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EFFECT OF HYDROPHILIC POLYMERS ON INVITRO RELEASE RATE OF BUPROPION FLOATING TABLETS BY EMPLOYING EFFERVESCENT METHOD

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Abstract:
Formulation and evaluation of floating tablets of Bupropion. In the present study the formulations were prepared by direct compression method using different proportions of Chitosan, Carbopol, Ethyl Cellulose as Swellable polymers. Sodium bicarbonate is used as buoyancy-imparting agent. The prepared formulations were evaluated for different parameters during its pre-compression and Post-compression stages. The release characteristics of the formulations were studied in in-vitro conditions. The in-vitro dissolution study of formulation F5 was 98.31 % within 12 h for good release and was fitted to kinetics of drug release for R^2 value of Zero order release mechanism model is 0.982. As an extension of this work for formulation F5, bioavailability, pharmacokinetic, and in-vivo studies can be done in future to develop as suitable candidate for a novel drug delivery system.

Key words: *Bupropion, Chitosan, Carbopol, Ethyl Cellulose and Floating Tablets.*

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INTRODUCTION:

Oral delivery of drugs is the most preferable route of drug delivery. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient compliance and flexibility in formulation and cost effective manufacturing process [1]. Many of the drug delivery systems, available in the market are oral drug delivery type systems Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as:

1. Drugs with short half-life require frequent administration, which increases chances of missing dose of drug leading to poor patient compliance.
2. A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult.
3. The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the C_{ss} values fall or rise beyond the therapeutic range.
4. The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs. [2]

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits. [3]

Controlled Drug Delivery Systems:

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue. [4]

Controlled drug delivery or modified drug delivery systems are divided into four categories.

1. Delayed release
2. Sustained release
3. Site-specific targeting
4. Receptor targeting

More precisely, controlled delivery can be defined as:-

1. Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.
2. Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.
3. Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.
4. Provide physiologically/therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body. [5]

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug (Figure 1). [6] Controlled drug deliveries usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient.

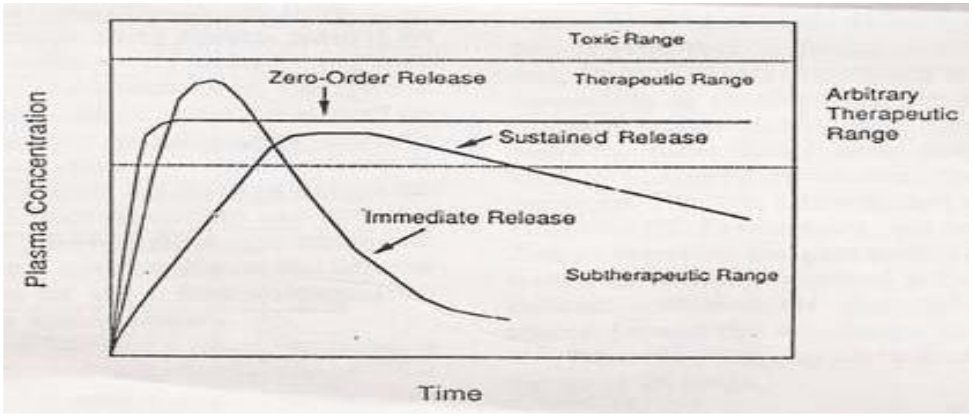

Figure 1.1: Drug level verses time profile showing differences between zero order, controlled releases, slow first order sustained release and release from conventional tablet

Oral drug delivery systems have progressed from immediate release to site-specific delivery over a period of time. Every patient would always like to have a ideal drug delivery system possessing the two main properties that are single dose or less frequent dosing for the whole duration of treatment and the dosage form must release active drug directly at the site of action. [7]

Thus the objective of the pharmacist is to develop systems that can be as ideal system as possible. Attempts to develop a single- dose therapy for the whole duration of treatment have focused attention on controlled or sustained release drug delivery systems. Attention has been focused particularly on orally administered sustained drug delivery systems because of the ease of the administration via the oral route as well as the ease and economy of manufacture of oral dosage forms. Sustained release describes the delivery of drug from the dosage forms over an extended period of time. It also implies delayed therapeutic action and sustained duration of therapeutic effect. Sustained release means not only prolonged duration of drug delivery and prolonged release, but also implies predictability and reproducibility of drug release kinetics. A number of different oral sustained drug delivery systems are based on different modes of operation and have been variously named, for example, as dissolution controlled systems, diffusion controlled systems, ion-exchange resins, osomotically controlled systems, erodible matrix systems, pH- independent formulations, swelling controlled systems, and the like.

An orally administered controlled drug delivery system encounters a wide range of highly variable conditions, such as pH, agitation intensity, and composition of the gastrointestinal fluids as it passes down the G.I tract. Considerable efforts have been made to design oral controlled drug delivery systems that produce more predictable and increased bioavailability of drugs. However, the development process is precluded by several physiological difficulties, like inability to retain and localize the drug delivery system within desired regions of the G.I tract and highly variable nature of the gastric emptying process. An important factor, which may adversely affect the performance of an oral controlled drug delivery system, is the G.I transit time. The time for absorption in the G.I transit in humans, estimated to be 8-10 hr from mouth to colon, is relatively brief with considerable fluctuation. G.I transit times vary widely between individuals, and depend up on the physical properties of the object ingested and the physiological conditions of the gut. This variability may lead to predictable bioavaialability and times to achieve peak plasma levels. One of the important determinants of G.I transit is the residence time in the stomach.

Majority of the drugs are well absorbed from all the regions of the G.I tract while some are absorbed only from specific areas, principally due to their low permeability or solubility in the intestinal tract, their chemical instability, the binding of the drug to the gut contents, as well as to the degradation of the drug by the microorganisms present in the colon. Therefore, in instances where the drug is not absorbed uniformly over the G.I tract, the rate of drug absorption may not be constant in spite of the drug delivery system delivering the drugs at a constant rate into the G.I fluids. More particularly, in instances where a drug has a clear cut absorption window, i.e., the drug is absorbed only from specific regions of the stomach or upper parts of the small intestine; it may not be completely absorbed when administered in the form of a typical oral controlled drug delivery system. It is due to the relatively brief gastric emptying in humans, which normally averages 2-3 hrs through the major absorption zone. It may cause incomplete drug release from the dosage form at absorption sites leading to diminished efficacy of the administered dose. It is apparent that for a drug having such an absorption window, an effective oral controlled drug delivery system should be designed not only to deliver the drug at a controlled rate, but also to retain the drug in the stomach for a long period of time. For this drug, increased or more predictable availability would result if controlled release systems could be retained in the stomach for extended periods of time.

It is suggested that compounding narrow absorption window drugs in a unique pharmaceutical dosage form with gastro retentive properties would enable an extended absorption phase of these drugs. After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of controlled release dosage form for these drugs.

Incorporation of the drug in a controlled release gastroretentive dosage form (CRGRDF) can yield significant therapeutic advantages due to a variety of pharmacokinetic and pharmacodynamic factors.

MATERIALS:

Bupropion-Procured From Aurobindo Laboratory, Hyderabad.. Provided by SURA LABS, Dilsukhnagar, Hyderabad.,Chitosan-Colorcon Asia Pvt. Limited,Carbopol-Colorcon Asia Pvt. Limited,Ethyl Cellulose-Colorcon Asia Pvt. Limited,Lactose-Indchem International Ltd, Mumbai, India,NaHCO3-S.D. Fine Chemicals, Mumbai, India,MgS-S.D. Fine Chemicals, Mumbai, India.,Talc-S.D. Fine Chemicals, Mumbai, India.

METHODOLOGY:

a) Determination of absorption maxima:

A solution containing the concentration 10 µg/ mL drug was prepared in 0.1N HCL UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

b) Preparation calibration curve:

10mg Bupropion pure drug was dissolved in 10ml of methanol (stock solution1) from stock solution 1ml of solution was taken and made up with10ml of 0.1N HCL (100µg/ml). From this 1ml was taken and made up with 10 ml of 0.1N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 5, 10, 15, 20, 25 µg /ml of per ml of solution. The absorbance of the above dilutions was measured at 254 nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R2) which determined by least-square linear regression analysis.

Preformulation parameters:

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone , r = Radius of the cone base

Formulation composition for tablets

INGREDIENTS (mg)	FORMULATION CHART								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bupropion	100	100	100	100	100	100	100	100	100
Chitosan	30	60	90	120	-	-	-	-	-
Carbopol	-	-	-	-	30	60	90	120	-
Ethyl Cellulose	-	-	-	-	-	-	-	-	30
Lactose	147	117	87	57	147	117	87	57	147
NaHCO3	15	15	15	15	15	15	15	15	15
MgS	5	5	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3	3	3
Total Weight	300	300	300	300	300	300	300	300	300

All the quantities were in mg

RESULTS AND DISCUSSION:

a. Determination of absorption maxima

The standard curve is based on the spectrophotometry. The maximum absorption was observed at 254 nm.

b. calibration curve

Graphs of Bupropion was taken in 0.1N HCL (pH 1.2)

Table no : Observations for graph of Bupropion in 0.1N HCl

Conc [µg/mL]	Abs
0	0
5	0.128
10	0.254
15	0.368
20	0.478
25	0.591

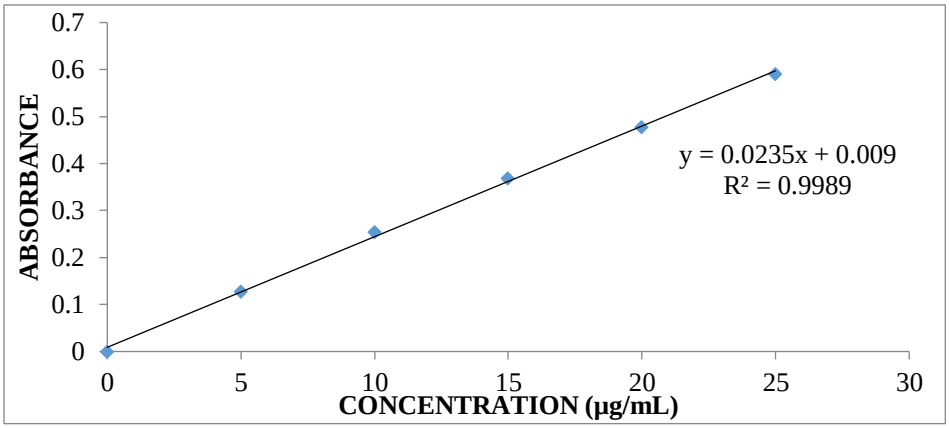

Fig 8.1 : Standard graph of Diltiazem HCl in 0.1 N HCl

Standard graph of Bupropion was plotted as per the procedure in experimental method and its linearity is shown in Table 8.1 and Fig 8.1. The standard graph of Bupropion showed good linearity with R^2 of 0.998, which indicates that it obeys "Beer- Lamberts" law.

Preformulation parameters of powder blend:

Table : Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
F1	29.73±0.02	0.449±0.05	0.518±0.06	13.32±0.02	1.15±0.03
F2	30.96±0.06	0.405±0.05	0.468±0.06	13.46±0.01	1.15±0.04
F3	32.01±0.04	0.409±0.04	0.478±0.07	14.43±0.02	1.16±0.02
F4	28.01± 0.04	0.469±0.04	0.525±0.08	10.66±0.02	1.11±0.03
F5	26.32 0.06	0.45±0.08	0.548±0.02	17.88±0.03	1.21±0.02
F6	27.07±0.02	0.471±0.04	0.569±0.02	17.22±0.02	1.20±0.04
F7	25.17±0.03	0.459±0.02	0.57±0.02	19.47±0.02	1.24±0.01
F8	29.98±0.01	0.458±0.01	0.54±0.011	15.18±0.02	1.17±0.03
F9	23.75 ±0.01	0.446±0.05	0.539±0.09	17.25±0.07	1.20±0.02
F10	28.1±0.03	0.461±0.08	0.539±0.09	14.47±0.01	1.16±0.04
F11	26.57±0.05	0.405±0.06	0.5±0.04	19±0.02	1.23±0.03
F12	28.07±0.02	0.418±0.01	0.505±0.02	17.22±0.08	1.20±0.01

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations

was found to be in the range of 0.45±0.08 to 0.471±0.04 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.5±0.04 to 0.569±0.02 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 19.47 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 1.11 to 1.24 indicating the powder has good flow properties.

***In-Vitro* Dissolution studies:**

Tablet quality control tests such as weight variation, hardness, and friability, thickness, Drug content and drug release studies were performed for floating tablets.

Table:. *In -vitro* dissolution data

Formulation codes	Average Weight (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (Sec)	Total Floating Time(Hrs)
F1	300.4	5.2	0.32	4.15	98.31	59	8
F2	298.3	5.9	0.43	4.96	97.28	62	10
F3	295.1	5.4	0.15	4.22	99.62	35	7
F4	299.8	5.1	0.68	4.35	98.55	46	12
F5	986.2	5.6	0.25	4.18	96.38	26	9
F6	297.05	5.7	0.11	4.39	95.89	19	7
F7	300.1	5.0	0.75	4.75	99.72	34	8
F8	295.9	5.9	0.29	4.39	97.19	20	12
F9	299.2	5.7	0.56	4.12	98.83	43	11
F10	300.3	5.2	0.41	4.82	99.25	56	12
F11	297.1	5.0	0.62	4.75	98.41	21	10
F12	298.6	5.6	0.32	4.21	97.68	62	9

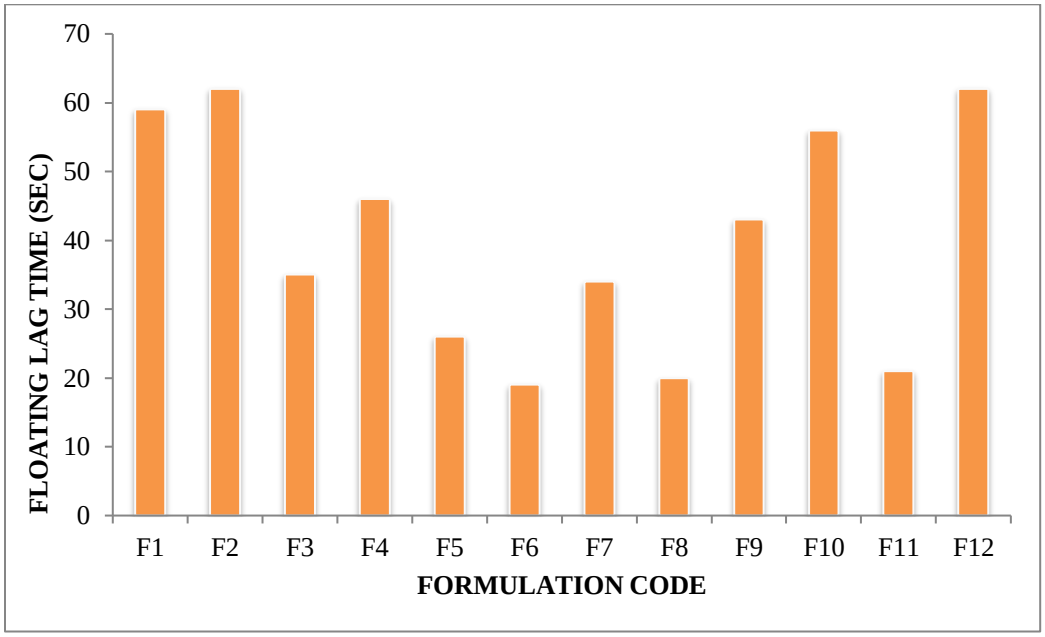

Figure : Floating lag time (Sec)

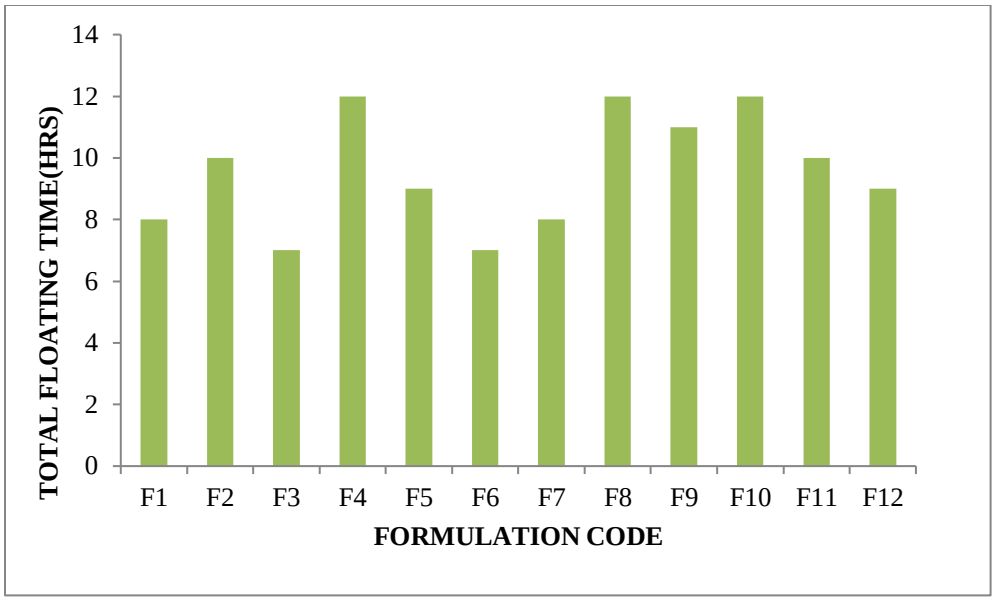

Figure : Total Floating Time (Hrs)

***In Vitro* Drug Release Studies**

Dissolution data of Floating Tablets

ime (Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	21.36	23.53	15.78	12.19	15.89	08.75	10.86	5.93	14.95	17.19	08.15	11.13
1	31.92	29.90	21.53	19.10	20.65	13.18	15.19	10.24	26.60	23.16	12.56	16.46
2	38.71	37.15	26.97	26.67	27.31	20.96	21.27	16.15	33.52	30.25	18.28	21.11
3	43.56	42.49	38.65	31.71	36.78	25.81	26.70	22.97	49.90	36.76	23.66	28.58
4	51.17	51.14	42.12	38.32	42.52	31.76	30.13	32.65	57.34	43.42	30.76	34.64
5	68.83	57.28	50.79	42.17	51.16	36.51	35.91	41.10	64.12	57.31	35.12	42.12
6	76.49	67.91	56.20	48.82	57.90	45.86	42.78	47.74	78.59	65.86	47.82	45.14
7	80.21	74.80	62.56	53.96	67.15	51.79	46.65	55.86	83.62	76.91	53.95	53.28
8	97.65	81.75	68.37	59.81	75.36	57.56	54.91	59.25	89.65	79.72	60.57	61.74
9		86.14	72.91	66.94	80.92	65.27	57.15	63.17	93.91	82.93	68.12	68.59
10		98.11	78.86	71.25	85.60	71.98	61.50	66.93	98.35	87.45	72.82	74.64
11			83.97	75.31	91.15	77.31	68.14	69.34		95.76	86.31	82.54
12			91.65	87.52	98.31	81.18	76.62	72.21			90.14	86.46

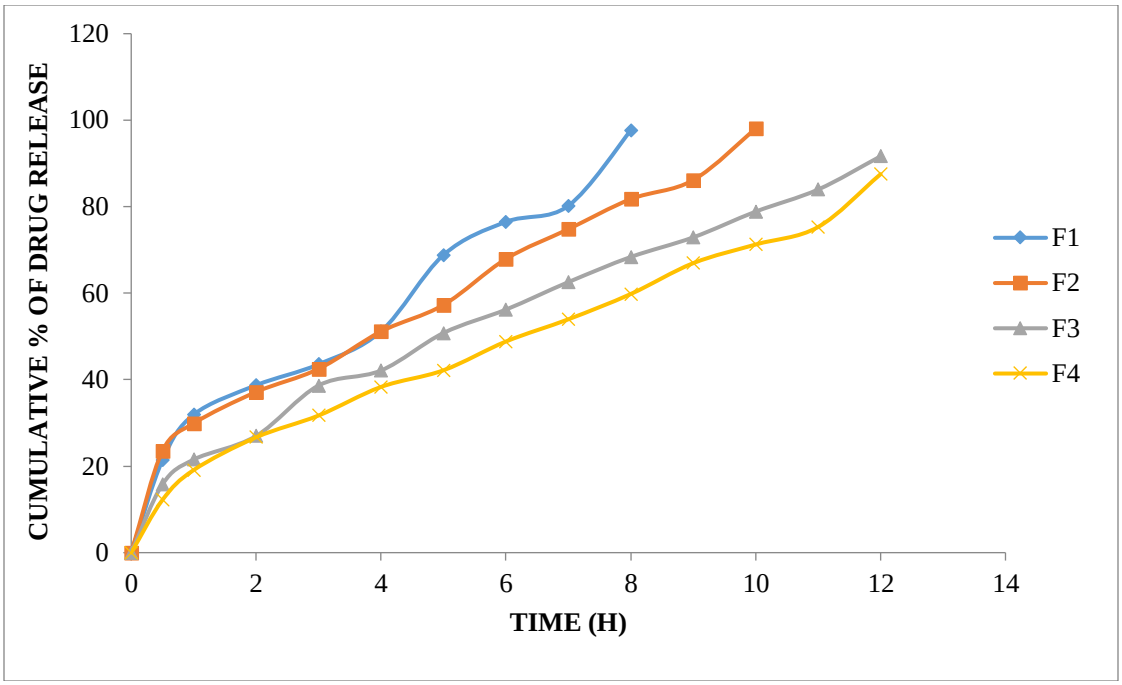

Fig 8.4 : Dissolution data of Bupropion Floating tablets containing Chitosan

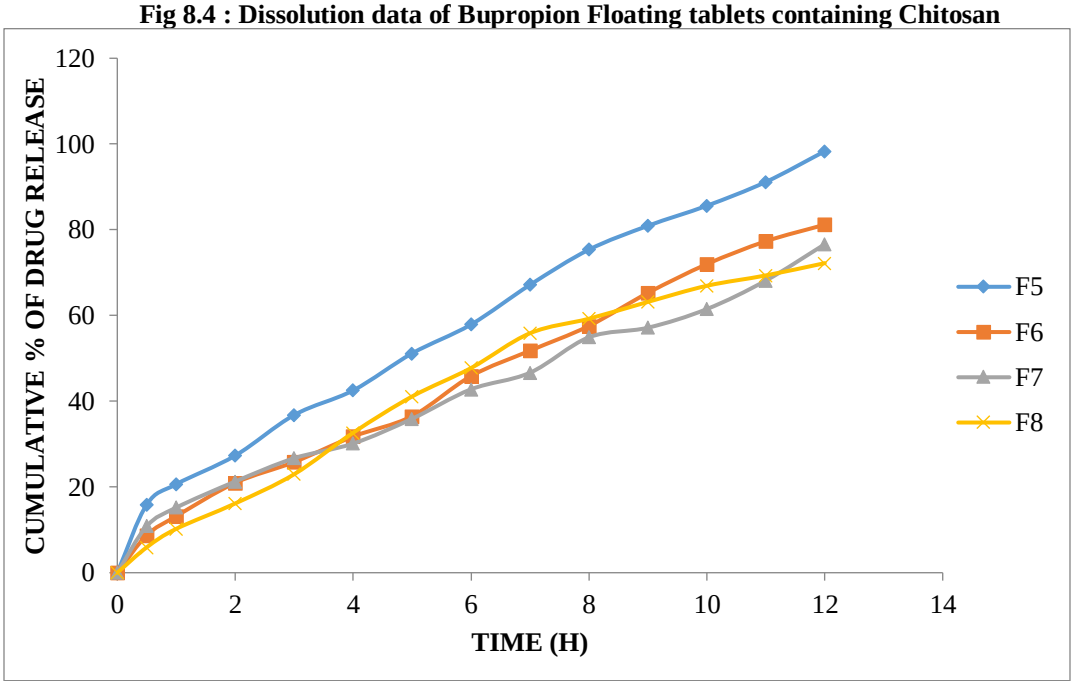

Fig: 8.5 : Dissolution data of Bupropion Floating tablets containing Carbopol

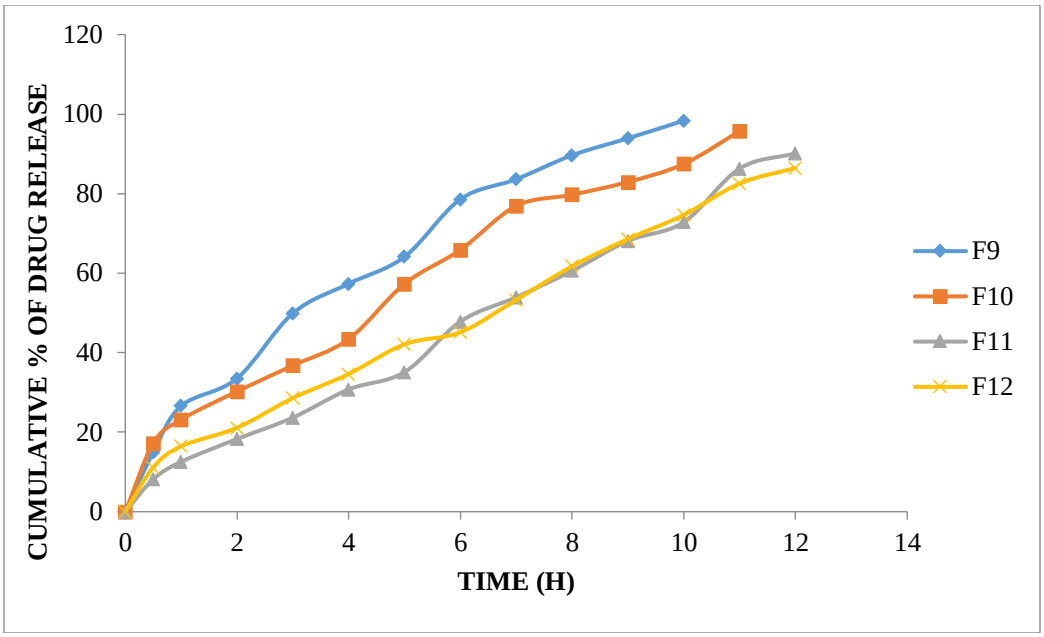

Fig: 8.6 : Dissolution data of Bupropion Floating tablets containing Ethyl Cellulose

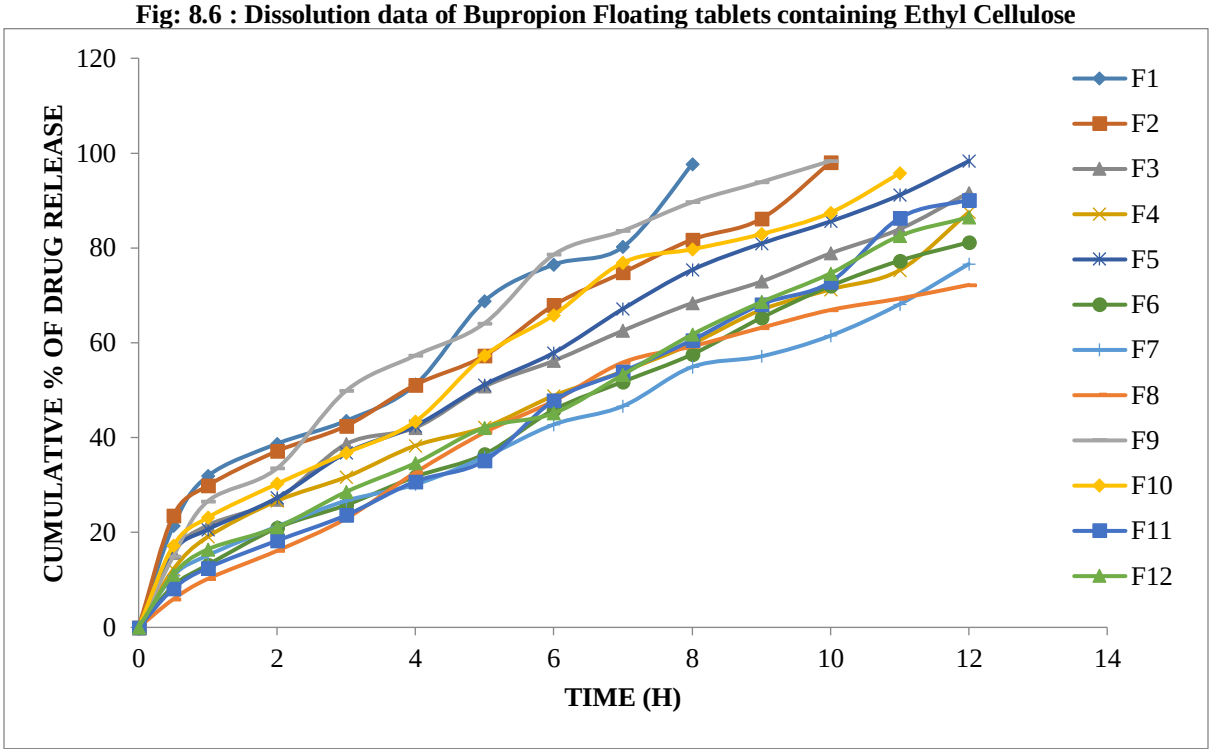

Fig: 8.7: Dissolution data of Bupropion Floating tablets containing all formulations (Chitosan, Carbopol, and Ethyl Cellulose)

From the dissolution data it was evident that the formulations prepared with Chitosan as polymer were retarded the drug release more than 12 hours.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release mode

Table : Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
15.89	0.5	0.707	1.201	-0.301	1.925	31.780	0.0629	-0.799	84.11	4.642	4.381	0.260
20.65	1	1.000	1.315	0.000	1.900	20.650	0.0484	-0.685	79.35	4.642	4.297	0.344
27.31	2	1.414	1.436	0.301	1.861	13.655	0.0366	-0.564	72.69	4.642	4.173	0.468
36.78	3	1.732	1.566	0.477	1.801	12.260	0.0272	-0.434	63.22	4.642	3.984	0.658
42.52	4	2.000	1.629	0.602	1.760	10.630	0.0235	-0.371	57.48	4.642	3.859	0.782
51.16	5	2.236	1.709	0.699	1.689	10.232	0.0195	-0.291	48.84	4.642	3.655	0.986
57.9	6	2.449	1.763	0.778	1.624	9.650	0.0173	-0.237	42.1	4.642	3.479	1.163
67.15	7	2.646	1.827	0.845	1.517	9.593	0.0149	-0.173	32.85	4.642	3.203	1.439
75.36	8	2.828	1.877	0.903	1.392	9.420	0.0133	-0.123	24.64	4.642	2.910	1.732
80.92	9	3.000	1.908	0.954	1.281	8.991	0.0124	-0.092	19.08	4.642	2.672	1.969
85.6	10	3.162	1.932	1.000	1.158	8.560	0.0117	-0.068	14.4	4.642	2.433	2.209
91.15	11		1.960	1.041	0.947	8.286	0.0110	-0.040	8.85	4.642	2.068	2.573
98.31	12	3.317	1.993	1.079	0.228	8.193	0.0102	-0.007	1.69	4.642	1.191	3.450

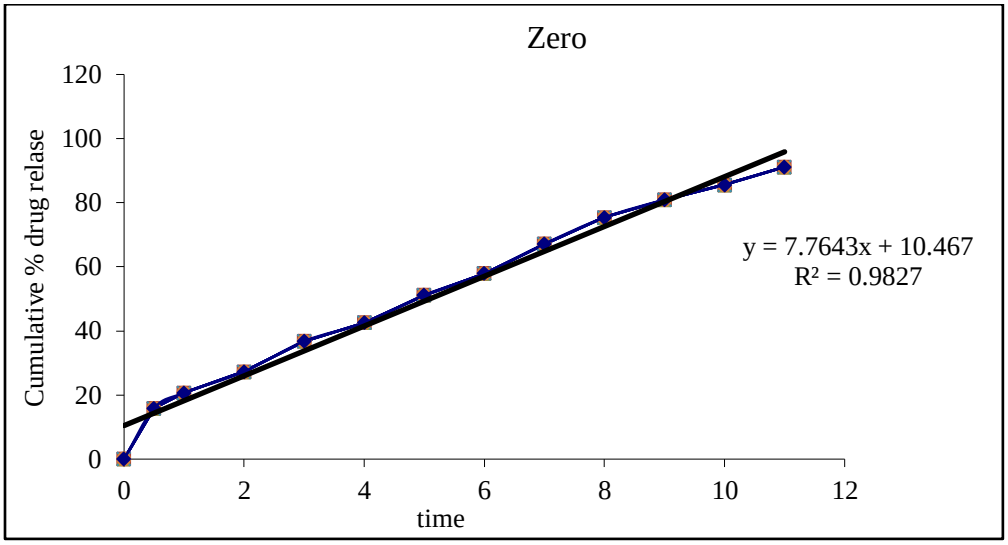

Fig no 8.8: Zero order release kinetics

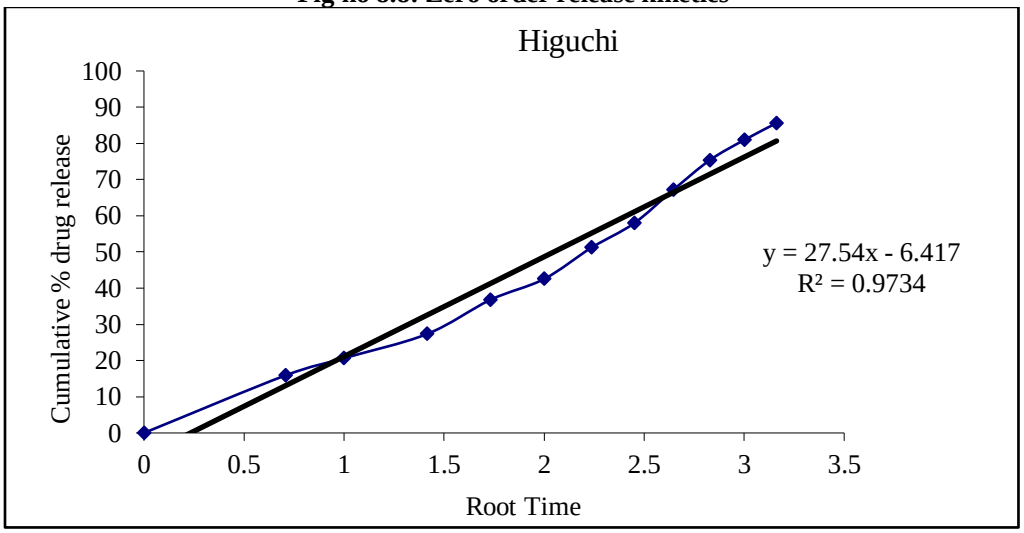

Fig no 8.9: Higuchi release kinetics

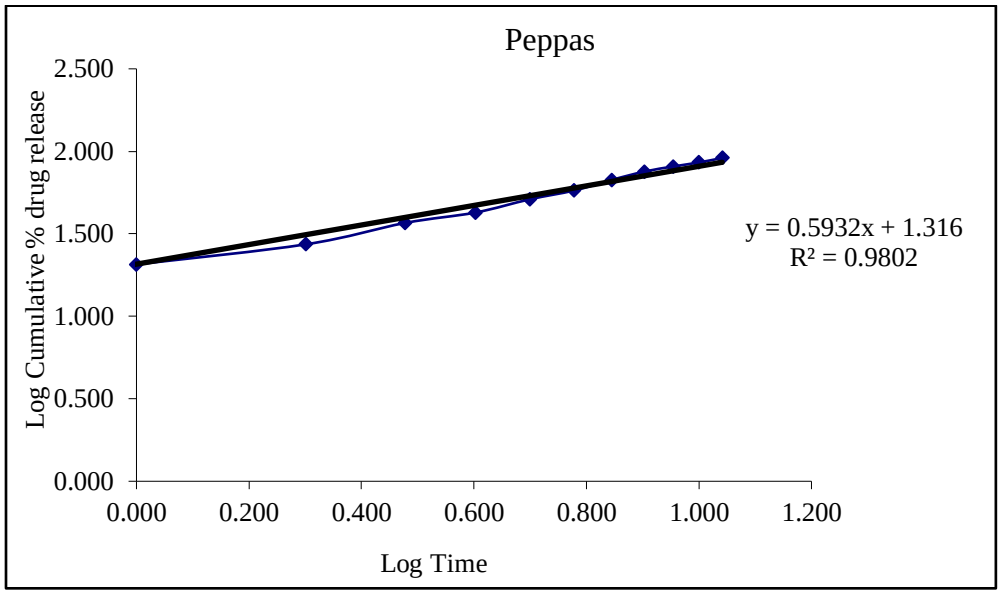

Fig 8.10 : Kors mayer peppas release kinetics

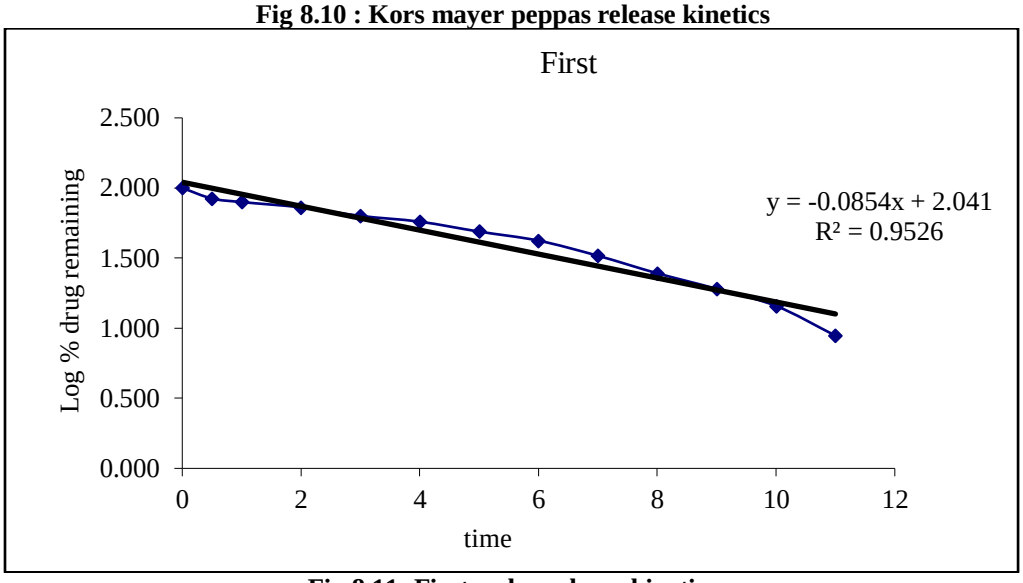

Fig 8.11: First order release kinetics

Optimised formulation F5 was kept for release kinetic studies. From the above graphs it was evident that the formulation F5 was followed Zero order release mechanism.

Drug and excipient compatibility studies
Fourier Transform-Infrared Spectroscopy:

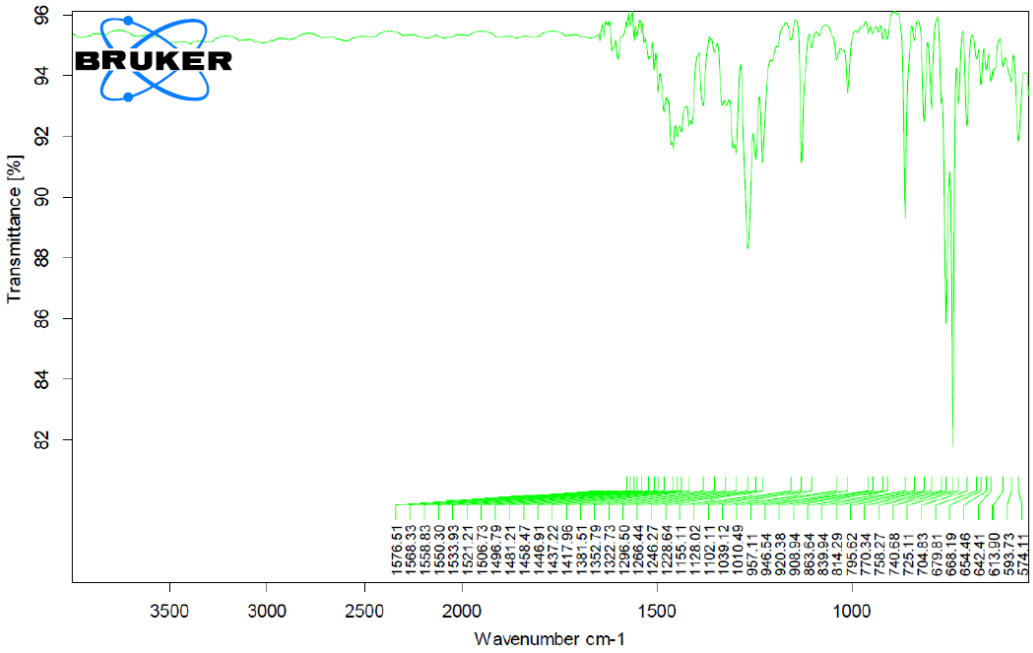

Figure 8.12: FTIR Spectrum of pure drug

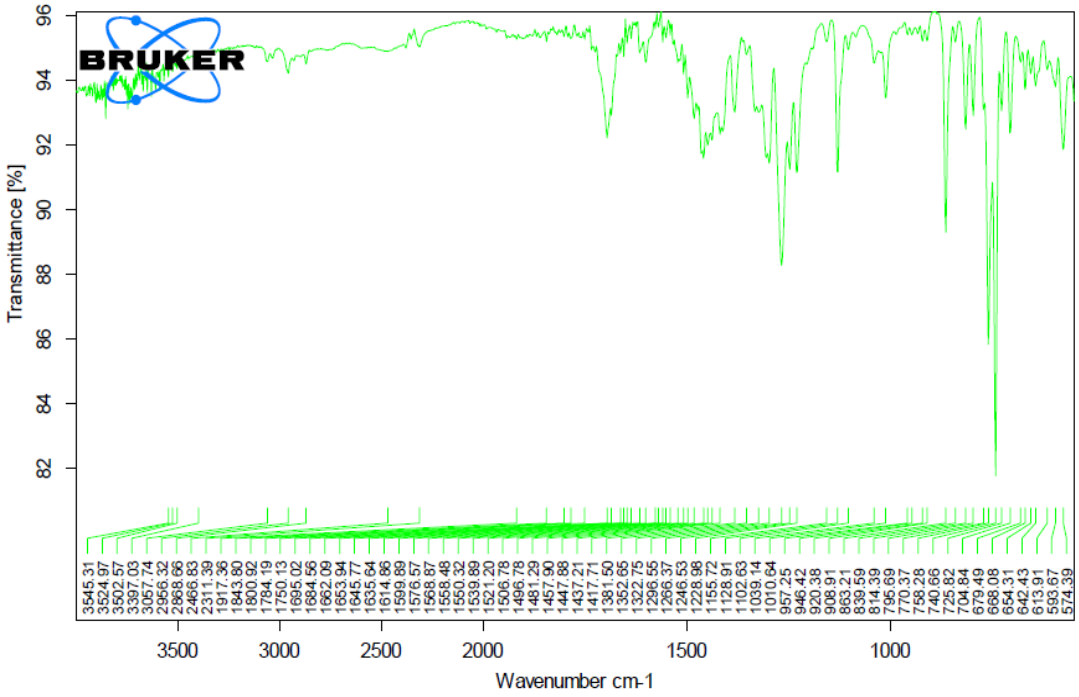

Fig 8.13: FTIR Spectrum of optimized formulation

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

CONCLUSION:

Over the years, various attempts have been made to control the time course of drug in the body through a variety of drug modifications and dosage forms. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the gastrointestinal tract is to control the GRT.

The approach of the present study was to formulate floating tablets of Bupropion and hence for theevaluate the release profiles of these formulations. From the results obtained in the present study, the following conclusions are drawn:

- The IR spectrum of pure drug and drug-polymer mixture revealed that there was no interaction between polymer and drug. The prepared floating tablets are industrially feasible method.
- Bulk density and tapped density shown good packability, and Carr's index results shown excellent compressibility.
- Formulation F5 containing 30 mg of Carbopol was found to release a maximum of 98.31 % at the 12th hour.
- Comparison of all formulations of Bupropion revealed the fact that developed formulation F5 showed comparable release characteristics, and thus, it may have fair clinical efficacy. Hence, the formulation F5 has met the objectives of the present study.

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