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FORMULATION, DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF REPAGLINIDE

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Abstract: To Formulate, Develop and evaluate sustained release matrix tablets of Repaglinide, to reduce the frequency of dosage administration for long term therapy and control drug release. Repaglinide sustained release matrix tablets using HPMC K100M and Guargum were prepared by wet granulation method. A 32 full factorial design was employed to optimize the concentration of HPMC K100M(X1) and concentration of Guargum(X2) was selected as independent variables and Q_2, Q_{12} and T_{90} were selected as dependent variables. There lease data were subjected to different models in order to evaluate their release kinetics and mechanisms. The tablets were subjected to evaluation for physical characteristics like weight variation, drug content uniformity and *in vitro* drug release. Formulation was optimized on the basis of *in vitro* drug release for 12hrs. The optimization study indicates that dependent variable depends on concentration of HPMC K 100M and Guargum. Batch N4 contains 20mg of HPMC K 100M and 10mg of Guargum shown best results of 99.67% drug release in 12 hrs.After the *In vitro* dissolution study of prepared sustained release tablet of Repaglinide, it was concluded that the combination of HPMC K100M (Synthetic polymer) and Guargum (Natural polymer) shown better sustained release effect. There lease kinetics data implies that there lease mechanism of the all formulations was follow zero order. The optimized formulation was subjected to stability studies for one month at 40℃ temperature with 75±5%RH and showed there was no significant change in drug content, physicochemical parameters and release pattern.
Keywords: Repaglinide, Sustained Release, Matrix Tablets, HPMC K100M, Guargum, Wet Granulation

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INTRODUCTION

Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in developing a sustained-release drug delivery system. Matrix systems are the most popular method among innumerable methods used in the development of controlled release formulations. Hydrophilic polymeric matrix systems are widely used in controlled drug delivery, since they make it easier to achieve a desirable drug release profile, are cost effective and have broad FDA acceptance.[1] Increased compliance and expense involved in marketing of new drug entities has focused greater attention on development of sustained release or controlled release drug delivery systems.[2] The aim of any drug delivery system is to provide therapeutic amount of drug to appropriate site in the body to achieve immediate therapeutic response and to maintain the desired drug concentration. In the recent years sustained release (SR) dosage forms continue to draw attention in the research for improved patient compliance and decreased incidence of adverse drug reactions.[3] In general the goal of sustained release dosage form is to maintain therapeutic blood or tissue level of the drug for extended period of time. This is generally accomplished by attempting to obtain "zero order" release from the dosage form. Zero order release constitutes drug release from the dosage form which is independent of the amount of drug in the delivery system. Sustained release system generally do not attain this type of release and usually try to mimic zero order release by providing drug in slow "first order" fashion (i.e. concentration dependent).[3]

Repaglinide is the first member of new class of oral hypoglycemic designed to normalize the meal time glucose excursions. Repaglinide induces rapid onset short lasting insulin release. It is administered before each major meal to control postprandial hyperglycemia; the dose may be omitted if a meal is missed. Because of short lasting action it may have a lower risk of serious hypoglycemia. Side effects are mild headache, dyspepsia, arthralgia, and weight gain. After oral administration, Repaglinide is rapidly and completely absorbed from the gastrointestinal tract. After single and multiple oral doses inn healthy subjects or in patients, peak plasma drug levels (Cmax) occurs within 1 hour (Tmax). Repaglinide is rapidly eliminated from the blood stream with a half life of approximately 1-hour. The mean absolute bioavailability is 56%, when repaglinide was given with food .

The present study was designed to formulate matrix tablets using HPMC K15 M,HPMC K 100 M, Guar gum and Xanthan gum , pectin, EC(ethyl cellulose) as hydrophilic and hydrophobic matrix polymers for controlling release of poorly water soluble drug Repaglinde

MATERIALS AND METHODS:

Repaglinide obtained from torrent pharmaceuticals ltd., Ahmedabad, india as a gift sample. HPMC k 15 M HPMC K100 M, pectin, ethyl cellulose obtained from chemdyes corporation,

ahmedabad, india. guar gum and xanthan gum were obtained from h. b. gum India ltd, ahmedabad, talc ,lactose ,magnsium sterate obtained from powder pack chem. India, pvp k 30 obtained from s.d. fine. chemady, mumbai, India all other reagents used were of analytical grade.

Theoretical Drug Release Profile:- Calculation of theoretical drug release profile

Robinson Erikson equation using available p'cokinetic data

k_0 = zero order drug release, ke = 0.693/$t_{1/2}$,D_i = initial dose/conventional dose, D_l =loading dose, $D_m$maintenance dose, T = time for sustained action, T_p = time to reach peak plasma concentration; D_t = total dose of drug.

$K_0=Dik_e=1.125 * 0.693 /1=0.7796$ mg

$Dm=K_0T=0.076 * 12=9.35$ mg

$D_l=D_i-k_0T_P=1.125-(0.076*1)=0.3454$ mg

$D_t=D_l+D_m=0.3454+9.35=9.70$ mg=10 mg

Hence the matrix tablet should contain a total dose of 10 mg for 12 h. sustained release dosage form and it should release 0.3454 + 0.7796 = 1.125 (11.25%) mg in 1st hour. remaining dose (10 - 1.125 mg) in remaining 11 hours, i.e. 0.8068 (8.07%) mg per hour up to12 hr.

Table 1.1 Theoretical Drug Release Profile

Time (hrs)	Drug Release (mg)	Drug Release (%)
0	0	0
1	1.125	11.25
2	1.931	19.31
3	2.737	27.37
4	3.543	35.43
5	4.349	43.49
6	5.155	51.55
7	5.961	59.61
8	6.767	67.67
9	7.573	75.73
10	8.379	83.79
11	9.185	91.85
12	9.991	99.91

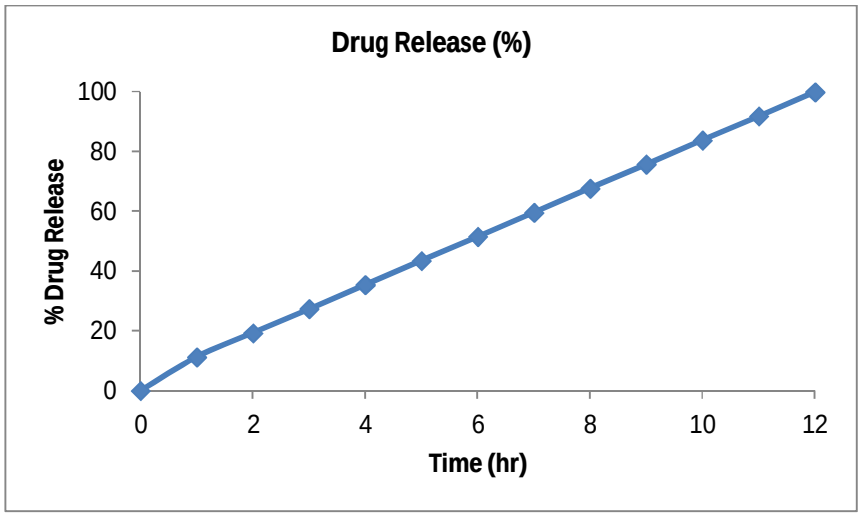


Fig:1 Theoretical Drug Release Profile:-

Standard Plot for Repaglinide

In 0.1N HCL Repaglinide 100 mg was dissolved in 0.1N HCl and volume was made up to 100 ml in 100 ml volumetric flask i.e.1000µg/ml. This Stock solution was diluted with 0.1N HCl to make the concentration of 0, 5, 10, 15, 20 and 25 µg/ ml. Absorbance of each solution was measured at 223 nm using Shimadzu UV/Visible double beam spectrophotometer by using 0.1N HCl as a reference standard. Standard curve was generated for the entire range from 10 to 30 µg/ ml.

Table 1.2 Calibration Curve of Repaglinide in 0.1N HCl at 223nm

Concentration (µg/ml)	Absorbance			Average Absorbance	STD Deviation
	I	II	III		
0	0.000	0.000	0.000	0.000	0.000
5	0.115	0.112	0.118	0.115	0.003
10	0.227	0.224	0.231	0.227	0.004
15	0.312	0.318	0.308	0.313	0.005
20	0.445	0.441	0.444	0.443	0.002
25	0.551	0.548	0.554	0.551	0.003

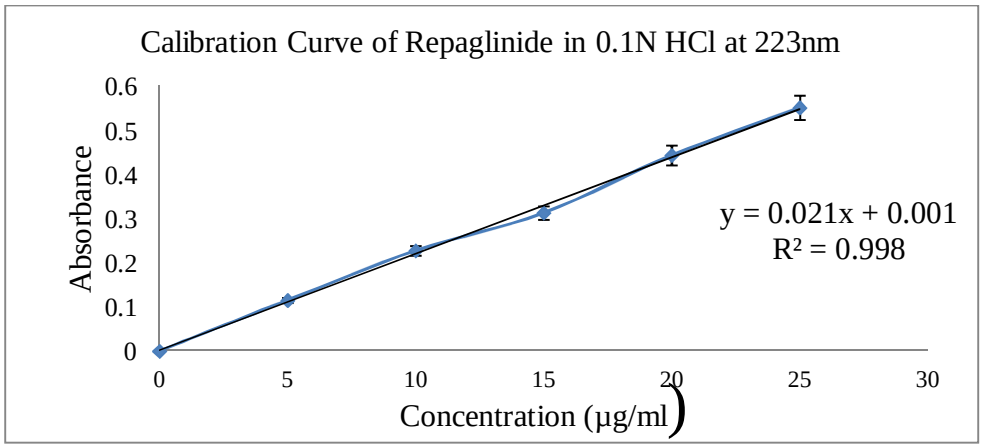


Fig:2 Calibration Curve of Repaglinide in 0.1N HCl at 223nm

Standard Plot for Repaglinide

IN pH 7.4 Phosphate buffer

Repaglinide 100 mg was dissolved in Phosphate Buffer pH 7.4 and volume was made up to the mark in 100 ml volumetric flask. i.e.1000µg/ml. This Stock solution was diluted with 7.4pH Phosphate Buffer to make the concentration of 0, 5, 10, 15, 20 and 25 µg/ ml. Absorbance of each solution was measured at 247 nm using Shimadzu UV/Visible double beam spectrophotometer by using Phosphate Buffer pH 7.4 as a reference standard. The standard curve was generated for the entire range from 10 to 50 µg/ ml.

Table 1.3 Calibration Curve of Repaglinide in pH 7.4 Phosphate buffer at 247nm

Concentration (µg/ml)	Absorbance			Average Absorbance	STD Deviation
	I	II	III		
0	0.000	0.000	0.000	0.000	0.000
5	0.118	0.119	0.119	0.119	0.001
10	0.209	0.208	0.205	0.207	0.002
15	0.322	0.319	0.328	0.323	0.005
20	0.421	0.417	0.423	0.420	0.003
25	0.530	0.525	0.524	0.526	0.003

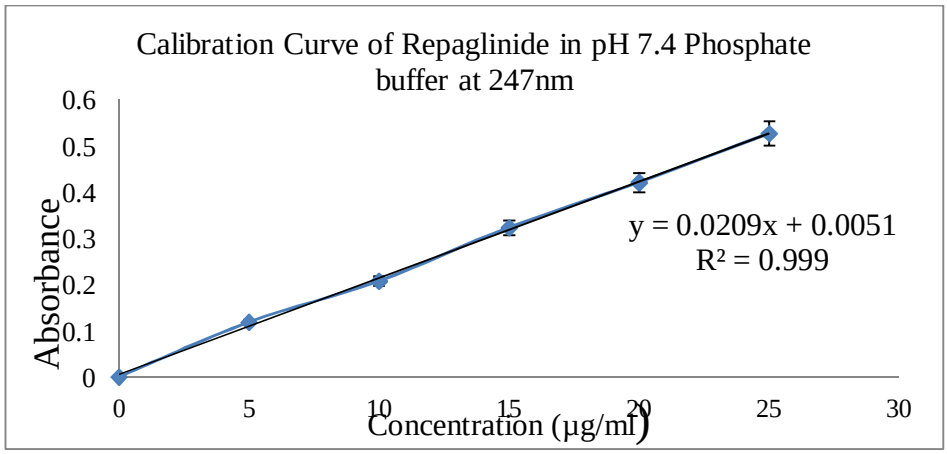


Fig 3 : Calibration Curve of Repaglinide in pH 7.4 Phosphate buffer at 247nm

PRELIMINARYSCREENING

Optimization of polymer

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
Repaglinide	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
HPMCK 15M	10	-	-	-	-	-	20	-	-	-	-	-	30	-	-	-	-	-
HPM K 100M	-	10	-	-	-	-	-	20	-	-	-	-	-	30	-	-	-	-
Ethyl Cellulose	-	-	10	-	-	-	-	-	20	-	-	-	-	-	30	-	-	-
Guar gum	-	-	-	10	-	-	-	-	-	20	-	-	-	-	-	30	-	-
Xanthan Gum	-	-	-	-	10	-	-	-	-	-	20	-	-	-	-	-	30	-
Pectin	-	-	-	-	-	10	-	-	-	-	-	20	-	-	-	-	-	30
PVP K 30 (5%)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
LACTOSE	125.5	125.5	125.5	125.5	125.5	125.5	125.5	115.5	115.5	115.5	115.5	115.5	105.5	105.5	105.5	105.5	105.5	105.5
Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150

Preliminary screening for optimization of bioadhe polymer was carried out using SIX different polymers for selection of good release in sustained manner.The formulas of batch f1to f18 [5]are shown in [Table 1.4].

Table 1.4 Composition of Sustained released matrix tablets of repaglinide preliminary baches

OPTIMIZATION USING FULL FACTORIAL DESIGN

A 3^2 randomized full factorial design was used in present study. In this design, 2 factors were evaluated, each at 3 levels, and experimental trials were performed for all 9 possible combinations. Ratio of HPMC K100 M to (10,20,30 mg) (X_1) and guargum also(10,20,30 mg) (X_2) were chosen as two factors. The formulation layout for the factorial design batches (F1-F9) is shown in [Table 1.5]. Prepared tablets were evaluated for content uniformity, *in vitro dissolution*, thickness, hardness, weight variation ,friability, ,swelling study, carried out for optimized.

CODED VALUES

LEVEL	X1(CONCENTRATION OF HPMC K1OO)	X2(CONCENTRATION OF GUAR GUM)
-1	10	10
0	20	20
1	30	30

Table 1.5 Formulation of 3^2 Factorial design batch

Ingredients	N1	N2	N3	N4	N5	N6	N7	N8	N9
Rapaglinide	10	10	10	10	10	10	10	10	10
HPMC K 100M	10	10	10	20	20	20	30	30	30
Guar gum	10	20	30	10	20	30	10	20	30
PVP K 30 (5%)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
LACTOSE	115.5	105.5	95.5	105.5	95.5	85.5	95.5	85.5	75.5
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	150	150	150	150	150	150	150	150	150

- **Method of Preparation of Repaglinide SR matrix Tablet**

The wet granulation process was used to form granules with using a Repaglinide was mixed with HPMC K 15M, HPMC K 100M, Pectin, Guargum, Xanthan gum and Ethyl Cellulose taking in concentration of (10mg, 20mg, 30mg) and binder PVP K30 was dissolved in IPA than after lactose was used as diluents for final blend. After that wet mass pass from sieve no 20# and wet granules were dried at 50°c in over for 30 minutes. Dried granules were sized by passing it though sieve no.15# and lubricated with magnesium state and talc for 1 minute. Tablets were

compressed using rotary tablet machine with 8mm diameter standard concave punch. Tablet weight is 150 mg.

Determination of physicochemical parameters:-

- **Drug Excipient Compatibility Study**

- **FTIR Spectra:**

IR spectra of drug in KBr pellets at moderate scanning speed between 4000-400 cm^{-1} was carried out using FTIR. The peak values (Wave number) and the possibility of functional group shown in spectra were compared with standard value. The comparison of these results with Repaglinide chemical structure shows that the sample was pure Repaglinide Sample.

- **Weight Variation:**

20 tablets were weighed individually and then collectively, average weight of the tablets was calculated.

- **Hardness**

The hardness of the tablets was determined using a Hardness testing apparatus (Monsanto Type). A tablet hardness of about 5-7kg/cm^2 was considered adequate for mechanical stability.[58]

- **Friability**

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai, India). Tablets of a known weight (W) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 % w/w.[59]

% Friability = (W í W)/W × 100 ---------- (7)

- **Thickness:**

The thickness of ten randomly selected matrix tablets was determined using a digital vernier caliper. The results were expressed as mean values of 10determinations.[57]

- **% Drug Content**

Weigh and powder 20 tablets. Weigh accurately a Quantity of the powder equivalent to 100 mg of Repaglinide, transfer to a 250 ml volumetric flask. Add about 150 ml of 0.1N HCL, shake well and sonicate it for 25-30 min. Make up the volume up to 250 ml with 0.1N HCL. Filter the

solution, take 10 ml of filtrate in 100 ml volumetric flask and make up the volume with 0.1N HCL. Measure the Absorbance. of the resulting solution at the maxima at about 247 nm spectrophotometrically. Weigh accurately 100mg of Repaglinide pure drug and transfer to a 250 ml volumetric flask. Add about 150 ml of 0.1N HCL, shake well until it dissolves. Make up the volume up to 250 ml with 0.1N HCL. Filter the solution, take 10 ml of filtrate in 100 ml volumetric flask and make up the volume with 0.1N HCL. Measure the Absorbance of the resulting solution at the maxima at about 247 nm spectrophotometrically. Measure the concentration of drug in tablet powder using following equation:

Cu/Cs = Au/As * dilution factor

Where, Cu = Concentration of unknown sample

Cs = Concentration of Standard sample

Au = Absorbance of unknown sample

As = Absorbance of standard sample.[59]

- **Swelling Index**

Swelling index was taken on tissue paper at ph 7.4 phosphate buffer in petridish at an interval of 1hr to 12hr. The tablet was withdrawn and the excess water was blotted with tissue paper. This procedure was repeated until the tablet reches constant weight.

% swelling index=wt-wo/wt*100

Wt is the weight of the swollen tablet

Wo is the initial weight of the tablet

- **In-vitro dissolution study:**

Dissolution tests were performed in a USP Dissolution Test Apparatus II (Paddle method) at 37 ± 0.5°C. The Paddles were rotated at a speed of 50 rpm. The prepared tablets of Repaglinide tablets were placed in the baskets and then submerged into 0.1 N HCl solutions (pH 1.2) for 2 hrs. These were then transferred to phosphate buffer (pH 7.4) and continue dissolution. Aliquots of 10 ml were withdrawn at different time intervals, filtered through 0.45 µm filter paper and the content of Repaglinide was determined spectrophotometrically at a wavelength of 223nm for first 2 hr and than after take in 247nm. At each (hr) time of withdrawal, 10 ml of fresh corresponding medium was replaced into the dissolution flask. The release studies were conducted and results were noted in respective tables.

Comparison of dissolution profiles for selection of optimum batch

The similarity factor (f_2) given by SUPAC guidelines for a modified release dosage form was used as a basis to compare dissolution profiles. The dissolution profiles are considered to be similar when f_2 is between 50 and 100. The dissolution profile of products were compared using a f_2 which is calculated from following formula,

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

Where, n is the dissolution time and R_t and T_t are the reference (here this is the theoretical dissolution profile of repaglinide) and test dissolution value at time t.

- **Kinetic modeling of dissolution data**

The dissolution profile of all factorial batches were fitted to various models such as zero order, first order, Higuchi, Hixon Crowell, Korsemeyer and Peppas, to ascertain the kinetic of drug release. The method described by Korsemeyer and Peppas was used to describe mechanism of drug release.

- **Stability Studies of the Optimized Formulation**

Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life."

To assess the drug and formulation stability, stability studies were done according to ICH guidelines Q_1C. The stability studies were carried out on the most satisfactory formulations as per ICH guidelines Q_1C. The optimized formulation were sealed in aluminum packaging coated inside with polyethylene and kept in humidity chamber maintained 40 ± 2 °C / 75 ± 5 % RH for 1month.

RESULT AND DISSCUTION

- **RESULTS OF PRELIMINARY SCREENING**

OPTIMIZATION OF POLYMER

Table 1.6 Pre compression parameter of Preliminary Trail Batches

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
Bulk Density (gm/ml)	0.43	0.37	0.39	0.36	0.37	0.44	0.47	0.52	0.42	0.49	0.47	0.48	0.37	0.44	0.45	0.46	0.37	0.48
Tapped density (gm/ml)	0.49	0.43	0.44	0.42	0.44	0.52	0.54	0.6	0.49	0.56	0.53	0.55	0.48	0.42	0.41	0.39	0.34	0.6
Angle of Repose (θ)	29.42	27.62	28.12	28.44	29.44	29.4	29.39	26.08	25.12	26.42	25.08	24.12	26.46	28.64	29.13	24.13	29.44	23.08
Carr's index (%)	12.24	13.95	13.36	14.29	15.91	15.38	14.96	15.33	14.29	13.5	13.32	14.73	13.24	14.94	13.33	14.27	15.92	13.34
Hausner's Ratio	1.22	1.28	1.26	1.22	1.84	1.23	1.87	1.17	1.23	1.15	1.29	1.27	1.25	1.23	1.22	1.25	1.24	1.24

Table 1.7 Postcompression parameter of Preliminary Trail Batches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diameter (mm)	6±0.2	6±0.2	6±0.2	6±0.2	6±0.2	6±0.2	6±0.2	6±0.2	6±0.2
Thickness (mm)	4.7±0.2	4.6±0.3	4.65±0.2	4.7±0.2	4.67±0.1	4.65±0.2	4.7±0.2	4.65±0.2	4.66±0.1
Hardness (kg/cm^3)	5±0.3	5±0.5	6±0.2	4±0.4	5±0.3	5±0.6	5.5±0.2	7±0.4	6±0.5
Wt. Variation	pass	pass	pass	pass	pass	pass	pass	pass	pass
Friability test (%)	0.76±0.2	0.74±0.2	0.91±0.1	0.89±0.3	0.80±0.2	0.77±0.4	0.71±0.2	0.54±0.2	0.61±0.3
Swelling Test	16.6±0.9	18.4±0.8	15.2±1	24.4±0.6	23.3±0.9	12±0.8	17.7±0.7	22.5±0.6	19.1±0.1
Drug content	98.33±1.2	97.32±1.3	96.33±1	98.78±1.1	98.88±1.4	99.1±1.2	98.77±1	99.23±0.9	97.77±1.2

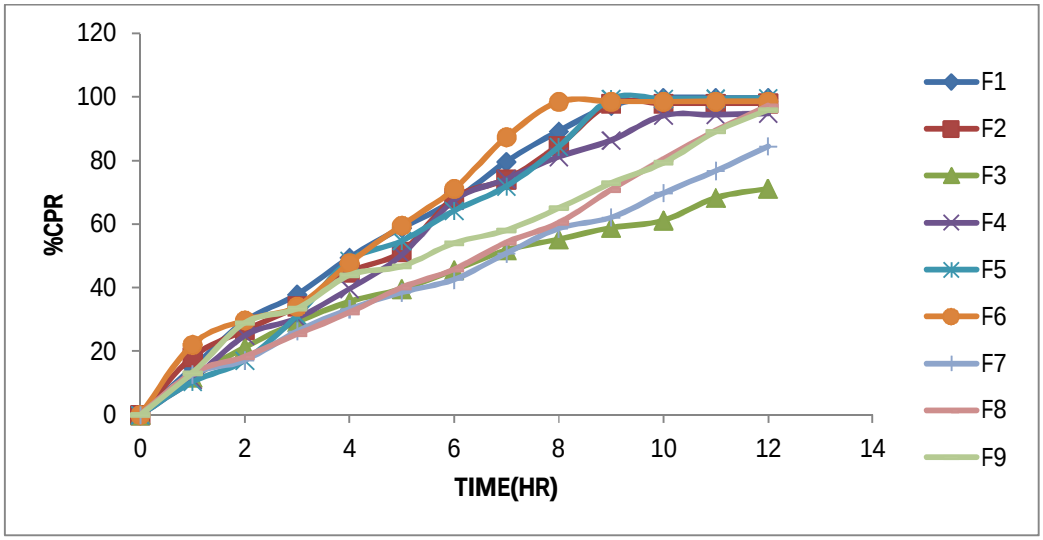
Table 1.8 Post compression parameter of Preliminary Trail Batches

Ingredients	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
Diameter (mm)	6±0.2	6±0.2	6±0.2	6±0.2	6±0.2	6±0.2	6±0.2	6±0.2	6±0.2	6±0.2
Thickness (mm)	4.66±0.1	4.71±0.2	4.65±0.2	4.69±0.3	5±0.2	6±0.2	5±0.3	5.8±0.2	5.7±0.1	5.7±0.3
Hardness (kg/cm^3)	6±0.5	7±0.3	7±0.8	6±0.6	7±0.3	6±0.5	6.5±0.2	6±0.4	5±0.3	5±0.6
Wt. Variation	pass	pass	pass	pass	Pass	Pass	Pass	Pass	Pass	Pass
Friability test (%)	0.61±0.3	0.49±0.3	0.53±0.2	0.64±0.2	0.60±0.2	0.69±0.2	0.65±0.1	0.70±0.3	0.81±0.2	0.82±0.4
Swelling Test	19.1±0.1	24.9±0.8	34.8±0.7	25.7±0.6	25.6±0.9	32.4±0.8	24.2±1	27.4±0.6	24.3±0.9	21±0.8
Drug content	97.77±1.2	98.32±0.8	98.56±1.3	98.78±1.2	99.56±1.4	97.04±1.3	98.78±1.2	99.96±1.3	96.78±1	97.88±1.2

Table 1.9 :Dissolution profile of Preliminary Trail Batches

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	14.8	18.2	11.8	11.1	10.4	22.1	12.73	13.21	13.21	13.21	12.97	15.83	12.7	14.5	13.7	12.7	13	15.8
2	29.4	26.6	21.2	24.9	17.1	29.8	17.17	18.26	28.95	18.26	19.8	26.94	17.3	18.3	20.3	17.4	19.8	26.9
3	37.9	34.2	29.2	30.5	31.2	34.1	26.3	25.36	33.46	24.36	27.29	31.93	26.4	25.3	28.8	26.4	27.2	31.9
4	49.5	44.9	35.6	39.7	48.5	47.8	33.3	32.2	43.98	30.91	39.08	37.02	33.3	32.3	30.7	32.2	38.8	37
5	58.8	51.3	39.6	50.3	54.7	59.6	38.55	40.02	46.75	38.81	41.17	41.63	38.6	38.8	39.1	38.4	40.9	41.6
6	67.4	68.2	45.6	67.5	64.2	71.1	42.58	45.74	54.07	48.6	43.42	48.75	44.5	44.5	41.6	44.3	43.5	48.8
7	79.6	74.1	51.8	74.2	71.9	87.4	50.84	54.25	58.11	54.48	49.94	52.47	50.9	54.2	55.6	50.9	49.3	52.5
8	89.2	84.7	55.3	81.2	84.3	98.5	58.62	60.41	65.11	61.9	52.29	58.9	58.7	57.9	62.3	58.4	56.5	58.9
9	97.2	97.9	58.9	86.4	99.4	98.5	62.14	70.74	72.93	71.42	60.79	72.76	63.6	70.6	68.5	63.3	60.9	72.8
10	99.7	97.9	61.2	94.2	99.4	98.5	69.84	80.4	79.36	80.23	69.94	74.21	72.7	77.5	71.1	72.5	71.3	77.7
11	99.7	97.9	68.3	94.4	99.5	98.6	76.77	89.35	89.19	88.42	77.99	87.68	76.4	83.3	77.5	76.1	78.2	84.9
12	99.7	98	71.2	94.9	99.6	98.6	84.51	97.17	95.94	96.7	86.9	92.14	84.7	86.5	81.6	84.5	87.1	87.8

Fig 4. Comparison of Dissolution Profile of Batches F1TO F9



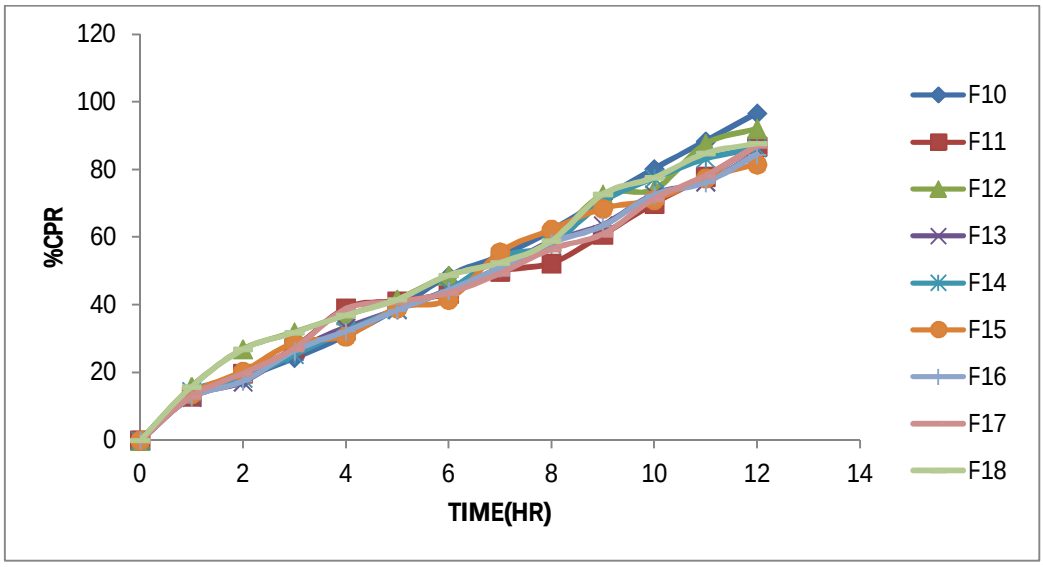


Fig 5. Comparison of Dissolution Profile of Batches F10 TO F18

Result of Preliminary Trails:

From the Preliminary Batches, F8 and F10 gave good result in dissolution as compared to other batches in medium concentration. Optimization was done on the basis of % Drug release within 12 hours. Batch F8 and F10 gave 97.17% to 96.70% release in 12 hrs respectively.In the F8 batch HPMC K 100M (20mg) and in F10 batch Guar gum (20 mg) were used. So these two polymers were selected for the further studies. Selected F8 batch shows friability, swelling index and drug content of 0.54, 22.5 and 99.23% respectively while that of F10 batch with Guargum polymer was 0.49, 24.9 and 98.32% respectively.

RESULT OF FULL FACTORIAL DESIGN

Drug Excipient Compatibility Study

It was observed that there were no changes in these main peaks in the IR spectra of a mixture of drug and excipient **[Figure 6], [Figure 7], [Figure 8]**and [**Figure 9] .** Hence, it was concluded that there is no interaction between drug and excipients.

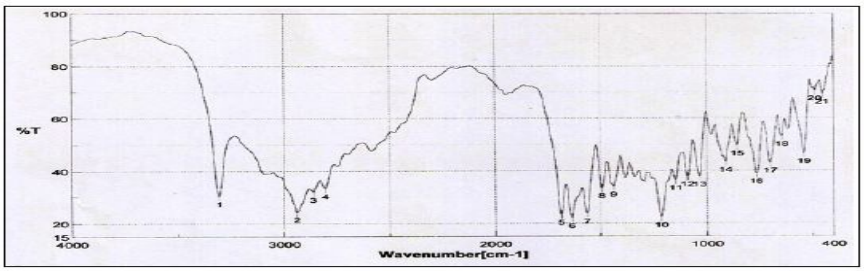


Figure 6 (a) FTIR Spectra of Repaglinide

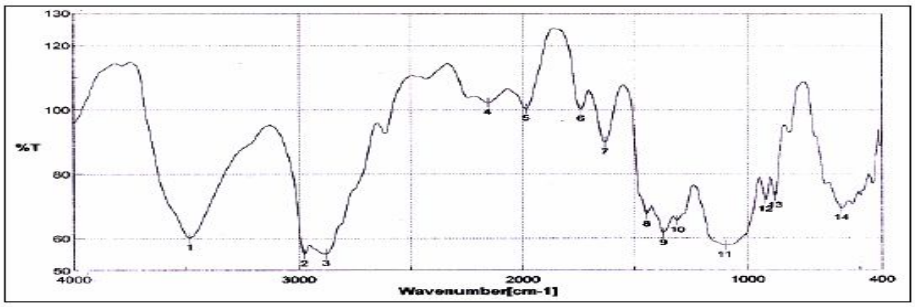


Figure 7 (b) FTIR Spectra of Repaglinide + HPMC K 100M

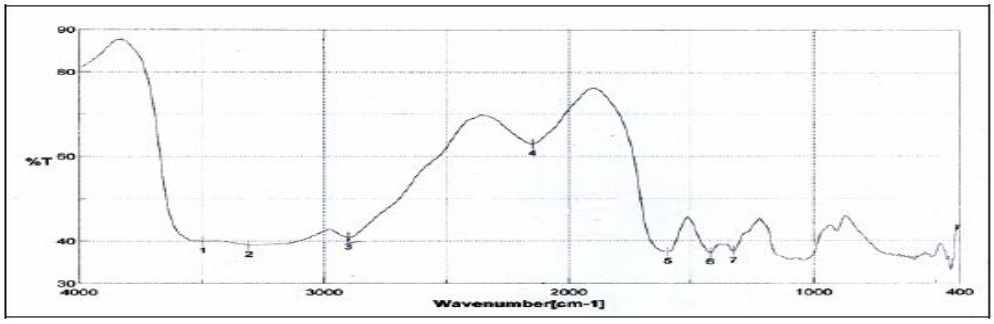


Figure 8 (c) FTIR Spectra of Repaglinide + Guargum

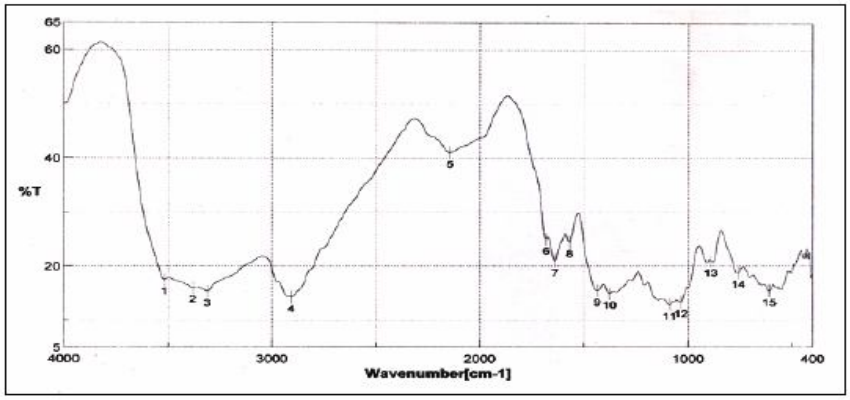


Figure 9 (d) FTIR Spectra of Repaglinide + HPMC K 100M + Guargum

TABLE 2 Evaluation Parameters for Batches

Ingredients	N1	N2	N3	N4	N5	N6	N7	N8	N9
Diameter (mm)	6±0.2	6±0.2	6±0.2	6±0.2	6±0.2	6±0.2	6±0.2	6±0.2	6±0.2
Thickness (mm)	4.6±0.2	4.5±0.3	4.6±0.2	4.65±0.2	4.6±0.3	4.5±0.4	4.53±0.5	4.57±0.6	4.51±0.7
Hardness (kg/cm3)	7±0.4	6±0.3	5±0.2	6±0.5	5±0.8	5±0.11	5±0.5	6±0.17	5±0.2
Wt Variation	pass	pass	pass	pass	pass	pass	pass	pass	pass
Friability test %	0.56±0.2	0.68±0.3	0.74±0.2	0.57±0.3	0.74±0.3	0.65±0.4	0.71±0.4	0.85±0.5	0.77±0.5
Swelling Test	21.6±0.9	19.4±0.6	20.2±1	26.4±0.8	24.2±2	18.4±0.9	22.2±3	26.4±0.1	22.2±4
Drug content	97.22±1	98.23±1.2	97.25±1.3	99.67±0.9	98.09±1.4	97.51±1.2	96.93±1	96.35±0.9	95.77±1

Table 2.1 Dissolution profile of Batches N1 to N9

Time (hrs)	N1	N2	N3	N4	N5	N6	N7	N8	N9
0	0	0	0	0	0	0	0	0	0
1	13.1	9.17	11.67	13.69	10.36	11.67	12.5	8.57	13.1
2	14.32	15.32	16.27	16.32	16.03	15.32	19.35	18.67	19.35
3	27.44	26.37	25.68	27.21	23.96	28.72	26.29	22.37	29.94
4	32.99	30.26	29.66	35.62	30.63	31.94	33.3	26.6	37.33
5	38.35	33.51	33.26	43.2	36.77	36.37	38.54	35.1	41.48
6	41.62	37.73	39.59	52.03	42.49	40.93	42.57	40.02	48.23
7	47.34	42.69	44.99	59.03	46.26	45.25	50.83	45.33	52.32

8	51.1	56.42	49.43	67.98	50.25	52.18	58.61	52.3	57.51
9	60.33	66.51	56.49	75.7	58.58	59.45	66.51	65.86	64.58
10	69.73	72.81	74.38	83.39	71.67	68.69	73.14	74.77	73.98
11	77.67	80.26	83.79	91.04	88.34	81.09	81.32	87.69	83.67
12	91.49	92.32	94.43	98.99	97.22	98.65	96.67	97.21	96.21

Figure 10 Dissolution Profile Bach N1 To N9

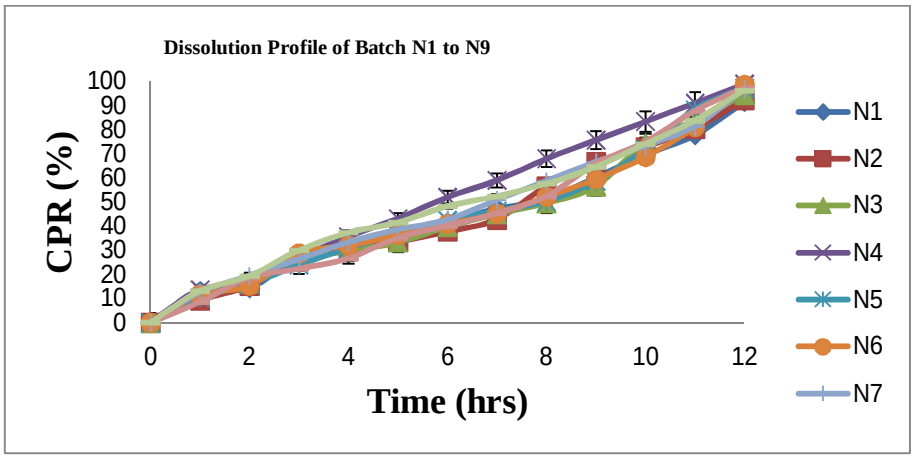


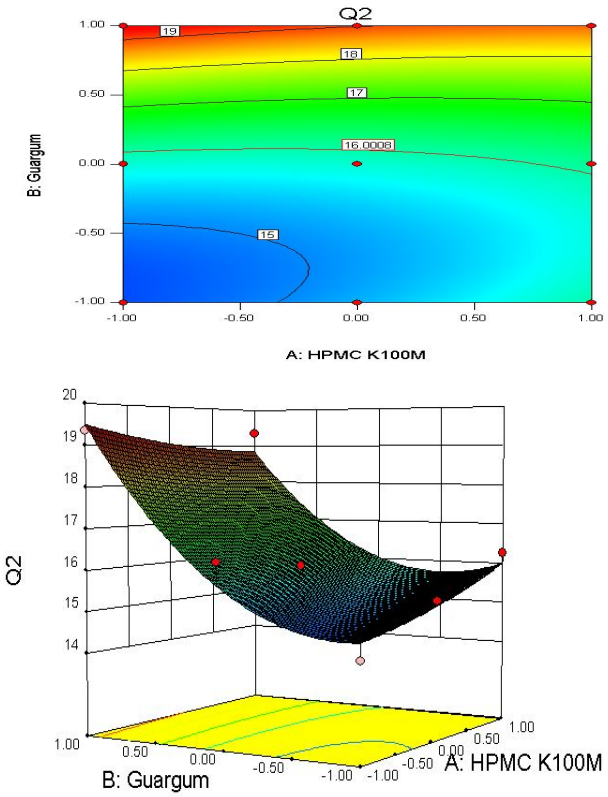
Table 2.2 Translation of coded levels in actual units

Independent Variables	Real Value		
	Low (-1)	**Medium (0)**	**High (+1)**
HPMC K 100 M (X1)	**10 mg**	**20 mg**	**30 mg**
Guargum (X2)	**10 mg**	**20 mg**	**30 mg**

Q2 = % Drug release at 2 hrs.

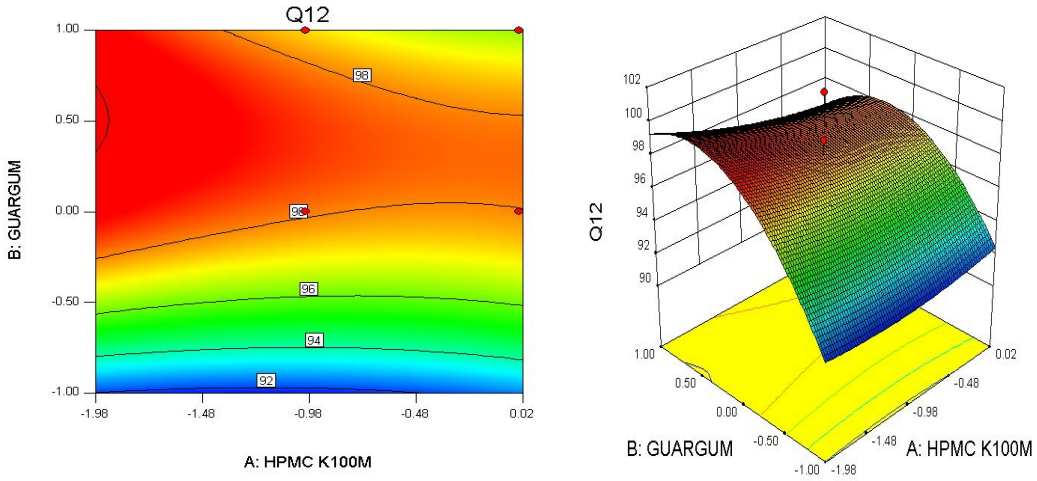
Q12= % Drug release at 12 hrs.

T_{90}= 90% Drug release in hrs



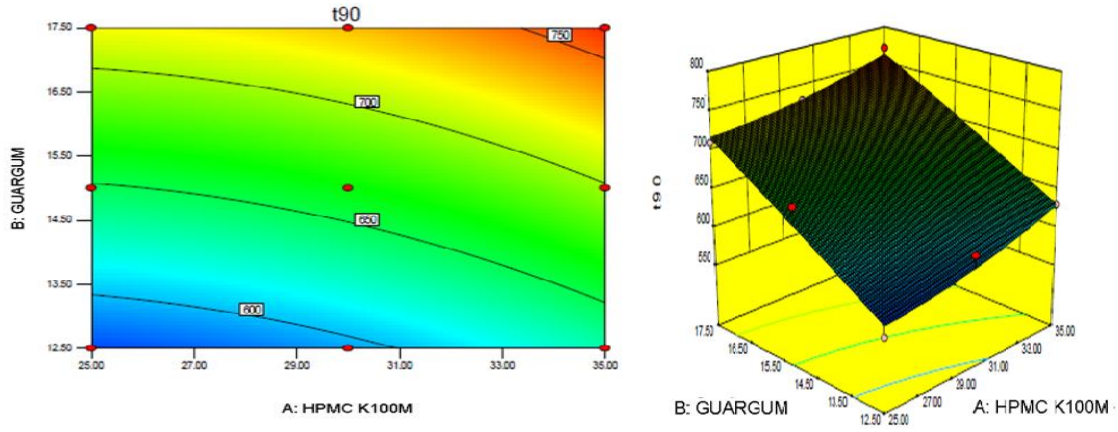
$$Q2=+15.79+0.16A+1.91B-0.49AB+0.15A^2+1.32B^2$$

Figure 11 Counter plot and 3d for Q2 = % Drug release at 2 hrs.



$$Q12=97.96+0.356667A+1.575B-0.85AB+0.41A^2+3.56B^2$$

Figure 12 Counter plot and 3d for Q12 = % Drug release at 12 hrs.



$T90=666.44+25A+68.33B-2.5AB+8.33A^2-8.67B^2$

Figure 13 Counter plot and 3d for Q90 = 90% Drug release in hrs

2. Kinetic modeling of dissolution data

Table 2.3: Kinetic study of dissolution data of all batches

Coefficient of Determination						
Batch no	Higuchi	Zero order	First order	K-peppas		Best fit model
	R^2	R^2	R^2	R^2	n	
N1	0.9653	0.9877	0.9647	0.9799	0.79	Zero order
N2	0.9644	0.9892	0.9639	0.9902	0.9	K-peppas
N3	0.9464	0.979	0.99811	0.9815	0.82	K-peppas
N4	0.9863	0.9991	0.9635	0.9896	0.86	Zero order
N5	0.9514	0.98	0.9727	0.9891	0.88	K-peppas
N6	0.9492	0.977	0.9679	0.9827	0.82	K-peppas
N7	0.971	0.9934	0.9754	0.9927	0.8	Zero order
N8	0.9564	0.9868	0.9704	0.9892	0.93	K-peppas
N9	0.9753	0.9921	0.9616	0.991	0.78	Zero order

Formulation of check point batch

Table 2.4: Formulation of check point batch

Ingredients	C1
Repaglinide	10
HPMC K 100M	14.4
Guar gum	15.3
PVP K 30 (5%)	q.s
Lactose	115.8
Magnesium Stearate	3
Talc	1.5

Total weight(mg)	150

➢ **Evaluation of check point batch**

To assess the reliability of above described factorial batches, a check point batch was experimented that varied the independent variable and estimated the dependent variable. The response values of Q2, Q_{12} and T90 of check point batch were compared with the response values of the optimized batch (N4) and it showed that the Q2, Q_{12} and T90 was found to be nearer to Q2, Q_{12} and T90 of optimized batch (N4) as shown in table 2.5 and 2.6.

Table 2.5: Comparision of Evaluation parameters of check point batch with optimized batch.

Batch	Thickness	hardness	Diameter	Friability	Wt variation	Swelling index	Drug content
C1	4.51	6.5	6	0.63	Pass	25.91	98.97
N4	4.65	6	6	0.57	Pass	26.45	99.67

Table 2.6 Comparison of Check point batch with optimum batch

Time (hrs)	C1	N4
0	0	0
1	13.25	13.69
2	15.96	16.32
3	26.21	27.21
4	32.36	35.62
5	42.66	43.2
6	51.98	52.03
7	58.55	59.03
8	66.78	67.98
9	77.31	75.7
10	86.11	83.39
11	90.42	91.04
12	98.06	98.99
Similarity Factor f2= 88.56		

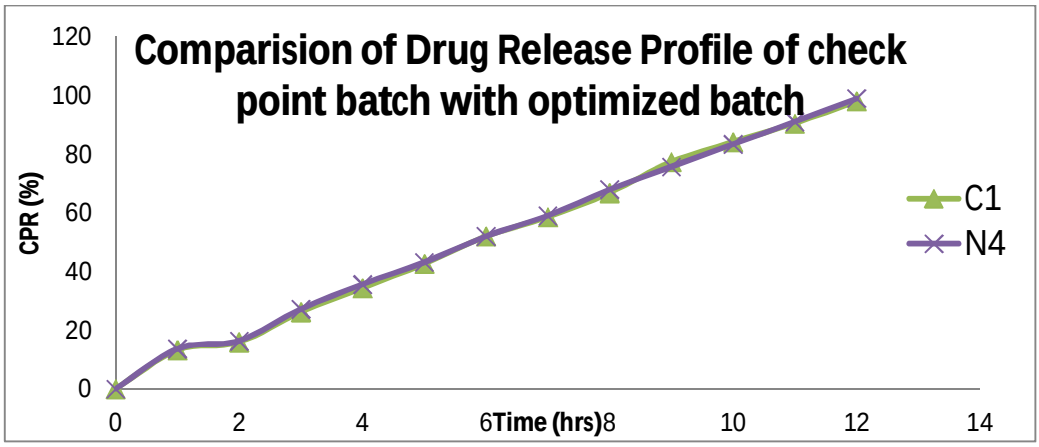


Fig 14 comparision of drug release profile of check point batch with optimized back

Table 2.7 Stability study

Batch	Thickness	hardness	Diameter	Friability	Wt variation	Swelling index	Drug content
N4 (initial)	4.65	6	6	0.57	Pass	26.45	99.67
N4 (Final)	4.53	5.75	6	0.61	Pass	25.86	99.15

Time (hrs)	N4 (initial)	N4 (Final)
0	0	0
1	13.69	13.98
2	16.32	15.97
3	27.21	26.31
4	35.62	36.31
5	43.2	45.2
6	52.03	55.61
7	59.03	62.01
8	67.98	69.23
9	75.7	74.81
10	83.39	81.33
11	91.04	89.17
12	98.99	98.09

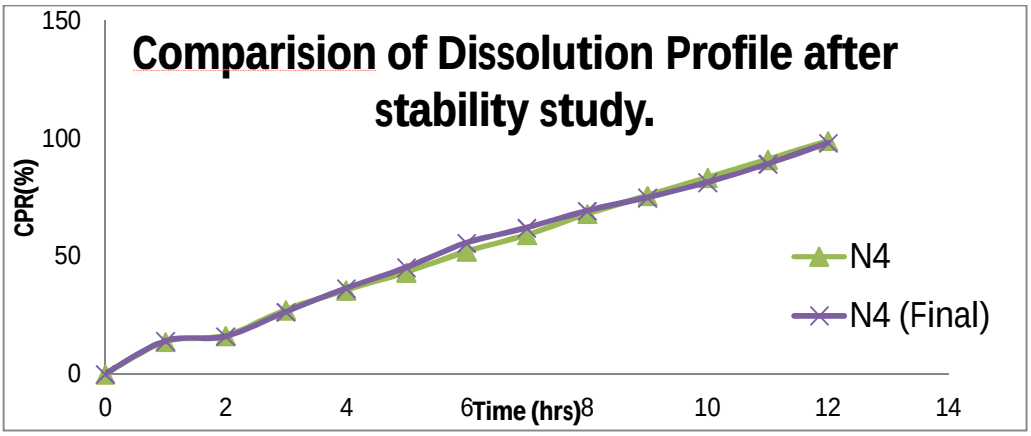


Fig 15 COMPARISON OF DISSOLUTION PROFILE AFTER STABILITY STUDY

CONCLUSION

The present study deals with formulation and evaluation of sustained release tablets of Repaglinide. Repaglinide sustained release tablets were prepared by wet granulation method using HPMC K 100M (Synthetic polymer) and Guargum (Natural polymer). All the prepared tablets were evaluated for physicochemical parameters such as angle of repose, carr's index, hausner ratio, friability, drug content, *in-vitro* dissolution studies and stability studies. All the evaluation parameter of the formulations was found to be well within the limits and official standards. FTIR studies revealed that there is no chemical interaction between Repaglinide and the excipients used in the study.

The addition of gel forming polymer like HPMC K 100M and Guargum caused an enhancement in drug release. The type of polymer affects the drug release rate and mechanism.

The systemic using a 3^2 factorial design revealed that by selecting a suitable composition of HPMC K 100M and Guargum, the desired dissolution profile could be achieved up to 12 hr. It shows 99.67 % drug release in 12 hrs. Regulated drug release in zero-order manner attained in the current study indicates that the sustained release tablets of Repaglinide prepared using HPMC K 100M and Guargum can successfully be employed as a controlled release drug delivery system. The response surface obtained showed significant effect of Q2, Q_{12} and the time required for 90% drug release (T_{90}). Different batches were prepared for optimization and factorial design was applied. Data shows that N4 batch gave good results and Followed Zero order kinetic release. Check point batch was prepared and evaluated. It was also compared with the results of N4 batch.f_2 value was observed to be 88.56.

Repaglinide was successfully formulated as a sustained release matrix tablet using HPMC K 100M and Guargum, as sustained release polymers. The optimized formulation N4 (20mg

HPMC K100M and 10mg Guargum) provided sustained in vitro release of drug over an extended period of 12 hrs. The optimized formulation can be a competent alternative to conventional tablets as the formulation provides sustained release of Repaglinide. The drug release of all batches was compared with theoretical profile. Stability study was carried out for optimized formulation for 1 month. The formulations were found to be stable for defined period of study.

Thus conclusion can be made that stable sustained release matrix tablet of Repaglinide can be made using reported technology.

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