

Preliminary formulation development of silicone elastomer vaginal rings for sustained release of metronidazole, sucrose and lactobacillus



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Key points

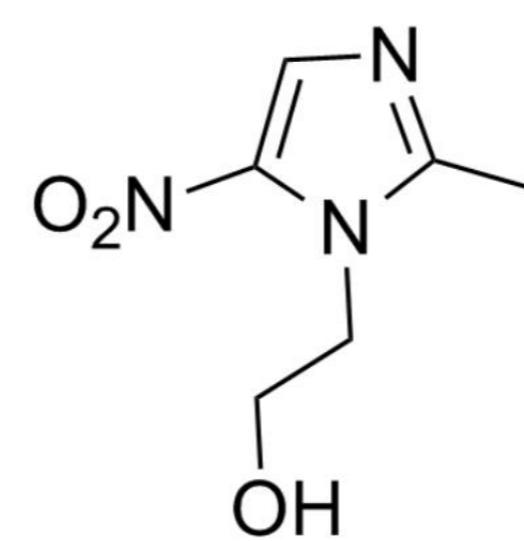
- Matrix-type Elkem 15 rods loaded with lyoprotectants, and combination of MET and lyoprotectants can be manufactured by molding injection.
- Swelling ratio values (Q_{wt}) indicates the hydrophilicity of the material. As the concentrations of lyoprotectants increased, the hydrophilicity of silicone elastomer increase.
- In this 14-day release study, cumulative release for all rods increased as the lyoprotectant loading increased.

Background

Bacterial vaginosis (BV) is a common dysbiosis of the human vagina in which commensal vaginal lactobacilli are displaced by mixed pathogenic bacterial populations. Current treatments for – including metronidazole (MET) and clindamycin – result in short-term cure but often lead to recurrence. New treatment options are needed. Lactobacilli are being actively developed as a probiotic treatment option for BV, given their ability to inhibit growth of pathogenic microorganisms and to maintain the health and stability of the vaginal tract microbiota. Also, prebiotic sucrose gels have shown promise for treatment of BV in clinical studies. Here, we report preliminary formulation work as part of our efforts to develop sustained-release vaginal ring formulations for simultaneous release of MET, a prebiotic lyoprotectant and lactobacillus. Specifically, the influence of incorporating various lyoprotectants into silicone elastomer rings is investigated.

Objectives

- To manufacture and characterize matrix-type rods (as prototype vaginal rings) having various antibiotic and prebiotic components, including MET, maltodextrin (MD), mannitol (MT), sucrose (SC), polyethylene glycerol 4000 (PEG) and 20% freeze-dried sucrose (FDSC).
- To evaluate the relationship between concentration of lyoprotectants and hydrophilicity of silicone elastomer.
- To evaluate the in vitro release profiles of MET from rods containing different lyoprotectants.



Metronidazole (MET)

Methods

- Matrix-type Elkem 14 rods loaded with (i) no active ingredients (blank), (ii) lyoprotectants (5%w/w, 10%w/w and 20%w/w), and (iii) a combination of 12.5%w/w MET and lyoprotectants (5%w/w, 10%w/w and 20%w/w) were manufactured by injecting into PVC tubing and then curing in an oven at 40°C.
- All rod formulations (n=13) were assessed for swelling test into SVF in the shaking incubator (60 rpm, 37°C) over 14 days.
- All rod formulations (n=13) were evaluated for in vitro release testing in 200ml water over 14 days (37°C and 60 rpm).

Results & Discussion

The image of matrix-type silicone elastomer Elkem 14 rods were presented in Figure 1. The mean rod weight and cross-sectional diameter were 3.0g and 8mm.

In the swelling test, The blank rods did not show significant change in their weight change (Figure 2). The swelling ratio is the value that can directly demonstrate the hydrophilicity of the material. The addition of lyoprotectant increased the hydrophilicity of the silicone elastomer (Figure 3). For MT, MD and SC, as concentration of lyoprotectant increased, the hydrophilicity of silicone elastomer increased (Figure 3a), (Figure 3b) and (Figure 3c). From 5% to 10% of PEG4000, the hydrophilicity increased, while from 10–20% the hydrophilicity had no significant difference (Figure 3d).

Mean daily release vs. time and cumulative release vs. time profiles of metronidazole from matrix-type silicone elastomer Elkem 15 rods into reverse osmosis water medium were presented in (Figure 4 and 5). Cumulative release vs. square root of time profiles of metronidazole from matrix-type silicone elastomer Elkem 15 rods into reverse osmosis water medium were presented in (Figure 6). All rods indicated a burst release on day 1 followed by a slightly decreasing daily release with time and a linear cumulative release vs. square root time (all $R^2 > 0.9$), confirmed to a permeation-control drug release mechanism from a polymeric matrix device containing excess solid drugs. In this 14-day release, cumulative release for all rods increased as the lyoprotectant loading increased, consistent with hypothesis that the lyoprotectant can facilitate the release of metronidazole.

The experimental results obtained to date are encouraging, and support the continued development of these ring formulations as a novel and interesting strategy for improving treatment of BV.

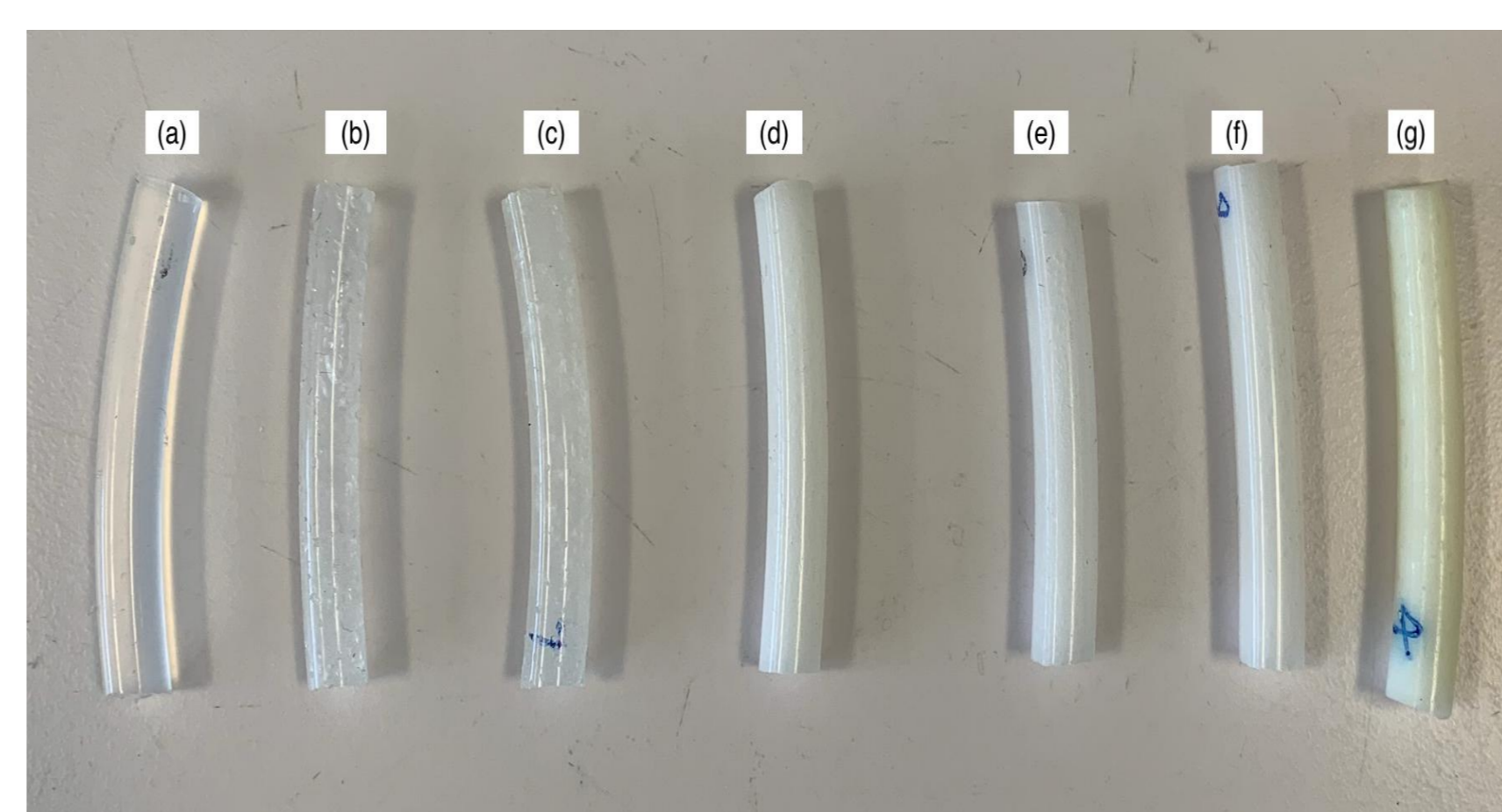


Figure 1. Representative images of matrix-type silicone elastomer Elkem 15 rods (a) Blank, (b) SC20, (c) PEG20, (d) MD20, (e) MT20, (f) FDSC and (g) MET + 20SC.

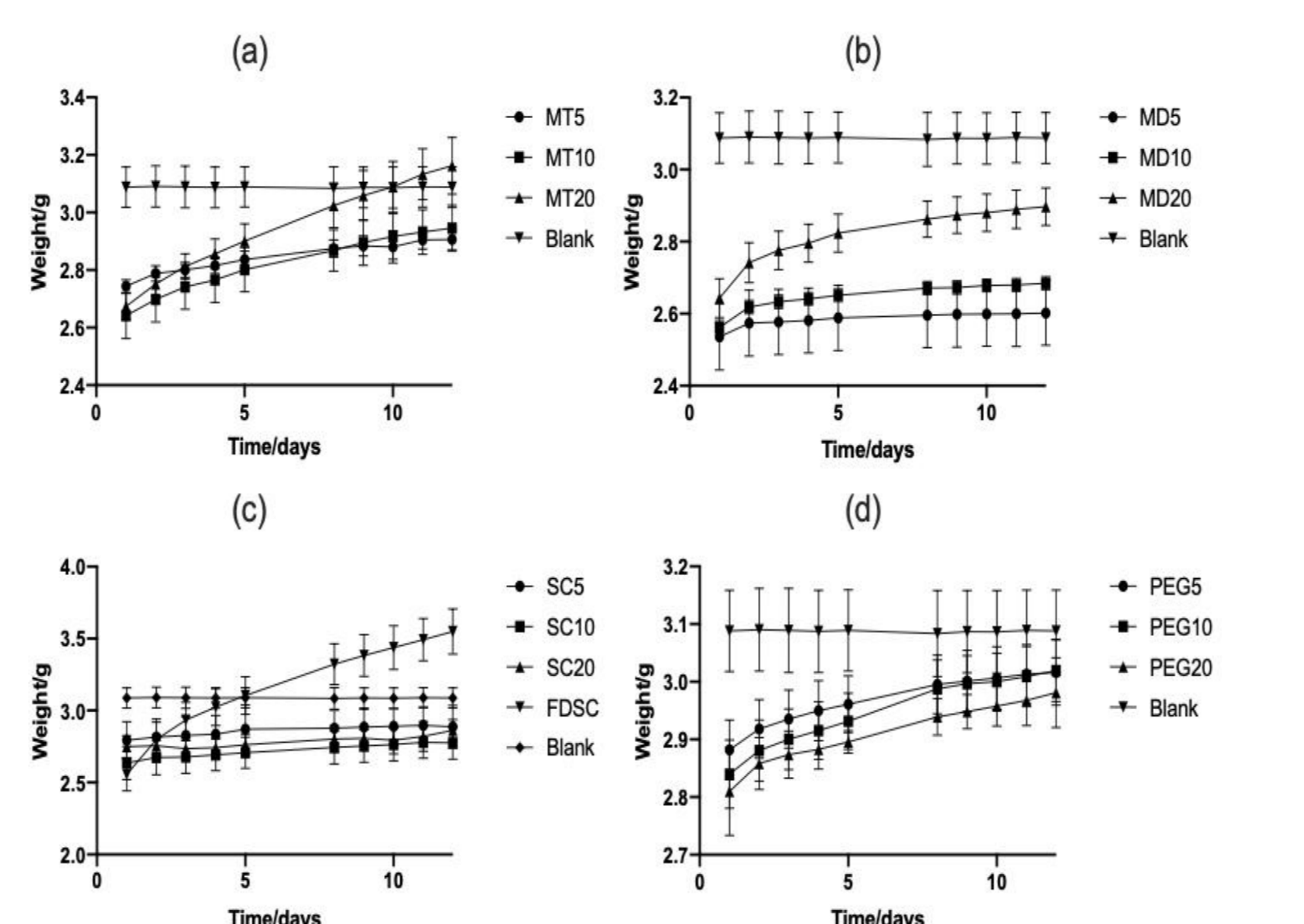


Figure 2. Weight vs. time of MT (a), MD (b), SC (c) and PEG (d) rods in SVF medium (pH = 4.2) for 14 days.

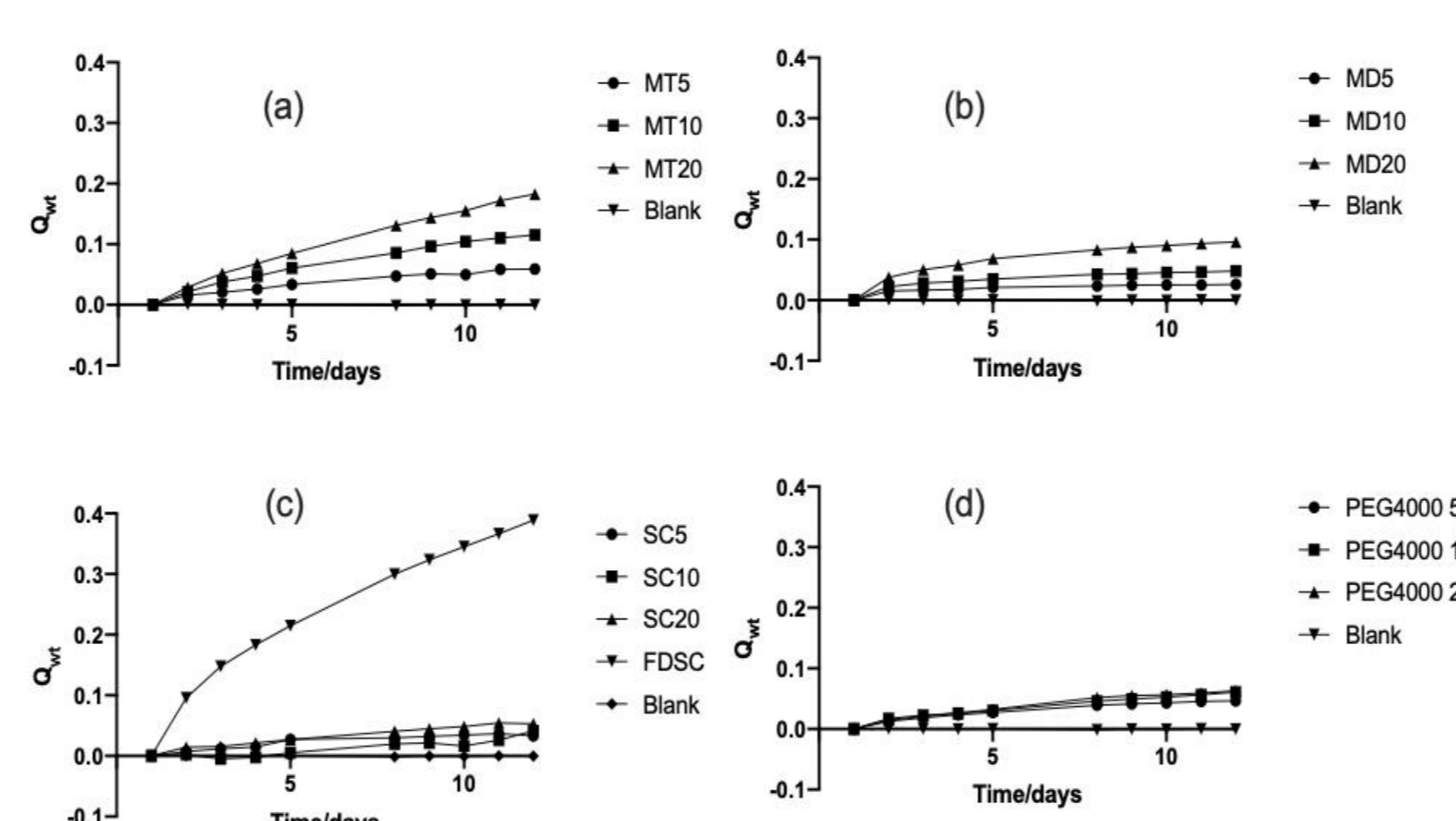


Figure 3. Q_{wt} vs. time of MT (a), MD (b), SC (c) and PEG (d) rods in SVF medium (pH=4.2) for 14 days.

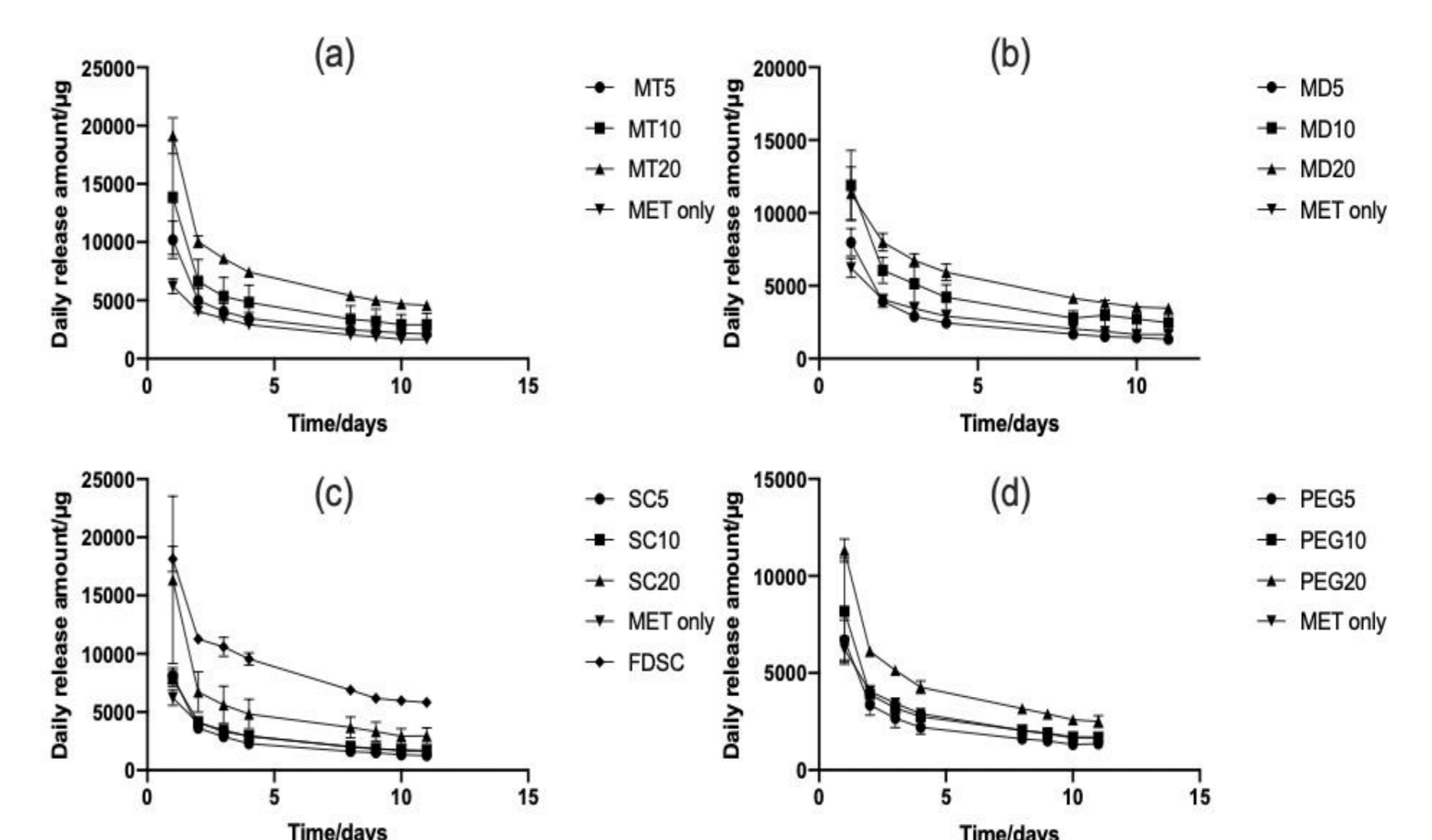


Figure 4. Mean daily release vs. time profiles of metronidazole release into reverse osmosis water (pH=5.5) of (a) MT, (b) MD, (c) SC and (d) PEG contained Elkem 15 silicone elastomer matrix-type rods over 14 days

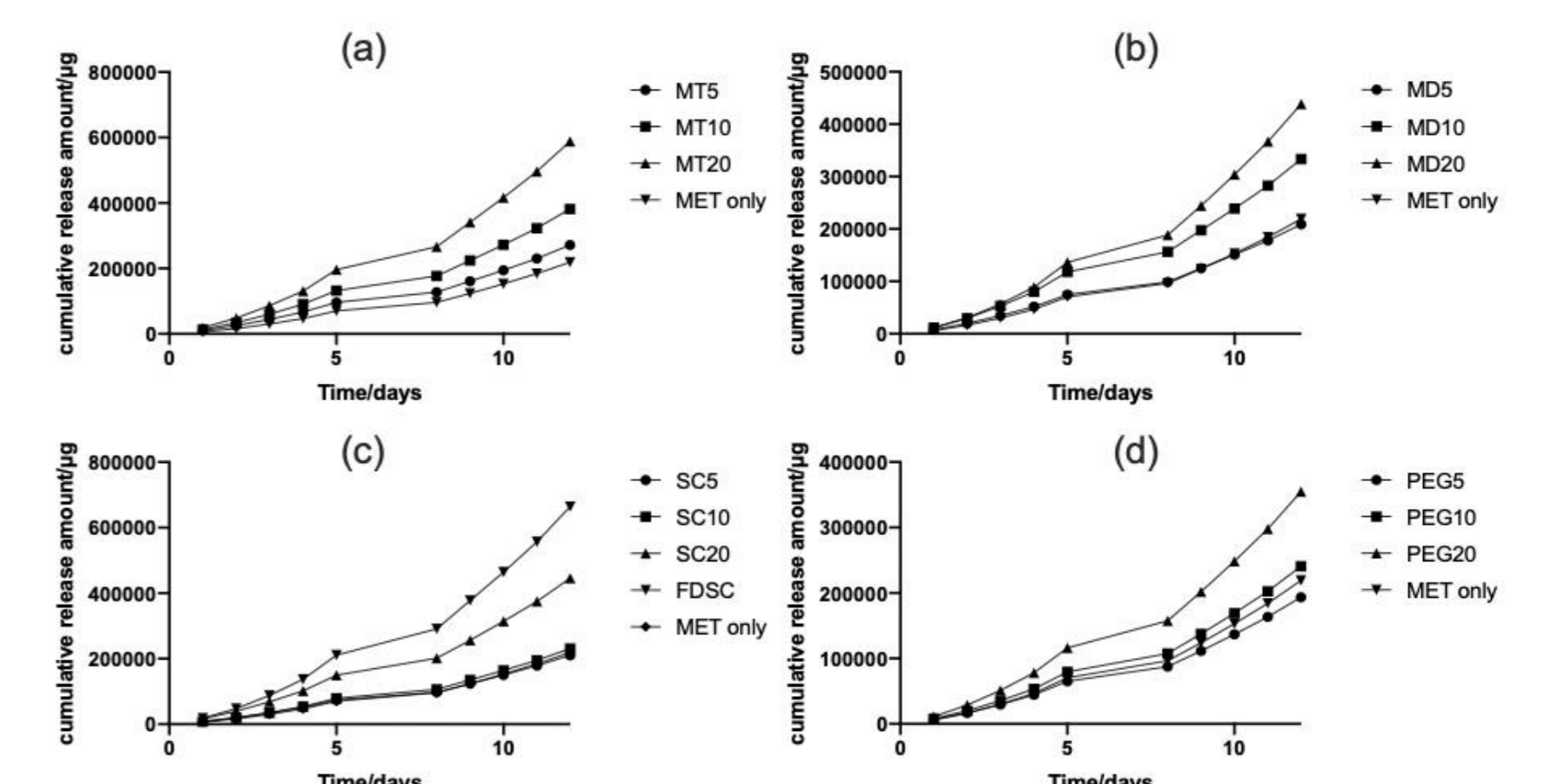


Figure 5. Cumulative release vs. time profiles for metronidazole release into reverse osmosis water (pH=5.5) of (a) MT, (b) MD, (c) SC and (d) PEG contained Elkem 15 silicone elastomer matrix-type rods over 14 days

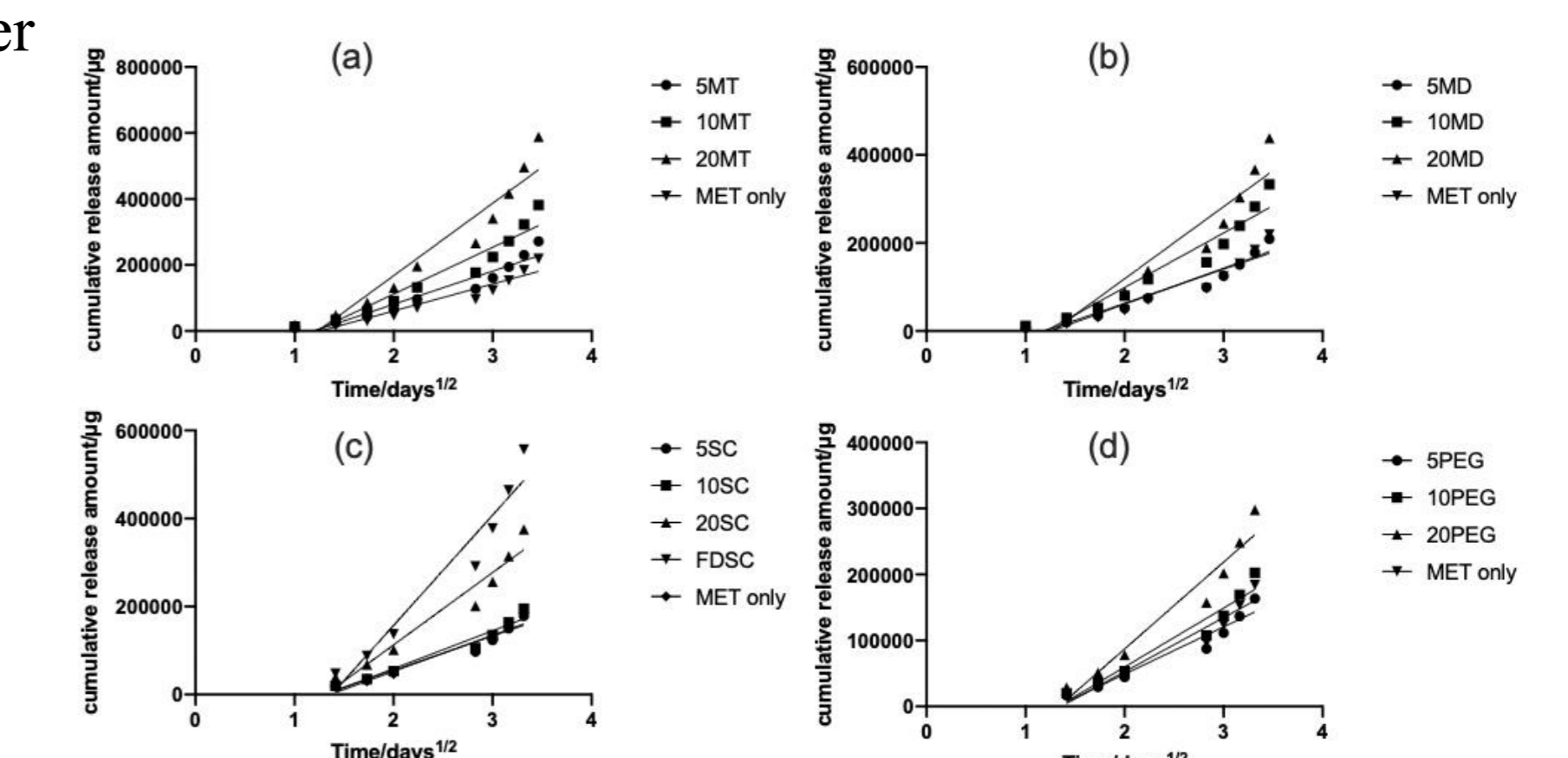


Figure 6. Cumulative release vs. root time profiles of metronidazole release into reverse osmosis water (pH = 5.5) of (a) MT, (b) MD, (c) SC and (d) PEG contained Elkem 15 silicone elastomer matrix-type rods over 14 days.