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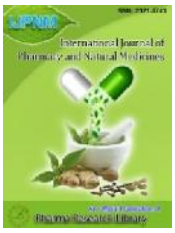

Research Article **Open Access**

Design and *In-Vitro* Characterization of Repaglinide Tablets for Controlled Release Drug Delivery System

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A B S T R A C T

Oral drug delivery is the most preferred and convenient option as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs. The attractiveness of these dosage forms is due to awareness to toxicity and ineffectiveness of drugs when administered by oral conventional method in the form of tablets & capsules. The aim of the present study was to develop and controlled release formulation of Repaglinide to maintain constant therapeutic levels of the drug for over 12 hrs. Various grades of HPMC were employed as polymers. Repaglinide dose was fixed as 2 mg. Total weight of the tablet was considered as 75 mg. Polymers were used in the concentration of 12 and 16 mg concentration. 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 (F11) showed better and desired drug release pattern i.e., 97.82 % in 12 hours. It followed zero order release kinetics mechanism.

Keywords: Repaglinide, different grades of HPMC polymers, Controlled Release tablets

A R T I C L E I N F O

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1. Introduction

Oral Drug Delivery:

Over the past 30 years, as the expense and complications involved in marketing new entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery of, greater attention has been focused on development of controlled release drug delivery systems. It is generally been recognized that for most disease states, a substantial number therapeutically effective compounds already exists. The effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting. 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. 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.

Oral Controlled Release Drug Delivery Systems

Oral ingestion is traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is very little control over release of drug. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses, which in most situations, often results in constantly changing, unpredictable and often sub or supra therapeutic plasma concentrations leaving the marked side effects. 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.

An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled release (CR) delivery system provides a uniform concentration or amount of the drug at the absorption site and thus, after absorption allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration. In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits [6].

Advantages of Controlled Drug Delivery System:

- Maintenance of plasma drug concentration within an optimal therapeutic range for prolonged duration of treatment.
- More consistent and prolonged therapeutic effect is observed.
- Maximization of efficiency-dose relationship.
- Employ less total drug than that in combined conventional dosage forms.
- Reduction of adverse side effects.
- Minimization of the need for frequent dose intake.
- Improved patient compliance.
- Improves control of condition i.e., reduced fluctuation in drug level.
- Minimize or eliminate local side effects
- Minimize drug accumulation with chronic dosing.
- Make use of special effects, e.g. Sustained-release aspirin for morning relief of arthritis by dosing before bedtime.
- Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period may be less, with lesser frequency of dosing, enhanced therapeutic benefits and reduced side effects.

Disadvantages of Controlled Drug Delivery Systems:

- Increased variability among dosage units.
- *In vitro – in vivo* correlation.
- Toxicity due to dose dumping may occur when more than usual fraction is being released.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- More rapid development of tolerance.
- Need for additional patient education and counselling.
- Reduced potential for dose adjustment of drugs normally administered in varying strengths.

2. Materials and method

Materials:

Repaglinide, Different grades of HPMC polymers, Xanthan gum, Different grades of eudragit polymers, Different grades of carbopol polymers, gnesium stearate,Micro crystalline cellulose, Talc**.**

Methodology

Pre--formulation studies

Before formulation of drug substances into a dosage form, it is essential that drug and polymer should be chemically and physically characterized. Pre-formulation 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.

Calibration curves of Repaglinide in different media:

Principle:

The calibration curve is based on the spectrophotometry. The maximum absorption of Repaglinide was observed at 228 nm. It obeyed Beer's law in the concentration range of 1 -10 µg/ml.

Calibration curve of Repaglinide in phosphate buffer of pH 6.8: The stock solution of Repaglinide was freshly prepared by dissolving 100 mg of Repaglinide in few ml of phosphate buffer pH 6.8 (5 ml) in a 10 0ml volumetric flask and then make up the solution upto the mark using phosphate buffer for obtaining the solution of strength 1000 µg/ml (stock I). 10 ml of this solution is diluted to 100 ml

with of phosphate buffer pH 6.8 to obtain a solution of strength 100 µg/ml (stock II). From this secondary stock 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2 ml, were taken separately in 10 ml volumetric flasks and made up to 10 ml with of phosphate buffer pH 6.8, to produce 2,4, 6, 8 10 and 12 µg/ml respectively. The absorbance was measured at 228 nm using a UV spectrophotometer. A plot of concentrations of drug versus absorbance was plotted. The linear regression analysis was done on absorbance data points. A straight-line equation was generated to facilitate the calculation of amount of drug. This procedure is repeated 3 times and the average value will be taken into consideration.

Calibration curve of Repaglinide in 0.1 N HCl:

The stock solution of Repaglinide was freshly prepared by dissolving 100 mg of Repaglinide few ml of 0.1 N HCl (5 ml) in a 100 ml volumetric flask and then make up the solution upto the mark using 0.1N HCl for obtaining the solution of strength 100 0µg/ml (stock I). 10 ml of this solution is diluted to 100 ml with of 0.1 N HCl to obtain a solution of strength 100 µg/ml (stock II). From this secondary stock 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 ml, was taken separately in a 10 ml volumetric flask and made up to 10 ml with of 0.1 N HCl, to produce 5, 10, 15, 20, 25 and 30 µg/ml respectively. The absorbance was measured at 228 nm using a UV spectrophotometer. A plot of concentrations of drug versus absorbance was plotted. The linear regression analysis was done on absorbance data points. A straight-line equation was generated to facilitate the calculation of amount of drug. This procedure is repeated 3 times and the average value will be taken into consideration.

Fourier transform infrared spectrophotometry (FTIR):

Compatibility study of drug with the excipients was determined by FTIR Spectroscopy. The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100. The pellets thus prepare were examined and the spectra of drug and other ingredients in the formulations were compared with that of the original spectra.

Formulation

Preparation of Repaglinide tablets

Direct compression method: Different tablets formulations were prepared by direct compression technique. All powders were passed through 60 mesh. Required quantities of drug and polymers were mixed thoroughly Magnesium stearate was added as lubricant. Talc was used as glidant. Microcrystalline cellulose was used as diluent. Finally, the powder mix was subjected to compression after mixing uniformly in a poly-bag. Prior to compression, the blends were evaluated for several tests.

Evaluation:

Pre-compression parameters:

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. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force.

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

Ingredients	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	F9	F10	F11	F12
Repaginide	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

The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured.

Bulk density*:*

Density is defined as weight per unit volume. Bulk density, ρb, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 15 g powder blend introduced into a dry 100 ml cylinder, without compacting.

Tapped density: After carrying out the procedure as given in the measurement of bulk 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.

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. In theory, the less compressible a material the more flow able it is. As such, it is measures of the relative importance of inter-particulate interactions. In a free flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions and a greater difference between the bulk and tapped densities will be observed.

Hausner's ratio*:*

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

Hausner's ratio=Tapped density (ρ_t) / Bulk density (ρ_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: Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

Following parameters were evaluated:

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.

Weight variation: Twenty Tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of three batches were calculated. It passes the test for weight variation, if not more than two of the individual Tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown.

Tablet hardness: Hardness of Tablet is defined as the force applied across the diameter of the Tablet in order to break the Tablet. The resistance of the Tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its 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.

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.

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±0.5°c, 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

$$\%\text{swelling index} = \{(W_t) - (W_o) / (W_t)\} \times 100$$

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.

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 pH of the dissolution medium was kept for 2 h with 0.1 N HCl was prepared by taking 8.5 ml of HCl in 1000 ml of water. Then, 6.8 g of KH_2PO_4 and 0.8 g of NaOH. were added, adjusting the pH to 6.8. The release rate analysis was done. 1 ml 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.

Model fitting for drug release kinetics: Drug release kinetics can be analyzed by various mathematical models, which are applied considering the amounts of drug released from 0 to 24 hrs. Following equations presents the models tested. Depending on these estimations, suitable mathematical models to describe the dissolution profiles were determined. The following plots were made: cumulative % drug release versus time (zero order kinetic model); log cumulative % drug remaining versus time (firstorder kinetic model); cumulative % drug release versus square root of time (Higuchi model).

Zero order kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions. are obtained) can be represented by the following equation:

$$Q_1 = Q_0 + K_0 t$$

Where Q is the amount of drug dissolved in time t, Q is the initial amount of drug in the solution (most times, Q 50) and *K* is the zero order release constant.

First order kinetics

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967) and later by Wagner (1969). This model has been also used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism in a theoretical basis. The following relation can also express this model:

$$\text{Ln } Q_t = \ln Q_0 - k_1 t$$

Where Qt is the amount of drug released in time t, Q0 is the initial amount of drug in the solution and *K* is the first order release constant. In this way, a graphic of the decimal logarithm of the released amount of drug versus time will be linear. The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

Higuchi model

Higuchi (1961, 1963) developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semi-solid and/or solid. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. In a general

way it is possible to resume the Higuchi model to the following expression:

$$Q_t = K_H t_{1/2}$$

Where Qt is amount of drug released in time t and KH is release rate constants. Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems (Costa et al., 1996) and matrix Tablets with water soluble drugs.

Korsmeyer–Peppas model

Korsmeyer et al. (1983) developed a simple, semi empirical model, relating exponentially the drug release to the elapsed time (*t*). An equation that can be described in the following manner:

$$M_t / M_\infty = at^n$$

where a is a constant incorporating structural and geometric characteristics of the drug dosage form, n is the release exponent, indicative of the drug release mechanism, and the function of t is M /M (fractional release of drug). Peppas (1985) used this n value in order to characterize different release mechanisms, concluding for values for a slab, of n =0.5 for Fick diffusion and higher values of n, between 0.5 and 1.0, or n=1.0, for mass transfer following a non-Fickian model.

3. Results and Discussion

Pre-formulation Studies

Calibration curves of Repaglinide in different media:

Standard graph of Repaglinide in different media was plotted by taking concentration ranging from 1 to 30 µg/ml.

Calibration of Repaglinide in* PBS pH *6.8: Standard graph of repaglinide in PBS pH 6.8 was plotted by taking concentration ranging from 2 to 12 µg/ml. The absorbance values for their respective concentration were shown in Table 3 and the standard graph was shown in Figure 1.

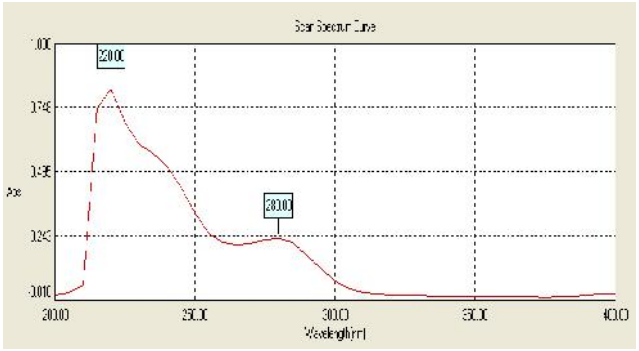

Figure 1: Repaglinide peak in 6.8 phosphate buffer

Table 3: Calibration of Repaglinide in PBS pH 6.8

Concentration (µg/ml)	Absorbance
0	0
2	0.103
4	0.252
6	0.381
8	0.557
10	0.699
12	0.911

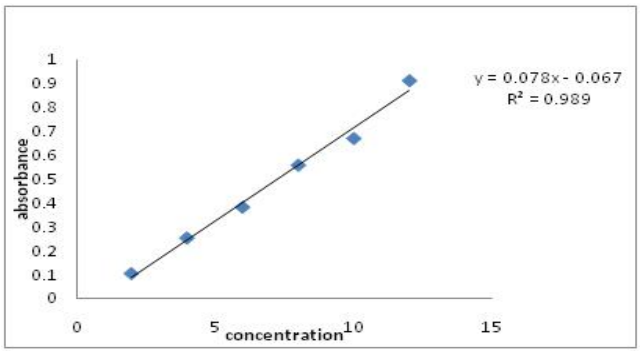

Figure 2: Calibration graph of Repaglinide PBS pH 6.8

The calibration curve of Repaglinide in PBS pH 6.8 was constructed by taking 2, 4, 6, 8, 10, 12 µg/ml as the serial concentrations and then finding the corresponding absorbance values by spectrometrically at 220 nm. The slope and intercept values were found to be 0.078 and 0.067 and the Coefficient of Correlation (R^2) was found to be 0.989. From the slope and intercept values it was found that the curve is having a positive slope and intercept. As the coefficient of correlation value is 0.989 the values are acceptable.

Calibration of Repaglinide in 0.1N HCl:

Standard graph of Repaglinide in 0.1 N HCl was plotted by taking concentration ranging from 5 to 30 µg/ml. The absorbance values for their respective concentration were shown in Table 4 and the standard graph was shown in Figure 3 **The** calibration curve of Repaglinide in 0.1 N HCl was constructed by taking 5, 10,15,20, 25 and 30 µg/ml as the serial concentrations and then finding the corresponding absorbance values by spectrometrically at 240 nm.

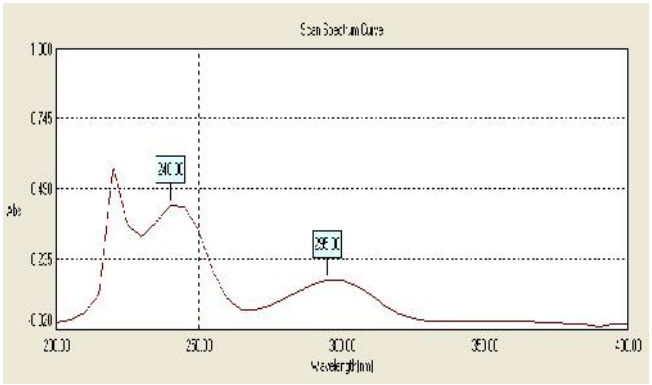

Figure 3: Repaglinide peak in 0.1 N HCl

Table 4: Calibration of Repaglinide in 0.1N HCl

Concentration (µg/ml)	Absorbance
0	0
5	0.103
10	0.222
15	0.342
20	0.463
25	0.568
30	0.693

The slope and intercept values were found to be 0.023 and 0.012 and the Coefficient of Correlation (R^2) was found to be 0.999. From the slope and intercept values it was found

that the curve is having a positive slope and intercept. As the coefficient of correlation value is 0.999 the values are acceptable**.**

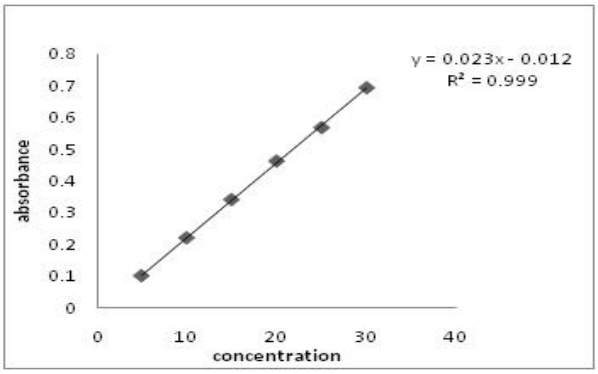

Figure 4: Calibration graph of Repaglinide in 0.1N HCl

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. 1447.77 Aromatic (C=O), 2934 CH3 Streching, 1339.19 CH2 bending, 3306.35 N-H Streching, 1685.30-Cyclic C=0.By observing the IR spectra of pure drug and the all physical mixtures of drug and polymers was found out that none of the above mentioned groups were affected by those polymers. Thus it can be said that there was no interaction between the drug and any of the polymers. The following table 5 shows the wave number for the characteristic bands in the IR spectra of pure Repaglinide. 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.

Table 5: Wave number for the characteristic bands in the IR spectra of pure Repaglinide

Wave number in cm^{-1}	Characteristic bands
1447.77	Aromatic(C=C)
2934	CH3 Streching
1339.19	CH2 bending
3306.35	N-H stretching
1685.30	Cyclic c=0

Bulk density of all formulations was in the range of 0.4 1gm/cc to 0.48 gm/cc. Tapped density of all formulations was in the range of 0.57 gm/cc to 0.6 6gm/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 ethyl Eudragit had an angle of repose ranging from 31.2 to 35.9 indicates that all of the formulations made with Eudragit had excellent flow properties.

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.

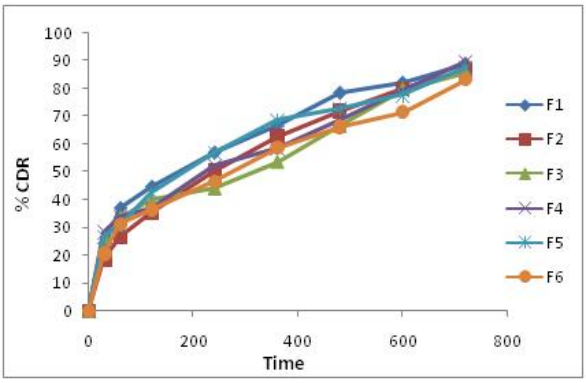

Figure 8: Dissolution graphs of F1, F2, F3, F4, F5 & F6

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 considerd as the best formulation among all the formulations.

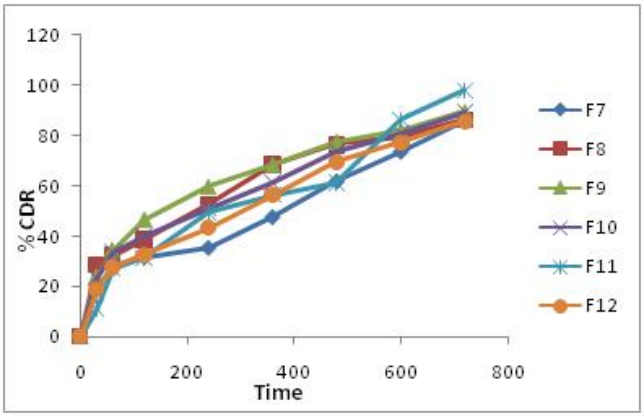

Figure 9: Dissolution graphs of F7,F8,F9,F10,F11 & F12

Different formulations were compressed by using different polymers in different ratios. These formulations weight variation was found to be is in the range of 74-76 mg. Hardness is in the range of 2.5-3.2 kg/cm^2. Thickness is about 1.0-1.6 mm. Friability is in the range of 0.04-0.09%.

Tablet thickness: Tablet thickness is one of the important physical parameter as it may affect the uniformity and pose different problems in packing. Tablet thicknesses of

randomly selected Tablets from each formulation were measured using a screw gauge and the thicknesses of Tablets of all the formulations were in the range of 1.0-1.6 mm.

Weight variation*:* The weight variation test was performed to see whether all the Tablets punched have uniform weight. The total weight of each formulation was maintained constant. The average weights of all formulations were within the permissible limits.

Hardness: Hardness of the Tablet was between 2.5-3.2 kg/cm^2 and was maintained for all the batches in order to minimize the effect of hardness on the drug release because the effect of polymer concentration is the only area of interest. The hardness of the Tablets was measured using Monsanto hardness tester. The force required to break the Tablet across its diameter is recorded as the hardness for the Tablet. The hardness values of the Tablets were shown in Table 4.11. The results showed that the hardness of the Tablets were almost the same. This was done because the effect of polymer and its concentration on the drug release was the area of interest.

Friability*:*

Friability test was performed using Roche-type friabilator. The results obtained in the friability test are indicated in Table 4.11. Friability test of all the formulations was found satisfactory showing enough resistance to the mechanical shock and abrasion. The weight loss was found to be in between 0.04-0.09% which shows that all the formulations comply with the friability test.

Release kinetics:

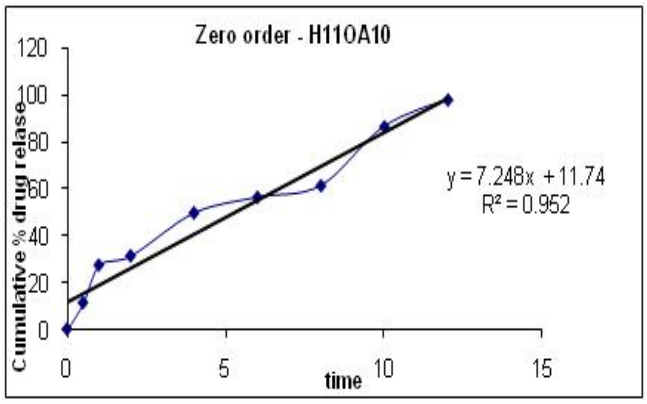

Figure 10: Zero order graph

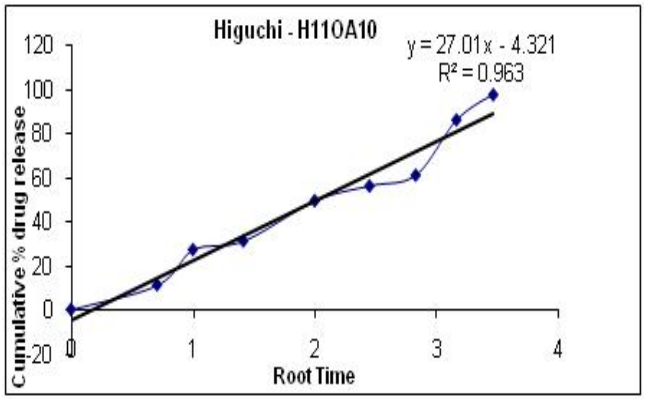

Figure 11: Higuchi graph

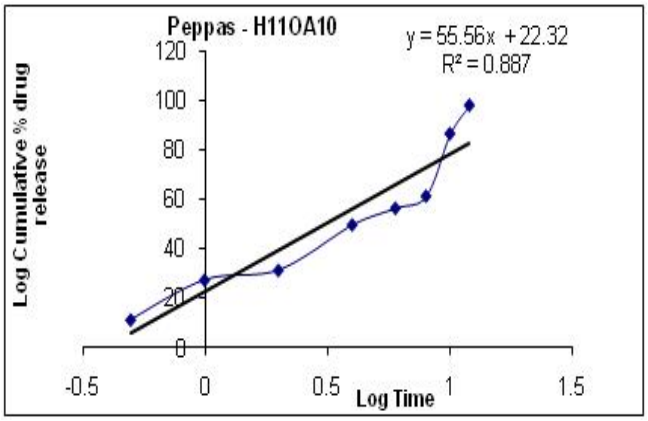

Figure 12: Peppas graph

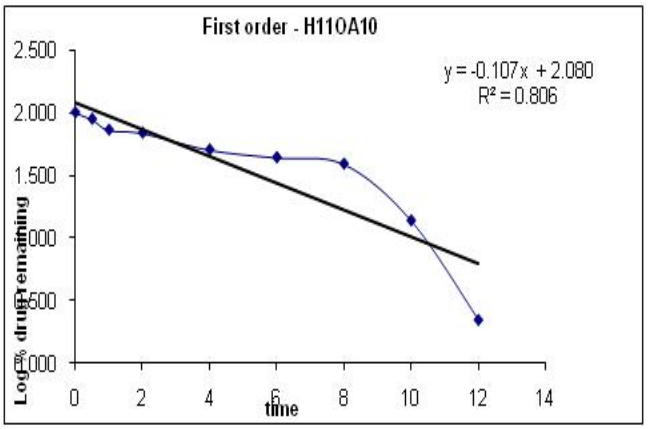

Figure 13: First order graph

The results of dissolution data were fitted to various drug release kinetic equations. Regression coefficient (R^2) value was highest for Higuchi release equation in formulation F11.The kinetics of dissolution data with R^2 value obtained from formulation F1,F2,F3,F4,F5,F6,F7,F8,F9,F10 ,F11 & F12 are tabulated in Table. Formulation F11 plots of Zero order, First order, Higuchi and Korsmeyer-peppas are depicted. The Zero order drug release graph is plotted time taken on x-axis and the cumulative percentage of drug released on y-axis. The First order drug release graph is plotted between by time taken on x-axis and the log cumulative percentage of drug remaining on y-axis. Higuchi's graph is plotted between the square root of time taken on x-axis and the cumulative percentage of drug released on y-axis. Korsmeyer-peppas drug release graph is plotted between the log time taken in x-axis and the log cumulative percentage of drug released on y-axis. Among the various formulations studies, formulations F11 is considered as ideal formulation, which exhibited 97.82% of drug, release in 12 hours. The R^2 values of Higuchi model were found to be highest among all other models for this formulation.

4. Conclusion

The aim of the present study was to develop and controlled release formulation of Repaglinide to maintain constant therapeutic levels of the drug for over 12 hrs. Various grades of HPMC were employed as polymers. Repaglinide

dose was fixed as 2 mg. Total weight of the tablet was considered as 75 mg. Polymers were used in the concentration of 12 and 16mg concentration. 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 (F11) showed better and desired drug release pattern i.e.,97.82 % in 12 hours.It followed zero order release kinetics mechanism. In present work the formulations was carried out in single polymer with single drug, In future the studies that can be carried out on this formulations are usage of combination of polymers, Preclinical Studies in animals to know the bioavailability of the drug and Clinical Studies to know bioavailability of the formulation with that of the formulations available in the market and for the release of the formulation in to the market.

FT-IR (Fourier Transform Infrared Spectrophotometry)

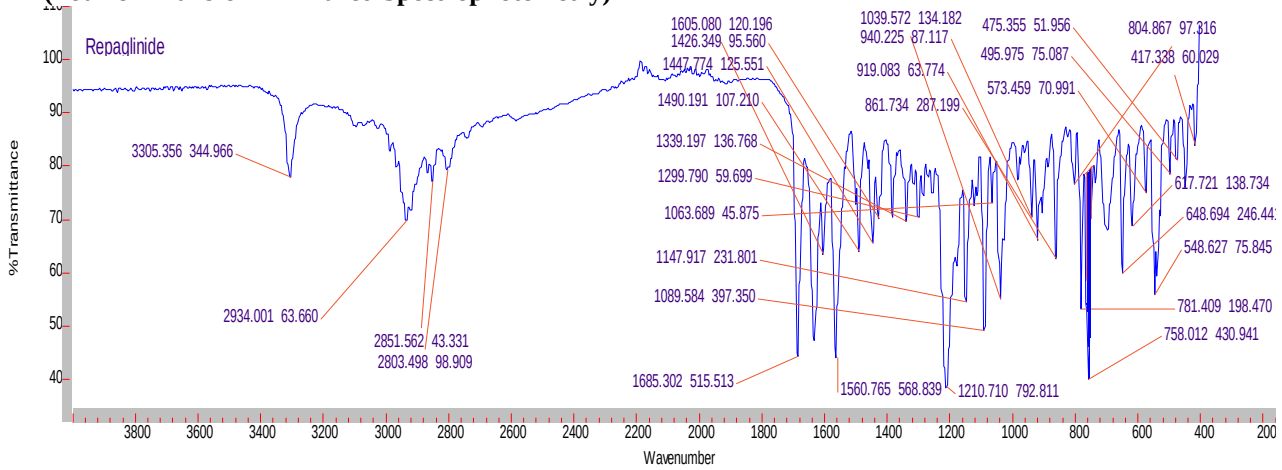

Figure 5: FT-IR Spectra of Repaglinide

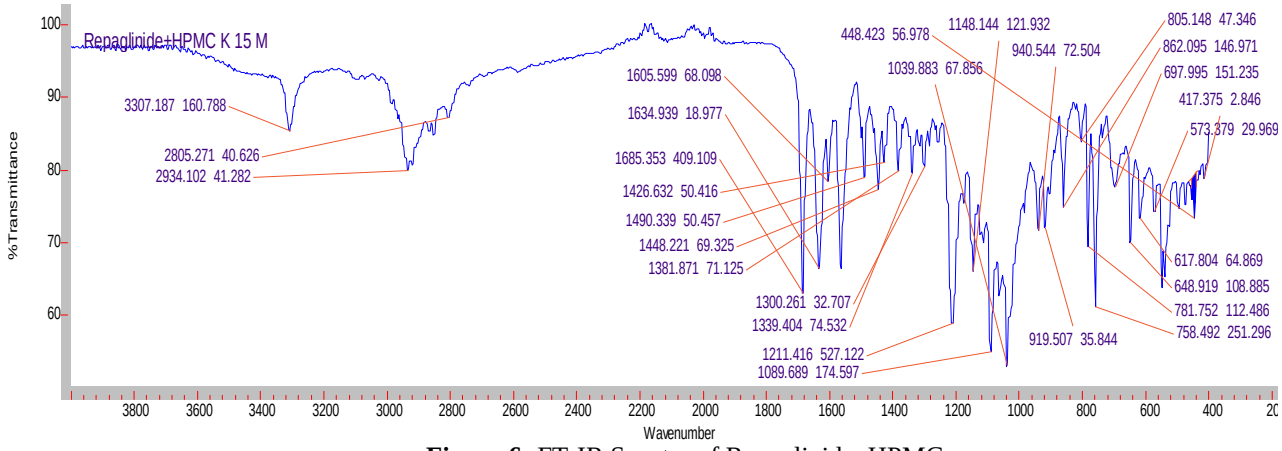

Figure 6: FT-IR Spectra of Repaglinide, HPMC

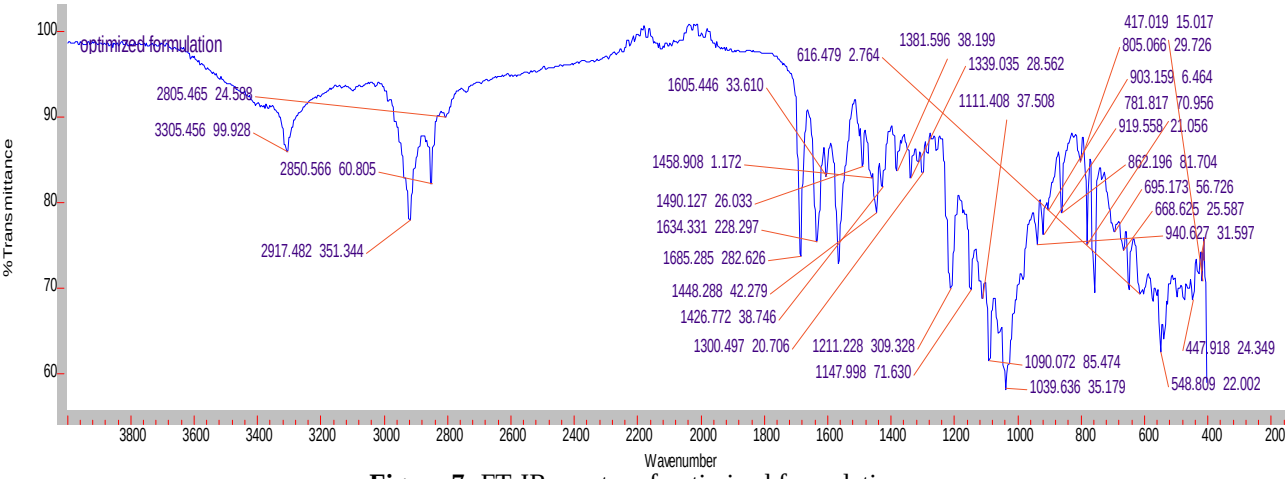

Figure 7: FT-IR spectra of optimized formulation

Table 6: Comparitive FT-IR Interpretation of Repaglinide with Excipients

S.NO.	pure drug	Drug + polymer	Optimized formulation	Frequency range	Mode of vibration
1.	1447.77	1490.33	2916.43	1600-1475	C=C Aromatic
	2934	2934.10	2917.48	3000	CH3 Streching
2.	1339.19	1381.87	1381.59	1400	CH2 bending
	3306.35	3307.18	3305.45	3500-3000	N-H
3.	1685.30	1685.35	1685.28	1715	C=O
	1339.19	1381.87	1381.59	1400	O-H
4.	1147.91	1211.41	1211.22	1270	C-H Ring

From the above table, the wave number of mixture of drug with excipients is within the range of wave number of pure drug. This implies that the excipients are compatible with the drug since their combination did not alter the functional groups of pure drug.

Evaluation of Powders:

Table 7: A comprehensive report on flow properties of Powders

Formulation	Bulk	Tapped	Hausner	Compressibility	Angle
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

***In-vitro* drug release study:**

Table 8: 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 9: 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

Table 10: 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

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

Table 11: 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

5. Acknowledgement

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