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FORMULATION AND *IN VITRO* EVALUATION OF SOLID DISPERSION SUSTAINED RELEASE TABLETS OF BENDROFLUMETHIAZIDE USING NATURAL AND SYNTHETIC POLYMER

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ABSTRACT

The aim of the present study was to develop sustained release formulation of Bendroflumethiazide to maintain constant therapeutic levels of the drug for over 12 hrs. Guar gum and HPMC grades were employed as polymers. The formulations prepared by direct compression method containing different concentration of polymers. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation F8 showed better and desired drug release pattern i.e., 99.15% in 12 hours. It contains the HPMC K100M as sustained release material. It followed First order release kinetics mechanism.

KEYWORDS: Bendroflumethiazide, Solid dispersion, Sustained release system, HPMC, Guar Gum.

INTRODUCTION

Sustained release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. The advantage of administering a single dose of a drug that is released over an extended period of time to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.[1,2]

As a diuretic, bendroflumethiazide inhibits active chloride reabsorption at the early distal tubule via the Na-Cl cotransporter, resulting in an increase in the excretion of sodium, chloride, and water. Thiazides like bendroflumethiazide also inhibit sodium ion transport across the renal tubular epithelium through binding to the thiazide sensitive sodium-chloride transporter. This results in an increase in potassium excretion via the sodium-potassium exchange mechanism. The antihypertensive mechanism of bendroflumethiazide is less well understood although it may be mediated through its action on carbonic anhydrases in the smooth muscle or through its action on the large-conductance calcium-activated potassium (KCa) channel, also found in the smooth muscle.[3,4]

The aim of the present work is to formulate and evaluate the Bendroflumethiazide solid dispersion sustained release tablets using natural and synthetic polymers such as Guar gum, HPMC K15M and HPMC K100M.

MATERIALS AND METHODS

Bendroflumethiazide was a gift sample from (Dr.Reddys Laboratories, Hyderabad, India). HPMC K15M, Guar Gum and HPMC K15M were obtained from Hetro Pharmaceuticals, Hyderabad, India). Micro crystalline cellulose, Talc, Magnesium stearate was procured from Loba chemie Private Ltd. All other chemicals and reagents were analytical grade and used as received.

Fourier Transform Infrared (FTIR) spectroscopy

Drug excipient interaction studies are significant for the successful formulation of every dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the assessment of physicochemical compatibility and interactions, which helps in the prediction of interaction between drug and other excipients. In the current study 1:1 ratio was used for preparation of physical mixtures used for analyzing of compatibility studies. FT-IR studies were carried out with a Bruker, ATR FTIR facility.[5]

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.[6,7,8]

Formulation development of solid dispersion sustained release Tablets

Bendroflumethiazide and polymer were weighed accurately and mix it then add methanol and keep aside at room temperature for evaporate the solvent then to get dried form powder, scrap the powder and the powder was pass through sieve 22 then to get uniform size powder. Add diluents such as microcrystalline cellulose and mit it properly for 10 mins then add to glident and lubricant to mixture and mix for 10 mins .compress the powders by using labpress tablet compression machine.[9,10,11]

Table 1: Formulation of solid dispersion sustained release tablets.

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bendroflumethiazide	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Guar gum	10	20	30	-	-	-	-	-	-
HPMC K15M	-	-	-	10	20	30	-	-	-
HPMC K100M	-	-	-	-	-	-	10	20	30
Mg.stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total tablet weight	100	100	100	100	100	100	100	100	100

Evaluation of post compression parameters for prepared Tablets.[12,13,14,15]

The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test

Twenty tablets were randomly selected and weighed, to estimate the average weight and that were compared with individual tablet weight. The percentage weight variation was calculated as per Indian Pharmacopoeial Specification. Tablets with an average weight 250 mg so the % deviation was ±5 %.

Friability test

Twenty tablets were weighed and subjected to drum of friability test apparatus. The drum rotated at a speed of 25 rpm. The friabilator was operated for 4 minutes and reweighed the tablets. % loss (F) was calculated by the following formula.

F =100 (W0-W)/W0

Where W0 = Initial weight, W = Final weight

Hardness test

The hardness of tablets was measured by using Monsanto hardness tester. The results were complies with IP specification.

Thickness test

The rule of physical dimension of the tablets such as sizes and thickness is necessary for consumer acceptance and maintain tablet uniformity. The dimensional specifications were measured by using screw gauge. The thickness of the tablet is mostly related to the tablet hardness can be used as initial control parameter.

Drug content

The amount of drug in tablet was important for to monitor from tablet to tablet, and batch to batch is to evaluate for efficacy of tablets. For this test, take ten tablets from each batch were weighed and powdered. Weighed equivalent to the average weight of the tablet powder and transferred into a 100 ml volumetric flask and dissolved in a suitable quantity of media. The solution was made up to the mark and mixed well. Then filter the solution. A portion of the filtrate sample was analyzed by UV spectrophotometer.

***In vitro* drug release studies**

Apparatus -- USP-II, Paddle Method

Dissolution Medium -- 0.1 N HCl, pH6.8 Phophate buffer

RPM -- 50

Sampling intervals (hrs) -- 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 11 and 12

Temperature -- 37°c $\pm$ 0.5°c

Procedure

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The media was allowed to equilibrate to temp of 37°c $\pm$ 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours. Then 0.1 N HCl was replaced with pH 6.8 phosphate buffer and process was continued upto 12 hrs at 50 rpm. At specific time intervals, withdrawn 5 ml of sample and again 5ml media was added to maintain the sink condition. Withdrawn samples were analyzed at wavelength of drug using UV-spectrophotometer.[16,17,18]

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 model.

Zero order release rate kinetics

To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

$$\mathbf{F = K_o t}$$

Where, 'F' is the drug release at time't', and 'K_o' is the

zero order release rate constant. The plot of % drug release versus time is linear.[19]

First order release rate kinetics: The release rate data are fitted to the following equation
Log (100-F) = kt

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.
F = k t1/2

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.[20]

Korsmeyer and Peppas release model
The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t / M_\infty = K t^n$$

Where, M_t / M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t / M_∞) versus log (time) is linear.[21]

RESULTS AND DISCUSSION

Drug – Excipient compatability studies
It is observed that the peaks of major functional groups of Bendroflumethiazide which are present in spectrum of pure drug. There was no appearance or disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. It means that there are no interactions between drug and other ingredients in a physical mixture and drug is compatible with other ingredients.

FTIR study

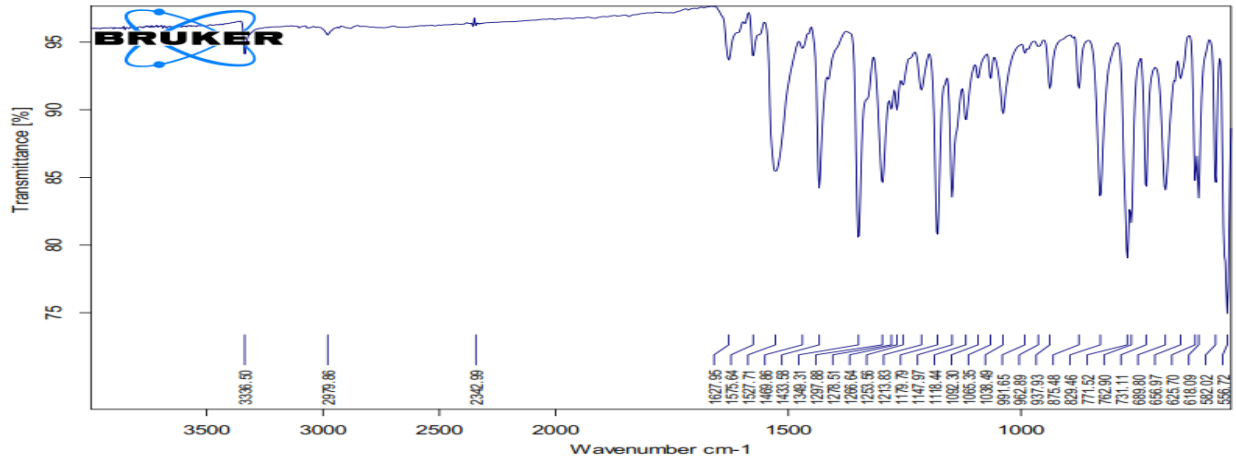

Figure 1: Bendroflumethiazide Pure Drug FTIR.

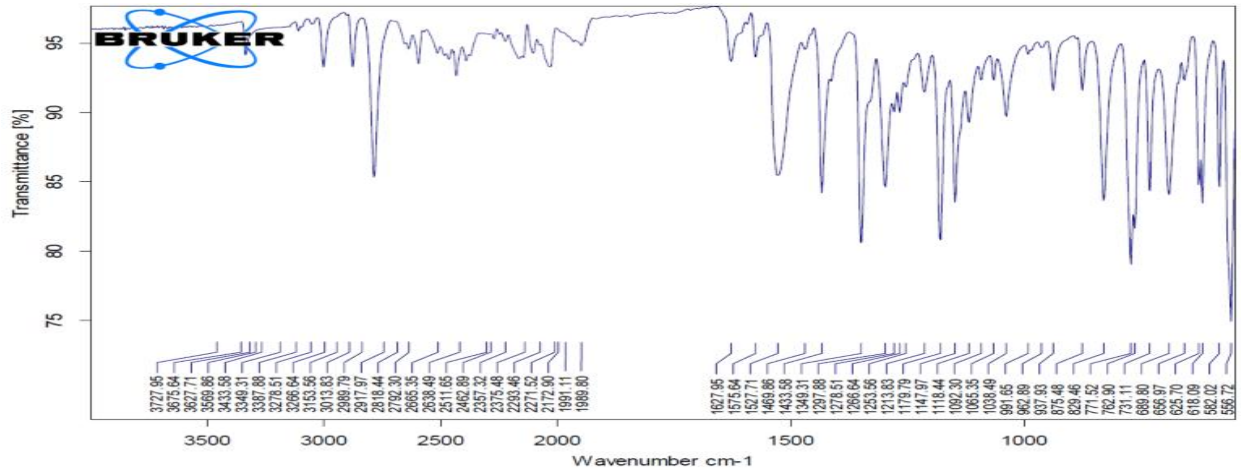

Figure 2: Bendroflumethiazide optimised formula FTIR.

Pre-formulation parameters of powder blend

Table 2: Pre-compression parameters of powder blend.

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	23.12 ± 0.1	0.45 ± 0.03	0.51± 0.061	11.76 ± 0.58	1.13 ± 0.012
F2	25.53 ± 0.57	0.47 ± 0.06	0.55 ± 0.08	14.54 ± 0.47	1.17 ± 0.032
F3	22.46 ± 0.57	0.53 ± 0.08	0.59 ± 0.011	10.16 ± 0.57	1.11 ± 0.015
F4	26.61 ± 0.63	0.51 ± 0.09	0.60 ± 0.071	15 ± 0.15	1.17 ± 0.021
F5	23.15 ± 0.58	0.48 ± 0.01	0.55 ± 0.08	12.72 ± 0.21	1.14 ± 0.012
F6	27.08 ± 0.51	0.53 ± 0.011	0.61 ± 0.06	13.11 ± 0.35	1.15 ± 0.023
F7	24.38 ± 0.56	0.46 ± 0.08	0.53 ± 0.01	13.20 ± 0.42	1.15 ± 0.031
F8	22.26 ± 0.56	0.50 ± 0.055	0.58 ± 0.08	13.79 ± 0.57	1.16 ± 0.026
F9	26.43 ±1 0.62	0.55 ± 0.07	0.64 ± 0.012	14.06 ± 0.12	1.16 ± 0.056

Tablet powder blend was subjected to various pre-compression parameters. The angle of repose values was showed from 20 to 30; it 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±0.03 to 0.53 ± 0.08 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.51± 0.061to 0.64 ± 0.012 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 11 to 16 which showed that the powder has good flow properties. All the formulations were showed the hausner ratio ranging from 0 to 1.25 indicating the powder has good flow properties.

Quality Control Parameters For tablets

Table 3: Post Compression Parameters of Tablets.

Formulation codes	Average Weight (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	98.95 ± 1.22	4.8±0.11	0.45±0.05	4.1±0.05	98.3±0.14
F2	99.15 ± 1.31	4.7±0.15	0.54±0.07	4.2±0.04	99.3±0.13
F3	100.26 ± 0.81	4.5±0.27	0.55±0.02	3.5 ±0.06	98.2±0.15
F4	105.36 ± 1.17	4.7±0.24	0.56±0.04	4.1±0.08	99.2±0.17
F5	97.25 ± 2.02	4.6±0.29	0.48±0.08	3.8±0.09	99.3±012
F6	96.26 ± 2.25	4.7±0.21	0.45±0.02	4.2±0.05	97.2±0.19
F7	102.5 ± 1.15	4.9±0.14	0.51±0.04	3.9±0.03	102.3±0.21
F8	103.63 ± 1.64	4.8±0.13	0.52±0.03	4.1±0.04	103.5±0.14
F9	99.53 ± 1.13	4.5 ± 0.22	0.561 ±0.03	3.8 ±0.02	99.56 ± 0.22

Weight variation and thickness: All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table 7.4. The average tablet weight of all the formulations was found to be between 96.26 ± 2.25to 105.36 ± 1.17**.** The maximum allowed percentage weight variation for tablets weighing >80 mg is 7.5% and no formulations are not exceeding this limit. Thus all the formulations were found to comply with the standards given in I.P. And thickness of all the formulations was also complying with the standards that were found to be between 3.8 ±0.02 to 4.2±0.04.

Hardness and friability: All the formulations were evaluated for their hardness, using monsanto hardness tester and the results are shown in table 7.4. The average hardness for all the formulations was found to be between **(**4.5 ± 0.22 to 4.9±0.14**)** Kg/cm^2 which was found to be acceptable.

Friability was determined to estimate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the formulations were evaluated for their percentage friability using roche friabilator and the results were shown in table 7.4. The average percentage friability for all the formulations was between 0.51±0.04 and 0.56±0.04, which was found to be within the limit.

Drug content: All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown in table 7.4. The drug content values for all the formulations were found to be in the range of **(**97.2±0.19 **to** 103.5±0.14**).** According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the FDT formulations comply with the standards given in IP.

***In Vitro* Drug Release Studies**

The formulations prepared with different natural polymer, Synthetic Polymer by direct compression method. The tablets dissolution study was carried out in paddle dissolution apparatus using 0.1N HCl for 2 hours

and 6.8 pH phosphate buffers for remaining hours as a dissolution medium.

Table 4: Dissolution Data of Bendroflumethiazide Tablets Prepared With Guar gum In Different Concentrations.

Time (hr)	Cumulative Percent Drug Released		
	F1	F2	F3
0	0	0	0
0.5	23.46 ± 1.58	16.45 ± 2.14	12.54 ± 2.16
1	40.24 ± 2.01	21.38 ± 1.56	20.15 ± 1.25
2	61.38 ± 1.57	32.45 ± 1.34	26.72 ± 1.68
3	80.15 ± 1.63	43.83 ± 1.34	39.26 ± 2.05
4	99.51 ± 1.82	59.64 ± 1.82	48.59 ± 1.37
5	-	70.15 ± 2.14	56.15 ± 1.86
6	-	82.47 ± 1.86	68.53 ± 2.05
7	-	99.85 ± 1.75	67.49 ± 1.48
8	-	-	79.34 ± 1.67
9	-	-	88.63 ± 2.14
10	-	-	99.34 ± 1.43
11	-	-	-
12	-	-	-

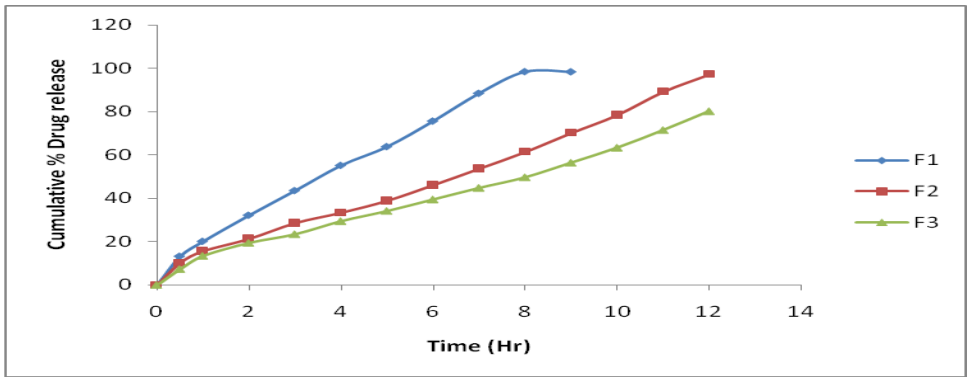

Figure 3: Dissolution study of bendroflumethiazide sustained tablets (F1 to F3).

The % drug release of formulations (F1 to F3) containing guar gum depends on the concentration of polymer. The concentration of guar gum 10% and 20% was unable to retard the drug release up to desired time. When the concentration of polymer increased to 30% was able to retard the drug up to 10 hours. In F3 formulation 30 mg polymer concentration was used, showed maximum % drug release up to 10 hours i.e., 99.34%.

Table 5: Dissolution Data of bendroflumethiazide Tablets Prepared With HPMC K15 M In Different Concentrations.

Time (hr)	Cumulative percent drug released		
	F4	F5	F6
0	0	0	0
0.5	18.26 ± 1.85	12.48 ± 1.26	10.38 ± 1.63
1	32.14 ± 1.34	19.81 ± 1.67	16.47± 2.15
2	50.16 ± 1.52	25.46 ± 2.15	25.49 ± 1.31
3	73.54 ± 1.46	33.46 ± 1.46	31.64 ± 2.15
4	88.49 ± 1.73	42.15 ± 2.07	38.76 ± 1.62
5	99.86 ± 1.34	51.49 ± 1.85	44.57 ± 1.74
6		62.48 ± 1.92	50.15 ± 1.63
7		71.34 ± 2.14	55.64 ± 1.42
8		83.46 ± 1.45	61.49 ± 1.11
9		99.25 ± 2.14	70.56 ± 2.14
10			76.48 ± 1.56
11			87.52 ± 1.72
12			98.11 ± 1.34

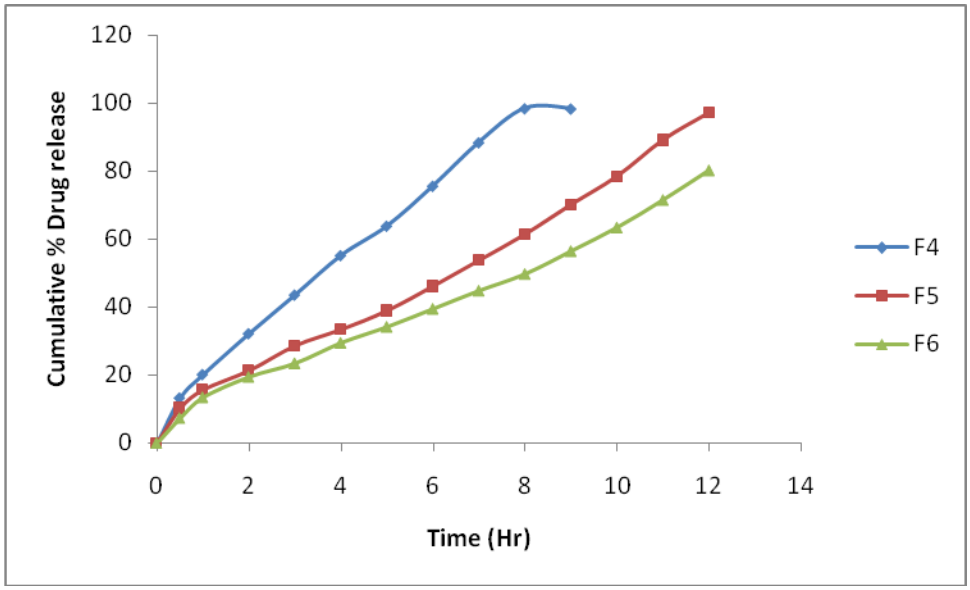

Figure 4: Dissolution study of Bendroflumethiazide tablets (F4 to F6).

The % drug release of F4 to F8 formulations depends on concentration of polymer in the solution. The concentration of HPMC k15M polymer 10% was unable to retard the drug release up to desired time. When the concentration of polymer 20% was retard the drug up to desired time period i.e 99.25% at 9 hours. In F8 formulations, polymer concentration is 30% showed maximum % drug release i.e 98.11% at 12 hours.

Table 6: Dissolution Data of Bendroflumethiazide Tablets Prepared With HPMC K100 M in Different Concentrations.

Time (hr)	Cumulative percent drug released		
	F7	F8	F9
0	0	0	0
0.5	13.24 ± 1.25	10.25 ± 2.05	7.35 ± 1.46
1	20.15 ± 1.65	16.67 ± 1.34	13.45±2.05
2	32.18 ± 2.05	23.34 ± 1.58	19.46 ± 1.35
3	43.56 ± 1.95	30.63 ± 2.04	23.45 ± 1.48
4	55.18 ± 2.15	37.41 ± 1.37	29.48 ± 1.25
5	63.84 ± 1.56	44.95 ± 2.15	34.15 ± 2.05
6	75.61 ± 2.31	50.15 ± 1.64	39.46 ± 1.63
7	88.43 ± 1.48	58.73 ± 1.73	44.78 ± 1.75
8	98.43 ± 1.23	66.42 ± 2.14	49.68 ± 2.15
9	98.36 ± 2.09	73.15 ± 2.35	56.41 ± 2.13
10		81.47 ± 1.64	63.34 ± 1.46
11		90.15 ± 1.85	71.45 ± 2.17
12		99.15±1.63	80.15 ± 1.63

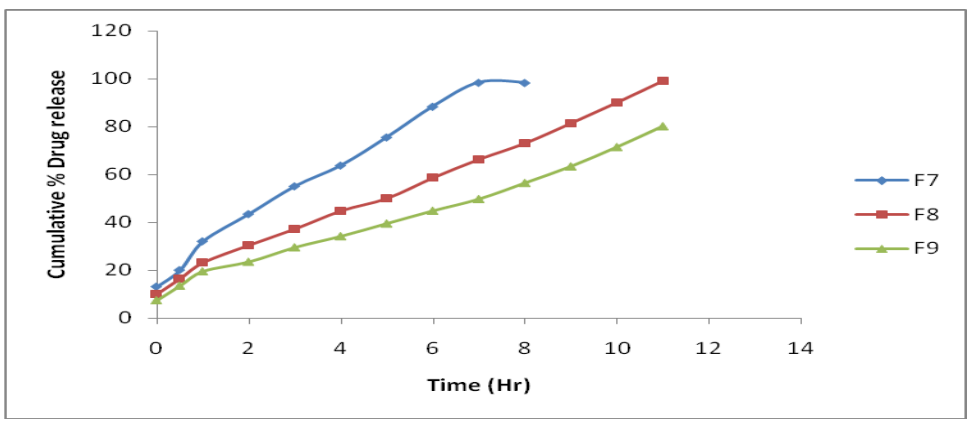

Figure 5: Dissolution study of Bendroflumethiazide tablets (F7 to F9).

The % drug release of F7 to F9 formulations depends on concentration of polymer in the solution. The concentration of HPMC K100M polymer 10% was unable to retard the drug release up to desired time. When the concentration of polymer 20% was retard the drug up to desired time period i.e., 97.15% at 12 hours. In F9 formulations, polymer concentration is 30% showed more retardation up to 12 hours.

From the above results of F7, F8, F9. In that F8 formulation showed good release up to 12 hours so in these F8 formulation was good formulation.

Hence based on dissolution data of 9 formulations, F8 formulation showed better release up to 12 hours. So F8 formulation is optimised formulation.

Application of Release Rate Kinetics To Dissolution Data

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Bendroflumethiazide release from sustained tablets. The data was fitted into various kinetic models such as zero, first order kinetics, higuchi and korsmeyer peppas mechanisms and the results were shown in below table.

Table 7: Release kinetics data for optimized formulation (F8).

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
0	0	0			2.000				100
10.25	0.5	0.707	1.011	-0.301	1.953	20.500	0.0976	-0.989	89.75
16.67	1	1.000	1.222	0.000	1.921	16.670	0.0600	-0.778	83.33
23.34	2	1.414	1.368	0.301	1.885	11.670	0.0428	-0.632	76.66
30.63	3	1.732	1.486	0.477	1.841	10.210	0.0326	-0.514	69.37
37.41	4	2.000	1.573	0.602	1.797	9.353	0.0267	-0.427	62.59
44.95	5	2.236	1.653	0.699	1.741	8.990	0.0222	-0.347	55.05
50.15	6	2.449	1.700	0.778	1.698	8.358	0.0199	-0.300	49.85
58.73	7	2.646	1.769	0.845	1.616	8.390	0.0170	-0.231	41.27
66.42	8	2.828	1.822	0.903	1.526	8.303	0.0151	-0.178	33.58
73.15	9	3.000	1.864	0.954	1.429	8.128	0.0137	-0.136	26.85
81.47	10	3.162	1.911	1.000	1.268	8.147	0.0123	-0.089	18.53
90.15	11	3.317	1.955	1.041	0.993	8.195	0.0111	-0.045	9.85
99.15	12	3.464	1.996	1.079	-0.071	8.263	0.0101	-0.004	0.85

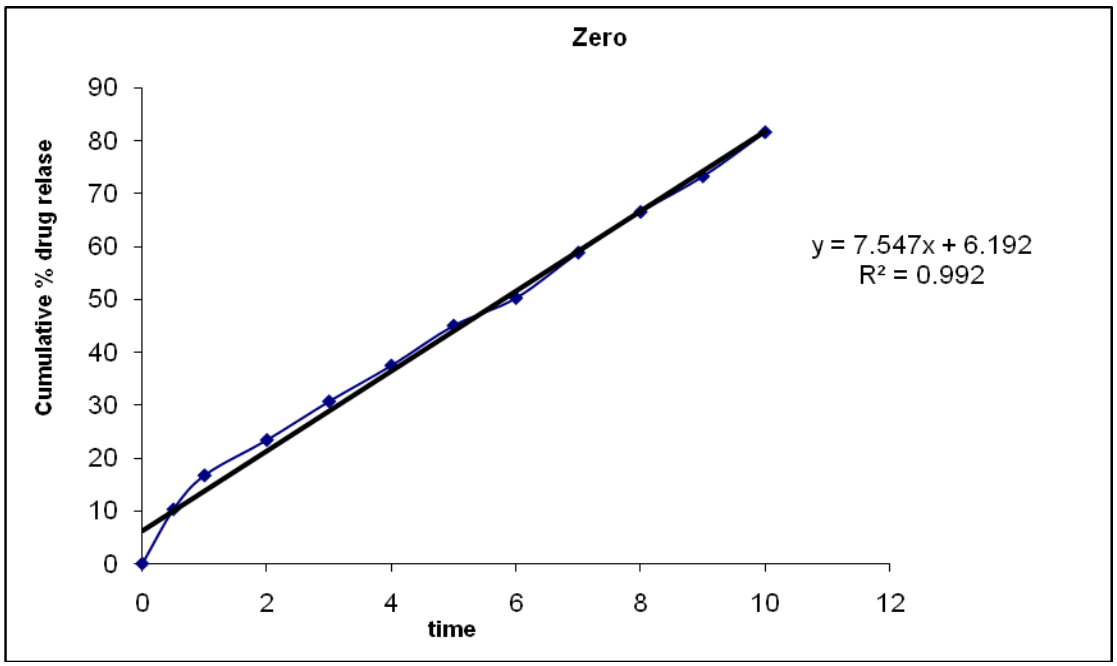

Figure 6: Graph of zero order kinetics.

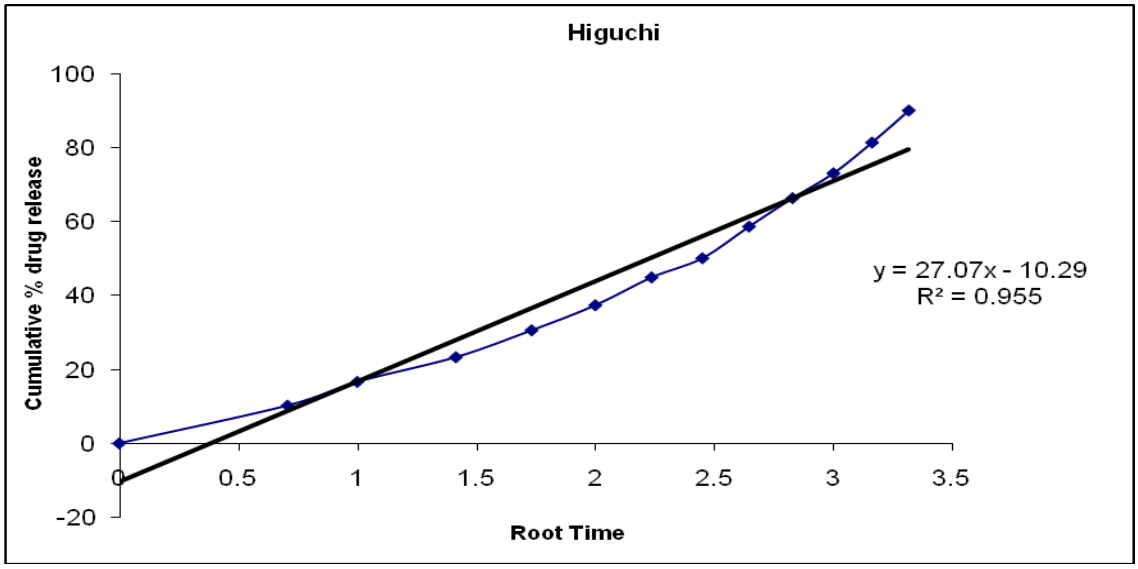

Figure 7: Graph of higuchi release kinetics.

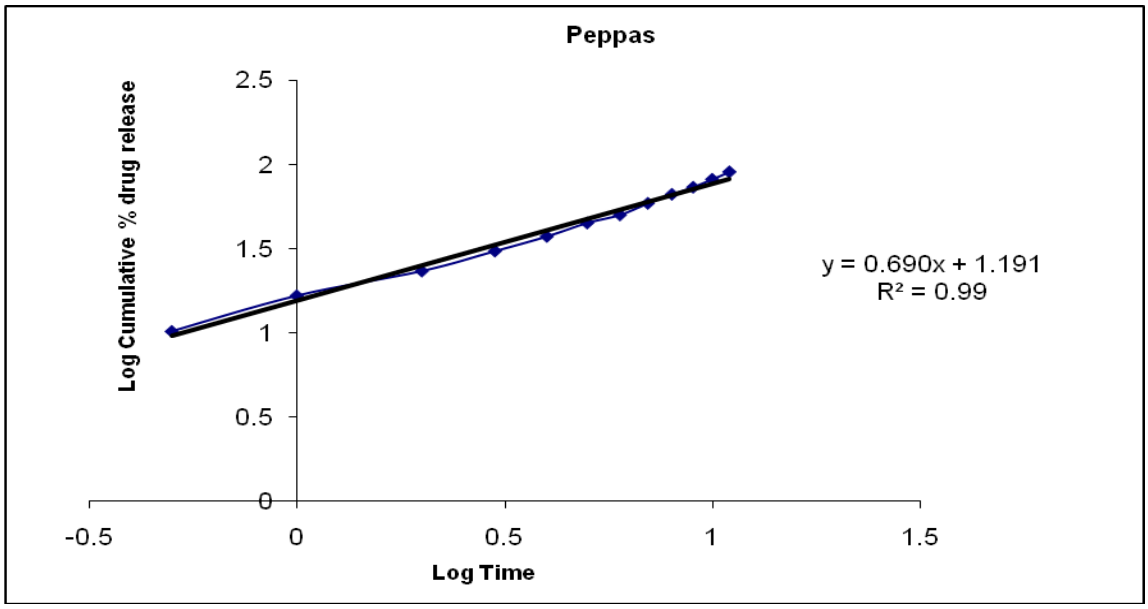

Figure 8: Graph of peppas release kinetics.

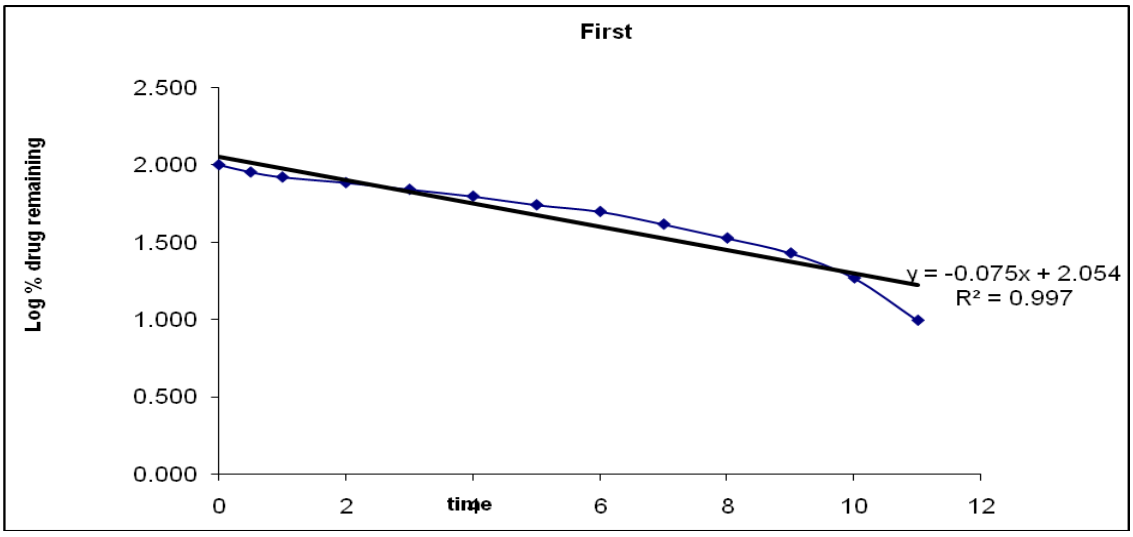

Figure 9: graph of first order release kinetics.

Based on the data above results the optimised formulation followed First order release kinetics.

CONCLUSION

FTIR studies concluded that there was no interaction between drug and excipients. The physico-chemical properties of all the formulations prepared with different polymers like Guar gum, HPMC K15M and HPMC K100M were shown to be within limits. Properties and from the results, it was concluded that the *in vitro* drug release of the optimised formulations is suitable for solid dispersion sustained drug delivery system. The present study concludes that sustained drug delivery of Bendroflumethiazide tablets can be a good way to prolong duration of action of drug by reducing the frequency of dosing of Bendroflumethiazide. Present study concludes that solid dispersion sustained drug delivery system should be a suitable method for Bendroflumethiazide administration. The optimised formulation was found to be F8 formulation. The optimised formulation F8 followed First order release kinetics.

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