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Formulation and *In-vitro* Evalaution of Repaglinide Controlled Release Tablets

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A B S T R A C T

The purpose of present research work was to prepare and evaluate the controlled release tablets of Repaglinide. Direct compression method was used to prepare the tablets using different polymers like Eudragit S-100, Eudragit RSPO, Eudragit RLPO, Eudragit L-100, HPMC K4M and HPMC K15M. Twelve formulations (F1-F12) were prepared by varying the amount of polymers. The prepared tablets were evaluated for both pre-compression and post-compression parameters. Among all the formulation, F11 is considered as ideal formulation which exhibited 97.82% drug release in 12 hours. The results of dissolution data were fitted to various drug release kinetics and the optimized formulation F11 follows Higuchi's kinetics with R^2 value 0.99 and diffusion exponent values (n) of all repaglinide controlled release tablets were found to be 0.35-0.50 which indicates fickian diffusion.

Keywords: Repaglinide, Eudragit S-100, Eudragit RSPO, Eudragit RLPO, Eudragit L-100, HPMC K4M and HPMC K15M, Direct compression method.

A R T I C L E I N F O

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1. Introduction

The goal in designing a controlled delivery system is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery [1, 2]. Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects [3].

An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms [4][5]. Oral controlled release drug delivery is a system that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action [6]. Repaglinide is an oral blood glucose-lowering drug of the meglitinide class used in the management of type 2 diabetes mellitus. Repaglinide is rapidly eliminated from the blood stream with a half-life of approximately 1 hour. The mean absolute bioavailability is 56%. So in the present research work controlled release tablets of Repaglinide were prepared by direct compression method by using different polymers like Hydroxy propyl methyl cellulose K100M (HPMC K100M), HPMC K15M, Carbopol, Eudragit L-100, RSPO, S-100, RLPO.

2. Materials and Methods

Materials

Best possible grade available were used as supplied by the manufacturer without further purification or investigation. Repaglinide was purchased from Natco Pharma. HPMC K4M, HPMC K15M, xanthane gum, carbopol and microcrystaline cellulose was obtained from S.D. Fine Chem. Ltd., Mumbai. L.R. HPMC K100M, magnesium stearate was obtained from Degussa India Pvt. Ltd., Mumbai L.R. Eudragit L-100, Eudragit S-100, Talc is obtained from Merck Specialities Pvt. Ltd, Mumbai, India.

Method

All the formulations were prepared by direct compression technique as shown in table no-1 & 2. All powders were passed through 60 mesh. Required quantities of drug and polymers were mixed thoroughly and Magnesium stearate was added as lubricant. Talc was used as glidant. Micro crystalline cellulose was used as diluent. Finally the powder mix was subjected to compression after mixing uniformly in a polybag. Prior to compression, the blends were evaluated for several tests.

Evaluation

Preformulation studies [9, 10]

Before formulation of drug substances into a dosage form, it is essential that drug and polymer should be chemically and physically characterized. Preformulation studies give the information need to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the fabrication of a dosage form.

Precompression parameters [9, 10]:

i. Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose (θ). It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The fixed funnel method was employed to measure the angle of repose. The angle of repose (θ) was calculated using the following formula:

$$\mathbf{Tan\ \theta = h/r}$$

Where; θ = Angle of repose, h = Height of the cone, r = Radius of the cone base

ii. Bulk density:

Density is defined as weight per unit volume. Bulk density, ρ_b, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3.

$$\mathbf{\rho_b = M / Vo}$$

Where; ρ_b = Apparent bulk density, M = Weight of sample, V = Apparent volume of powder

iii. Tapped density:

The cylinder containing the sample was tapped 500 times initially followed by an additional taps of 750 times until difference between succeeding measurement is less than 2% and then tapped volume, $V_f$was measured, to the nearest graduated unit. The tapped density was calculated, in gm per ml, using the following formula.

$$\mathbf{\rho_{tap} = M / V_f}$$

Where; ρ_{tap} = Tapped density, M = Weight of sample, V_f = Tapped volume of powder

iv. Carr's index (%):

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. The differences are reflected in the carr's index which is calculated using the following formulas:

$$\mathbf{Compressibility\ index = [(\rho_{tap} - \rho_b) / \rho_{tap}] / \times 100}$$

Where; ρ_b = Bulk density, ρ_{tap} = Tapped density

v. Hausner's ratio:

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\mathbf{Hausner's\ ratio = Tapped\ density\ (\rho_t) / Bulk\ density\ (\rho_b)}$$

Where ρ_t tapped density and ρ_b is bulk density. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones, between 1.25 to 1.5 showing moderate flow properties and more than 1.5 poor flow.

Post compression parameters [9, 10]:

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

i. Tablet thickness:

The thickness in millimeters (mm) was measured individually for 10 pre weighed Tablets by using micrometer (screw gauge). The average thickness and standard deviation were reported.

ii. Weight variation:

Twenty Tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of three batches were calculated according to the weight variation limits prescribed in the pharmacopoeia.

iii. Tablet hardness:

For each formulation, the hardness of 6 Tablets was determined using Monsanto hardness tester and the average is calculated and presented with standard deviation.

iv. Friability:

The friability values of the Tablets were determined using a Roche-type friabilator. Accurately weighed six Tablets were placed in Roche friabilator and rotated at 25rpm for 4 min. The Tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original Tablets.

Percentage friability was calculated using the following equation.

Friability = ([w_O – w] /w_O) ò 100, Range: 0.5-1.0

Where,

w_O = weight of the Tablet at time zero before revolution.

w = weight of the Tablet after 100 revolutions.

v. Swelling Index:

Swelling index of the dosage form is conducted by using USP dissolution apparatus-II in 900 ml of pH 7.4 phosphate buffer which is maintained at 37±0.5c, rotated at 50 rpm. At selected regular intervals, the tablet is withdrawn the excess water was blotted with tissue paper. This procedure was repeated until the tablet reaches constant weight. The swelling index was calculated by using following formula

% swelling index = {(W_t) – (W_o) / (W_t)} × **100**

vi. Water uptake:

A piece of tissue paper folded twice was placed in a petridish containing 5ml of water. A pre weighed tablet was placed on the paper and time for complete wetting was measured which is characterized by coloring of tablet.

R was determined according to the following formula.

$R = (W_a – W_b / W_b)\ 100$

vii. *In-vitro* Drug release study:

The drug release was studied using USP type II apparatus at 37 ± 0.5°C and at 50 rpm using the phosphate buffer pH 6.8 & 0.1NHCl. The dissolution medium was kept for 2 h with 0.1NHCl and replaced with phosphate buffer pH 6.8 after 2 hours. The release rate analysis was done. 1ml of the sample solution was withdrawn at predetermined time intervals, filtered, diluted suitably and analyzed spectrophotometrically. Equal amount of the fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percentage drug dissolved was calculated.

viii. Model fitting for drug release kinetics:

Drug release kinetics was analyzed by various mathematical models, which are applied considering the amounts of drug released from 0 to 24hrs. Depending on these estimations, suitable mathematical models were used to describe the dissolution profiles. The following plots were made: cumulative % drug release versus time (Zero order kinetics); log cumulative % drug remaining versus time (First order kinetics); cumulative % drug release versus square root of time (Higuchi model).

Table 1: Composition of Formulations of repaglinide containing Eudragit (L-100, RSPO, RLPO, S-100)

Ingredients in (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Repaglinide	2	2	2	2	2	2	2	2
Eudragit L-100	4	8	-	-	-	-	-	-
Eudragit RSPO	-	-	4	8	-	-	-	-
Eudragit RLPO	-	-	-	-	-	-	4	8
Eudragit S-100	-	-	-	-	4	8	-	-
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
MCC	66	52	66	52	66	52	66	52
Total weight	75	75	75	75	75	75	75	75

Table 2: Composition of Formulations of repaglinide containing HPMC K4M, HPMC K15M

Ingredients in (mg)	F9	F10	F11	F12
Repaglinide	2	2	2	2
HPMC k4M	12	16	-	-
HPMC K15M	-	-	12	16
Magnesium stearate	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5
MCC	58	54	58	54
Total weight	75	75	75	75

3. Results and Discussion

The spectra for pure Repaglinide and for the physical mixture of Repaglinide and all the polymers were determined to check the intactness of the drug in the polymer mixture using FTIR – Spectrophotometer by disc method. The comparative FTIR studies of Drug and excipients combination had shown negligible variation in the values as compared with that of only pure form of Drug. Therefore it implies good compatibility of drug and excipients. Spectra was shown in fig no- 1,2,3. Bulk density of all formulations was in the range of 0.41gm/cc to 0.48gm/cc. Tapped density of all formulations was in the range of 0.57gm/cc to 0.66gm/cc.

Carr's index of all the formulations of with Eudragit and HPMC were between 21.4% and 34.7% respectively, which indicates the flow properties of the powders of all formulations are excellent. Hausner's Ratio of all the formulations of powders with Eudragit and HPMC were between 1.35 and 1.56 respectively which indicates the flow properties of the powders of all formulations are excellent. The powders with Eudragit had an angle of repose ranging from 31.2 to 35.9 indicates that all of the formlations made with Eudragit had excellent flow properties. The results are shown in table no-3.

Different formulations were compressed by using different polymers in different ratios. Weight variation was found to be is in the range of 74-76mg. Hardness is in the range of 2.5-3.2 kg/cm^2. Friability is in the range of 0.04-0.09%. Tablet thickness of all the formulations were in the range of 1.0-1.6mm. The average weights of all formulations was within the permissible limits. The results showed that the hardness of the tablets were almost the same and this was done to analyze the effect of polymer and its concentration on the drug release. Friability test of all the formulations was found satisfactory showing enough resistance to the mechanical shock and abrasion. The results are shown in table no-4. Formulations F1, F2 were prepared by using Eudragit L-100 is in the ratio of 1:2 and 1:4 shows drug release is about 88.69%, 86.57% up to 12th hr. Formulations F3, F4 were prepared by using Eudragit RSPO is in the ratio of 1:2, 1:4 shows drug release is abot 85.8%, 89.57% up to 12th hr. Formulations F5, F6 were prepared by using Eudragit S-100 is in the ratio of 1:2, 1:4 shows drug release is abot 87.48%, 83.25% at the end of the 12th hr. Formulations F7, F8 were prepared by using Eudragit RLPO is in the ratio of 1:2 and 1:4 shows drug release is about 85.65%, 86.29% up to 12th hr. Formulations F9, F10 were prepared by using HPMC K4M is in the ratio of 1:6, 1:8 shows drug release is abot 89.54%, 89.37% up to 12th hr. Formulations F11, F12 were prepared by using HPMC K15M is in the ratio of 1:6, 1:8 shows drug release is abot 97.82%, 85.69% at the end of the 12th hr. Among all these formulations F11 formulation shows highest amount of drug release upto 12hrs. so it is considered as the best formulation among all the formulations. The results are give in table no-5,6 and fig no-4,5. The kinetics of dissolution data with R^2 value obtained from formulation F1 to F12 are tabulated in table no-7. The optimized formulation F11 follows Higuchi's kinetics with R^2 value 0.99 and diffusion exponent values (n) of all repaglinide controlled release tablets were found to be 0.35-0.50 which indicates fickian diffusion. The results are shown in fig no-6 to 9.

Table 3: A comprehensive report on flow properties of Powders

Formulation	BulkDensity* G/CC	Tapped Density*	Hausner Ratio	Compressibility Index %	Angle of Repose
F1	0.427±0.003	0.577±0.00	1.35	30.7	31.2±1.001
F2	0.43±0.036	0.663±0.00	1.54	35.6	31.6±0.5
F3	0.412±0.003	0.646±0.00	1.56	32.75	35.8±0.95
F4	0.423±0.006	0.623±0.00	1.47	33.8	32.6±0.5
F5	0.435±0.001	0.634±0.00	1.45	32.4	33.4±0.4
F6	0.421±0.001	0.652±0.00	1.54	33.4	35.9±0.458
F7	0.423±0.003	0.632±0.00	1.49	33.9	32.3±0.3
F8	0.462±0.004	0.648±0.00	1.40	34.7	34.2±0.34
F9	0.453±0.003	0.655±0.00	1.44	29.4	32.5±0.5
F10	0.441±0.002	0.648±0.00	1.46	21.4	36.8±0.529
F11	0.437±0.002	0.638±0.00	1.45	32.1	33.1±0.624
F12	0.423±0.006	0.623±0.00	1.47	33.8	32.6±0.5

Table 4: Post compression parameters

Formulation Code	Hardness (kg/cm^2)	Friability (%)	Avg Weight (mg)	Thickness	Swelling index	Water Uptake (%)
F1	2.5	0.09	75	1.5	10	20.7
F2	3.0	0.06	75	1.0	25.6	22.4
F3	3.1	0.06	74	1.5	37.8	25.7
F4	3.2	0.11	74	1.5	33.5	29.9
F5	2.8	0.07	75	1..3	24.4	24.4
F6	2.5	0.04	75	1.5	40.9	21.7
F7	2.5	0.08	75	1.6	45.3	30.6
F8	2.3	0.07	76	1.5	33.6	32.5
F9	2.6	0.05	75	1.4	34.6	28.6

F10	2.5	0.04	75	1.5	39.7	27.9
F11	2.5	0.06	74	1.3	23.3	30.8
F12	3.2	0.09	74	1.5	43.7	25.8

Table 5: Cumulative % drug release of F1, F2, F3, F4, F5, F6

Formulation	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
30	22.62	18.59	26.57	28.36	26.58	20.72
60	36.95	26.59	33.57	33.57	30.57	31.25
120	44.59	35.27	39.84	36.95	42.59	36.59
240	56.85	50.29	44.14	52.29	56.87	46.58
360	66.63	62.57	53.68	58.28	68.52	58.67
480	78.25	71.58	66.59	68.74	72.59	66.27
600	81.89	79.68	79.86	79.48	77.59	71.43
720	88.69	86.57	85.8	89.57	87.48	83.25

n=3±S.D (All the values are average of three determinations)

Table no 6: Cumulative % drug release of F7, F8, F9, F10, F11, F12

Formulation	F7	F8	F9	F10	F11	F12
0	0	0	0	0	**0**	0
30	18.62	28.59	23.87	23.25	**11.25**	18.97
60	28.57	32.45	34.36	33.57	**27.30**	27.57
120	31.59	38.64	46.57	40.19	**31.24**	32.54
240	35.27	52.59	59.67	51.05	**49.57**	43.29
360	47.58	68.57	68.39	61.29	**56.27**	56.27
480	61.85	76.38	77.59	73.59	**61.20**	69.57
600	73.72	79.41	81.98	81.25	**86.37**	77.45
720	85.65	86.29	89.54	89.37	**97.82**	85.69

n=3±S.D (All the values are average of three determinations)

Table 7: Kinetic model fitting data for all formulations

Formulation code	Zero-order		First-order		Higuchi		Korsmeyer-Peppas		Best fit model
	Slope	R^2	slope	R^2	slope	R^2	slope	R^2	
F1	6.263	0.867	-0.070	0.983	24.71	**0.984**	0.404	0.984	Higuchi
F2	6.499	0.928	-0.066	0.992	24.98	**0.999**	0.484	0.999	Higuchi
F3	5.855	0.904	-0.061	0.950	22.40	**0.965**	0.352	0.942	Higuchi
F4	6.054	0.906	-0.067	0.940	23.30	**0.978**	0.358	0.960	Higuchi
F5	6.046	0.867	-0.064	0.971	23.85	0.984	0.385	**0.991**	Korsmeyer-Peppas
F6	5.754	0.905	-0.054	0.968	22.28	**0.989**	0.408	0.987	Higuchi
F7	6.045	0.947	-0.058	0.930	22.49	**0.955**	0.437	0.928	Higuchi
F8	6.122	0.8795	-0.010	0.9821	23.98	**0.983**	0.369	0.968	Higuchi
F9	6.283	0.861	-0.010	0.981	24.89	0.984	0.408	**0.993**	Korsmeyer-Peppas

F10	6.316	0.910	-0.010	0.975	24.41	**0.991**	0.398	0.988	Higuchi
F11	7.248	0.952	-0.014	0.806	27.01	**0.963**	0.587	0.946	Higuchi
F12	6.349	0.946	-0.009	0.981	24.06	**0.991**	0.454	0.981	Higuchi

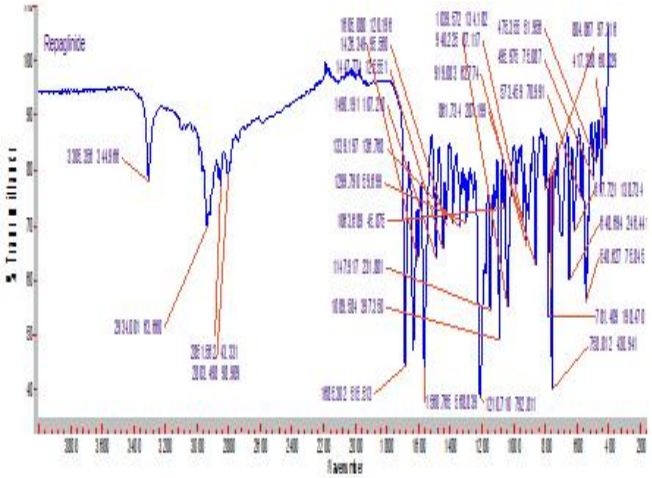

Figure 1: FT-IR Spectra of Repaglinide

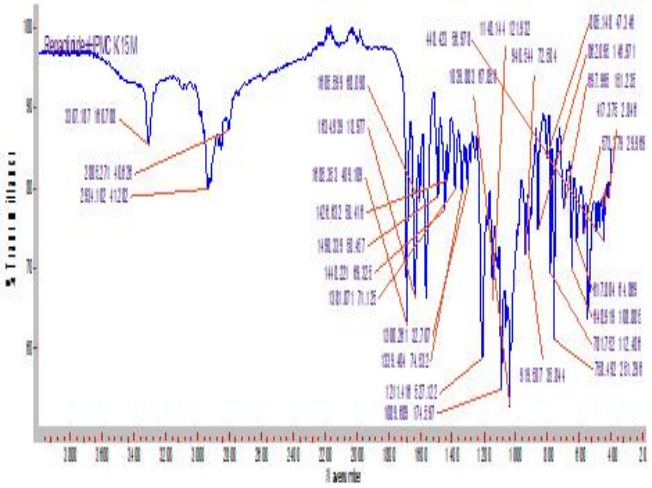

Figure 2: FT-IR Spectra of Repaglinide, HPMC

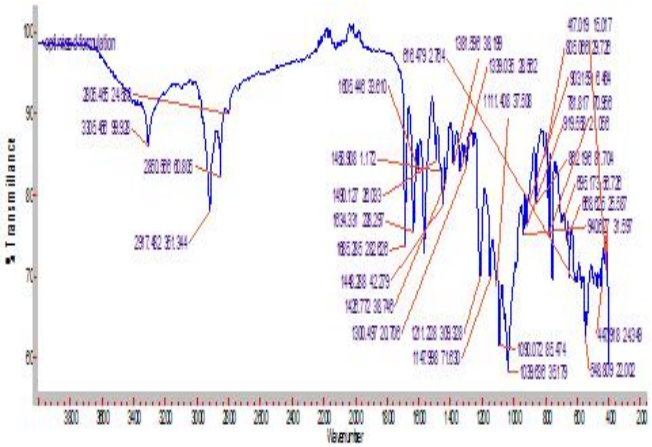

Figure 3: FT-IR spectra of optimized formulation

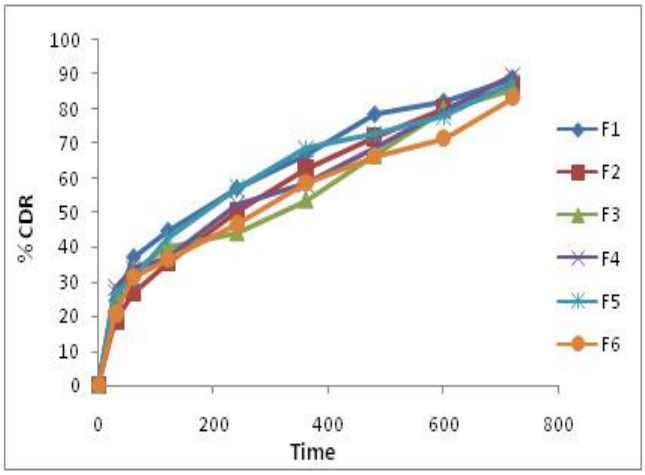

Figure 4: Dissolution graphs of F1, F2, F3, F4, F5 & F6

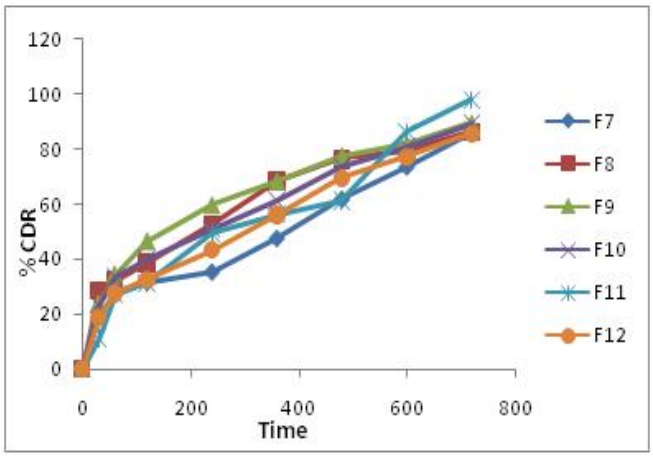

Figure 5: Dissolution graphs of F7, F8,F9,F10,F11 & F12

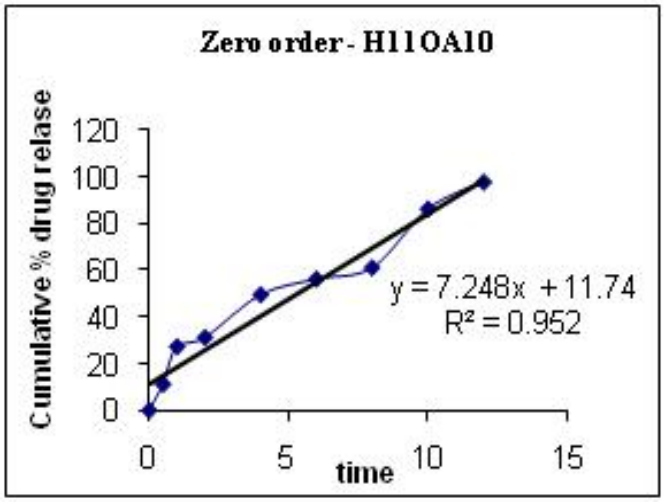

Figure 6: Zero order graph for F11

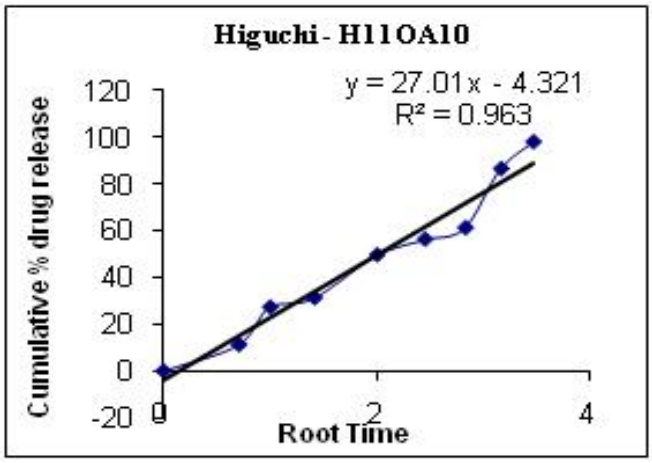

Figure 7: Higuchi graph for F11

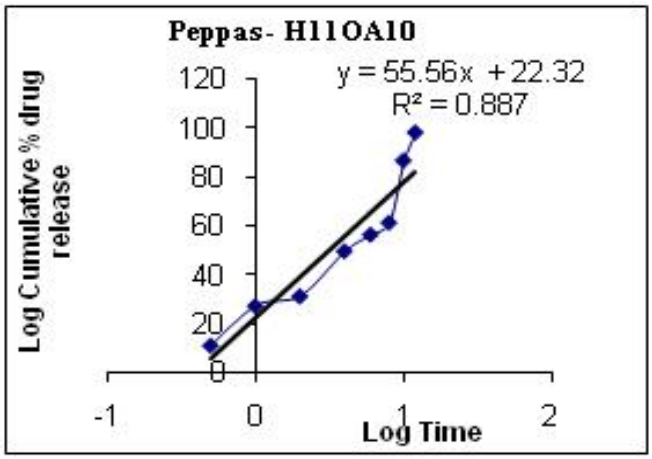

Figure 8: Peppa's graph for F11

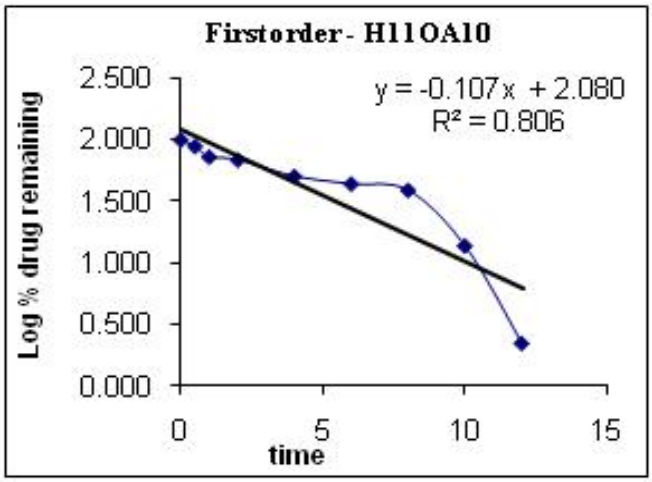

Figure 9: First order graph for F11

4. Conclusion

From the present research it was concluded that the formulation F11 (HPMC K15M is in the ratio of 1:6) of Repaglinide controlled release tablets has achieved 97.82% drug release for 12 Hrs which was found to be the best. The above formulation may also decrease the gastric irritation and may improve patient compliance with reduction in dosage frequency.

5. Acknowledgements

We sincerely thank principal Dr. P. Mani chandrika and **K.P labs (A DIVISION OF KDPL)** for their cooperation and support throughout the project.

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