Nanoporous Magnesium Aluminometasilicate Tablets for Precise, Controlled, and Continuous Dosing of Chemical Reagents and Catalysts: Applications in Parallel Solution-Phase Synthesis

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Mechanically robust tablets of nanoporous magnesium aluminometasilicate with high surface area and porosity can be loaded with a variety of organic and inorganic reagents and catalysts. The scope of this novel dosing methodology is demonstrated through the evaluation of 14 diverse organic reactions, including Mitsunobu, Suzuki, and bromination reactions.

Introduction

Various technologies for automated and parallel synthesis of biological active molecules have been adopted as standard laboratory techniques by the pharmaceutical industry.[1] A prerequisite for efficient parallel synthesis is the precise and safe dosing of reagents and catalysts. This is especially true when dosing of toxic or obnoxious reagents necessitates extensive and often expensive safety precautions. Conventionally, liquid reagents or solutions are dispensed either by (automated) pipetting techniques or manually by weighing. However, specific technologies are not readily available for the slow and continuous dosing of reagents, as required in "high dilution principle" procedures or in exothermic reactions, and for accurate high-throughput dosing of small quantities (e.g., transition metal catalysts). We have previously described the potential for dosing solids as tablets based on a polystyrene matrix for use in parallel solid- and solution-phase synthesis.[2] As a continuation of this research, we describe an alternative and novel dosing methodology for liquid and solid reagents that might offer new synthetic possibilities.[3] In the following discussion, it is shown that tablets based on a nanoporous matrix can be loaded directly with a diverse set of reagents and are then able to release those reagents slowly and continuously into a solvent of choice (Figure 1). The inorganic, nanoprous absorbent, Neusilin US2, is a commercially available, inexpensive powder possessing a highly rigid magnesium aluminometasilicate architecture (formula $Al_2O_3 \cdot MgO \cdot 2SiO_2 \cdot xH_2O$).[4] The powder is nontoxic and consists of highly porous spherical particles with a median size of 110 μm (based on volume) and a specific surface area of approximately 370−420 m^2/g.[5] Due to its excellent fluidity and compressibility, Neusilin powder can be mechanically compacted into stable tablets. We envisioned that the relatively high chemical inertness of Neusilin combined with its high thermostability (above 450 °C) would allow the use of loaded Neusilin tablets in diverse chemical reactions and under a broad range of reaction conditions.[6]

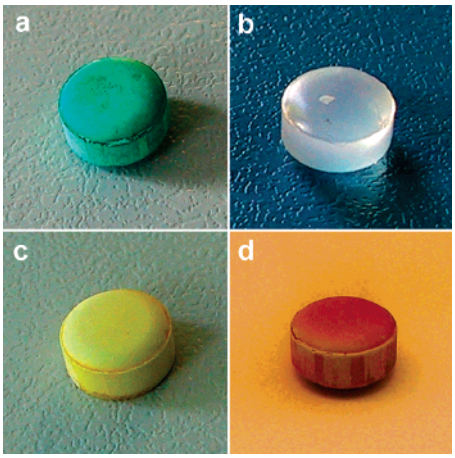

Figure 1. Neusilin US2 tablets (∅ = 9 mm): (a) Cu(II) pivalate tablet (0.2 mmol/tablet), (b) toluene tablet (2.1 mmol/tablet), (c) diethyl azodicarboxylate (DEAD) tablet (1.4 mmol/tablet), and (d) bromine tablet (4.7 mmol/tablet).

Results and Discussion

Formation of tablets from the Neusilin powder was achieved by generating a blend with magnesium stearate (0.5% w/w) prior to compression. The additive was required during the tabletting process to avoid undesired adhesion of Neusilin powder to the tablet punches when under compression. The then obsolete magnesium stearate was subsequently

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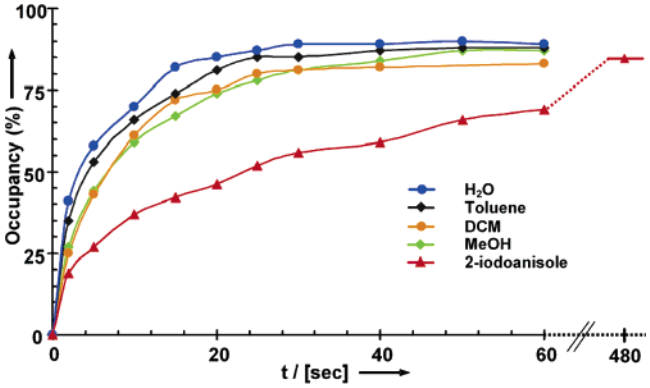


Figure 2. Absorption of different liquids into pure nanoporous Neusilin tablets as a function of exposure time.[7]

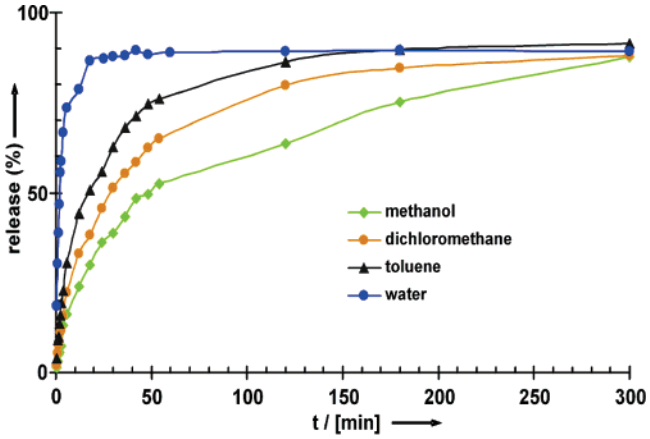


Figure 3. Release of absorbed 2-iodoanisole from completely saturated Neusilin tablets into water, toluene, DCM, and methanol.

removed by solvent extraction to avoid any contamination with this additive in the later reactions. In this manner, tablets with a diameter of 9 mm, a volume of 333 μL, and a weight of 144 mg $\pm$ 2% were reproducibly prepared, while various shapes and sizes are equally possible. The tablet void was calculated to be 265 μL based on its porosity of 80%.[7] The mechanical stability of the unloaded tablets was determined in a tablet hardness tester to be 33 N $\pm$ 9%.

A series of model experiments was conducted to explore both the absorption characteristics of a set of liquid solvents and reagents into the tablets and the release profiles of a representative reagent, 2-iodoanisole, into a selection of common solvents. Figure 2 illustrates the absorption profiles of different liquids into the tablets as a function of exposure time. The observed fast absorption is caused by capillary suction and is determined (according to the Washburn equation) by both the pore size of Neusilin and the nature of the liquid (viscosity, liquid−solid contact angle).[8] In all model experiments, tablets were completely loaded with liquids within 8 min.[7]

In comparison to the absorption of reagents into the tablets, the release of reagents from the tablets into a solution is progressing much slower. Figure 3 illustrates the release profile of 2-iodoanisole from tablets into water, toluene, DCM, and methanol. First within 5 h, 2-iodoanisole is completely released in all test solvents. The release of 2-iodoanisol in the solvents was determined by measuring the loss of tablet weight over time. The slow release rates

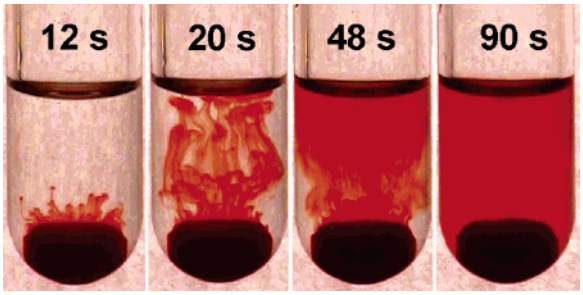
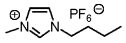
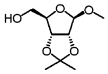
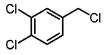
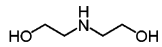


Figure 4. Visualization of the release of 1,10-phenanthroline (phen) over time from a phenanthroline tablet (0.17 mmol/tablet) into a 0.1 M solution of $Fe(II)SO_4$ in aqueous acetic acid (pH = 2) without agitation. The red color is caused by formation of the iron complex $(phen)_3Fe(II)SO_4$.

(as expressed by the slope of the curves) would allow precise microscale dosing (e.g., in methanol, ~50 mg/s after 50% release). It should be noted that the release rate of 2-iodoanisole is relatively fast in water in comparison to other solvents. This effect can be explained by the huge capillary suction for water (approximately 150 bar). These experiments clearly show that loaded reagents are slowly and continuously released from tablets and that tailored release rates can be achieved by appropriate selection of the solvent. In addition, release rates can be adjusted by changing tablet size and shape, which will influence the length of the diffusion path, by altering the concentration of the reagent in the tablets, which controls the concentration gradient, or by both. Finally, it should be noted that the entire amount of reagent within a tablet will never be completely released, since a steady-state concentration will be reached inside the tablet. Thus, quantitative release from the tablets is expected only if the reagent is fully consumed in a chemical reaction. Figure 4 visualizes the release of 1,10-phenanthroline into an aqueous solution of $Fe(II)SO_4$.

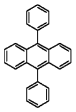
Neat liquid reagents were readily absorbed by the unloaded tablets occupying typically 77−91% of the maximum available pore volume (Table 1), resulting in a loading of between 0.9 and 4.7 mmol/tablet. It was observed (as expected) that the extent of loading is dependent mainly on the molar density (mol/mL) of the individual reagent.[7] Tablets were successfully loaded with (see Table 1) an ionic liquid (entry 2), a perfluorinated liquid (entry 4), an acid (entry 17), a base (entry 16), a viscous organic oil (entry 5), and with inorganic materials (e.g., entry 22). Solid and thermally stable reagents were absorbed as their melts (Table 2). For example, molten bismuth(III) chloride (mp 230 °C) was absorbed into unloaded tablets at 260 °C (Table 2, entry 4). The tablets are robust and do not lose their structural integrity, even under challenging conditions of high temperature and acidity. The loading of reagents that have either a high melting point (>300 °C) or low thermostability was achieved by absorption of a solution of the reagent. Tablets with thermolabile organic reagents, such as PyBOP (Table 3, entry 2) and high-melting, inorganic salts (e.g., KCN, entry 17), were produced with loadings of between 0.1 and 3.3 mmol/tablet. Loading capacities of these tablets are clearly dependent on the partitioning of the solvent and reagent within the tablets. Finally, the loading of tablets with substances that are both thermally unstable and poorly soluble (e.g.,

Table 1. Loading of Neat, Liquid Organic and Inorganic Chemicals

Entry	Substrate[a]	Loading[b] [mmol/tablet]	Occupancy[7] [v/v %]
1	n-Bu_3SnH	0.9 ± 0.7%	91
2		1.1 ± 0.6%[c]	87
3	15-crown-5	1.2 ± 1.3%	89
4	$CF_3(CF_2)_4CF_3$	1.2 ± 1.7%	88
5		1.3 ± 0.5%	89
6	HMPA	1.3 ± 0.6%	90
7	DEAD	1.4 ± 0.3%	83
8		1.5 ± 0.6%	78
9		1.7 ± 0.6%	84
10	$(EtO)_2POH$	1.8 ± 3.4%	87
11		2.0 ± 0.9%	88
12		2.2 ± 1.0%	86
13	PhNCO	1.9 ± 0.9%	89
14		2.1 ± 1.6%	77
15		2.3 ± 1.0%	82
16		2.5 ± 0.3%[c]	85
17	$CH_3(CH_2)_2CO_2H$	2.5 ± 0.4%	90
18		2.6 ± 0.2%	88
19	CH_3I	2.9 ± 1.3%	87
20	CH_2I_2	3.8 ± 0.3%	87
21	CS_2	3.5 ± 0.6%	79
22	Br_2	4.7 ± 1.3%	91

[a] Substrates are ranked according to increasing molar density [mmol/cm^3]. [b] Loading time 1−2 h, at room temperature if not otherwise noted. [c] Loading for 2 h at 80 °C.

Table 2. Loading of Neat, Solid Organic and Inorganic Chemicals

Entry	Substrate	Temperature[a] [°C]	Loading[b] [mmol/tablet]
1		260	0.7 ± 0.8%
2	PhSeSePh	80	1.2 ± 0.5%
3	S_8	165	1.7 ± 0.5%
4	$BiCl_3$	260	2.9 ± 3.6%
5	$NH_4^+SO_3NH_2^-$	145	3.4 ± 0.6%

[a] Temperature at which molten substrates were absorbed into tablets. [b] Loading time 2 h.

Table 3. Loading of Solid Organic and Inorganic Chemicals in Solution

Entry	Substrate	c/[mol/L] (solvent)	Loading[a] [mmol/tablet]
1		0.3 (DCM)	0.04
2	PyBOP	1.3 (DCM)	0.3
3	$K_2Cr_2O_7$	0.4 (H_2O)	0.1
4	$Cu(piv)_2$	0.8 (acetone)	0.2
5	$B_{10}H_{14}$	2.0 (DCM)	0.6
6	$CuSO_4{\cdot}5H_2O$	2.5 (H_2O)	0.4
7	$HgCl_2$	3.3 (acetone)	1.0
8	$ZnCl_2$	3.7 (EtOH)	0.8
9	$LiClO_4$	3.9 (H_2O)	2.5
10	Cs_2CO_3	5.0 (H_2O)	1.2
11	$CeCl_3{\cdot}7H_2O$	5.0 (H_2O)	0.6
12	$BiPh_3$	5.1 (THF)	0.7
13	$SnCl_2{\cdot}2H_2O$	5.5 (EtOH)	0.8[b]
14	$NH_4^+PF_6^-$	6.7 (H_2O)	1.4
15	K_2CO_3	9.0 (H_2O)	1.3
17	KCN	10.0 (H_2O)	3.3
19	H_2O_2	10.3 (H_2O)	2.7

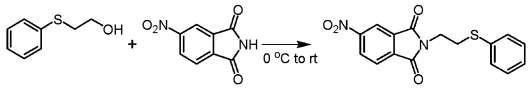
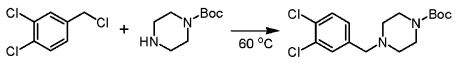
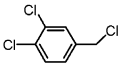
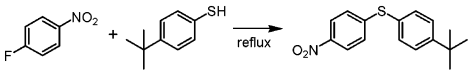
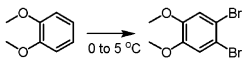
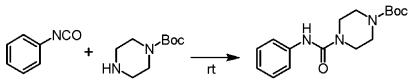
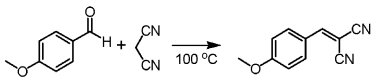
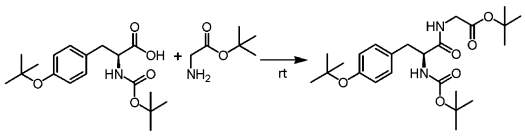
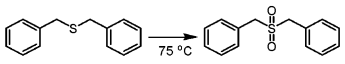
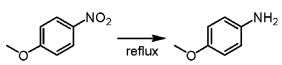
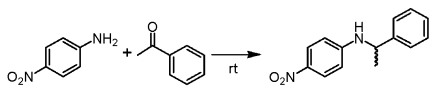
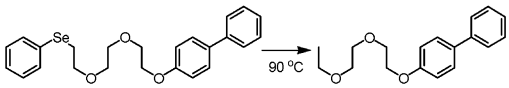
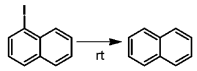
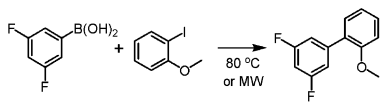
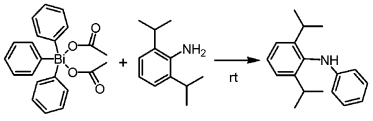
[a] Loading after removal of the solvent; loading time 1−2 h, at room-temperature if not otherwise noted. [b] Loading for 2 h at 70 °C.

($Ph_3P)_2PdCl_2$) was achieved by co-compression with the Neusilin powder. Loading of the tablets with more than one reagent has not been investigated.

For liquids or solutions, a loading time of 1−2 h was chosen to ensure complete absorption by the tablets. In all cases, robust tablets with dry surface and of reproducible loading, size, and shape were obtained. The tablet hardness was determined for a selection of the loaded tablets to provide an indication of likely mechanical stability. Compared to the blank tablets, tablets loaded with liquids are equally or even slightly more mechanically stable (e.g., HMPA tablet: 37 N), and tablets loaded with solids are generally much more mechanically stable (e.g., $NH_4SO_3NH_2$ tablet: 402 N).

This work has demonstrated that Neusilin tablets can be accurately and directly loaded with a diverse selection of reagents without tablet disintegration, loss of tablet hardness, or change in tablet shape or size. A few exceptions were observed and are, therefore, of interest. Elemental mercury, molten selenium (at 230 °C), and (diethylamino)sulfur trifluoride were not absorbed by the tablets. These materials obviously establish an unfavorable liquid−solid contact angle (>90°) with Neusilin that makes absorption, according to the Kelvin equation, at atmospheric pressure impossible.[8] In one other case, instantaneous tablet disintegration occurred when loading of the tablets with a 10 M aqueous solution of KI was attempted. Long-term shelf life stability tests of reagents within tablets have not been carried out systematically. We have observed by NMR spectroscopy that 3,4-dichlorobenzylchloride and 2-iodoanisole remained un-

Table 4. Application of Tablets in Diverse Chemical Reactions

Entry	Reaction	Scale/[mmol] (solvent)	Reagent-Tablet	Yields [%][a]		
				+	-	Lit.[11]
1		1.3 (THF)	DEAD	85	84	100
2		1.3 (THF)		76	77	100
3		15.0 (THF)	K_2CO_3	96	96	99
4		50.0 (CCl_4)	Br_2	90	86	83
5		1.6 (THF)		88	86	94
6		10.0 (neat)	$ZnCl_2$	97	98	97
7		1.0 (DCM)	PyBOP	81	80	80-97
8		16.8 (AcOH)	H_2O_2	94	89	98
9		5.0 (THF)	$SnCl_2{*}2H_2O$	94	94	82-97
10		1.4 (MeOH)	$B_{10}H_{14}$	76	100	97
11		0.8 (Toluene)	n-Bu_3SnH	54	82	89
12		2.0 (THF)	HMPA	80	85	95
13		0.6 3.8 0.5 (DMF/H_2O 5:1)	$(Ph_3P)_2PdCl_2$ $(Ph_3P)_2PdCl_2$ 	86 86[b] 85	 87	 >80
14		2.0 (DCM)	$Cu^{II}(piv)_2$	87	90	100

[a] Isolated yields after purification for reactions carried out with (+) or conventionally without (-) tablets. [b] Carried out under microwave irradiation (150 °C/10 min).

changed after storage in tablet form for more than 1 year at ambient temperature in air. However, some chemicals showed decomposition; namely, phenylisocyanate, which trimerised to 1,3,5-triphenyl-[1,3,5]triazane-2,4,6-trione within a few weeks, diethylazodicarboxylate (DEAD), which decomposed (20% decomposition within 4 months), and indan-1-one, which underwent aldol condensation (50% conversion within 4 months).[9] An interesting observation was made with

tablets containing decaborane(14) (Table 3, entry 5). The tablets ignited spontaneously at room temperature when exposed to air, even though this borane is known to be relatively stable to hydrolysis in air as well as at elevated temperature (up to 150 °C).[10] Possible explanations include enhanced reactivity of decaborane(14) toward atmospheric oxygen either due to the huge increase in surface area, or due to activation by the Brøndsted-basic sites within the Neusilin pores.

The tablets were applied to the following reaction types (Table 4): acylation (entry 7), condensation (entry 6), transition metal catalysis (entry 13), nucleophilic substitutions (S_N entries 1 and 2; and S_NAr, entry 3), electrophilic aromatic substitution (entry 4), oxidation (entry 8), reduction (entry 9), and radical reaction (entry 11). The reaction conditions cover a range of temperatures (−5 to 90 °C, including microwave heating), solvents (e.g., CCl_4, DMF/H_2O, acetic acid, and neat), and scales (0.5−50 mmol).

To evaluate the tablet-dosing methodology, parallel reactions were carried out under identical conditions with reagents added either conventionally or in tablet form. For the experiments performed with tablets, a small excess of the reagent was present. Tablets were removed after the reaction by simple filtration. In general, isolated yields for experiments performed by tablet dosing were comparable to those obtained under conventional dosing (Table 4). In particular, dosing of small amounts (e.g., catalysts) by tablets was very convenient, allowing the precise dosing of very small amounts of substance in a simple and reproducible manner.[12] The Pd-catalyzed C−C coupling (Suzuki reaction, entry 13) and the Cu-catalyzed N−C coupling (Barton reaction, entry 14) proceeded in excellent yields. Interestingly, the tablet-mediated dosing of reagents into exothermic reactions provides a practical solution to control the reaction temperature. For example, we demonstrated that the reaction temperatures both for the oxidation of dibenzyl sulfide with H_2O_2 (entry 8) and for the bromination of 1,2-dimethoxybenzene with bromine (entry 4) were better regulated by controlled dosing. Even though phenylisocyanate and DEAD are not stable upon prolonged storage in Neusilin tablets, as mentioned before, use of freshly prepared phenylisocyanate tablets and DEAD tablets smoothly leads to the desired products in yields similar to those obtained without tablet dosing (entries 8 and 4, respectively). Only in the deselenization reaction (entry 11) and in the reductive amination reaction (entry 10) were significantly lower yields reproducibly obtained (52 and 76%, respectively), in comparison to those obtained without tablets (82% and 100%, respectively).

We have developed a novel reagent and catalyst dosing methodology for parallel synthesis. Tablets based on a nanoporous magnesium aluminometasilicate (Neusilin US2) can be loaded directly with a very broad range of solid and liquid reagents. The versatility of the dosing method was demonstrated in loading experiments and in 14 representative organic reactions. Since tablets are able to release reagents slowly and continuously in a solvent of choice, this dosing methodology might have many advantages in comparison with more sophisticated and expensive solutions currently available. The slow and continuous release of reagents enables, for example, microscale dosing (micrograms per second) applicable in "high dilution" conditions for parallel synthesis of, for example, macrocycles. Sealing of the tablet surface by coating would protect embedded reagents, and storage of tablets under inert gas in, for example, a 96-blister package would enable simultaneous and precise dosing of small quantities (e.g., catalysts) to a 96-reactor block. This would not only speed up parallel synthesis and optimization experiments but would also improve the reproducibility of reactions.

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Note Added after ASAP Publication. This article was released ASAP on January 20, 2007, with errors in captions for Figures 1 and 4. The version posted on February 8, 2007, and the print version are correct.

Supporting Information Available. Preparation and loading of tablets. Analytical data: ^{1}H NMR, ^{13}C NMR, GC/MS, CHN analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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(4) Neusilin US2 is commercially available from Fuji Chemical Industries Co. Ltd.
(5) The specific surface area was determined by nitrogen absorption.
(6) For details, see safety data information from Fuji Chemical Industries Inc., U.S.A.
(7) The pore volume of the tablets determined by filling with water is ∼10% lower than the calculated pore volume. This is a normal behavior that suggests not all void is accessible to liquids. The tablet porosity before loading (ϵ; defining the relative free voids of the tablet) is calculated on the basis of the density of the tablet ρ_t and the skeleton density ρ_s of Neusilin. The porosity, ϵ, is calculated according to $\epsilon = 1 - \rho_t/\rho_s$. The density of the tablet is based on the ratio between weight and volume of the tablet. The skeleton density ($\rho_s = 2.14 g/cm^3$) of Neusilin powder was determined by gas pycnometrical density determined in helium using Micromeritics Accupyc 1330. Occupancy is defined as filling of the tablet voids with the loaded liquid (v/v %).
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(11) References for compounds or representative procedures are listed in the Supporting Information.
(12) Unpublished results by Dr. A. Stewart Liddon and Dr. Michael Pitts. for further information, please write to info@reaxa.com.

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