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Research Article

FORMULATION AND EVALUATION OF ITOPRIDE HCL SUSTAINED RELEASED PELLETS

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ABSTRACT

The present work was aimed at formulation development, evaluation and comparative study of the effects of ethyl cellulose in Itopride HCL CR pellets. The controlled release polymers used for the present study were Ethylcellulose N-14 and Ethylcellulose N-20. The formulated pellets were evaluated for various pellet properties, like hardness, bulk density, tapped density, cars index and dissolution rate. Comparative evaluation of the above-mentioned parameters established the superiority of the pellets formulated with Ethylcellulose those formulated with different grades.

Keywords: "PPI"s, Laryngopharyngeal,

INTRODUCTION

A peptic ulcer is a hole in the Gut lining of the stomach, duodenum, or esophagus. A peptic ulcer of the stomach is called a gastric ulcer of the duodenum, a duodenal ulcer, and of the esophagus, an esophageal ulcer. An ulcer occurs when the lining of these organs is corroded by the acidic digestive juices which are secreted by the stomach cells.

Peptic ulcer disease is common, affecting millions of Americans yearly Proton pump inhibitors (or "PPI"s) are a group of drugs whose main action is a pronounced and long-lasting reduction of gastric acid production.

These drugs are utilized in the treatment of many conditions such as Dyspepsia, Peptic ulcer disease (PUD), Gastroesophageal reflux disease Laryngopharyngeal Reflux Disease, Barrett's esophagus, prevention of stress gastritis. Gastrinomas and other conditions that cause hypersecretion of acid, Zollinger-Ellison syndrome.

Proton pump inhibitors act by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system (the H+/K+ ATPas) or more commonly just gastric proton pump) of the gastric parietal cell. The proton pump is the terminal stage in gastric acid secretion, being directly responsible for secreting H+ ions into the gastric lumen, making it an ideal target for inhibiting acid secretion.

MATERIALS AND METHODS

Materials

Itopride HCL (purity 99%) was procured from Cipla pharmaceutical, Mumbai and PVPK_30 from VAV Life Science Pvt. Ltd. Mumbai, India. Hydroxy Propyl Methyl Cellulose (grade 1) (AR), Buffer Solution pH-7 (LR), Chloroform (LR), Di-methyl Sulphoxide (LR), Buffer Solution pH-4 (LR), Dichloromethane (AR) was purchased from Central Drug House (P) Ltd. New Delhi, India. Hydroxy Propyl Methyl Cellulose (grade 2) (LR) and Talc was purchased from E. Merck Ltd., Mumbai, India. All other chemicals and solvents were of analytical reagent grade.

Methods

Pre-formulation Study

Physical Characteristic

Determination of bulk density and tap density

An accurately weighted quantity of the powder (W) was carefully poured into the granulated cylinder and volume (V_o) was measured. Then the graduated cylinder was closed with lid .set into the density determination apparatus (bulk density apparatus)the density apparatus was set for 500 taps,750 taps , and 1250 taps.

After that the volume (V_f) was measured and continued the operation till the two consecutive reading were equal. The bulk density and the tapped density were calculated using the formulas.

Bulk Density – W/V_o

Tapped Density- W/V_f

Where W- Weight of the powder

V_o - Initial volume (s)

V_f - Final volume.

Bulk density of ItoprideHCl powder was found to be 0.39g/ml.

Tap density of ItoprideHCl powder was found to be 0.62g/ml.

Hausner ratio

It indicates the flow properties of the powder and measured by the ratio of Tapped density to bulk density.

Hauser ratio- Tapped density /Bulk density

Table No 1: Range of hausner ratio and its properties

No.	Hausner ratio	Properties
1	0-1.2	Free flowing
2	1.2-1.6	Cohesive powder

Itopride HCl is cohesive powder .And hausner ratio was found to be 0.63g/ml.

Sieve Analysis

The main aim of sieve analysis was to determine the different size of drug Particles present. series of standard sieve were stacked one above the other so that sieves with larger pore size (less sieve number)occupy top position followed by sieve of decreasing pore size (large sieve number) towards the bottom.

Procedure

A series of sieves were arranged in the order of their deceasing pore diameter (increasing sieve number) i.e. sieve no. ASTM 40, 60, 80, 100 with 40grams of drug were weighed accurately and transferred

to sieve 40 which were kept on top. The sieves were shaken for about 5-10 minutes.
Then the drug retained on each sieves were taken, Weighted separately and expressed in terms of percentage 69.4% itoprideHCl powder pass through sieve 100 (NLT 65% should pass through 100 mesh).

Solubility- freely soluble in water, methanol.
Melting Point-192°C
Description- white power.

METHODS OF PREPARING PELLETS

Compaction and drug layering are the most widely used pelletization techniques in harmaceutical industry. Of the compaction techniques, extrusion and spheronization is the most popular method. Recently, however, melt pelletization has been used frequently in making compaction pellets using a different type of equipment, e.g. a high-shear mixer. Other pelletization methods such as Solution Layering

SOLUTION LAYERING

Solution and suspension layering involves the deposition of successive layers of solution or suspensions of drug substances and binder over the starter and non-peril seeds, which is an inert material or crystals and granules of the same drug. In fact the coating process involved in general is applicable to solution or suspension layering technology.

Consequently conventional coating pans, fluidized beds, centrifugal granulators, wurster coaters have been used successively to manufacture pellets by this method. The

Formulation and development of pellets

In this method mainly 3 steps

A. Drug Loading
B. Seal Coating
C. S.R Coating

Drug Loading

Solution1: Required quantity of drug (Itopride hcl)was dissolved in isopropyl alcohol (IPA).to this solution add tri ethyl citrate , pvpk_30,talc, titanium dioxide, mix properly then filtrate the solution .

Drying

Dry the solution at 45c for 2hours.

Soiution2 (Seal coating):

Required quantity of HPMC in isopropyl alcohol and add methyl dichloride

Drying

S.R Coating

In S.R Coating ethyl cellulose dissolved in isopropyl alcohol and methiline dichloride. HPMC is soluble in water and then add isopropyl alcohol.

Spraying

Drying

Shifting or sieving

Filling capsule according to weight

Table 2: Formulation of Itopride HCl pellets

Ingredients	IPF
Itopride HCl	9g
PVPK-30	3g
Talc	3g

COATING EQUIPMENTS

CONVENTIONAL PAN SYSTEM

The standard coating pan system consists of a circular metal pan mounted somewhat angularly on a stand, the pan is rotated on its horizontal axis by a motor, the hot air is directed into the pan and onto the bed surface, and is exhausted by means of ducts positioned through the front of the pan .Coating solutions are applied by spraying the material on the bed surface.

EVALUATION OF ENTERIC COATED PELLETS:

DISSOLUTION STUDIES OF ITOPRIDE PELLETS

Parameter for Dissolution Study
Apparatus Tablet dissolution tester USP
Method USP Type II Apparatus (Paddle Method)

Dissolution medium 0.1 N Hydrochloric acid (900 ml)

Temperature -37 + 0.5° C

Speed-50 rpm

in-vitro release studies were carried out in the dissolution test apparatus (USP Type II). The tests were carried out in 900 ml of 0.1N HCl for 12 hrs at 50 rpm at 37±0.5oC. 10 ml of the aliquot were withdrawn at different predetermined time intervals (0.5, 1, 2, 4, 6, 8, 10, 12 hr) and filtered.

The required dilutions were made with 0.1N HCl and the solution was analyzed for the drug content by UV spectrophotometer detecting at λ max 247 nm, 0.1N HCl was replaced in the vessel after each withdrawal to maintain sink condition. From this percentage drug release was calculated and this was plotted against function of time to study the pattern of drug release.

PROCEDURE

One tablet was placed to each of the six dissolution vessel containing 900 ml of dissolution medium. The apparatus was run for 24 hours. After each specified interval, 10 ml of sample was withdrawn and the solution was filtered through membrane filters.

Table 3: Release studies of Coating of Itopride HCl pellets with Ethyl cellulose N-20

Time(Hrs)	IPF1	IPF2	IPF3	IPF4	IPF5	Marketed
1	61	46	26	12	10	19
3	76	58	44	36	26	35
6	95	72	63	45	34	65
9	95	88	81	59	51	76
12	95	96	94	76	66	87

Table 4: Release studies of Coating of Itopride HCl pellets with Ethyl cellulose N-50

Time(Hrs)	IPF6	IPF7	IPF8	IPF9	IPF10	Marketed
1	55	35	18	11	8	19
3	72	56	38	25	19	35
6	88	69	67	42	32	65
9	92	82	83	57	49	76
12	94	95	97	71	62	87

RESULTS AND DISCUSSION

STANDARD CURVE FOR ITOPRIDE HCL

Table No.5: Conc. and absorbance for standard curve

Conc	Abs
10	0.124
20	0.241
30	0.346
40	0.465
50	0.587
60	0.715

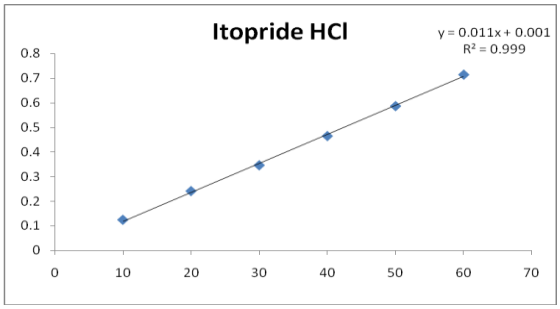


Fig 1: Standard Curve of Etopride HCL

in-vitro DISSOLUTION TEST

The percentage of drug release of the no. of pellets in each capsule in Different Trials

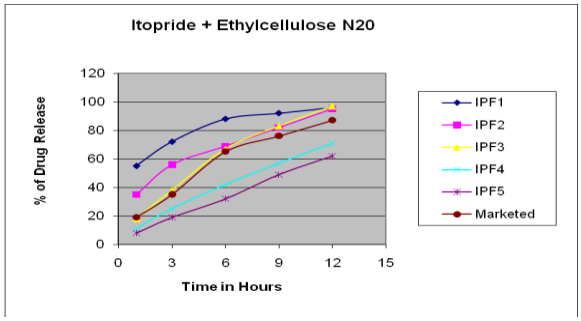


Fig 2: Comparative study of percentage drug release with Innovator product

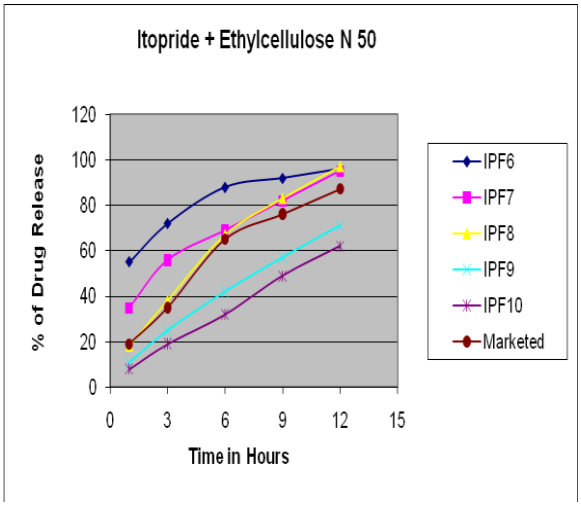


Fig 3: Comparative study of percentage drug release with Innovator product from Top-spray, Tangential-spray Bottom-spray equipment

DESCRIPTION– Fine Spherical shape having sr coated pellets.

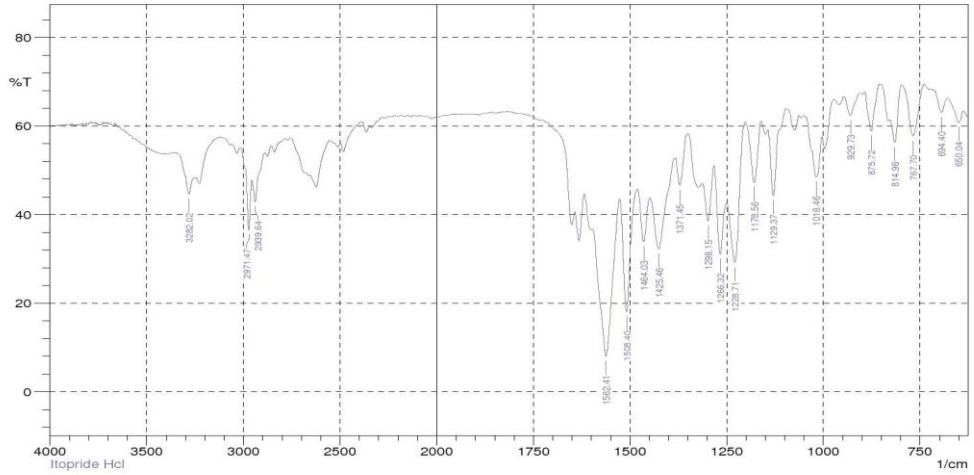
DIMENSIONS– Size of the pellets in the range of 1.28 -1.40 mm determine by using vernier caliper.

HARDNESS– Hardness of pellets in the range of 9 -17 N determined by Dr.Schieuniger hardness tester.

Table No.6 Hardness of pellets of different formulation

Formulation	F1	F2	F3	F4	F5
Hardness (N)	9	N10	N14	N17	N17 N

SPECTRAL ANALYSIS



No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	650.04	60.77	3.414	680.9	638.47	8.396	0.403
2	694.4	63.016	3.917	722.37	680.9	7.534	0.401
3	767.7	57.725	11.646	797.6	738.77	11.42	2.075
4	814.96	56.271	8.547	828.46	797.6	6.549	0.815
5	875.72	58.836	9.7	893.08	855.47	7.342	1.184
6	929.73	62.387	4.575	946.12	904.65	7.791	0.587
7	1018.46	48.458	10.689	1050.29	1003.03	12.315	1.808
8	1129.37	44.267	16.257	1142.87	1096.58	11.973	2.2
9	1178.56	47.201	13.808	1201.7	1161.2	10.74	2.042
10	1228.71	29.141	21.478	1249.93	1201.7	18.793	4.761
11	1266.32	31.088	15.73	1282.72	1249.93	13.47	2.604
12	1298.15	38.546	10.523	1313.58	1282.72	11.075	1.522
13	1371.45	46.635	7.969	1382.06	1350.23	9.105	0.958
14	1425.46	32.295	14.627	1448.6	1382.06	25.602	4.433
15	1464.03	33.889	10.843	1480.43	1448.6	12.877	1.763
16	1508.4	18.066	26.303	1526.72	1481.39	22.424	6.522
17	1562.41	8.084	32.048	1598.09	1527.69	46.899	18.874
18	2939.64	42.829	6.391	2955.07	2888.53	20.952	1.36
19	2971.47	36.576	13.195	3015.83	2955.07	19.888	2.285
20	3282.02	44.685	5.546	3354.35	3246.34	32.935	1.45

Comment;
Itopride Hcl

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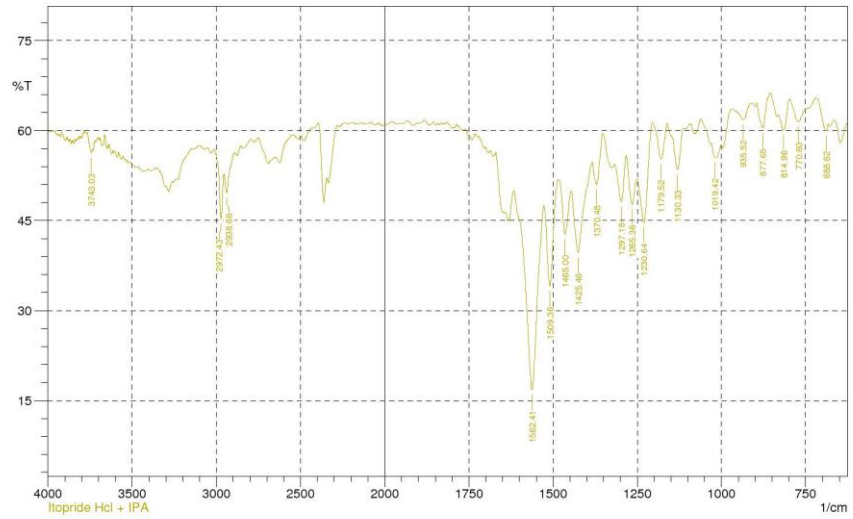
ITOPRIDE HCL



No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	688.62	60.044	1.695	717.55	683.79	6.92	0.204
2	770.6	61.495	2.989	797.6	743.59	10.846	0.553
3	814.96	60.096	3.717	830.39	797.6	6.821	0.438
4	877.65	60.438	4.856	895.01	854.5	8.106	0.638
5	935.52	61.841	2.287	967.34	909.48	11.584	0.399
6	1019.42	55.5	2.285	1031	1001.1	7.453	0.322
7	1130.33	53.523	7.146	1161.2	1112.97	11.601	1.173
8	1179.52	55.214	6.046	1204.6	1161.2	10.151	0.919
9	1230.64	44.621	11.551	1251.86	1204.6	13.859	2.126
10	1265.36	47.692	5.947	1282.72	1251.86	9.119	0.822
11	1297.18	48.087	7.147	1317.44	1282.72	9.992	1.007
12	1370.48	51.044	5.828	1383.98	1353.12	8.292	0.786
13	1425.46	39.694	11.841	1445.71	1383.98	20.421	3.052
14	1465	42.713	8.194	1483.32	1445.71	12.318	1.278
15	1509.36	34.06	15.21	1527.69	1483.32	16.417	2.908
16	1562.41	16.832	31.608	1616.42	1527.69	42.167	14.425
17	2938.68	49.614	4.059	2955.07	2890.45	17.812	0.797
18	2972.43	45.328	8.681	3011.98	2955.07	16.312	1.436
19	3743.03	56.298	0.813	3750.74	3737.24	3.331	0.051

Comment;
Itopride Hcl + IPA

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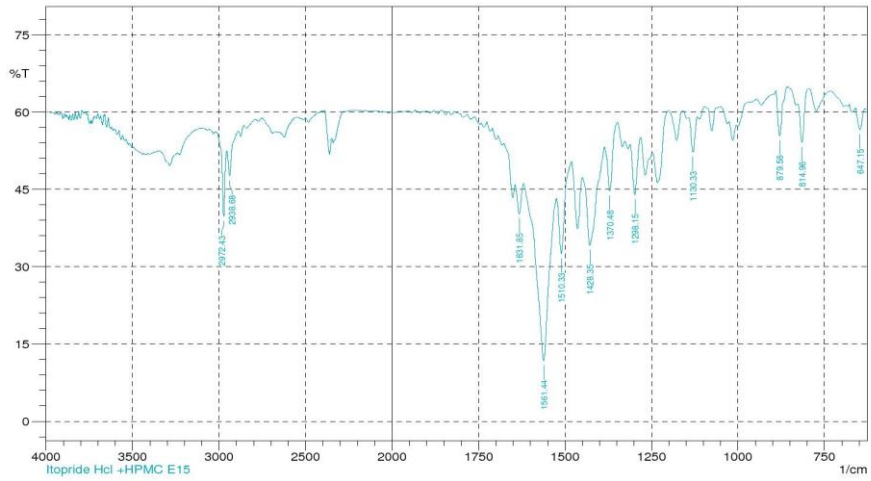
ITOPRIDE HCL with IPA



No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	647.15	56.634	4.107	659.68	630.75	6.696	0.428
2	814.96	54.15	8.553	827.5	794.71	7.33	0.759
3	879.58	55.398	8.963	890.19	857.4	7.165	0.922
4	1130.33	52.243	6.76	1142.87	1117.8	6.361	0.616
5	1298.15	43.944	10.355	1311.65	1281.75	9.177	1.262
6	1370.48	44.683	10.501	1385.91	1348.3	10.902	1.303
7	1428.35	34.13	15.128	1449.57	1385.91	23.429	4.353
8	1510.33	32.545	13.099	1524.79	1481.39	16.499	2.149
9	1561.44	11.78	32.575	1619.31	1524.79	50.68	17.573
10	1631.85	40.244	5.737	1644.39	1619.31	9.135	0.674
11	2938.68	47.619	5.757	2955.07	2888.53	18.512	0.873
12	2972.43	39.735	13.671	3021.62	2955.07	19.632	1.968

Comment;
Itopride Hcl +HPMC E15

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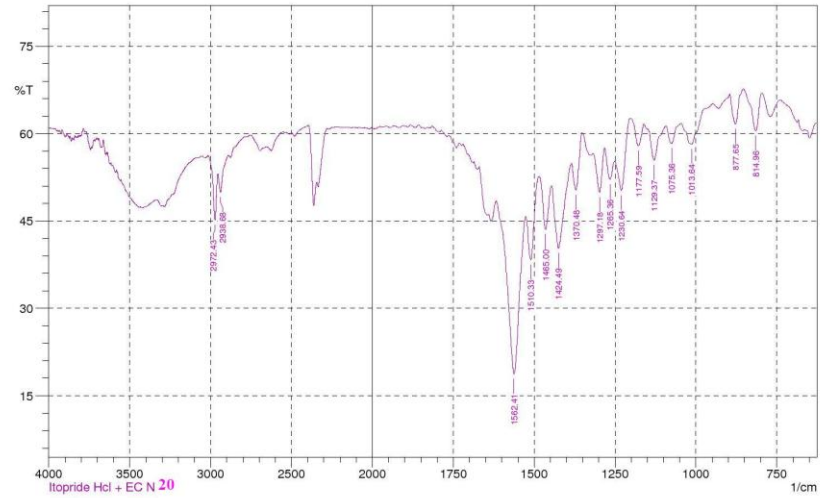
ITOPRIDE HCl with HPMC E15



No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	814.96	60.495	6.713	853.54	796.64	10.898	1.124
2	877.65	61.639	5.526	895.01	853.54	7.874	0.725
3	1013.64	58.195	2.117	1031.96	999.17	7.503	0.304
4	1075.36	58.325	3.12	1091.76	1045.46	10.22	0.449
5	1129.37	55.441	6.036	1160.23	1091.76	15.601	1.125
6	1177.59	57.916	4.115	1203.63	1160.23	9.54	0.569
7	1230.64	50.263	8.168	1250.89	1203.63	12.279	1.395
8	1265.36	52.148	4.14	1282.72	1250.89	8.458	0.537
9	1297.18	49.973	7.162	1317.44	1282.72	9.452	0.992
10	1370.48	50.356	6.788	1383.98	1352.16	8.576	0.922
11	1424.49	40.284	12.096	1445.71	1383.98	20.279	3.239
12	1465	43.531	8.308	1484.29	1445.71	12.306	1.296
13	1510.33	38.311	10.025	1525.76	1484.29	14.549	1.736
14	1562.41	18.755	28.043	1616.42	1526.72	42.836	13.452
15	2938.68	49.975	3.915	2955.07	2889.49	17.913	0.708
16	2972.43	45.167	8.797	3016.8	2955.07	17.758	1.545

Comment;
Itopride Hcl + EC N 15

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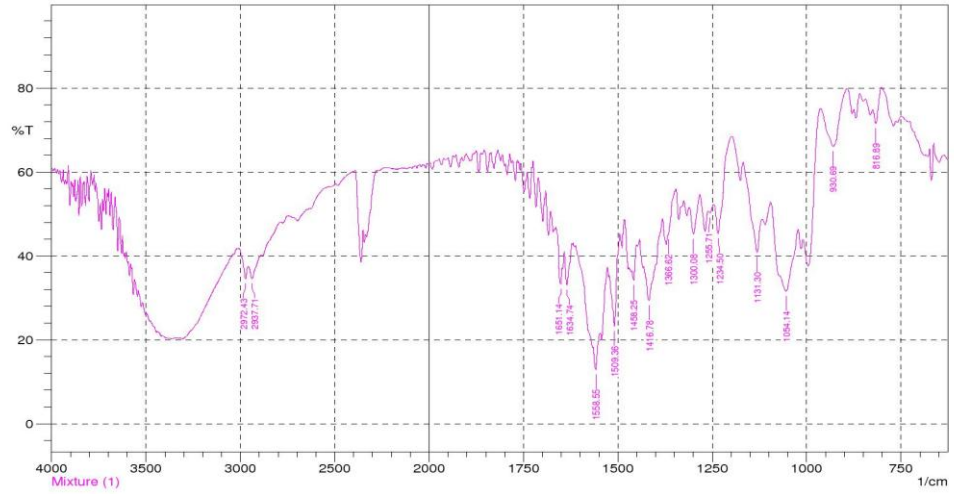
ITOPRIDE HCL WITH EC N20



No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	816.89	71.565	5.034	824.6	801.46	2.875	0.305
2	930.69	66.145	11.21	963.48	893.08	10.14	2.338
3	1054.14	31.583	7.616	1071.5	1022.32	21.622	2.29
4	1131.3	40.817	11.52	1168.91	1117.8	15.454	2.229
5	1234.5	45.325	10.86	1246.07	1197.85	12.074	1.324
6	1255.71	50.27	0.993	1260.54	1246.07	4.227	0.06
7	1300.08	45.204	7.547	1310.69	1282.72	8.6	0.91
8	1366.62	45.025	0.526	1367.59	1346.37	6.204	-0.146
9	1416.78	29.337	8.383	1431.24	1399.42	15.064	1.598
10	1458.25	34.2	4.63	1463.07	1450.53	5.401	0.332
11	1509.36	23.253	16.845	1522.87	1494.9	13.799	2.659
12	1558.55	12.957	6.529	1565.3	1547.94	13.527	1.306
13	1634.74	33.064	8.632	1641.49	1622.2	8.327	1.056
14	1651.14	33.289	6.354	1659.82	1647.28	5.454	0.603
15	2937.71	34.552	3.713	2958.93	2888.53	30.181	1.226
16	2972.43	34.58	4.075	3007.15	2958.93	20.251	0.828

Comment;
Mixture (1)

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MIXTURE

- There is no interaction in between Drug and excipients.
- In the Dissolution report Ethylcellulose N-50 (4%) IPF8 shows better release studies.

CONCLUSION

The present work on as controlled drug delivery system for ItoprideHCl from the present study, it can be concluded that Ethylcellulose N-50 grade was shows better Drug release studies using 4% Solution for controlled release of ItoprideHCl and there is no interaction observed in Infrared Spectroscopy.

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