

Preparation of Stable, Gastro-Resistance Diclofenac Sodium Tablets, Utilizing Optimized Film Coating Combinations with Acryl-EZE[®]

INTRODUCTION

The stability of alkaline pharmaceutical actives enteric film coated with acidic polymers, can be compromised due to deprotonation of the acidic polymer by the alkaline drug.¹ In addition the inclusion of pigmentation into acrylic coating dispersions can lead to instability of the dispersion and the resultant polymer film.^{2&3} To investigate these effects, Acryl-EZE[®], aqueous acrylic enteric system, was prepared with and without aluminum lake pigmentation. Acryl-EZE was developed to meet market need for a simple, fully-formulated, pigmented, aqueous-enteric, coating system. Market demand requires the ability to meet a wide range of color demands. We, therefore, initiated this work as complimentary to the white/iron oxide pigmentation perfected in the original development. Diclofenac sodium was utilized as both a model drug and in support of customer projects. The diclofenac sodium tablets were film coated with varying combinations of a seal-coat layer, enteric layer, and/or a coloring layer, to determine the process that provided a stable, gastro-resistant dosage form. For each combination of coating layers, tablet samples were tested for delayed release diclofenac sodium dissolution, assay, total impurities, and acid uptake.

METHODS

Coating Dispersion Preparation

Acryl-EZE pigmented with titanium dioxide (93O18359) or FD&C Yellow #6 aluminum-lake (93O13864) was dispersed in water to achieve a solids content of 20%w/w. Following a mixing time of 20 minutes the resultant dispersion was passed through a 250-micron sieve prior to initiation of the coating process. Seal-coat (85F18378) and coloring layer (85F13854; Opadry[®] II, high performance film coating system) dispersions also were prepared at 20%w/w. The coloring layer was formulated to match the color of the aluminum lake-pigmented Acryl-EZE sample.

Enteric Film Coating

All samples were prepared in an O'Hara Labcoat II side vented coating unit equipped with a 15" perforated pan and a VAU spray nozzle. Tablets were enteric coated to a theoretical 5.2-8.7 mg/cm² (6-10% weight gain) from dispersions containing 20% solids. (See Table 1 for the process parameters utilized to apply the enteric coat.) Where applicable a 1.7 mg/cm² (2% weight gain) seal-coat layer and/or a 2.6 mg/cm² (3% weight gain) coloring layer were also applied.

Table 1.

Parameter	Value
Bed Temperature (°C)	30
Inlet Temperature (°C)	45
Outlet Temperature (°C)	32
Atomization Pressure (psi/bar)	20/1.4
Pattern Air Pressure (psi/bar)	20/1.4
Pan Speed (rpm)	17
Pan Charge (kg)	2.5
Fluid Delivery Rate (g/min)	20
Drying Air Volume (m ³ /hr)	300-3400

Analytical Methodology

The following methods were employed for sample analysis:

- Acid Uptake – Colorcon Internal Method
- USP Delayed Release Diclofenac Sodium Tablet Monograph

Diclofenac Sodium Assay – 90-110%

Dissolution <724>

- Apparatus II (Paddles), 50 rpm
- Acid Phase
 - 0.1N HCL
 - NMT 10% dissolved after 120 min.
- Buffer Phase
 - pH 6.8 phosphate buffer
 - NLT 80% dissolved after 45 minutes

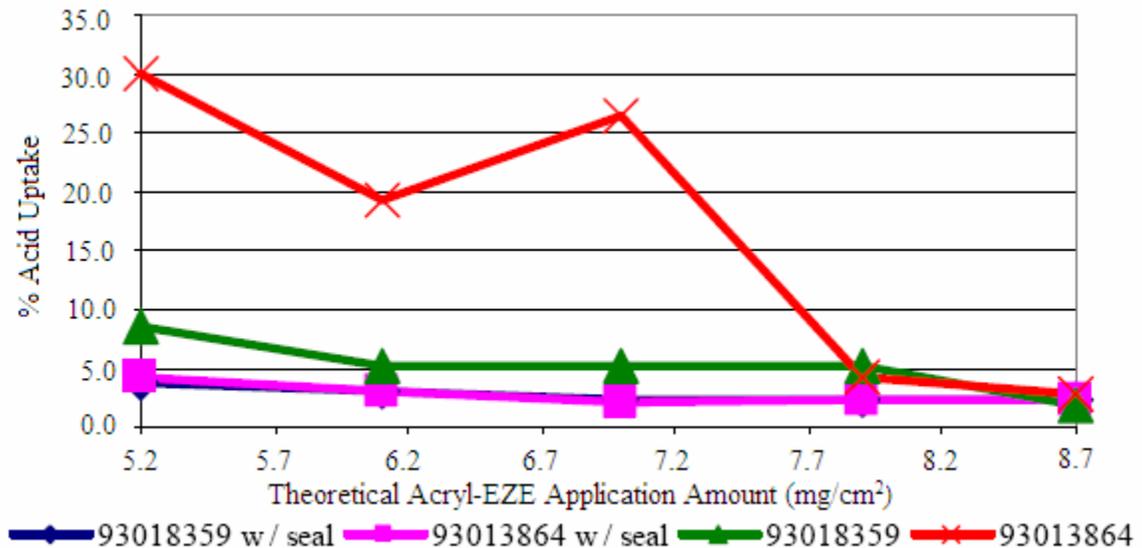
Chromatographic Purity

- Individual Impurity – NMT 1.0%
- Sum of Impurities – NMT 1.5%

RESULTS

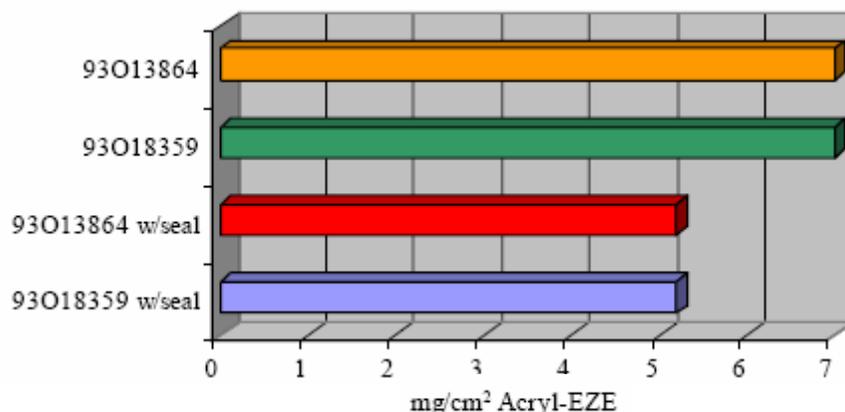
Acid uptake results indicated that application of a seal coating prior to enteric coating significantly reduced the amount of acid permeation through the enteric film, across the range of theoretical enteric coating applied (Figure 1)

Figure 1. Delayed Release Diclofenac Sodium 50 mg



This was found to be the case for both the aluminium lake and titanium dioxide pigmented enteric layers. This trend is likely to be due to an increase in the mechanical strength of the dosage form prior to deposition of the enteric layer. There was a direct correlation between the acid uptake results and the delayed release dissolution data for enteric coated diclofenac sodium, as shown in Figure 2. Samples containing a seal-coat met the USP dissolution requirements at a theoretical 5.2 mg/cm² Acryl-EZE, whereas, samples without a seal-coat required upwards of 7.0 mg/cm² to meet the USP dissolution criteria.

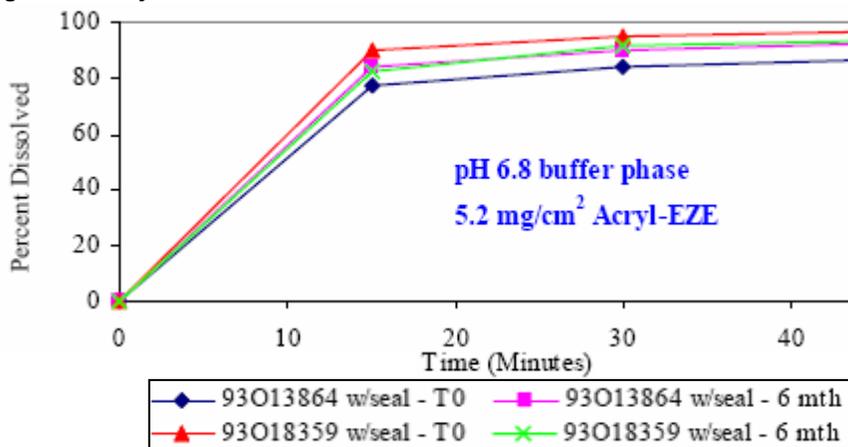
Figure 2. Quantity of Acryl-EZE required to Meet USP Dissolution Criteria



The results of a 6-month stability study at accelerated conditions (40°C/75% RH) demonstrates how the use of a seal-coat can enhance product stability while allowing for a significant reduction in the quantity of enteric coating applied. Figure 3 shows that the release profile for diclofenac sodium enteric coated with either the titanium dioxide or aluminum-lake pigmented Acryl-EZE formulations to a theoretical 5.2 mg/cm² with seal-coat, meets the USP dissolution criteria. Important to note is that enteric coated samples without a seal-coat did meet criteria, but required a minimum Acryl-EZE quantity of 7.9 mg/cm². As mentioned previously this difference is believed to be due to an increase in the mechanical strength of the dosage form prior to deposition of the enteric layer.

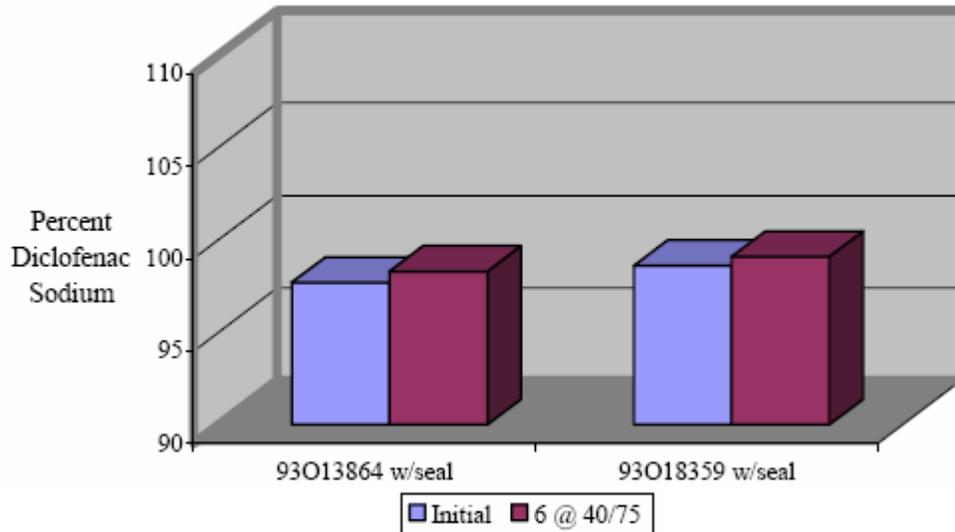
In this study the stability data supports the use of a fully-formulated, colored Acryl-EZE coating system as a replacement for separate enteric and non-functional colored coating layers. Coloring layers separate from the enteric layer are typically only required in situations where an incompatibility is identified with the active ingredient.

Figure 3. Delayed Release Diclofenac Sodium Dissolution at 6 month 40C/75%RH



Stability of the active ingredient was monitored via drug assay and impurity level. Results in Figure 4 through 6 months at accelerated conditions indicate that all samples meet the USP diclofenac sodium assay criterion with no issues observed. Impurity levels through 6 months showed no appreciable quantity present with typical values less than 0.01%. Further studies have shown similar stability performance with a variety of aluminum lake pigments.

Figure 4. USP Diclofenac Sodium Assay



This study provided a stepwise approach to determine the minimum number of coating layers required to yield stable, enteric protection of diclofenac sodium. The use of a seal-coat reduced the quantity of enteric coating necessary to yield gastric protection. The length of the coating process was reduced 25% by combining the aluminum lake pigments directly into the Acryl-EZE formulation and removing the need for a coloring layer, without adverse effects on the tablet or dispersion properties. Additional development work targeted at utilization of other aluminum lake-pigments has resulted in stable dispersion and enteric-film properties, thus continuing to expand the range of the world's first, fully-formulated, acrylic-enteric, coating system, Acryl-EZE.

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