Supporting Information

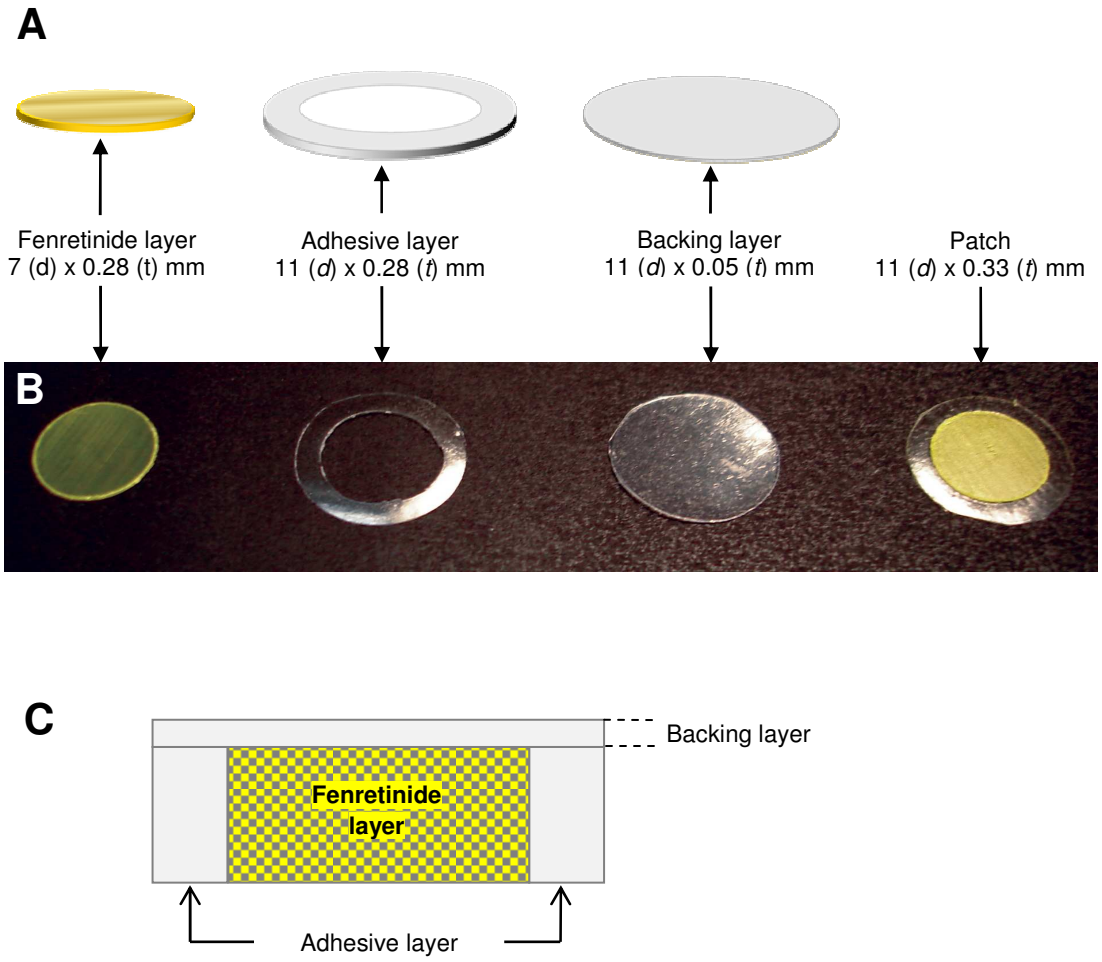

Figure S1. Schematic diagram (A), photographic image (B), and schematic cross-sectional diagram (C) of a mucoadhesive patch comprising drug (fenretinide/Eudragit® RL PO/solubilizers with or without permeation enhancers), adhesive (HPMC 4KM: polycarbophil (3:1), and backing (Tegaderm™ adhesive film) layers.

Methods

Preparation of Oral Mucoadhesive Patches for Delivery of Fenretinide

Preparation of an adhesive layer

An adhesive layer based on the blend of HPMC 4KM and PC at a weight ratio of 3:1 was prepared by a casting method. Briefly, 1.5% polymer solution was prepared in ddH_2O containing required amount (20 wt% based on polymer mass) of propylene glycol by stirring the polymer/water mixture overnight. About 50 mL of polymer solution was then casted onto glass petri dish (150 × 20 mm) and incubated at 50 ºC for 48 h. Then, the polymer film was cut into required size and stored in a desiccator at room temperature until further use.

Preparation of drug release (fenretinide) layer

Preparation of fenretinide films was performed under the protection from light. Required quantity of solubilizer (Tween® 80 and sodium deoxycholate), permeation enhancers (1, 2.5, 5, and 10 wt%) and Eudragit® RL PO were weighed in 15 mL polypropylene tubes to which 8 mL of a 50:50 (v/v) acetone-ethanol mixture was added. The quantity of plasticizer or solubilizer added was calculated based on the mass of polymer. The resulting mixture was vortexed until all ingredients were dissolved. The required quantity (5 wt% based on the total mass of polymer + excipients) of fenretinide was then added to above prepared polymer-solubilizer or polymer-solubilizer-permeation enhancer(s) solution, vortexed again, and the volume was adjusted to 10 mL with the same solvent mixture. Five milliliter of fenretinide-polymer solution was added onto Teflon (Scientific Commodities, Inc., Lake Havasu City, AZ, USA) overlaid glass petri dish (60 × 15 mm) and incubated at 38 ºC for 48 h. After sufficient drying, fenretinide loaded polymer film was cut into required size (7 mm diameter), packed in aluminum foil, and stored in a desiccator at -20 ºC until further use.

Assembly of oral mucoadhesive patches of fenretinide

An annular adhesive layer with 11 (outer diameter) and 7 (inner diameter) mm dimensions were formed by cutting the film with 11 and 7 mm cork borers, respectively. The adhesive layer was then placed onto adhesive side of the Tegaderm™ film (backing layer), followed by insertion of previously cut 7 mm fenretinide/Eudragit® layer into open region of adhesive layer to obtain oral mucoadhesive patch of fenretinide (see Supplementary Fig. 1).

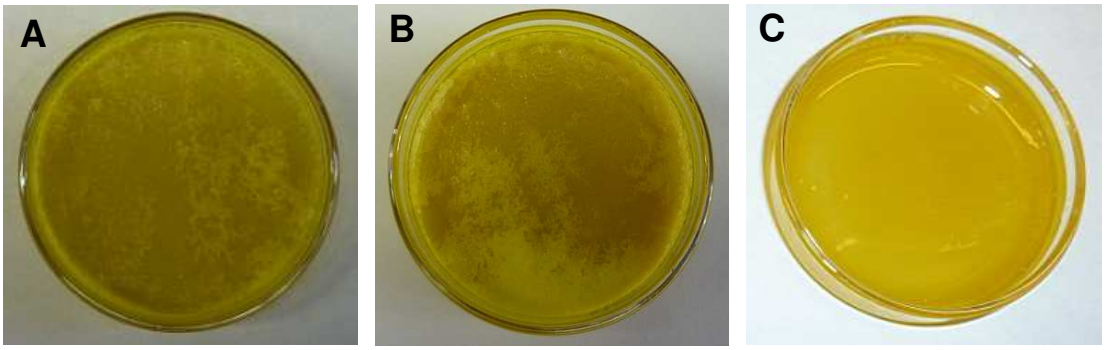

Figure S2. Physical appearance of the fenretinide/Eudragit® (drug release) layer loaded with 5 wt% menthol (A), 10% menthol (B), and 1 wt% PG + 5 wt% menthol (C).

Discussion

Effect of Co-incorporation of Menthol on Fenretinide/Eudragit® RL PO Film Morphology

Fenretinide/Eudragit® RL PO (drug release) films without menthol exhibited good film forming and physical appearance. Fenretinide/Eudragit® RL PO films loaded with 5% or 10% menthol did not exhibit good film forming and physical appearance (see Supplementary Fig. 2 A and B). It appeared that that phase separation occurred during the film formation due to formation precipitation and/or aggregation of menthol. As shown in Supplementary Fig. 2C, the addition of 1% PG as a co-solvent facilitated better film formation.