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Performances of Homogeneous and Heterogenized Methylene Blue on Silica Under Red Light in Batch and Continuous Flow Photochemical Reactors

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Methylene blue was efficiently immobilized on silica micro- and nanoparticles by electrostatic interactions and the performances of the heterogenized photocatalysts were compared against the homogeneous conditions using the photooxidation of citronellol as a model reaction under red light, in a batch and a continuous flow photochemical reactor. In batch, the heterogeneous photocatalyst outperforms the homogeneous one, presumably due to kinetic and stability effects. The two catalytic systems are also compared in a flow reactor displaying improved mass transfer properties. We demonstrate that this results in a dramatic enhancement in photocatalyst stability, reactivity and productivity. This study highlights the importance of photocatalyst stability under homogeneous versus heterogenized conditions and in batch versus flow photochemistry.

Keywords: photochemistry, flow chemistry, green chemistry, heterogeneous photocatalysis, catalysis, singlet oxygen, process intensifcation

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INTRODUCTION

Visible-light photochemistry is a promising approach in the development of greener synthetic chemistry. This technology has been widely developed over the past two decades as it promotes a variety of powerful transformations under very mild conditions with increased selectivity and safety. The general principle is based on the use of a colored material, which is able to capture and transfer the energy of visible light to enable chemical reactivity. The basis of most of the developments in visible-light photochemistry is therefore linked to the properties of excited states dyes, so called photocatalysts (PCs), which are able to transfer energy or electrons to other reactants and catalyze a photochemical transformation (Prier et al., 2013). Excited state chemistry allows for conventional reactions to occur at close to ambient temperature, a landmark example being the photo-Ullmann reaction (Ziegler et al., 2013; Yoo et al., 2015), but also to generate unconventional electronic transitions, leading to completely new reactivity such as for instance [2 + 2] cycloadditions which are impossible *via* thermal activation (Sarkar et al., 2020).

However, these molecular systems have important efficiency issues, which must be solved to make them more productive and ultimately applicable in an industrial context. PCs can generate important toxicity, cost and sustainability issues. They often display poor stability with low to mediocre turn over numbers (TONs) and their utilization often requires additional downstream purifications. In addition, an important issue in photocatalysis, which is often overlooked, is the problem of solubility of these reactive dyes, which makes them incompatible with the use of green solvents (Clarke et al.,

2018) and often impairs the overall benefit of visible-light photochemistry in terms of green chemistry.

To counter such sustainability issues, our group and others have developed recyclable photocatalytic systems, such as heterogenized solid PCs (Mori et al., 2010; Mori and Yamashita, 2016; Tambosco et al., 2018; Choi et al., 2020; Gisbertz and Pieber, 2020; Soria-Castro et al., 2020; Materna and Hammarström, 2021). In particular, we investigated the straightforward non-covalent immobilization of PCs on silica particles which resulted in an improved reactivity and stability (Tambosco et al., 2018), and provided additional physical properties such as magnetism (Terra et al., 2020) or plasmonic resonance (Gellé et al., 2021). We also developed a continuous flow photochemical process with a fixed photocatalytic bed reactor to leverage productivity issues (Blanchard et al., 2020). Important efforts have been made to intensify photochemical processes by means of flow chemistry and this technology is the most promising for larger-scale photochemical manufacturing. However, this approach remains limited to homogeneous or gas/liquid conditions and yet, processing heterogeneous solid/liquid and solid/liquid/gas reactions is still underdeveloped (Carofiglio et al., 2008; Woźnica et al., 2014; Amara et al., 2015; Mendoza et al., 2018; Pieber et al., 2018; Blanchard et al., 2020; Mendoza et al., 2020; Radjagobalou et al., 2020).

Another important parameter in photochemistry is the choice of the irradiation wavelength. Recent developments in photocatalysis have shown that red light is a powerful mean to increase productivity because of its excellent penetration depth even in highly concentrated colored or turbid media (Mei et al., 2020; Ogura et al., 2020). In addition, red light is also more thermally efficient since less energy is wasted in the PS compared to UV/Vis-PS. Therefore, for a given quantum yield, the energy efficiency is only related to the energy of the incident photons as non-radiative dissipation is less energetic. At the same time, if the reaction matrix absorbs less light, there will be less of a cooling requirement compared to UV/Vis-light. These factors explain why lower energy light photochemistry can be more successfully intensified in batch or flow reactors compared to actual UV/Vis-light photochemistry.

Methylene blue (MB) is one of the most important red-light photocatalysts with applications such as type I and type II photooxidations and in photoredox catalysis (Patel et al., 2021) such as hydroxylation of boronic acid (Pitre et al., 2013), trifluoromethylation reactions (Romero and Nicewicz, 2016), photo-induced thiophosphonate synthesis (Zhang et al., 2018), dehydrosulfurization of thioamides to nitriles (Xu et al., 2020), acyl radical epoxyacylation of olefins (de Souza et al., 2018) and acyl radical-mediated intramolecular cyclization of aromatic acids (Hu et al., 2020). It is commercially available in large quantities at a low cost and it is relatively nontoxic and FDA approved for diagnostic applications (Oz et al., 2011). It is also available with very high purity which is useful for studying its photochemical properties. However, it is known to be relatively unstable and therefore it represents an interesting model for understanding which reaction parameters affect PC stability the most (Nassar et al., 2019).

In this paper, we report on the development of a new photocatalytic system, displaying high efficiency under red-light, which is based on the immobilization of methylene blue (MB) on silica (SiO_2). The performances of the homogeneous and heterogeneous PCs (using micro- and nanoparticles) are compared in a batch and in a continuous flow photo-reactor under red light, using the benchmark photo-oxidation of β-citronellol (**1**), a key step in the industrial synthesis of the commercial fragrance rose oxide (Ravelli et al., 2011).

RESULTS AND DISCUSSION

MB produces singlet oxygen ($^1O_2$) with a good quantum yield (Φ_Δ = 0.60 in CH_3CN, Rossi et al., 2008) and has been applied in $^1O_2$ photooxidation reactions on several occasions (Nilsson et al., 1972; Matheson et al., 1975; Jahnke and Frenkel, 1978; Cocquet et al., 2000; Oelgemöller et al., 2006; Lancefield et al., 2012; Schachtner et al., 2016). The main drawback of MB is its tendency to agglomerate and its intermolecular reactivity leads to the formation of leuco-forms which account for a low stability in solution (Nassar et al., 2019). Building on our previously developed non-covalent immobilization approach of cationic dyes on SiO_2, we succeeded in dispersing MB on micro- and nano-SiO_2 particles by simply mixing the two components together in water (**Figure 1A**). The microparticles are commercially available and widely utilized in gel chromatography with a size of 40–60 μm. The nanoparticles were obtained by the Stöber method with an average size of 187 nm determined by SEM and 190 ± 50 by DLS (Thomassen et al., 2010). MB has a large absorption band at 653 nm in CH_3CN and a weaker band at 605 nm. We observed after immobilization of 1.25 mg of MB on 1 g of SiO_2 micro- (MB@SiO_2 MPs) and nano-particles (MB@SiO_2 NPs), a blue shift of the maximum absorbance from 653 to 647 nm (MB@SiO_2 MPs), and to 642 nm (MB@SiO_2 NPs) (**Figure 1B**). This blue shift has been described in the literature and could be due to electrostatic interactions between MB and surface groups (He et al., 2009; Veerapandian and Yun, 2013) or to disaggregation *via* surface interaction. We confirmed the non-covalent nature of the interaction by fluorescence microscopy by adding pure SiO_2 particles to a slurry of MB@SiO_2 (1.25 mg/g) and by observing the homogeneous fluorescence of all particles (**Figure 1C**). This experiment is in agreement with an adsorption/desorption equilibrium occurring in between the solid and liquid phases. We have previously shown (Terra et al., 2020) that the excited state lifetime of Ru $(bpy)_3Cl_2$ was not affected by immobilization on silica or on magnetic iron/silica nanoparticles and believe that, the excited state properties of MB remain the same whether in solution or immobilized on silica nanoparticles.

With these characterizations in hand, we used MB under homogeneous and heterogeneous conditions as a PC in the photooxidation of β-citronellol (**1**) (**Figure 2**). This reaction was first performed in a batch reactor with a concentration of **1** of 0.1 M in CH_3CN, 0.016 mol% of PC under red light irradiation (630 nm, 304 LEDs, 30.4 W) for 4 h.[1] As shown in **Figure 2A**, homogeneous MB

[1]We initially performed control experiments on the conversion of 1,5-dihydroxynaphthalene to produce juglone, a natural product and important intermediate in the synthesis of anthraquinones. In these experiments the performances of various MB@SiO_2 density were assessed (see ESI) and we found that 1.25 mg/g of MB@SiO_2 was the optimal concentration.

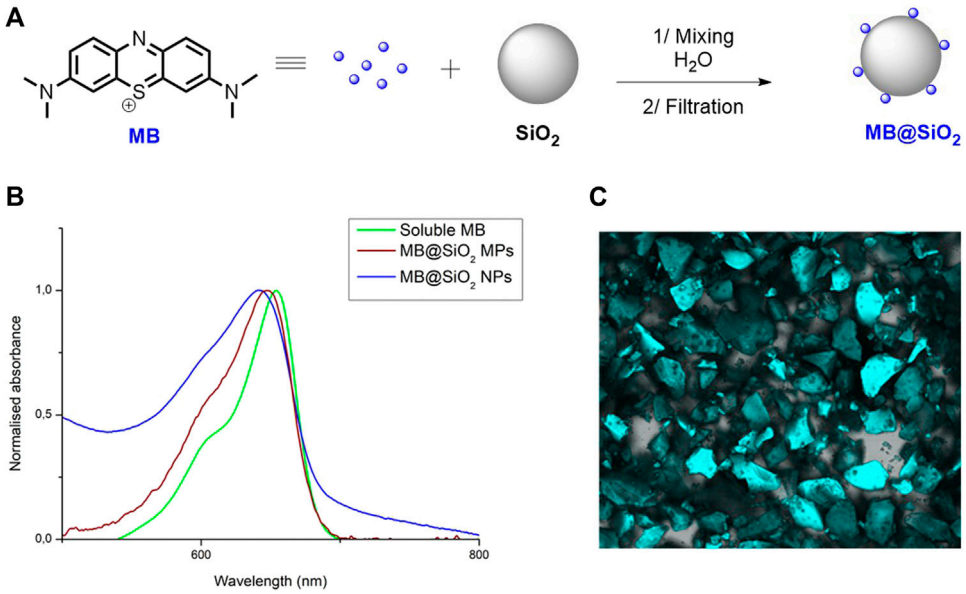


FIGURE 1 | (A) Structure of MB and process for the heterogenization of MB on SiO_2; **(B)** Absorption spectra of MB (green) and dispersed MB@SiO_2 MPs (blue) and MB@SiO_2 NPs (red) in CH_3CN; **(C)** Fluorescence microscopy snapshot of MB@SiO_2 MPs treated with pure SiO_2 MPs in CH_3CN.

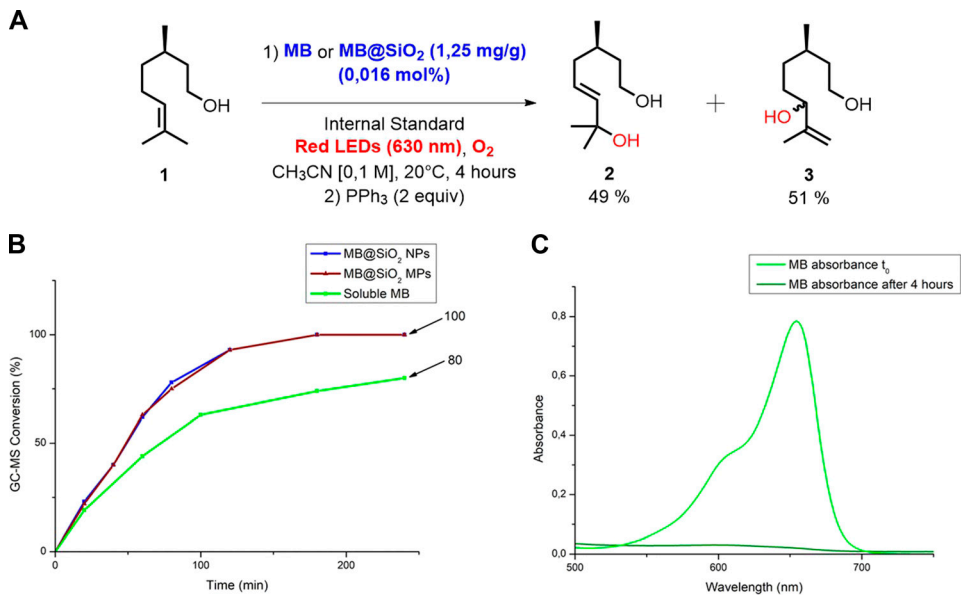


FIGURE 2 | (A) Photooxidation of **1** using MB or MB/SiO_2 as a PC under red light irradiation (630 nm) **(B)** Monitoring of the conversion of **1** to **2** and **3** in a batch reactor, in function of time by GC-MS analysis (Internal Standard = 1,3-dimethoxybenzene). The ratio between **2** and **3** is measured by ^{1}H NMR spectroscopy. **(C)** Absorption spectra of the homogeneous reaction media obtained at t_0 and after 4 h of reaction.

provided 80% conversion and a 49/51 selectivity to the regio-isomers **2** and **3** after 4 h of reaction, which corresponds to a turnover number (TON) of 5,000 and a space-time yield (STY) of 3.44 g h^{-1} L^{-1}. On the other hand, we tested the supported PCs MB@SiO_2 MPs and MB@SiO_2 NPs and found a very close reactivity between the two immobilized systems, reaching 100% conversion within 3 h, which corresponds to a TON of 6,250 and a STY of 5.74 g h^{-1} L^{-1}. In these experiments, free MB is easily deactivated which explains the plateau obtained at 80%, while MB@SiO_2 enables full conversion of **1** (**Figure 2B**). The complete deactivation of homogeneous MB is confirmed by the flattening of the absorption curve in the absorption spectra of the crude reaction medium taken at the end

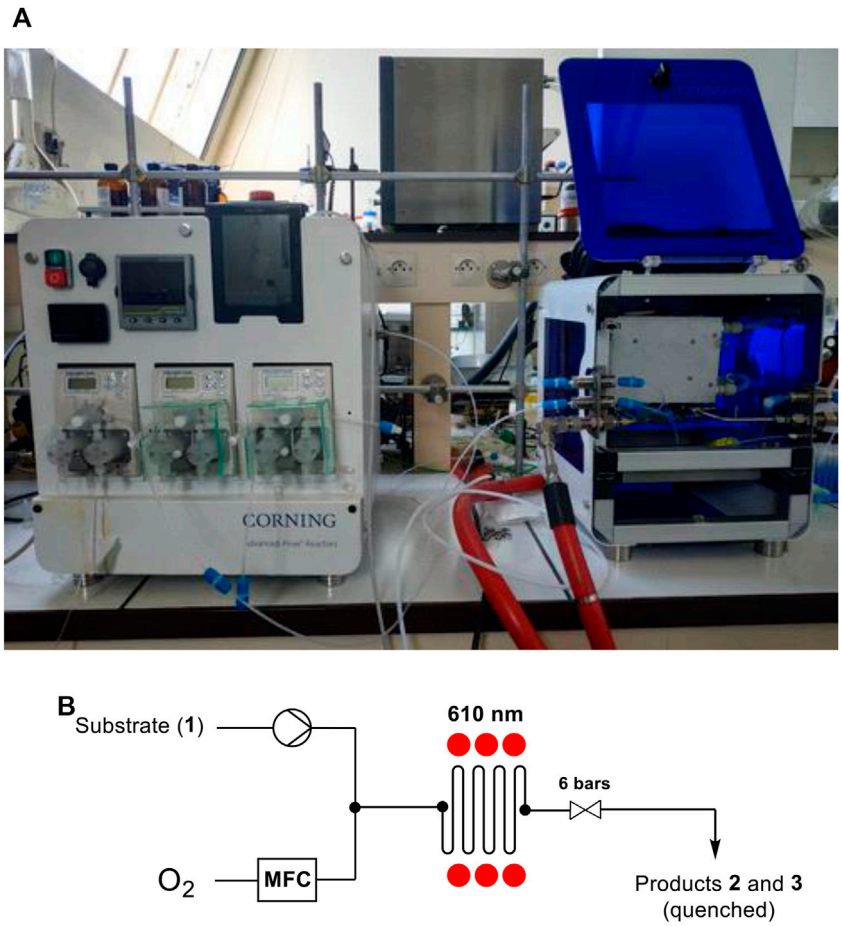


FIGURE 3 | (A) Picture of Corning ®Advanced-Flow Lab Photoreactor (AFR) **(B)** Schematic diagram of the photoreactor.

of the reaction, after 4 h (**Figure 2C**). We compared the performances of these photocatalytic systems at 0°C and 40°C and found no difference in conversion rates compared to the close to ambient temperature (20°C) reactions. Control experiments performed in the dark or under red-light without MB did not show any conversion of the starting material.

We next investigated the performances of the homogeneous and heterogeneous systems, using the same model reaction, in a continuous flow photoreactor consisting of a 2.7 ml transparent plate with narrow channels and a heart-shaped static mixer with optimized mass transfer properties. (Horn and Gremetz, 2020). The plate is irradiated with interchangeable tunable LEDs and connected upstream to an HPLC pump, a mass flow controller (MFC), which is itself connected to an O_2 cylinder, and downstream to a back pressure regulator (**Figure 3**).

Unfortunately, this reactor was not compatible with the use of micro-sized SiO_2 particles due to clogging issues but nano-sized SiO_2 particles were utilized without blockage. The first parameter we optimized for was the residence time, by fixing the O_2 flowrate at 2.0 ml(n)·min^{-1}, the temperature at 20°C and the system pressure at 6 bars. The selected wavelength was 610 nm and the lamp was operated at full power. We first operated under homogeneous conditions, with soluble MB (0.016 mol%), by fixing the organic flowrate to 1.0 ml·min^{-1} (**Table 1**, entry 1), corresponding to a 2.4 min residence time. Such conditions yielded 35% conversion of **1** and a 48/52 selectivity between **2** and **3**. Reducing the organic flow rate to 0.5 ml·min^{-1} (4.9 min residence time) and then to 0.25 ml·min^{-1} (10.0 min residence time) resulted in an increase in conversion to 57 and 81% respectively (Entries 2 and 3). Finally, decreasing the oxygen flowrate from 2.0 ml(n)·min^{-1} to 1.0 ml(n)·min^{-1} led to a further increase in conversion to up to 92% (Entry 4). This last result corresponds to a STY of 88 g h^{-1} L^{-1} which is 26 times more important compared to the STY measured with the batch reactor. We then turned our attention to study the heterogeneous nano-sized PC system. MB@SiO_2 NPs (1.25 mg/g) provided a 26% conversion at 1.0 ml·min^{-1} for the organic and 2.0 ml·min^{-1} for the O_2 flowrates (**Table 1**, entry 5). When the residence time was increased to 4.9 and 10 min (corresponding to a 0.5 and 0.25 ml·min^{-1} flowrates) the conversions were increased to 49 and 75% respectively (Entries 6 and 7). Finally, while maintaining the organic flowrate at 0.25 ml·min^{-1} and decreasing the O_2 flowrate to 1.0 ml·min^{-1}, an 86% conversion was obtained

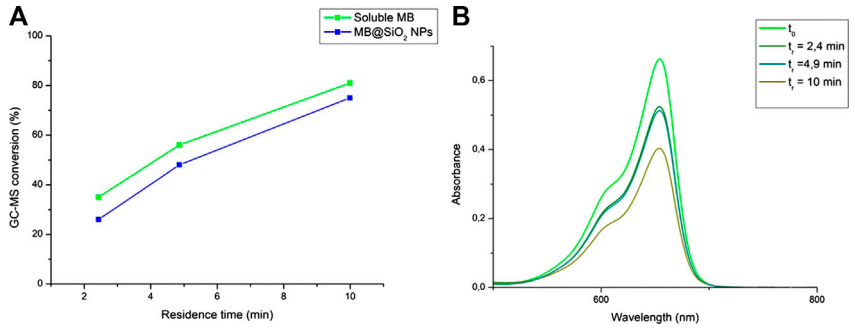


FIGURE 4 | (A) Plots of the conversions of **1** as a function of residence times under homogeneous and heterogeneous conditions in flow (in CH_3CN [0.1 M], Q (O_2) = 2 ml(n)·min^{-1}, p = 6 bars) **(B)** Absorption spectra of the homogeneous reaction media obtained at the outlet of the flow reactor at different residence times (in CH_3CN [0.1 M], Q (O_2) = 2 ml(n)·min^{-1}, p = 6 bars).

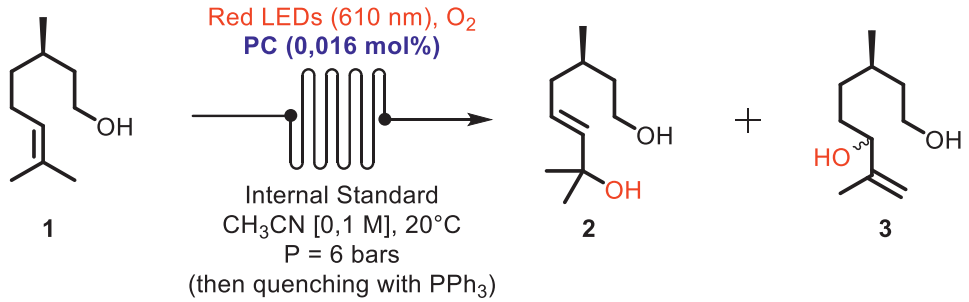


TABLE 1 | Conversions of **1** in a continuous flow reactor using MB and MB@SiO_2 NPs.

Entry	PC	Org Flow rate (ml·min^{-1})	O_2 Flow rate (ml(n)·min^{-1})	Residence time (min)	Conversion (%)[a]
1	MB	1.0	2.0	2.4	35
2	MB	0.5	2.0	4.9	57
3	MB	0.25	2.0	10.0	81
4	MB	0.25	1.0	10.3	92
5	MB@SiO_2 NPs	1.0	2.0	2.4	26
6	MB@SiO_2 NPs	0.5	2.0	4.9	49
7	MB@SiO_2 NPs	0.25	2.0	10.0	75
8	MB@SiO_2 NPs	0.25	1.0	10.3	86

[a]*Measured by GC-MS using an internal standard (1,3-dimethoxybenzene).*

(Entry 8). This corresponds to a STY of 82 g h^{-1} L^{-1} which is 14 times more important than in our previous batch reactor studies with the heterogeneous PCs.

These results show inverted performances of the homogeneous versus heterogeneous PCs in flow compared to batch (although this difference is less significant than with the results obtained in batch). Indeed, the heterogeneous PC systematically provides lower conversions compared to the homogeneous system in flow ((<10%), see **Figure 4A**), which is the opposite as what we observed in batch. Our assumption is that improved mass-transfer properties make the reaction much more efficient in flow which minimizes the influence of catalyst deactivation, as opposed to batch where the poorer reactivity makes catalyst deactivation a dominating kinetic effect. The latter also accounts for the non-linear increase in conversion in function of residence time as observed in **Figure 4A**, as a longer residence time should induce higher catalyst deactivation. In order to assess this hypothesis, we compared the absorption spectra of the crude homogeneous reaction media obtained at the outlet of the flow reactor at different residence times (**Figure 4B**). Indeed, we observed a marked difference in the absorption intensity of MB of the starting solution and 4.9 and 10.0 min residence times. However, the stability of MB appears to be the same at 2.4 and 4.9 min residence times.

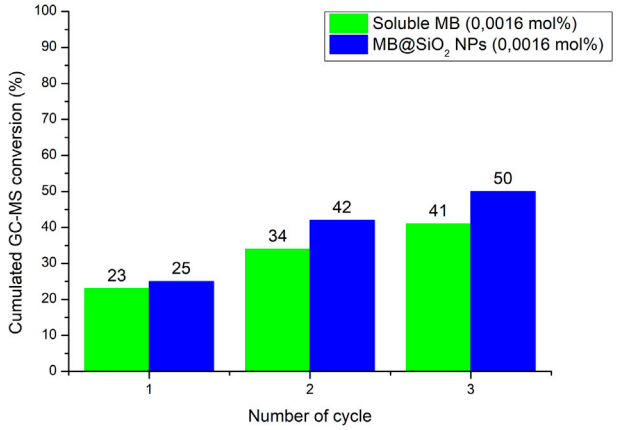


FIGURE 5 | Cumulated conversions of **1** as measured after *n* cycles in the continuous flow photoreactor under the following conditions: in CH_3CN [0.1 M], Q (organic) = 0.25 ml·min^{-1}, Q (O_2) = 1.0 ml(n)·min^{-1}, p = 6 bars, T = 20°C).

TABLE 2 | Summary of stability and productivity values obtained in batch and flow photoreactors using MB and MB@SiO_2 NPs as PCs under red light irradiation.

	Batch		Flow	
PC	MB	MB@SiO_2 NPs	MB	MB@SiO_2 NPs
TON	5,000	6,250	25,625	31,250
STY (g h^{-1} L^{-1})	3.44	5.74	88	82

Although the process was not optimized in terms of productivity, these results already compare well with literature data. Our best productivity was calculated to be around 0.025 mmol/min which is close to a previously reported study using MB, although with a higher MB loading, providing around 0.031 mmol/min at 1 mol% MB loading in the same reactor (Park et al., 2011). Other examples of higher productivity have been reported, however these required higher photocatalyst loading (1–20 mol%) and were essentially performed on microchip reactors which offer a largely improved surface to volume ratio and therefore a much more improved irradiation of the reaction (Hamami et al., 2019).

In order to further evaluate these stability parameters under homogeneous and heterogenized conditions, we studied the photooxidation of **1** in the flow reactor under stressed catalytic conditions with a PC concentration 10 times lower than in our previous experiments (0.016 mol%). The purpose of these experiments is to determine cumulated TON (tTON) values in flow by recirculating the crude solution mixture and measuring the cumulated conversion after each cycle. The same experiment was carried out with MB and MB@SiO_2 NPs and the results are plotted in **Figure 5** These indicate a tTON of 25,625 for the homogeneous system *vs* 31,250 for the heterogeneous system and demonstrate that photocatalyst stability is enhanced in the flow system, presumably due to less intense/prolonged exposure to light.

As a conclusion, we have reported in a systematic study the performances of a well-known PC (Methylene Blue) in a photooxidation reaction under homogeneous and heterogeneous conditions in a batch and in a flow reactor under red light (**Table 2**). Although the two reactors do not have the same photon throughput, the study highlights stability factors influencing the performances of the homogeneous and heterogeneous systems. Indeed, the homogeneous system seems to be less effective in a batch reactor due to rapid catalyst deactivation while this "unproductive" pathway is limited in flow compared to the "productive" photooxidation pathway, due to the improved mass transfer performances. On the other hand, the heterogeneous system provides a "protective" environment against catalyst deactivation which is leading to better performances in batch or in flow under stressed catalytic conditions, because in both experiments the photooxidation pathway is less efficient. Overall, we believe this study provides interesting data for the design and scale up of photochemical operations in industry, taking into account sustainability and process intensification parameters. In addition, this study indicates that high performance photocatalysis can be developed using low energy red light, which represents another important step towards the design of more environmentally benign photochemical manufacturing.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

ML and ZA designed the project and experiments with the help of CG and MP. ML performed all the experiments. ML prepared and characterized the nanoparticles, with the help of CG. ML and ZA drafted the manuscript and all authors edited it.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fceng.2021.752364/full#supplementary-material

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