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FORMULATION DEVELOPMENT AND INVITRO EVALUATION OF IMMEDIATE RELEASE TABLETS OF BIPERIDEN HCL CYCLODEXTRIN COMPLEXES

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ABSTRACT

Biperiden HCl is an Anticholinergic agent using in the management of all kinds of Parkinson's disease. It is very slightly soluble in water. In the present study attempt has been made to prepare and characterize inclusion complex of Biperiden HCl with β-Cyclodextrin. The phase solubility analysis indicated he formation of 1:1 molar inclusion complexes. Apparent stability constant (Kc) was found o be 164.557 M-1. The inclusion complexes prepared by different methods viz. Physical mixture, Kneading and Solvent evaporation methods. The prepared complexes were characterized using FT-IR. For the development of Biperiden HCl tablets, the excipients selected were Starlac as diluents, Croscarmellose sodium and Sodium Starch Glycolate, crosprovidon as super disintegrants, microcrystalline cellulose (MCC) as binding agents, Aerosil as glidant, Magnesium Stearate as lubricant. The formulation blend was evaluated for Precompression studies and compressed tablets were evaluated for post compression studies and the results were found to be within the limits. The compatibility studies were performed which resulted in no interactions between drug and excipients.

KEYWORDS

Biperiden Hydrochloride, β-Cyclodextrin, Starlac, Crospovidone and Croscarmellose sodium.

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INTRODUCTION

The poor dissolution of relatively insoluble drugs has a major pharmacokinetic problem in the oral dosage form. This limits aspects such as absorption and bioavailability. Therefore several approaches have been followed in improving the solubility of drugs, on being complexation using cyclodextrin1-2. Amongst the existing Cyclodextrin, β-Cyclodextrin (β-CD) has been used extensively to modify their physicochemical properties3-4.

Biperiden HCl is a piperidine derivative coming under the class of anticholinergics commonly used in the management of all kinds of Parkinson's diseases (PD).

MATERIAL AND METHODS[1,2,4,5,6]

Materials

Biperiden HCl was obtained as a gift sample from S.K Healthcare Pvt. Ltd, Hyderabad, β-Cyclodextrin was obtained from NU Therapeutics Pvt Ltd, Hyderabad, Sodium starch glycolate, Cross povidone, SSG, MCC, Starlac, Magnesium Stearate, Aerosil were obtained from Richer Pharmaceuticals Pvt Ltd, Hyderabad.

Methods

Phase-solubility-studies

Phase solubility studies were carried out at room temperature (25°) in triplicate according to the method reported by Higuchi and Conners[5]. Excess amount of Biperiden HCl was added to distilled water containing various concentrations of β -CD (0-15 mM) in a series of stoppered conical flasks and shaken for 48 h on a rotary flask shaker. The suspensions were filtered through Whatman No.1 filter paper and assayed for Biperiden HCl using a UV/Vis spectrophotometer (Shimadzu, UV 1601) at 258 nm against blanks prepared using same concentration of β -CD in distilled water[7-9].

Preparation of complex of Biperiden HCl with βcyclodextrin.

Physical mixture

Biperiden HCl with β-CD in different molar ratios (i.e. 1:1M, 1:2M) were mixed in a mortar for about one hour with constant trituration, passed through sieve No. 80 and stored in a desiccators over fused calcium chloride in Table No.1.

Kneading method

Biperiden HCl with β-CD in different molar ratios (1:1M, 1:2M) were taken. First cyclodextrin is added to the mortar, small quantity of 50 % ethanol is added while triturating to get slurry like consistency. Then slowly drug is incorporated into the slurry and trituration is further continued for one hour. Slurry is then air dried for 24 h, pulverized and passed through sieve No. 80 and stored in desiccators over fused calcium chloride.

Solvent evaporation Method

Drug and cyclodextrin in different molar ratio are dissolved in a common solvent to get a clear solution. Mixed the both solutions than the clear solution was kept for stirring on a magnetic stirrer till all the solvent got evaporated. The mass obtained was dried at 50°C and further sieved No. 80 or 100 sieve.

Evaluation of Bi-Hcl Inclusion Complexes

Drug Content Estimation[4]

Inclusion complexes prepared by above methods were assayed for Bi-HCL content by dissolving a specific amount of the complexes (Drug Equivalent to 2mg) in methanol and analyzing for the Bi-HCL content spectrophotometrically at 258 nm on a spectrophotometer.

In-vitro dissolution profile

Dissolution studies were carried out by USP Paddle method at 37 ± 0.5°C, taking 500 ml of 0.1 N HCl as dissolution medium. Speed of rotation of the paddle was set at 50 rpm. The absorbance was measured at 258 nm in a Shimadzu UV-Spectrophotometer in Table No.2.

Compression of biperiden hcl-β-cyclodextrin inclusion complexes into immediate release tablets by direct compression method

After elucidation of best inclusion complex of drug with β-cyclodextrin which shows the most satisfactory *in vitro* dissolution criteria and better solubility criteria, the particular complex was formulated as Immediate Release Tablets of Bi-HCL β-cyclodextrin Inclusion Complex by mixing it with selected excipients. In this present study, the best superdisintegrant among sodium starch glycolate (SSG), Crospovidone (CP), and croscarmellose sodium (CCS) were also screened out. Starlac selected as diluent, MCCPH101 as binder, Aerosil as glidant and Magnesium stearate selected as lubricant in Table No.3 and 4.

Evaluation of Pre-Compression Characteristics of Tablet Blend

Pre compression parameters

The prepared tablet blend was evaluated for Precompression parameters like Bulk density, Tapped density, compressibility index, Angle of repose and Hausner's ratio to know the flow ability of blend[10-12].

Evaluation of prepared tablets

The IR tablets so prepared were evaluated for parameters like hardness, friability, drug content uniformity, weight variation, wetting time, *in vitro* disintegration and *in vitro* drug release studies. Hardness of the three tables of each batch was checked by using Monsanto hardness tester and the data were shown in table.

***In-vitro* dissolution profile**

Dissolution studies were carried out by USP Paddle method at 37 ± 0.5°C, taking 500 ml of 0.1 N HCl as dissolution medium. Speed of rotation of the paddle was set at 50 rpm. The absorbance was measured at 258 nm in a Shimadzu UV-Spectrophotometer.

Mathematical Modeling of Dissolution Data The release data obtained were fitted into various mathematical models to know which mathematical model was best to fit the obtained release profile. The parameters; the time exponent (n), the release 2 rate constant (k), the regression coefficient (R), were determined for Korsmeyer-Peppas equation to know the release mechanism. The various models studied were,

- Zero order
- First order
- Higuchi model and
- Peppas model

The results of in-vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows,

1. Cumulative % of drug released Vs Time (zero order kinetic model).
2. Log cumulative percent drug remaining to be absorbed Vs Time (First order model).
3. Cumulative % of drug released Vs Square root of time (Higuchi model).
4. Log % drug release Vs Log time (Peppas model).

RESULTS AND DISCUSSION

Dissolution, assay and Physical appearance studies of selected formulation F6 and of Bi-Hcl complexes prepared by Kneading method (BK2) were carried out after subjecting the formulation for stability study. From the data, the formulation is found to be stable under the conditions mentioned before since there was no significant change in the percentage amount of drug content. In the present work, complexation of Biperiden HCl with β-cyclodextrin was tried in an attempt to improve its solubility and dissolution rate, he phase solubility studies revealed a linear relationship between the aqueous drug solubility with increasing in β-CD concentration shown in Table No.5 to 11 and Figure No.1 to 4.

Table No.1: Drug content Estimation

S. No	Complexation method	Drug: cyclodextrin Ratio	Complex Code	Amount of drug present in 2mg Equivalent powder	%Drug content
1	Physical Mixture Method	1:1	BP1	2.02	101
		1:2	BP2	1.967	98.35
2	Kneading Method	1:1	BK1	2.044	102.2
		1:2	BK2	1.988	99.4
3	Solvent Evaporation Method	1:1	BS1	2.002	101.1
		1:2	BS2	2.04	102

Table No.2: Comparison of In-vitro dissolution data of all complexes (Pure drug-BS2)

S.No	Time (min)	% CDR						
		Pure drug	BP1	BP2	BK1	BK2	BS1	BS2
1	0	0	0	0	0	0	0	0
2	5	6.52322	36.5778	39.6516	42.0423	53.6543	38.9685	47.8483
3	10	20.5479	55.3620	58.4357	58.4357	74.1461	56.3866	56.0450
4	15	25	59.8019	63.5587	76.1953	82.3429	72.4385	77.2199
5	30	26.0274	62.1926	78.2445	82.0013	85.4166	76.5368	79.2691
6	45	27.7397	74.1461	81.3183	83.3674	90.8811	80.2937	82.6844
7	60	28.0821	79.6106	83.3674	86.0997	93.9549	82.0013	87.4658

Table No.3: Batches prepared for screening of superdisintegrant

S.No	Ingredients	F1	F2	F3	F4
1	Complexed drug (Bi-HCL : β-CD)	5.89	5.89	5.89	5.89
2	Starlac	68.51	66.91	66.91	66.91
3	MCCPH101	20	20	20	20
4	SSG	-	1.6		
5	Crospovidone	-	-	1.6	-
6	CCS	-	-	-	1.6
7	Mag. Stearate	3.6	3.6	3.6	3.6
8	Aerosil	2	2	2	2
9	Total Wt	100	100	100	100

Table No.4: Batches prepared for screening of concentration of superdisintegrant

S.No	Ingredients	F5	F6	F7	F8
1	Biperiden HCl	-	-	-	2
2	Complexed drug **(Bi-HCL - β-CD**)	5.89	5.89	5.89	-
3	Star Lac	65.31	63.71	67.4	67.6
4	MCCPH101	20	20	20	20
5	SSG	3.2	4.8	7	4.8
6	Mag. Stearate	3.6	3.6	3.6	3.6
7	Aerosil	2	2	2	2
8	Total Wt	100	100	100	100

Table No.5: Results of pre-compression parameters of tablet blend

S.No	Formulation code	F1	F2	F3	F4	F5	F6	F7	F8
1	**Angle of repose (Avg±S.D)**	34.61±0.923	33.28±0.395	33.55±0.596	34.21±0.602	34.45 ±0.4	32.08± 0.78	33.48± 0.39	33.55±0.596
2	**Bulk density (Avg±S.D)**	0.563±0.0097	0.553±0.0069	0.565±0.004	0.572±0.0034	0.574 ± 0.006	0.572 ±0.007	0.563± 0.0069	0.545 ±0.004
3	**Tapped density (Avg±S.D)**	0.627 ±0.004	0.635 ±0.0046	0.646±0.0046	0.651±0.0046	0.660 ± 0.005	0.663 ±0.007	0.625± 0.0046	0.624 ±0.0046
4	**Compressibility index**	13.20	12.91	12.53	11.82	12.63	12.20	13.19	13.23
5	**Hausner's ratio**	.113	1.148	1.143	1.134	1.14	1.15	1.158	1.153

Table No.6: Results of Post-compression parameters

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8
Hardness (avg ±S.D)	3.46±0.0577	3.23±0.0577	3.26±0.057	3.3±0.057	3.33±0.057	3.23±0.115	3.23±0.0577	3.26±0.057
Thickness (avg ±S.D)	2.513±0.0057	2.503±0.0057	2.513±0.0057	2.513±0.0057	2.513±0.0057	2.513±0.0057	2.503±0.0057	2.513±0.0057
Friability (avg ±S.D)	0.497±0.0995	0.231±0.0571	0.264±0.0577	0.069±0.00579	0.231±0.151	0.296±0.25	0.231±0.0571	0.264±0.0577
Weight variation (avg ±S.D)	100.55 ±2.459	100.15 ±1.773	99.95 ±1.848	99.8 ±1.794	100.3 ±1.719	99.8 ±1.609	100.15 ±1.77	99.95 ±1.848
Wetting Time (Sec) (avg ±S.D	38±1.123432	24±0.3245	28±0.674302	29±0.126242	18±0.428645	10±0.224322	22±0.3245	28±0.674302
Disintegration time(avg ±S.D)	43±0.965445	27±0.624536	32±0.524238	33±0.864042	19±0.964246	16±0.452678	15±0.624536	20±0.524238
% Drug content (avg ±S.D)	101.35±008425	99.78±0.065428	99.89±0.041286	101.54±0.126422	100.62±0.102264	100.62±0.102264	99.97±0.065428	99.8±0.081286

Values are mean ± SD, n=3

Table No.7: *In vitro* drug release for all tablets formulation

S.No	Time (Min)	Formulations							
		F1	F2	F3	F4	F5	F6	F7	F8
1	0	0	0	0	0	0	0	0	0
2	5	53.9959	55.36202	54.33743	54.33743	56.38661	56.04508	56.72814	7.206284
3	10	70.7308	73.80464	72.43852	71.0724	74.82923	76.19536	75.5123	23.9726
4	15	82.6844	86.09973	84.05055	83.36749	87.46585	87.80738	88.83197	27.39726
5	30	84.7331	89.1735	86.09973	85.07514	94.29645	94.97951	95.32104	39.0411
6	45	87.8073	92.24727	88.83197	89.1735	95.66257	96.68716	96.0041	42.12329
7	60	92.9303	95.32104	94.29645	93.61339	96.34563	98.73634	97.02869	46.23288

Table No.8: Curve fitting data analysis for all tablet formulations

S.No	Formula -tion	Zero order		First Order			Higuchi		Korsemeyer-Peppas	
1		Slope (K)	R^2	Slope	(K)	R^2	Slope(K)	R^2	Slope(n)	R^2
2	F1	42.76	0.521	-0.015	1.724	0.817	22.63	0.79	0.195	0.864
3	F2	44.59	0.514	-0.0119	1.705	0.845	23.54	0.786	0.198	0.850
4	F3	43.47	0.517	-0.016	1.719	0.828	23.03	0.786	0.196	0.852
5	F4	42.98	0.524	-0.016	1.725	0.833	22.67	0.793	0.197	0.868
6	F5	48.03	0.376	-0.022	1.685	0.839	23.89	0.788	0.204	0.852
7	F6	45.67	0.528	-0.028	1.742	0.936	23.59	0.799	0.212	0.859
8	F7	46.21	0.508	-0.004	1.957	0.878	24.25	0.783	0.204	0.846
9	F8	9.504	0.824	-0.023	1.676	0.839	6.409	0.947	0.665	0.847

Table No.9: Stability data of optimized formulation BK2 stored at Room temperature and at 40^0C for six weeks

S.No	Time	Stability data of BK2 stored at Room temperature		Stability data of BK2 stored at 40^0C	
		Physical appearance(Colour)	% Drug Content at Room temperature	Physical appearance(Colour)	% Drug Content
1	First day	White	101.41	White	101.41
2	1st week	White	99.97	White	99.97
3	3rd week	White	100.46	White	100.46
4	6th week	White	101.79	White	99.89

Table No.10: Stability data of optimized formulation F6 stored at Room temperature and at 40^0C for six weeks

S.No	Time	Characteristics of optimized formulation-F6 stored at Room temperature		Characteristics of optimized formulation-F6 stored at 40^0C	
		Physical appearance (Colour)	% Drug Content	Physical appearance(Colour)	% Drug Content
1	First day	White	100.41	White	101.41
2	1st week	White	100.97	White	99.97
3	3rd week	White	99.46	White	100.46
4	6th week	White	101.59	White	99.89

Table No.11: Dissolution studies of Biperiden HCl Betacyclodextrin complex (BK2) after storage for six weeks at room temperature and at 40^0C

S.No	Time in min	%CDR of BK2 at room temperature	%CDR of BK2 at 40^0C	%CDR of F6 at room temperature	%CDR of F6 at 40^0C
1	0	0	0	0	0
2	5	54.33743	55.02049	53.2543	54.129
3	10	74.82923	74.14617	73.4223	73.546
4	15	80.97678	83.02596	80.95278	83.259
5	30	84.05055	84.05055	82.040	85.0050
6	45	90.19809	89.51503	89.98	90.1150
7	60	94.29645	94.97951	94.12	94.728

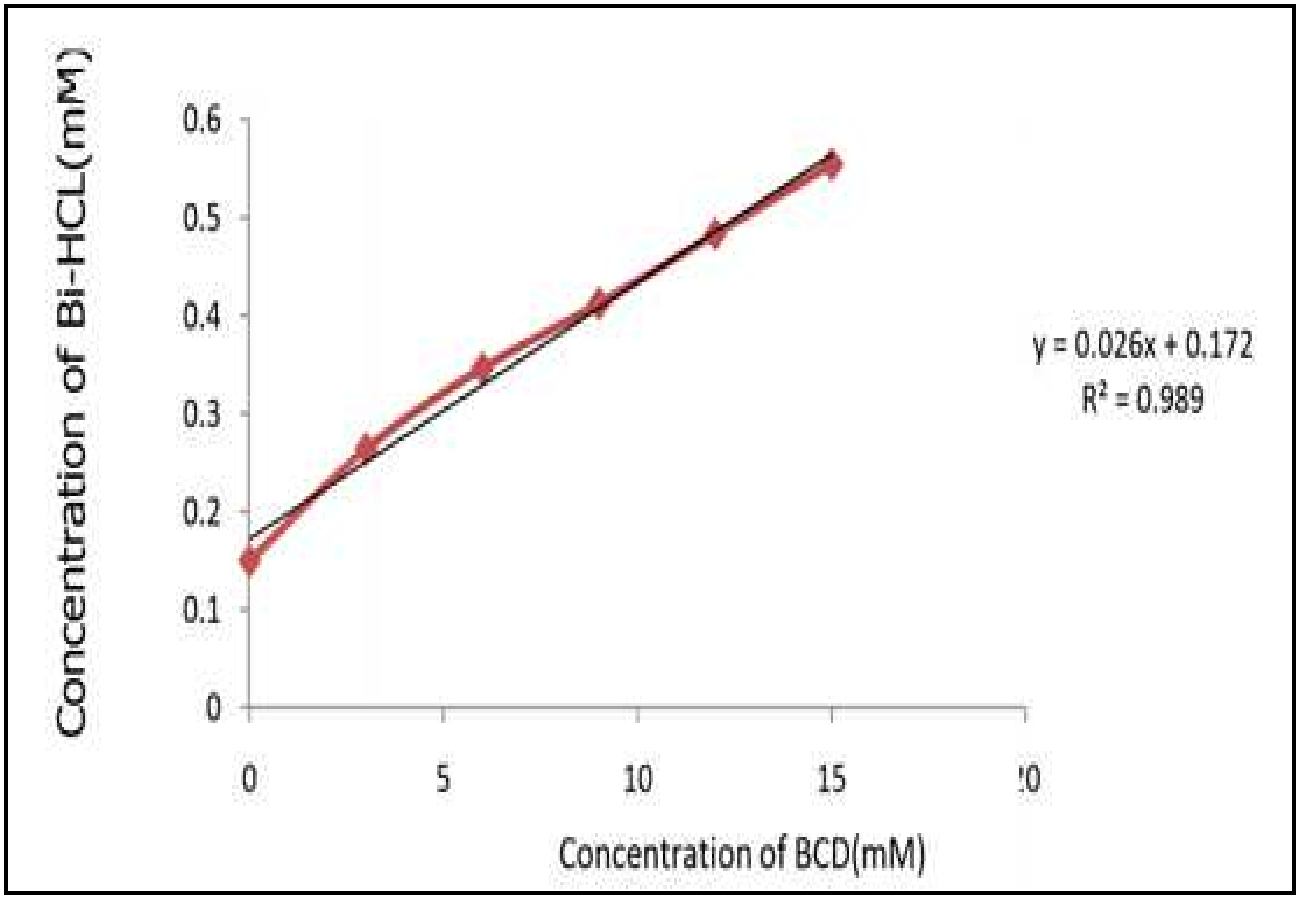

Figure No.1: Phase Solubility study

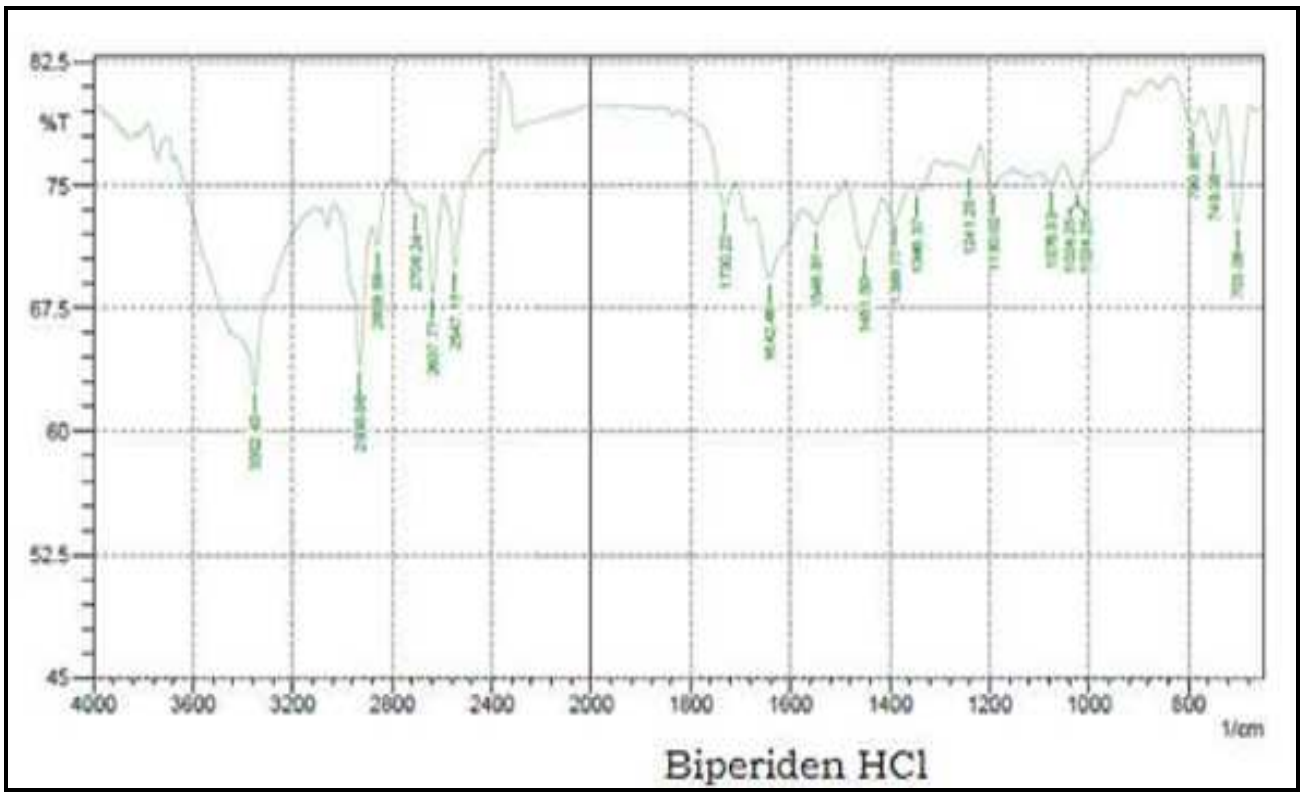

Figure No.2: FTIR of Biperiden HCl Pure drug

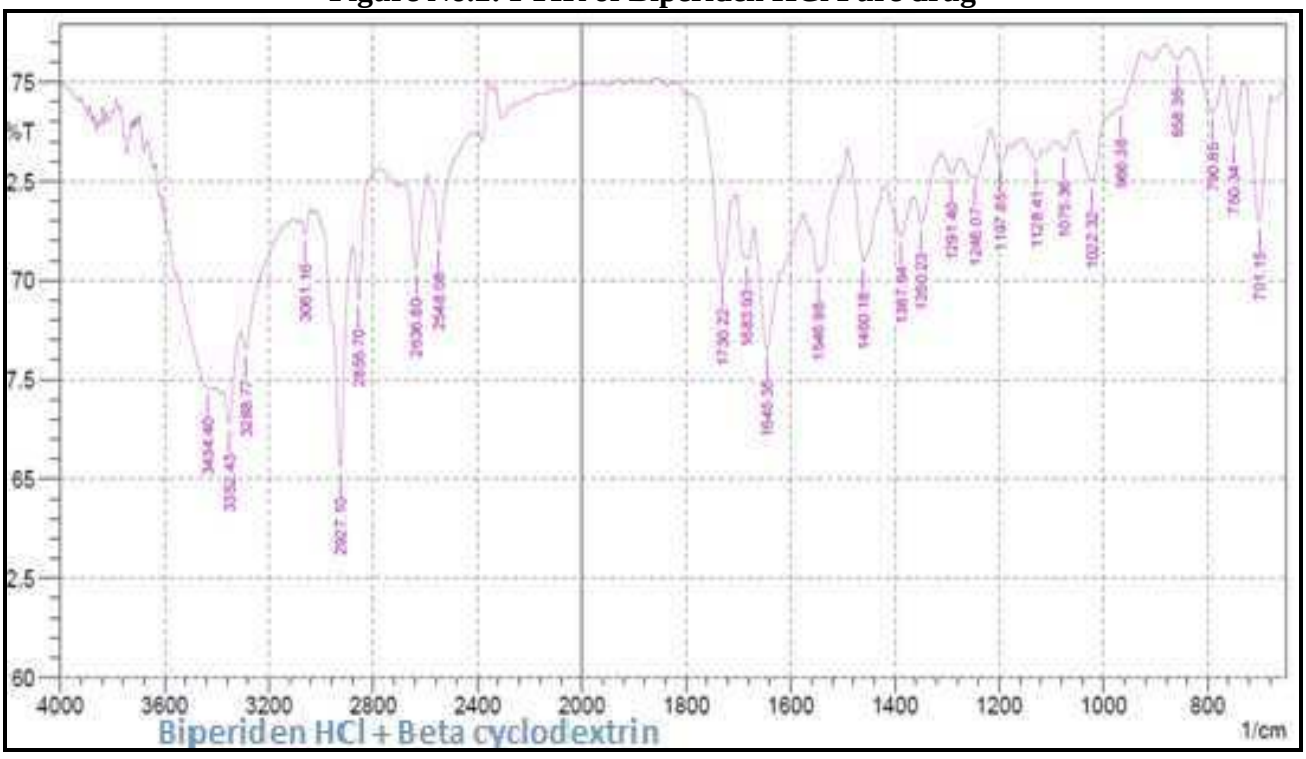

Figure No.3: FTIR of Biperiden HCl-Beta Cyclodextrin complex

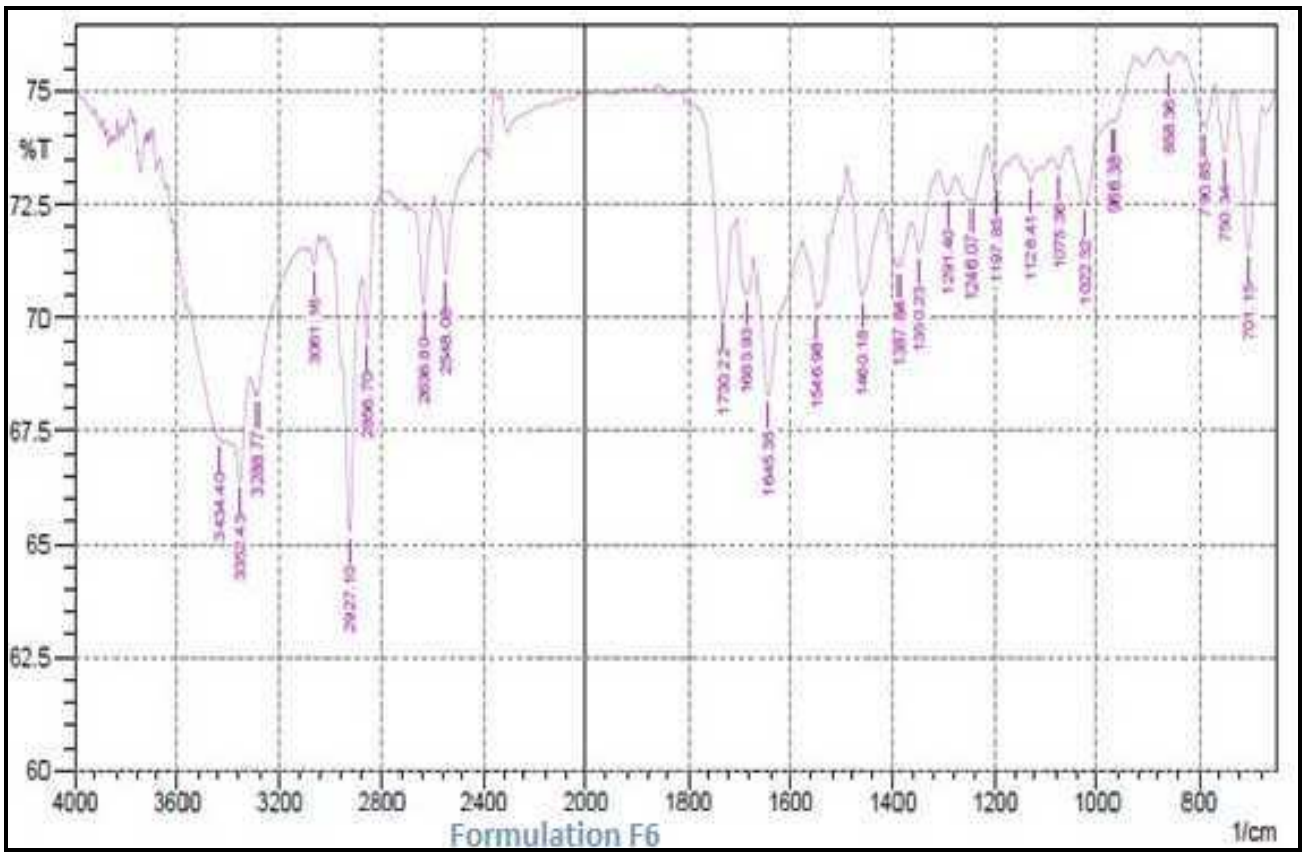

Figure No.4: FTIR of Formulation F6

CONCLUSION

The phase solubility diagram can be classified as AL type, according to Higuchi and Connors. The extent of complexation is characterized by the apparent 1:1 stability constant was calculated based on the solubility diagram and was found to be 164.557 M-1. The inclusion complex of Biperiden HCl and β-CD in molar ratio of 1:2 were prepared by kneading method (BK2) showed 93.9549 % of drug release in 60 min.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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