**ANALYTICAL METHOD VALIDATION COMMITTEE FOR NON PHARMACOPOEIAL PRODUCT**

# DEPARTMENT OF DRUG ADMINISTRATION

## Antacid Suspension with Oxetacaine & Simethicone

| S.No. | **Test Parameter** | **Limit** |
|---|---|---|
| 1. | Identification | Positive for<br>Dried Aluminum Hydroxide Gel<br>Magnesium hydroxide<br>Simethicone<br>Oxetacaine |
| 2. | Fill volume variation | as per Pharmacopoeia |
| 3. | pH | 7.0 to 8.6 |
| 4. | wt/ml | As per the manufacturer's specification |
| 5. | Acid Neutralizing Capacity | NLT 5 mEq |
| 6. | Assay:<br>Each 10 ml suspension contains:<br>Dried Aluminum Hydroxide Gel IP 300 mg<br><br>Magnesium Hydroxide IP 150 mg<br><br>Oxetacaine BP 10 mg<br><br>Simethicone USP 125 mg | <br><br>NLT 270 mg and NMT 345 mg<br>(90 % to 115 % of the stated amount)<br>NLT 135 mg and NMT 172.5 mg<br>(90 % to 115 % of the stated amount)<br>NLT 9 mg and NMT 11 mg<br>(90 % to 110 % of the stated amount)<br>NLT 112.5 mg and NMT 137.5 mg<br>(90 % to 110 % of the stated amount) |

**1. Identification:**

**1.1. Magnesium**

Dissolve an amount of suspension containing about 0.8 g of anhydrous magaldrate in 20 ml of 3M hydrochloric acid, dilute with water to 50 ml, add 3 drops of methyl red solution and heat to boiling. Add dilute ammonia solution until the color changes to just yellow, continue boiling for 2 minutes and filter; the filtrate gives the reaction of magnesium salt. (IP 2014)

**1.2 Aluminium**

Wash the precipitates obtained in the test A with 50 ml of hot 2 % solution of ammonium chloride, then dissolve the precipitate in 15 ml of 3 M hydrochloric acid; the solution gives the reaction of aluminium salt. (IP 2014)

**1.3 Oxetacaine**

The retention time of the standard and sample preparation of assay preparation should resemble each other.

**1.4 Simethicone (As per USP 2017)**

**2. pH**

Operate the pH meter according to the manufacturer's instruction. Calibrate the pH meter using the standard buffer solution. Determine the pH of the syrup by using the calibrated pH meter.

**3. wt/ml**

First dry the pycnometer in the hot air oven and cool it in dessicator for 5 to 10 minutes. Take the weight of the empty pycnometer together with its stopper ($W_1$). Fill the pycnometer with water, put the stopper, wipe it dry outside with the help of tissue paper. Now take the weight of pycnometer and water ($W_2$). Throw water, dry the pycnometer and fill the pycnometer with the syrup, put the stopper, wipe it dry outside with the help of tissue paper. Take the weight of pycnometer and suspension ($W_3$). The calculate wt/ml

$$\textbf{wt/ml (g/ml)} = \frac{W3-W1}{W2-W1} \textbf{ x volume of 1 g of water at various temperature}$$

**4.0 Acid-neutralizing capacity**

Note: All tests shall be conducted at 37 ºC ± 3 ºC

Theoretical mEq value: [0.55 X (0.0385 A)] + [0.8 X (0.0343 X M)]

Where, 0.0385 and 0.0343 are the theoretical acid neutralizing capacity in mEq of Aluminium Hydroxide and Magnesium Hydroxide, and A and M are quantities in mg of Aluminum hydroxide and Magnesium hydroxide, based on the label claim.

Standardize the pH Meter before performing the test.

**Test Preparation:** Shake the container until the contents are uniform, and determine the density. Transfer an accurately weighed quantity of the uniform mixture, equivalent to 10 ml to a 250 ml beaker; add water to make a total volume of about 70 ml, and mix on the magnetic stirrer for 1 minute.

**Procedure:** Pipette 30 ml of 1.0 N hydrochloric acid VS into the test preparation while continuing to stir with the magnetic stirrer. Stir for 15 minutes, accurately timed, after the addition of the acid, begin to titrate immediately, and in a period not to exceed and additional 5 minutes, titrate the excess hydrochloric acid with 0.5 N sodium hydroxide VS to attain a stable (for 10 to 15 seconds) pH of 3.5. Calculate the number of mEq of acid consumed by the formula:

**Total mEq = (30 X Normality of HCl) – (Volume of NaoH X Normality of NaOH)**

**5. Assay**

**5.1 Aluminum Hydroxide**

**5.1.1 Reagent preparation**

5.1.1.1 Acetic acid ammonium acetate Buffer: Dissolve 77.1 g of ammonium acetate in water and add 57 ml of glacial acetic acid and dilute with water to 1000 ml.

5.1.1.2 Disodium Edetate, xM: Solution of any molarity xM may be prepared by dissolving 372.2x g of disodium edetate in sufficient water to produce 1000 ml.

5.1.1.3 Zinc Sulphate, xM : Solution of any molarity xM may be prepared by dissolving 289x g of zinc sulphate in sufficient water to produce 1000 ml.

5.1.1.4 Dithizone solution : A 0.05% w/v solution of dithizone in chloroform .

**5.1.2 Assay Preparation**

Weigh the sample equivalent to 250 mg of Dried Almunium Hydroxide gel in a 100 ml volumetric flask, add 10 ml water, shake and add slowly 5 ml of HCl. Heat gently, if necessary, and dilute to 100 ml with water.

**5.1.3 Procedure**

Pipette 20 ml of the assay preparation in to 250 ml conical flask, add 20 ml of water and then with stirring 25.0 ml of 0.05 M disodium edetate, mix and add 20 ml of acetic acid-ammonium acetate buffer, and heat near the boiling temperature for 5 minutes. Cool and add 40 ml ethanol (95%) and add 2 ml of dithizone solution and titrate with 0.05 M zinc sulphate to a bright rose-pink color. Repeat the procedure without the substance being examined. The difference between the titrations represents the amount of disodium edetate required.

Each ml of 0.05 M disodium edetate is equivalent to 3.900 mg of $Al(OH)_3$.

**5.2 Magnesium Hydroxide**

**5.2.1 Reagent Required**

**5.2.1.1** Ammonium- Ammonium Chloride Buffer: Dissolve 67.5 g of ammonium Chloride in about 200 ml of water, add 570 ml of strong ammonia solution and dilute with water to 1000 ml.

**5.3 Assay preparation**

Prepared as directed in the assay for aluminum hydroxide.

**5.3.1 Procedure**

Pipette 20 ml of the sample obtained in the assay preparation of almunium hydroxide, add 40 ml of water and 20 ml of triethanolamine and stir. Add 10 ml of ammonia-ammonium chloride buffer and 3 drops of an erichrome black T solution. Cool the solution to between $3^{\circ}$ and $4^{\circ}$ C by immersion of the flask in an ice bath, then remove and titrate with 0.05 M disodium edetate to blue color. Repeat the procedure without the substance being examined.

The difference between the titration represents the amount of disodium edetate required.

Each ml of 0.05 M disodium edetate is equivalent to 0.002916 g of $Mg(OH)_2$.

Net Vol. consumed (V) = Vol. consumed in sample - Vol. consume in blank.

**5.4 Oxetacaine**

**5.4.1 Reagent Preparation**

4.3.1.1 Buffer: 0.01 M Potassium hydrogen phosphate and pH adjusted to pH 6.5 ± 0.1 with orthophophoric acid.
4.3.1.2 Mobile Phase:
A mixture of Acetonitrile and Buffer (78:22) and filter through membrane filter of 0.45 µm.

**5.4.2 Chromatographic Condition**

**Column:** Octadecylsilane (C18), (150*4.6 mm), 5 µm
**Flow rate:** 1.0 ml/min
**Detector:** UV Detector
**Wavelength:** 220 nm
**Injection volume:** 50 µl
**Oven temperature:** 30 °C

**5.4.3 Standard Preparation:**

Weigh accurately about 25 mg of working standard of Oxetacaine and transfer into 100 ml volumetric flask. Dissolve with mobile phase and make up the volume to 100 ml with mobile phase. Dilute 2 ml of the resulting solution to 50 ml with mobile phase.

**5.4.4 Sample Preparation:**

Weigh accurately about the sample equivalent to 5 mg of Oxetacaine in 100 ml volumetric flask. Dissolve with mobile phase by sonicating for about 10 minutes and make up the volume to 100 ml with mobile phase. Centrifuge or filter the resulting sample. Dilute 5 ml of the clear solution to 25 ml with mobile phase.

**5.4.5 Chromatographic Procedure:**

Inject 50 µl of standard and sample solution separately and obtain the respective chromatogram. Measure the peak responses.

**5.4.6 System suitability:**

Inject 50µl of standard solution of oxetacaine as per above mentioned chromatographic condition. In the chromatogram obtained from the standard preparation, the column efficiency determined from the major peak should not be less than 2000 theoretical plates, the tailing factor should be not more than 2.0 and the relative standard deviation of replicate injections should not more be than 2.0 %. Inject 20µl of the sample preparation and chromatograph as per above mentioned chromatographic condition. Calculate the result from the formula given.

**5.4.7 Calculations:**

**Content of Oxetacaine in the suspension:**

$$\frac{\textbf{Spl Peak Area}}{\textbf{Std Peak Area}} \textbf{ X } \frac{\textbf{Std wt}}{\textbf{Std Dil.}} \textbf{ X } \frac{\textbf{Spl Dil.}}{\textbf{Spl wt}} \textbf{ X Claimed volume X } \frac{\textbf{wt}}{\textbf{ml}} \textbf{ X Std Potency } (\%) \textbf{X} \frac{(\textbf{100} - \textbf{Std LOD})}{\textbf{100}}$$

**5.5 Polydimethylsiloxane**

**By IR Spectrophotometry as per USP 2017 (Simethicone oral suspension).**