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DESIGN AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF METFORMIN BY NATURAL POLYMERS

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ABSTRACT

The aim of the present study was to develop sustained release matrix formulation of Metformin to maintain constant therapeutic levels of the drug for over 12 hrs. Guar gum, Xanthane gum and Carbomer were employed as polymers. Formulations were prepared by wet granulation technique. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. From the dissolution studies it was evident that the formulation (F2) showed better and desired drug release pattern i.e., 99.65±0.05% in 12 hours. It contains the guar gum polymer. It followed Higuchi order release kinetics mechanism.

KEYWORDS: Carbomer, Guar gum, Metformin, Sustained release tablets, Xanthane 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.[1] The advantage of administering a single dose of a drug that is released over on Sustained 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.[2,3]

Advantages of SR tablets

1. Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.
2. If the active compound has a long half-life, it is sustained on its own.
3. If the pharmacological activity of the active is not directly related to its blood levels.
4. If the absorption of the drug involves an active transport and.
5. If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose.[4]
6. Aim of the study was to formulation and *in vitro* characterization of sustained release matrix tablets of Metformin using natural polymers. The main objective of this study was to prolong the drug release of metformin to reduce the dosage frequency. Metformin was a antidiabetic drug for type –I diabetes.

MATERIALS AND METHODS

Metformin was obtained as a gift sample from Aurobindo Ltd., (Hyderabad). Guar gum, Xanthane gum, Carbomer was used as polymers. Micro Crystalline Cellulose (SD Fine Chemicals) served as diluents. PVP K-30, Talc, Magnesium stearate is obtained from SD Fine Chemicals.

Preparation method

Intra granular: Drug and required ingredients were individually passed through sieve no # 60. All the ingredients were weighed ascending order and mixed thoroughly by triturating up to 15 min. IPA was added little amount as granulating agent. Wet mass prepared and sifted through the sieve no #60 to get granules. Obtained granules were kept a side for air drying.[5]

Extra granular: After drying the granules, Lubricant (Mg. stearate) and glidant (talc) was added to increase the flow properties. The tablets were compressed using a sixteen station rotary tablet-punching machine.[6]

Table 1: Formulation of SR Matrix tablets of Metformin.

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metformin	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**
Guar gum	100	150	200	-	-	-	-	-	-
Xanthane gum	-	-	-	100	150	200	-	-	-
Carbomer	-	-	-	-	-	-	100	150	200
PVP K-30	20	20	20	20	20	20	20	20	20
Magnesium stearate	06	06	06	06	06	06	06	06	06
Talc	06	06	06	06	06	06	06	06	06
MCC pH 102	168	118	68	168	118	68	168	118	68
Total wt	800	800	800	800	800	800	800	800	800

Evaluation

Preformulation studies

Selection of wavelength for analysis of metformin: The prepared concentration of 10 µg/ml was used for initial spectral scan in the UV range of 200-400 nm to detect maximum wavelength and further dilutions for linearity were prepared from the stock solution by allegation method.[7]

FTIR Compatibility Studies

FTIR spectra of pure drug and formulation with other ingredients were recorded by using FTIR Spectroscopy.[8,9]

Post-compression parameters

Thickness, Weight variation test, Friability study, Hardness, Drug content, and *in-vitro* dissolution studies were performed for prepared sustained release tablets.[10,11,12]

RESULTS AND DISCUSSION

The present study was aimed to developing Sustain release tablets of Metformin using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method

Graphs of Metformin were taken in 0.1N HCl and pH 6.8 phosphate buffers at 235 nm and 237 nm respectively.

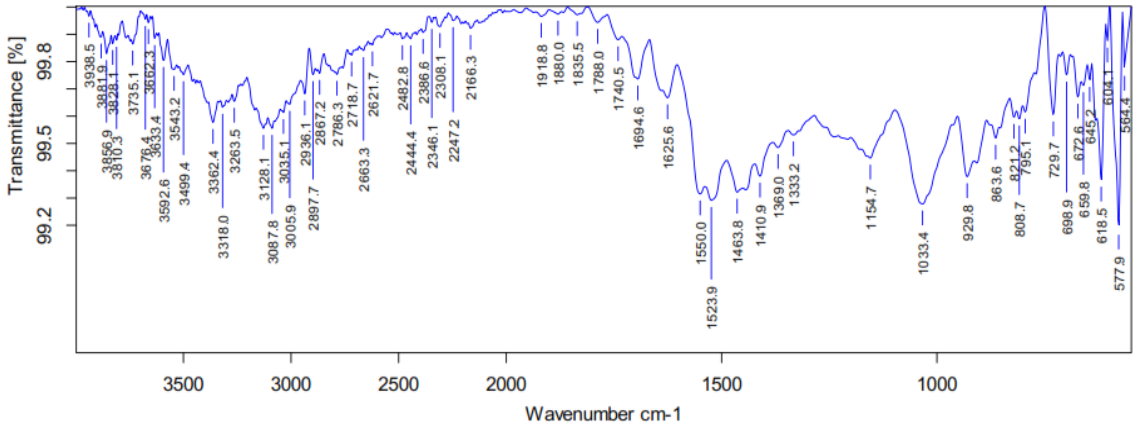


Figure 1: FTIR studies of pure drug Metformin.

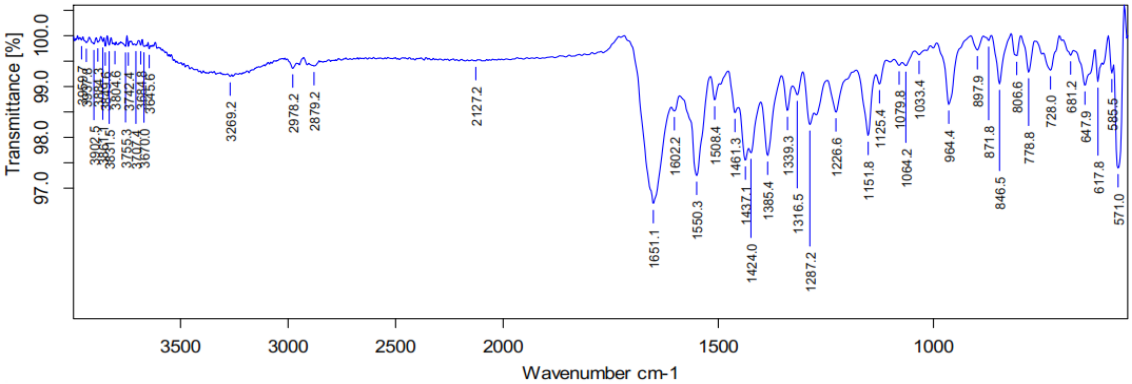


Figure 2: FTIR compatibility studies of optimized formulation (F2).

It is observed that the peaks of major functional groups of Metformin 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.

Table 2: Physical properties of precompression blend.

Batch Code	Angle of repose (θ)	Bulk density (g/mL)	Tapped density (g/mL)	Carr's Index (%)	Hausner's ratio
F1	26.01±0.21	0.59±0.05	0.67±0.06	11.94±0.01	1.13±0.02
F2	27.8±0.35	0.46±0.04	0.54±0.08	14.81±0.00	1.17±0.05
F3	24.7±0.42	0.62±0.09	0.74±0.02	16.21±0.09	1.19±0.06
F4	25.33±0.48	0.54±0.05	0.63±0.04	14.28±0.05	1.16±0.08
F5	26.24±0.52	0.63±0.02	0.74±0.05	14.86±0.09	1.17±0.07
F6	27.12±0.35	0.48±0.03	0.57±0.02	15.78±0.02	1.18±0.05
F7	28.08±0.47	0.58±0.01	0.66±0.05	12.12±0.01	1.13±0.04
F8	26.12±0.51	0.68±0.09	0.76±0.05	10.52±0.05	1.11±0.06
F9	26.45±0.65	0.64±0.02	0.73±0.04	12.32±0.04	1.14±0.07

Each value represents the mean ± Standard deviation (n=3)

Pre-formulation parameters of blend

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 0.46±0.04 to 0.68±0.09 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.54±0.08 to 0.76±0.05 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below18 which shows that the powder has good flow properties. All the formulations have shown the hausner ratio below 1.2 indicating the powder has good flow properties.

Table 3: Post compression properties of SR Matrix tablets of Metformin.

Batch Code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Assay (%)
F1	799.8±2.48	5.79±0.05	5.5±0.06	0.40±0.08	95.1±0.15
F2	796.32±2.42	5.08±0.06	5.0±0.05	0.19±0.05	96.8±0.24
F3	803.88±2.28	5.05±0.06	5.5±0.07	0.08±0.04	98.34±0.32
F4	801.72±1.74	5.93±0.05	5.4±0.03	0.29±0.05	96.55±0.41
F5	797.42±2.85	5.79±0.07	5.5±0.05	0.30±0.05	98.13±0.15
F6	795.02±1.88	5.76±0.01	5.7±0.01	0.72±0.03	99.30±0.18
F7	802.9±2.01	5.74±0.06	5.3±0.03	0.41±0.04	97.82±0.32
F8	804.48±1.37	5.75±0.04	5.9±0.04	0.20±0.04	95.86±0.45
F9	803.4±1.19	5.76±0.06	5.5±0.06	0.19±0.04	96.55±0.25

Each value represents the mean ± Standard deviation (n=3)

Weight variation test: Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet. The average weight of the tablet is approximately in range of 795.02±1.88 to 804.48±1.37 mg, the results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test: Hardness of the three tablets of each batch was checked by using Monsanto hardness tester. The results showed that the hardness of the tablets is in range of 5 to 5.5 kg/cm^2, which was within IP limits.

Thickness: Thickness of three tablets of each batch was checked by using screw gauge and data shown. The result showed that thickness of the tablet is raging from 5.05±0.06 to 5.93±0.05 mm.

Friability: Tablets of each batch were evaluated for percentage friability. The friability of all the formulations was found to be less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

Assay: Tablets of each batch were evaluated for percentage of purity. The assay performed as per IP and the drug was estimated spectrophotometrically at 235 nm. The result showed that the percentage of purity from of the tablet is raging from 95.1±0.15 to 99.30±0.18.

Table 4: *In vitro* Drug Release from Formulations F1-F3.

Time (hrs)	Cumulative percentage drug release		
	F1	F2	F3
	Mean ± SD	Mean ± SD	Mean ± SD
0	0	0	0
0.5	28.18	23.93	18.4
1	34.47	31.68	22.3
2	50.38	39.77	29.5
3	79.33	44.51	32.3
4	84.38	52.97	41.3
5	89.45	59.84	52.6
6	93.4	65.81	59.4
7	96.8	70.91	65.2
8	99.2	78.29	72.3
9		83.94	79.5
10		89.88	82.5
11		93.82	89.1
12		99.65	91.2

Each value represents the mean ± Standard deviation (n=3)

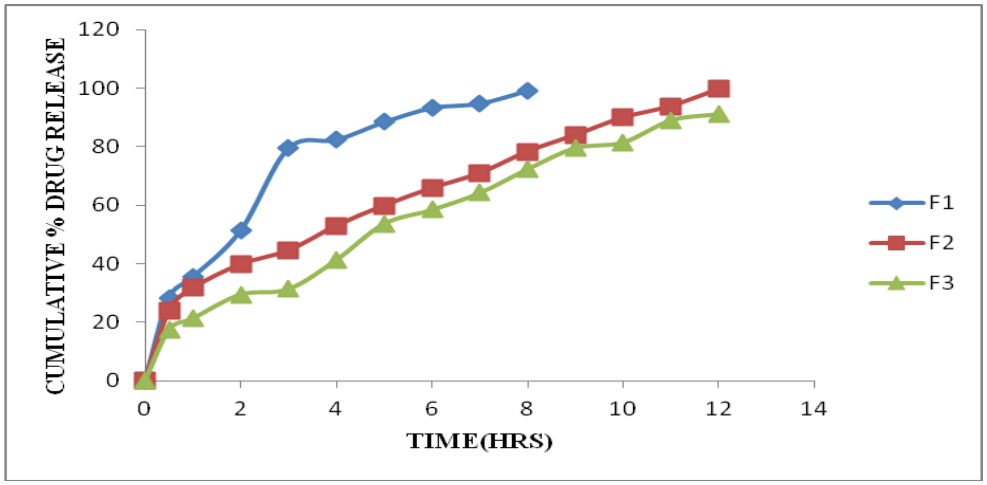


Figure 3: *In vitro* drug release of SR Matrix tablets of Metformin with guar gum.

Table *5: In vitro* Drug Release from Formulations F4-F6.

Time (hrs)	Cumulative percentage drug release		
	F4	F5	F6
	Mean ± SD	Mean ± SD	Mean ± SD
0	0	0	0
0.5	37.21	37.24	31.62
1	48.25	41.37	33.86
2	52.16	47.63	41.35
3	70.01	64.04	47.45
4	89.26	72.25	54.82
5	99.10	88.33	59.23
6		93.41	65.27
7		98.56	70.72
8			78.24
9			85.42
10			99.17
11			
12			

Each value represents the mean ± Standard deviation (n=3)

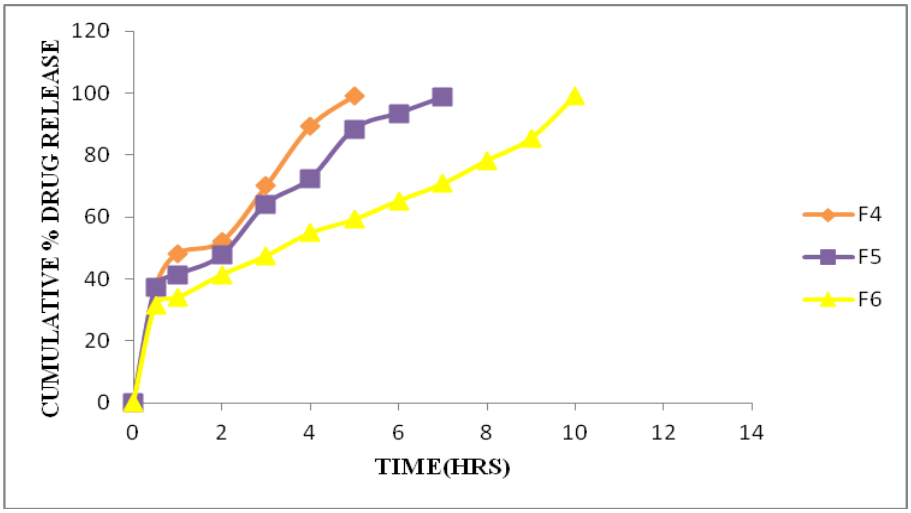


Figure 4: *In vitro* drug release of SR Matrix tablets of Metformin with Xanthane gum.

Table *6: In vitro* Drug Release from Formulations F7-F9.

Time (hrs)	Cumulative percentage drug release		
	F7	F8	F9
	Mean ± SD	Mean ± SD	Mean ± SD
0	0	0	0
0.5	8.21	3.20	1.90
1	13.23	8.91	4.23
2	16.36	12.33	8.37
3	22.47	17.45	12.31
4	26.39	19.34	17.46
5	29.55	22.45	19.38
6	32.81	25.61	22.49
7	38.44	32.31	25.65
8	42.56	37.69	32.90
9	48.15	42.87	37.55
10	56.37	52.68	42.76
11	73.47	62.33	52.38
12	85.51	72.30	62.80

Each value represents the mean ± Standard deviation (n=3).

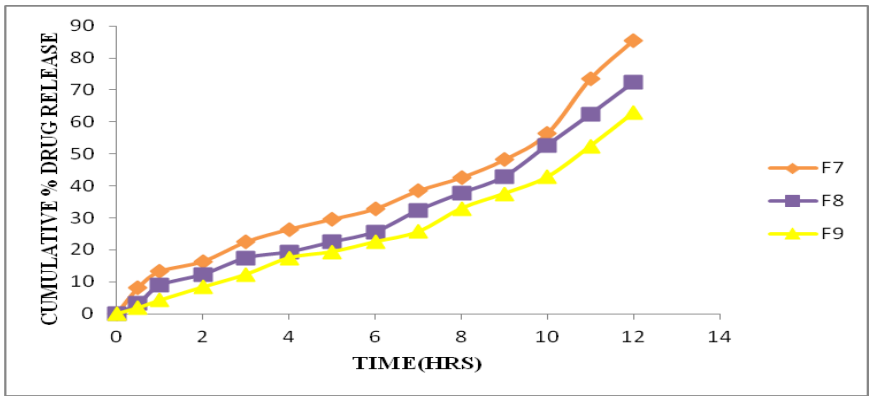


Figure 5: *In vitro* drug release of SR Matrix tablets of Metformin with Carbomer.

From the dissolution data, it was revealed that formulations prepared with Xanthane gum did not retard the drug release up to 12 hrs. Hence those formulations did not take into consideration. Formulations prepared with Carbomer retards the drug release more than 12hrs. These formulations also did not take into consideration. Formulations prepared with guar gum were revealed that increase in the concentration retards the drug release. Among all formulations F2 formulation was considered as optimized formulation. It was shown 99.65% drug release at 12hrs.

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 7: Release kinetics data for optimized formulation of SR Matrix tablets.

Time (T)	Root (T)	Log (%) Release	Log (T)	Log (%) remain	Release rate (cumulative % release / t)	1/cum. percentage release	Peppas log Q/100	% Drug Remaining
0	**0**			**2.000**				**100**
0.5	0.707	1.379	0.301	1.881	47.860	0.0418	-0.621	76.07
1	1.000	1.501	0.000	1.835	31.680	0.0316	-0.499	68.32
2	1.414	1.600	0.301	1.780	19.885	0.0251	-0.400	60.23
3	1.732	1.648	0.477	1.744	14.837	0.0225	-0.352	55.49
4	2.000	1.724	0.602	1.672	13.243	0.0189	-0.276	47.03
5	2.236	1.777	0.699	1.604	11.968	0.0167	-0.223	40.16
6	2.449	1.818	0.778	1.534	10.968	0.0152	-0.182	34.19
7	2.646	1.851	0.845	1.464	10.130	0.0141	-0.149	29.09
8	2.828	1.894	0.903	1.337	9.786	0.0128	-0.106	21.71
9	3.000	1.924	0.954	1.206	9.327	0.0119	-0.076	16.06
10	3.162	1.954	1.000	1.005	8.988	0.0111	-0.046	10.12
11	3.317	1.972	1.041	0.791	8.529	0.0107	-0.028	6.18
12	3.464	1.998	1.079	-0.456	8.304	0.0100	-0.002	0.35

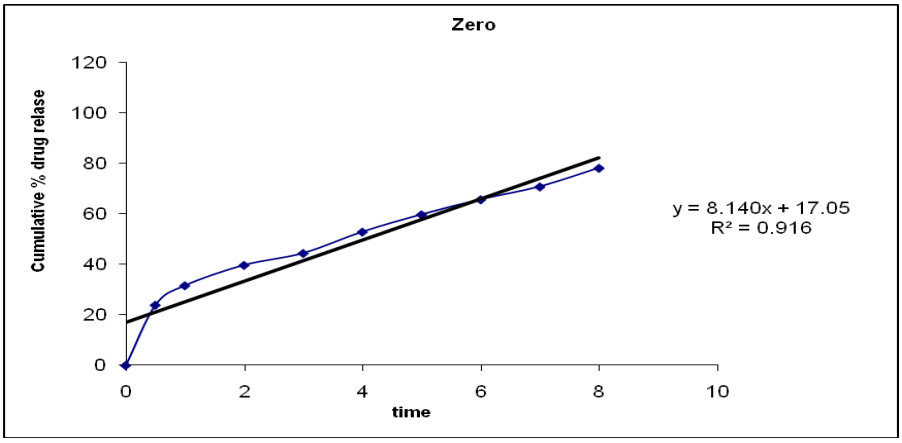
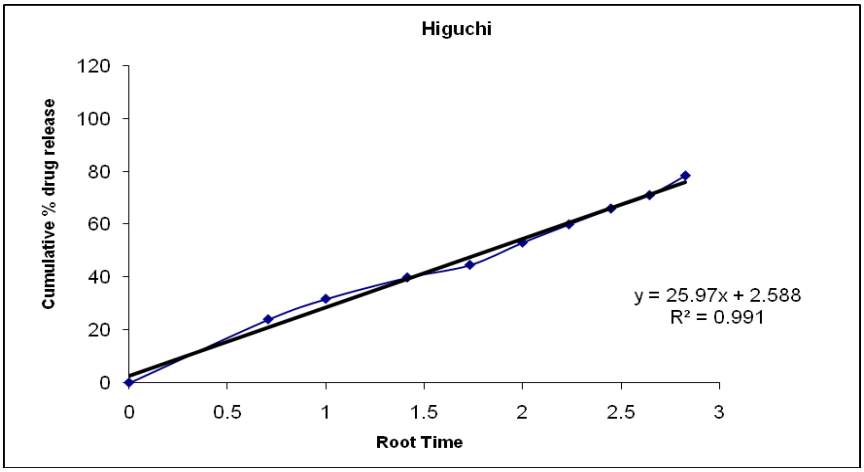


Figure 6: Zero order release kinetics graph.



Fiogure 7: Higuchi release kinetics graph.

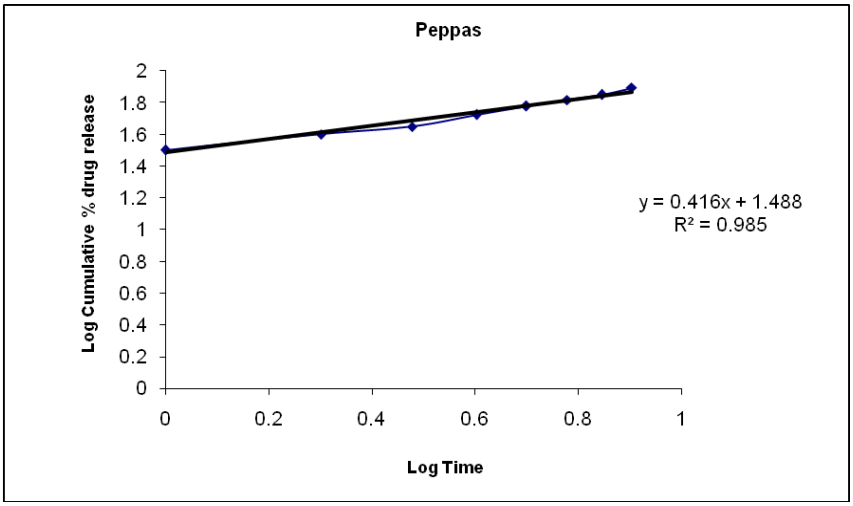


Figure 8: Korsmeyer peppas graph.

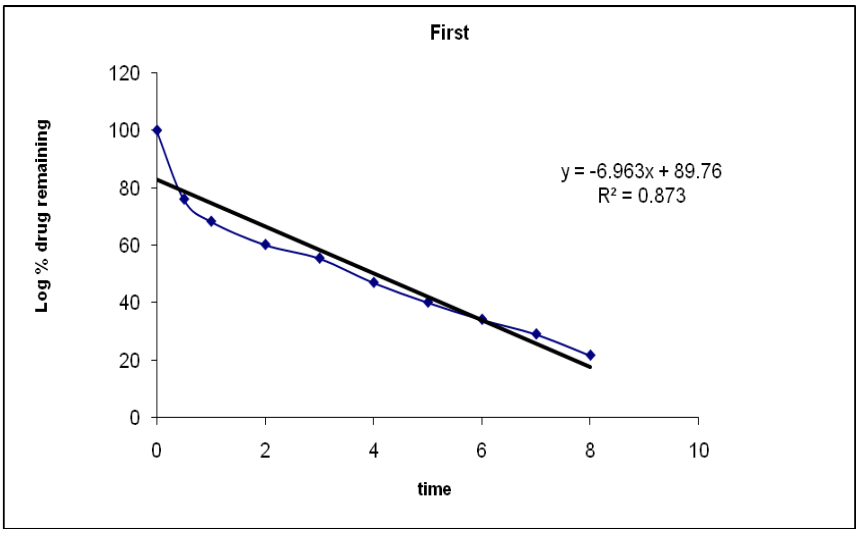


Figure 9: First order release kinetics graph.

From the above graphs it was evident that the formulation F2 was followed Higuchi release kinetics.

CONCLUSION

In vitro dissolution data revealed that formulations prepared with Xanthane gum were not retarded the drug release up to 12 hrs and formulations prepared with Carbomer retard the drug release more than 12 hrs. Hence those formulations did not take into consideration. Among all formulations F2 formulation prepared with guar gum was shown maximum drug release within 12 hrs i.e. 99.65%. The formulation F2 was followed Higuchi release kinetics.

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