CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.8206298

Available online at: http://www.iajps.com *Research Article*

FORMULATION DEVELOPMENT AND *IN VITRO* CHARACTERIZATION OF FAMOTIDINE SUSTAINED RELEASE MATRIX TABLETS

Rekadi Vinay Kumar*[1], Mrs. M.Vineela[1], Mr. D.Appalaraju[1]

[1]Department of Pharmaceutics, Pydah College of Pharmacy Patavala, Andhra University, Kakinada, Andhra Pradesh.

Article Received: May 2023 **Accepted:** June 2023 **Published:** July 2023

Abstract:

The aim of the present study was to develop sustained release formulation of Famotidine to maintain constant therapeutic levels of the drug for over 12 hrs. By using different ratios of synthetic polymers like HPMC K100M, Ethyl cellulose Natural polymer like Xanthan gum was employed as 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 (F3) showed better and desired drug release pattern i.e., 96.61% in 24 hours. It contains the HPMC K100M 1:3 ratios as sustained release material. It followed Higuchi release kinetics mechanism.

Keywords: *Famotidine, Sustained release tablets*

Corresponding author:

Rekadi Vinay Kumar,
Department of Pharmaceutics,
Pydah College of Pharmacy
Kakinada, Andhra Pradesh
Email Id- vinaykumarhv2830@gmail.com

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Please cite this article in press Rekadi Vinay Kumar et al, ***Formulation Development And In Vitro Characterization Of Famotidine Sustained Release Matrix Tablets,*** *Indo Am. J. P. Sci, 2023; 10 (07).*

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.

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].

MATERIALS:

Famotidine Provided by SURA LABS, Dilsukhnagar, Hyderabad. ,HPMC K100M Merck Specialities Pvt Ltd, Mumbai, India ,Ethyl cellulose Merck Specialities Pvt Ltd, Mumbai, India Xanthan gum Merck Specialities Pvt Ltd, Mumbai, India ,PVP Merck Specialities Pvt Ltd, Mumbai, India ,Iso propyl ,alcohol Merck Specialities Pvt Ltd, Mumbai, India ,Talc Merck Specialities Pvt Ltd, Mumbai, India ,Magnesium ,Stearate Merck Specialities Pvt Ltd, Mumbai, India ,Microcrystalline cellulose Merck Specialities Pvt Ltd, Mumbai, India

METHODOLOGY:

Analytical method development:

a) Determination of absorption maxima:

100mg of Famotidine 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 Famotidine 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 5 ml of solution and make up to 10ml with 0.1N HCL to obtain 10, 20, 30, 40 and 50 µg/ml of Famotidine per ml of solution. The absorbance of the above dilutions was measured at 271nm 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.

Table1: Formulation of Sustained release tablets

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Famotidine	20	20	20	20	20	20	20	20	20	20	20	20
HPMC K100M	30	60	90	120	-	-	-	-	-	-	-	-
Ethyl cellulose	-	-	-	-	30	60	90	120	-	-	-	-
Xanthan gum	-	-	-	-	-	-	-	-	30	60	90	120
PVP	15	15	15	15	15	15	15	15	15	15	15	15
Iso propyl alcohol	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3	3
MCC	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
Total weight	200	200	200	200	200	200	200	200	200	200	200	200

RESULTS AND DISCUSSION:

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

Analytical Method:

Standard graph of Famotidine in 0.1N HCL:

The scanning of the 10µg/ml solution of Famotidine in the ultraviolet range (200-400nm) against 0.1 N HCL the maximum peak observed at λ_{max} as 271 nm. The standard concentrations of Famotidine (10-50 µg/ml) was prepared in 0.1N HCL showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

Table 2: Standard curve of Famotidine in 0.1N HCL

Concentration (µg/ ml)	Absorbance
0	0
10	0.119
20	0.221
30	0.323
40	0.431
50	0.531

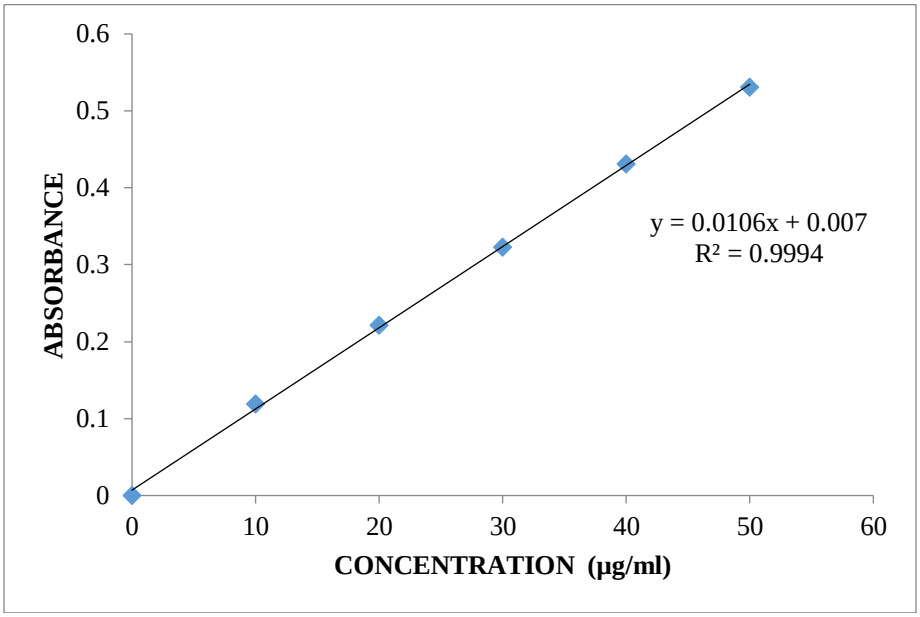

Fig. 1: Calibration curve of Famotidine in 0.1 N HCL at 271 nm

Table3: Standard curve of Famotidine in Phosphate buffer pH 6.8

Concentration (µg / ml)	Absorbance
0	0
10	0.125
20	0.22
30	0.333
40	0.440
50	0.536

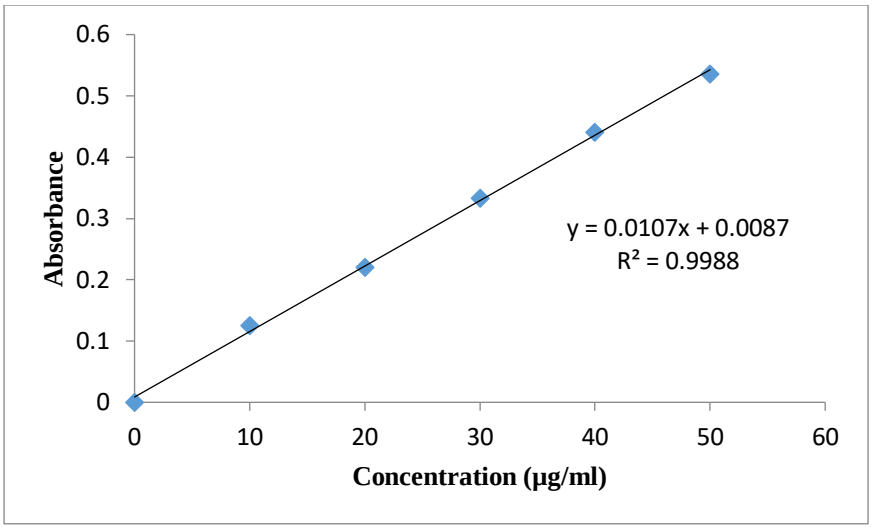

Fig.2: Calibration of Famotidine in Phosphate buffer pH 6.8

Pre-compression parameters

Table4: 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	25.15 ± 0.58	0.49 ± 0.01	0.56 ± 0.08	12.5 ± 0.21	1.14 ± 0.012
F2	28.53 ± 0.57	0.48 ± 0.06	0.56 ± 0.08	14.28 ± 0.47	1.16 ± 0.032
F3	28.38 ± 0.56	0.47 ± 0.08	0.54 ± 0.01	12.96 ± 0.42	1.14 ± 0.031
F4	27.61 ± 0.63	0.53 ± 0.09	0.61 ± 0.071	13.1 ± 0.15	1.15 ± 0.021
F5	25.41 ±0.65	0.52 ±0.091	0.59 ±0.064	14.21 ±0.17	1.25 ±0.022
F6	26.08 ± 0.51	0.55 ± 0.011	0.62 ± 0.06	11.29 ± 0.35	1.12 ± 0.023
F7	25.25 ±0.52	0.43 ±0.022	0.61 ±0.033	11.20 ±0.03	1.10 ±0.06
F8	25.46 ± 0.57	0.55 ± 0.08	0.62 ± 0.011	11.29 ± 0.57	1.12 ± 0.015
F9	26.43 ±0.62	0.56 ± 0.07	0.63 ± 0.012	11.11 ± 0.12	1.12 ± 0.056
F10	24.16 ±0.68	0.54 ± 0.051	0.64 ±0.013	11.21 ±0.21	1.14 ±0.051
F11	26.12 ± 0.1	0.44 ± 0.03	0.50± 0.061	12 ± 0.58	1.13 ± 0.012
F12	27.26 ± 0.56	0.52 ± 0.055	0.59 ± 0.08	11.86 ± 0.57	1.13 ± 0.026

Post Compression Parameters For tablets

Table.5: Post Compression Parameters of Tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (% loss)	Thickness (mm)	Drug content (%)
F1	200.23 ±0.25	4.8±0.03	0.52±0.03	4.7±0.04	103.5 ± 0.14
F2	201.53 ± 0.34	4.5±0.02	0.56±0.03	4.2 ±0.02	99.50 ± 0.22
F3	199.25 ± 2.02	4.6±0.09	0.48±0.08	4.6 ±0.09	104.3 ± 012
F4	198.25± 1.15	4.7±0.01	0.45±0.02	4.3 ±0.05	97.2 ± 0.19
F5	202.5 ± 0.86	4.7±0.04	0.55±0.07	4.3 ±0.05	98.3 ± 0.20
F6	203.26 ± 1.25	4.7±0.01	0.45±0.02	4.4±0.05	98.2 ± 0.19
F7	199.5 ± 0.95	4.8±0.07	0.51±0.04	4.3 ±0.03	102.3 ± 0.28
F8	202.26 ± 0.81	4.5±0.01	0.55±0.02	4.6±0.06	98.2 ± 0.15
F9	201.36 ± 1.17	4.7±0.04	0.56±0.04	4.7±0.08	100.8 ± 0.17
F10	199.95 ± 1.72	4.8±0.01	0.45±0.05	4.4 ±0.05	98.8 ± 0.14
F11	202.15 ± 1.31	4.7±0.05	0.54±0.07	4.6±0.04	99.3 ± 0.13
F12	201.5 ± 0.25	4.8±0.04	0.51±0.04	4.6±0.03	102.3 ± 0.21

Quality control parameters for tablets:

Table6: Dissolution Data of Famotidine Tablets Prepared with HPMC K100M in Different Ratios

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED			
	F1	F2	F3	F4
0	0	0	0	0
1	21.56	22.67	38.31	28.20
2	29.56	27.19	46.57	36.58
3	35.43	33.86	53.86	45.69
4	44.95	39.60	58.48	53.55
5	52.12	47.86	65.77	59.38
6	63.76	56.78	71.68	65.60
7	68.27	62.41	79.54	71.42
8	72.54	79.17	85.43	78.31
10	78.45	84.33	90.38	86.34
12	89.14	91.01	96.61	90.29

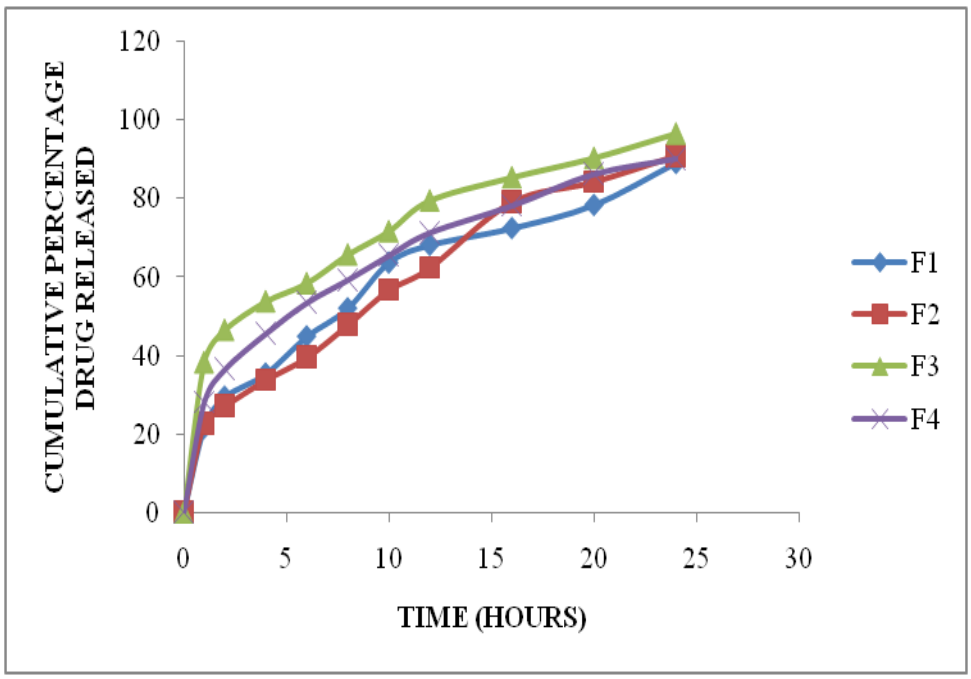

Figure 3: Dissolution study of Famotidine Sustained tablets (F1 to F4)

Table7: Dissolution Data of Famotidine Tablets Prepared With Ethyl cellulose in Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED			
	F5	F6	F7	F8
0	0	0	0	0
1	19.32	20.16	27.50	19.55
2	26.49	28.33	31.50	28.17
3	31.42	36.45	37.41	36.27
4	36.50	45.62	48.34	47.44
5	39.56	54.89	59.49	59.15
6	44.24	61.30	63.56	67.80
7	51.45	66.31	67.65	72.83
8	59.50	72.79	74.42	75.61
10	65.72	79.31	80.43	77.86
12	71.34	85.66	89.25	80.10

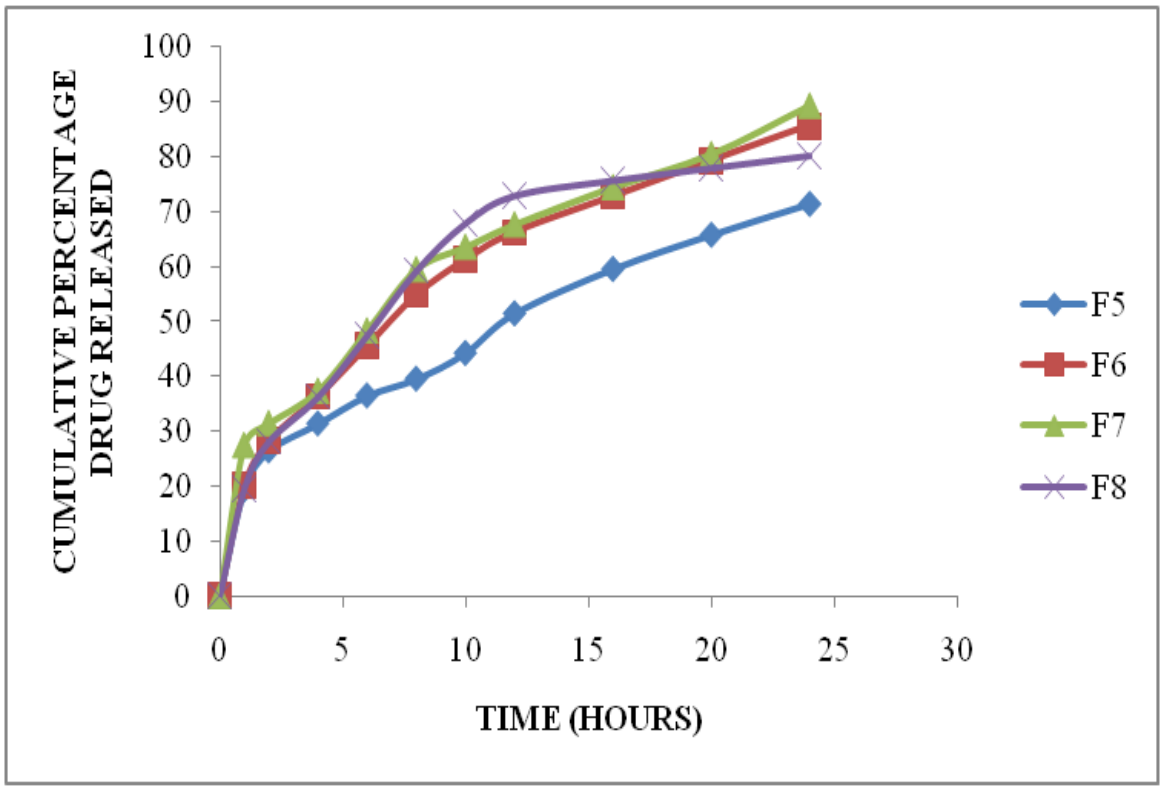

Figure 4: Dissolution study of Famotidine tablets (F5 to F8)

Table 8 :Dissolution Data of Famotidine by using Xanthan gum

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED			
	F9	F10	F11	F12
0	0	0	0	0
1	20.97	25.78	14.93	12.71
2	31.94	38.13	26.93	22.99
3	43.31	49.00	35.41	31.96
4	50.41	56.10	45.22	42.28
5	57.48	68.11	55.72	51.60
6	66.42	75.56	63.16	59.19
7	70.09	81.95	67.84	63.19
8	74.56	86.79	71.30	67.67
10	80.06	88.71	83.55	70.44
12	83.53	90.78	86.64	71.83

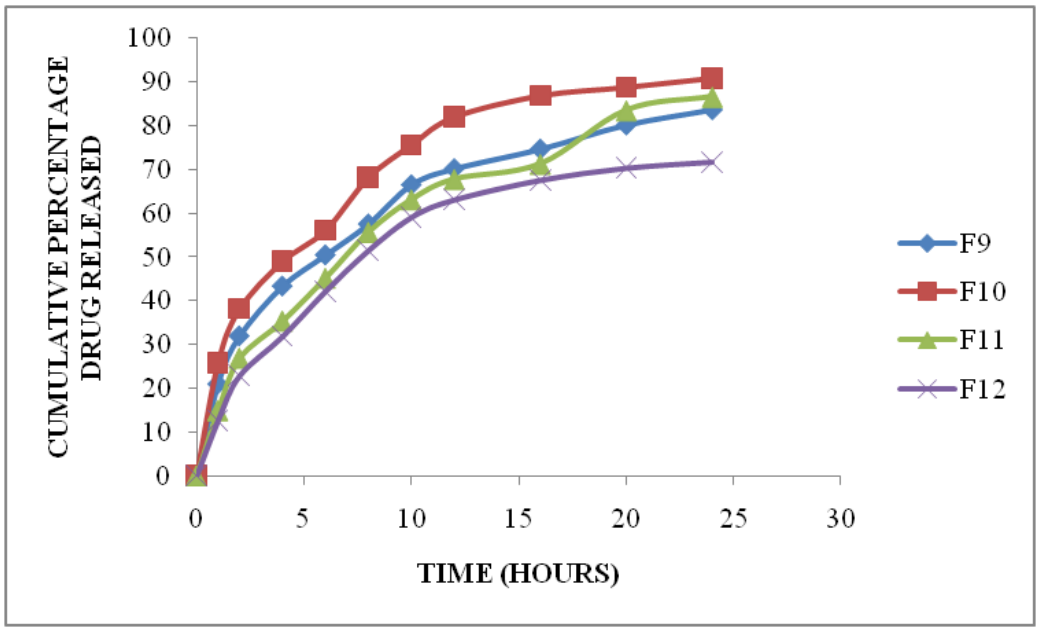

Figure 5: Dissolution study of Famotidine tablets with different ratios of Xanthan gum (F9 to F12)

Table 9: Release kinetics data for optimized formulation (F3)

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
38.31	1	1.000	1.583	0.000	1.790	38.310	0.0261	-0.417	61.69	4.642	3.951	0.690
46.57	2	1.414	1.668	0.301	1.728	23.285	0.0215	-0.332	53.43	4.642	3.766	0.875
53.86	3	1.732	1.731	0.477	1.664	17.953	0.0186	-0.269	46.14	4.642	3.587	1.055
58.48	4	2.000	1.767	0.602	1.618	14.620	0.0171	-0.233	41.52	4.642	3.463	1.179
65.77	5	2.236	1.818	0.699	1.534	13.154	0.0152	-0.182	34.23	4.642	3.247	1.395
71.68	6	2.449	1.855	0.778	1.452	11.947	0.0140	-0.145	28.32	4.642	3.048	1.593
79.54	7	2.646	1.901	0.845	1.311	11.363	0.0126	-0.099	20.46	4.642	2.735	1.907
85.43	8	2.828	1.932	0.903	1.163	10.679	0.0117	-0.068	14.57	4.642	2.442	2.199
90.38	10	3.162	1.956	1.000	0.983	9.038	0.0111	-0.044	9.62	4.642	2.127	2.515
96.61	12	3.464	1.985	1.079	0.530	8.051	0.0104	-0.015	3.39	4.642	1.502	3.139

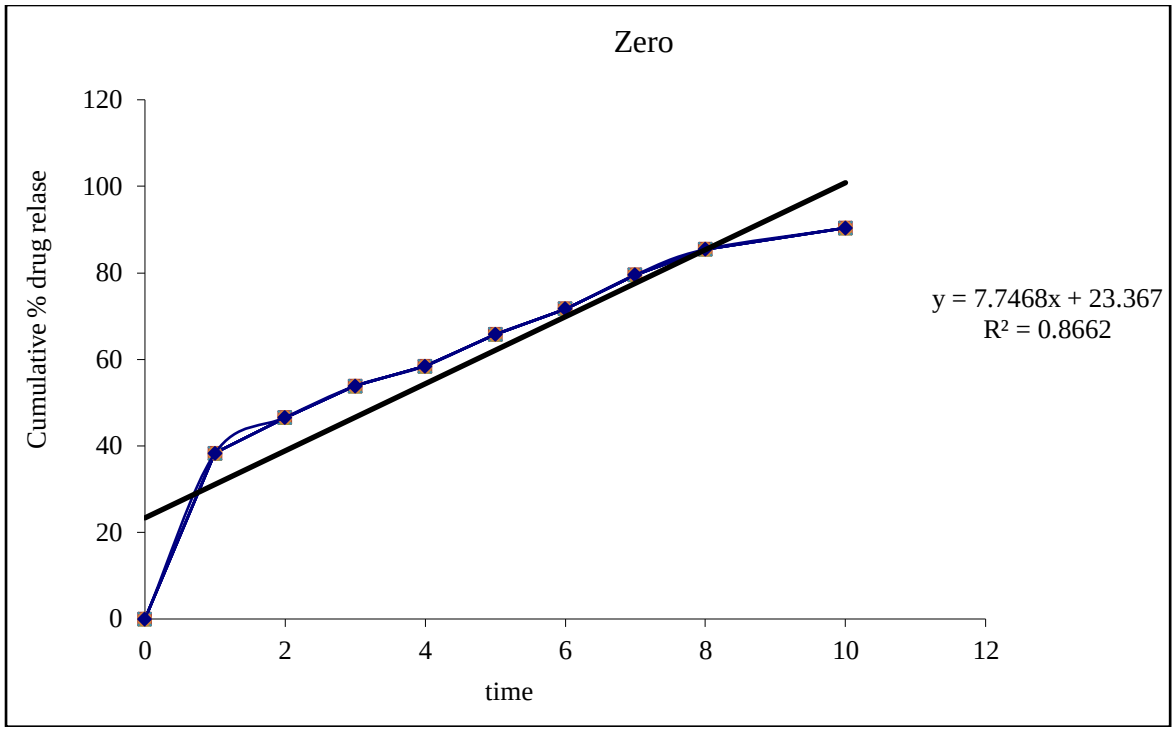

Figure 6: Graph of Zero order kinetics

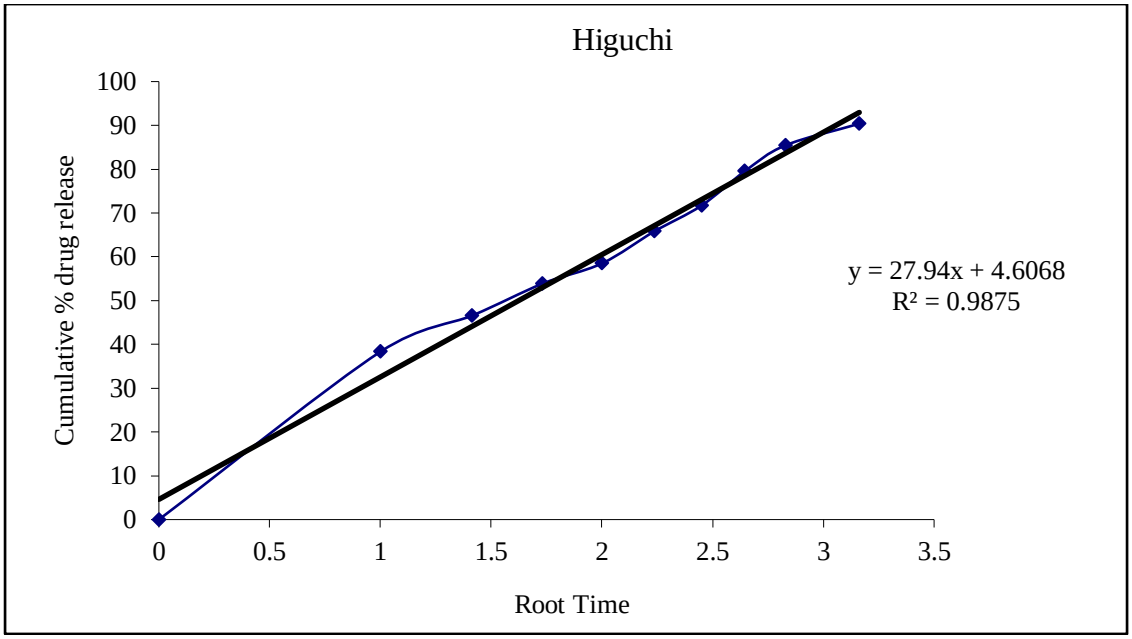

Figure7 : Graph of Higuchi release kinetics

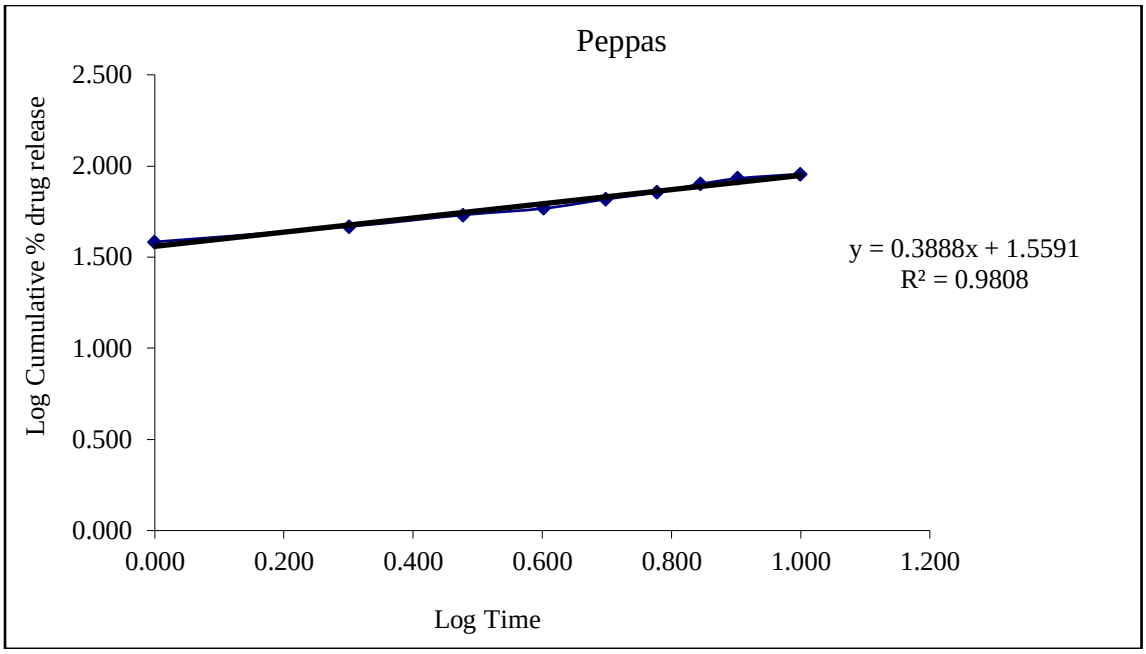

Figure 8: Graph of Peppas release kinetics

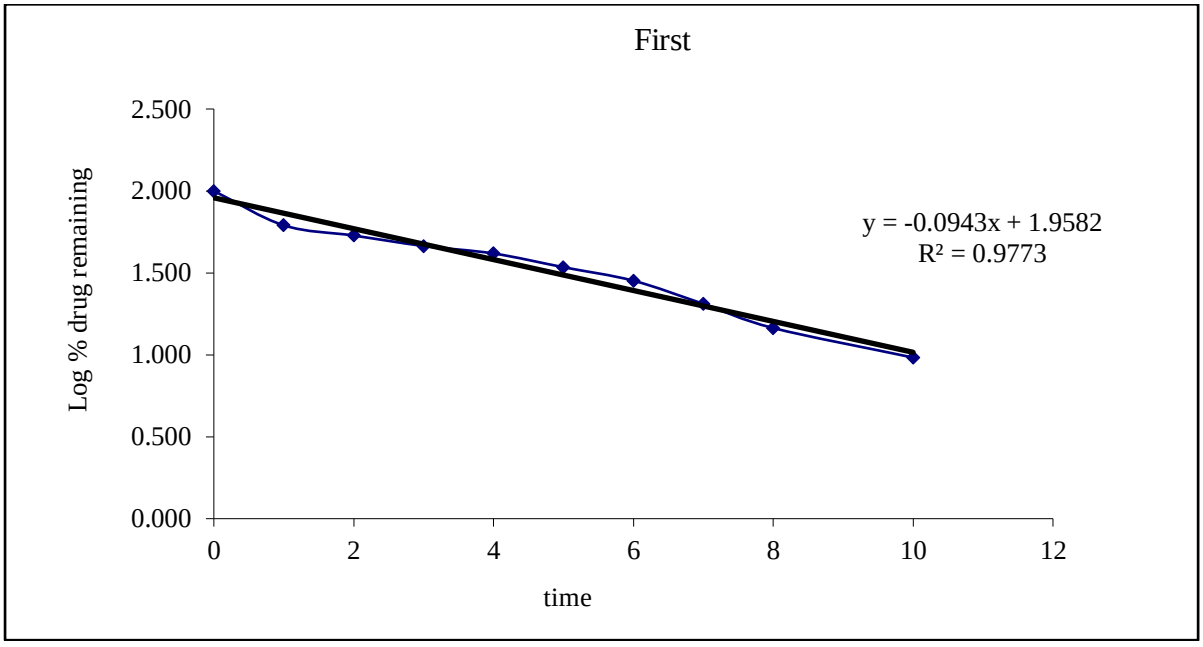

Figure 9: Graph of First order release kinetics

Drug – Excipient compatibility studies

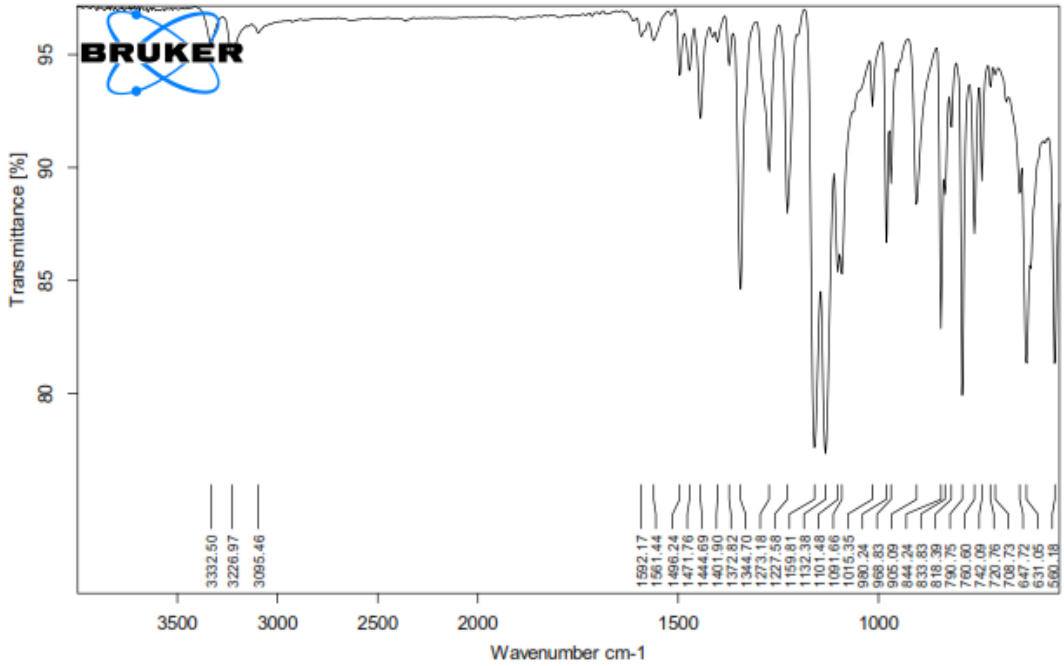

Fig. 10: FTIR GRAPH OF PURE DRUG

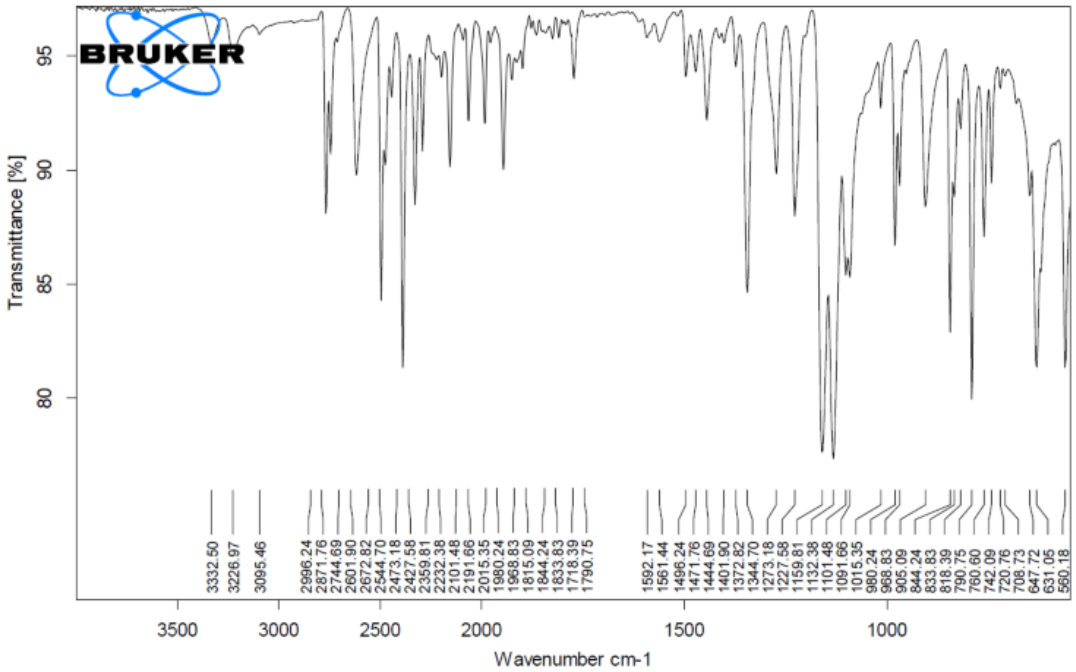

Fig. 11: FTIR GRAPH OF OPTIMISED FORMULATION

SUMMARY:

Development of Sustained release tablets is one of the alternative routes of administration to prolonged Sustained release of drug.

Sustained release tablets of Famotidine were prepared by wet granulation method using various synthetic polymers like HPMC K100M, Ethyl cellulose, Xanthan gum in different ratios. The formulation containing 1:3 ratio of (Famotidine: HPMC K100M)

showed maximum % drug release i.e. 96.61% at 12 hours.

The formulated sustained release tablets were evaluated for different parameters such as drug excipient Compatability studies, weight variation, thickness, hardness, content uniformity and *In vitro* drug release. *In vitro* drug release studies performed in pH 1.2 and phosphate buffer pH 6.8 for 12 hrs in standard dissolution apparatus. The data was subjected to zero order, first order, Zero and First diffusion models.

The following conclusions could be drawn from the results of various experiments

- 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 HPMC K100M, Ethyl cellulose, Xanthan gum were shown to be within limits.
- Properties and from the results, it was concluded that the *in vitro* drug release of the optimized formulations is suitable for Sustained drug delivery system.

CONCLUSION:

The present study concludes that sustained drug delivery of Famotidine can be a good way to prolong duration of action of drug by reducing the dosing frequency of Famotidine. Present study concludes that Sustained drug delivery system should be a suitable method for Famotidine administration. The optimised formulation was found to be F3 formulation.

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