Development of a novel drug in adhesive transdermal analgesic patch: 
Formulation optimization and characterization

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ABSTRACT SUMMARY
A novel drug in adhesive transdermal analgesic patch formulation was developed with codeine and acetaminophen. This may potentially treat moderate pain in children and may overcome the poor patient compliance and other limitations of the conventional oral and intravenous routes of analgesic drug administration. Three analgesic drugs hydrocodone bitartrate, codeine and acetaminophen were screened, among which codeine patch showed maximal drug permeation through the human skin and may have the potential to deliver a dose adequate to relieve moderate pain in infants weighing upto 3-4 kg. A combination patch made with codeine and acetaminophen may have synergistic analgesic effects by acting via multiple (opiate and nonopiate) mechanisms1 and also could prevent the misuse of the narcotic drug.

INTRODUCTION
Drugs such as hydrocodone bitartrate, codeine and acetaminophen are being widely used as analgesics and are traditionally given as oral or intravenous solid/liquid dosage formulations to mitigate mild to moderate pain in patients. However, patient compliance is a serious issue while administering drugs via oral or i.v routes to treat post-operative pain especially in pediatric patients. Furthermore, other factors such as differences in gastrointestinal blood circulation and dietary factors may influence oral bioavailability and might result in inconsistent analgesic effects. All these limitations emphasize the need to develop an alternative route and delivery system to treat moderate pain in children.

Transdermal route of drug administration is being proven to be successful in delivering potent analgesic drugs such as fentanyl. Fentanyl patches are available in the market for treatment of chronic pain. However, potent drugs such as fentanyl are discouraged for use in pediatric patients and are not suggested for mild or moderate pain because of their high risk potential and severe side effects such as loss of vision and impaired breathing3. Our current investigation aims for delivery of relatively less potent analgesic drugs such as codeine and acetaminophen and their combination via the skin route through a drug-in-adhesive transdermal patch to potentially treat acute, mild to moderate pain in children.

EXPERIMENTAL METHODS
Solubility of hydrocodone bitartrate, codeine and acetaminophen was tested by adding increasing amounts of drug in different solvent/cosolvent mixtures to identify suitable vehicles for the donor and receptor solutions for the in vitro permeation studies on vertical Franz cells. Saturation solubility (Cs) was determined by adding excess drug in a known volume of propylene glycol (PG) with/ without 5% oleic acid (OA) as a solubility enhancer and quantified by a validated HPLC method.

Passive permeation of the drugs was studied in vitro using dorsal flap of porcine full thickness ear skin obtained from a local slaughter house and/or human skin and/or epidermis obtained from a skin bank and mounted on a Franz cell whose jacket temperature was maintained at 37°C. A saturated solution (200 µL) of drug in PG with or without 5% OA was added to the donor compartment of Franz diffusion cells. Samples (500 µL) were obtained from the receptor compartment at different time points until 24 hours and analyzed by a validated HPLC method.

Transdermal patch formulations have been made by dissolving analgesic drug in appropriate pressure sensitive adhesive selected from Henkel’s Durotak™ product range. Selection of an acrylate adhesive (DT-87-9301) that allows greater drug loading was made by considering theoretical saturation solubility (Cs) of the drug estimated using Henkel’s drug-in-adhesive solubility calculator.

Slide crystallization studies were performed to identify the appropriate drug concentration in the patch at which the drug does not crystallize during its shelf life. Different formulations of drug-in-adhesive at various w/w ratios were made and smeared on histological slides and were examined for crystal formation for 3 days under polarized light microscope (Leica DM 750).

Codeine base used for patch was prepared by adding codeine phosphate (2.5 g) to a saturated solution of sodium bicarbonate which was allowed to stir at 500 rpm for 15 min. To this solution, methylene chloride (50 mL) was added and was stirred for 1 hr. The immiscible methylene chloride layer is collected and two more cycles of extraction were carried for better yield. The combined methylene chloride extracts were dried under nitrogen gas for 2 hrs. Purity of the free codeine base was confirmed with a sharp endothermic peak at its melting point (155.86 °C) by differential scanning calorimetry (DSC).

The drug in adhesive patches were prepared by dissolving the previously determined amount of drug(s) in the adhesive (with or without 5% OA) and stirred overnight in an air-tight glass vial, and later cast with a BYK-Gardner film casting knife on a polypropylene release liner (3M™ Scotchpak™ 9741). The cast sheet was dried at 60°C for 20 minutes in an oven to allow crosslinking of adhesive monomers. A polyester film laminate (3M™ Scotchpak™ 9733) was spread as the backing membrane with a roller taking care to avoid air bubbles. The patches made were observed for 3 days to
confirm there is no crystal formation and were used for *in vitro* permeation studies on human skin and/or epidermis. Studies are in progress to characterize the optimized patches for drug release profile, weight and thickness variation, content analysis and tack and peel adhesion.

**RESULTS AND DISCUSSION**

Preliminary screening of three analgesic drugs by flux studies with drug in solution were promising for codeine and hence was chosen as the drug of choice. Slide crystallization studies suggested 40% Cs of codeine as the optimum concentration for making the patch.

![Figure 1](image1.png)

Figure 1. Slide crystallization study with formulations made in 10%, 20%, 40% and 50% Cs of codeine in DT 87-9301 adhesive visualized under polarized microscope.

Figure 2. Patch crystallization study: No crystals were observed in the patch at 40% Cs codeine for a period of 3 days and hence was chosen for skin permeation studies.

![Figure 2](image2.png)

Figure 3. The patch made with 40% saturation solubility (Cs) of codeine (CDB) in DT 87-9301 acrylate adhesive resulted in permeation of 105.48 µg of codeine per sq. cm over a period of 24 hours across dermatoine human skin.

The required therapeutic dose of codeine in children is 0.4-0.6 mg/kg body weight/day. Assuming the average weight of an infant to be 4 kg, the minimum amount of codeine that need to be delivered across the skin is estimated as 1.6 mg/day. Also, the current permeation profile of codeine (figure 3) from the standalone patch suggests that 1.6 mg codeine can be delivered to infants weighing 4 kg in 1 day from a patch sized 15.16 cm².

![Figure 4](image3.png)

Figure 4. A combination patch of codeine (CDB, 40% Cs) and acetaminophen (ACP, 200% Cs) with 5% Oleic acid as a permeation enhancer in DT 87-9301 adhesive resulted in permeation of 151.53 µg of CDB and 58.12 µg of ACP per sq. cm/day across human epidermis.

Similar dose calculations for the combination patch (figure 4) suggest that it would also be able to deliver the required dose of codeine to infants weighing up to 3.4 kg. But, acetaminophen dose may not be enough to reach required plasma levels. However it may have synergistic effect since both drugs act by different mechanisms and also could help in preventing the misuse of narcotic.

**CONCLUSION**

A novel, drug in adhesive type transdermal patch formulation was developed to deliver codeine and acetaminophen and their combinations via transdermal route that may potentially treat mild to moderate pain in children weighing 3-4 kg and may overcome the poor patient compliance of oral and i.v route formulations.

**REFERENCES**


**ACKNOWLEDGMENTS**

We acknowledge Little Innovations LLC., Knoxville, TN for their generous financial support for this project and Ludeka Neely Group, P.C Knoxville, TN for their kind assistance with the patent application (serial no.13/644,080) filed on October 3, 2012 with the USPTO. Our thanks are also due to Dr. Piyush Jain, Meera Gujjar and Pavilion compounding Pharmacy, Atlanta, GA for their assistance to our research.