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effects of monomer on PLGA based long-acting injectables' release and stability

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PURPOSE

Long acting injectables (LAI's) frequently utilize bio-resorbable polymers to control the release of active pharmaceutical ingredients via tunable degradation rates. One commonly used bioresorbable polymer is poly (lactic-co-glycolic acid), or PLGA because they allow for tuning of co-monomer ratio, molecular weight, and end capping group to meet a characteristic degradation rate. Degradation rates, geometric constraints and, API characteristics such as hydrophobicity and loading help determine the pharmacokinetic profile of the long-acting injectable product. A less studied aspect of PLGA bio-resorbable polymers is the effect monomers can have on the degradation rate and drug stability. The purpose of this study is to examine the effects monomer has on long-acting injectable formulations release and stability and how to minimize these effects.

METHODS

Analysis of the development of an acidic microenvironment was performed using Viatel™ DL 07 E and Viatel™ DL 07 E ultrapure, they were cast into films and incubated at 37 ° in 20 mL scintillation vials with 15 mL of 10 mM phosphate buffer at pH 6.95. API stability was assessed using solutions composed of Pharmasolve™ (NMP), Viatel™ DL 02 A, Viatel™ DL 02 A ultrapure with 10 mg/g omeprazole or 10 mg/g atorvastatin to assess degradation of the API. In situ forming depots were composed of Pharmasolve™ (NMP), Viatel™ DL 07 E, Viatel™ DL 07 E ultrapure and, Viatel™ DL 07 E + monomer and atorvastatin to assess the burst release of the API, by directly injecting the depot forming solution into a bath containing 900 mL pH 7.4 PBS and stirring at 100 rpm after initially forming the depot.

Figure 1: *Omeprazole appearance after 30 minutes*

RESULTS

Fig.1 shows the color change in solutions containing omeprazole, the least change is observed in the Viatel™ DL 07 E ultrapure. In the cases of the thin film a significant drop in pH is observed immediately for samples containing elevated monomer which is to be expected as the monomer hydrolyses to lactic acid in solution. The high monomer sample has a more erratic and rapid degradation compared to the Viatel™ DL 07 E ultrapure sample that degrades in a more gradual and controlled manner as seen in figure 2 with little pH change seen over 13 weeks. Stability of the in-situ system shows the degradation of atorvastatin was far more pronounced with increasing concentrations of monomer compared to the low monomer equivalent. At 72 hours nearly 10% of API had been degraded in the high monomer sample compared to <2% in the low monomer sample, Fig. 3. Release of atorvastatin was monitored up to 48 hours from in situ depot. The high monomer depot demonstrates initial burst and greater release overall. The Viatel™ ultrapure sample had much lower burst and less release in the time analyzed to demonstrate burst release in Fig. 4.

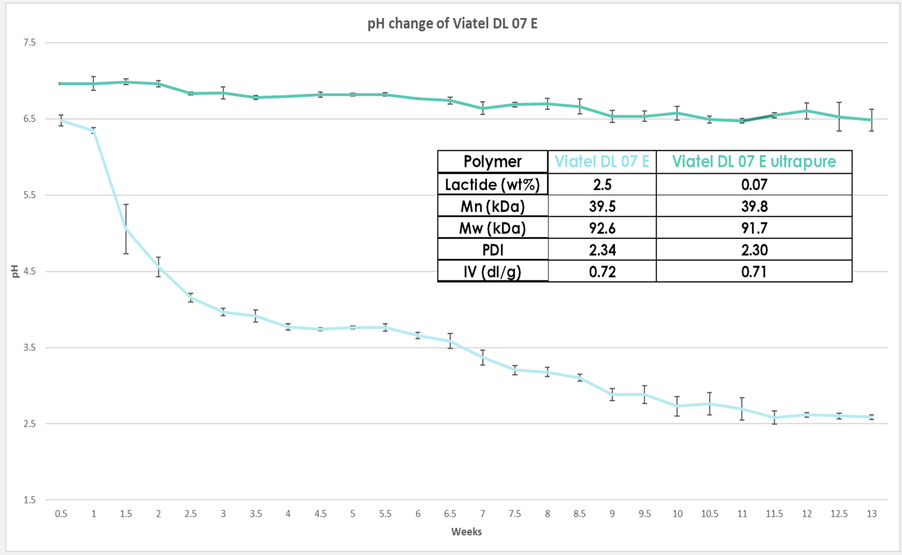

Figure 2: *Viatel DL 07 E: pH change of phosphate buffer*

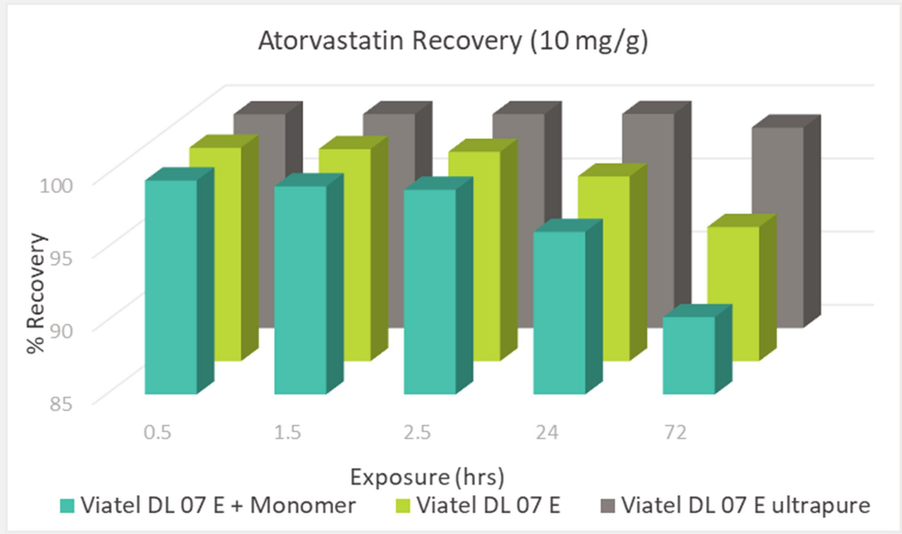

Figure 3: *Atorvastatin recovery after exposure to in situ system, shows substantial degradation with high monomer content.*

CONCLUSIONS

The presence of monomer contributes to acid-catalyzed hydrolysis of the PLGA backbone accelerating the degradation rate by means of molecular weight drop and influencing burst release and API stability. This effect may contribute to dissolution profiles observed in products on the market and must be accounted for in product design and deformulation. Viatel™ ultrapure, with very low monomer content, yields a dissolution and release profile that best demonstrates the effects exerted by composition and API characteristics alone.

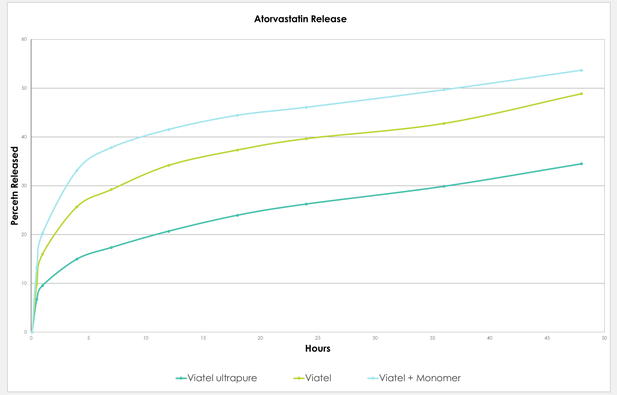

Figure 4: *in vitro release of atorvastatin through 7 hours, indicating burst release in high monomer sample. 900 mL pH 7.4 PBS, 37C, 100 rpm*

Image 1: *Comparison of Viatel DL 07 E polymer (left) and Viatel DL 07 E Ultrapure polymer (right)*

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