TECHNICAL PAPER

# ADVANCING TRANSDERMAL APIXABAN STABILITY WITH UPLC ANALYSIS

## RESOLVING EXCIPIENT INCOMPATIBILITY CHALLENGES WITH ANALYTICAL INNOVATION

### OVERVIEW

ARx developed a once-weekly transdermal apixaban patch to demonstrate how our drug delivery technologies can unlock new opportunities for partners. By replacing the burden of twice-daily oral dosing with a convenient patch, this program showcases ARx's ability to solve complex formulation challenges and create patient-friendly, commercially viable products.

### THE CHALLENGE

During development, initial formulation analysis revealed critical excipient incompatibility issues that threatened product stability. The complex pharmaceutical formula utilizes three key excipients (E1, E2, and E3) to optimize apixaban delivery through skin, but these components exhibited incompatibility, which promoted the production of unwanted byproducts and reduced product quality.

Excipient 1 (E1) promoted the degradation of Excipients 2 and 3 (E2 and E3). While E1 degraded E3 via an oxidative pathway requiring an antioxidant (AO) addition, the interaction between E1 and E2 proved more challenging. E1 and E2 interactions caused the rapid formation of two degradation species (E2.1 and E2.2), with E2 partially degrading despite the presence of an antioxidant. A comprehensive analytical investigation was essential to enable successful formulation optimization.

### THE METHOD

ARx's Analytical R&D team conducted comprehensive excipient compatibility studies using a high-throughput UPLC method capable of assaying API, E2, AO, and associated degradants in a single analytical run. The method utilized a gradient in which an organic mobile phase gradually replaced aqueous mobile phase over time to allow for elution, UV detection at 278 nm, and temperature-controlled analysis.

Key study parameters included:

- **Stability Testing:** Monthly formulation monitoring under normal (5°C, 25°C) and accelerated (45°C) conditions to assess degradation profiles
- **Excipient Compatibility:** Systematic evaluation of binary and ternary excipient combinations to identify potential excipient interactions
- **Placebo Studies:** Single-excipient and API-only placebo formulations to isolate specific degradation sources and differentiate drug versus excipient degradation
- **Process Optimization:** Temperature-controlled manufacturing evaluation and pH adjustment strategies using optimized neutralizers to minimize degradation formation

## THE RESULTS

UPLC investigation revealed that E1 and E2 heavily interact to generate two specific degradants (E2.1 and E2.2). While E1 and E3 also interact, this interaction is controlled through antioxidant addition and was not the focus of this UV-based analytical study.

### TEMPERATURE-DEPENDENT DEGRADATION (E2.1):

Stability monitoring confirmed that heat exposure significantly increases E2.1 formation, with this degradant comprising over half of total related substances under accelerated conditions:

| STORAGE CONDITION | E2.1 FORMATION (%) |
|---|---|
| 5°C (1 month) | 1.5 |
| 25°C (1 month) | 1.9 |
| 45°C (1 month) | 3.4 |

### PH-DEPENDENT DEGRADATION (E2.3):

The original patch formulation (pH 2.1) generated significant E2.3 formation, this degradant was found to be pH dependent, because as the pH of the formulation increased, the amount of E2.3 decreased.

| FORMULATION | PH | E2.3 FORMATION (%) |
|---|---|---|
| Original Patch | 2.1 | 1.0 |
| Improved Patch | 4.2 | 0.1 |

### PLACEBO STUDY INSIGHTS:

Single-excipient studies demonstrated that most unknown chromatographic peaks originated from E2 degradation rather than apixaban API. The apixaban remained stable in the initial formulation mixture, generating only minor degradation (0.02%) after one month. Notably, the API combined with E2 provided a mutual stabilizing effect, with E2.2 degradation reduced in the presence of apixaban.

## FORMULATION OPTIMIZATION SUCCESS:

The optimized patch formulation achieved remarkable stability improvements through:

- Room temperature drying protocols, reducing E2.1 degradation from 3.4% to 1.1% under stressed conditions
- pH optimization to 4.2, reducing E2.3 formation from 1.0% to 0.1%
- Lower molecular weight neutralizer implementation, reducing overall patch weight requirements

## THE BENEFITS

ARx's comprehensive UPLC investigation offers significant advantages over traditional stability approaches, enhancing formulation development and manufacturing reliability. By systematically identifying and resolving temperature- and pH-dependent degradation pathways, the analytical and formulation development teams at ARx were able to improve unstable formulations to create robust, commercially viable products with dramatically improved shelf life.

Additionally, the investigation provides AR's manufacturing department with clear process controls and optimization strategies that streamline production while ensuring regulatory compliance. This approach significantly reduces development timelines and manufacturing risks, making it especially valuable for complex transdermal systems where excipient interactions could compromise product stability and patient outcomes.

## CONTACT

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