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Research

Formulation and Invitro Evaluation of Floating Pulsatile Drug Delivery System of Repaglinide

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Abstract

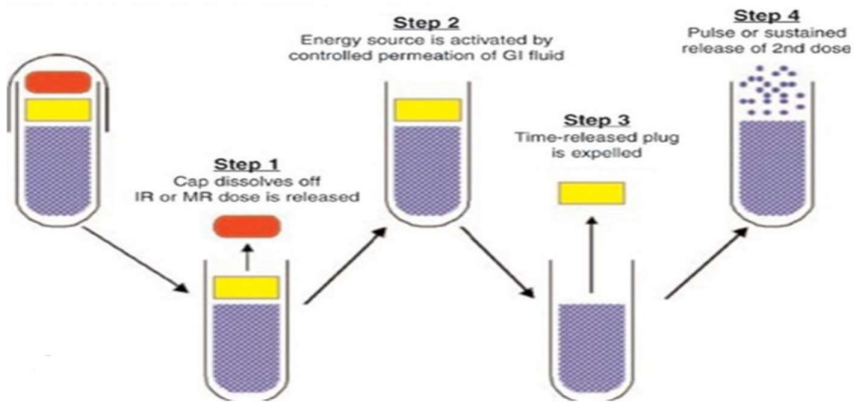
The main objective of the present research work was to develop chronomodulated, floating-pulsatile drug delivery system to release the drug in distal small intestine part of the GIT in order to achieve chronotherapeutics release of Repaglinide without releasing the drug during floating, for the treatment of rheumatoid arthritis, osteoarthritis, spondylitis and to improve the patient compliance. A chronodelivery system, based on biological rhythms, is a state-of-the-art technology for drug delivery to increase safety, efficacy and also improves overall drug performance. In this research work preparation of pulsatile drug delivery system was prepared using super disintegrants like Crospovidone, croscarmellose sodium and SSG were selected in the system. Whereas coated tablets were prepared by using HPMC K100M, and HPMC K200M. All the prepared formulations were analysed for Pre-compression parameters were conducted for all formulations blend and were found to be satisfactory. From the Invitro drug release data of the core tablets it was concluded that the formulation F9 of core tablet containing 15 mg of Sodium Starch glycolate shows immediate release while compared with other super disintegrants. From the drug release data of the press coated tablet it was concluded that the formulation M5F11 maintains lag phase for 5-6 hours and the drug release was bursted at the end of 9 hours. It follows first order release and follows super case II transport mechanism.

Keywords: Repaglinide, Crospovidone, croscarmellose sodium, HPMC100M, HPMC K200M.

INTRODUCTION

The Pulsatile drug delivery systems (PDDS) show great importance, interest due to complete drug release and follow the pattern of drug release after Lag time. So, the pulsatile systems are based on time, site-specific systems. Hence, these systems are designed to deliver the medication quickly and bursts in a short period after a

predetermined off-release Period. So, drug release from the dosage form as a pattern of "pulse" after the lag time. Two phases characterize the PDDS release: In that, the initial phase shows the release of small amount of the drug and is continued by the next phase, in which the complete release of the drug takes place in a short period of lag time. Chronobiology is the study of science concerned with biological rhythms and mechanisms. The presence of body biological rhythms is categorized into three categories as follows, **Circadian,** Oscillations of a Day (Completed within a day or 24 hours), **Ultradian,** Oscillations are shorter durations type (>01cycle/24 hours)**, Infradian,** Oscillations are longer durations type (<01 cycle/24 hours). Circadian rhythms are endogenous oscillations that occur periodically for about 24 hours and involve regulating many body functions of metabolism, sleep pattern, and hormone production. The mechanism involved in release of drug from the dosage form follows: Diffusion type, Erosion type, and Osmosis type. The methods used for Pulsatile Drug Delivery System are Time controlled, Stimuli induced and External regulated. The number of recent technologies are used for various disease treatments to release the required drug amount at different intervals. Hence, mostly multiparticulates are used compared to single unit dosage form due to greater flexibility in blending with different release patterns, dose dumping is not possible, and reproducible short gastric residence time. Various PDDS technologies developed on the basis of methodologies. The pulsatile systems are very beneficial and increase the therapeutic effectiveness of the medication and improve the patient compliance effect in chronic problems. The circadian time structure, disease rhythm pathophysiology, and medicine Chrono pharmacology knowledge help develop and design chronotherapeutic dosage forms and effective treatment of disease with minimizing the undesirable effects, target drug delivery, and non-constant dosing.



METHODOLOGY & MATERIALS

Materials

The following materials that were either AR/LR grade or the best possible grade available were used as supplied by the manufacturer without further purification or investigation.

Table 1: Materials Used

S. No.	Materials	Grade	Manufacturer
1.	Repaglinide	A.R.	Gift sample
2.	Sodium Starch Glycolate	L.R.	N.R. chemicals,Mumbai.
3.	MCC	L.R.	N.R. chemicals,Mumbai.
4.	Talc	L.R.	N.R. chemicals,Mumbai.
5.	Magnesium stearate	L.R.	N.R. chemicals,Mumbai.
6.	HPMCK100M	L.R.	B.M.R. chemicals,Hyderabad.
7.	HPMCK200M	L.R	B.M.R. chemicals,Hyderabad.
8.	NAHCO3	L.R	B.M.R. chemicals,Hyderabad.
9.	Citric acid	L.R	B.M.R. chemicals,Hyderabad.

Equipment's Used

Table 2: Equipment's Used

S. No.	Instruments	Manufacturer
1.	Electronic Weighing Balance	Essae-Teraoka Ltd, Model No. ND/09/2001/28
2.	UV-Vis Spectrophotometer (UV-1800)	PG Instruments T60
3.	FTIR Spectrophotometer	Shimadzu, Japan.
4.	Electronic Weighing Balance	Remi Equipments, Mumbai.
5.	Disintegration Test Apparatus ED-2L	ElectroLab, Mumbai.
6.	Dissolution test apparatus	Lab India DS8000, Mumbai.
7.	Mitutoyo Digital Caliper	Mitutoyo, Japan.
8.	Digital pH meter 7007	Digisun Electronics Hyderabad.
9.	Test Sieve (No.16, 22, 40, 60, 80)	Scientific Engineering Corp. Delhi.
10.	Hot Air Oven	Servewell Instrument PVT LTD, Bangalore.
11.	Stability Chamber	Lab Control Equipment Co. Mumbai.
12.	Friabilator USP EF-2	ElectroLab, Mumbai.
13.	Tablet punching machine, Rimek mini press-1	KarRepaglinidevati Engineering Ltd, MehsaRepaglinide, Gujarat.
14.	Monsanto Hardness Tester	Ketan engineering Ltd, Mumbai
15.	Melting Point Apparatus	SETCO Ltd, Bangalore

Preparation of Standard Calibration Curve of Repaglinide in 0.1 N HCL

10mg of Repaglinide was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 0.1 N HCL buffer to give stock solution containing 1000µg/ml.

The standard stock solution was then serially diluted with 0.1 N HCL buffer to get 2 to 12µg/ml of Repaglinide. The absorbance of the solution were measured against 0.1 N HCL buffer as blank at 240 nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Preformulation studies

It is one of the important pre-requisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination, solubility and compatibility studies.

Determination of Melting Point

Melting point of Repaglinide was determined by capillary method. Fine powder of Repaglinide was filled in glass capillary tube (previously sealed at one end). The capillary tube was tied to thermo meter and the thermometer was placed in the Thais tube and this tube was placed on fire. The powder at what temperature it melted was noticed.

Solubility

Solubility of Repaglinide was determined in pH 1.2 buffers. Solubility studies were performed by taking excess amount of Repaglinide in different beakers containing the solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no. 41. The filtered solutions were analyzed spectrophotometrically at 240 nm.

Compatibility Studies

FTIR analysis

The drug-polymer interactions were studied by FTIR spectrometer, Shimadzu 8400 S. 2% (w/w) of the sample, with respect to a potassium bromide (KBr; SD Fine Chem. Ltd., Mumbai, India) was mixed with dry KBr. The mixture was ground into a fine powder using mortar and then compressed into a KBr discs in a hydraulic press at a pressure of 10000 PSI. Each KBr disc was scanned 10 times at a resolution of 2 cm–1 using Happ-Genzel apodization. The characteristic peaks were recorded.

Formulation of Compressed Tablets of Repaglinide

The methodology adopted includes:

1) Preparation of core tablets of Repaglinide.
2) Coating of the core tablets

Formulation Table of Core Tablets

Table 3: Formulation Table of Core Tablets

Ingredients	F1	F2	F3	F4
Repaglinide (Equivalent to 2mg)	10	10	10	10
Sodium Starch glycolate (SSG)	5	10	15	20
MCC	Q. S	Q. S	Q. S	Q. S
Lactose	20	20	20	20
Mg. stearate	4	4	4	4
Talc	2	2	2	2
Total wt	75	75	75	75

Formulation of core tablet of Repaglinide

The inner core tablets were prepared by using direct compression method as per the developed formulation table which was shown above. Accurately weighed amounts of Repaglinide, MCC, Crospovidone, SSG, croscarmellose sodium, and Talc were dry blended for about 15min followed by addition of magnesium stearate. The mixture was then further blended for 10 min. Now the resultant powder blend was manually compressed using punching machine and finally the core tablet was obtained.

Evaluation of Preformulation parameters

Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\tan\theta = h/r$

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

Where,

h and r are the height and radius of the powder cone respectively.

Table 4: 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

Determination of Bulk Density and Tapped Density

5 g of the granules (W) from each formula were introduced into a 100 ml measuring cylinder, and the initial volume was observed. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 Sec intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following formulae.

Bulk density = W / V_O

Tapped density = W / V_F

Where,

W = weight of the granules, V_O = initial volume of the granules, V_F = fi Repaglinide volume of the granules.

Hausner's Ratio

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

Hausner's Ratio = Tapped density/Bulk density

Table 5: Hausner's Ratio

S. No.	Hausner's Ratio	Property
1.	0-1.2	Free flowing

2.	1.2-1.6	Cohesive powder

Compressibility index (Carr's Index)

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20% has good flow property.

$$C_I = \frac{(Tapped\ Density - Bulk\ Density)}{Tapped\ Density} \times 100$$

Table 6: Carr's index

S. No	Carr's Index	Properties
1	5-12	Free flowing
2	12-16	Good
3	18-21	Fair
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

Formulation of tablets of Repaglinide

The optimized core tablets were coated with coating ingredients like Xanthan gum, HPMCK100M. Now accurately weighed amount of barrier layer material was transferred into a 16mm die then the core tablet was placed manually at the center. The remaining amount of the barrier layer material was added into the die and compressed. Compression of tablets was done in rotary compression tablet machine using 16.4x8mm flat oval shape punch. The prepared tablet of each batch was evaluated for the tablet properties.

Evaluation of Tablet Properties

Tablets were subjected to evaluation of properties including drug content uniformity, weight variation, tablet hardness, friability, and thickness, and in-vitro drug release with different media.

Weight variation

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in the Table -10.

Table 7: Weight variation limits

S. No	Average weight of tablet (mg)	Maximum % difference allowed
1	130 or less	10
2	130-324	7.5
3	324<	5

Tablet hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 3 tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded.

Friability

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients.

Method

20 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded.

$$\% \text{ Friability} = \frac{Initial\ weight\ of\ tablet - Final\ weight\ of\ tablets}{Initial\ weight\ of\ tablet} x100$$

Tablet thickness

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten tablets of each formulation.

Content Uniformity

The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 20 mg was weighed accurately and dissolved in 10ml of buffer used. The solution was shaken thoroughly. The un dissolved matter was removed by filtration through Whattman's filter paper No.41. Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured at 240 nm. The concentration of the drug was computed from the standard curve of the Repaglinide in 6.8 phosphate buffer.

Disintegration time

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in Electrolab USP disintegration test apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top, and held against a 10 mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 litre beaker containing 6.8pH Buffer solution at 37°C ± 0.5°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

Invitro Dissolution time

In-vitro dissolution study of core and coated tablets of Repaglinide was carried out using Lab India DS8000 USP dissolution test apparatus. The details are given as below:

Procedure

Tablet was introduced into the basket of the Lab India DS8000 USP dissolution test apparatus and the apparatus was set in motion, 5 ml of sample was withdrawn for half a n hour at 5 min intervals. Samples withdrawn were a analyzed by UV spectrophotometer for presence of drug using buffer solution as blank.

Table 8: Composition of compression coated tablets

Formulation	M1F3	M2F3	M3F3	M4F3	M5F3
Core	75	75	75	75	75
HPMCK100M	125	175	75	150	100
HPMC K200M	125	75	175	100	150
NAHCO3	45	45	45	45	45
Citric acid	30	30	30	30	30
Total weight	**400**	**400**	**400**	**400**	**400**

Evaluation of Pulsatile Drug Delivery Systems

Characteristics of coated tablets of Repaglinide

Characteristics of tablets of Repaglinide such as hardness and disintegration test were conducted. 3 tablets were taken and hardness of formulations was determined by using Monsanto hardness tester. Average of three determinations was noted down.

Thickness of coated Repaglinide tablet formulations was determined by using digital Vernier calipers. 3 tablets of each type of coated formulation were determined for thickness and average thickness of the formulation was determined. Similarly the thickness of the coating on the formulation was determined by deducting the thickness of core tablets from thickness of the coated formulation.

A successful Pulsatile drug delivery system is one that remains intact in the physiological environment of stomach and small intestine for up to six hours, releasing no or minimum amount of drug, but completely releases the drug after six hours.

***In-vitro* Dissolution method**

Dissolution testing of pulsatile delivery systems with the conventional paddle method at 50 rpm and 37±0.5°C has usually been conducted in 0.1N HCL to simulate the GI tract pH. The ability of the coats/carriers to remain intact in the physiological environment of the stomach is generally assessed by conducting drug release studies in 0.1N HCL using USP dissolution rate test apparatus. The samples were withdrawn at regular intervals and analyzed by UV spectrophometer (PG Instruments T60) for the presence of the drug at 241nm. Dissolution tests were performed in triplicate.

Despite the simplicity and convenience, conventional dissolution testing primarily provides essential information on the processing specifications of a Pulsatile drug delivery system rather than on the validity of the system design.

Release kinetic models

One of the most important and challenging areas in the drug delivery field is to predict the release of the active agent as a function of time using both simple and sophisticated mathematical models. The importance of such models lies in their utility during both the design stage of a pharmaceutical formulation and the experimental verification of a release mechanism. In order to identify a particular release mechanism, experimental data of statistical significance are compared to a solution of the theoretical model. It is therefore clear that only a combination of accurate and precise data with models accurately depicting the physical situation will provide an insight into the actual mechanism of release.

To analyse the mechanism for the drug release and drug release rate kinetics of the dosage form, the data obtained was fitted in to Zero order, First order, Higuchi matrix, Krosmeyers-Peppas and Hixson Crowell model. In this by comparing the R-values obtained, the best-fit model was selected.

Zero Order Kinetics

This model describes the system where the release rate is independent of the concentration of the dissolved species.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-

$$W_O - W_t = K\,t$$

Where,

Wo = Initial amount of drug in pharmaceutical dosage form, Wt = Amount of drug in the dosage form at time t, K = Proportionality constant.

Dividing this equation by Wo and simplifying

$$ft = Kot$$

Where,

ft = 1-(Wt/Wo) which represents the fraction of drug dissolved in time t,

Ko= Apparent dissolution rate constant or zero order release constant

The pharmaceutical dosage forms following this profile release the same amount of drug by unit time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. This following relation can in a simple way express this model

$$Qt = Qo + Kot$$

Where,

Qt= Amount of drug dissolved in time t, Qo = Initial amount of drug in the solution and Ko = Zero order release constant.

First Order Kinetics

The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species.

To study the first order release rate kinetics, the release rate data were fitted to the following equation.

$$\log Q_t = \log Q_o + K_1 t / 2.303$$

Where,

Q_t = Amount of drug released in time t, Q_o = Initial amount of drug in the solution and K_1 = First order release constant.

The pharmaceutical dosage forms following this dissolution profile, release the drug in a way that is proportional to the amount of drug remaining in its interior, in such a way that the amount of drug released by unit of time diminished.

Higuchi Model

Higuchi developed several theoretical models to study the release of water soluble and low-soluble drugs incorporated in semisolids and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. The Higuchi equation is

$$f_t = K_H \times t_{1/2}$$

Where,

f_t = Amount of drug released in time t and

K_H = Higuchi dissolution constant.

The equation describes the release from systems where solid is dispersed in an insoluble matrix, and the rate of drug release is related to the rate of drug diffusion.

Korsemeyer-Peppas Model

Korsemeyer et al. developed a simple, semi-empirical model, relating exponentially the drug release to the elapsed time. To study this model the release rate data is fitted to the following equation

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

Where,

M_t / M_∞ = Fraction of drug release, K= Release constant, t = Drug release time and

n = Diffusional exponent for the drug release that is dependent on the shape of the matrix dosage form.

This mathematical model has been used very frequently to describe the drug release from several different pharmaceutical modified release dosage forms.

The results obtained from in vitro drug release studies were plotted adopting four different mathematical models of data treatment as follows:

- % Cum. Drug Release v/s Time (Zero order rate kinetics).
- Log % Cum. Drug Retained v/s Time (First order rate kinetics).
- % Cum. Drug release was plotted against √T (root time). (Higuchi model)
- $\sqrt[3]{\text{Initial concentration}}$ - $\sqrt[3]{\%\ \text{drug remaining}}$ v/s Time (Hixen-Crowell)
- Log % Cum. Drug Release v/s Log Time (Korsmeyer-Peppas exponential equation).

Stability Studies

Stability is defined as the capacity of drug product to remain within established specifications to maintain its identity, strength, quality and purity throughout the retest or expiration dating periods.

Stability studies provide an evidence on how the quality of the drug product varies with time under the influence of a variety of environmental factors such as

- Temperature
- Humidity
- Light

These studies establish the

- Re-test period of the drug product
- Shelf life for the drug product
- Recommended storage conditions

In any rationale design and evaluation of dosage forms for drugs, the stability of the active component will be a major criteria in determining their acceptance or rejection. So, in the present study, the stability of the drug product is assessed by exposing the product to various temperatures and humidity conditions.

The optimized matrix tablets were subjected to stability studies at 25^0C+_2^0C/ 60%_+5%RH and 40^0C+_2^0C/75%_+5%RH the product were evaluated for their physical characteristics drug content and in-vitrodrug release profiles over a period of 3 months.

Table 9: Stability Study Details acc. to ich guidelines

Study	Storage Condition	Duration
Long term	25^0C+_2^0C/60%_+5%RH	12 months
Intermediate	30^0C+_2^0C/65+_5%RH	12 months
Accelerated Temperature	40^0C+_2^0C/75%_+5%RH	6 months

In the present study optimized formulation was selected for the study and formulations were packed in amber-colored bottles tightly plugged with cotton and capped. They were exposed to 40ºC temp and 75% RH for 30 days.

RESULTS & DISCUSSION

Pre formulation studies

Determination of Melting Point

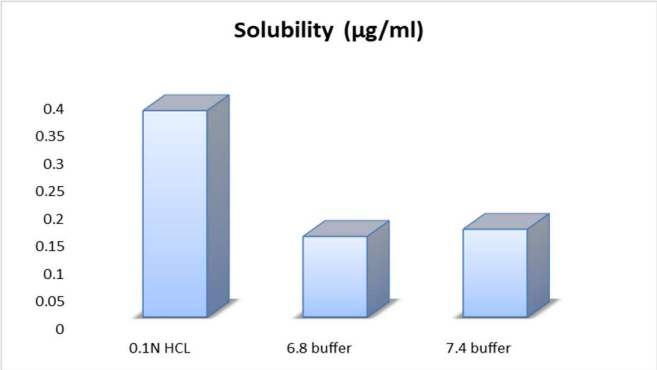
Melting point of Repaglinide was found to be in the range of 126 to 128 °C

Solubility

Solubility of Repaglinide was determined in pH 1.2, water, & pH 6.8 phosphate buffers.

Table 10: Data for Solubility Curve for Repaglinide

S.No	Buffers	Solubility (mg/ml)
1	0.1N HCL	0.374
2	6.8 buffer	0.146
3	7.4 buffer	0.159



From the above obtained solubility data we can say that 0.1N HCL is having more solubility than 6.8 ph buffer.

Uv spectrum of Repaglinide

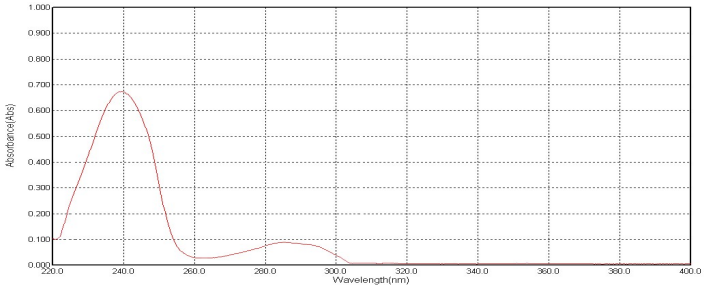


Fig 1: Uv spectrum of Repaglinide

Preparation of Standard Calibration Curve of Repaglinide

Table 11: Standard Calibration Curve of Repaglinide at 240 nm

S.NO	Concentration(µg/ml)	Absorbance
1	0	0
2	2	0.136
3	4	0.264
4	6	0.386
5	8	0.528
6	10	0.671
7	12	0.789

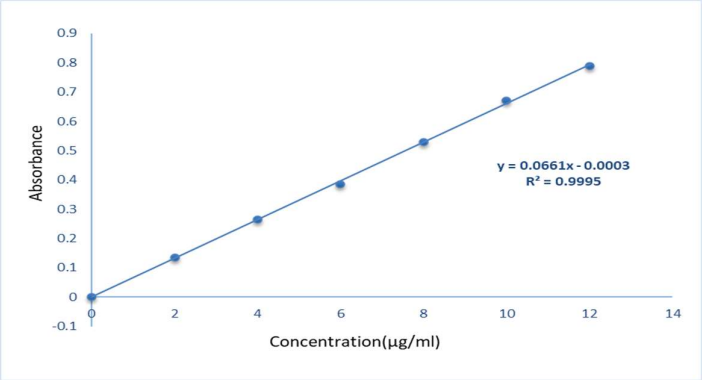


Fig 2: Calibration curve of Repaglinide

Compatibility Studies

Compatibility with excipients was confirmed by FTIR studies. The pure drug and polymers were subjected to FTIR studies. In the present study, the potassium bromide disc (pellet) method was employed.

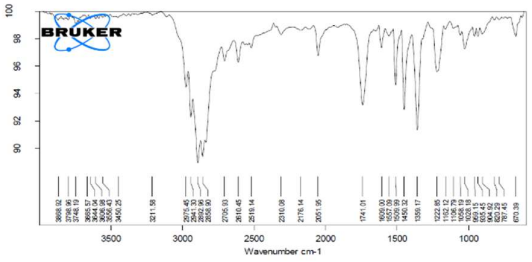


Fig 3: FTIR Spectrum of pure Repaglinide

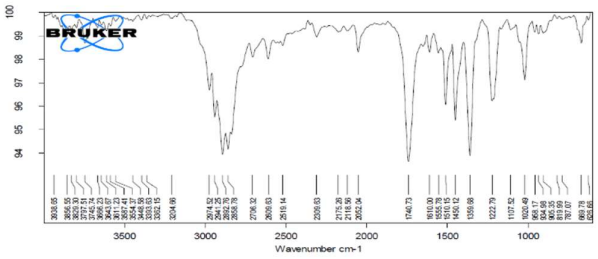


Fig 4 : FTIR Spectrum of Repaglinide best formulation

Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Repaglinide) and optimized formulation (Repaglinide+ excipients) which indicates there are no physical changes.

Table 12: Pre Compression parameters

Formulation Code	Derived properties		Flow properties		
	Bulk density (mean±SD)	Tapped density (mean±SD)	Angle of repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
F1	0.58±0.36	0.69±0.12	24.64±0.42	15.64±0.18	1.21±0.52
F2	0.55±0.18	0.68±0.26	25.74±0.26	17.47±0.17	1.18±0.25

F3	0.56±0.14	0.67±0.24	26.84±0.48	19.85±0.16	1.27±0.36
F4	0.57±0.16	0.68±0.29	24.12±0.37	18.85±0.18	1.15±0.41

The angle of repose of different formulations was ≤ 28.59 which indicates that material had good flow property. So, it was confirmed that the flow property of blends was free flowing. The bulk density of blend was found between 0.53g/cm^3 to 0.59g/cm^3.Tapped density was found between 0.63g/cm^3 to 0.70g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 13.90-22.31 and Hausner's ratio from 1.14-1.27 which reveals that the blends have good flow character.

Table 13: Post compression parameters of core tablet

Formula	Post compression parameters of core tablet				
	Avg. Wt (mg)	**Hardness (kg/cm^2)**	**Thickness (mm)**	**Friability(%)**	**Disintegration time(secs)**
F1	74.98	3.68	3.27	0.22	63
F2	75.18	3.75	3.24	0.36	72
F3	75.15	3.87	3.20	0.51	41
F4	74.26	3.48	3.15	0.37	69

Weight Variation Test

The percentage weight variations for all formulations were given. All the formulated (F1 to F12) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits. The weights of all the tablets were found to be uniform with low standard deviation values.

Hardness test

The measured hardness of tablets of all the formulations ranged between 3-4 kg/cm2. This ensures good handling characteristics of all batches.

Disintegration test for core tablets

It was found between 63 – 104 seconds ensuring that all the cores of different formulations were rapid disintegrating type.

Friability Test

The % friability was less than 1 % in all the formulations ensuring that the tablets were mechanically stable.

Table 14: Content uniformity of different formula (F1 to F12)

Formulation code	Drug content
F1	98.42±0.48
F2	97.24±0.42
F3	**99.75±0.25**
F4	98.26±0.41

The percentage of drug content for F1 to F12 was found to be between 85.14% - 99.75%. It complies with official specifications.

Table 15: Cumulative percent drug release of core Repaglinide tablets of different formulations (F1 to F4)

TIME (MINS)	F1	F2	F3	F4
0	0	0	**0**	0
5	24.38	30.62	42.26	39.18
10	41.82	49.69	54.71	54.52
15	52.66	68.38	63.15	64.23
20	63.58	82.22	78.29	82.64

25	74.28	90.98	86.12	92.85
30	82.56	94.41	98.78	98.12
45	93.68	98.91		
60	99.22			

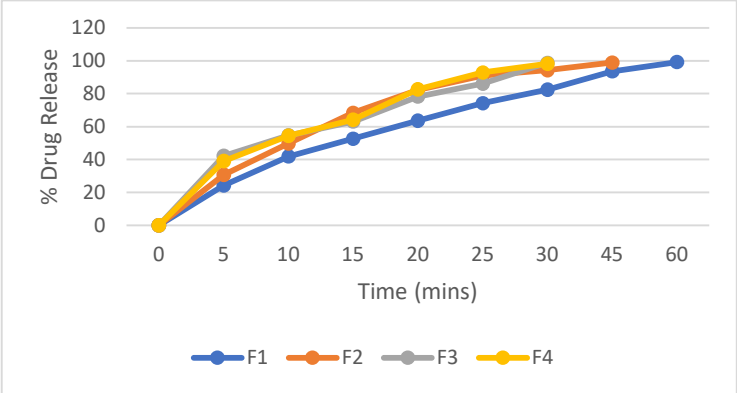


Fig 5: Cumulative percentage drug release of core formulation F1 – F4

Drug Release Kinetics Mechanisms

Zero Order Release Kinetics

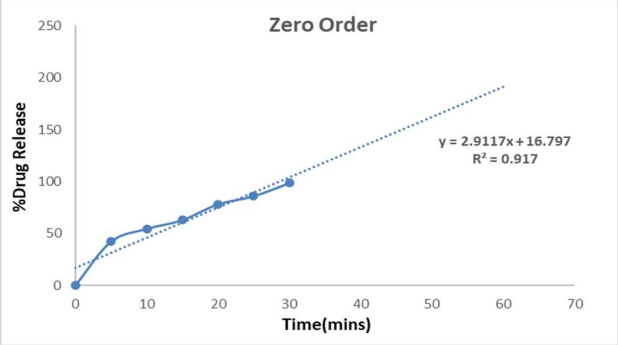


Fig 6: Zero Order Release Kinetics for Best Formulation (F3)

First Order Release Release Kinetics

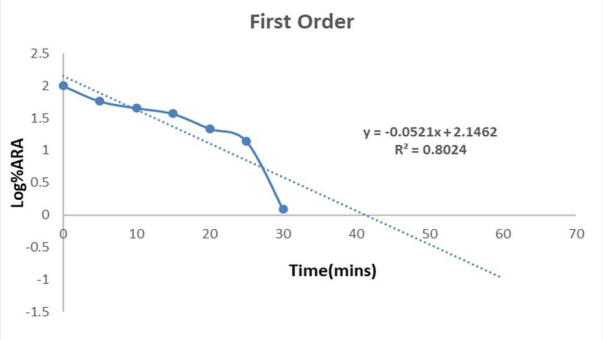


Fig 7: First Order Release Kinetics for Best Formulation (F3)

Table 16: I*n-vitro* drug release mechanism of best core formulation

Batch	Zero Order	First Order
Code	r^2	r^2
F3	0.917	0.802

Table 17: Evaluation of Physical Parameters of compressed tablets of Repaglinide

Formula	Weight variation (mean ± SD, mg)	Hardness	Friability (%)	Thickness
M1F3	398.30±0.18	4.88	0.28	4.24
M2F3	400.56±0.36	5.15	0.49	4.36
M3F3	402.66±0.47	5.36	0.67	4.15
M4F3	397.98±0.28	5.47	0.56	4.68

M5F3	400.29±0.35	6.84	0.24	4.35

Weight Variation Test: The percentage weight variations for all formulations were given. All the formulated (M1F11 to M5F11) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits. The weights of all the tablets were found to be uniform with low standard deviation values.
Hardness test: The measured hardness of tablets of all the formulations ranged between 4.88 – 6.84 kg/cm2. This ensures good handling characteristics of all batches.
Thickness: The measured thickness of tablets of all the formulations ranged between 4.15 - 4.68 mm. This ensures good handling characteristics of all batches.
Friability Test: The % friability was less than 1 % in all the formulations ensuring that the tablets were mechanically stable.

Table 18: Content uniformity of different formula (M1F3 to M5F3)

Formulation code	Drug content
M1F3	84.29±0.24
M2F3	88.78±0.69
M3F3	95.15±0.36
M4F3	95.36±0.40
M5F3	98.48±0.22

The percentage of drug content for M1F11 to M5F11 was found to be between 84.24% - 98.48%. It complies with official specifications.

In vitro drug release studies of press coated tablets

Table 19: Cumulative % drug release of coated different formulation (M1F3 to M5F3)

Time(hrs)	M1F3	M2F3	M3F3	M4F3	M5F3
0	0	0	0	0	**0**
1	0.98	0.48	0.49	0.41	**0.22**
2	1.53	1.89	1.25	1.97	**0.48**
3	2.23	2.58	1.85	1.75	**0.76**
4	17.12	7.98	2.38	2.98	**0.92**
5	23.65	24.65	11.49	13.69	**2.79**
6	36.36	42.87	34.29	38.79	**3.58**
7	48.47	66.3	58.45	52.65	**79.36**
8	77.12	85.9	73.38	68.78	**88.45**
9	86.28	98.22	88.46	79.96	**99.23**
10	98.85		97.28	84.64	

From the Invitro drug release studies it was observed that the formulation M1F11 containing HPMC K100M and HPMC K200M in 1:1 ratio releases maximum drug at the end of 10 hours and maintains the lag phase for only 3hours.

whereas the formulation M2F11 containing HPMC K100M and HPMC K200M concentrations lesser than the M1F11 releases maximum drug at the end of 9 hours due to the higher HPMC K100M concentration.

whereas the formulation M3F11 containing altered HPMC K100M and HPMC K200M concentrations than the M2F11 releases maximum drug at the end of 10 hours due to the higher HPMC K100M concentration, and it maintains the lag phase for upto 5 hours.

By changing the polymer ratios of HPMC K200M and HPMC K100M in 0.8:1.2 ratio the drug release was found to be satisfactory as it maintains the lag phase for upto 5-6hours and the complete drug was released within 9hours of time, when compared to M5F9 where the ratios were taken as vice versa.

By comparing the drug release profiles of the formulations M1F11-M5F11 formulated using natural polymers the drug release was found to be lagged upto 5-6hrs in case of M5F11 containing HPMC K200M and HPMC K100M in the ratio of (0.8:1.2)

So, the drug release kinetics were performed for the M5F11 formulation and the results were tabulated below.

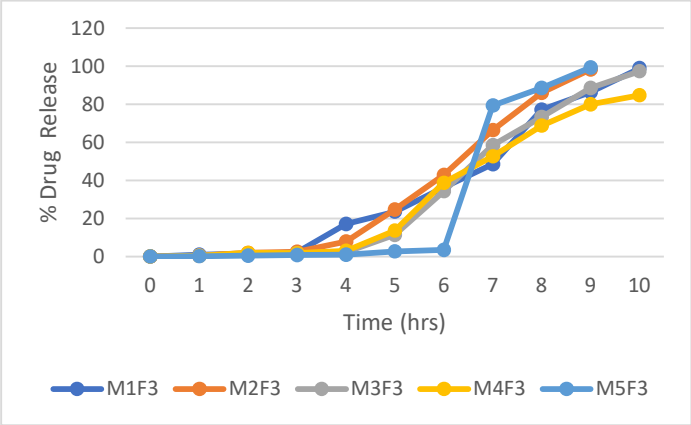


Fig 8: Cumulative percentage drug release of coated formulation M1F3 –M5F3

Drug Release Kinetics Mechanisms

Fig 9: Zero order release kinetics for best formulation (M5F3)

Fig 10: First order release kinetics for best formulation (M5F3)

HIGUCHI PLOT

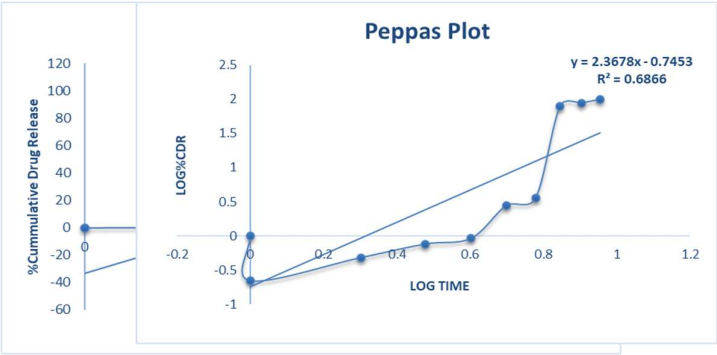


Fig 11: Higuhi Plot for Best Formulation (M5F3)

PEPPAS

Table 20: *in-vitro* drug release mechanism of best formulation

Fig 12: Peppas Plot for Best Formulation (M5F3)

Batch	Zero Order	First Order	Higuchi	Peppas	Peppas
Code	r^2	r^2	r^2	r^2	n
M5F3	0.678	0.582	0.472	0.686	2.367

From the drug release kinetics of the press coated tablet it was concluded that the formulation M5F11 maintains lag phase for 5-6 hours and the drug release was bursted at the end of 9hours. It follows first order release and follows super case II transport mechanism.

CONCLUSION

The aim of this study was to explore the feasibility of time dependent pulsatile drug delivery system of Repaglinide for treatment of non-insulin-dependent diabetes mellitus. A satisfactory attempt was made to develop pulsatile system of Repaglinide and evaluated it. From the reproducible results obtained from the executed experiments it can be concluded that: On the basis of drug content, *in-vitr*o release studies and its kinetic data F3 of core tablet and M5F3 of coated tablet were selected as optimized formulations for designing Pulsatile device. Therefore, the study proved that coated Repaglinide can be successfully used as a time dependent modified Chrono pharmaceutical formulation. Finally, from the above results we can conclude that pulsatile drug delivery system of Repaglinide can be formulated using polymers like HPMC K100M and HPMC K200M.

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