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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF REPAGLINIDE

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ABSTRACT

Repaglinide is a novel oral hypoglycaemic agent chemically unrelated to the sulphonyl urea's, metformin or Acarbose. Repaglinide stimulates the release of insulin from pancreatic beta-cells by inhibition of potassium efflux resulting in closure of ATP regulated K+ channels thus the main objective of sustained release drug delivery systems was to ensure safety and to improve efficacy of drugs as well as patient compliance. To increase the stay period of drug in its absorption area and decrease the dosing interval by increasing the bio availability. Sustained release tablets were prepared by direct compression technique using polymer like HPMC, Carbopol, PEG (Polyethylene glycol enhances the solubility of the drug in the water, therefore enhancing the dissolution rate and bio availability) in different ratios. It was also concluded that the formulations which contains only HPMC & Carbopol was more promising in modifying the drug release pattern as compared to the other formulations. Amongst the 8 formulations, formulation F4 was found to be most promising formulation. Because it has shown most consistent drug release (97.4%) at the end of 20 hours as compared to remaining formulations as well as formulation F4 showed. As the drug release was best fitted in First order kinetics, indicating that the rate of drug release is concentration dependent.

KEYWORDS: Repaglinide, Sustained release, Matrix tablets.

1. INTRODUCTION

Sustained release dosage forms are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects. This can be achieved through a variety of formulations, including liposomes and drug-polymer conjugates (an example being hydro gels). Sustained release's definition is more akin to a "controlled release" rather than "sustained".

Sustained released means that the drug will be released under first order kinetics. Therefore if a drug starts out at 100 mg and releases at a rate of 10% per unit time.
100mg --> 90mg --> 81mg -->72.9 mg.

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drug or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of Tablet.

Nowadays very few drugs are coming out of research and development and already existing drugs are suffering the problem of resistance due to their irrational use of drugs. Hence, changes in the operation are a suitable and optimized way to make drugs more effective by a slight alteration in the drug delivery. Sustained release provides a promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body.

The advantage of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, has been obvious to the pharmaceutical industry for some time. The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as

the enhanced clinical efficacy of the drug for its intended use.[1]

Advantages of sustained release drug delivery system
Clinical advantages:

- Patient compliance can be improved.
- Reduction in fluctuation in steady levels and better control of disease condition and reduced intensity of local and systemic side effects.
- Increased safety of margin of high potency of drugs.
- Maximum utilization of drug enabling reduction in total amount of dose.
- Improve therapy cost
- Shorter treatment period
- Lower frequency of dosing.[2]

Commercial / Industrial advantages

- Illustration of innovative /technological
- Product life-cycle extension
- Product differentiation
- Market expansion
- Patent extension.[3]

Matrix system is 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. In fact, matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers.[4]

The aim of present work was to formulate and evaluate sustained release tablets of Repaglinide. The main objective of sustained release drug delivery systems was to ensure safety and to improve efficacy of drugs as well as patient compliance. Initial trials were conducted with various polymers like HPMC, Carbopol, and PEG which were used alone and in combination, based on which the best formulation was selected. Polyethylene glycol enhances the solubility of the drug in the water, therefore enhancing the dissolution rate and bioavailability. Carbopol and HPMC acts as sustained release agents. So, they are designed to provide a therapeutic amount of drugs on the specific-site of absorption, and then to maintain the desired drug concentration.

2. MATERIALS

Table 1: List of materials used in preparation of repaglinide tablet.

S. no.	Ingredients	Functional category	Manufacturer
1	Repaglinide	API	Lara drugs Pvt. Ltd.
2	Polyethylene glycol 6000	Solubility enhancer	Lara drugs Pvt. Ltd
3	Hydroxy propyl methyl cellulose E15	Sustained- release agent	Lara drugs Pvt. Ltd
4	Carbopol 971P	Sustained- release agent	Lara drugs Pvt. Ltd
5	Micro crystalline cellulose	Binder, diluent	Lara drugs Pvt. Ltd
6	Magnesium stearate	Lubricant	Lara drugs Pvt. Ltd

3. METHOD

3.1. Preformulation study

Standard plot of repaglinide

An accurately weighed quantity of Repaglinide (50 mg) was dissolved in 10 ml of methanol and made up to 100 ml with water to generate stock solution having a concentration of 0.5 mg/ml. One ml of the primary stock solution was further diluted to 100 ml to produce a secondary stock solution having a concentration of 5µg/ml. 0.5-1.5ml aliquots of the secondary stock solution was further diluted 100ml to produce standard solutions. The absorbance of the solutions was measured at 240 nm using double beam UV- Visible spectrophotometer against as a blank. The plot of absorbance vs concentration (%) was plotted and data were subjected to linear regression analysis in Microsoft Excel.

3.2. Drug- Excipients interaction study

Fourier transform infrared (FTIR) spectroscopy

Infrared spectrophotometry is a useful analytical technique utilized to check the interaction between the drug and other excipients employed in the formulation. One mg of the sample was powdered and intimately mixed with 10mg of dry powdered potassium bromide. The powdered mixture was taken in a diffuse reflectance sampler and the spectrum was recorded by scanning within the wavelength region of 4000-400cm^{-1} in an FTIR spectrophotometer. The IR spectrum of the drug was compared therewith of the physical mixture to check for any feasible drug- excipients interaction.

3.3. Formulation of sustained release tablets

Tablets were prepared by direct compression method. Briefly, the compositions of different sustained release formulations were prepared using varying amounts of the polymers. The Drug was blended thoroughly after adding each polymer for 5 min and blended homogeneously for about 5 min with constant mixing. This blend subsequently compressed into a round shaped tablets (300 mg, 10mm diameter) using rotary tablet press.

Table 2: Composition of sustained release tablets.

Formulations	API (mg)	PEG6000 (mg)	HPMC K15 (mg)	Carbopol 971p (mg)	MCC (mg)	Magnesium Stearate (mg)	Avg (mg)
F1	4	24	12	-	255	5	300
F2	4	32	16	-	243	5	300
F3	4	40	20	-	231	5	300
F4	4	40	8	4	239	5	300
F5	4	40	-	8	243	5	300
F6	4	40	-	16	235	5	300
F7	4	40	-	20	231	5	300
F8	4	24	-	12	255	5	300

3.4. Evaluation of sustained release tablets

The powder was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. The tablets were evaluated for thickness, hardness, friability, weight variation test, drug content and in-vitro release studies.

3.4.1. Pre-Compression parameters

The following tests were performed for polymers as well as drug substance.

Bulk density (D_b)

It is the ratio of the whole mass of powder to the bulk volume of powder. It was measured by pouring the weighted powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

$D_b = m/v_0$

Where, M is the mass of powder

Vo is the bulk volume of the powder.

Tapped density (Dt)

It is the ratio of the whole mass of the powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to a constant volume. It is expressed in gm/ml and is given by

$D_t = M/v_t$

Where, 'M' is the mass of powder;

'V_t' is the tapped volume of the powder

Angle of repose (θ)

The frictional forces in a loose powder can be measured by the angle of repose, Which is the maximum angle possible between the surface of a pile of powder and the horizontal plane

$\theta = \tan^{-1}$ (h/r)

Where, θ' is the angle of repose

'h' is the height of heap of powder in cm

$'\theta'$ is the radius of the heap of powder.

Weighed quantity (10 g) of granules was passed through the funnel from the fixed height onto the graph paper. The height of the heap was measured and circumference of the heap was marked by pencil. The angle of repose was calculated using the above mentioned formula.

Table 3: Limits for angle of repose.

S. no.	Angle of repose (θ)	Type of flow
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very poor

Carr's Index (I)

It indicates the ease with which a material can be induced to flow. It is expressed in percentage and is given by

$$I = \frac{Dt - Db}{Dt} \times 100$$

Where, D_t is the tapped density of the powder.

D_b is the bulk density of the powder

Table 4: Limits for Carr's index.

S. no.	Carr's index	Type of flow
1	5-15	Excellent
2	12-15	Good
3	18-21	Fair
4	23-30	Poor
5	33-38	Very poor
6	>40	Extremely poor

Hausner's ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Values of Hausner‟s ratio: < 1.25: good flow and > 1.25: poor flow

If Hausner‟s ratio is between 1.25-1.5, flow property can be improved by addition of glidants.

3.4.2. Post compression parameters

Weight variation test

The weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablet meets the pharmacopoeia requirements if no more than 2 tablets are outside the percentage limits and if no tablets differs by more than 2 times the percentage limit. IP official limits of percentage deviation of tablet are presented in the given Table- 5.

Table 5: Limits for weight variation.

S. no.	Average weight of tablet	Percentage deviation
1	80 mg or less	10
2	More than 80 mg but less than 250 mg	7.5
3	250 mg or more	5

Hardness

The hardness of the tablet was determined using a Monsanto hardness tester. It is expressed as Kg/cm^2.

Friability (F)

20 tablets were weighed and initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 4min.

Then tablets were removed from the friabilator, redusted and weighed and the weight was recorded.

Percentage friability was calculated by using the formula

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

$W_{initial}$ = Initial weight of 20 tablets.

W_{final} = Final weight of 20 tablets.

Thickness

The thickness of tablet was measured by screw gauge. It is expressed in mm.

Drug content

Ten Tablets from each formulation were selected randomly and crushed and mixed. From the mixture powder equivalent to 300mg of Repaglinide was weighed and dissolved to 50ml and sonicated for 60 seconds. The resulting solution was filtered through Whatmann filter paper and diluted suitably with distilled water. The absorbance of the resulting solution was measured spectrophotometrically at 240nm using water as blank. Drug content was estimated by the formula.

$$\text{Drug content} = \frac{\text{concentration} \times \text{dilution factor}}{1000}$$

$$\%\text{Drug content} = \frac{\text{Practical yeild}}{\text{Theoretical yeild}} \times 100$$

This procedure was repeated thrice and average percent drug content was taken.

In vitro dissolution study

Apparatus: Dissolution Apparatus USP - II

Medium: pH 7.4 phosphate buffer

Time: 24 hrs

Temperature: 37±0.5 °C

Dissolution of the tablets of each batch was carried out using USP type-II apparatus using paddle. The dissolution medium consisted of p^H 7.4 phosphate buffer for the 24hrs maintained at 37± 0.5℃. One tablet was placed in each dissolution vessel and the paddle rotation speed was set at 50 rpm. 10ml of the sample was withdrawn at specific time intervals (2, 4, 6, 10, 16, 20 hrs) and the same volume of the fresh medium was replaced every time. The samples were analyzed for drug content at a wavelength of 240 nm for the sample at specific time intervals using UV-Visible spectrophotometer. The percentage of drug release was calculated.[5]

Kinetic analysis of dissolution data

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration (Hadjiioannou *et al.*, 1993). The first order Eq. (2) describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

$$C = K_0 t \quad (1)$$

where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\text{Log}C = \text{Log}C_0 - K_1 t / 2.303 \quad (2)$$

Where, C_0 is the initial concentration of drug and K_1 is first order constant.

$$Q = K_H t^{1/2} \quad (3)$$

Where, K_H is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t \quad (4)$$

Where, Q_t is the amount of drug remained in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

The following plots were made using the in-vitro drug release data

- Cumulative % drug release vs. time (Zero order kinetic model);
- Log cumulative of % drug remaining vs. time (First order kinetic model);
- Cumulative % drug release vs. square root of time (Higuchi model);
- And cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs. time (Hixson-Crowell cube root law).

Mechanism of drug release

Korsmeyer *et al* (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model.

$$M_t / M_\infty = Kt^n \quad (5)$$

where $M_t / M\infty$ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent. The n value is used to characterize different release mechanisms.

A plot of log cumulative % drug release vs. log time was made. Slope of the line was n. The n value is used to characterize different release mechanisms as given in Table 6., for the cylindrical shaped matrices. Case-II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release (Peppas, 1985).

Table 6: Diffusion exponent value ranges for different drug release mechanisms.

S. no.	Diffusion exponent value (n)	Drug release mechanism
1	< 0.45	Fickian release
2	0.45 to 0.89	Non fickian release
3	0.89	Case II transport
4	> 0.89	Super case II transport

4. RESULTS

Evaluation of sustained release tablets of repaglinide

1. Calibration curve of repaglinide

Table 7: Calibration data of repaglinide.

S. no.	Concentration (%)	Absorbance
1	50	0.2454
2	75	0.368
3	100	0.4907
4	125	0.6134
5	150	0.750

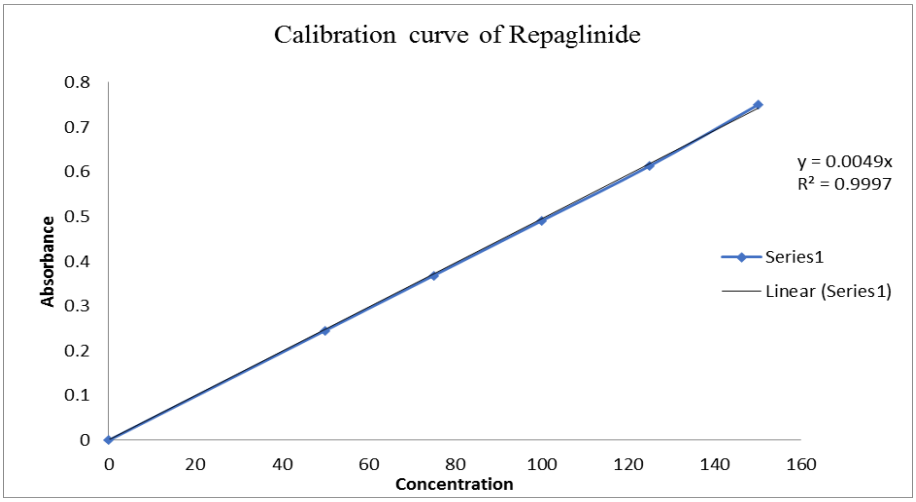

Figure 1: Calibration curve of repaglinide.

2. Drug excipients interaction study

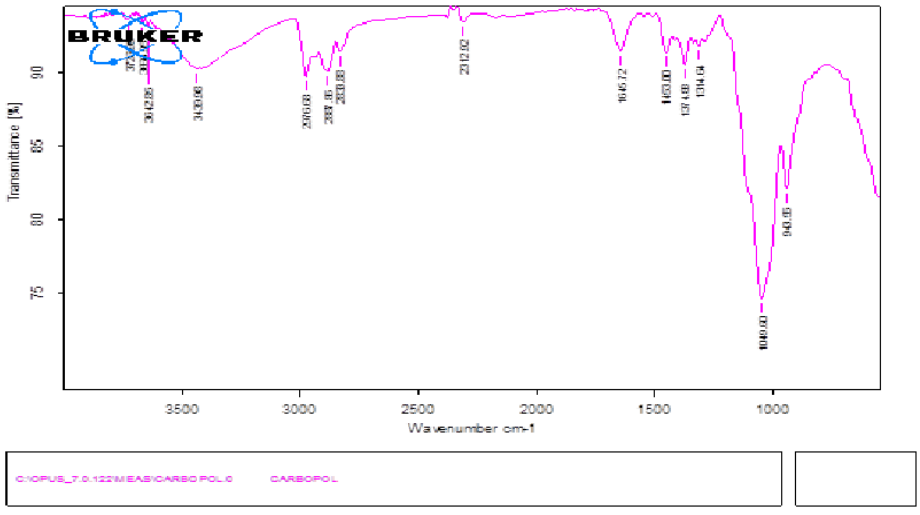

Figure 2: FTIR spectra of physical mixture of Repaglinide and Carbopol.

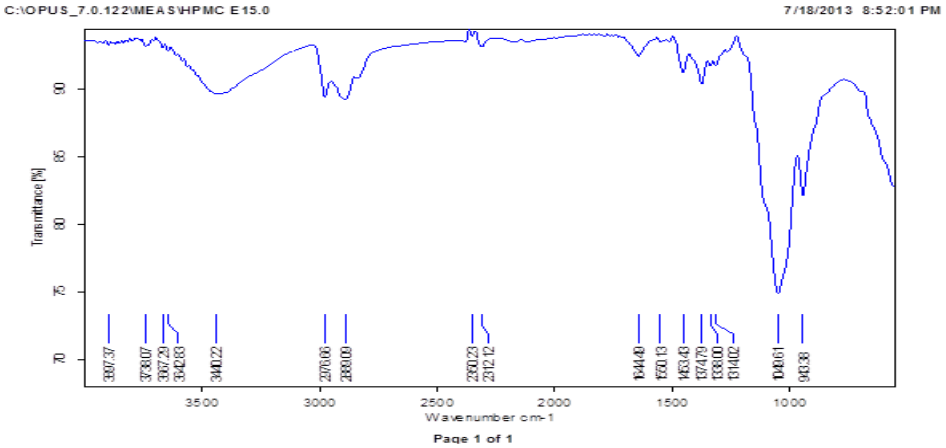

Figure 3: FTIR spectra of physical mixture of Repaglinide and Magnesium stearate.

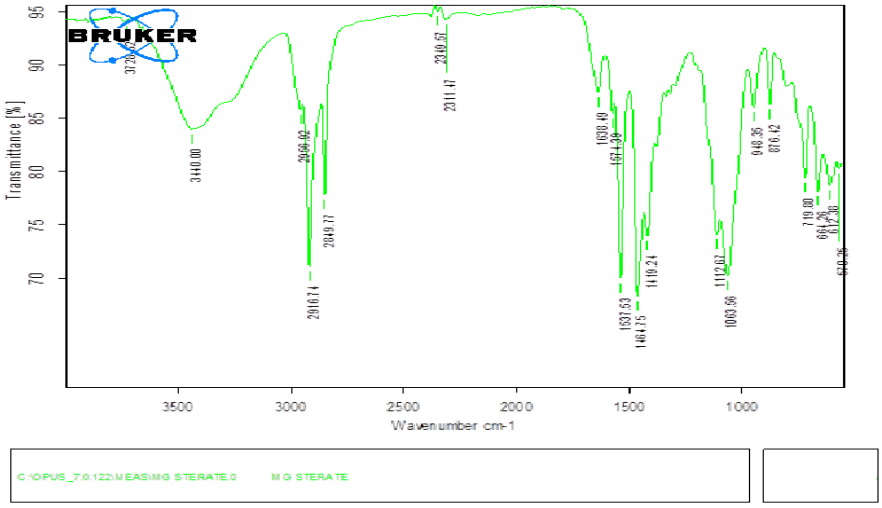

Figure 4: FTIR spectra of physical mixture of Repaglinide and Hydroxy propyl methyl cellulose.

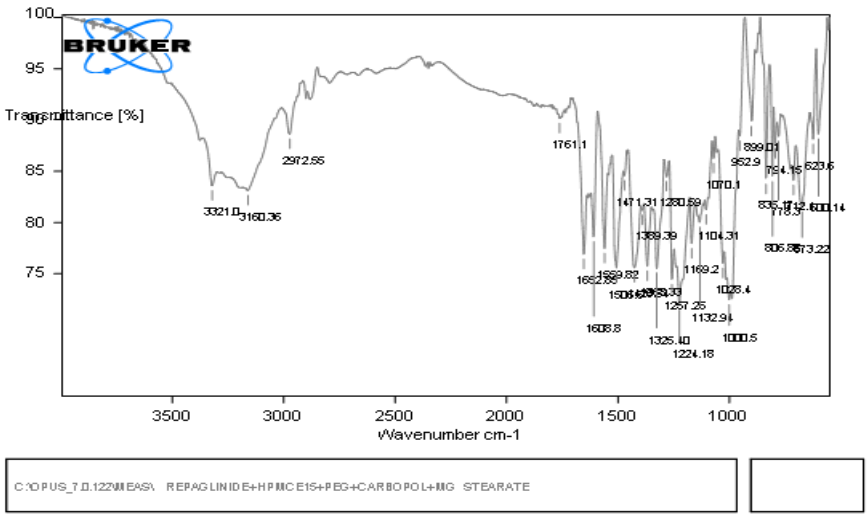

Figure 5: FTIR spectra of best formulation 4.

1. Pre compression parameters

The powder properties like bulk density, tapped density, carr's index, Hausner's ratio and angle of repose, for all formulations, were determined and the results were reported, as shown in table 8.

Table 8: Powder properties of formulations F1 to F8.

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio (%)	Angle of repose (degree)
F1	0.428	0.504	15	1.17	16.77
F2	0.44	0.50	11.11	1.12	18.15
F3	0.44	0.50	11.11	1.12	18.12
F4	0.42	0.50	15.35	1.18	16.89
F5	0.40	0.49	17.28	1.20	16.46
F6	0.41	0.48	14.13	1.16	17.84
F7	0.38	0.46	17.41	1.21	16.33
F8	0.42	0.50	15.35	1.18	16.75

2. Post compression parameters

The evaluation parameters like thickness, hardness and friability of formulations F1-F8 are indicated in table 9. The drug content and weight variation values of these formulations are indicated in table 10. Dissolution data of the formulations are indicated in table 10.

Table 9: Physical properties of tablets.

Formulation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
F1	10	3.92	0.057
F2	9.98	3.86	0.028
F3	9.97	3.98	0.025
F4	9.95	3.97	0.01
F5	10.1	4.12	0.08
F6	9.96	3.99	0.021
F7	9.98	4.11	0.028
F8	9.94	3.94	0.026

Table 10: Drug content uniformity and weight variation for formulations.

Formulation	Drug content in percentage	Weight variation(mg)
F1	98%	Pass
F2	102%	Pass
F3	99%	Pass
F4	100%	Pass
F5	98%	Pass
F6	98%	Pass
F7	98%	Pass
F8	99%	Pass

Table 11: % Drug release of formulations.

S. no.	Time (hrs)	% drug release							
		F1	F2	F3	F4	F5	F6	F7	F8
1	2	23.8	22.8	19.5	14.5	17.7	17.0	18.8	23.4
2	4	44.1	44.2	22.4	32.2	22.4	33.5	34.9	44.8
3	6	51.5	51.2	36.5	57.6	40.6	50.2	48.1	50.7
4	10	68.6	67.7	55.0	74.1	55.0	74.1	59.4	69.2
5	16	87.4	72.8	78.9	83.8	64.1	78.9	78.9	89.5
6	20	91.2	94.6	84.2	97.4	83.1	91.5	91.6	93.7

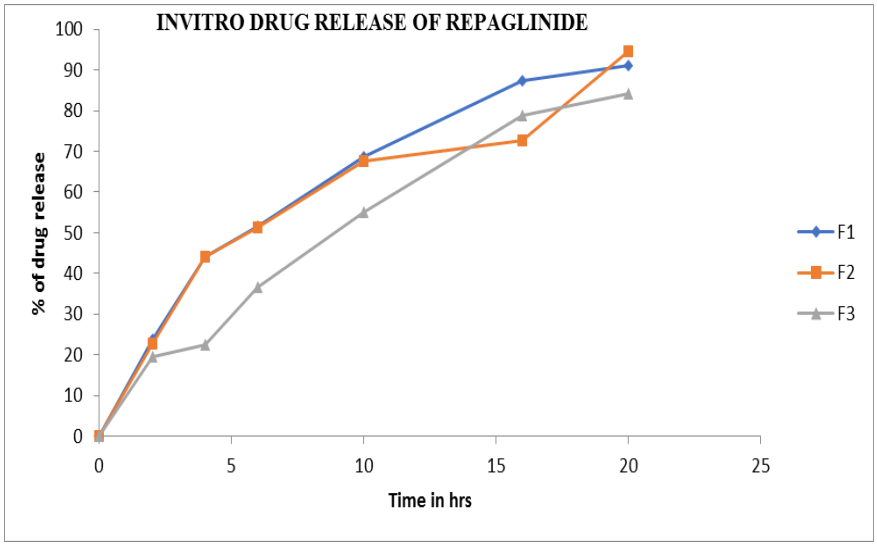

Figure 6: In-vitro dissolution profile of formulations F1 to F3.

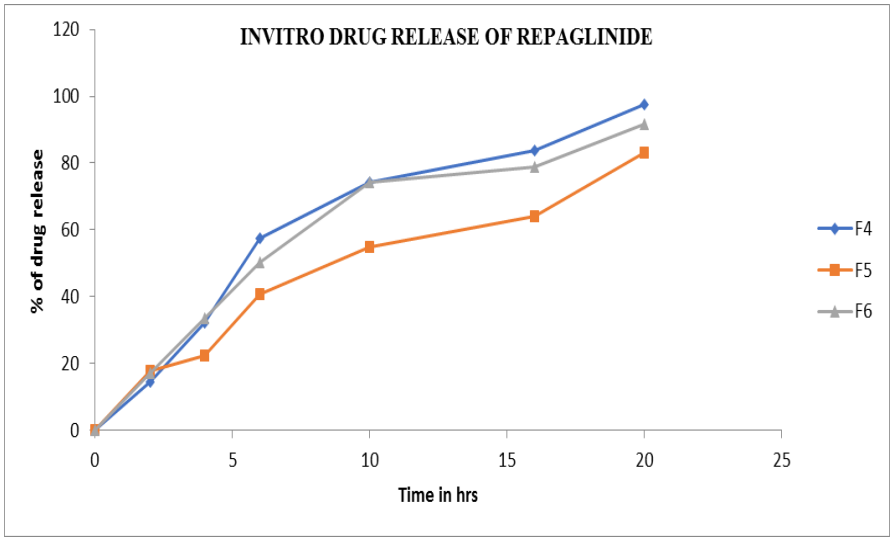

Figure 7: In-vitro dissolution profile of formulations F4 to F6.

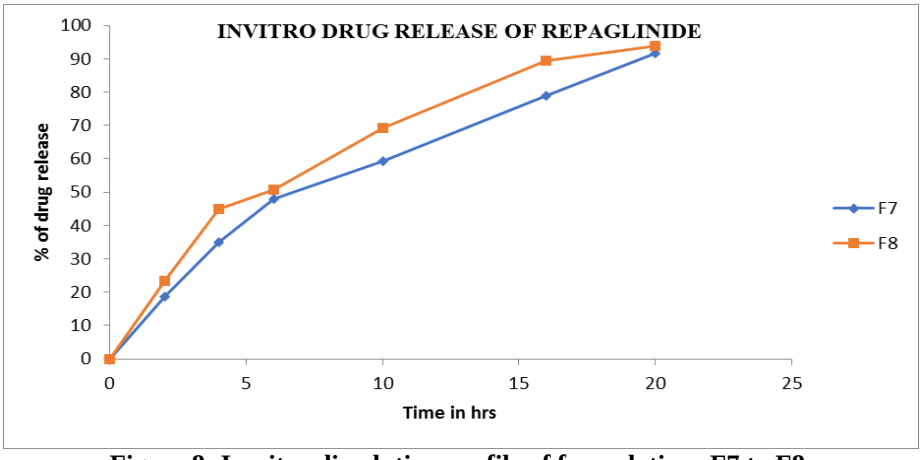

Figure 8: In-vitro dissolution profile of formulations F7 to F8.

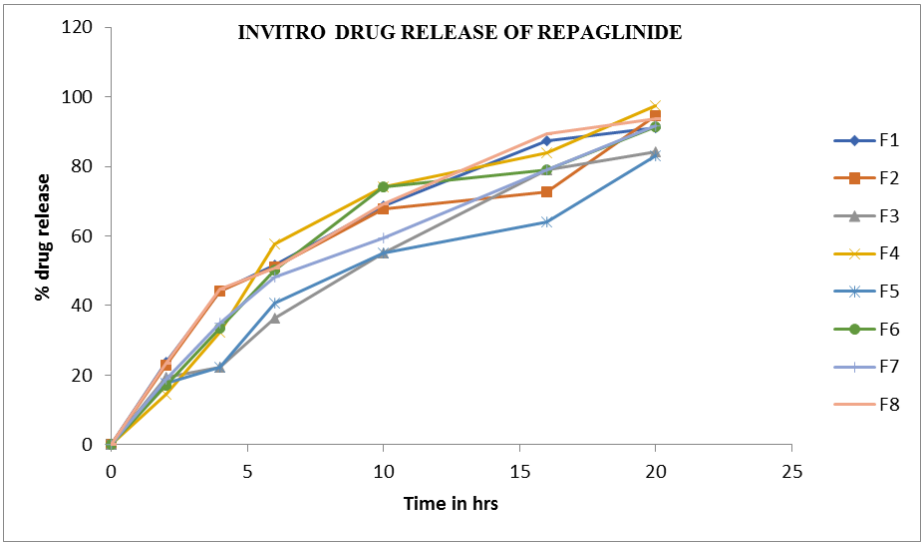

Figure 9: In-vitro dissolution profile of formulations F1 to F8.

3 Mechanism of drug release

Drug release kinetics

Table 12: Dissolution kinetics of optimized batch F4.

Time	Square root	Log time	% drug relesed	log % drug released	% drug remaining	log % d remaining
0	0		0		100	2
2	1.414214	0.30103	14.5	1.161368	85.5	1.931966115
4	2	0.60206	32.2	1.5078559	67.8	1.831229694
6	2.44949	0.778151	57.6	1.7604225	42.4	1.627365857
10	3.162278	1	74.1	1.8698182	25.9	1.413299764
16	4	1.20412	83.8	1.923244	16.2	1.209515015
20	4.472136	1.30103	97.4	1.988559	2.6	0.414973348

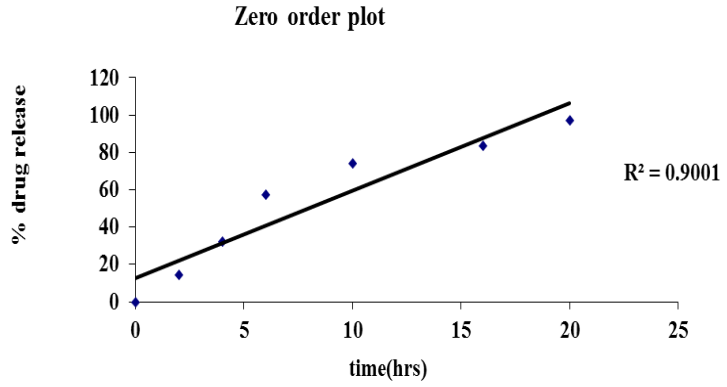

Figure no. 10: Zero order kinetics plot of optimized formulation F4.

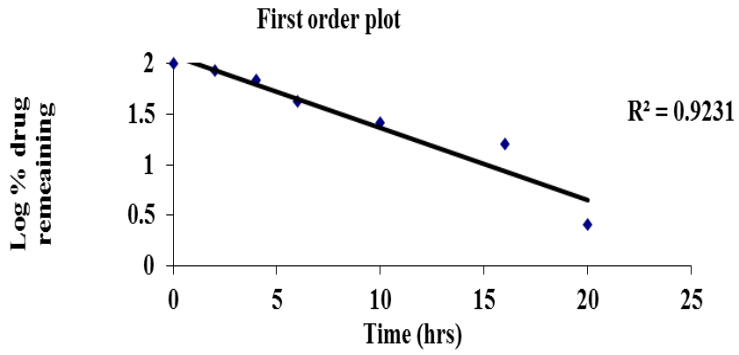

Figure no. 11: First order kinetics plot of optimized formulation F4.

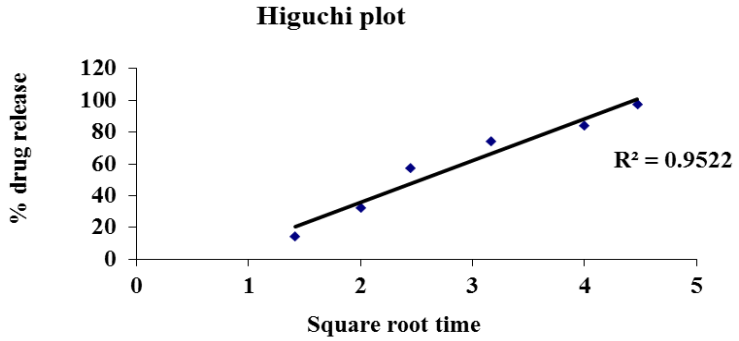

Figure no. 12: Higuchi order kinetics plot of optimized formulation F4.

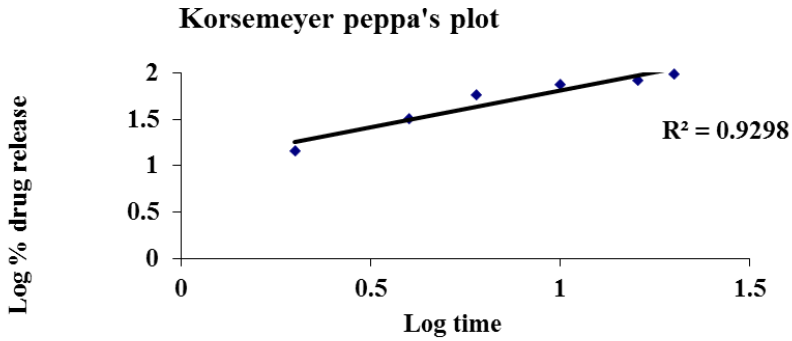

Figure no. 13: Korsemeyer peppa's order kinetics plot of optimized formulation F4.

5. DISCUSSION

The present work was an attempt to formulate and evaluate Sustained release tablets of Repaglinide 4 mg. Repaglinide stimulates the release of insulin and decreases the treatment regimen.

Pre-formulation studies of drug was performed to characterize the Repaglinide. Repaglinide was freely soluble in methanol.

The powder flow property of Repaglinide was studied to evaluate compressibility, since it has to be formulated as Tablet. The results obtained are Bulk density 0.44mg/ml, Tapped density was 0.50mg/ml and Hausner's ratio 1.21 for Repaglinide. The results showed that the compressibility of Repaglinide which indicates that it has excellent flow properties.

Compatibility studies showed that, there is no physical interaction between drug and excipients. So based on the physical compatibility results the excipients like Polyethylene glycol, Hydroxy propyl methyl cellulose, Carbopol, Micro crystalline- cellulose were selected for formulation development experimental work.

Repaglinide was formulated by using direct compression; because the results showed that the repaglinide has excellent flow properties does not show sticking problem. So that I selected direct compression technique for formulate the Repaglinide tablets. The tablet formulation was carried out in eight trials by varying the concentration of excipients.

Comparative in-vitro dissolution studies were carried out for all the eight formulations. The eight formulations F1,F2,F3,F4,F5,F6,F7,F8 exhibited the % drug release of 91.2%, 94.6%, 84.2%,97.4%, 83.1%, 91.5%,91.6 %,93.7% respectively. Among the eight formulations F5 formulation exhibited poor drug release.

Among the eight formulations F4 formulation has shown the highest release of Repaglinide with the optimum amount of Polyethylene glycol, Hydroxy propyl methyl cellulose and Carbopol prepared by using direct compression method.

The drug release data obtained were extrapolated by zero order, Highuchi, First order, Korsemeyer peppa's to know the mechanism of drug release from the formulations. The release rate kinetic data for all the formulations was shown in Table 12. The release kinetics shows that the release of drug followed First order release in all the formulations. As the drug release was best fitted in First order kinetics, indicating that the rate of drug release is concentration dependent.

6. CONCLUSION

The present study was aimed at an attempt to develop sustained release drug delivery system for Repaglinide. Repaglinide tablets were formulated into a sustained release dosage form using the optimum amount of PEG, HPMC and Carbopol along with other common tabulating occupants to sustain as well as extend the drug release over a period of 20 hours. The present study was undertaken to develop sustained release matrix tablets of 4 mg.

Eight formulations of sustained release matrix tablets were developed and evaluated. The formulation F4 showed a drug release 97.4% whereas the other formulation showed that 83 to 94.6. In-vitro drug release studies revealed that the drug was sustained over a period of 20 hours.

To conclude the In-vitro dissolution profile of Formula 4 has shown the highest release of Repaglinide with the optimum amount of PEG, HPMC and Carbopol prepared by using direct compression method. As the drug release was best fitted in First order kinetics, indicating that the rate of drug release is concentration dependent. Hence the further work of this formulation can bring a marketable product.

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