# Development of a pH Dependent Colon Targeted Drug Delivery System for Mesalamine Delayed Release Tablets

**Vaibhav Ambudkar[1], Hemant Bankhede[1], Shantanu Damle[1], Daniel To[2], Ali Rajabi Siahboomi[2]**

**[1] Colorcon Asia. Pvt. Ltd. Verna, Goa, India, [2] Colorcon Inc. Harleysville, PA, USA**

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## Introduction

Mesalamine (5-aminosalicylic acid, 5-ASA) is commonly used in the treatment of mild-to-moderate ulcerative colitis.[1] It acts locally on the colonic mucosa to achieve its therapeutic effect. However, if it is released in the upper gastrointestinal tract (GIT), it is rapidly and extensively absorbed in the small intestine which may lead to the less efficient delivery of the mesalamine in the colon, resulting in lower efficacy, along with significant systemic side effects.[2] To overcome these challenges pH-dependent enteric coating of solid oral dosage forms is commonly used for oral delivery of mesalamine to the colon. The pH of GIT increases progressively from stomach (pH 2.0 - 3.0), through small intestine (pH 6.5 - 7.0) to the colon (pH 7.0 - 8.0) based on physiological conditions.[3]

The purpose of this work was to investigate the use of fully formulated enteric coating systems to impart acid resistance to a mesalamine tablet formulation in pH 1.2 and pH 6.0, while achieving complete drug release at pH 7.2 as per the USP monograph of mesalamine delayed release (DR) tablets.

## Methods

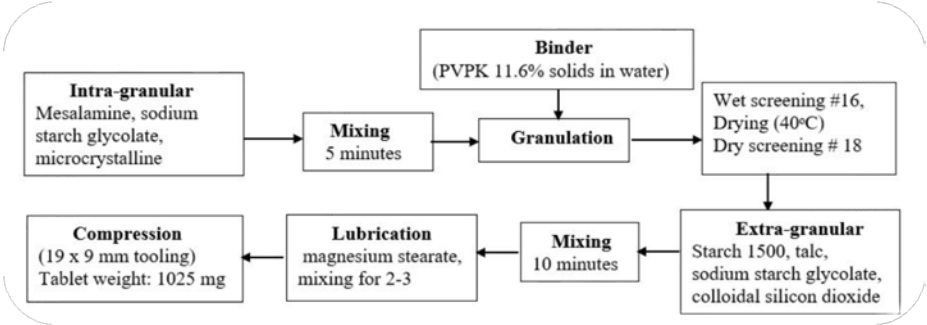
### Core Tablet Manufacture

A high shear wet granulation (HSWG) process was used to granulate part of the formulation as shown in Table 1 and Figure 1. The lubricated blend was compressed on a rotary tablet press (Rimek, Mini Press II) using 19 x 9 mm plain, oval standard concave tablet tooling at a target weight of 1025 mg.

**Table 1: Composition of Mesalamine Tablets, 800 mg**

| Ingredients | % W/W | mg/dosage |
|---|---|---|
| **Intragranular** | | |
| **Mesalamine USP** | 78.05 | 800.0 |
| **Sodium Starch glycolate Type A** | 3.51 | 36.0 |
| **MCC PH 102** | 5.06 | 52.0 |
| **PVP K30** | 4.09 | 42.0 |
| **Extragranular** | | |
| **Starch 1500** | 5.07 | 52.0 |
| **Sodium Starch glycolate Type A** | 2.54 | 26.0 |
| **Colloidal Silicon Dioxide** | 0.58 | 6.0 |
| **Talc** | 0.56 | 5.8 |
| **Magnesium stearate** | 0.50 | 5.2 |
| **Total** | 100.0 | 1025.0 |

**Figure 1: Flowchart for Manufacturing of Mesalamine Tablets**




## Coating of Tablets

Mesalamine tablets were seal-coated with an HPMC-based clear Opadry® complete film coating system to 3.5% weight gain using 10% w/w solids in water. The seal-coated tablets were subsequently enteric coated with Opadry Enteric using below sequential steps (Figure 2 and Table 2)

**Step 1**: Opadry Enteric 95K (dissolution trigger pH > 7.0) to a weight gain of 3% using 10% w/w solids in IPA: Water (88:12 by weight).
**Step 2**: Opadry Enteric 94O (dissolution trigger pH > 6.0) to a weight gain of 3% using 10% w/w solids in IPA: Water (88:12 by weight).

**Table 2: Coating Process Parameters**

| Parameter | Seal-coat | Enteric coat Step 1 (95K) | Enteric coat Step 2 (94O) |
|---|---|---|---|
| **Tablet load (kg)** | 1 | 1 | 1 |
| **Weight gain (% w/w)** | 3.5 | 3 | 3 |
| **Atomization air pressure (bar)** | 1.2 – 1.3 | 0.5 – 0.7 | 0.5 – 0.7 |
| **Pattern air pressure (bar)** | 1.2 – 1.3 | 0.5 – 0.7 | 0.5 – 0.7 |
| **Pan speed (rpm)** | 9 | 9 | 9 |
| **Inlet air temperature (˚C)** | 58 – 61 | 31 – 32 | 31 - 32 |
| **Exhaust air temperature (˚C)** | 44 - 47 | 29 – 31 | 29 – 31 |
| **Bed temperature (˚C)** | 44 - 46 | 29 – 30 | 29 – 30 |
| **Air volume ($m^3$/hr)** | 107 | 115 | 113 |
| **Spray rate (gm/min)** | 2 - 4 | 2 – 4 | 2 - 4 |

**Figure 2: Coating Layers and Appearances of Tablet (Core vs. Coated)**

### Enteric Performance Testing

Enteric protection performance of coated tablets (n=6) was evaluated using a USP disintegration bath (Electrolab, ED-2L) containing 0.1 N HCl for 2 hours; followed by buffer stage I with phosphate buffer pH 6.0 for 1 hour at 37 ± 2˚C and media uptake calculated as % of initial weight. The intact tablets were then reciprocated in the disintegration apparatus using pH 7.2 phosphate buffer (buffer Stage II), at 37.0˚C. The time taken for all the tablets to disintegrate completely was recorded. Buffer stage medium 1 and 2 were prepared as per USP general chapter “Buffer Solutions”.

### Assay, Impurities and Dissolution

Drug assay and impurities testing was performed per the USP monograph for mesalamine delayed release tablets. Dissolution testing was carried out per the USP monograph for mesalamine delayed release tablets (n=6). Drug release was determined using a USP dissolution bath (Electrolab, EDT-08LX) using the following dissolution media sequence at 37.0 ± 0.5

### Drug Release Testing

Dissolution testing was carried out per the USP monograph for mesalamine delayed release tablets (n=6). Drug release was determined using a USP dissolution bath (Electrolab, EDT-08LX) using the following dissolution media sequence at 37.0±0.5˚C.

1. Acid Stage: 500 mL of 0.1M HCl, Apparatus II at 100 rpm for 120 min,
2. Buffer Stage I: 900 mL of phosphate buffer pH 6.0, Apparatus II at 100 rpm for 60 min
3. Buffer Stage II: 900 mL of phosphate buffer pH 7.2, Apparatus II at 50 rpm for 90 min

At the end of the acid stage, (120 min) and buffer stage I (60 min), an aliquot was taken and tested for % mesalamine released. Further dissolution testing was continued with buffer stage II and sample aliquots were withdrawn at 15, 30, 60, and 90 min and analyzed for the amount of mesalamine released.

### Stability Testing

Coated tablets were packaged in 100 cc HDPE bottles (Shriji Polymers, India), and stored at 30°C/65% RH and 40°C/75% RH for 1, 3 and 6 months. Stability was monitored by testing drug release, assay, impurities, liquid uptake as described above, and disintegration time of enteric coated tablets.

## Results

### Testing of Physical Properties of Tablets

The physical parameters for the compressed tablets are summarized in Table 3.

**Table 3: Physical Properties of Mesalamine Core Tablets**

| Test | Result |
|---|---|
| **Tablet weight (mg)** | 1026.8 ± 1.13 |
| **Tablet Width (mm)** | 9.02 ± 0.0 |
| **Tablet thickness (mm)** | 7.2 ± 0.01 |
| **Length (mm)** | 19.04 ± 0.01 |
| **Disintegration time (min)** | 3 - 4 |
| **Hardness (kPa)** | 13.7 ± 0.8 |
| **Friability (%)** | 0.08 |

## Enteric Performance Test

Enteric performance test showed that mesalamine tablets remained intact during the acid stage (0.1 M HCl) and buffer stage I (buffer pH 6.0) indicating low liquid uptake (less than 5%) followed by rapid disintegration in buffer stage II (buffer pH 7.2) (Table 4).

**Table 4: Assessment of Enteric Performance Test with Liquid Uptake in 0.1 N HCl and Buffer Stage 1**

| Media | Observations |
|---|---|
| **Acid stage (0.1 M HCl); 2h** | All Tablets intact<br>Acid uptake (%): 2.1 to 2.7 |
| **Buffer Stage I (pH 6.0); 1h** | All Tablets intact<br>Acid uptake (%): 2.5 to 4.0 |
| **Buffer Stage II (pH 7.2)** | All tablets disintegrated in 32 to 52 min |

## Assay and Impurities

The assay content and total impurities for mesalamine tablets were 102.0% and 0.012% ($t_0$), respectively (Table 5).

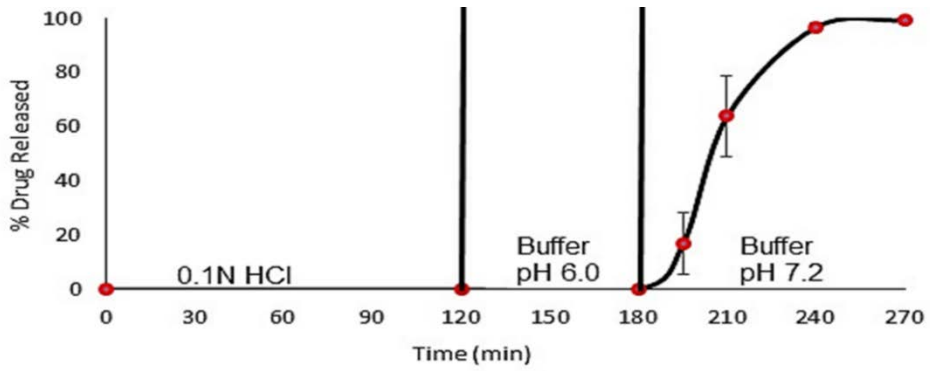
**Table 5: Assay and Impurities Test Result**

| Test | Result | Limit (%) |
|---|---|---|
| **Assay (%)** | 102.0 | 90-110 |
| **Impurities** | | |
| **Salicylic acid (%)** | 0 | NMT 1.0 |
| **3-amino salicylic acid (%)** | 0 | NMT 1.0 |
| **Total impurities (%)** | 0.0121 | NMT 2.0 |

## Drug Release Test

Mesalamine tablets complied with the dissolution test for all media sequences. Results indicated that the drug loss was <1% at the end of 3 hours, 2 hours in the acid media (0.1N HCl) and 1 hour in the buffer stage I. This was followed by a rapid release of drug in phosphate buffer, pH 7.2 (Figure 3).

**Figure 3: Release from Mesalamine DR tablets, 800 mg coated with Opadry Enteric Systems**



## Stability Testing

The results of accelerated stability studies at 1, 3 and 6 months showed no significant change in enteric performance (Table 6), assay content, total impurities (Table 7) and release profiles (Figure 4) regardless of storage conditions, confirming that the final dosage forms were stable in accelerated conditions.

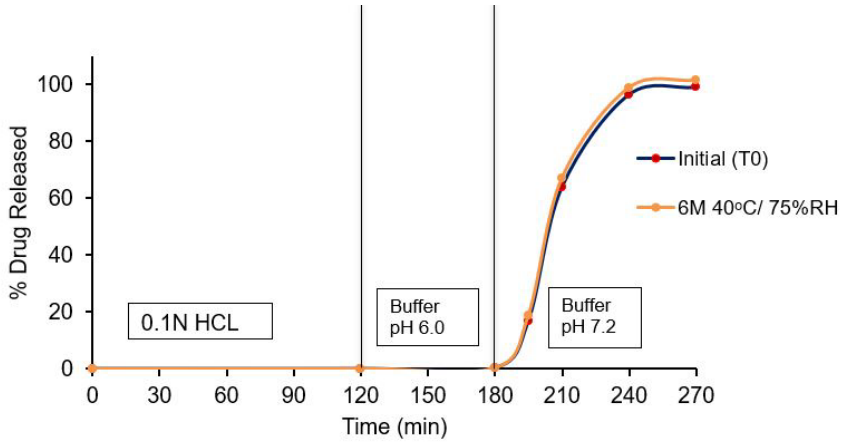
**Table 6: Enteric Performance Over Stability Conditions of 40°C/75% RH and 30°C/65% RH**

| Media | T0 / Initial | 40°C/75% RH | 30°C/65% RH |
|---|---|---|---|
| Acid stage (0.1 M HCl); 2 hr | 2.1 to 2.7 % | 2.0 to 2.7% | 2.1 to 2.4% |
| Buffer stage 1 (pH 6.0); 1 hr | 2.5 to 4.0 % | 3.0 to 4.9% | 3.1 to 3.7% |
| Buffer stage 2 (pH 7.2) | 32 to 51 min | 29 to 51 min | 33 to 57 min |

**Table 7: Assay and Impurities Test Result at 30°C/65% RH and 40°C/75% RH**

| Media | T0 / Initial | 40°C/75% RH | 30°C/65% RH |
|---|---|---|---|
| **Assay (%)** | 102.0 | 103.1 | 99.8 |
| Salicylic acid (%) | 0 | 0.01 | 0.01 |
| 3-amino salicylic acid (%) | 0 | 0 | 0 |
| **Total impurities (%)** | 0.012 | 0.033 | 0.0169 |

## Figure 4: Dissolution Profile of Mesalamine DR Tablets Over Stability



## Conclusions

Opadry Enteric 95K (Step1) followed by Opadry Enteric 94O (Step 2) offered excellent enteric protection in both 0.1 M HCl and pH 6.0 buffer. Complete drug release was observed in phosphate buffer, pH 7.2 for mesalamine tablets (800 mg), which remained stable over the period of 6 months at accelerated storage conditions. These results show that Opadry Enteric 95K and 94O can be successfully used to achieve colon targeted delivery of drugs.

## References

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