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Title:
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Date:
2018-10-01

Citation:
Nothling, M. D., McKenzie, T. G., Reyhani, A. & Qiao, G. G. (2018). Tunable, Quantitative Fenton-RAFT Polymerization via Metered Reagent Addition. Macromolecular Rapid Communications, 39 (19), https://doi.org/10.1002/marc.201800179.

Persistent Link:
https://hdl.handle.net/11343/283936

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DOI: 10.1002/marc.201800179

Communication

Tunable, Quantitative Fenton-RAFT polymerization via metered reagent addition[1]

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A continuous supply of radical species is a key requirement for activating chain growth and accessing quantitative monomer conversions in RAFT polymerization. In Fenton-RAFT, activation is provided by hydroxyl radicals, whose indiscriminate reactivity and short-lived nature poses a challenge to accessing extended polymerization times and quantitative monomer conversions. Here, we present

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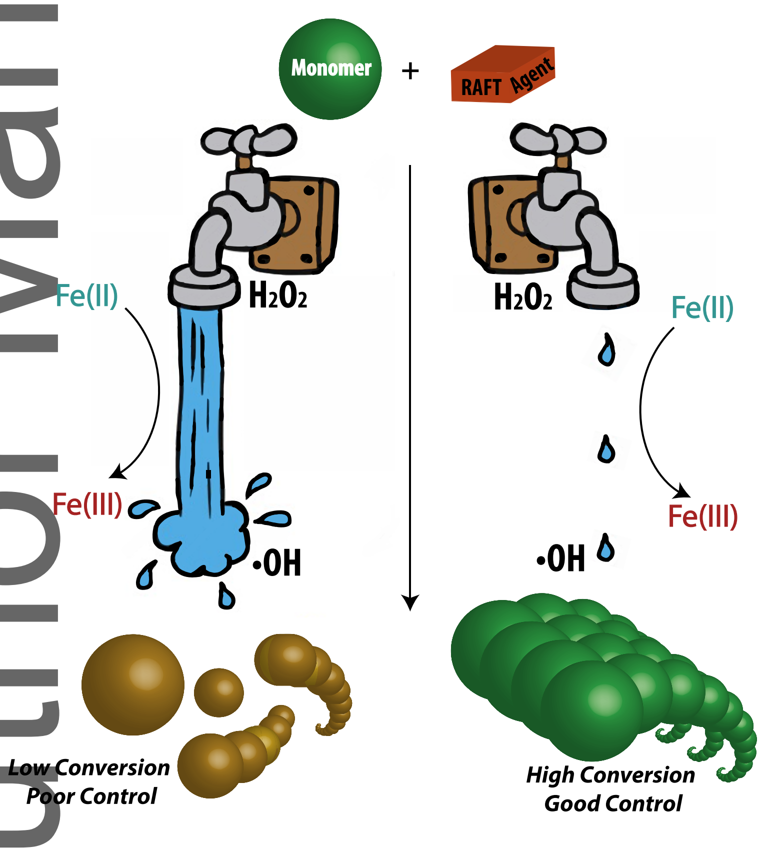
an alternative Fenton-RAFT procedure whereby radical generation can be finely controlled via metered dosing of a component of the Fenton redox reaction (H_2O_2) using an external pumping system. By limiting the instantaneous flux of radicals and ensuring sustained radical generation over tunable time periods, metered reagent addition reduces unwanted radical 'wasting' reactions and provides access to consistent quantitative monomer conversions with high chain-end fidelity. Fine tuning of radical concentration during polymerization is achieved simply via adjustment of reagent dose rate, offering significant potential for automation. This modular strategy holds promise

for extending traditional RAFT initiations toward more tightly regulated radical concentration profiles, and affords excellent prospects for the automation of Fenton-RAFT polymerization.



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1. Introduction

The development of reversible deactivation radical polymerization (RDRP), including atom transfer radical polymerization (ATRP),[1-2] nitroxide-mediated polymerization (NMP),[3-4] and reversible addition-fragmentation chain transfer polymerization (RAFT)[5-6] has afforded access to a remarkable array of predetermined polymer architectures for diverse academic and industrial applications.[7] However, even the most promising RDRP processes suffer from the requirement for labor intensive, multi-step syntheses that must be conducted by expert operators, while maintaining reproducibility in the final polymer products.[8] A long-standing challenge to address these issues is the development of quantitative polymerization reactions that maintain excellent chain end fidelity for future integration into automated, programmable and high throughput RDRP protocols.[9]

A key requirement for the successful automation of RDRP is the development of suitable chemical procedures that can be readily translated into a program design. Such procedures should demonstrate a number of characteristics, chiefly including quantitative monomer conversion and high chain-end fidelity, to facilitate preparation of complex polymeric architectures.[10-13] A significant challenge unique to RAFT polymerizations is the requirement for a constant supply of radicals during the reaction to (re)activate the chain transfer agent and compensate for radical-radical termination between propagating chains.[14] This has traditionally been achieved via the thermal decomposition of a radical initiator, such as AIBN, to continuously supply radicals over the duration of the polymerization. This approach is defined by the temperature dependent half-life for the initiator homolysis, leading to a high initial radical flux followed by a decreasing radical production and eventual halting of the associated polymerization.[15] A constant supply of radicals has been achieved in RAFT activated by light[16-18] or acoustic cavitation (sonochemistry),[19]

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displaying excellent temporal control over polymer chain growth. A similar constant supply of radical species in a purely chemical initiation system could afford greater scalability and automation to the RAFT procedure.

Previous study in our group has established the technique of Fenton-activated RAFT polymerization for the “on-demand” preparation of a range of predefined polymer structures.[20] Fenton-RAFT employs the redox pairing of hydrogen peroxide (H_2O_2) and ferrous ions (Fe(II)) in solution, which catalytically generates hydroxyl radicals that subsequently initiate a controlled radical polymerization in the presence of a chain transfer agent (CTA) *via* RAFT. However, similar to the thermal initiator systems described above, access to consistent quantitative monomer conversions while maintaining chain-end fidelity remained challenging with this technique, due to the short-lived nature of the highly reactive hydroxyl radical initiating species.[21] While the high flux of hydroxyl radicals rapidly generated by the Fenton reaction is sufficient to begin polymerization, the rapid exhaustion of initiating species by the various hydroxyl radical side reactions results in the polymerization stopping after a short time interval and with incomplete monomer conversion.[22] This effect was subsequently managed via the addition of multiple doses of H_2O_2, however limited control was available over the H_2O_2 concentration profile during the reaction. The development of an automated, finely-adjustable system for customized individual polymerization reactions using RDRP requires a system which can achieve quantitative monomer conversion without loss of chain-end fidelity as the first milestone step.

In this study, we sought to achieve this goal in Fenton-RAFT via finely controlling the H_2O_2 addition – and hence the radical concentration profile – via an external pumping system (syringe pump)

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(**Scheme 1**). Using the polymerization of *N,N*-dimethylacrylamide (DMA) as an illustrative example, several reagent dosing parameters were explored, including the concentration and ratio (i.e. H_2O_2:Fe(II)) of Fenton reagents, H_2O_2 dose rate and H_2O_2 dosing profile (instantaneous, linear, non-linear increasing/decreasing). Quantitative monomer conversions while maintaining chain-end fidelity, tunable reaction times and low dispersity is afforded by this approach, with the simple, readily-available experimental apparatus making this technique particularly appealing for future exploration of automated Fenton-RAFT polymerization.

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2. Results and Discussion

Following our recent work developing Fenton-RAFT as a robust, versatile controlled radical polymerization technique, our next goal was two-fold: to extend the protocol to consistently achieve quantitative monomer conversions while maintaining low dispersity and chain-end fidelity; and to probe the maximum polymerization rate that could be achieved by the system while maintaining control over radical propagation and subsequently the resultant polymer product. Focus was directed toward the aqueous polymerization of *N,N*-dimethylacrylamide in the presence of a water soluble chain transfer agent (*bis*-TTC) as a model reaction system for this study, as these reagents previously showed good compatibility with the Fenton-RAFT protocol. Initially, polymerization was attempted by combining monomer, CTA, water (as solvent) and ammonium ferrous sulfate (Fe(II) source) in a sealed round bottom flask, followed by vigorous degassing via N_2 sparging. A separately degassed aliquot of H_2O_2 solution was then rapidly injected into the monomer/CTA/Fe(II) solution to initiate the Fenton redox reaction and begin polymerization.

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Despite exploring multiple different Fenton reagent concentrations and ratios, instantaneous addition of H_2O_2 to initiate chain growth consistently resulted in the polymerization stopping after short time intervals (<3 mins) with sub-quantitative monomer conversion (**Table S1**). It appears that the high flux of hydroxyl radicals formed during the Fenton redox pairing is sufficient to initiate polymerization and sustain a level of chain propagation. However, the highly indiscriminate reactivity of the hydroxyl radicals results in various undesired 'wasting' reactions, quickly removing the initiating species from the reaction mixture, resulting in cessation of the polymerization. The presence of such undesired hydroxyl radical side reactions is well known in the literature (refer to Supporting Information for further discussion). We initially hypothesized that this effect could be reduced by increasing the total concentration of Fenton reagents in the polymerization mixture. This effectively increases the initial flux of hydroxyl radicals such that there are sufficient radicals available to afford complete conversion of available monomer, before the hydroxyl radicals can be exhausted by the undesired side reactions. Using this methodology, increased monomer conversions were achieved, however increases in polydispersity of the polymer product and eventual gelling of the reaction mixture was observed at higher Fenton reagent concentrations (Table S1). It appears that the high initial radical to RAFT agent ratio under this protocol leads to chain-chain coupling reactions, an increase in the concentration of 'dead' polymer chains and the uncontrolled crosslinking of polymer chains due to hydroxyl radical attack along the polymer backbone. In addition, the highest H_2O_2 concentrations studied here could result in RAFT agent degradation leading to uncontrolled polymerization.[23]

To address these issues, a temporally regulated H_2O_2 addition profile was envisaged whereby the concentration of initiating hydroxyl radicals within the polymerization mixture could be finely tuned, limiting the instantaneous radical concentration as well as the accompanying radical wasting reactions, and allowing the polymerization to proceed over longer time periods. We believe that the

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gradual addition of H_2O_2 via the action of glucose oxidase results in quantitative monomer conversions in the presence of an Fe(II) source as a Fenton redox pair. Therefore, we hypothesized that the time-controlled, metered addition of H_2O_2 via an external pumping system could achieve a similar effect, re-establishing control over polymer chain growth while allowing for complete monomer conversion. A syringe pump was programmed to infuse H_2O_2 solution constantly over specified time periods, and several reactions were examined with varied Fenton reagent concentrations, ratios and H_2O_2 infusion rates (**Table S1–S3**). Intriguingly, our first scenario with monomer:CTA:Fe(II): H_2O_2 of 200:1:0.15:1 displayed a significant increase in monomer conversion, from ~1% when H_2O_2 was added instantaneously, to 72% when the same volume of H_2O_2 was infused over 3 minutes (**Figure 1A**).

By extending the time over which the H_2O_2 aliquot was delivered to 90 mins, quantitative conversion could be achieved, with the resulting polymer displaying very low polydispersity ($Đ$ = 1.05) and a molecular weight in agreement with the theoretical value (**Figure 1B**). By simultaneously varying both the volume of H_2O_2 infused and the H_2O_2 delivery rate, fine control of the polymerization rate could be achieved with longer reaction times required for lower H_2O_2 addition rates and shorter reaction times when H_2O_2 infusion rates were increased (**Figure 1C**). Extremely fast (<3 mins) and quantitative polymerizations were observed with the highest Fenton reagent concentrations (monomer:CTA:Fe(II): H_2O_2 = 200:1:1:3), however control over these systems was reduced, as evidenced by broader molecular weight distributions and elevated molecular masses (**Figure 1D**). Limiting the instantaneous hydroxyl radical flux by infusing lower volumes of H_2O_2 over longer periods appeared to result in the greatest control over the polymerization in terms of the molecular weight and dispersity of the final polymer product. Importantly, polymer chain-end fidelity and excellent “livingness” of the PDMA product was demonstrated via a successful chain extension

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experiment, resulting in a monomodal polymer with a clear shift to higher molecular mass and low dispersity (**Figure S1**).

An examination of monomer conversion as a function of time for two systems where the H_2O_2 infusion rate and volume have been balanced to achieve near-quantitative monomer conversion over different reaction times is illustrated in **Figure 2**. Comparing these dosing scenarios qualitatively reveals a slower rate of polymerization with a reduced H_2O_2 dose rate, indicative of a lower flux of hydroxyl radicals. In addition, a lower H_2O_2 dose rate results in a longer induction period before polymerization is observed, implying the presence of a threshold H_2O_2 concentration required to initiate polymerization. Nevertheless, the PDMA prepared under the two dose rate scenarios is almost identical when analyzed via GPC_{DRI}.

The relative independence of the final PDMA molecular mass, dispersity and molecular mass distribution (MWD) on the H_2O_2 dose rate is a direct result of the RAFT mechanism.[24][25] Under a RAFT regime, initiation of the polymerization is primarily undertaken by the chain transfer agent (CTA), and a continued supply of radicals is required to (re)activate the CTA-derived radical species. As the CTA is not added continuously in our experiments, no impact is observed on the final polymer molecular mass or dispersity. This contrasts with alternative RDRP processes such as NMR and ATRP that proceed with a discrete initiating species, whereby polymer MWD can be selectively skewed via the temporally regulated dosing of initiator.[26] However, the rate of irreversible chain termination in RAFT – a process that should lead to a skewing of the MWD towards lower molecular weight species – is known to be directly proportional to the concentration of exogenous radical initiator in the system.[10] Therefore, as the profile of this exogenous initiator species is changed throughout the course of polymerization via syringe pump addition, a resultant impact on the MWD may be expected.

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To probe the potential for this effect in the Fenton-RAFT system, we explored a number of additional, non-linear H_2O_2 dosing profiles (**Figure 3**). Under these dosing scenarios, the rate of H_2O_2 infusion increased or decreased non-linearly while the dosing period and total volume of H_2O_2 was kept constant (Table S2; S4–S7). Once again, the non-linear dosing profiles also displayed little impact on the molecular weight or MWD of the resulting PDMA polymers. A slightly elevated molecular mass was observed for the PDMA sample prepared with an increasing H_2O_2 dose rate, which may due to the higher instantaneous H_2O_2 concentration near the end of the reaction, consistent with results discussed previously (Table S1). It appears that the H_2O_2 dosing profile impacts the rate of polymerization only, with a negligible effect observed on the final polymer product when the H_2O_2 dose rate and volume is minimized. This effect points toward an approximately constant radical concentration that results from a concurrent increase in deleterious radical side reactions balancing the overall greater radical production at high H_2O_2 dose rates, again consistent with the well-established mechanism of RAFT.[27]

As achieved with light– and sono–activated RAFT, extending metered reagent addition to other RAFT polymerization initiator systems may afford a finely-tuned, continuous supply of radical species necessary to sustain chain propagation. This effect should be tunable independent of the kinetics of bond homolysis and radical formation in alternative initiator systems, and further work in this direction is ongoing in our lab.

4. Conclusions

In summary, we outline an optimized Fenton-RAFT method for preparing controlled PDMA with quantitative monomer conversion and low dispersity via metered H_2O_2 addition. By tuning the

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volume and rate of addition of H_2O_2, a constant supply of hydroxyl radicals could be sustained for the duration of the polymerization resulting in well-defined polymers with consistent molecular weight, dispersity and MWD characteristics. Importantly, this technique delivers quantitative monomer conversions while maintaining chain-end fidelity, highlighting the controlled nature of the procedure. Metered reagent addition holds significant promise for extending the utility of traditional radical initiators (such as AIBN) to longer polymerization times and quantitative monomer conversions, and represents a versatile technique for quantitatively accessing well-controlled polymers via Fenton-RAFT.

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Acknowledgments

G.G.Q. acknowledges the Australian Research Council Future Fellowship (FT110100411) and Discovery Project schemes (DP170104321). A.R is supported by the Melbourne International Research Scholarship (MIRS) and the Melbourne International Fee Remission Scholarship (MIFRS) schemes.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Fenton; RAFT; Initiation; Metered; Quantitative

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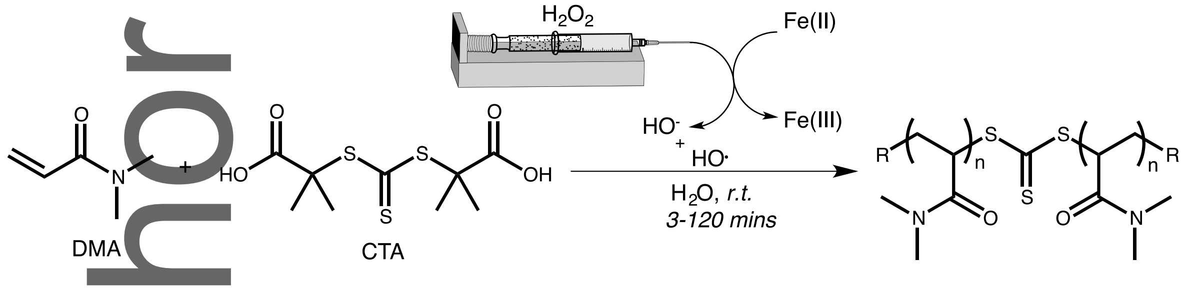
Figures



Scheme 1. Fenton-RAFT synthesis of PDMA incorporating metered H_2O_2 addition.

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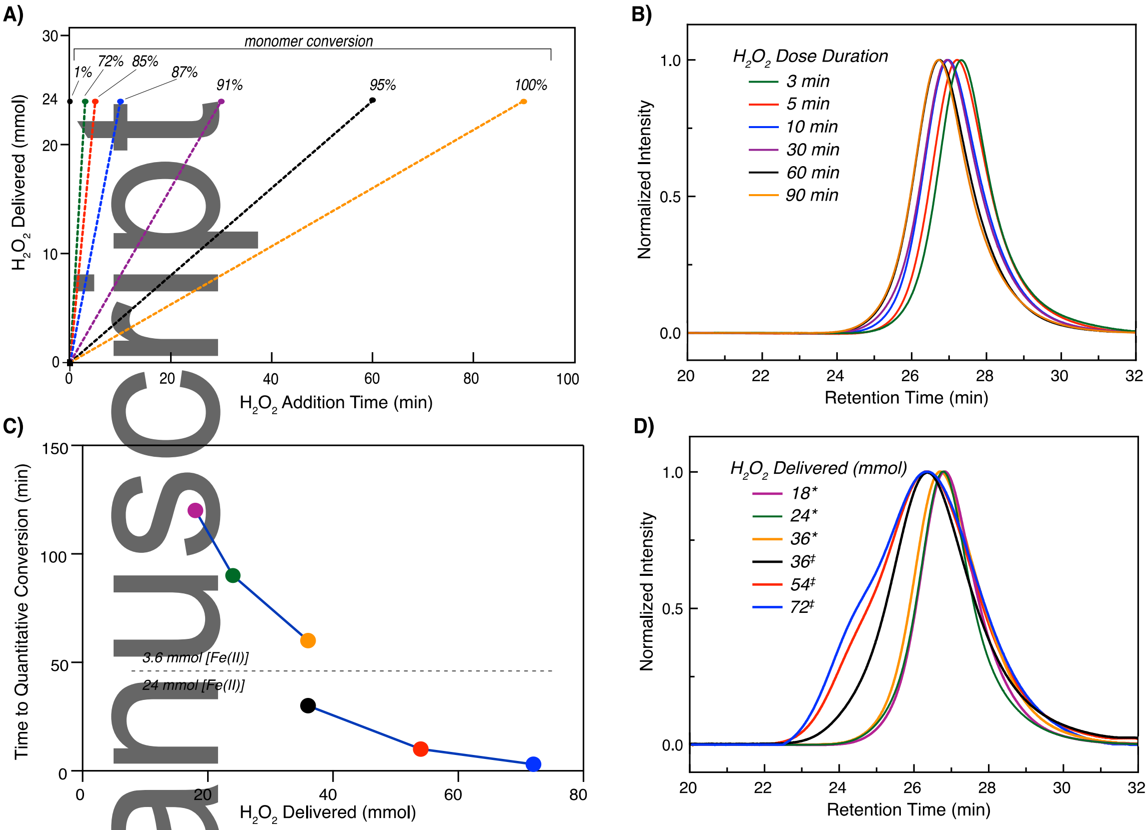

***Figure 1.* Constant Dosing of H_2O_2 in Fenton-RAFT. (A)** Linear dose profiles for addition of H_2O_2 (24 mmol) over varying time intervals, illustrating increased monomer conversions with extended dosing times (where dose time (0) represents instantaneous addition and CTA:Fe(II):H_2O_2 = 1:0.15:1). **(B)** Size exclusion chromatograms (GPC$_{DRI}$) for PDMA resulting from different H_2O_2 dosing times. **(C)** A comparison between the total volume of H_2O_2 dosed and reaction time required to reach quantitative monomer conversion for two Fe(II) concentrations, highlighting increased polymerization rates with increasing Fenton reagents addition. (Coloured points correspond with chromatographs in panel (D)). **(D)** Increasing both Fe(II) and H_2O_2 addition results in an increased PDMA molecular weight (M_n) by GPC$_{DRI}$, with broadening of the chromatogram peaks and appearance of a high molecular weight 'shoulder' indicating reduced control over the polymerization. (*[Fe(II)] = 3.6 mmol, ‡[Fe(II)] = 24 mmol, Fe(II) added as $(NH_4)_2Fe(SO_4)_2{\cdot}6H_2O$).

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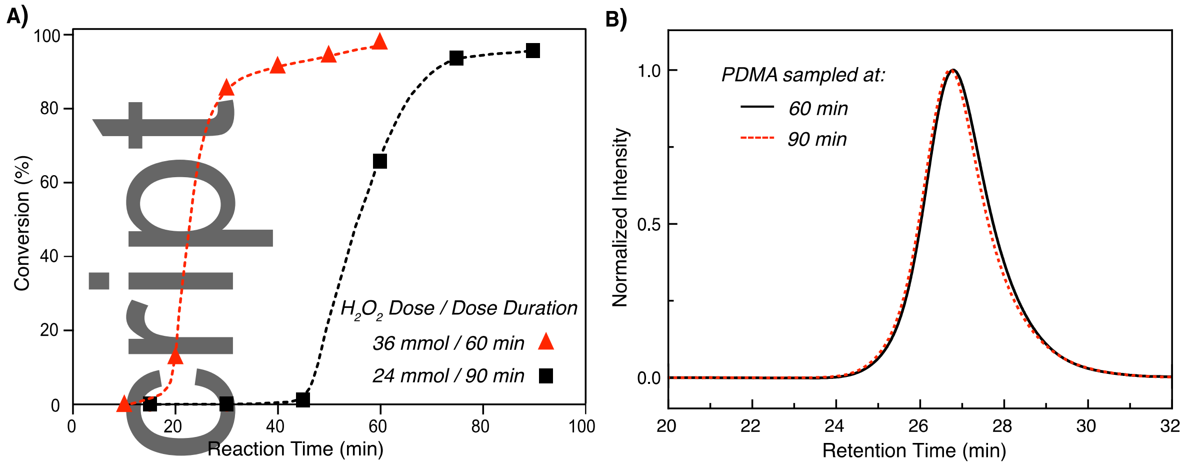

***Figure 2.* Varied H_2O_2 Addition Rates Result in Near-Quantitative Conversions (A)** Monomer conversion as a function of time for polymerization of DMA with alternate H_2O_2 addition rates. **(B)** Resulting PDMA mass and polydispersity with near-quantitative monomer conversion appears to be independent of H_2O_2 addition rate when analyzed by GPC_{DRI}.

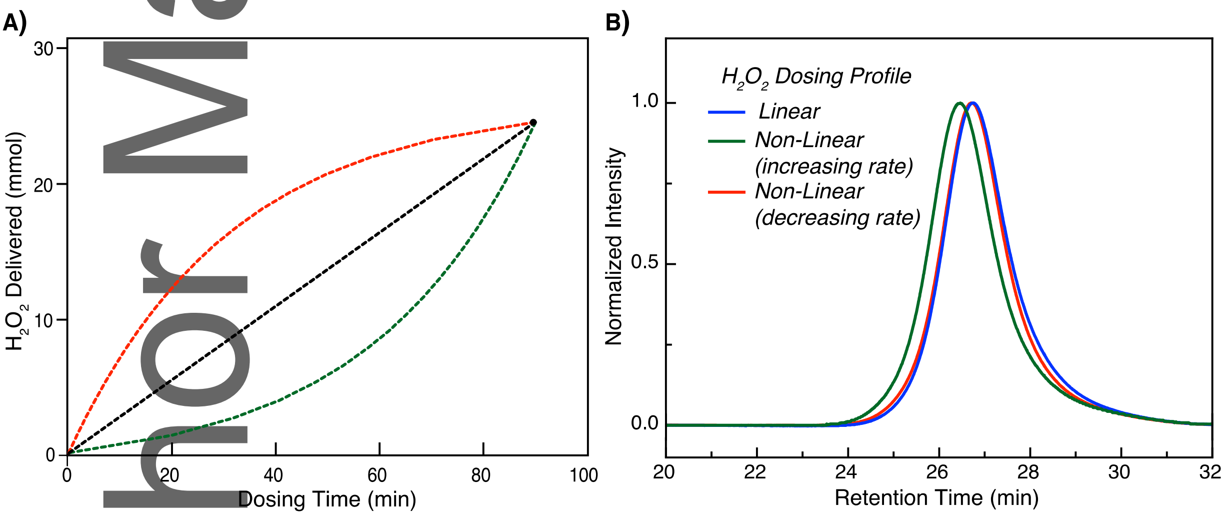

***Figure 3.* Alternative H_2O_2 addition profiles. (A)** Linear (black), non-linear (*decreasing rate*) (red), non-linear (*increasing rate*) (green) H_2O_2 addition profiles examined. **(B)** H_2O_2 addition profile does not appear to significantly affect the resultant polymer sample, with very similar monomodal, low dispersity PDMA formed under each scenario.

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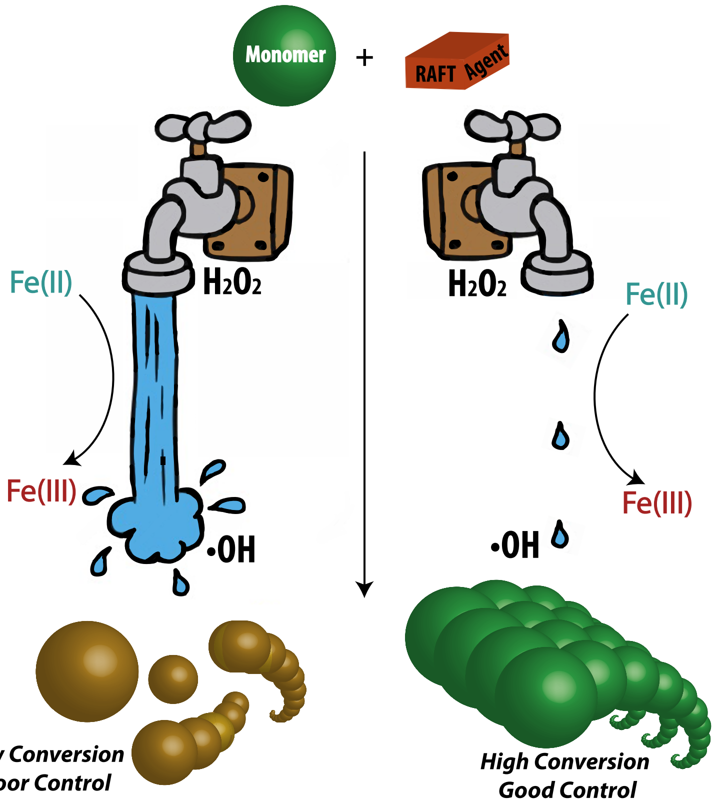
Tunable, Quantitative Fenton-RAFT polymerization via metered reagent addition

In RAFT polymerization, a constant supply of radical species is essential for maintaining chain growth and achieving high monomer conversions. Here, we present a method for sustained radical generation in a RAFT polymerization by way of metered reagent addition. Tuning of the reagent dose rate enables polymerizations to proceed to quantitative monomer conversions while maintaining 'livingness' in the polymer products.

ToC & Abstract Figure



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