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FORMULATION AND EVALUATION OF BACLOFEN EXTENDED RELEASE TABLETS.

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ABSTRACT

The aim of the present study was to develop Extended release formulation of Baclofen to maintain constant therapeutic levels of the drug for over 12 hrs. Guar gum, sodium alginate and carbopol 940 were 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 (F6) showed better and desired drug release pattern i.e., 96.32% in 12 hours. It contains the sodium alginate as Extended release material. It followed Zero order release kinetics mechanism.

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INTRODUCTION

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

Baclofen is a gamma-amino-butyric acid (GABA) derivative used as a skeletal muscle relaxant. Baclofen stimulates GABA-B receptors leading to decreased frequency and amplitude of muscle spasms. It is especially useful in treating muscle spasticity associated with spinal cord injury. It appears to act primarily at the spinal cord level by inhibiting spinal polysynaptic afferent pathways and, to a lesser extent, monosynaptic afferent pathways.

The aim of the study is to Formulation and Evaluation of Baclofen Tablets by Using Carbopol 904, Guar Gum and Sodium Alginate. The main objective is to formulate and evaluate Baclofen extended release tablets using different polymers such as Xanthan gum, Chitosan, HPMC K15M[1,2].

MATERIALS AND METHODS

Baclofen was a gift sample from (Aurobindo Pharmaceuticals Limited, Hyderabad, India). Carbopol 904, Guar Gum and Sodium Alginate were obtained from Hetro Pharmaceuticals, Hyderabad, India). Micro crystalline cellulose, Talc, Magnesium stearate was procured from Loba chemie Private Ltd. All other chemicals and reagents were analytical grade and used as received.

Fourier Transform Infrared (FTIR) spectroscopy:

Drug excipient interaction studies are significant for the successful formulation of every dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the assessment of physicochemical compatibility and interactions, which helps in the prediction of interaction between drug and other excipients. In the current study 1:1 ratio was used for preparation of physical mixtures used for analyzing of compatibility studies. FT-IR studies were carried out with a bruker FTIR facility[3,4].

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[4,5]

Formulation development of floating 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 Baclofen. Baclofen and all other ingredients were individually passed through sieve no ≠ 60.All the ingredients were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with talc. The tablets were prepared by using direct compression method[6,7,8].

Table 1: Formulation composition for Extended Releae tablets.

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Baclofen	10	10	10	10	10	10	10	10	10
Guar gum	10	20	40	-	-	-	-	-	-
Sodium alginate	-	-	-	10	20	40	-	-	-
Carbopol 940	-	-	-	-	-	-	10	20	40
Mg.stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total tablet weight	100	100	100	100	100	100	100	100	100

Evaluation of post compression parameters for prepared Tablets

The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content[9,10,11].

Weight variation test:

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

Friability test

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

$$F = 100\ (W0-W)/W0$$

Where W0 = Initial weight, W = Final weight

Hardness test

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

Thickness test

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

Drug content

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

***In vitro* drug release studies**

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	0.1 N HCl , p H 6.8 Phophate buffer
RPM	--	50
Sampling intervals (hrs)	--	0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 11 and 12
Temperature	--	37°c $\pm$ 0.5°c

Procedure:

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The media was allowed to equilibrate to temp of 37°c $\pm$ 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours. Then 0.1 N HCl was replaced with pH 6.8 phosphate buffer and process was continued upto 12 hrs at 50 rpm. At specific time intervals, withdrawn 5 ml of sample and again 5ml media was added to maintain the sink condition. Withdrawn samples were analyzed at wavelength of drug using UV-spectrophotometer[12,13].

Application of Release Rate Kinetics To Dissolution Data [47]

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics:

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

$$F = K_o\ t$$

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[14,15,16].

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. [17,18]

Korsmeyer and Peppas release model:

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

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

Where, M_t / M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t / M_∞) versus log (time) is linear[19,20].

RESULTS AND DISCUSSION

Drug – Excipient compatability studies

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

Etodolac also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug. The results are shown in Fig.1 & 2

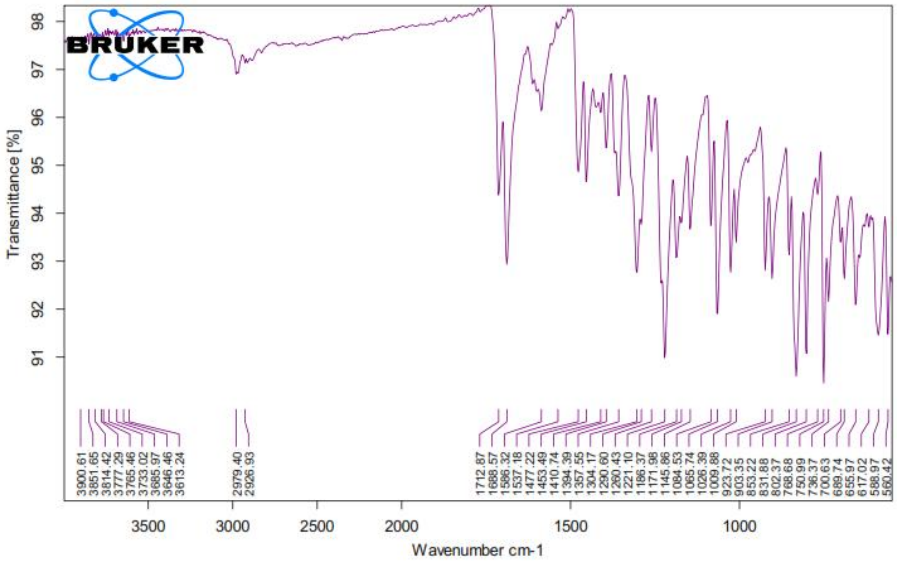

Fig : Pure Drug Of Baclofen.

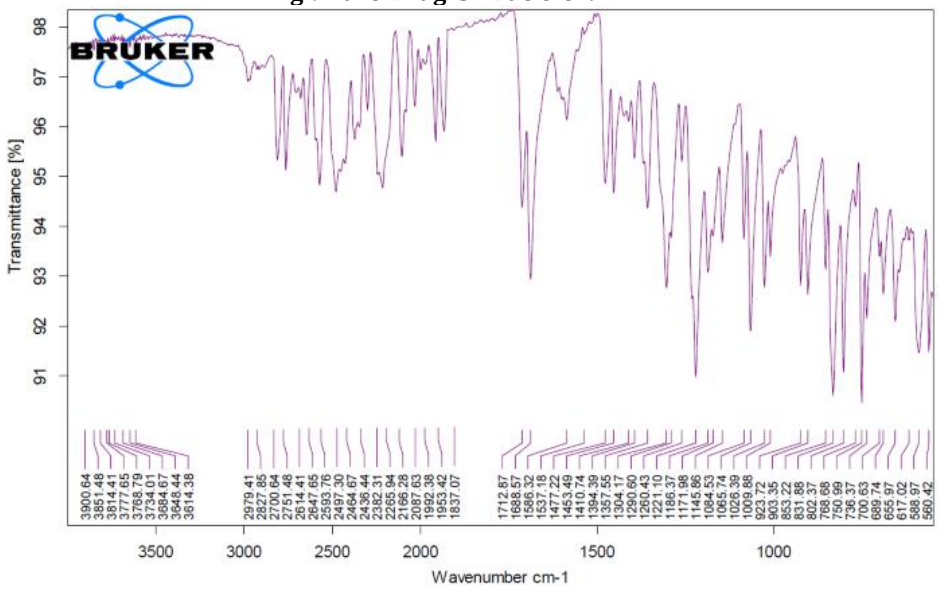

Fig : Pure Drug Of Baclofen Optimised Graph.

Pre-formulation parameters of powder blend:

Table 7.3: Pre-compression parameters of powder blend.

Formulation Code	Angle of Repose	Bulk density (gm/cm^3)	Tapped density (gm/ cm^3)	Carr's index (%)	Hausner's Ratio
F1	26.12 ± 0.1	0.44 ± 0.03	0.50± 0.061	12 ± 0.58	1.13 ± 0.012
F2	28.53 ± 0.57	0.48 ± 0.06	0.56 ± 0.08	14.28 ± 0.47	1.16 ± 0.032
F3	25.46 ± 0.57	0.55 ± 0.08	0.62 ± 0.011	11.29 ± 0.57	1.12 ± 0.015
F4	27.61 ± 0.63	0.53 ± 0.09	0.61 ± 0.071	13.1 ± 0.15	1.15 ± 0.021
F5	25.15 ± 0.58	0.49 ± 0.01	0.56 ± 0.08	12.5 ± 0.21	1.14 ± 0.012
F6	26.08 ± 0.51	0.55 ± 0.011	0.62 ± 0.06	11.29 ± 0.35	1.12 ± 0.023
F7	28.38 ± 0.56	0.47 ± 0.08	0.54 ± 0.01	12.96 ± 0.42	1.14 ± 0.031
F8	27.26 ± 0.56	0.52 ± 0.055	0.59 ± 0.08	11.86 ± 0.57	1.13 ± 0.026
F9	26.43 ±1 0.62	0.56 ± 0.07	0.63 ± 0.012	11.11 ± 0.12	1.12 ± 0.056

Tablet powder blend was subjected to various pre-compression parameters. The angle of repose values was showed from 25 to 30; it indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.44±0.03 to 0.56 ± 0.07 (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 0.50± 0.061to 0.63 ± 0.012 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 11 to 14.28 which showed that the powder has good flow properties. All the formulations were showed the hausner ratio ranging from 0 to 1.25 indicating the powder has good flow properties.

Quality Control Parameters For tablets:

Table7.4: Post Compression Parameters of Tablets.

Formulation codes	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	99.95 ± 1.22	4.8±0.01	0.45±0.05	4.0 ±0.05	98.8 ± 0.14
F2	99.15 ± 1.31	4.7±0.05	0.54±0.07	3.9 ±0.04	99.3 ± 0.13
F3	101.26 ± 0.81	4.5±0.07	0.55±0.02	3.8 ±0.06	98.2 ± 0.15
F4	103.36 ± 1.17	4.7±0.04	0.56±0.04	4.1±0.08	99.8 ± 0.17
F5	97.25 ± 2.02	4.6±0.09	0.48±0.08	3.8 ±0.09	99.3 ± 012
F6	98.26 ± 1.25	4.7±0.01	0.45±0.02	3.8 ±0.05	97.2 ± 0.19
F7	100.5 ± 0.95	4.8±0.04	0.51±0.04	4.0 ±0.03	102.3 ± 0.21
F8	103.63 ± 1.04	4.8±0.03	0.52±0.03	4.1±0.04	103.5 ± 0.14
F9	99.53 ± 0.53	4.5 ± 0.02	0.561 ±0.03	3.9 ±0.02	99.56 ± 0.22

Weight variation and thickness:

All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table 7.4. The average tablet weight of all the formulations was found to be between 97.25 ± 2.02 to 103.63 ± 1.04**.** The maximum allowed percentage weight variation for tablets weighing >80-250 mg is 7.5% and no formulations are not exceeding this limit. Thus all the formulations were found to comply with the standards given in I.P. And thickness of all the formulations was also complying with the standards that were found to be between 3.8 ±0.06 to 4.1±0.08.

Hardness and friability:

All the formulations were evaluated for their hardness, using monsanto hardness tester and the results are shown in table 7.4. The average hardness for all the formulations was found to be between **(**4.5 ± 0.07 to 4.8±0.04**)** Kg/cm^2 which was found to be acceptable.

Friability was determined to estimate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the formulations were evaluated for their percentage friability using roche friabilator and the results were shown in table 7.4. The average percentage friability for all the formulations was between 0.45±0.04 and 0.56±0.04, which was found to be within the limit.

Drug content:

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

***In Vitro* Drug Release Studies**

The formulations prepared with different natural polymers by wet granulation 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 7.5: Dissolution Data of Baclofen Tablets Prepared With Guar gum In Different Concentrations.

TIME	CUMULATIVE PERCENT DRUG RELEASED		
(hr)	F1	F2	F3
0	0	0	0
0.5	35.32	30.04	24.63
1	54.53	47.56	30.63
2	69.90	54.35	42.52
3	74.96	63.52	50.31
4	86.14	74.75	58.25
5	92.85	82.54	65.78
6		89.26	70.17
7		95.95	75.79
8			82.27
9			89.64
10			94.87
11			
12			

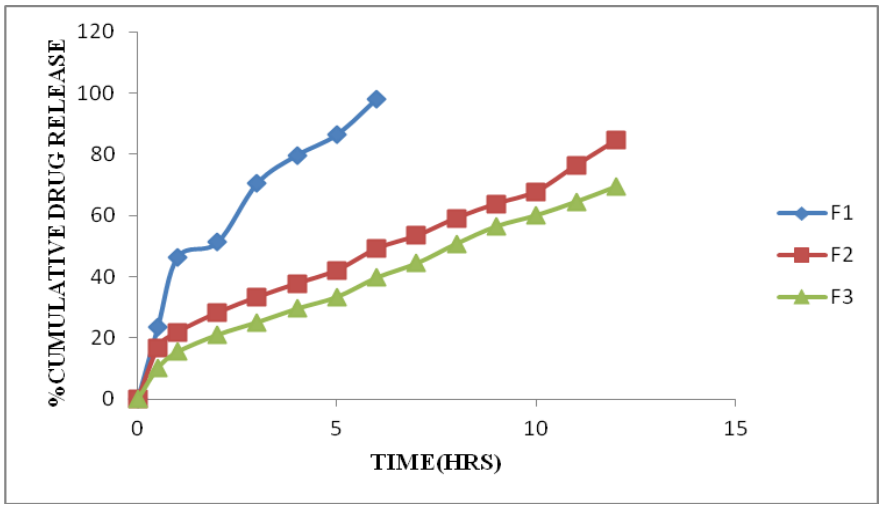

Figure 7.3: Dissolution study of Baclofen Extended tablets (F1 to F3).

Table 7.6: Dissolution Data of Baclofen Tablets Prepared With sodium alginate in Different Concentrations.

TIME	CUMULATIVE PERCENT DRUG RELEASED		
(hr)	F4	F5	F6
0	0	0	0
0.5	19.17	14.90	10.49
1	24.12	20.45	17.63
2	38.64	32.02	26.55
3	50.20	39.31	32.84
4	69.56	47.82	39.39
5	75.43	53.47	44.71
6	83.01	59.74	53.05
7	95.57	64.05	60.87
8		79.93	67.02
9		84.26	74.15
10		95.45	79.24
11			87.54
12			96.32

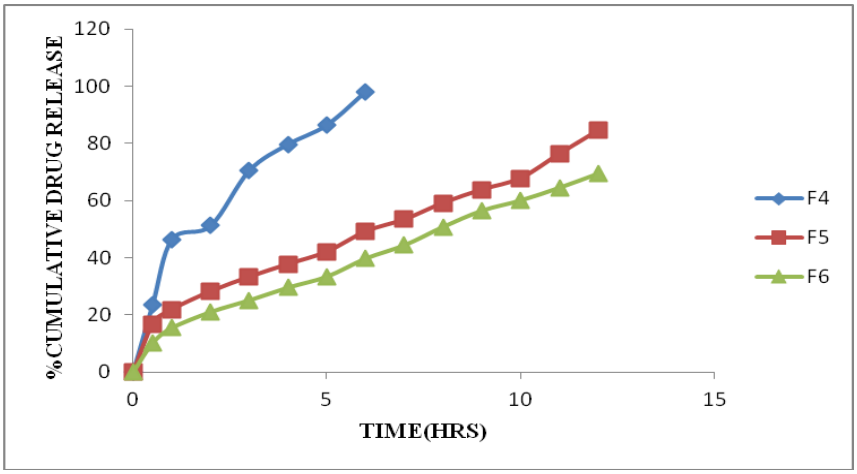

Figure 7.4: Dissolution study of Baclofen tablets (F4 to F6).

Table 7.6: Dissolution Data of Baclofen Tablets Prepared With HPMC K100 M in Different Concentrations.

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F7	F8	F9
0	0	0	0
0.5	23.56	16.76	10.15
1	46.45	21.89	15.41
2	51.23	28.24	20.98
3	70.54	33.32	25.09
4	79.73	37.75	29.54
5	86.46	42.09	33.36
6	98.12	49.16	39.67
7		53.36	44.36
8		59.12	50.77
9		63.78	56.42
10		67.79	60.02
11		76.31	64.46
12		84.45	69.39

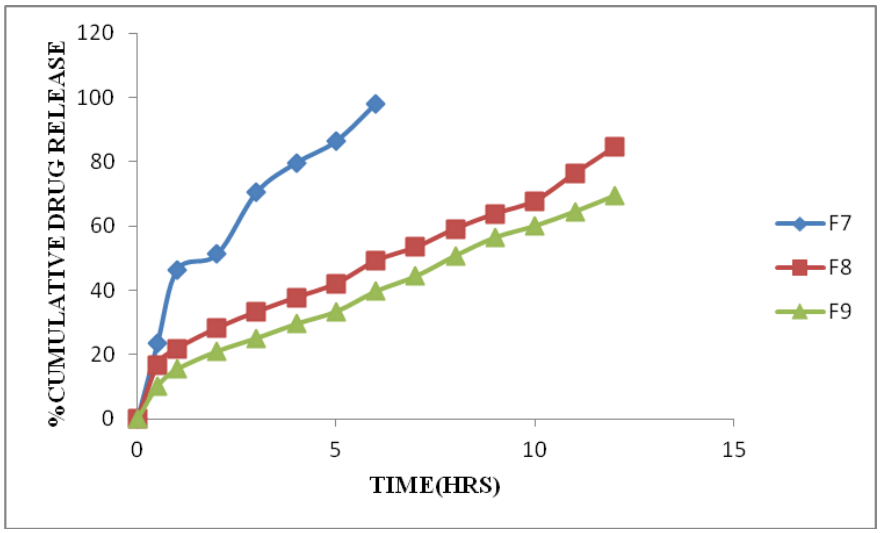

Figure 7.5: Dissolution study of Baclofen tablets (F7 to F9).

From the dissolution data it was evident that the formulations prepared with Carbopol 940 as polymer were retarded the drug release more than 12 hours.

Whereas the formulations prepared with higher concentration of Sodium alginate retarded the drug release up to 12 hours in the concentration 40 mg. In lower concentrations the polymer was unable to retard the drug release.

The formulations prepared with Guar gum showed very less retardation capacity hence they were not considered.

Hence from the above dissolution data it was concluded that F6 formulation was considered as optimised formulation because good drug release (96.32%) in 12 hours.

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 Baclofen release from Extended tablets. The data was fitted into various kinetic models such as Zero, First order kinetics; Higuchi and Korsmeyer peppas mechanisms and the results were shown in below table

Table 7.7: Release kinetics data for optimised formulation (F6).

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
10.49	**0.5**	0.707	1.021	-0.301	1.952	20.980	0.0953	-0.979	89.51	4.642	4.473	0.168
17.63	1	1.000	1.246	0.000	1.916	17.630	0.0567	-0.754	82.37	4.642	4.351	0.291
26.55	2	1.414	1.424	0.301	1.866	13.275	0.0377	-0.576	73.45	4.642	4.188	0.454
32.84	3	1.732	1.516	0.477	1.827	10.947	0.0305	-0.484	67.16	4.642	4.065	0.577
39.39	4	2.000	1.595	0.602	1.783	9.848	0.0254	-0.405	60.61	4.642	3.928	0.713
44.71	5	2.236	1.650	0.699	1.743	8.942	0.0224	-0.350	55.29	4.642	3.810	0.832
53.05	6	2.449	1.725	0.778	1.672	8.842	0.0189	-0.275	46.95	4.642	3.608	1.034
60.87	7	2.646	1.784	0.845	1.593	8.696	0.0164	-0.216	39.13	4.642	3.395	1.247
67.02	8	2.828	1.826	0.903	1.518	8.378	0.0149	-0.174	32.98	4.642	3.207	1.435
74.15	9	3.000	1.870	0.954	1.412	8.239	0.0135	-0.130	25.85	4.642	2.957	1.685
79.24	10	3.162	1.899	1.000	1.317	7.924	0.0126	-0.101	20.76	4.642	2.748	1.893
87.54	11	3.317	1.942	1.041	1.096	7.958	0.0114	-0.058	12.46	4.642	2.318	2.323
96.32	12	3.464	1.984	1.000	0.566	8.027	0.0104	-0.016	3.68	4.642	1.544	3.098

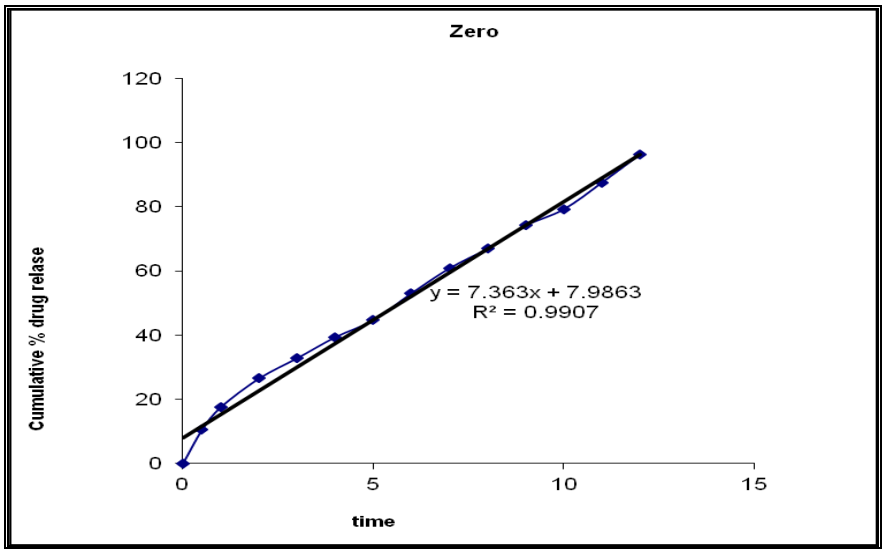

Figure 7.6: Graph of zero order kinetics.

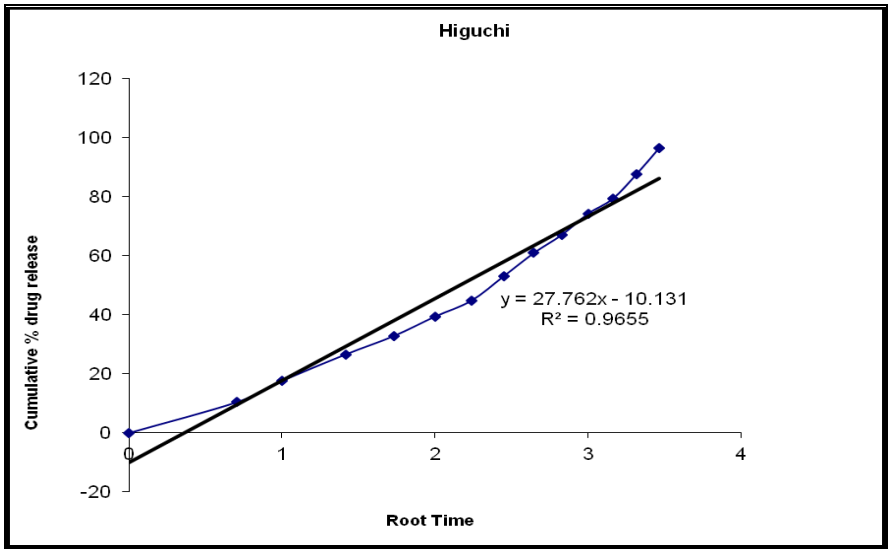

Figure 7.6: Graph of higuchi release kinetics.

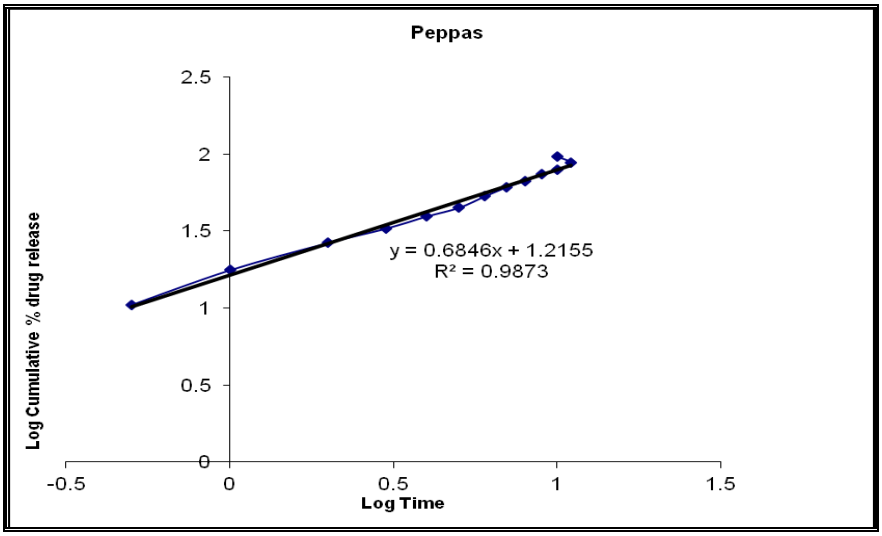

Figure 7.7: Graph of peppas release kinetics.

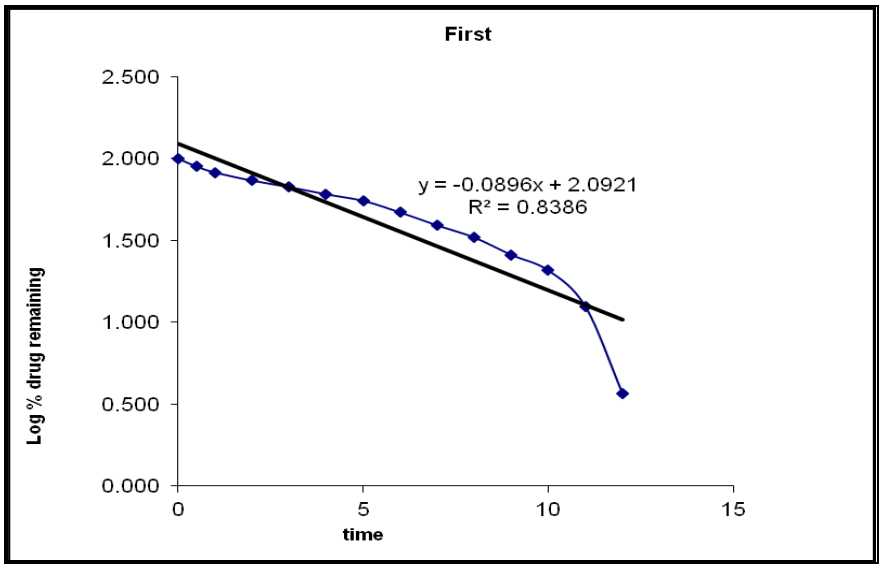

Figure 7.8: Graph of first order release kinetics.

Optimised formulation F6 was kept for release kinetic studies. From the above graphs it was evident that the formulation F6 was followed Zero order release mechanism.

CONCLUSION

The present study concludes that Extended drug delivery of Baclofen tablets can be a good way to prolong duration of action of drug by reducing the frequency of dosing of Baclofen. Present study concludes that extended drug delivery system should be a suitable method for Baclofen administration. The optimised formulation was found to be F6 formulation.

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ABBREVIATIONS

HPMC : Hydroxy Propyl Methyl Cellulose
IP : Indian Pharmacoepia
FTIR : Fourier transmission infrared spectroscopy
HCl : Hydrochloric acid
UV : Ultraviolet

CONFLICT OF INTEREST

The authors declare none

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