\geq$ 10 seconds) when dispensing polystyrene beads (D-mannitol, L-proline, sodium chloride and thiamine HCl in Figure 4) mostly at the 50.0 and 10.0 mg target mass using the GDU-Pfd when compared to the same solids on glass beads. From the characterization data, it was observed that polystyrene beads have a density approximately half that of glass beads, potentially explaining their longer dispense time as larger volume of ChemBeads will need to be dispensed.

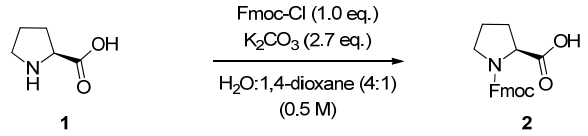
Using the calibrated scoops for manual dispensing demonstrated the shortest dispense time among the three methods studied and comparable % error (±10%) for the 10 mg and 50 mg target masses (Figure 3). These scoops can be used for fast manual dispensing of ChemBeads to deliver native solid at sub-milligram scale. This confirmed that the calibrated scoops were as effective as the automated platforms for solid dispensing and would be

practical for setting up high-throughput experimentation when automation equipment was not readily available.

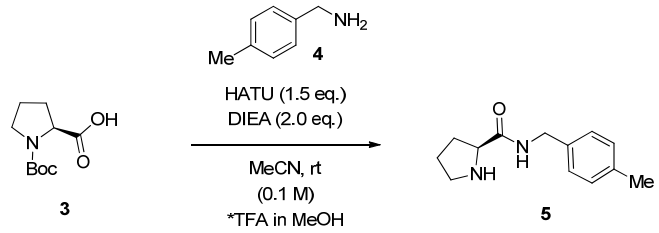
Application of ChemBeads for Chemical Reactions

To demonstrate the utility of ChemBeads in setting up chemical reactions, two chemical transformations using L-proline and *Boc*-L-proline ChemBeads and their corresponding native solid reagents were set up and the isolated yields recorded.

Scheme 1: Fmoc protection of L-proline **1**[14]



Scheme 2: Acylation of **3**[15]



The comparative study of the reactivity between native L-proline, *Boc*-L-proline and their corresponding ChemBeads versions (both on glass and polystyrene beads) showed no major difference in the % isolated yields (Table 3). These results indicated that the inert nature of the glass and polystyrene beads do not interfere with the chemical reactivity of the native solid reagents.

Table 3. Comparative study of chemical reactivity of the native solids and ChemBeads.

Chemical Transformation	Material	% Yield
Protection with L-proline	native	89
	1.8 % of L-proline on glass ChemBeads	89
	4.0 % of L-proline on polystyrene ChemBeads	85
Acylation with *Boc*-L-proline	native	70
	1.9 % of *Boc*-L-proline on glass ChemBeads	67
	4.0 % of *Boc*-L-proline on polystyrene ChemBeads	67

CONCLUSIONS AND OUTLOOK

SDU, GDU-Pfd, as well as the calibrated scoops were successfully applied to dispense different types of ChemBeads with comparable mean mass values and relatively consistent dispense time for each target mass examined. This study proved that the ChemBeads technology is a practical approach to dispense sub-milligram amounts of solid reagents using either automation platforms or calibrated scoops. The level of accuracy for the different target masses was relatively consistent for the seven types of ChemBeads at 2.0, 10.0 and 50.0 mg using the automated solid dispensing platforms. The calibrated scoops demonstrated similar and consistent accuracy for the 10.0 and 50.0 mg target mass with shorter dispense time, validating its general utility as a fast and effective manual solid dispensing method on the bench without the need of an analytical balance and automation equipment.

With this novel technology, over 450 ChemBeads of different solid reagents have been prepared and used exclusively in our internal HTE efforts with great success. As shown in this study, the process was straightforward, general and applicable to different solid reagents, regardless of its physical and chemical nature. The uniform physical property of the ChemBeads, regardless of the original form of the native solid reagent, facilitated solid dispensing at low targeted masses using the GDU-Pfd tool. With the ability to deliver sub-milligram quantities of the native solid reagents in vials, screening multiple reaction conditions in parallel can be done without exhausting precious starting materials. No major difference in target mass accuracy was observed for dispensing solid reagents coated on glass or polystyrene beads using both SDU and GDU-Pfd platforms. After the 6910 dispenses recorded, the material was observed to remain on the beads throughout the

dispensing process. We also demonstrated that we could use the calibrated scoops with the ChemBead technology to manually dispense sub-milligram quantities of solid reagents depending on their loadings using the 5, 10 and 50 mg scoops. These calibrated scoops with the ChemBeads technology would be an asset to increase applications of HTE in laboratories not equipped with automated solid dispensing platforms. The inert nature of the glass and polystyrene beads did not interfere with the reactivity of the solid reagents coated on them hence rendering them suitable to set up microscale high-throughput experimentation. When choosing a host material (glass or polystyrene) for coating, glass beads should be the first choice due to their availability from multiple vendors, lower price and solvent compatibility. Polystyrene beads should be considered as host when glass beads do not achieve the desired reagent loading.

ChemBeads technology, when coupled with a suitable solid dispensing platform, would be a solution for the development of a single solid dispensing protocol for solid reagents of various physical properties. We fully anticipate that the ChemBead technology will find broad application in both academic and industrial laboratories

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Chemspeed Swave and Chemspeed Swing Isynth solid dispensing platforms; Calibrated scoops; Dry powder coating using Resonant Acoustic Mixer; Tables containing dispensed data using Chemspeed Swave and Swing Isynth and calibrated scoops; quantitative NMR data for thiamine HCl and D-mannitol; Quantification data for thiamine HCl using calibration curve; Tables of mean mass and % RSD mass values from dispenses on the Chemspeed Swave and Swing Isynth as well as calibrated scoops; Physical characterization data of ChemBeads.

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Competing interests: None declared.

Data and materials availability: All data is available in the manuscript or the supplementary materials.

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(15) General Procedure used for acylation reaction: To three 4 mL vials each containing Boc-L-proline **3** (native solid, 1.9 % coated on glass beads and 4.5 % coated on polystyrene beads, 0.12 mmol, 1.0 equiv.) was added HATU (0.17 mmol, 1.5 equiv.), DIEA (0.23 mmol, 2.0 equiv.) and acetonitrile (0.1 M) and allowed to shake using an orbital heater shaker for 5 min at 60°C, followed by addition of *p*-tolylmethanamine **4** (0.17 mmol, 1.5 equiv.) and allowed to shake overnight. Upon completion water was added to the resulting mixture and extracted with ethyl acetate. The combined extracts were dried down using Biotage® V-10 and treated with TFA in methanol to remove the Boc group. The crude product was dissolved in 1.5 mL DMSO/H_2O (1:1), filtered, and the solid washed with additional 1.5 mL of DMSO. The crude product was purified using reverse phase preparative HPLC to yield pure (*S*)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide **5** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.36 (t, J = 5.7 Hz, 1H), 4.58 (d, J = 9.5 Hz, 1H), 4.33 (d, J = 5.8 Hz, 2H), 3.38 – 3.22 (m, 2H), 2.30 (s, 4H), 1.95 (pt, J = 9.0, 4.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.6, 137.2, 134.4, 129.3, 127.4, 59.6, 46.4, 43.6, 30.1, 24.4, 21.0.