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FORMULATION CHARACTERIZATION AND OPTIMIZATION OF BENDROFLUMETHIAZIDE CONTROLLED RELEASE MATRIX TABLETS USING VARIOUS POLYMERS

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ABSTRACT
In the present study Controlled release matrix tablets of bendroflumethiazide is investigated to optimize drug release up to 24hrs. These tablets were prepared by wet granulation method using various polymers like Guar gum, Sodium Alginate, Eudragit-S100, Carnauba Wax, Ethyl Cellulose. The formulated Controlled release matrix tablets were evaluated for different parameters such as Drug-excipient compatibility studies, weight variation, thickness, hardness, content uniformity, In-vitro Buoyancy studies, In vitro drug release studies performed in 0.1N HCl for 2hrs, 22hrs in 6.8PH Phosphate buffer and the data was subjected to Zero order, first order, Higuchi release kinetics and Korsmayer peppas graph. All pre and post compression parameters were found to be within limits. From the drug release data among formulations F_{12} formulation was found to be optimized.

KEYWORDS: Bendroflumethiazide, Controlled Release Matrix Tablets, Carnauba wax, Guar gum, Sodium Alginate, Eudragit S_{100}, Ethyl Cellulose.

INTRODUCTION
Historically, oral drug administration has been the predominant route for drug delivery. It is known to be the most popular route of drug administration due to the fact the gastrointestinal physiology offers more flexibility in dosage form design than most other routes (Chen et al. 2010, Gupta and Robinson 1992, Maderuelo et al. 2011, Tongwen and Binglin 1998). A major challenge for the pharmaceutical industry in drug development is to produce safe and efficient drugs, therefore properties of drugs and the way in which they are delivered must be optimised.

A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time (Chen et al. 2010, Nair et al. 2010, Rajput et al. 2010). The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels (Chen et al. 2010, Grundy and Foster 1996, Lordi 1986). Drug release is dependent on polymer properties, thus the application of these properties can produce well characterised and reproducible dosage forms (Levina and Rajabi-Siahboomi 2004).

Controlled release systems can be influenced by physiological conditions such as motility, ions, pH and enzymes (Abrahamsson et al. 2004, Singh et al. 1968).

Hydrophillic matrix systems are among the most commonly used means for oral controlled drug delivery as they can reproduce a desirable drug profile and are cost effective (Prajapati and Patel 2010). The primary mechanism of drug release from hydrophilic matrices occurs when the polymer swells on contact with the aqueous medium to form a gel layer on the surface of the system. The drug then releases by dissolution, diffusion and/or erosion (Colombo 1993, Siepmann and Peppas 2001a, Tiwari and Rajabi-Siahboomi 2008).

MATERIALS AND METHODS
Bendroflumethiazide was obtained at Sura Labs, Hyderabad, India. Guar gum, Sodium alginate, Eudragit S_{100}, PVP K_{30} and other ingredients were procured from Merck Specialities Private Ltd, Mumbai, India.

1. Formulation development of Tablets
All the formulations were prepared by wet granulation method. The compositions of different formulations are given in Table 1. The tablets were prepared as per the procedure given below and aim is to prolong the release of Benzoflumethiaide. Total weight of the tablet was considered as 100mg. Bendroflumethiazide and all others excipients were mixed thoroughly by triturating up to 15min. Granulating liquid was added to the powder mixture. The powder mixture was then passed through

Sieve#14 and dried in the oven. Tablets were prepared by using wet granulation method.

Table 1: Formulation composition for tablets.

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg
Guar gum	10mg	20mg	30mg	_	_	_						
Sodium alginate	_	_	_	10mg	20mg	30mg						
Eudragit S_{100}		_	_	_	_	_	10mg	20mg	30mg	_	_	
Carnauba Wax										2.5mg	2.5mg	2.5mg
Ethyl Cellulose										10mg	20mg	30mg
PVP-K_{30}	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg
Isopropyl Alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Mg. Stearate	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg
Talc	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg
MCC-P^H102	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

All the quantities were taken in **mg.**

2. Analytical method development

a) Determination of absorption maxima

10mg of Bendroflumethiazide pure drug was dissolved in 10ml of Methanol (stock solution). 1ml of above solution was taken and made up to 10ml by using 0.1N HCl (100µg/ml). From this 1ml was taken and made up to 10 ml of 0.1N HCl (10µg/ml) and the solution was scanned in the range of 200 – 400. Similar procedure was repeated for pH 6.8 Phosphate buffer. UV spectrum was taken using Double beam UV/VIS spectrophotometer.

b) Preparation calibration curve

2.5mg of Bendroflumethiazide pure drug was dissolved in 10ml of methanol (stock solution). 1ml of above solution was taken and made up to10ml by using 0.1N HCl (100µg/ml). From this 1ml was taken and made up to 10 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions containing 2,4,6,8 and 10µg/ml of Bendroflumethiaide per ml of solution. The absorbance of the above dilutions was measured at 277 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 (R^2) which was determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffers.

3. Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

The formulations were subjected to FTIR studies to find out the possible interaction between the drug and the excipients during the time of preparation. FTIR analysis of the Pure drug and optimised formulation were carried out using an FTIR spectrophotometer (Bruker FT-IR - USA).

4. 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.

$$\tan\theta = h/r \quad \tan\theta = \text{Angle of repose.}$$

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

Table 2: Angle of Repose values (as per USP).

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved

and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, V_0, was read.
The bulk density was calculated using the formula:
Bulk Density = M/V_0

Where, M = weight of sample.
V_0 = apparent volume of powder.

Tapped density
After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2% and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula.
Tap = M/V.

Where, Tap= Tapped Density.
M = Weight of sample.
V= Tapped volume of powder.

Measures of powder compressibility
The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:
Carr's Index = [(tap - b)/tap] × 100.
Where, b = Bulk Density.
Tap = Tapped Density.

Table 3: Carr's index value (as per USP).

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
21 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Evaluation of post compression parameters for prepared tablets
The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight Variation Test
To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.
% Deviation = (Individual weight – Average weight/Average weight) × 100.

Table 4: Weight Variation Values.

Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than 250	More than 324	5

Hardness
Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness
Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability
It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Pre-weighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as
% Friability = [(W1-W2) / W] × 100.

Where, W1 = Initial weight of three tablets.
W2 = Weight of the three tablets after testing.

Determination of drug content
Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of drug were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with media. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* drug release studies**
Dissolution parameters

Apparatus (Paddle Type)	--	USP-II
Dissolution Medium	--	0.1N HCl, 6.8 pH Phosphate buffer
RPM	--	50
Sampling intervals (hrs)	--	1hr, 2hr, 4hr, 6hr, 8hr, 10hr, 12hr, 22hr, 23hr, 24hr
Temperature	--	37°C± 0.5°C

Procedure
900ml 0f 0.1N HCl was placed in vessel and the USP apparatus–II (Paddle Type) was assembled. The medium was allowed to equilibrate to temp of 37°C ± 0.5°C. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCl was removed and 6.8pH phosphate buffer was added process was continued up to 12 hrs at 50 rpm. At definite time intervals 5ml of sample was withdrawn, and was replaced with 5ml of buffer. The same was repeated up to 12hrs.Suitable dilutions were done with media and analysed at 277nm (for 0.1N HCl) and 272 nm (for 6.8pH buffer) using UV-spectrophotometer.

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 are fitted to the following equation.
$$F = K_0 t.$$

Where, 'F' is the drug release at time't' and 'K_0' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics
The release rate data are fitted to the following equation.

$$\text{Log (100-F)} = k_t.$$

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.

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.
$$M_t / M_\infty = Kt^n.$$

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 super case II transport, n > 1. In this model, a plot of log (M_t / M_∞) versus log (time) is linear.

Hixson-Crowell release model
$$(100-Q_t)^{1/3} = 100^{1/3} - K_{HC}.t.$$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

RESULTS AND DISCUSSIONS

1. Analytical Method
The graph of bendroflumethiazide was taken in 0.1N HCl at 277nm.

Table.5 Observations for graph of bendroflumethiazide in 0.1N HCL (277 nm)

Conc [µg/ml]	Abs
0	0
2	0.173
4	0.345
6	0.484
8	0.635
10	0.790

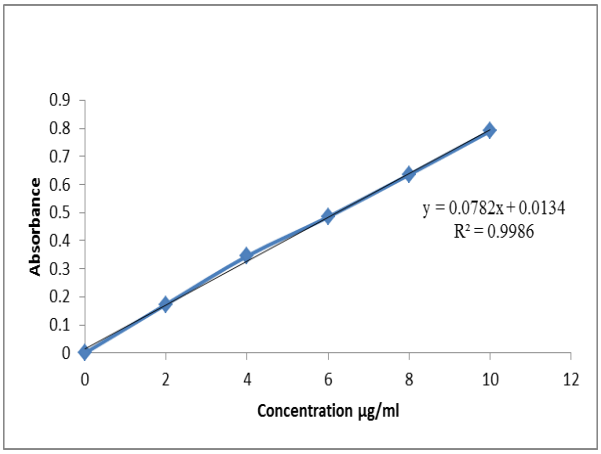

Figure 1: Standard graph of bendroflumethiazide in 0.1N HCL (277 nm)

Table.6 Observations for graph of bendroflumethiazide in 6.8P^{H}(272nm)

Conc [µg/ml]	Abs
0	0
2	0.144
4	0.288
6	0.432
8	0.576
10	0.728

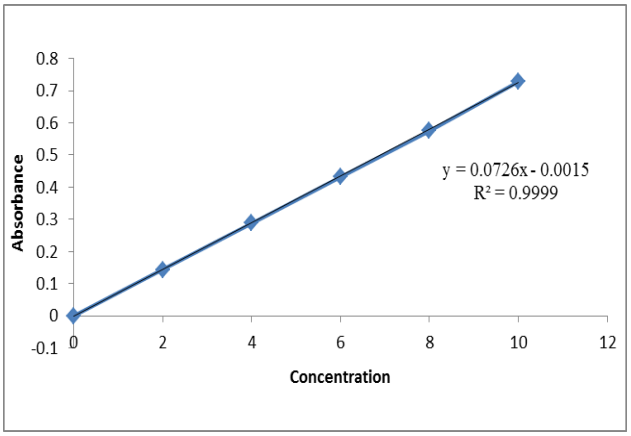

Figure 2: Standard graph of bendroflumethiazide in 6.8P^{H}(272 nm)

2. Drug-Excipient compatibility studies

Fourier Transform-Infrared Spectroscopy:

Fourier transform infrared (FTIR) spectroscopy was employed to characterize further the possible interactions between the drug and the carrier in the solid state on a FTIR spectrophotometer by the ATR (attenuated total reflectance) technique. For this technique ZnSe crystal was used to know the wavelength of those drug and carriers. The spectra were scanned over a frequency range 4000-550 cm-1.

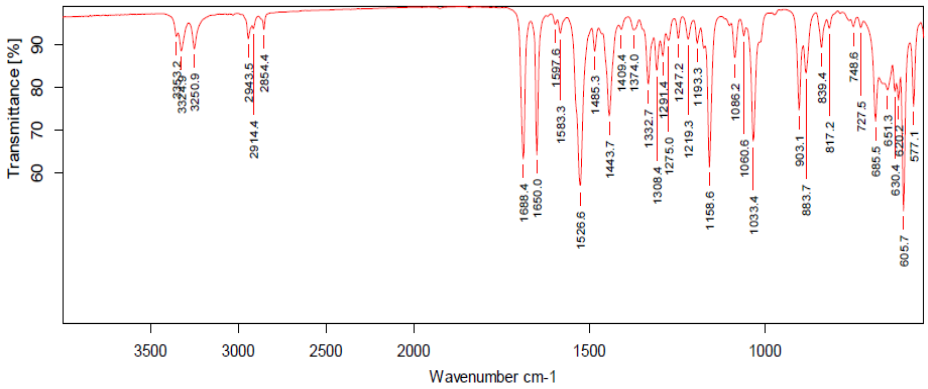

Figure 3: FT-IR Spectrum of bendroflumethiazide pure drug.

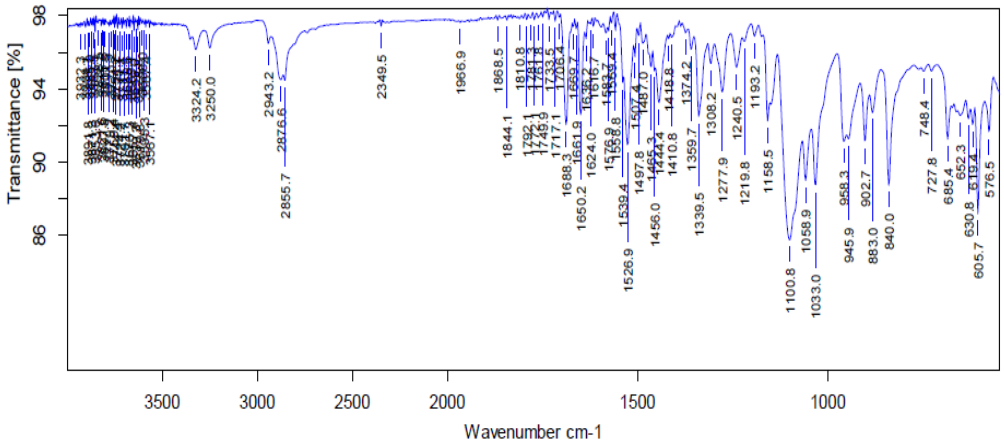

Figure 4: FT-IR Spectrum of Optimized Formulation.

3. Preformulation parameters of powder blend

Table 7:Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	23.01±0.60	2.27±0.15	2.67±0.12	14.98	1.132
F2	24.12±0.51	2.02±0.45	2.32±0.35	12.93	1.148
F3	27.22±0.55	1.85±0.52	2.15±0.45	13.95	1.162
F4	26.31±0.45	2.22±0.21	2.56±0.16	13.28	1.153
F5	25.72±0.72	1.56±0.69	1.78±0.51	12.35	1.141
F6	22.81±0.77	1.23±0.36	1.43±0.23	13.98	1.162
F7	23.41±0.82	1.47±0.16	1.76±0.11	16.47	1.197
F8	27.52±0.65	2.15±0.49	2.42±0.32	11.15	1.125
F9	23.21±0.33	1.69±0.23	1.98±0.19	14.64	1.171
F10	26.47±0.95	2.07±0.74	2.34±0.69	11.53	1.130
F11	27.58±0.24	2.25±0.54	2.51±0.33	10.35	1.115
F12	28.63±0.68	1.99±0.94	2.23±0.29	10.76	1.120

Tablet powder blend was subjected to various pre-formulation parameters.

4. Post compression Parameters for tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

Table 8. *In vitro* quality control parameters for tablets

Formulation code	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	95.54±0.23	5.4±0.36	0.22%	2.2±0.037	96.47%
F2	97.52±0.36	5.2±0.53	0.39%	2.6±0.058	95.55%
F3	95.23±0.16	5.5±0.23	0.52%	3.0±0.023	97.66%
F4	99.37±0.29	5.6±0.28	0.63%	2.3±0.047	98.49%
F5	95.33±0.12	5.3±0.79	0.84%	2.9±0.012	95.28%
F6	99.45±0.33	5.5±0.68	0.49%	2.1±0.05	96.86%
F7	96.55±0.20	5.2±0.74	0.74%	2.4±0.041	98.37%
F8	96.20±0.13	5.2±0.52	0.13%	3.1±0.043	96.57%
F9	99.23±0.65	5.5±0.19	0.44%	2.5±0.082	97.61%
F10	99.75±0.39	5.7±0.89	0.77%	2.3±0.079	99.05%
F11	98.27±0.36	5.4±0.68	0.32%	2.5±0.074	98.23%
F12	96.39±0.44	5.3±0.42	0.52%	3.2±0.37	97.39%

Weight variation: 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 95.23±0.16 to 99.75±0.39.The maximum allowed percentage weight variation for tablets weighing 80-250mg 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.

Thickness: And thickness of all the formulations was also complying with the standards that were found to be between 5.2±0.52 to5.6±0.28.

Hardness: 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 from 2.1±0.05 to 3.2±0.37Kg/cm^2 which were found to be acceptable.

Friability: 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's Friabilator and the results were shown in table 7.4.The average percentage friability for all the formulations was between 0.22 and 0.84,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 7.3. The drug content Values for all the formulations were found to be in the range of **(**95.28 to 99.05**).** 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 formulations comply with the standards given in IP.

5. *In-Vitro* Drug Release Studies

Table 9: Dissolution Data of Bendroflumethiazide Tablets Prepared With Guar Gum (F_1, F_2, F_3 Formulations)

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED (n=3 ±SD)		
	F_1	F_2	F_3
0	0	0	0
1	52.22±1.25	34.29±1.64	25.27±1.92
2	70.29±1.54	52.22±1.47	39.47±1.33
4	86.34±2.15	65.17±1.42	50.12±1.49
6	99.49±1.55	74.29±1.28	66.18±1.45
8		86.39±2.28	75.30±1.63
10		99.44±1.12	86.42±1.85
12			99.51±1.22
22			
23			
24			

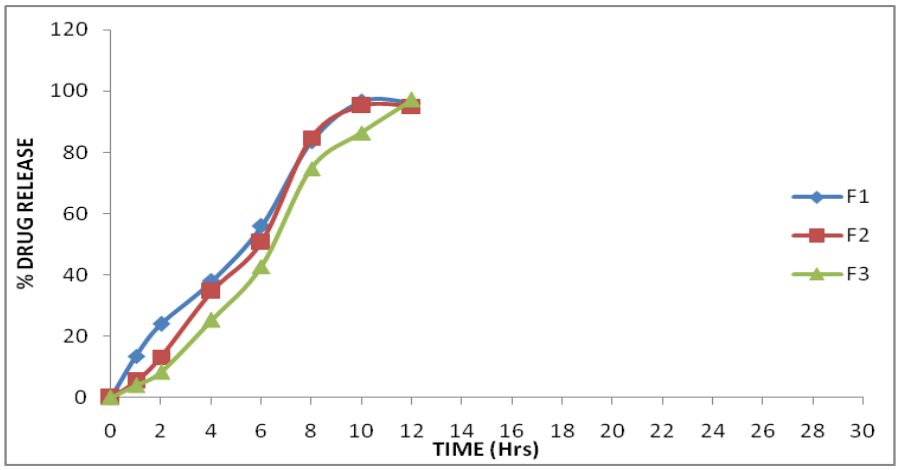

Fig 5: Dissolution profile of Bendroflumethiazide controlled release matrix tablets (F_1, F_2, F_3 formulations).

Table 10: Dissolution Data of Bendroflumethiazide Tablets Prepared With Sodium Alginate (F_4, F_5, F_6 Formulations)

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED (n=3 ± SD)		
	F_4	F_5	F_6
0	0	0	0
1	30.54±1.12	24.21±1.34	17.52±1.54
2	54.25±1.25	39.58±1.59	29.88±1.89
4	74.21±1.33	58.39±1.95	40.85±1.93
6	87.55±1.54	66.86±1.69	57.43±1.34
8	99.21±1.85	74.28±2.58	67.87±1.81
10		86.21±1.32	75.31±2.64
12		94.55±1.54	82.12±2.18
22		99.59±1.57	89.21±2.32
23			99.39±1.85
24			

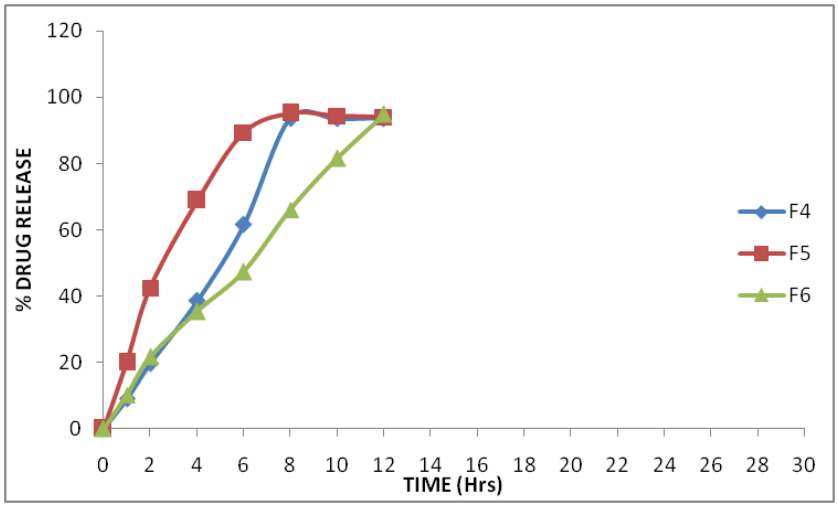

Fig 6: Dissolution profile of Bendroflumethiazide controlled release matrix tablets (F_4, F_5, F_6 formulations).

Table 11: Dissolution Data of Bendoflumethiazide Tablets Prepared With Eudragit-S_{100} (F_7, F_8, F_9 formulations).

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED (n=3 ± SD)		
	F_7	F_8	F_9
0	0	0	0
1	36.21±1.56	24.52±1.52	19.23±2.24
2	48.27±1.49	39.21±1.94	25.24±2.12
4	63..72±1.57	54.12±1.63	40.57±1.42
6	74.24±2.15	68.49±1.49	52.49±1.94
8	85.22±2.24	75.25±2.51	69.51±1.52
10	99.11±1.87	86.32±2.42	76.52±2.49
12		94.19±1.38	87.43±2.59
22		99.54±1.57	94.44±1.74
23			99.18±1.89
24			

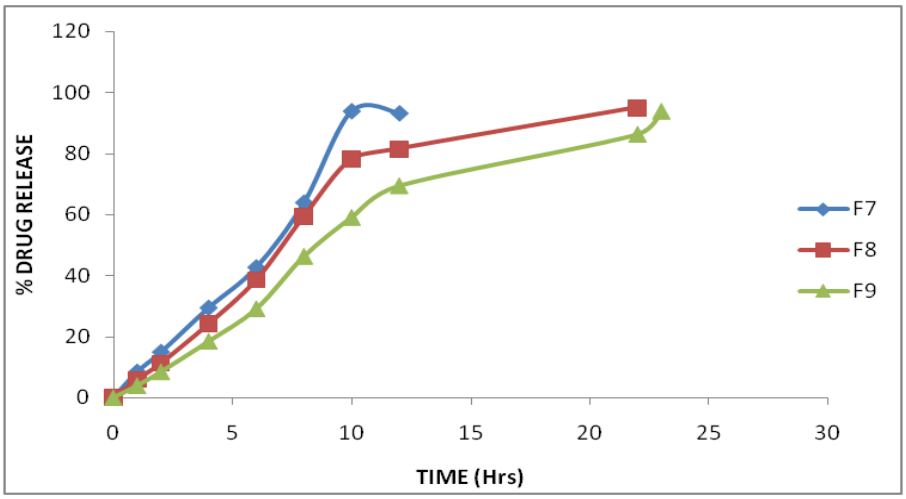

Fig 7: Dissolution Profile of Bendroflumethiazide Prepared With Eudragit S100 Controlled Release Matrix Tablets (F_7, F_8, F_9 Formulations).

Table 12: Dissolution Data of Bendroflumethiazide Tablets Prepared with Carnuba wax (F_{10}, F_{11}, F_{12} Formulations).

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED (n=3 ± SD)		
	F10	F11	F12
0	0	0	0
1	33.19±1.89	21.49±1.47	15.47±1.49
2	42.29±1.98	33.94±1.94	22.97±2.14
4	54.41±1.74	43.34±1.43	32.91±1.59
6	63.44±1.51	51.55±2.42	44.47±1.24
8	72.92±1.48	62.79±1.76	51.23±1.78
10	86.41±1.86	74.19±1.24	62.97±1.67
12	98.95±2.64	82.74±1.39	73.39±1.41
22		91.27±1.56	83.76±1.66
23		99.55±1.74	92.72±1.93
24			99.86±1.76

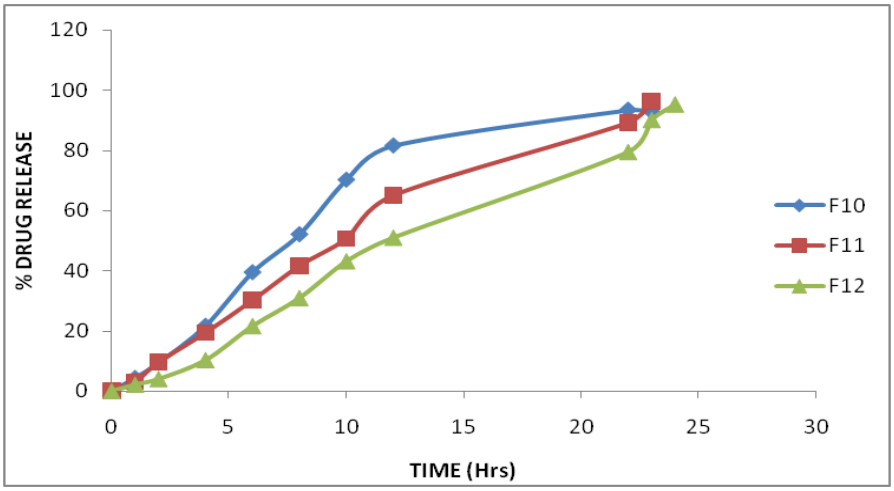

Fig 8: Dissolution Profile of Bendroflumethiazide Controlled Release Matrix Tablets (F_{10},F_{11},F_{12} Formulations)

6 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.

Table 13: Release Kinetics Data for Optimized Formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG (%) RELEASE	LOG(T)	LOG (%) REMAIN
0	0	0			2.000
2.16	1	1.000	1.229	0.000	1.919
4.01	2	1.414	1.400	0.301	1.874
10.31	4	2.000	1.538	0.602	1.816
21.62	6	2.449	1.660	0.778	1.735
30.96	8	2.828	1.724	0.903	1.672
43.18	10	3.162	1.811	1.000	1.549
51.04	12	3.464	1.874	1.079	1.401
79.55	22	4.690	1.932	1.342	1.164
90.16	23	4.796	1.976	1.362	0.728
95.34	24	4.899	2.007	1.380	0

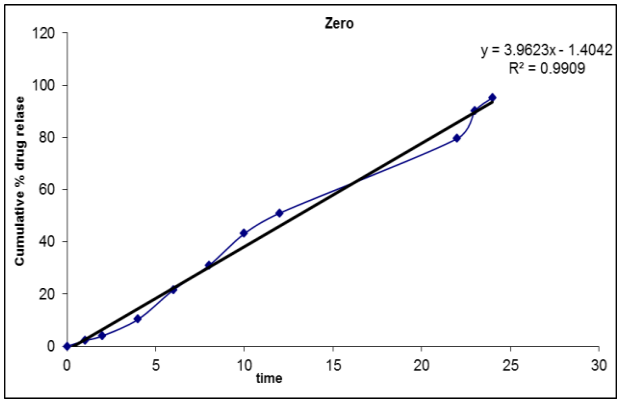

Fig 9: Zero Order Release Kinetics Graph

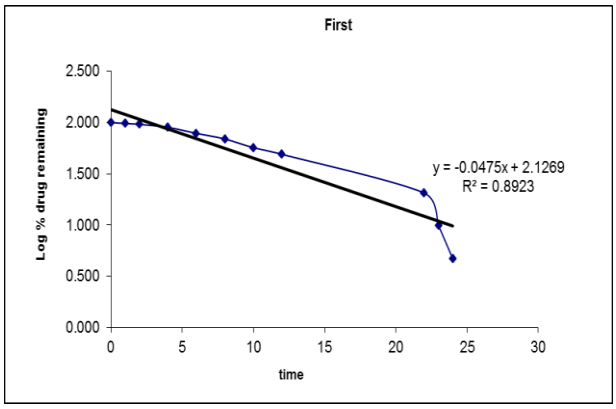

Fig 10: First Order Release Kinetics Graph

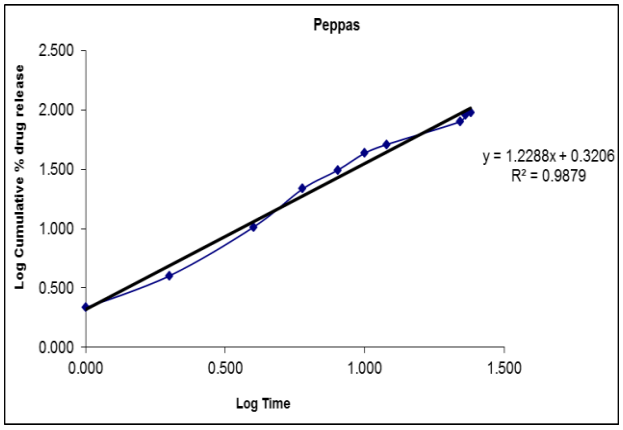

Fig 11: Karsmayer Peppas Graph

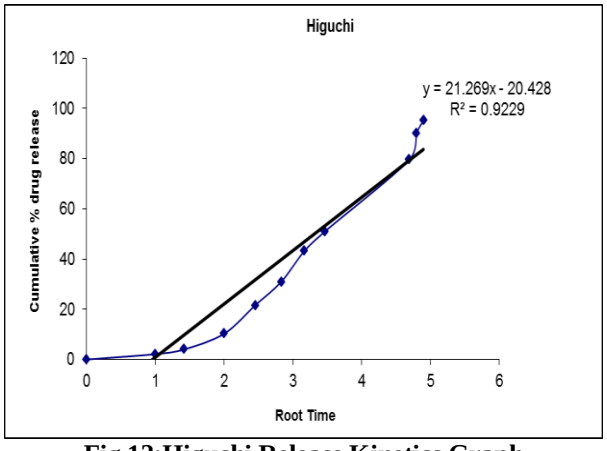

Fig 12:Higuchi Release Kinetics Graph

7. Differential Scanning Calorimetry

The possibility of any interaction between the drug and the carriers during preparation of solid dispersion was assessed by carrying out thermal analysis of drug and polymer alone as well as physical mixture and solid dispersion using DSC. DSC analysis was performed using Hitachi DSC 7020, on 5 to 15 mg samples. Samples were heated in sealed aluminum pan at a rate of 10°C/min conducted over a temperature range of 30 to 350°C under a nitrogen flow of 50 mL/min.

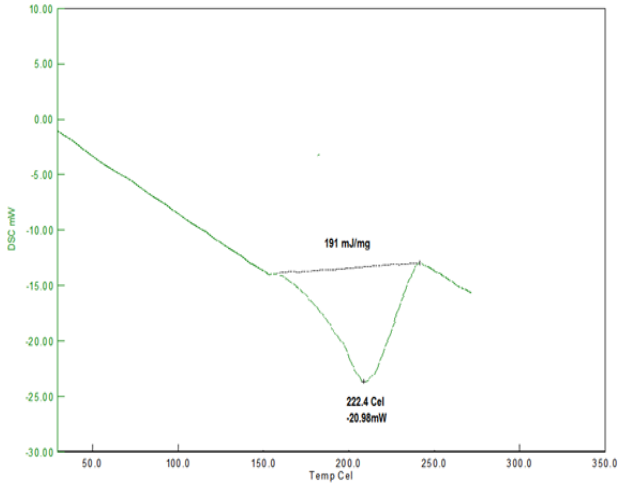

Fig 13: DSC of Pure Drug

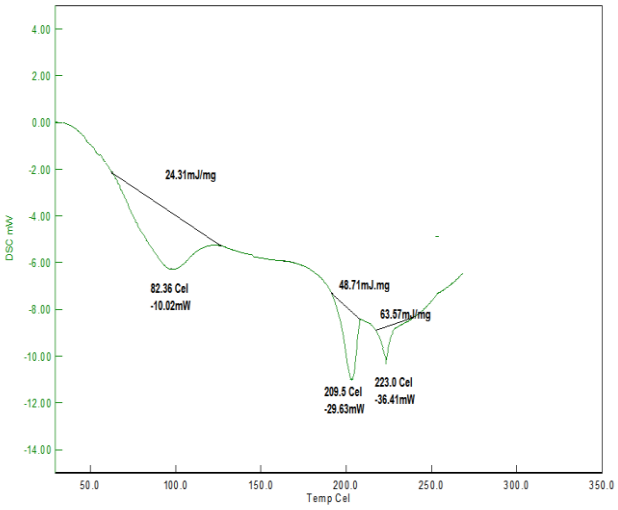

Fig 14: DSC of Drug+ Carnauba Wax + Ethyl Cellulose

8. Accelerated stability studies

Stability is defined as the extent to which a product retains with in specified limits and throughout its period of storage and use *i.e.*, shelf life. Stability studies were carried out on optimized formulation according to International Conference on Harmonization (ICH) guidelines.

The formulation packed in aluminium foil was subjected to accelerated stability testing for 3 months as per ICH

norms at a temperature 40 ± 2°C and relative humidity 75 ± 5%. Samples were taken at regular time intervals of 1month for over a period of 3months and analyzed for the change in physical appearance and drug content by procedure stated earlier. Any changes in evaluation parameters, if observed were noted. Tests were carried out in triplicate and mean value of the observed values was noted along with standard deviation.

Accelerated Stability Studies

The optimized formulation was taken for accelerated stability studies. That formulation was shown for drug content for every month up to 3 months. These studies were given good results (shown in Table 7.14) which mean optimized formulation had good stability up to 3months period.

Table 14: Accelerated stability studies of Optimized formulation F12

	Initial	After 1month	After 2 month	After 3 month
Drug content	97.39%	97.23%	97.07%	96.86%
Physical Appearance	White color	No Change	No change	No change

CONCLUSION

The present study concludes that controlled release matrix tablets prepared using Guar gum, Sodium alginate, EudragitS_{100}, Carnuba wax and Ethyl Cellulose as retarding polymers. Among all the formulations, F12 formulation has shown optimized results. Present study concludes that controlled drug system may be a suitable method for bendroflumethiazide.

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