

# HYDROXYPROPYL CELLULOSE-CARBOPOL AND HYDROXYPROPYL CELLULOSE -NOVEON COMPOSITE MOUTH DISSOLVING FILMS OF AMBROXOL HYDROCHLORIDE

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## ABSTRACT

Ambroxol hydrochloride is a choice of drug in acute and chronic lung infections. In the COVID-19 situation, ambroxol played a crucial role in treating bronchitis and potentiating, the effect of antibiotics in lung infections. In the present study, a patient-friendly drug delivery system of ambroxol hydrochloride was prepared by solvent casting method to produce better mechanical strength in the film. To impart better mechanical strength without affecting disintegration and dissolution, composite films of hydroxypropyl cellulose - Carbopol-981NF and hydroxypropyl cellulose – Noveon-AA1 were developed and evaluated. Nine formulations were prepared using varying levels of film formers. The evaluated film formulations were in folding endurance range  $32 \pm 2.00$  to  $92 \pm 8.05$ , tensile strength range  $27.51 \pm 1.22$  to  $130.32 \pm 0.98$  g cm<sup>-2</sup>, % elongation range  $14.12 \pm 0.32$  to  $26.54 \pm 0.08$  and disintegration time range  $54 \pm 1.42$  to  $114 \pm 1.52$  seconds, and more than 90% drug dissolution occurred within 5 min. All the prepared formulations showed compatibility between ambroxol hydrochloride and ingredients of film.

**Keywords:** Composite mouth dissolving films, ambroxol hydrochloride, respiratory infection, solvent casting, and tensile strength

## INTRODUCTION

Patients with prevalent conditions of respiratory infections with acute cough, running nose, pain, fever, and swelling of the body are commonly visiting physician clinics<sup>1</sup>. Pandemic environments increase the worries among respiratory sufferers. In specific, the control of respiratory tract infections has wriggled many of the patients subjected to identical clinical symptoms between COVID-19 and non-COVID infections like allergies, influenza, flu, pneumonia and lung failures<sup>2</sup>. Common cold or acute bronchitis recurrently precipitate in acute cough and the distinction of causes is becoming difficult<sup>3</sup>. In children, acute cough can cause high fever, cough lasting for greater than four weeks leads to a chronic condition of pneumonia and subsequently asthma. The principle cause of mortality in low-income countries is observed with acute respiratory infections which further precipitate into pneumonia<sup>4</sup>. Over the counter (OTC) antitussives, antihistamines, and mucolytic formulations are the primary care medication in the intimal cough secretions in the respiratory tract which are repeatedly

given to the patients<sup>5</sup>. Mucoactive agents can modify the viscoelasticity of the cough or mucus which initiates mucociliary clearance<sup>6</sup>. Mucoactive drugs can be classified as expectorants, much regulators, mucolytics or mucokinetics, based on their potential mechanism of action<sup>7</sup>. Ambroxol hydrochloride salt form, chemically trans-4-(2-amino-3,5-dibromobenzylamino)-cyclohexanol hydrochloride, is used as a muco-active in the cure of acute and long-lasting respiratory infections. Ambroxol hydrochloride lowers bronchial hyper-sensitivity by exciting alveolar type II cell surfactant secretion, which results in better penetration of antibiotics and produces anti-inflammatory activity<sup>8,9</sup>.

Ambroxol, an active metabolite of parent compound bromhexine<sup>10</sup>, possesses mucokinetic and mucociliary effects<sup>11</sup>. In addition to this, ambroxol bears hydroxyl group at cyclohexyl ring in para-trans site, cyclohexyl ring attached with hydroxyl functional group at para-trans site and the methyl group elimination in the structure produces activation of cellular surfactant secretion, thus reduces respiratory inflammations and produces local anesthesia<sup>12</sup>. Besides pharmacology physicochemical properties of ambroxol hydrochloride reveal a white crystalline powder with astringent taste, molecular weight 414.6, good absorption from Gastro-intestinal tract (GIT), bioavailability

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70-80 %, pKa value 8.69, biphasic elimination with alpha half-life about 1.3 h and beta half-life 8.8 h, poor water solubility, BCS class-II drug, and dose 30 mg 2-3 times daily makes it a suitable candidate for oral film drug delivery system<sup>13</sup>. Oral films are advantageous over conventional tablets as films are ready to swallow, cost-effective, patient-friendly dosage form with no need to compress polymorphic drugs, can incorporate hygroscopic drugs, and better absorption from mouth cavity within a minute<sup>14</sup>.

In the present study, an attempt has been made to develop an alternative dosage form for the existing conventional system as oral dissolving film (ODF) of ambroxol hydrochloride for treating broncho pulmonary complications, pain relief of acute sore throat, and abnormal mucus secretion from the respiratory system of all age groups patients. No research was found on the composite film of ambroxol hydrochloride with Hydroxy Propyl Cellulose (HPC), Carbopol, and Noveon. Composite films will be prepared to improve folding endurance, fast dissolution, better mouth texture or feel, and retention in the buccal cavity till dissolution. Carbopol and Noveon at very low concentration act as mucoadhesive agents in combination with HPC<sup>15</sup>. HPC is good water-soluble film, formerly widely used in fast-dissolving films which impart good mouth feel and film strength<sup>16</sup>.

## **MATERIALS AND METHODS**

Ambroxol hydrochloride as a gift sample was the received from Medley Pharmaceuticals Ltd., Jammu, India. Hydroxy Propyl Cellulose (HPC) of Vishal Chemicals Pvt. Ltd. was obtained as gift sample from LNJD COP Kalwan, Nashik. Carbopol 981-NF and Noveon-AA1 Polycarbophil were obtained from Lubrizol Advanced Materials India Pvt. Ltd. Menthol, mannitol, and PEG 400 were purchased from Vishal Chemicals Ltd., Nashik, India. Distilled water, ethanol, other chemicals and reagents used were of analytical grade.

### **Formulation and development of ambroxol hydrochloride oral dissolving film**

Oral film of ambroxol hydrochloride was developed after screening developing blank films of the HPC, Carbopol 981NF, and Noveon-AA1. A solution of ambroxol hydrochloride, film-forming polymers, plasticizer, flavor and sweetener was formed in a water and ethanol mixture. Varying proportion of HPC at three levels with two levels of Carbopol 981 NF and Noveon-AA1 contributed to the development of the oral film to study the film-forming properties of polymers with ambroxol hydrochloride.

### **Drug and excipient compatibility test**

FTIR spectrum of ambroxol hydrochloride and oral dissolving films were compared for compatibility study. FTIR spectrum of ambroxol hydrochloride powder and film formulations F1, F4, and F7 were obtained using JASCO FTIR -4600 with ATR. Overlay of the spectrum was obtained to compare the spectra.

### **Preparation of drug-loaded mouth dissolving films**

Oral mouth dissolving films of ambroxol hydrochloride were prepared by the solvent casting technique on an aluminum foil-coated glass surface. Hydroxypropyl cellulose (HPC), Carbopol 981NF, Noveon-AA1 Polycarbophil, mannitol, and PEG 400 were dissolved in ethanol/water mixture (1:1) with the help of an orbital shaker (Neolab) at room temperature. Ambroxol hydrochloride solution was mixed drop wise with above solution of polymers and agitated. The solution was sonicated for the removal of air bubbles. From 60 mL, three batches of 20 mL were prepared. The 20 mL solution was then poured into an aluminum foil-coated glass casting surface and further dried at 30 °C for 16 h. The dry film was removed from the aluminum foil surface. The mouth dissolving film was sectioned into 2 cm × 2 cm film pieces using a sharp scissor. The films were wrapped using an aluminum foil and stored at room temperature in a desiccator until further use<sup>17</sup>.

### **Surface morphology, appearance and film thickness test**

Visual inspection of films was carried out for physical appearance and morphology. A digital vernier caliper measured the film thickness. Film was placed at anvils of vernier caliper on 3 random places on the film. The mean film thickness and standard deviation were determined.

### **Film surface pH**

The film sample was wetted with the help of few drops of water in a watch glass and mounted on the surface of the electrode of the pH meter. Film pH reading was noted.

### **Film weight variation**

Six film formulations of size 2cm x 2cm were randomly selected. Weight of each film was measured on digital balance (Shimadzu). Mean weight and standard deviation were calculated.

### **Film folding endurance**

Six film formulations of size 2cm x 2cm were randomly selected. Folding of film at identical place was repeatedly performed till the film breaks into two pieces. The number of folds required to break the film was noted as folding endurance<sup>18</sup>.

### **Film tensile strength**

Film tensile strength was determined manually gripping film at both ends of apparatus. Force in terms of weight was applied at the lower end of grip till break of the film. Force in gram applied for breaking the film at cross-section was noted as tensile strength of the film. Experiment was repeated three times. Mean and standard deviation was calculated<sup>18</sup>.

### **Film elongation test**

A film elongation test was performed by gripping both the ends of the film. Force in increment was applied at lower end of grip till the film broke. At each increment, film length was noted. The difference between the initial length and final length was measured as film elongation. Percentage film elongation was calculated<sup>18</sup>.

### **Film drug content test**

Six ambroxol hydrochloride films of size 2 cm x 2 cm were randomly selected. In 10 mL phosphate buffer, pH 6.8, the films were dissolved using a stirrer. Each film solution was filtered using filter paper. Dilutions of solutions were performed and the absorbance was noted at 244 nm. The % drug present in the film formulation was determined. The mean and standard deviation were reported<sup>19, 20, 21</sup>.

### **In vitro film disintegration**

10 mL phosphate buffer, pH-6.8, was placed in a glass petri plate. Each film formulation was horizontally placed over the surface of the buffer. The petri plate was swirled using orbital shaker at 10 rpm. The time required to disintegrate the film was noted<sup>22, 23</sup>.

### **In vitro film dissolution study**

The dissolution test apparatus USP (ELECTROLAB, TDT-08L) attached with a basket was used. 500 mL Phosphate buffer of pH 6.8 was added into each vessel. Temperature at 37°C ± 0.5°C was maintained and speed was adjusted to 50 rpm. Six films of 2 cm x 2 cm were randomly selected for dissolution study. Ambroxol hydrochloride samples of 5 mL were collected and fresh phosphate buffer of equal quantity was used

for replacement. The time intervals of 3,10,15, 20 min were selected for the study. The collected samples were filtered. The percentage drug released was determined with the help of a spectrophotometer (JASCOV-730) at wavelength 244 nm<sup>24, 25</sup>.

### **Stability study**

Film formulations F5 and F7 were packed in aluminum foil and kept in tightly closed glass container for 3 months at room temperature. After 3 months, drug content was tested.

## **RESULTS AND DISCUSSION**

Primary screening was performed for the development of film formulations. Films with HPC were easily prepared with water using the solvent casting method. The addition of Carbopol or Noveon and other ingredients to HPC film did not produce film in water. Water-ethanol at 1:1 ratio was developed as a solvent system to dissolve hydrophilic HPC and hydrophobic Carbopol-981NF and Noveon-AA1 polymers together. After the primary screening, the hydroxypropyl cellulose (HPC), Carbopol-981NF, and Noveon-AA1 were used in the mouth dissolving film formulation. Literature reported that Carbopol- 981NF and noveon- AA1 were widely used as viscosity modifier, film former and mucoadhesive polymers. In the present study, both polymers at very low concentrations were added in the mouth dissolving film for good adherence to oral mucosa, produce viscous feel, retain drug in oral mouth cavity for short time so that drug can get completely and fast absorption from oral buccal site. Addition of these viscosity modifiers in HPC can give better film strength without affecting fast dissolution. HPC alone produced poor film strength. Based on imparting better film strength, combination of HPC with Carbopol 981NF and HPC with Noveon-AA1 was selected. Mannitol was used to impart sweet taste and give better patient compliance. PEG 400 was utilized for imparting plasticity to the film formulation. Menthol stimulates salivation and produces cooling sensation in the mouth, hence it was used in the formulation. Total nine formulations F1 to F9 were developed, varying three levels of HPC and two levels of Carbopol-981NF and Noveon-AA1 polymers. Carbopol 981NF Carbomer homopolymer and Noveon-AA1 Polycarbophil are in the FDA's inactive ingredients guide (IIG) at a maximum potency of 195 mg and 2.06 mg respectively, and were used at lower concentrations in the prepared film formulations.

The compatibility of ambroxol hydrochloride with polymer was confirmed by FTIR spectroscopy. Overlay of

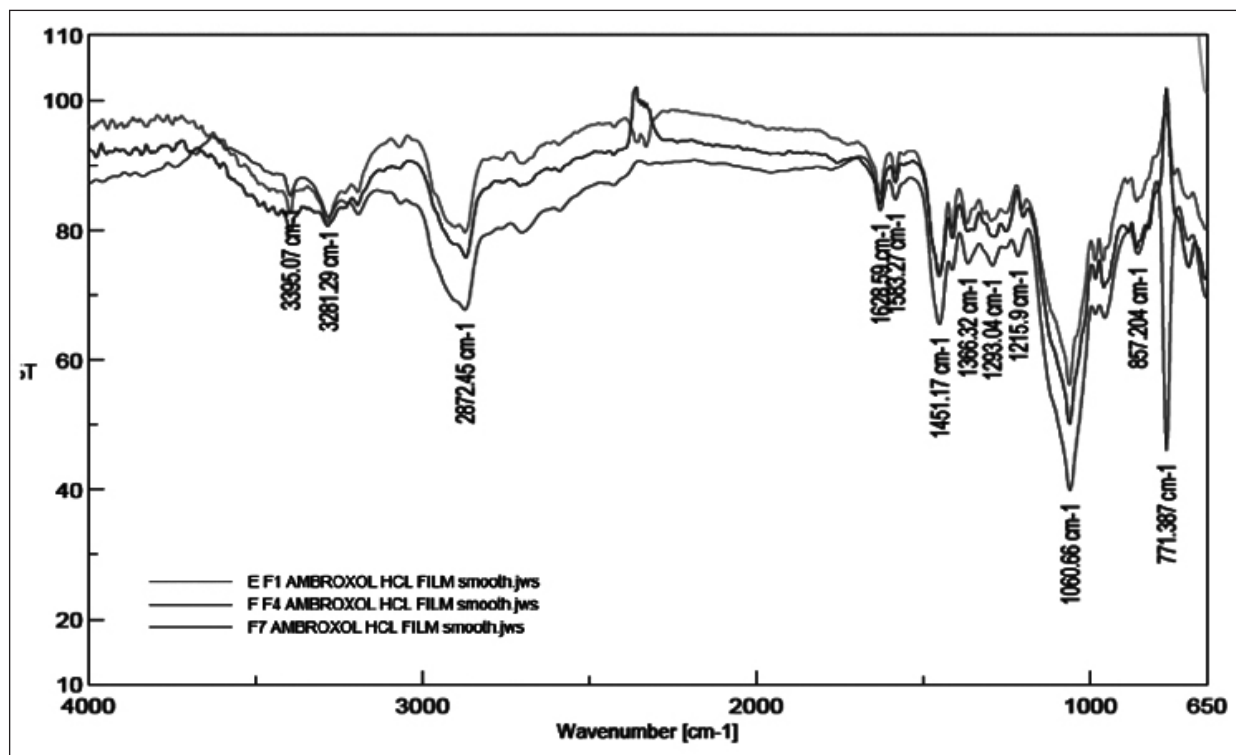


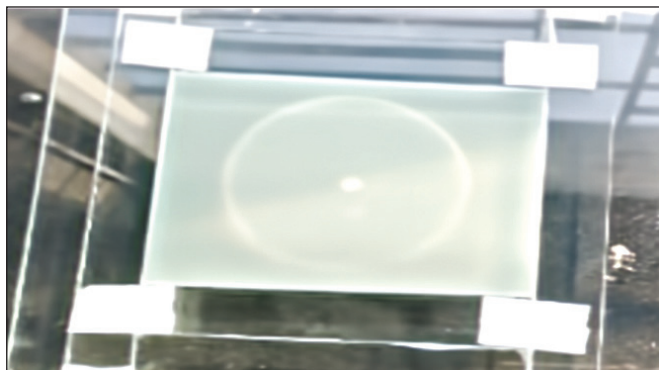
Fig. 1: Overlay spectra of ambroxol hydrochloride formulations F1, F4 and F7

Table I: Formulation and development of ambroxol hydrochloride oral dissolving film

Ingredient	Formulation batch								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ambroxol HCl (mg)	360	360	360	360	360	360	360	360	360
HPC (g)	2	1	2	3	2	1	2	3	2
Carbopol 981 NF (mg)	---	10	10	10	20	---	---	---	---
NOVEON-AA1 (mg)	--	--	--	---	---	10	10	10	20
PEG 400 (mg)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Menthol (mg)	10	10	10	10	10	10	10	10	10
Mannitol (mg)	200	200	200	200	200	200	200	200	200
Ethanol (mL)	qs	qs	qs	qs	qs	qs	qs	qs	qs
Water (mL)	qs	qs	qs	qs	qs	qs	qs	qs	qs

FTIR spectrum was obtained for ambroxol hydrochloride, Formulations F1, F4, and F7 contain all ingredients mentioned in formulation Table I. The overlay FTIR spectrum is shown in Fig. 1. Major peaks of ambroxol hydrochloride were exactly mapped with peaks observed in formulations. No shifting of the peak was observed. Mouth dissolving films of F1 to F9 formulations were prepared and evaluated for various tests. 3 batches of 12 films of each formulation

were prepared. The prepared films were kept to dry at 30 °C for 16 h. The mouth dissolving film formulation was evaluated for physical appearance, surface morphology, and thickness of the film, weight variation, *in vitro*, film disintegration time, film tensile strength, % elongation, folding endurance, film content uniformity, film surface pH, swelling index, and *in vitro* dissolution study. Results are shown in Tables II and III.



**Fig. 2: Photograph of formulation F5 mouth dissolving film**

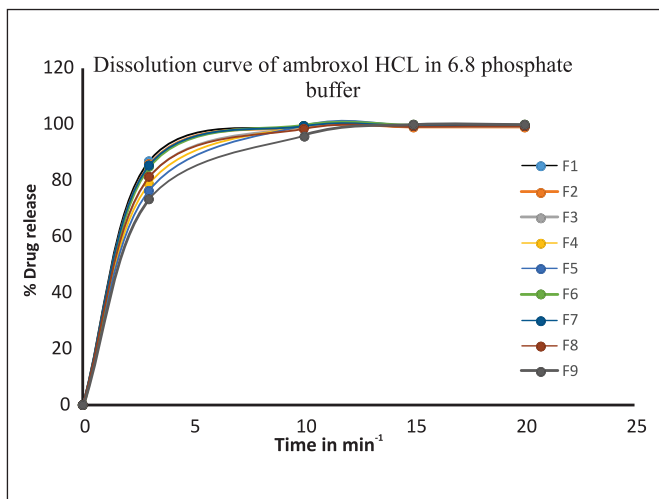
Mouth dissolving films of ambroxol hydrochloride were prepared easily using solvent casting method on glass plate. The prepared films are shown in Fig. 2 and were found thin smooth, even surfaced and flexible.

The surface pH of film formulations in batches F1-F9 was neutral, found in the range  $6.21 \pm 0.04$  to  $6.61 \pm 0.12$ , indicating that prepared films might not produce any potential irritation to the mucosa. The films were cut into 2 cm x 2 cm dimensions and weight of six individual films was taken. The weight of obtained films of developed formulations were found in the range of  $214.22 \pm 1.25$  to  $216.07 \pm 1.19$  mg, which contains 30 mg drug theoretically. The changes in weight of film were observed due to changes in levels of HPC, Carbopol, and Noveon. The variation in the weight of film affects, % film drug content. The content in the films ranged from  $98.33 \pm 0.37$  to  $101.83 \pm 0.13$  %. The film thickness was observed from  $0.23 \pm 0.035$  to  $0.27 \pm 0.026$  mm and depicted very thin films. It was observed, that an increase in the concentration of Carbopol and Noveon increased film thickness. Folding

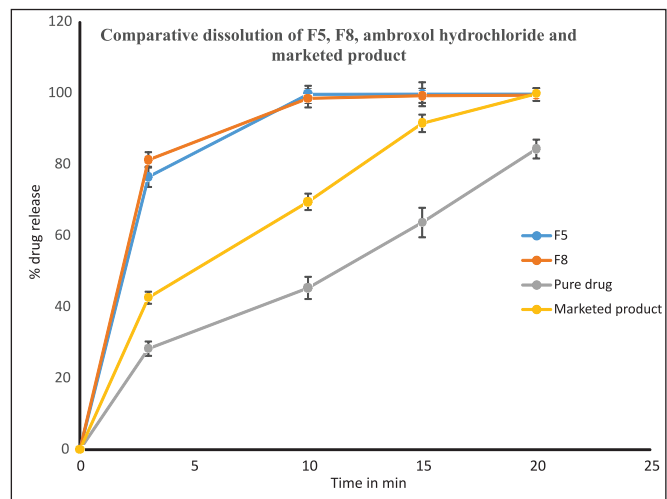
endurance studies showed improvement of folds with the increase of polymer concentration in films. Film F5 and F8 showed better folding endurance. Film F5 and F8 contain Carbopol and Noveon at the highest level and produced better folding endurance.

Film formulations F1 to F9 disintegrated within 114 seconds. Formulation F1 contains only HPC at a low level and showed fast disintegration at 54 seconds. As the concentration of Carbopol and Noveon increased, disintegration time increased. All formulations were disintegrated within 2 minutes, leading to compliance with official compendia. Formulation F5 has shown better tensile strength than formulation F8. Carbopol formulations were found superior to Noveon formulation for tensile strength. Also, Carbopol containing formulations have shown better elongation than Noveon formulations F6 to F9. The folding endurance, tensile strength, and elongation studies show that formulation F5 and F8 were having better mechanical strength than other formulations. All formulations F1-F9 dissolved more than 90% ambroxol hydrochloride within 5 minutes. The dissolution profiles of the film formulations is shown in Fig. 3. Formulations F5 and F8 were found to be better mouth dissolving films in the sense of mechanical strength of the film. The dissolution data of formulations F5 and F8 were compared with pure drug and marketed uncoated ambroxol hydrochloride tablet. It was observed that dissolution from films was faster than its pure drug and marketed uncoated tablet of ambroxol hydrochloride, as shown in Fig. 4 and Table IV.

Formulations F5 and F8 after 3 months were found stable for drug content. The samples of ambroxol hydrochloride films were kept at room temperature in



**Fig. 3: Dissolution curve of ambroxol hydrochloride mouth dissolving films F1 to F9**



**Fig. 4: Comparative dissolution of Formulations F5, F8, ambroxol hydrochloride and marketed product**

**Table II: Properties of mouth dissolving films of ambroxol hydrochloride**

Formulation code	Weight variation (mg)	Thickness (mm)	Folding endurance	Surface pH
F1	214.22±1.25	0.23±0.045	34±2.51	6.61±0.12
F2	215.01±1.82	0.24±0.020	48±4.50	6.34±0.06
F3	215.23±1.28	0.25±0.010	59±5.50	6.58±0.14
F4	215.53±1.50	0.26±0.032	52±3.05	6.23±0.09
F5	215.87±1.19	0.27±0.026	90±6.50	6.45±0.05
F6	215.11±1.82	0.23±0.035	32±2.00	6.21±0.04
F7	215.35±1.28	0.24±0.051	58±7.02	6.29±0.03
F8	215.75±1.50	0.25±0.050	92±8.05	6.45±0.07
F9	216.07±1.19	0.26±0.025	71±6.01	6.38±0.10

*n=6, ±standard deviation (S.D)*

**Table III: Evaluation parameters of mouth dissolving film of ambroxol hydrochloride**

Formulation code	Disintegration time (sec)	Tensile strength (g cm <sup>-2</sup> )	Elongation %	Drug content %
F1	54±1.42	27.51±1.22	14.12±0.32	99.36±0.39
F2	75±1.77	41.73±1.43	15.32±0.19	99.33±0.21
F3	95±1.72	50.18±1.71	17.29±0.17	98.83±0.28
F4	105±1.04	81.5±0.76	23.89±0.12	98.33±0.37
F5	114±1.52	130.32±0.98	26.54±0.08	100.46±0.15
F6	66±2.02	39.05±1.54	14.86±0.15	101.66±0.13
F7	88±2.08	51.16±1.52	16.67±0.18	99.96±0.18
F8	70±1.53	85.33±1.32	24.65±0.11	101.83±0.13
F9	108±1.83	84.22±1.15	24.21±0.10	99.96±0.22

*n=6, ±standard deviation (S.D)*

**Table IV: Dissolution data of film formulations F5, F8, ambroxol hydrochloride and marketed tablet**

Formulation batch	Time in mins			
	3	10	15	20
F5	76.55±1.11	99.72±1.39	99.74±1.49	99.75±1.43
F8	81.32±1.14	98.58±1.30	99.31±1.43	99.47±1.23
Pure ambroxol hydrochloride	28.26±1.58	45.39±2.13	63.34±1.94	84.36±1.88
Marketed tablet	42.66±2.57	69.55±1.87	91.58±1.14	99.86±2.33

*n=6, ±standard deviation (S.D)*

aluminum foil. The ambroxol hydrochloride films were found stable and showed drug content  $99.76 \pm 0.32\%$  and  $99.26 \pm 0.47\%$  respectively. Stability test of ambroxol hydrochloride film formulations suggested that the film should be packed in aluminum strip and stored in airtight packaged container.

## CONCLUSION

From the composite design formulation, better mechanical strength films can be obtained. The composite films can produce fast disintegration and dissolution of ambroxol hydrochloride in the presence of small quantity of sustained release mucoadhesive polymers Carbopol-981NF and Noveon-AA1. Composite films can result in better patient compliance and therapeutics in mouth dissolving film drug delivery systems.

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