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FORMULATION AND EVALUATION OF ORAL CONTROLLED RELEASE TABLETS OF BETAHISTINE HYDROCHLORIDE

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ARTICLE INFO

ABSTRACT

The present study involves in the formulation and evaluation of Controlled release tablets of Betahistine HCl (16mg). The objective ofthe present study was to formulate Betahistine HCl Controlled release tablets by direct compression method by using HPMC K4M, Ethyl cellulose and Eudragit S-100.MCC was used as diluting agent, Magnesium Stearate was usedas a lubricant and Talc was used as a glident. This Controlled release the drug up to 12 hours in predeterminedrate. The formulated powder blend was evaluated for bulk density, tapped density, compressibility index and angle of repose. Theformulated tablets were evaluated for physical characteristics of Controlled release tablets such as thickness, hardness, friability,weight variation and drug content. The results of the formulations found to be within the limits specified in official books. Thetablets were evaluated for *In-vitro* drug release studies by using USP type II dissolution test apparatus. The dissolution test wasperformed in 0.1 N HCL for 2 hr and phosphate buffer pH 6.8 for 12hrs. The *in-vitro* cumulative drug release profile of all formulations F1-F12 hours showed good drug release. Hence, Formulation F7 was the most promisingformulation as it gives satisfactory release (98.29 %) for 12 hours and F7 found to be the best formulation.

INTRODUCTION

Over the Past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention is being paid on development of oral controlled release drug delivery systems. The goal in designing controlled release drug delivery system is to reduce the frequency of the dosing, reducing the dose and providing uniform drug delivery. So, controlled release dosage form is a dosage form that releases one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ . Controlled release dosage forms provide better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. [1] The Important role of novel drug delivery system that improve the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and or targeting the drug to desired site. The aim of any drug delivery system is to provide a therapeutic amount of drug to the specific site in the body to achieve promptly and then maintain the desired drug concentration.[2,3] The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Sustain release system includes any drug delivery systems that achieves slow release of drug over prolong period of time.[4] Matrix tablets are considered to bethe commercially feasible sustained action dosageforms that involve the least processing variables,utilize the conventional facilities and accommodatelarge doses of drug. There remains an interest indeveloping novel formulations that allow forsustained the drug release using readily available,inexpensive excipient by matrix based formulation.During the last two decades there has beenremarkable increase in interest in sustained releasedrug delivery system. This has been due to variousfactors like the prohibitive cost of developing newdrug entities, expiration of existing internationalpatients, discovery of new polymeric materialssuitable for prolonging the drug release, and theimprovement in therapeutic efficiency and safetyachieved by these delivery systems. Now a days thetechnology of sustained release is also being applied to veterinary products also.[5]

Drawback of conventional dosage form

1) Poor patient compliance: Chances of missing ofthe dose of a drug.
2) The unavoidable fluctuations of drugconcentration may lead to under medication orover medication.
3) A typical peak-valley plasma concentration-timeprofile is obtained which makes attainment of Drawback of conventional dosage form.

4) The fluctuations in drug levels which causesprecipitation of adverse effects mainly the drugwhich having the small Therapeutic Indexwhenever over medication occur.[6,7,8]

Advantages

Patient compliance: Lack of compliance is mainly observed with chronic disease which required long term treatment, as success of drug therapy depends on the patient ability to comply with the drug treatment. Patient compliance is affected by a various factors, like knowledge of disease process, patient faith in treatment, and understanding of patient related to a strict treatment schedule. Also the complication of therapeutic regimens, the cost of therapy and local or systemic side effect of the dosage form. This problem can be resolved to some extent by administering sustained release drug delivery system.

Reduced 'see-saw' fluctuation: Drug concentration in the systemic circulation and tissue compartments show 'see saw' pattern frequently when the drug administration in conventional dosage form. The magnitudes of these fluctuations mainly depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see-saw' pattern is more prominent just in case of drugs with biological half-life less than four hours, since recommended dosing intervals arerarely less than four hours. A well designed sustained release drug delivery system can widely reduce the frequency of drug dosing and also mainta in a steady drug concentration in blood circulation and target tissue cells.

Total dose reduction: To treat a diseased condition less amount of total drug is used in Sustained release drug delivery systems. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.

Improvement of deficiency in treatment*: Optimal therapy of a disease requires an effective transfer of active drugs to the tissues, organs that need treatment. Very often doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This unfortunately may lead to undesirable, toxicological and immunological effects in non-target tissue. A sustained release dosage form leads to better management of the acute or chronic disease condition.

Economy: The initial unit cost of sustained release products is usually greater than that of conventional dosage form because of the special nature of these compounds but importantly average cost of treatment over an prolong period of time may be less.[9,10]

Disadvantages of sustained release dosage form

1. Dose dumping: Dose dumping may occur with faulty formulation.
2. Reduced potential for dose adjustment.
3. Cost is more than conventional dosage form.
4. Increase potential for first pass metabolism.
5. For proper medication patient education is necessary.
6. Possible reduction in systemic availability.
7. Poor in vivo and in vitro correlations.[11]

Terminology: Controlled drug delivery or modified release deliverysystems may be defined as follows:

Controlled release formulation: The controlled release system is to deliver a constantsupply of the active ingredient, usually at a zero-orderrate, by continuously releasing, for a certain period oftime, an amount of the drug equivalent to the eliminated by the body. An ideal Controlled drugdelivery system is the one, which delivers the drugs at apredetermined rate, locally or systematically, for aspecific period of time.[12]

Repeat action preparations: A dose of the drug initially is released immediatelyafter administration, which is usually equivalent to asingle dose of the conventional drug formulation. Aftera certain period of time, a second single dose isreleased. In some preparation, a third single dose isreleased after a certain time has elapsed, following the second dose [13]

Advantage: it provides the convenience of supplyingadditional Dose or doses without the need of readministration.

Disadvantage: that the blood levels still exhibit the"Peak and valley" characteristic ofconventionalintermittent drug therapy.

Extended-Release formulation: Extended-Releaseformulations are usually designed to reduce dosefrequency and maintain relatively constant or flatplasma drug concentration. This helps avoid the sideeffects associated with high concentration.

Delayed release preparations*: The drug is released at alater time after administration. The delayed action isachieved by the incorporation of a special coat, such asenteric coating, or other time barriers such as theformaldehyde treatment of soft and hard gelatincapsules. The purposes of such preparations are toprevent side effects related to the drug presence in thestomach, protect the drug from degradation in thehighly acidic pH of the gastric fluid [14].

Site specific targeting: These systems refer to targetingof a drug directly to a certain biological location. Inthis case the target is adjacent to or in the diseasedorgan or tissue.

Receptor targeting: These systems refer to targeting ofa drug directly to a certain biological location. In thiscase the target is the particular receptor for a drug within organ or tissue. Site specific targeting and receptortargeting systems satisfy the spatial aspect of drugdelivery and are also considered to be controlled drug delivery systems [15].

MATERIALS

Betahistine HCl Provided by SURA LABS, HPMC K4M Merck Specialities Pvt Ltd, Mumbai, India, Ethyl cellulose Merck Specialities Pvt Ltd, Mumbai, India, Eudragit S-100 Merck Specialities Pvt Ltd, Mumbai, India ,PVP K30   Merck Specialities Pvt Ltd, Mumbai, India, Mg-Stearate Merck Specialities Pvt Ltd, Mumbai, India, Talc Merck Specialities Pvt Ltd, Mumbai, India, MCC Merck Specialities Pvt Ltd, Mumbai, India.

METHODOLOGY

Analytical method development

Determination of absorption maxima: 100mg of Betahistine HCl pure drug was dissolved in 100ml of Methanol (stock solution) 10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100μg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10μg/ml)and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VISspectrophotometer. The solution was scanned in the range of 200 – 400 nm.

Preparation calibration curve: 100mg of Betahistine HCl pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100μg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10μg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 5,10,15,20 and 25 μg/ml of Betahistine HCl per ml of solution. The absorbance of the above dilutions was measured at 260nm 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 (R^2)which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy: The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes.The resultant disc was mounted in a suitable holder in Agilent spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 500 cm^{-1}. The resultant spectrum was compared for any spectrum changes.

Preformulation parameters: The quality of tablet, once formulated by rule, is generally dictated by thequality 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.

Table 1. Formulation composition for tablets

| Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Betahistine HCl	16	16	16	16	16	16	16	16	16	16	16	16
HPMC K4M	20	40	60	80	-	-	-	-	-	-	-	-
Ethyl cellulose	-	-	-	-	20	40	60	80	-	-	-	-
Eudragit S-100	-	-	-	-	-	-	-	-	20	40	60	80
PVP K30	10	10	10	10	10	10	10	10	10	10	10	10
Mg-Stearate	5	5	5	5	5	5	5	5	5	5	5	5
Talc	4	4	4	4	4	4	4	4	4	4	4	4
MCC	195	175	155	135	195	175	155	135	195	175	155	135
Total Weight	250	250	250	250	250	250	250	250	250	250	250	250

All the quantities were in mg

RESULTS AND DISCUSSION

Standard Calibration curve of Betahistine HCl

Table 2. Concentration and absorbance obtained for calibration curve of Betahistine HCl in 0.1 N hydrochloric acid buffer (pH 1.2)

S. No.	Concentration (μg/ml)	Absorbance* (at 260 nm)
1	0	0
2	10	0.148
3	20	0.284
4	30	0.411
5	40	0.538
6	50	0.667
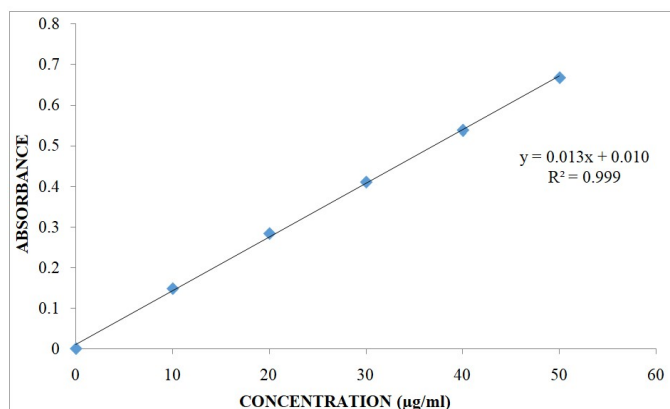
Fig. 1. Standard graph of Betahistine HClin 0.1 N HCl
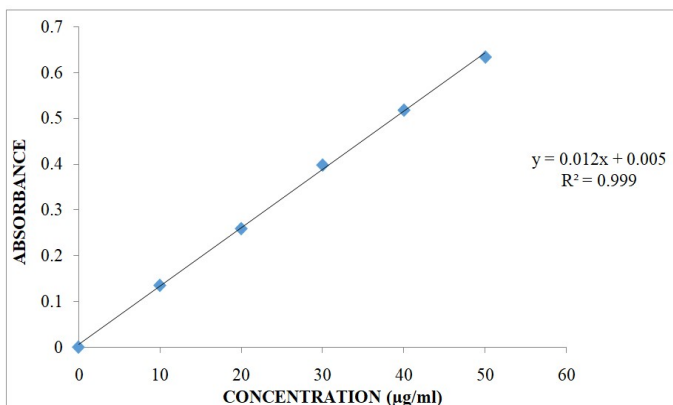
Fig. 2. Standard graph of Betahistine HClin pH 6.8 Phosphate buffer

Table 3. Concentration and absorbance obtained for calibration curve of Betahistine HCl in pH 6.8 Phosphate buffer

S. No.	Concentration (µg/ml)	Absorbance* (at 265 nm)
1	0	0
2	5	0.135
3	10	0.259
4	15	0.398
5	20	0.518
6	25	0.634

Preformulation parameters of powder blend

Table 4. Pre-compression parameters

Formulations	Bulk Density(gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner ratio	Angle Of Repose(Θ)
F1	0.32±0.0012	0.37±0.0023	13.1± 0.09	1.15±0.009	33.59±0.32
F2	0.31±0.0030	0.38±0.0015	18.4± 0.15	1.22±0.010	34.71±0.31
F3	0.30±0.0010	0.35±0.0060	14.2± 0.12	1.27±0.010	32.41±0.29
F4	0.29±0.0022	0.37±0.0011	21.6± 0.20	1.27±0.010	33.36±0.30
F5	0.33±0.0019	0.40±0.0026	17.5± 0.17	1.21±0.011	27.39±0.25
F6	0.31±0.0028	0.38±0.0014	13.2± 0.11	1.22±0.011	33.42±0.31
F7	0.33±0.0030	0.38±0.0037	13.1± 0.11	1.15±0.006	33.56±0.25
F8	0.26±0.0016	0.33±0.0023	21.2± 0.07	1.26±0.008	31.25±0.12
F9	0.28±0.0022	0.37±0.0019	24.3± 0.22	1.32±0.005	28.44±0.22
F10	0.26±0.0021	0.32±0.0025	18.7± 0.09	1.23±0.009	34.24±0.31
F11	0.28±0.0019	0.36±0.0023	22.0± 0.17	1.28±0.025	34.31±0.31
F12	0.28±0.0024	0.35±0.0033	20.0±0.12	1.25±0.011	32.15±0.26

All the values represent n=3

Quality control parameters for tablets

Table 5. Post compression parameter

Formulation codes	Weight variation(mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	250.2	5.2	0.58	2.15	96.36
F2	250.1	5.1	0.49	2.36	98.10
F3	248.4	6.3	0.50	2.87	96.91
F4	250.2	6.0	0.69	2.10	97.62
F5	249.6	5.0	0.48	2.25	96.31
F6	248.8	5.8	0.55	2.31	99.81
F7	250.0	6.2	0.57	2.10	98.72
F8	250.1	6.3	0.63	2.11	97.87
F9	249.9	5.3	0.47	2.08	96.21
F10	248.6	5.9	0.65	2.12	95.12
F11	249.5	6.7	0.59	2.09	99.32
F12	250.0	5.6	0.66	2.44	98.98

In Vitro Drug Release Studies

Table 6. *In -vitro* dissolution data

| Time (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	19.85	17.41	14.65	35.12	12.87	9.25	7.90	5.08	25.2	4.6	8.16	13.12
1	26.52	23.60	26.32	42.53	18.75	12.61	10.62	8.25	38.3	8.16	11.08	20.91
2	37.11	37.82	40.67	47.39	27.98	23.18	18.17	16.71	51.0	16.36	15.31	29.56
3	49.75	44.91	54.23	55.48	36.57	28.27	26.34	20.59	59.1	27.84	22.64	32.15
4	53.24	48.76	55.47	61.32	44.92	39.69	37.23	25.31	61.5	36.33	29.72	39.28
5	58.96	56.95	56.62	68.67	55.11	45.41	43.60	36.29	68.1	42.94	37.09	44.87
6	64.21	65.72	58.83	71.52	59.35	54.61	49.57	39.40	71.2	50.41	43.15	53.19
7	83.79	73.95	60.76	75.28	66.42	65.83	57.82	47.01	81.4	59.66	51.6	57.69
8	97.63	81.10	63.91	79.32	69.57	69.71	64.71	54.32	99.5	68.07	59.85	61.38
9		93.86	65.54	81.94	72.20	74.82	67.22	59.75		75.14	66.1	68.79
10		98.25	69.43	85.71	77.39	78.29	76.99	63.21		83.37	72.03	72.33
11			71.27	87.15	82.48	85.32	82.18	69.98		90.05	79.81	76.94
12			74.56	89.40	89.21	92.53	98.29	76.25		97.92	86.32	79.68
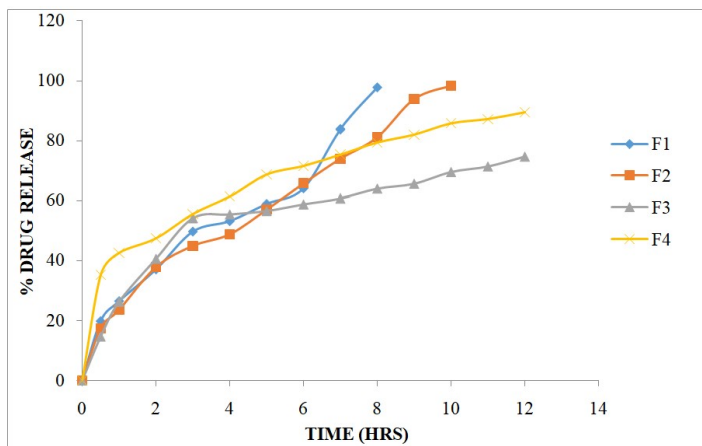
Fig. 3. Dissolution profile of formulations prepared with HPMC K4M polymer
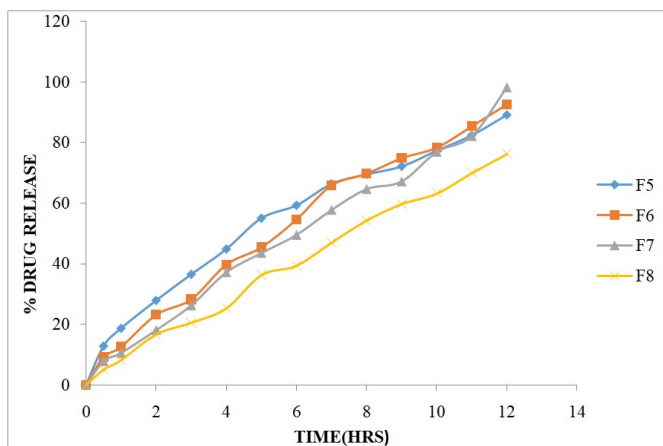

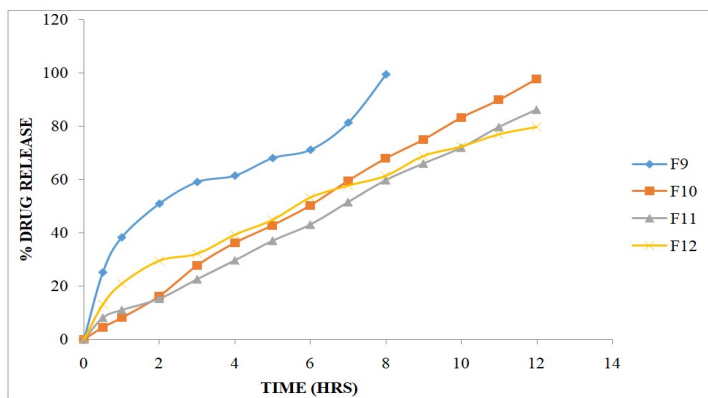**Fig. 4. Dissolution profile of formulations prepared with Ethyl cellulose polymer**

Fig. 5. Dissolution profile of formulations prepared with Eudragit S-100as polymer

Table 7. 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
7.9	0.5	0.707	0.898	-0.301	1.964	15.800	0.1266	-1.102	92.1	4.642	4.516	0.126
10.62	1	1.000	1.026	0.000	1.951	10.620	0.0942	-0.974	89.38	4.642	4.471	0.170
18.17	2	1.414	1.259	0.301	1.913	9.085	0.0550	-0.741	81.83	4.642	4.341	0.300
26.34	3	1.732	1.421	0.477	1.867	8.780	0.0380	-0.579	73.66	4.642	4.192	0.450
37.23	4	2.000	1.571	0.602	1.798	9.308	0.0269	-0.429	62.77	4.642	3.974	0.667
43.6	5	2.236	1.639	0.699	1.751	8.720	0.0229	-0.361	56.4	4.642	3.835	0.807
49.57	6	2.449	1.695	0.778	1.703	8.262	0.0202	-0.305	50.43	4.642	3.695	0.947
57.82	7	2.646	1.762	0.845	1.625	8.260	0.0173	-0.238	42.18	4.642	3.481	1.161
64.71	8	2.828	1.811	0.903	1.548	8.089	0.0155	-0.189	35.29	4.642	3.280	1.362
67.22	9	3.000	1.827	0.954	1.516	7.469	0.0149	-0.173	32.78	4.642	3.200	1.441
76.99	10	3.162	1.886	1.000	1.362	7.699	0.0130	-0.114	23.01	4.642	2.844	1.797
82.18	11	3.317	1.915	1.041	1.251	7.471	0.0122	-0.085	17.82	4.642	2.612	2.030
98.29	12	3.464	1.993	1.079	0.233	8.191	0.0102	-0.007	1.71	4.642	1.196	3.446
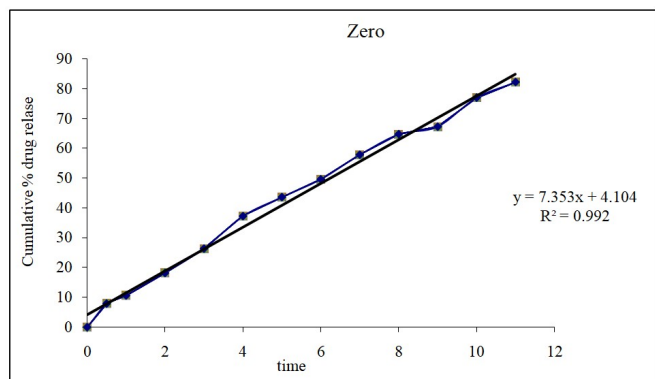
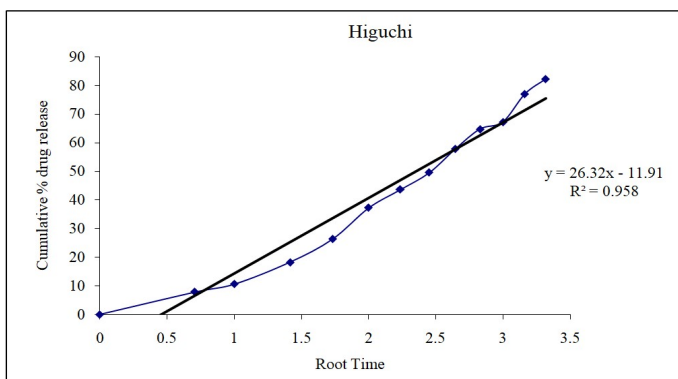**Fig. 6. Zero order release kinetics graph**

Fig. 7. Higuchi release kinetics graph
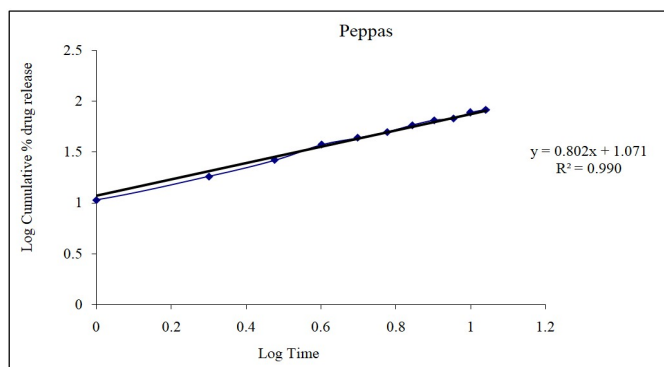
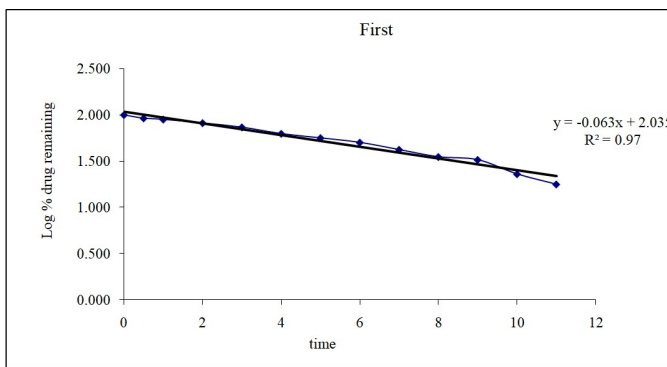**Fig. 8. Kars mayer peppas graph**

Fig. 9. First order release kinetics graph

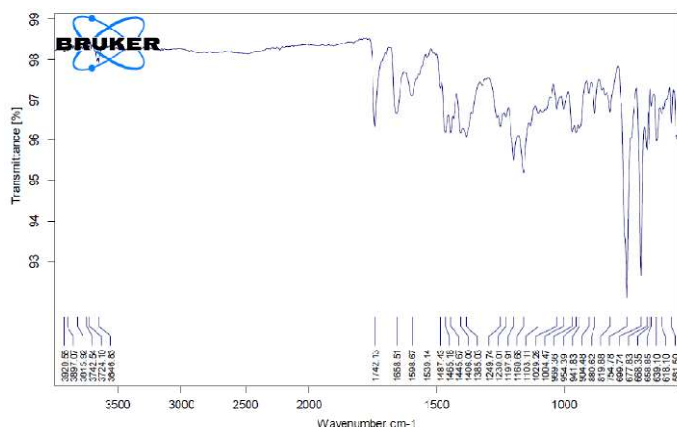**Drug – Excipient compatibility studies**

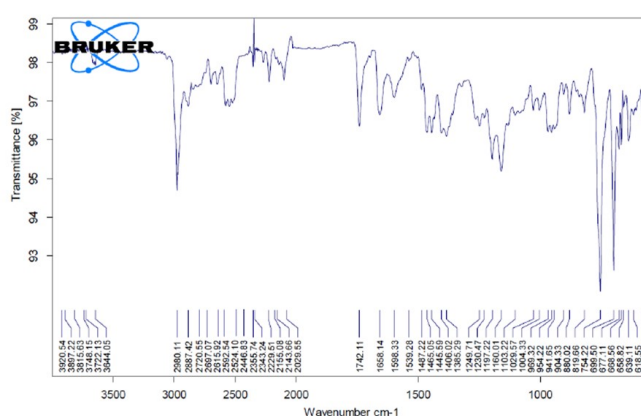**Fig. 10. FT-TR Spectrum of Betahistine HCl pure drug**

Fig. 11. FT-IR Spectrum of Optimised Formulation

CONCLUSION

In the present work, an attempt has been made to develop controlled release tablets of Betahistine HCl by selecting different grades of HPMC and Ethyl cellulose, Eudragit S-100 as retarding polymers. All the formulations were prepared by direct compression method. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F7 formulation showed maximum % drug release i.e., 98.29 % in 12 hours. Hence it is considered as optimized formulation F7 which contains Ethyl cellulose (60mg). Whereas the formulations with Ethyl cellulose showed more retarding with low concentration of polymer.

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