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BRIEF REPORT

A Thermo-Sensitive Delivery Platform for Topical Administration of Inflammatory Bowel Disease Therapies

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Systemic therapies for inflammatory bowel disease are associated with an increased risk of infections and malignancies. Topical therapies reduce systemic exposure, but can be difficult to retain or have limited proximal distribution. To mitigate these issues, we developed a thermo-sensitive platform, using a polymer-based system that is liquid at room temperature but turns into a viscous gel on reaching body temperature. After rectal administration to mice with dextran sulfate sodium–induced colitis, the platform carrying budesonide or mesalamine becomes more viscoelastic near body temperature. Mice given the drug-containing platform gained more weight and had reduced histologic and biologic features of colitis than mice given the platform alone or liquid drugs via enema. Image analysis showed that enemas delivered with and without the platform reached similar distances in the colons of mice, but greater colonic retention was achieved by using the platform.

Keywords: Mouse Model of IBD; Drug Delivery; TDDP; Technology.

Topical therapies delivered rectally are safe and effective treatments for colitis. Composed of mesalamine or corticosteroids, topical therapies can treat acute flares successfully as well as maintain remission for many patients. In fact, more than half of patients with ulcerative colitis and, based on expert opinion, a smaller fraction with Crohn's colitis may benefit from topical therapy alone because their disease is limited to the distal colon/rectum.[1–3] However, patients with active distal colitis often are unable to tolerate enemas owing in part to urgency and the associated inability to retain a liquid solution.[4] Foams and suppositories may be easier to retain, but have the marked disadvantage of being unable to reach the proximal areas of the left colon that often are accessible with an enema.[5] Despite the effectiveness of current topical therapies, adherence remains low because of the associated inconvenience and limitations; this lack of adherence leads to increased health risks and costs of care.[6]

We have developed a novel thermo-sensitive drug delivery platform (TDDP) that has the advantages of a liquid enema (more proximal delivery) and addresses retention issues associated with liquids. This is accomplished by a delivery platform that is a liquid near room temperature, but transitions into a viscous gel at body temperature. The platform is a nonionic surfactant copolymer consisting of hydrophilic polyethylene glycol and hydrophobic polypropylene glycol blocks (Supplementary Figure 1*A* and Supplementary Figure 2). In this report, we show the efficacy of this platform with 2 commonly used therapeutic agents: budesonide and mesalamine, prepared as described under Supplementary Materials and Methods.

Our first objective was to develop the TDDP with a therapeutic agent that transitions from a liquid at approximately room temperature to a viscous gel near 37°C. Such a formulation with budesonide, a corticosteroid with significant first-pass metabolism, becomes more viscoelastic near body temperature, as evidenced by the nonlinear increase in storage modulus or G′ at 37°C and 34°C for the 18% (G'18) and 20% (G'20) polymer solution/gels, respectively (Supplementary Figure 1*B*).[7]

We next tested the therapeutic potential of the TDDP with budesonide (budesonide, polymer, lipid [BPL]) in the dextran sulfate sodium colitis model. The BPL group reproducibly showed improvement vs water and polymer controls, as well as budesonide liquid (BL), as shown by the limited body weight loss (Figure 1*A* and *B*). In addition, BPL-treated mice had longer colons (with well-formed stool) and histologically reduced leukocyte infiltration and more preserved epithelial architecture (Figure 1*C*–*E*). Similar anti-inflammatory activity of BL and BPL was seen in cultured cells (Supplementary Figure 3), but animal studies showed that TDDP increases the effectiveness of budesonide in vivo.

We hypothesized that the BPL enema, as a liquid at instillation would have a noninferior distribution, and as a transitioned gel would have greater retention compared with a liquid enema. To determine the colonic distribution and retention kinetics of BPL, we gave standardized enemas with contrast to healthy and colitis mice, and imaged the mice at predetermined intervals. The BPL and BL enemas indeed reached a similar distance (at 0.25 h) (Supplementary Figure 4); however, interestingly, the

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Abbreviations used in this paper: **BL, budesonide liquid; BPL, budesonide polymer lipid; IBD, inflammatory bowel disease; TDDP, thermo-sensitive drug delivery platform.**

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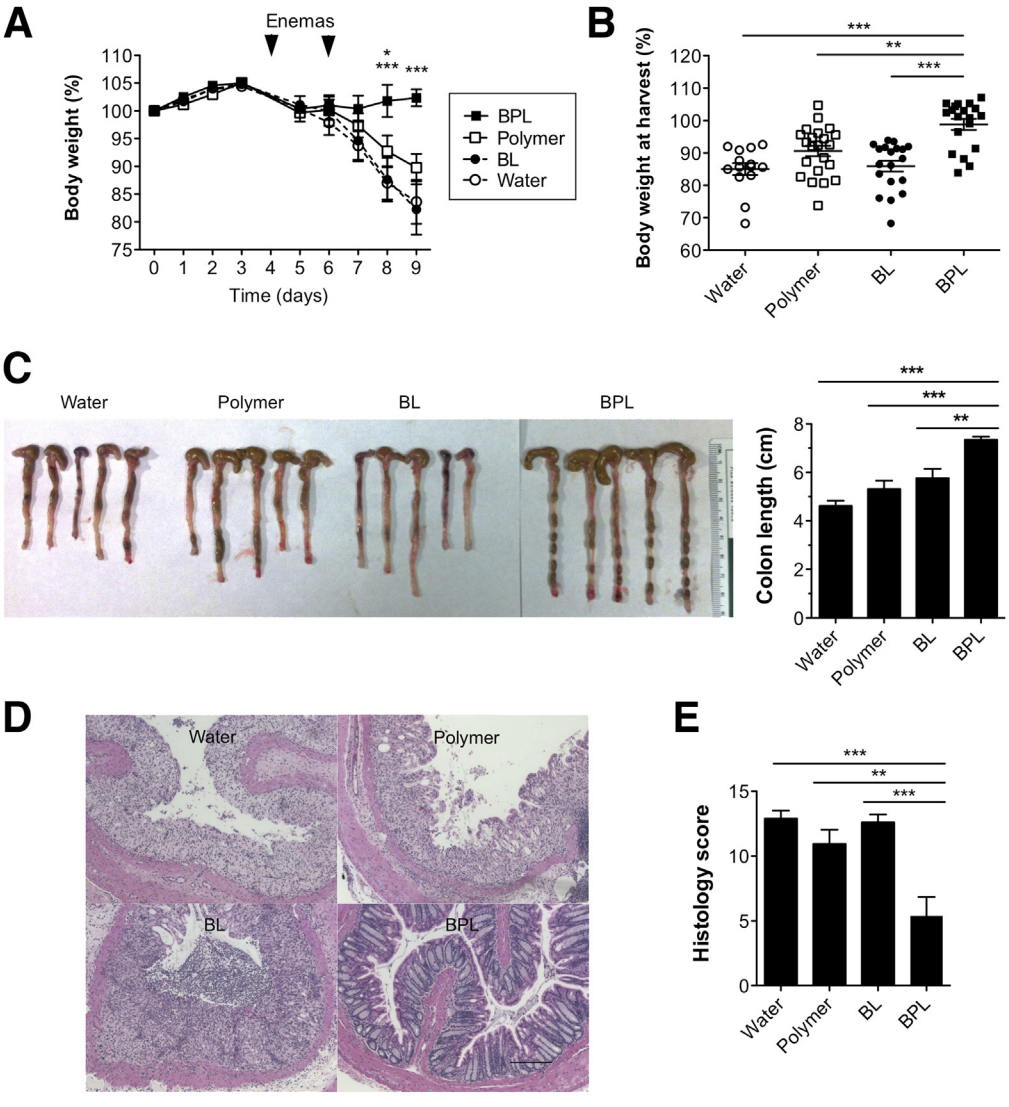

Figure 1. BPL improves dextran sodium sulfate–induced colitis. (*A*) Weight of mice given dextran sodium sulfate starting day 0 and water, polymer, and BL or BPL enemas on days 4 and 6 (representative of 4 experiments). n = 5 BL, BPL, and water; n = 3 polymer; means ± SEM. Two-way analysis of variance with Bonferroni post-tests. ***$P < .001$ between BPL and other treatments, except polymer on day 8, where *$P < .05$. (*B*) Body weight by end of 4 combined experiments. n = 14 water, 22 polymer, 19 BL, and 19 BPL; means ± SEM. One-way analysis of variance with the Tukey post-test. **$P < .01$, ***$P < .001$. (*C*) Gross colon morphology and length. n = 5; mean ± SEM. One-way analysis of variance with the Tukey post-test. **$P < .01$, ***$P < .001$. (*D*) H&E staining of colon. *Scale bar*: 20 μm. (*E*) Histopathology score from 3 combined studies. n = 14 water, 18 polymer, 14 BL, and 14 BPL; means + SEM. One-way analysis of variance with the Tukey post-test. **$P < .001$, ***$P < .0001$.

distance of BPL was better maintained (Figure 2*A* and Supplementary Figure 4*A*). Based on 3-dimensional imaging analyses, the volume of BPL (or polymer) enema retained was substantially greater than that of BL in both healthy and inflamed colons (Figure 2*B* and Supplementary Figure 4*B*), indicating possible mucoadhesiveness.

The TDDP did not appear to alter bowel function because BPL-treated mice observed for 4 additional weeks continued to gain weight and have normal bowel movements. In addition, multiple BPL applications did not increase the risk of obstruction in a model of trinitrobenzene sulfonic acid–induced strictures, as evidenced by imaging and the absence of mortality (Supplementary Figure 5, and data not shown).[8] However, long-term studies are needed to confirm the safety of its use in patients with colonic strictures. As with topical drugs, a potential benefit of the BPL enema is localized drug delivery without the systemic exposure.

To determine if our formulation could be used as a platform for other rectally administered drugs, we formulated TDDP with mesalamine. Unlike the standard mesalamine enema or vehicle controls, mesalamine polymer lipid minimized dextran sulfate sodium–associated weight loss, colon shortening, and histologic inflammation in multiple independent experiments (Supplementary Figure 6). The positive outcome of using TDDP is not model- or strain-specific because BPL also treated trinitrobenzene sulfonic acid–induced colitis in Balb/c mice (Supplementary Figure 7).

In summary, there is a clinical unmet need for better-targeted and localized therapies that can reach diseased areas and are easier to retain. In addition, major limitations in current inflammatory bowel disease (IBD) therapies include the side effects and intolerances associated with systemic therapies.[9] Our studies herein use TDDP, a novel thermo-sensitive platform that addresses these limitations. By using 2 IBD models, we show that TDDP with drug is superior to standard treatments by seemingly overcoming significant issues with current topical therapies.

The majority of IBD patients with colitis and all ulcerative colitis patients can benefit from topical therapies