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FORMULATION AND EVALUATION OF BILAYER TABLET OF AMBROXOL HCL AND DESLORATADINE FOR THE TREATMENT OF SEASONAL ALLERGIC RHINITIS ASSOCIATED WITH COUGH.

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ABSTRACT

The present study was intended at raising a bilayer drug delivery system containing Ambroxol HCL and Desloratadine for the treatment of moderate seasonal allergic rhinitis (SAR), to reduce the dose frequency and to improve the prolongation of action. The tablet is characterize by conventional release of Desloratadine and sustained release of Ambroxol HCl. The formulation containing sustained release layer of Ambroxol HCl, was designed using HPMC-5 CPS as sustained release polymer, MCC as drug binder, Aerosil to improve flow properties of powder, and Magnesium stearate as antiadherent agent. Crosspovidone was used as superdisintegrant for the preparation of conventional release layer. The prepared sustained release layer was evaluated for their pre-compression parameters, physical characteristics like hardness, friability, and weight uniformity, disintegration, and uniformity of drug content and *in- vitro* drug release. The release of Desloratadine from the conventional release layer was found to be within 30 min. The release of Ambroxol HCl for sustained release layer was found to be in 6 hours.

KEYWORDS: Ambroxol HCL, Desloratadine, bilayer tablet, crosspovidone, superdisintegrant.

INTRODUCTION

In the present era due to a great awareness in the pharmaceutical and medical field about the effective, safe and controlled use of drugs, much attention has been rewarded to develop the controlled drug delivery system. Oral route has been the most widely used and most convenient route for the delivery of drugs. Oral route of administration has acknowledged

more attention than any other dosage form in research field because of the flexibility in crafting of the dosage form and liberty from problems like sterility and prospective damage at the administration site. Oral drug delivery system is approximately 50% conveniently used system in the market. Drugs that are rapidly absorbed from the gastrointestinal tract with a short half life are eliminated rapidly from the blood stream, thus require a frequent dosing. To avoid this, the oral sustained controlled release formulation has been developed. It is an attempt to release the drug gradually into the gastrointestinal tract to maintain the therapeutic drug concentration in the serum for longer time period. The oral controlled release system is characterized by a distinctive pattern of drug release where the drug concentration is maintained in the therapeutic casement for a prolonged time period. Thereby ensuring sustained therapeutic action.[1] Allergic rhinitis is a common condition, disturbing more than 40 million people in the United States, including 10 to 30% of adults and as many as 42% of all children.[2,3] Further, its frequency is increasing.[4,5] Approx. 90% of the patients with seasonal allergic asthma at the same time as experience allergic rhinitis(6). Nasal congestion is a common symptom of SAR that is on the whole difficult to many patients. Airborne allergens activate the immediate release of histamine from mast cells, inspiring mucus secretion and vasodilatation.[2,3]

Desloratadine is a potent, nonsedating, oral H1 – receptor antagonist with multiple antiallergic properties.[7,8] In placebo- controlled trials, Desloratadine provided rapid and long lasting relief of a broad range of persistent nasal and non nasal SAR symptoms, including nasal congestion.[9]

A new formulation containing Ambroxol HCL and Desloratadine in combined form was designed to treat two major symptoms i.e. throat soreness and cough.[10] The combination is projected to provide relief when co-prescribed with more specific therapies, such as antibiotics. The Ambroxol- Desloratadine formulation is a long acting, non- sedating, anti histamine[11], and is a mucolytic-expectorant decongestant for oral administration in patients for indicative treatment of upper and lower acute allergic rhinitis.[12]

MATERIALS AND METHOD

Ambroxol HCl and Desloratadine were obtained as a gift sample from Morepen Laboratories Limited, Parwanoo Himachal Pradesh, HPMC 5 CPS were purchased from colorcon Asia Pvt. Ltd. Mumbai, Mcc Plain and MCC pH102 were purchased from S.P Enterprises, Bangalore, Aerosil and magnesium stearate were purchased from S.D fine chemicals Pvt.

Ltd. Pharmatose DCL-15 was purchased from Ekta International, Mumbai; Crosspovidone was purchased from Dr. Reddys Laboratories Ltd. Hyderabad and Starch 1500 was purchased from Colorcon Asia Pvt. Ltd. Mumbai. All other chemicals were of analytical grades.

Formulation of Bilayer Tablets

Bilayer tablet is prepared in two stages as following

- Formulation of Desloratadine immediate release layer.
- Formulation of Ambroxol HCl Sustained release layer.

Formulation of Desloratadine immediate release layer

Desloratadine immediate release layer was prepared by taking variable concentration of crosspovidone and MCC pH 102. This layer was prepared by using direct compression method. Desloratadine was weighed and passed (sieve) through mesh no. #40. Pharmatose DCL 15, MCC pH 102, starch- 1500, Aerosil, crosspovidone were also weighed and passed (sieve) through mesh no. #40. Now mix all these ingredients in double polybag for 5 minutes thoroughly. Now weigh Magnesium stearate and pass through (sieve) mesh no. #60. Add this magnesium stearate to mixed blend in double polybag and again mixed the blend for 3 min manually. The blend was directly compressed using single punch tablet compression machine. The composition of Desloratadine tablet layer is shown in Table No. 1.

Table No. 1: Composition of Desloratadine Tablet Layer.

	Formulation code					
Ingredients	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**
Desloratadine	5	5	5	5	5	5
Pharmatose (DCL-15)	10	13	17	16.5	17	16.5
MCC 102	30	20	24	30	30	30
Starch 1500	5	8	9	6	5	5
Crosspovidone	10	9.5	7	5	1	5
Aerosil	1	2	2	0.5	1	2
Magnesium Stearate	3	6	6	1	5	0.5
Total	64	64	64	64	64	64

Formulation of Ambroxol HCl Sustained release layer

The formulation of sustained release layer of Ambroxol HCl was prepared by using experimental design by altering the concentration of HPMC- 5 cps. Ambroxol hydrochloride, HPMC- 5 cps, MCC plain were weighed and passed through (sieves) mesh no. #40. The active ingredients of Ambroxol Hydrochloride, HPMC 5 cps and MCC plain were mixed in a double polybag for 5 min. Make granules by using sufficient water in rapid mixer granulator,

and dry the granules in Fluidized Bed Dryer for 20 minutes. Now pass the granules through (sieves) mesh no. #16 and final pass the granules through (sieves) mesh no. #24. After passing the granules check the LOD of the granules. Now dried granules are lubricated by using MCC pH102, Aerosil and mixed these in a double polybag for 5 minutes thoroughly. Now pass Magnesium stearate after weighing through (sieves) mesh no. #60.Again mixed the blend for 3 minutes manually. Check the final LOD of the blend. The blend was compressed using single punch 16 station tablet compression machine. The Composition of Ambroxol hydrochloride SR tablet is shown in table No. 2.

Table No. 2 Composition of Ambroxol Hydrochloride Tablet Layer.

	Formulation Code					
Ingredients	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**
Ambroxol Hydrochloride	75	75	75	75	75	75
HPMC 5 Cps	5	8	7	10	9	7
MCC Plain	20	20	20	17	19	20
MCC pH 102	32	29	35	35	30	35
Aerosil	1	1	1	1	2	1
Magnesium Stearate	7	7	2	2	5	2
Total	140	140	140	140	140	140

EVALUATION OF TABLET

Pre-compression parameters of powder blend

The evaluation of prepared powder blend was done with parameters like bulk density, tapped density, Carr's index, Angle of repose, and Hausner's ratio. The pre-compression parameters of powder blend of both the layers are shown in Table 3 and 4.

Table 3: Pre-compression parameters of powder blend for Desloratadine Tablet Layer.

Formulation Code	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Angle of Repose (Ɵ)	Hausner Ratio	Carr's Index (%)
Dry Granulation					
D1	0.436	0.635	23.10	1.45	31.63
D2	0.422	0.631	26.75	1.6	33.32
D3	0.412	0.610	28.56	1.45	31.85
D4	0.423	0.616	22.39	1.5	33.74
D5	0.420	0.632	26.42	1.43	32.82
D6	0.425	0.592	26.52	1.403	29.74

Table 4: Pre-compression parameters of powder blend for Ambroxol HCL Tablet layer.

Formulation Code	Angle of repose (Ɵ)	Bulk density (g/cm³)	Tapped density(g/cm³)	Hausner ratio	Carr's index(%)
Wet Granulation					
A1	32.10	0.63	0.678	1.07	7.07
A2	33.14	0.71	0.747	1.05	4.95
A3	30.20	0.75	0.810	1.08	7.40
A4	31.23	0.67	0.712	1.06	4.20
A5	29.34	0.59	0.636	1.07	7.23
A6	30.21	0.79	0.871	1.10	9.29

Post –compression parameters

Hardness

While handling the tablet, hardness indicates the ability of the tablet to withstand mechanical shocks. Monsanto hardness tester was used to determine the hardness of the tablet. Three tablets from each formulation were randomly picked to determine the hardness of the tablets. The hardness of Desloratadine tablet layer and Ambroxol HCL tablet layer is shown in table 5 and 6. The hardness of optimized bilayer tablet is reported in Table no. 7.

Table No. 5: Optimization parameters for Desloratadine tablet layer.

Formulation code	Hardness (kg/cm^2)	Friability (%)	Uniformity of weight (%)	Disintegration time (minutes)
D1	2.1 ± 1.3	0.46	1.31 ± 0.04	30 ± 1.2
D2	2.3 ± 1.2	0.49	1.41 ± 0.08	29 ± 1.2
D3	2.5 ± 1.4	0.66	1.56 ± 0.05	28 ± 1.1
D4	2.2 ± 1.7	0.45	1.28 ± 0.07	24 ± 1.1
D5	2.0 ± 1.2	0.55	1.30 ± 0.02	30 ± 1.5
D6	2.2 ± 1.2	0.56	1.80 ± 0.04	28 ± 1.3

Table No. 6: Optimization parameters of Ambroxol HCL tablet layer.

Formulation code	Hardness (kg/cm^2)	Friability (%)	Uniformity of weight (%)	Drug content (%)
A1	2.2 ± 0.65	0.53	1.26 ± 0.05	97.2
A2	2.1 ± 0.51	0.78	1.55 ± 0.07	93.6
A3	2.6 ± 0.44	0.85	1.47 ± 0.08	98.1
A4	2.3 ± 0.26	0.44	1.52 ± 0.06	96.3
A5	2.6 ± 0.22	0.67	1.36 ± 0.05	97.84
A6	2.2 ± 0.35	0.45	1.64 ± 0.07	98.9

Table No. 7: Evaluation parameters of optimized bilayer tablet.

Parameter	Observations
Hardness (kg/cm^2)	2.3 ± 0.35
Friability (%)	0.642
Weight variation (%)	1.30 ± 0.04
Disintegration time (minutes)	30 ± 1.2

Friability Test[13]

Roche friabilator was used to determine the friability of the tablet. Ten tablets were initially weighed ($w_{initial}$) and placed into friabilator. The friabilator is operated at 25 rpm for 4 min.i.e.100 revolutions. The tablets were then taken out, dusting the tablets and weighed again (W_{final}). The % age friability was calculated by using formula:

$\% F = W_i - W_f / W_i * 100$

The values of friability of Desloratadine tablet layer and Ambroxol HCL layer are shown in Table 5 and 6 respectively. The friability of optimized bilayer tablet is reported in Table No. 7.

WEIGHT UNIFORMITY[14]

20 tablets were arbitrarily selected from each batch, individually weighed and the average weight and standard deviation of 20 tablets were calculated. The data of weight variation test of Desloratadine tablet layer and Ambroxol HCL tablet layer are shown in table 5 and 6 respectively. The data of weight variation test of optimized bilayer tablet is reported in Table 7.

Disintegration Test

The disintegration time of optimized bilayer tablet is reported in Table 7. Disintegration test is performed to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. One tablet was placed in each tube and the basket rack was positioned in a 1 liter beaker of simulated gastric fluid at 37 ± 2ºC, such that tablet remains 2.5 cm on below the surface of the liquid on their upward movement and descends not closer than 2.5 cm from the bottom of the beaker. A standard motor driven device was used to move the basket assembly containing the tablets up and down through a distance of (5-6) cm at the frequency of 28 to 32 cycles per minute. Time at which there is no fraction of tablet present in the tube was noted. The disintegration time plot obtained for Desloratadine layer is shown in Table no.7.

In – vitro dissolution study

In –vitro dissolution study of Desloratadine immediate release tablet.

Time (min)	Dissolution (%)
30	Not less than 85%

In –vitro required release profile criteria for Ambroxol HCl SR tablet.

Time (hrs.)	Dissolution (%)
0 - 2	20 – 40 %
2 - 4	40 – 60 %
4 – 6	Not less than 85%

In –vitro drug release studies from the prepared sustained release tablets were conducted for a period of 6 hours using USP dissolution test apparatus (type 1-Basket) at 37 ± 0.5ºC and 50 rpm speed. The simulated gastric fluid (ph 1.2) for first 2 hours and intestinal fluid (ph 6.8) for next 4 hours without enzymes were used as a dissolution medium. Samples (10 ml) were withdrawn with replacement at fixed time intervals, the samples were then diluted with dissolution medium (when necessary).The concentrations of Ambroxol Hydrochloride released from the tablet formulations were determined at 244 nm using a UV spectrophotometer.(As per the USP).

RESULTS

Result of in –vitro dissolution study of Desloratadine immediate release layer.

	15 min.		20 min.		30 min.	
Tablet weight	**Absorbance**	**% Result**	**Absorbance**	**% Result**	**Absorbance**	**% Result**
64.2 mg	0.300	91.16	0.309	93.90	0.304	92.38
62.9 mg	0.243	73.84	0.277	84.17	0.288	87.53
64.7 mg	0.252	76.58	0.282	85.69	0.313	95.11
65.1 mg	0.265	80.53	0.295	89.64	0.310	94.20
63.6 mg	0.261	85.39	0.303	92.08	0.311	94.51
64.2 mg	0.257	77.51	0.285	85.71	0.316	95.14

	15 min	20 min	30 min
Average	82.15	90.30	93.44
Minimum	73.84	84.17	87.52
Maximum	91.16	96.33	96.94

Result of In-vitro dissolution study of Ambroxol HCl sustained release layer.

	2st Hrs.		4th Hrs.		6th Hrs.	
Tablet weight(mg)	**Absorbance**	**% Result**	**Absorbance**	**% Result**	**Absorbance**	**% Result**
140.9	0.102	28.47	0.149	41.59	0.225	62.80
142.7	0.100	27.91	0.171	47.73	0.226	63.08
141.6	0.110	30.70	0.164	45.78	0.225	62.80
141.9	0.190	53.03	0.264	73.69	0.319	89.04
141.2	0.125	34.89	0.197	54.99	0.239	66.71

	2st Hrs.	4th Hrs.	6th Hrs.
Average	35.00	52.76	68.89
Minimum	27.91	41.59	62.80
Maximum	53.03	73.69	89.04

According to the results of in –vitro dissolution studies more than 89% of the sustained release layer was released within 6 hrs. And 96.94% of the immediate release layer was released within 30 minutes. It means the tablet complies the dissolution release profile criteria successfully.

Determination of drug content in Ambroxol Hydrochloride layer[16]

To determine the drug content, 3 tablets were weighed and crushed and was dissolved in 0.1 N HCl. Stirr the solution for 20 minutes. Filter the solution with membrane filter and after diluting it, absorbance was measured at 245 nm using UV- visible spectrophotometer.

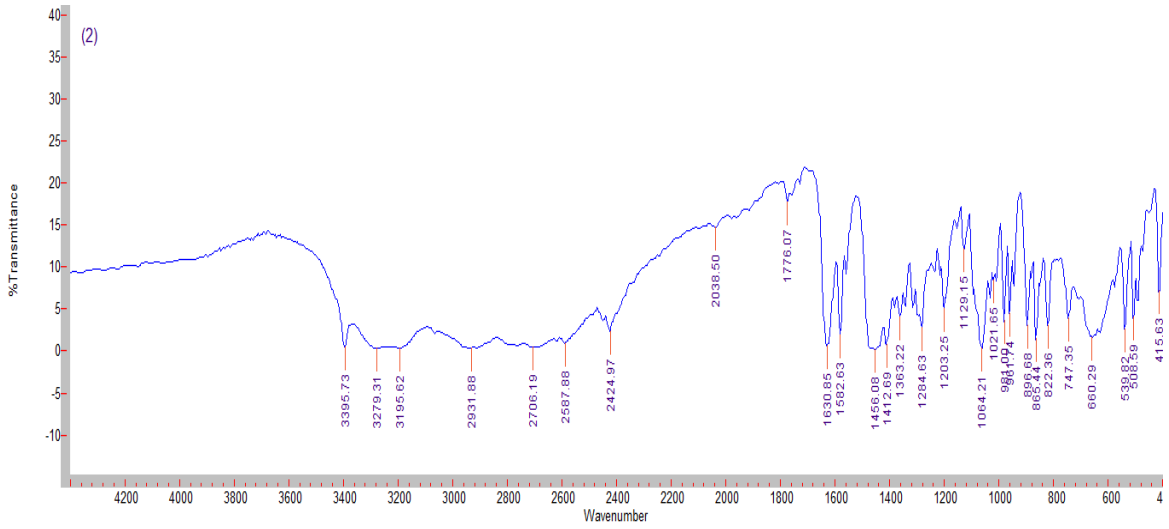
FTIR spectral Analysis

FTIR spectroscopy was used to investigate the interaction between drug – drug and drug and polymer. To produce a stable product, drug and polymers must be compatible with each other. FTIR (Shimadzu, model 8400, Japan) was used to study drug and polymer interaction as per the method. The similarity in the peaks when compared to pure drug indicates that there are no interactions between the drug and the excipients.

FTIR characteristic peaks of Ambroxol HCl.

Sr. No.	Functional groups	Characteristic peaks (nm)		Observed peaks (nm)	
		Stretching	Bending	Stretching	Bending
01	C-H	3150 -3050		3066	
02	=C-H			2966	
03	C-H Aromatic characteristic shapes	2000 -1667	900-850, 860-790	1760-1700	866,896
04	C-N (Aromatic)	1350-1250		1284	
05	C-N (Aliphatic)	1220-1020, 1410		1130, 1413	
06	Aromatic NH2 (2 Bands)	3500,3400	1650-1590	3396,3282	1633
07	N-H Secondary amines	3500-3310	1650-1550	3228	1543
08	O-H Intermolecular Hydrogen bonded	3400-3200	1100, 1350-1260	3196	1064,1284
09	C-O	1100-1070		1064	
10	C-Br (Aryl Bromide)	1250-1190	1075-1030	1203	1064

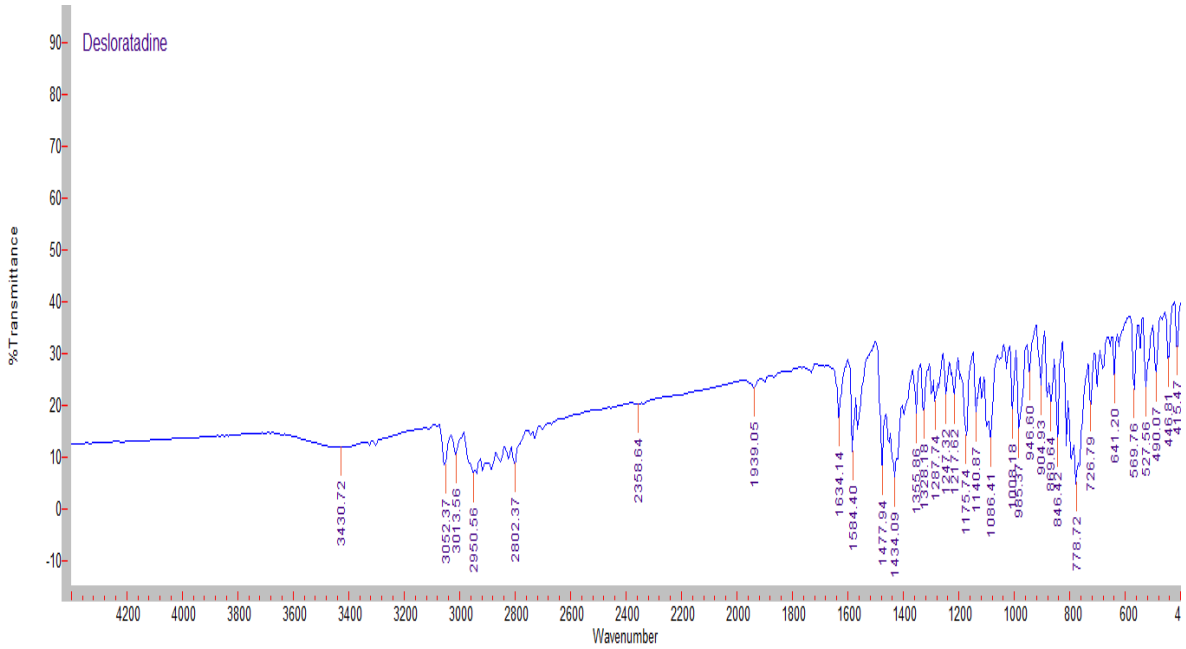
FTIR Peaks of Ambroxol HCl



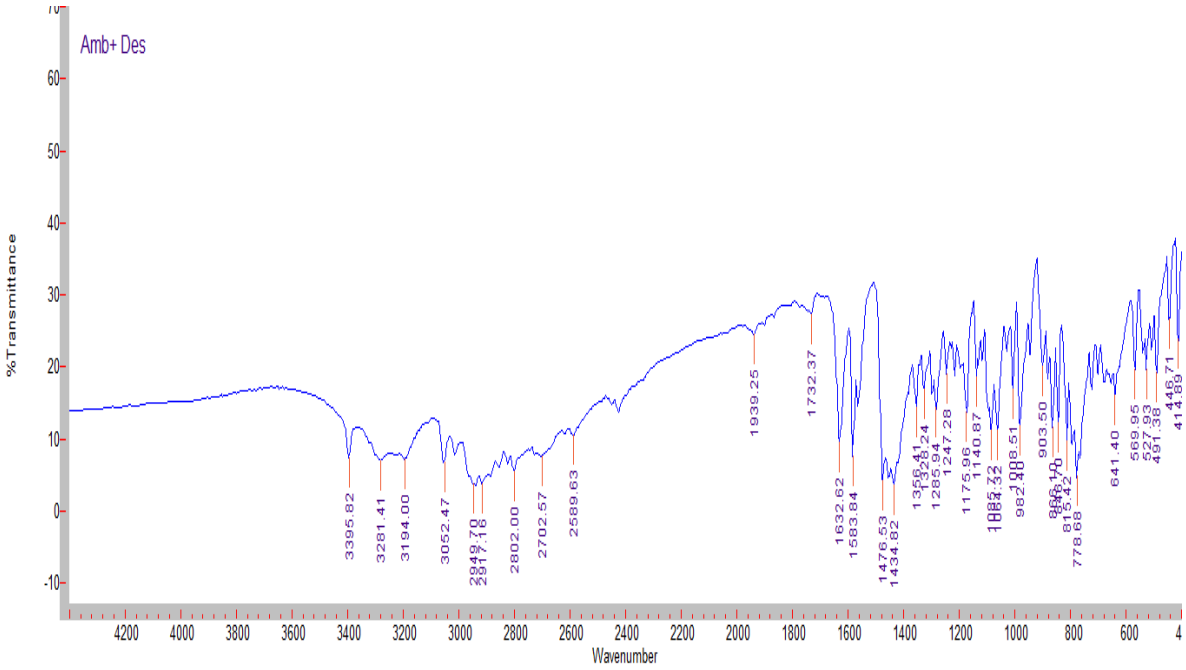
FTIR Characteristic peaks of Desloratadine

Sr. No.	Functional groups	Characteristic peaks (nm)		Observed peaks (nm)	
		Stretching	Bending	Stretching	Bending
1	**C=H**	3000-3100		3052,3013	
2	**N-H**	3100-3500		3430	
3	**O-H**	2400-3400		2950-2802	
4	**C=-N**	2240-2260		2368	
5	**C=O**	1630-1680			1634
6	**N-H**	1550-1640		1584	
7	**C=C**	1475-1600			1477
8	**-CH_3**		1375-1450		1434
9	**C-N**	1000-1350		1328	
10	**C-O**	1000-1300		1008,1140,1247,1287	

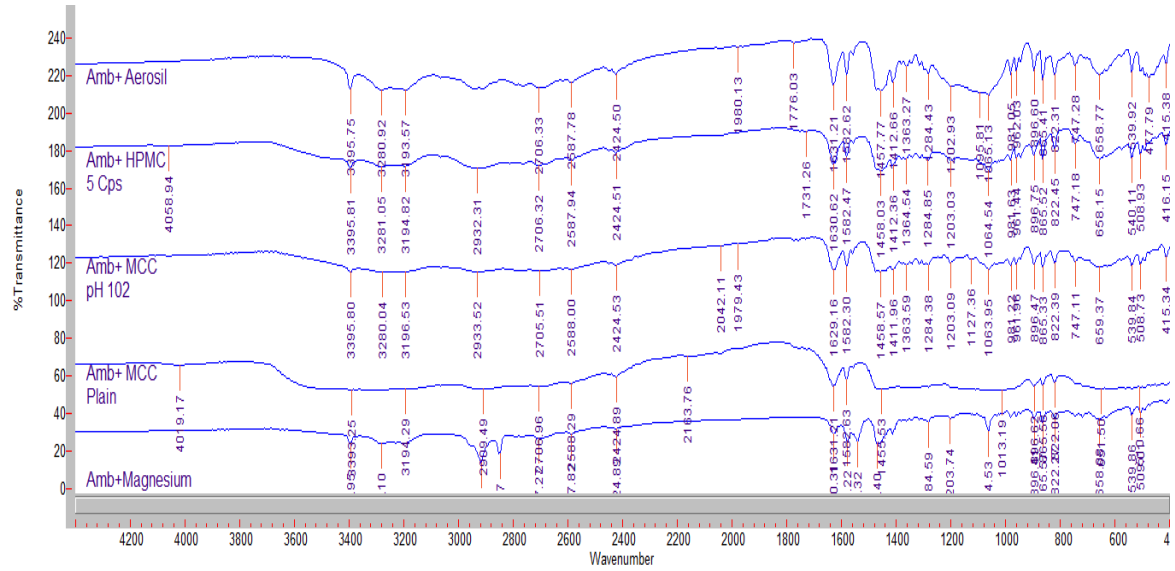
FTIR peaks of Desloratadine



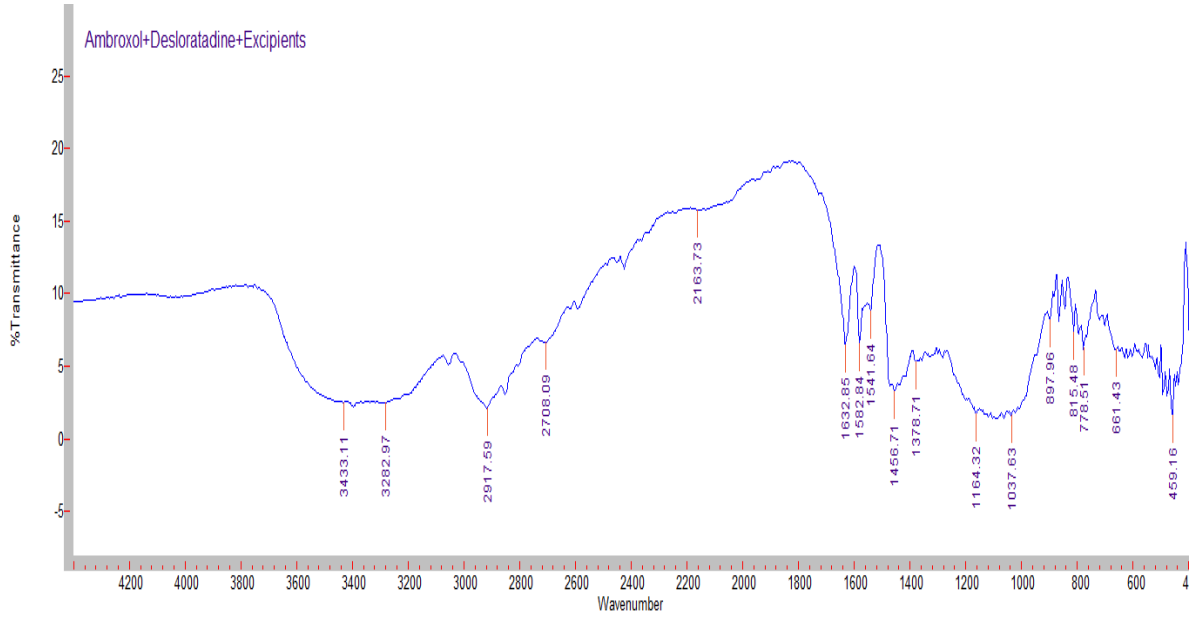
FTIR Study of Ambroxol HCl + Desloratadine



FTIR Spectra of Ambroxol HCl with various polymers.



FTIR study of Ambroxol HCl + Desloratadine + Excipients.



CONCLUSION

Finally, the present study attained successful formulation and evaluation of bilayer tablet of Ambroxol Hydrochloride for sustained release and Desloratadine for immediate release for moderate seasonal allergic rhinitis. Final prepared bilayer tablet in combination with HPMC polymer show sustained release of Ambroxol HCl in 6 hours (89.04%) and immediate release layer of Desloratadine shows dissolution of 96.94% in 30 minutes with superdisintegrant. The method employed for formulation was found to be economical and industrially feasible.

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