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Formulation and Evaluation of Sustained Release Matrix Tablet of Cimetidine

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Abstract: The aim of the present research study was to Formulate and Evaluate sustained release tablets of Cimetidine 500mg tablet using direct compression method. Nine formulations were prepared using different polymers like HPMC, Xanthan Gum and Sodium CMC. These Polymers were used in different proportion to control the released of the drug. All the formulations were evaluated of physicochemical tests. All the physicochemical characters of the formulated tablets were within the acceptable limits. The release pattern of the drug was observed over a period of 12 hours and determined the amount of drug by the UV- visible method. Dissolution data showed all formulations showed drug release for 12hrs. Among all the formulations C6 showed best drug release 99.08 %. The optimized formulations were followed zero – order kinetics, korsmeyer –peppas and Higuchi models.

Keywords: Cimetidine Sustained release Tablets.

1. INTRODUCTION:

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body[1]. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action[2, 3]. The term therapeutic substance also applies to an agent such as gene therapy that will induce in vivo production of the active therapeutic agent. 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[4]. 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[5, 6].

The first sustained release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida.

Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ[7, 8].

Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain considerations for the preparation of extended release formulations:

- If the active compound has a long half-life, it is sustained on its own,
- If the pharmacological activity of the active is not directly related to its blood levels,
- If the absorption of the drug involves an active transport and
- If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose.

The above factors need serious review prior to design.

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and Pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed[9].

In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

1.1. Rationale for extended release dosage forms:

Some drugs are inherently long lasting and require only once-a-day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate release dosage forms. However, many other drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. Multiple daily dosing is inconvenient for the patient and can result in missed doses, made up doses, and noncompliance with the regimen[10,11]. When conventional immediate-release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys (troughs) associated with the taking of each dose . However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administered too frequently, minimum toxic concentrations of drug may be reached, with toxic side effects resulting. If doses are missed, periods of sub therapeutic drug blood levels or those below the minimum effective concentration may result, with no benefit to the patient. Extended-release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended-release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period (Fig.1).

The sustained plasma drug levels provided by extended-release products oftentimes eliminate the need for night dosing, which benefits not only the patient but the caregiver as well[12].

7. METHODOLOGY

7.1. Analytical method development:

a) Determination of absorption maxima:

100 mg of Cimetidine pure drug was dissolved in 15ml of Methanol and make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCL (stock

solution-2 i.e 100µg/ml). From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). Scan the 10µg/ml using Double beam UV/VIS spectrophotometer in the range of 200 – 400 nm.

b) Preparation calibration curve:

100mg of Cimetidine pure drug was dissolved in 15ml of Methanol and volume make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCl (stock solution-2 i.e 100µg/ml). From this take 1, 2, 3, 4, and 5ml of solution and make up to 10ml with 0.1N HCl to obtain 10, 20, 30, 40 and 50 µg/ml of Cimetidine solution. The absorbance of the above dilutions was measured at 228nm 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.

7.2. Drug – Excipient compatibility studies

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 using direct sample technique.

7.3 Formulation development of Sustained release Tablets:

All the formulations were prepared by direct compression method. The compositions of different formulations are given in Table. The tablets were prepared as per the procedure given below and aim is to prolong the release of Cimetidine.

Procedure:

In the present work the Cimetidine tablets were prepared by direct compression method. The drug and the excipients were passed through 72# size mesh prior to the preparation of dosage form. The entire ingredients were weighed separately and mixed thoroughly for 10 minutes in double cone blender to ensure uniform mixing in geometric ratio. The tablets were prepared by direct compression technique using 9mm punch.

Table 7.1: Formulation of Cimetidinerelease tablets

Ingredients	C1	C2	C3	C4	C5	C6	C7	C8	C9
Cimetidine	200	200	200	200	200	200	200	200	200
Hpmc	40	80	120	-	-	-	-	-	-
Xanthan gum	-	-	-	40	80	120	-	-	-
Sodium cmc	-	-	-	-	-	-	40	80	120
Pvp	15	15	15	15	15	15	15	15	15
Talc	10	10	10	10	10	10	10	10	10
Mg sterate	5	5	5	5	5	5	5	5	5
Mcc	230	190	150	230	190	150	230	190	150
Total weight	500	500	500	500	500	500	500	500	500

7.4 Evaluation Parameters

7.4.1 Pre Compression parameters

Bulk density (D_B)

Bulk density is the ratio between a given mass of the powder and its bulk volume.

Bulk density = Mass of Powder / Bulk volume of the powder

Bulk density (D_B) = W /V_0

Procedure: An accurately weighed quantity of granules (w) (which was previously passed through sieve No: 40) was carefully transferred into 250 ml measuring cylinder and measure the bulk volume.

Tapped Density (D_T)

Tapped density is the ratio between a given mass of powder (or) granules and the constant (or) fixed volume of powder or granules after tapping.[67]

Tapped density = mass of the powder/ tapped volume

Procedure: An accurately weighed quantity of granules (w) (which was previously passed through sieve No: 40) was carefully transferred into 250 ml measuring cylinder and the cylinder was tapped on a wooden surface from the height of 2.5 cm at two second intervals. The tapping was continued until no further change in volume (until a constant volume) was obtained (V_f). The tapped density was calculated by using the formula

Tapped density (D_T) =W/V_f

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow and was calculated by the formula,

Hausner'sratio = D_T/D_B

Where, D_T is the tapped density
D_B is the bulk density

Compressibility index

Compressibility index (CI) was determined by measuring the initial volume (V_o) and final volume (V_f) after hundred tapping's of a sample in a measuring cylinder. It indicates the powder flow properties and expressed in terms of percentage and given in table no. 14 and calculated by using the formula

% Compressibility index = V_o - V/V_o x 100

Angle of repose

Angle of repose was measured by fixed funnel method. It determines flow property of the powder. It is defined as maximum angle formed between the surface of the pile of powder and the horizontal plane.

The powder was allowed to flow through the funnel fixed to a stand at definite height (h). By measuring the height and radius of the heap of powder formed (r), angle of repose was calculated by using formula given below and the calculated values obtained was shown in table no. 14

$\theta = \tan^{-1} (h / r)$

Where, θ is the angle of repose

h is the height in cm

r is the radius in cm

Flow property

Table 7.2: The flow property of powder blend

Flow property	Angle of repose	Compressibility index (%)	Hausner's ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45

Very poor	56-65	32-37	1.46-1.59
Very very poor	>66	>38	>1.60

7.4.2 Post Compression parameters

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 %.

Table 7.3: IP standards of uniformity of weight

S. No.	Average weight of tablet	% of deviation
1	≤ 80 mg	10
2	> 80 mg to <250 mg	7.5
3	≥ 250 mg	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 – p H 6.8 Phosphate buffer

RPM – 50

Sampling intervals (hrs) – 1, 2, 3, 4, 5, 6, 7, 8, 10, & 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 up to 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 332nm wavelength of drug using UV-spectrophotometer.

7.5 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.

$$F = K_o t$$

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.

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.

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 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.

RESULTS AND DISCUSSION

The present work was designed to developing Sustained tablets of Cimetidine using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

8.1 Analytical Method

8.1.1 Standard graph of Cimetidine in 0.1N HCl:

The scanning of the 10µg/ml solution of Cimetidine in the ultraviolet range (200-400nm) against 0.1 N HCl the maximum peak observed at λ_{max} as 228 nm. The standard concentrations of Cimetidine (5-25µg/ml) was prepared in 0.1N HCl showed good linearity with R^2 value of 0.998, which suggests that it obeys the Beer-Lamberts law.

Table 8.1: Standard curve of Cimetidine in 0.1N HCl

Concentration (µg/ ml)	Absorbance
0	0
5	0.125
10	0.243

15	0.375
20	0.502
25	0.627

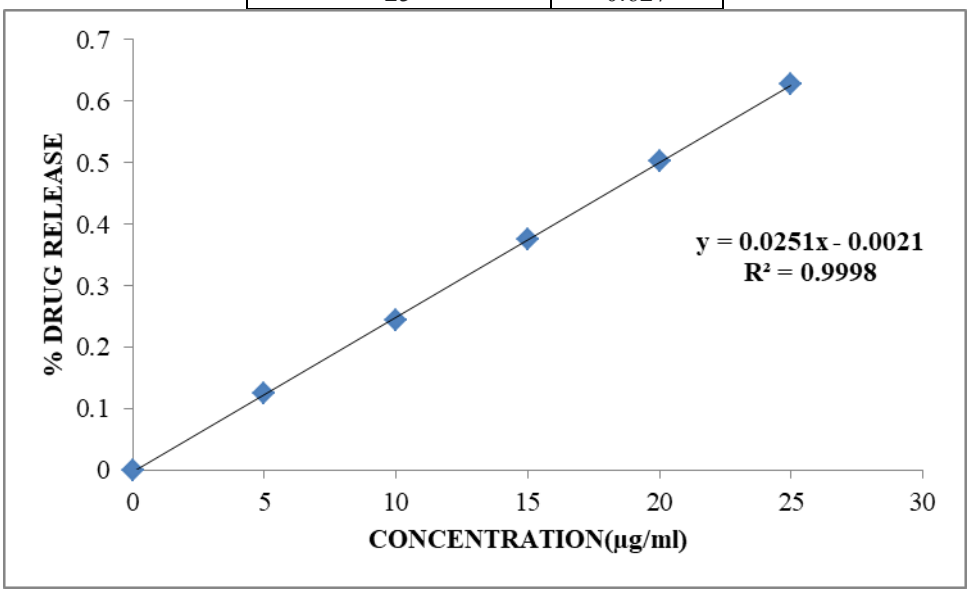

Fig. 8.1: Calibration curve of Cimetidine in 0.1 N HCl at 228nm

8.1.2 Standard Curve of Cimetidine in Phosphate buffer pH 6.8

The scanning of the 10µg/ml solution of Cimetidine in the ultraviolet range (200-400nm) against 6.8 pH phosphate the maximum peak observed at the λ_{max} as 228. The standard concentrations of Labetalol (5-25µg/ml) prepared in 6.8 pH phosphate buffer showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

Table 8.2: Standard curve of Cimetidine in Phosphate buffer pH 6.8

Concentration (µg / ml)	Absorbance
0	0
5	0.133
10	0.255
15	0.388
20	0.514
25	0.639

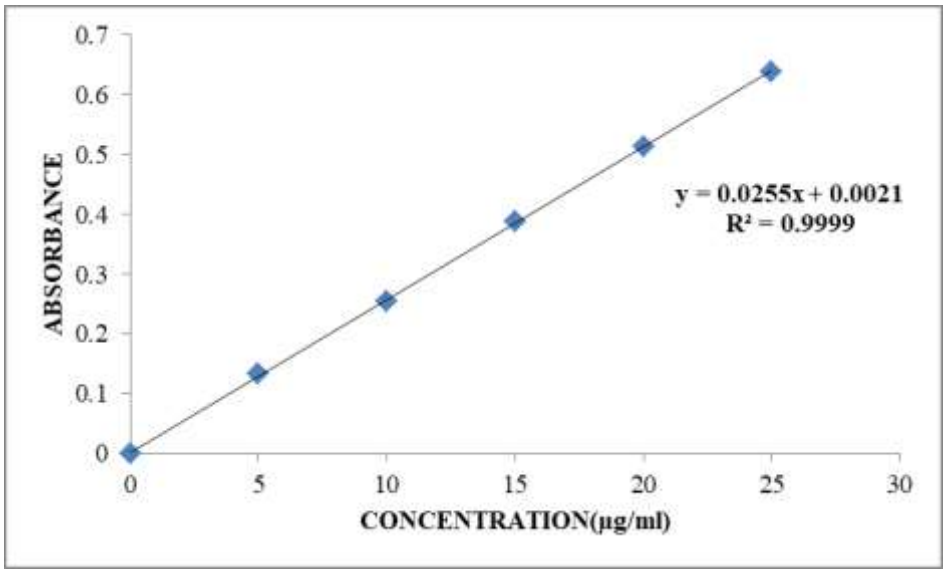

Fig.8.2: Calibration of Cimetidine in Phosphate buffer pH 6.8

8.2 Drug and Excipient Compatibility Studies

8.2.1 FTIR study

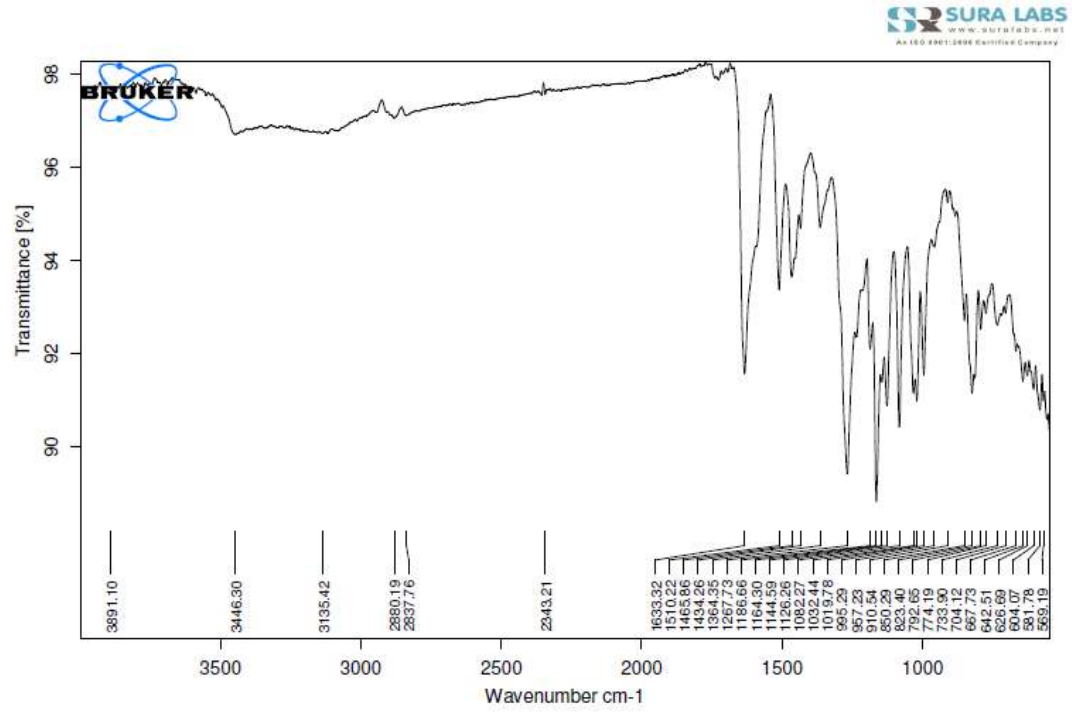

Fig. 8.3: FTIR Graph of Pure Drug

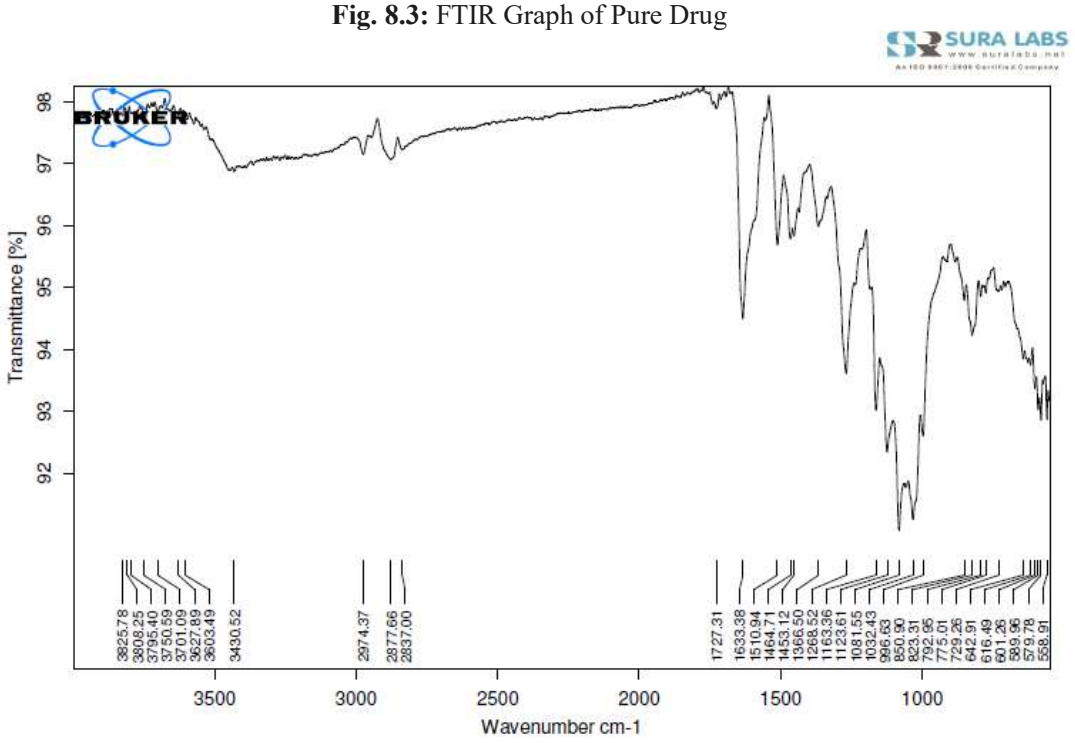

Fig. 8.4: FTIR Graph of Optimised Formulation

From the FTIR data it was evident that the drug and excipients does not have any interactions. Hence they were compatible.

8.3 EVALUATION PARAMETERS

8.3.1 Pre-compression parameters

Table 8.4: 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
C1	30.3 ± 0.09	0.52 ± 0.08	0.64 ± 0.04	22.5 ± 0.0	1.27 ± 0.10
C2	29.6 ± 0.17	0.51 ± 0.10	0.62 ± 0.06	19.5 ± 0.06	1.23 ± 0.15
C3	31.4 ± 0.08	0.50 ± 0.07	0.62 ± 0.03	19.8 ± 0.06	1.24 ± 0.14
C4	26.2 ± 0.12	0.54 ± 0.09	0.65 ± 0.06 2	21.4 ± 0.06	1.26 ± 0.13
C5	33.4 ± 0.07	0.51 ± 0.05	0.63 ± 0.06	20.4 ± 0.12	1.23 ± 0.07
C6	40.1 ± 0.12	0.48 ± 0.04	0.57 ± 0.03	17.4 ± 0.07	1.15 ± 0.04
C7	36.2 ± 0.13	0.52 ± 0.06	0.64 ± 0.07	21.5 ± 0.03	1.23 ± 0.07
C8	37.7 ± 0.12	0.50 ± 0.02	0.62 ± 0.04	18.3 ± 0.04	1.20 ± 0.12
C9	31.8 ± 0.03	0.51 ± 0.06	0.64 ± 0.03	20.1 ± 0.08	1.23 ± 0.10

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 0.48 ± 0.04 to 0.54 ± 0.09 (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 0.57 ± 0.03 to 0.65 ± 0.06 2 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 16.53 which show that the powder has good flow properties. All the formulations has shown the hausner ratio below 1.198 indicating the powder has good flow properties.

8.3.2 Post Compression Parameters For tablets

Table 8.5: Post Compression Parameters of Tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
C1	499.58	4.2	0.19	5.36	98.15
C2	500.22	4.9	0.24	5.64	97.36
C3	496.85	4.6	0.72	5.19	99.12
C4	495.14	4.3	0.48	5.85	96.49
C5	498.82	4.8	0.34	5.41	99.86
C6	499.78	4.1	0.52	5.75	99.0
C7	500.18	4.6	0.64	5.39	95.98
C8	497.82	4.9	0.38	5.54	98.34
C9	499.76	4.2	0.28	5.84	97.22

Weight variation and thickness:

All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table 9.5. The tablet weight of all the formulations was found to be between 495.14 to 500.35. The maximum allowed percentage weight variation for tablets weighing >500 mg is 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 5.16 to 5.85.

Hardness and friability:

All the formulations were evaluated for their hardness, using Monsanto hardness tester and the results are shown in table 9.5. The average hardness for all the formulations was found to be between **(**4.1 **to** 4.9) 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 9.5. The average percentage friability for all the formulations was between 0.19 and 0.72, 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 9.5. The drug content values for all the formulations were found to be in the range of **(**95.98 **to** 99.86**).** 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 polymers 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 8.6: Dissolution Data of Cimetidine Tablets Prepared with (Drug: polymer) Ratios of polymers like

TIME (hr)	CUMULATIVE PERCENT OF DRUG RELEASED		
	C1	C2	C3
0	0	0	0
1	13.57	15.81	15.61
2	19.58	21.32	19.59
3	26.57	25.61	28.12
4	38.69	34.15	38.45
5	45.97	39.29	50.61
6	57.62	52.84	56.18
7	65.48	63.26	68.92
8	68.74	74.82	73.29
9	71.38	79.81	82.72
10	75.35	84.96	86.24
11	79.42	88.21	90.17
12	85.75	91.55	95.54

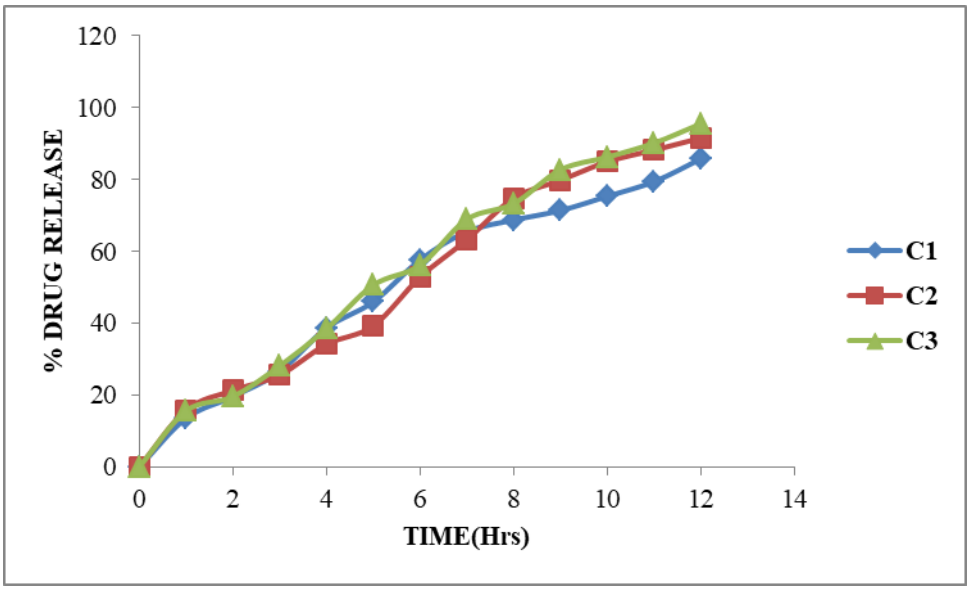

Figure 8.5: Dissolution study of Cimetidine Sustained tablets (C1 to C3)

The % drug release of formulations (C1 to C3) polymer like Xanthan gum depends on the concentration of polymer. In C3formulation was showed maximum % drug release up to 12 hours i.e., 95.54 %.

Table 8.7: Dissolution Data of Cimetidine Tablets Prepared with (Drug: polymer) Ratios of polymers like

TIME (hr)	CUMULATIVE PERCENT OF DRUG RELEASED		
	C4	C5	C6
0	0	0	0
1	24.28	18.93	28.28
2	32.47	22.66	35.15
3	38.59	38.31	40.55
4	47.26	42.69	49.47
5	54.12	55.74	52.82
6	59.63	59.98	68.83
7	66.81	65.82	72.02
8	72.27	74.21	86.52
9	78.44	78.84	90.91
10	83.11	83.23	92.11
11	88.75	91.52	96.22
12	90.81	98.99	99.08

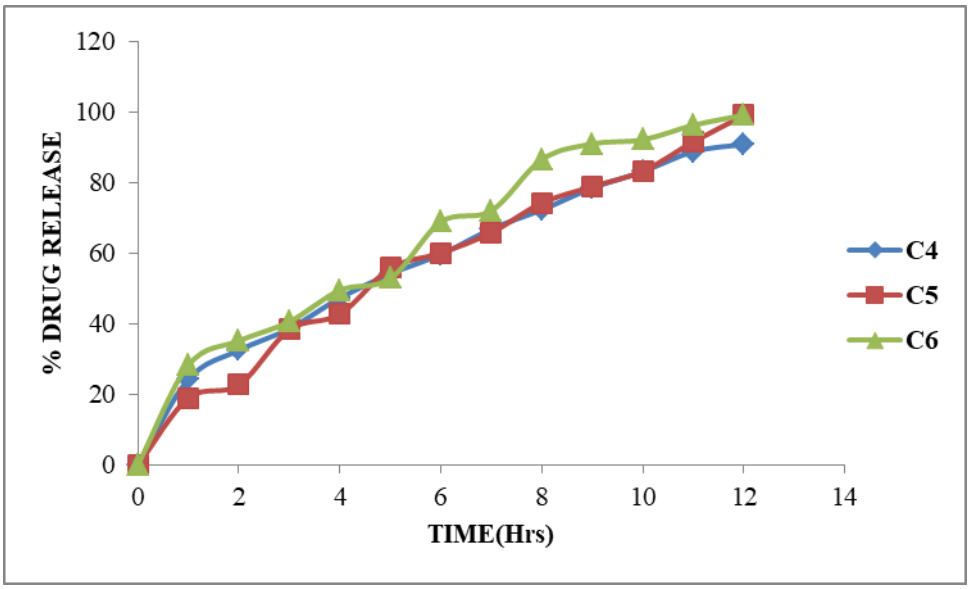

Fig 8.6: Dissolution study of Cimetidine (C4to C6)

The % drug release of F4to F6formulations depends on ratio of polymer in the solution. The concentration of polymer was unable to retard the drug release up to desired time C4 to C6Formulations. The formulation (C6) contains Xanthan gum (120mg) was retarding the drug up to desired time period i.e. 99.08 % at 12 hours.

Table 8.8: Dissolution Data of Cimetidine Tablets Prepared

TIME (hr)	CUMULATIVE PERCENT OF DRUG RELEASED		
	C7	C8	C9
0	0	0	0
1	8.28	10.97	13.40
2	12.26	15.22	19.75
3	18.62	22.35	26.05
4	24.72	28.10	30.58
5	30.73	32.34	36.57
6	35.48	39.23	40.04

7	41.29	45.76	47.96
8	48.68	50.38	58.45
9	56.30	69.45	76.11
10	67.74	74.56	82.74
11	75.19	78.15	86.04
12	77.56	82.12	98.74

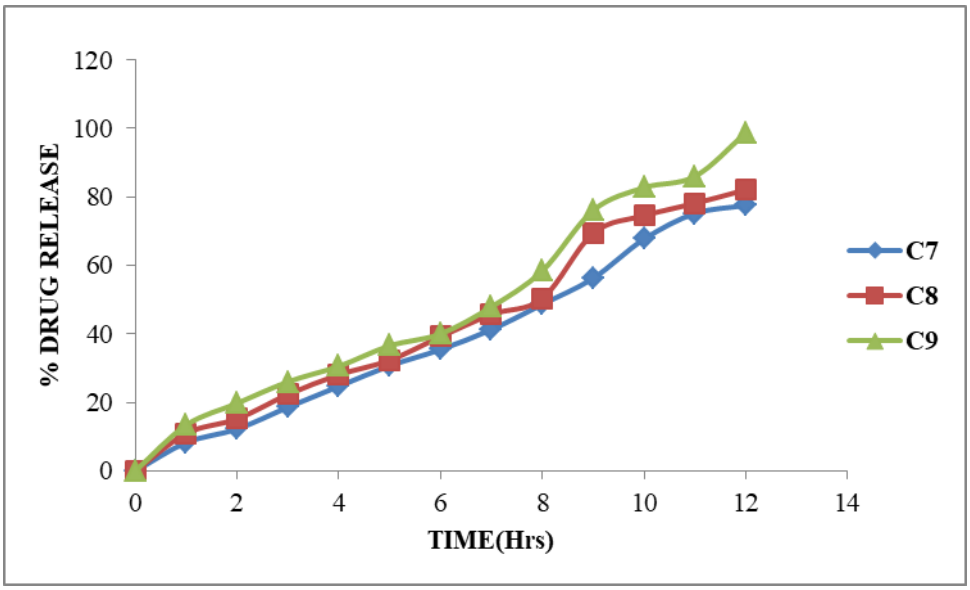

Fig 8.7: Dissolution study of Cimetidine (C7 to C9)

The % drug release of formulations (C7 to C9) polymer like Sodium Cmc depends on the concentration of polymer. In C9 formulation was showed maximum % drug release up to 12 hours i.e., 98.74 %.

Among these Nine Formulation shows better within the specified limits. So C6 formulation is optimised formulation. 99.08%.

8.4 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 Labetalol 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 it follows the zero order kinetics.

Table 8.9: Release kinetics data for optimized formulation (C6)

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
28.28	1	1.000	1.451	0.000	1.856	28.280	0.0354	-0.549	71.72	4.642	4.155	0.487
35.15	2	1.414	1.546	0.301	1.812	17.575	0.0284	-0.454	64.85	4.642	4.018	0.624
40.55	3	1.732	1.608	0.477	1.774	13.517	0.0247	-0.392	59.45	4.642	3.903	0.739
49.47	4	2.000	1.694	0.602	1.704	12.368	0.0202	-0.306	50.53	4.642	3.697	0.945
52.82	5	2.236	1.723	0.699	1.674	10.564	0.0189	-0.277	47.18	4.642	3.613	1.028
68.83	6	2.449	1.838	0.778	1.494	11.472	0.0145	-0.162	31.17	4.642	3.147	1.494
72.02	7	2.646	1.857	0.845	1.447	10.289	0.0139	-0.143	27.98	4.642	3.036	1.606
86.52	8	2.828	1.937	0.903	1.130	10.815	0.0116	-0.063	13.48	4.642	2.380	2.262
90.91	9	3.000	1.959	0.954	0.959	10.101	0.0110	-0.041	9.09	4.642	2.087	2.555
92.11	10	3.162	1.964	1.000	0.897	9.211	0.0109	-0.036	7.89	4.642	1.991	2.651
96.22	11	3.317	1.983	1.041	0.577	8.747	0.0104	-0.017	3.78	4.642	1.558	3.084
99.08	12	3.464	1.996	1.079	-0.036	8.257	0.0101	-0.004	0.92	4.642	0.973	3.669

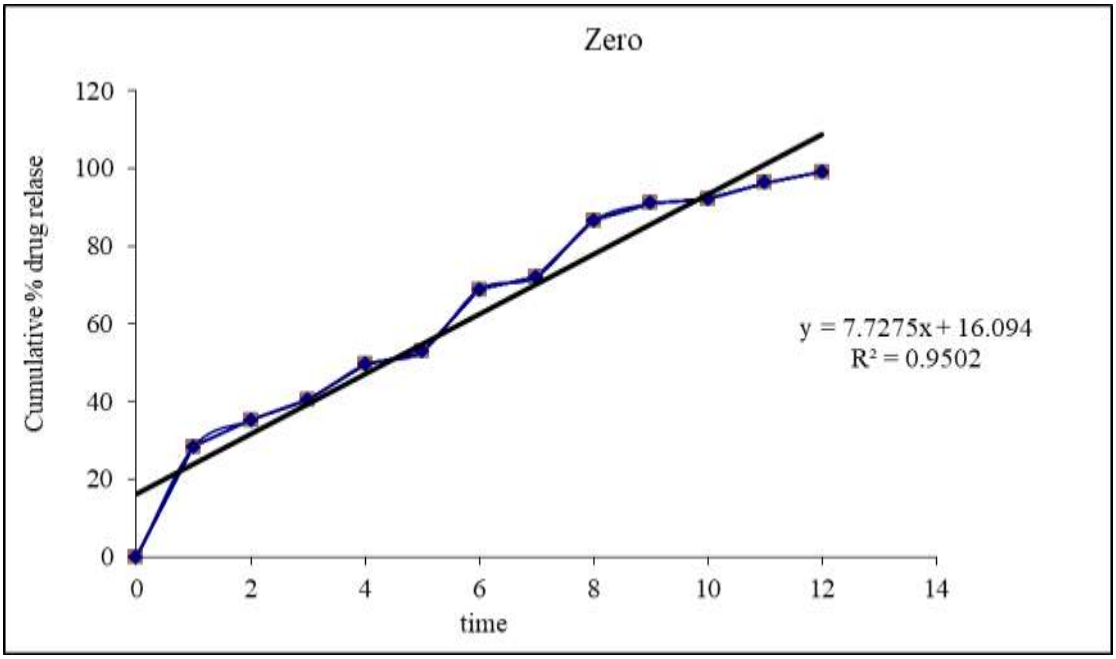

Fig 8.8: Graph of zero order kinetics

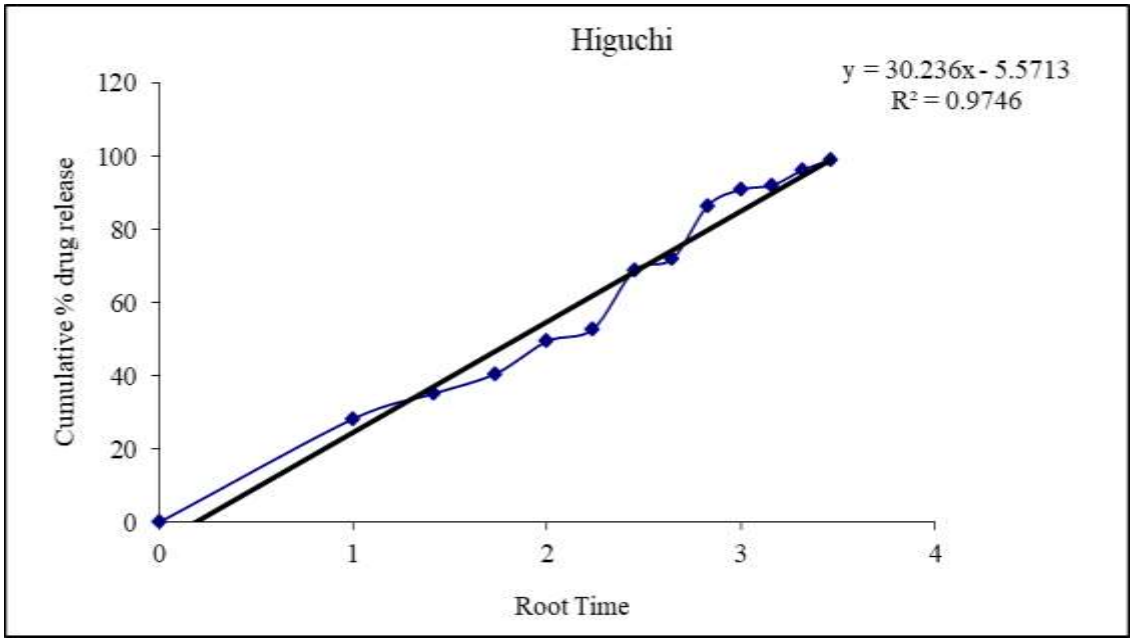

Fig 9.9: Graph of higuchi release kinetics

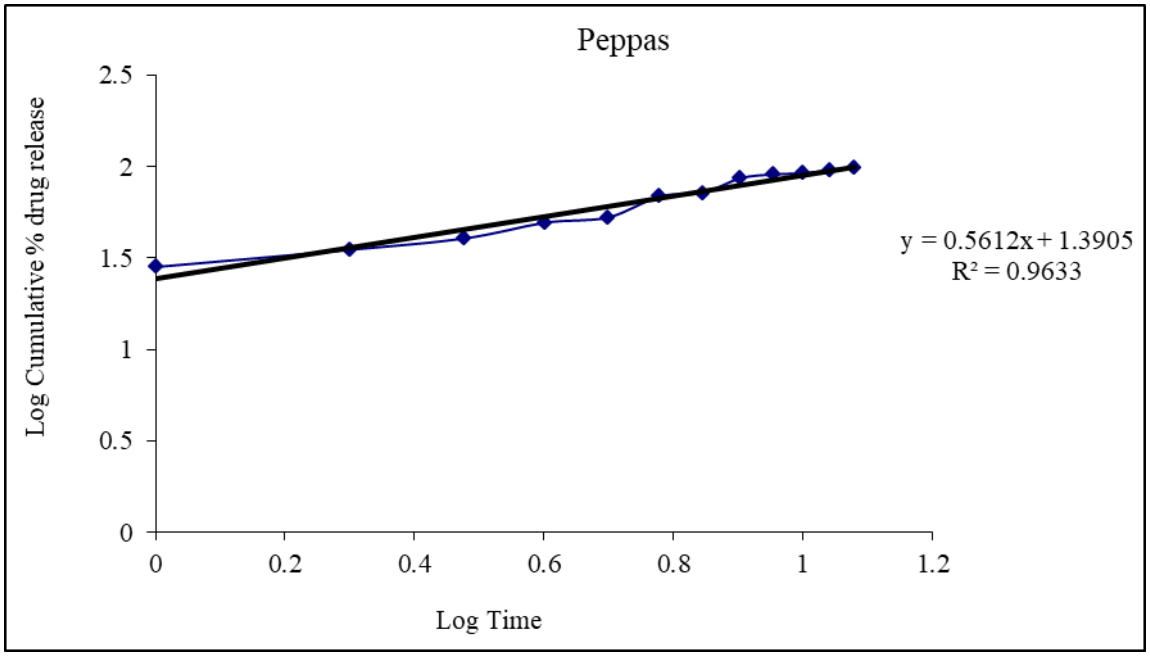

Fig 8.11: Graph of peppas release kinetics

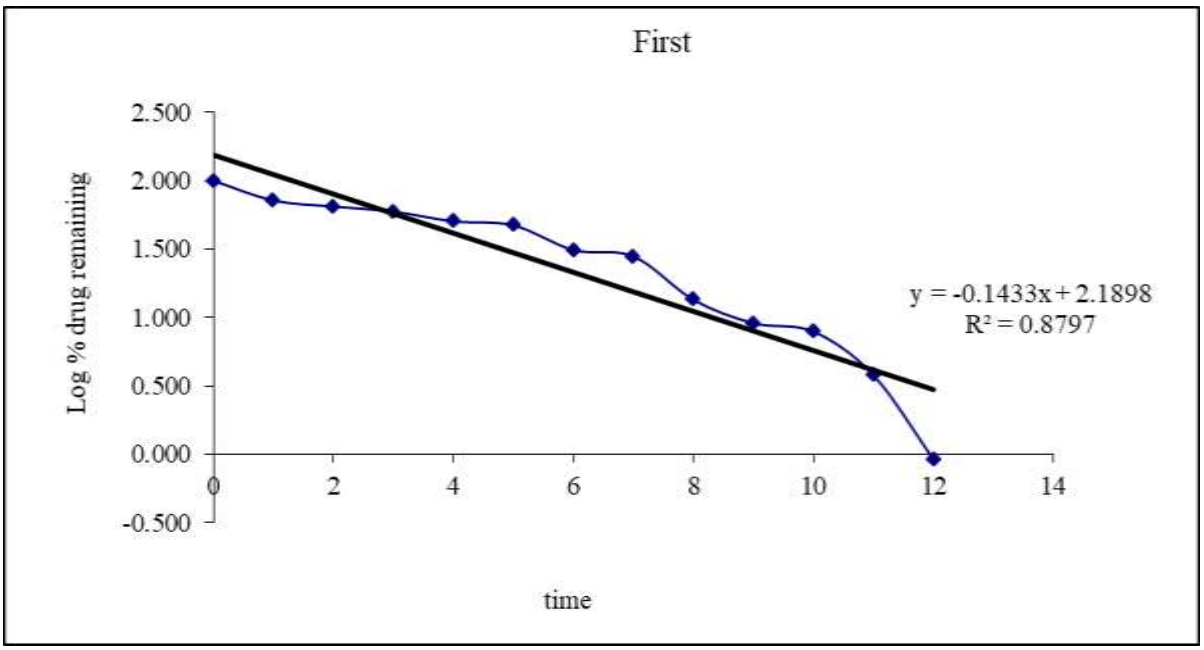

Fig 8.12: graph of first order release kinetics

Based on the data above results the optimized formulation followed Peppas release kinetics.

CONCLUSION

Sustained release tablets of Cimetidine were prepared successfully using polymers such as HPMC, Xanthan gum and Sodium cmc in various concentrations. The particle size and drift behavior of the granules were found to be in accordance with the official standards. Direct compression method was selected on the basis of Good compressibility index of the granules. The physical properties of compressed tablets like thickness, hardness, weight variation and friability were in compliance with the official limits. Free-flowing powder facilities the formulation of tablets with ideal properties. The drug release was primarily controlled by the type and concentration resulted in altered drug release. On the basis of these results it can be concluded that formulation was prolong duration. In vitro drug release was 99.08% was C6 it is consider as an optimized formulation.

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