FORMULATION AND EVALUATION OF EXTENDED RELEASETABLETS (REPAGLINIDE)

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Abstract:

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-deliver products result in relatively rapid medication absorption and onset of accompanying Pharmacodynamic effects. However, once absorption of the medicine from the dose type is complete, plasma drug concentrations decline per the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), leading to loss of therapeutic activity. Before this time is reached, another dose is typically given if a sustained therapeutic result is desired. An alternate to administering another dose is to use a dose type that may offer sustained drug release, and so maintain plasma drug concentrations, on that fare side generally seen mistreatment immediate- release dose forms. In recent years, varied modified-release drug products are developed to manage the release rate of the drug and/or the time for drug release.

1. Introduction

The term modified-release product is employed to explain products that alter temporal order and the speed release of the drug substance. A changed release form is defined "as one that the drug- release characteristics of your time course and/or location area time to accomplish therapeutic or convenience objectives not offered by typical dose form like solutions, ointments or promptly dissolving dose forms as presently recognized".

EXTENDED RELEASE CONCEPT

Over the past thirty years because the expense and complications concerned to making new drug entities have exaggerated , with concomitant recognition of the therapeutic benefits of extended drug delivery, larger attention has been centered on development of extended or controlled deliver drug delivery systems. The attractiveness or applied by standard technique with in the form of pills, capsules, injectables, ointments, etc. Typically standard indefinite quantity form conventional dosage forms produce wide range fluctuation in drug concentration with in the blood stream and tissues with resultant undesirable toxicity and poor potency. The factors like repetitive dosing and unpredictable absorption led to the semiconductor diode to the construct of extending drug delivery system.

The law states that the quantity of drug passing across a unit space is proportional to the engrossment distinctions across that plane.

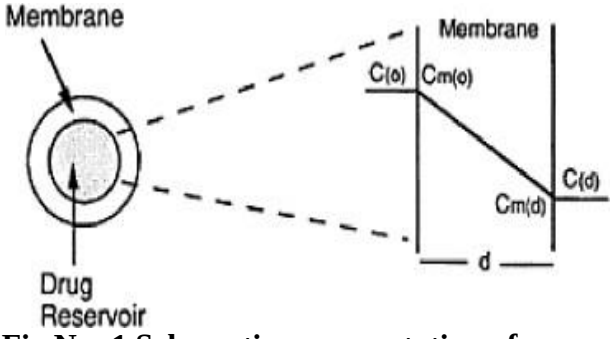


Fig No: 1 Schematic representation of reservoir diffusion device

Cm (o), and Cm (d) represent concentration of drug inside surfaces of membrane and C (o) & C

(d) represents concentration in adjacent ways.

The drug on the both side of membrane is in equilibrium with its respective

membrane surface which in equilibrium between the membrane surfaces and their bathing solutions as shown in Figure.

Therefore the engrossment just inside the membrane surface can be related to the concentration in the adjacent region by following expression.

K = Cm (o) /C(d) at X = o
K = partition coefficient.
If we consider K & D are constants then equation (1) becomes,J = D KΔC/d
Where,
ΔC = concentration difference across the membraned = path length of diffusion.
equation (1) is integrated and simplified to allow,J=DK ΔC /d (4)
Where,K = Partition constantD = diffusion constantΔC =Concentration distinctions across the membraneD = Thickness of the diffusion layer.
In the equation (4) it"s determined that „D" and „k" are constant.

Drug deliver can vary, betting on the geometry of the system. The only system to contemplate is that of a slab, wherever drug ransom is from only one surface.

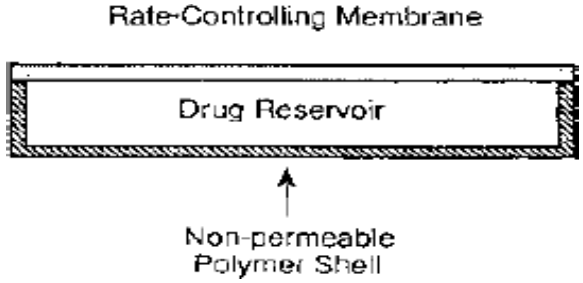


Fig No: 2Diagrammatic representation of the slab configuration of a reservoir diffusionalsystem.

In the case equation (4)

$dM_t/dt = ADk \Delta C /d$

5)

Where,Mt = mass of drug discharged after time"s" DM/dt = the steady-state ransom rate at time„t"A=the expanse of the device.

The left aspect of the equation (5) represents the speed of system. A controlled deliver system with a zero-order ransom rate may be potential if all the variables on the correct aspect of equation (5) stay constant. However it"s terribly very difficult to maintain all the parameters constant. A constant effective space of diffusion, diffusional path length, concentration distinctions and diffusional constant area need to get ransom rate that is constant.

(2)K = Cm (d) / C(d) at X = d (3)Where,

Objective

- ❖ Current work is to arrange and judge sustained-release (SR) matrix tablets of Repaglinideusing different polymers.
- ❖ To study the results of the compound and drug: chemical compound quantitative relationon the rate of drug ransom.
- ❖ To study the kinetic profile of drug deliver.

Plan of Work

- Construction of the calibration curve for Repaglinide in in 0.1N HCl and 6.8 pH phosphate buffer.
- Preparation of SR formulations of Repaglinide using MCC as agent, following polymers such as HPMC 100, Xanthum gumand Locust bean gumat totally different concentrations and combinations by Wet granulation method.
- Evaluation tests for the Precompression blend and prepared tablets.
- Selection of the most effective batch of medication based on the in-vitro release studies and similarity factor analysis.

To perform swelling and erosion studies, FTIR studies, and DSC studies for the

optimizedformulation.

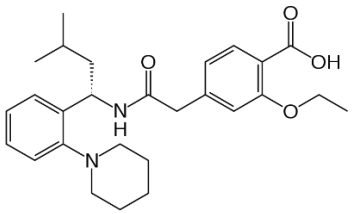
2. Drug Profile

REPAGLINIDE

Formula

- **Empirical Formula**
  $C_{27}H_{36}N_2O_4$

- **Structural Formula**



Physical and Chemical Properties

- **Mass weight** -452.86
- **Description** - White
- **Melting point** - 126 – 128^{0}C
- **Rout of**
- **Administration** **:** orally
- **Absorption** **:** speed and complete, 30%
- **Half-life** **:** fourteen hours
- **Bioavailability** **:** fifty six nada
- **Metabolism** **:** viscus
- **Excretion** **:** bile digestive juice
- **Protein binding** : >98% protein
- **Adverse Effects**
- Diarrhea
- Constipation
- Head ache
- Back pain
- Infections

Mechanism of Action

Repaglinide lowers blood sugar by stimulating the ransom of hormones from the beta isle cells of the exocrine gland. It achieves this by closing ATP-dependent metal channels within the membrane of the beta cells. This depolarizes the beta cells, opening the cells' atomic number 20 channel ad also the ensuing atomic number 20 inflow include hormone secretion.

EXCIPIENTS PROFILE

The following are the various polymers and excipients utilized in this work.

Hypromellose

Hypromellose is may be a partly *O*-methylated and *O*-(2- hydroxypropylated) polysaccharide.

Name : Benecel MHPC, Hydroxypropylmethylcellulose (HPMC),Methocel, Metolose, Tylopur.
Description: scentless and tasteless, white or creamy-whiteFibrous or granular powder.
Grade : Methocel K100 Premium LVEP, Methocel 100, K15M, K100M, Metolose 60SH, 65SH, 90SH.
Stability: Stable material, though it‟s absorbent whenDrying.
Solidity : 1.326 g/cm^3.
Liquefy point: Browns at 190–200°C; chars at 225–230°C. Glass transition temperature is 170–180°C.

Safety: Non-toxic and non-irritant material, though excessiveoral consumption could have a laxative effect.

Uses : As a pills binder (2% - 5% w/w),

Matrix former (10% - 80% w/w),

Thickening agent (0.45% - 1% w/w),

It is additionally used as an emulsifier, suspending agent, and in topical gels and ointmentsmatrix former, mucoadhesive compoundsas effective thickener.

<u>Cellulose, Microcrystalline</u> [Wade A, Weller PJ. 1994]

MCC is pure, part depolymerized polysaccharide that occurs as pearly, scentless, and flavorless and also the translucent grit possessed the porous particles. Commercially it‟s found within the completely different particle size and also the wet grades that have with the various properties and with different application.

- **Non property name :**
- BP : crystalline polysaccharide
- Ph Eur: CellulosesummicrocristalliumUSP **:** Microcrystalline cellulose
- **Synonyms :** Avicel PH, Celex, polysaccharide gel, Tabulose.
- **Chemical name :** Cellulose.
- **Molecular formula :** $(C_6H_{10}O_5)_n$
- **Functional class :** Adsorbent, suspending agent, pill disintegrating.
- **Angle of repose :** 498 for polysaccharide.
- **Frequency (bulk) :** zero.337 g/cm^3.
- **Frequency (tapped) :** 0.478 g/cm^3.
- **Flow ability :** one.41 g/s for Emcocel ninety M.
- **Melting purpose :** 260 to 270 ^{0}C
- **Moister content :** less than <5%
- **Solubility :** insoluble in water, acids, organic solvent.
- **Storage :** It is

often keep during a well closed instrumentally.

- **Incompatibilities** : Its incompatibilities with strong oxidizing agents.
- **Application in pharmaceutical dosage form**

Chiefly it"s used as binder and diluents within the preparation of the pills and therefore the capsules. Formulation is found within the both dry and the wet granulation. It has some lubricant substance and disintegrating property.

Talc

Talc [James .C. Bolyan, 1994]

- **Nonproprietary Name**
- BP - Purified talcUSP - Talc **Names** , Luzenac Pharma, magnesium hydrogen metasilicate

, pulverized talc.

- **Chemical Name** **:** Talc.
- **Atomic gross** **:** 144
- **Functional class** **:** Glidant, Anti-caking agent, pill & capsule diluents, lubricant

3.METHODOLOGY

Construction of Standard Graph of Repaglinide

Take the amount of 100 mg of medication was transferred into a 100 ml volumetric flask. Spirit was added to disband the drug and the primary stock solution was making to hundred ml of spirit. This gives a solution having concentration of 1 mg/ml of Repaglinide stock solution. Fromthis primary stock 10 ml was transferred in to another volumetric flask and made up to 100 ml with 6.8 pH phosphate buffer and this gives secondary stock solution. From this secondary stock 0.2, 0.4, 0.6, 0.8 and 1mL was taken individually and make up to 10 ml with 0.1N HCl and 6.8 pH phosphate buffer seperately. The absorbance was measured at 237 nm employing a UV photometer (Systronic, Hyderabad, India).

Preparation of 0.1N HCl

An 8.65 ml of Conc. HCl was placed during a 1000 ml volumetric flask and therefore volume was created up with water and pH was adjusted to 1.2.

5.1.1 Preparation of Standard Solution Repaglinide

Accurately weighed 100mg of Repaglinide was placed in a 100mL volumetrical flask and 50mL of 0.1 N HCl was more added to disband the medication. The volume was make up to 100mL HCl to grant 1000 µg/mL of solution (stock solution -I).

A 10mL aliquot from stock solution -I was taken and diluted to 100mL with in every volumetric flask to get 100µg/mL (stock solution -II).

Aliquotes of 0.2, 0.4, 0.6, 0.8 and 1mL of Repaglinide standard solution of 100mcg/ml (stock solution-II) was taken and diluted to 10ml to get concentrations from 2 to 10µg/mL with 0.1 N HCl. The absorbances of solutions were determined at 237nm against several media solutions as blank and a standard curve was plotted.

Preparation of pH 6.8 phosphate buffers: Accurately measured 50 ml of 0.2 M metallic element was taken in to a

200ml volumetric flask and 22.4 ml of 0.2 M sodium hydroxide was added to it. Volume was made up to 200 ml with distilled water, mixed and pH was adjusted to 6.8 with 0.2 M sodium hydroxide or 0.2 M othophosphoric acid.

Preparation of 0.2 M potassium dihydrogen phosphate solution: Accurately weighed a pair of 27.218 g of mono basic atomic number 19 dihydrogen phosphate was disband in 1000 ml of distilled water and mixed.

Preparation of 0.2 M sodium hydroxide solution: Accurately weighed 8 g of sodium hydroxide pellets were dissolved in 1000 ml of distilled water and mixed.

Preparation of Repaglinide Matrix Tablets

All the matrix tablets, each containing 5 mg of Repaglinide, were ready by direct compression methodology and also to check the impact of assorted ratios of various forms of polymers on the drug ransom.

LIST OF MATERIALS

S. No.	Material	
1.	Repaglinide	Gift sample from Aurobindo Pharma Ltd, Hyderabad, India
2.	HPMC 100	Dr.Reddy"s Laboratories, Hyderabad, India.
3.	Microcrystalline cellulose	Loba Chemie Pvt. Ltd, Mumbai.
4.	Talc	Qualikems Fine Chemicals Pvt. Ltd, New Delhi.
5.	Magnesium Stearate	Qualikems Fine Chemicals Pvt. Ltd, New Delhi
6.	Potassium Dihydrogen Orthophosphate Purified LR	S.D. Fine chemical Pvt. Ltd, Mumbai
7.	Sodium Hydroxide	Finar Chemicals Limited, Ahmedabad.

Table - list of material

LIST OF INSTRUMENTS

S. No.	Instrument	Manufacturer
1.	Electronic Weighing Balance	Shimadzu, AUX 220, Japan.
2.	16 Station Rotary compression Machine	Cadmach Machinery Co, Ahmedabad, India.
3.	Tap Density Tester (U.S.P.)	Electrolab, ETD-1020, India.
4.	Hardness Tester (Monsanto)	Cadmach Machinery Co, Ahmedabad, India.
5.	Sieves	Rolex standard sieves. Hyderabad, India.
6.	Dissolution Apparatus (U.S.P.)	Electrolab, TDT- 08L, India.
7.	UV/Visible Spectrophotometer	Systronics PC Based, 2202, Ahmedabad, India.
8.	Friability Test Apparatus	Campbell Electronics, Mumbai, India.

4.Formulations

In formulations ready, the ransom retardants enclosed (HPMCK100M), xanthum gum and carbon gum. Medication chemical compound ratios were 1:1, 1:2 and combination for all batches. Microcrystalline cellulose was used as diluents. Magnesium stearate 1% and talc 2 % were used as lubricants. Compositions of various preparations are given in the following Tables.

Table - Composition of Matrix medication

Ingredient					Formulation Code							
	Formulation1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Repaglinide	200	200	200	200	200	200	200	200	200	200	200	200
HPMC K1100	100	·	·	150	·	·	200	·	·	100	·	100
Xanthum gum	·	100	·	·	150	·	·	200	·	100	100	·
Locust bean gum	·	·	100	·	·	150	·	·	200		100	100
MCC PH102	197	197	197	147	147	147	97	97	97	97	97	97
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Mg. Stearate	One	One	1	1	1	1	1	1	1	1	1	1
Total	Five hundred	500	500	500	500	500	500	500	500	500	500	500

Evaluation of Precompression Blend

a) Angle of repose

It has the flow property of the solid materials. A tube was kept at a pek of approximately 2-4 cm over the platform. The dust was gently moved along with the wall of funnel, till hip is formed. It is decided by checking the hip of the cone powder by measure the culmination of the cone of the powder. **[[United States Pharmacopoeia .2002]**

$$\tan \theta = \frac{h}{r}$$

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

θ = angle of repose, h = height, r = radius.

- If repose is 25-30 the flow property is excellent.
- If repose is 31-35 the flow property is good
- If repose is 36-40 the flow property is fair
- If repose is 41-45 the flow property is passable
- If repose is 46-55 the flow property is poor
- If repose is 56-65 the flow property is very poor
- If repose is 66 the flow property is very very poor

b) Bulk density:

Bulk density of lipid lowering medicine was determined by pouring gently 30gm of sample (Atorvastatin) through a glass funnel into fifty milliliter graduated cylinder. The space is filled up with the samples was studied. **[United States Pharmacopoeia .2002]**

c) Tapped density:-

Tapped density was determined by victimization Electron lab density tester, that consists of a graduate mounted on a mechanical tapping device. Sample is added in the measuring barrel along with the funnel The initial original volume was noted, sample is also tapped for the reading (500, 650 or 1250 tapping) the percentage difference should not be more than 2%.

.Content was noted and the density was determined by applying the consecutive method.**[United States Pharmacopoeia .2002]**tapped volume

c) Compressibility Index (Carr's Index)

Compressibility Index and Hauser's ratio:-

In the recent year, the compressibility index is closely associate with the Haussler‟s ratio has become the best, quick and also the common technique of the predicting the powder flow characteristics. Each index of the Hauser‟s ratio was resolved by the bulk density and the tapped frequency of a particle. **[[United States Pharmacopoeia .2002]**

- Less than 10 percentages the flow of the fabric is excellent.
- If index percentage is 11-15 the flow of fabric is good.
- If index percentage is 16-20 the flow of fabric is fair.
- If index percentage is 21-25 the flow of fabric is passable.
- If index percentage is 26-31 the flow of fabric is poor.

Evaluation of Matrix Tablets

i) Thickness

Control of physical measurement of the tablets for example, size and thickness fundamental for purchaser acknowledgment and tablet-tablet consistency. The measurement size and punch size of tablets relies upon the pass on and punches chose for making the tablets. The thickness of tablet is estimated by Venire Calipers scale. With the tablet hardness and can be utilized an underlying control the thickness of the tablet identified parameter. The width of the pill should be controlled with in a range of ±5%. Furthermore thickness must be controlled to encourage bundling.

ii) Hardness

This is the force which is needed to shatter the tablet in polar pressure. Hardness of the tablet is dictated by Stock‟s Monsanto hardness analyzer which comprises of a barrel with a compressible spring. The arrow goes along with the gauze in the barrel crack. The pill firmness of five kg is considered as contemplate for handing the tablet.

iii) Friability Test

Rocher Friabilator is a machine which can tests a friable of the tablet. This is expressed in the percentage. Check the existing mass of tablets. They are placed in a plastic chamber that which is revolves at the twenty-five revolution per minute and fall from a elevation of six finger breadth in a instrument for about the 100 revolutions and take the tablets and then measure for the final weight and observe any difference in the weight of the tablet
Limits: If the tablet product is decreased in the mass not so great too 0.5 to 1% of the initial weight of the tablet should be considered as acceptable limits.
Rate of durability can check as

F= {(INITIAL WEIGHT- FINAL WEIGHT/ INITIAL WEIGHT)} x100

iv) Weight distinction of Tablets:

It is advisable that all the tablets of a

specific batch should be uniform in weight. If anyweight distinction is there, that should be within in limits.

Normal weight of tablet(mg)	Maximum % distinction permitted
80 or less than	10
80-250	7.5
Additional than 250	5

Table no .6. Acknowledgment basis for tablet mass distinction (IP)

Normal weight of tablet(mg)	Maximum % difference permitted
130 or small than	10
130-324	7.5
Additional than 324	5

Table - Acknowledgment basis for tablet mass distinction (USP)

Twenty tablets were taken arbitrarily and weighed precisely. The mean weight was evaluate by,Normal = weight of 20 tablets
20

v) Drug Content (Assay)

The drug content of the matrix medication determined in the standards and it meets the necessities if quantity of the active ingredient in each of the 3 tested medication lies inside the range of 90% to 110% of the quantity amount.

Three medications were weighed and brought into a mortar and crushed into fine powder.An accurately weighed portion of the powder like average weight of three medication of Repaglinide was taken to a 100 ml volumetric flask which contains 6.8 pH Phosphate buffer solutions and which the volume was created up to the mark. From this 10ml was taken and shaken by mechanical means using centrifuge at 3000rpm for 30min. Then it is absolutely filtered throughwhatman filter paper. From this resulted solution 1 ml was taken, diluted to 10 ml with 6.8 pH Phosphate buffer solution and absorbance was measured against blank at 237 nm.

In -vitro Drug Ransom Characteristics

Drug deliver was assessed by dissolution test under the following conditions: n = 3, USP type II dissolution equipment (paddle method) at 50 rpm in 900 ml of and the phosphate buffer pH 6.8 up to 24 hours and temperature was maintained at 37°C ± 0.5°C. An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of prewarmed (37°C ± 0.5°C) fresh dissolution medium. And medication content in each sample was analyzed by UV- visible spectrophotometer at 237 nm.

Mechanism of drug ransom

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

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

where M_t / $M\infty$ is fraction of medication 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 deliver mechanisms.

A plot of log cumulative % drug ransom vs. log time was made. Slope of the line was n. The n value is used to characterize different release mechanisms as given in Table11, 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).

Similarity Factor (f_2) Analysis

In vitro deliver profiles of the selected batches (F12 and F21) of sustained ransom medication were compared with the theoretical ransom profile which was calculated earlier. The data were analyzed by the following formula ((Bolton and Bon., 2004).

$$f_2 = 50 \log \{[1+ (1/N) \sum (R_i - T_i)^2]^{-0.5} \times 100\}$$

If f_2 is greater than 50 it is considered that 2 products share similar medication ransom behaviors.

Mean Dissolution Time

The other dissolution parameter used for comparing the formulations was mean dissolution time (MDT).This is calculated from the amount of medication deliver to the total cumulative medication . MDT is a measure of the speed of the dissolution method : the higherthe MDT,the slower the deliver speed. The following equation was used to calculate the MDT from the mean dissolution data

$$MDT = \frac{i=1\ t_{mid}}{\sum^{i=n} \Delta M}$$

Where i is the dissolution sample number, n is thenumber of dissolution sample time, t_{mid} is the time atthe midpoint between i and i-1 and ΔM is the additional amount of drug dissolved between i and i-1. (Gohel et al 2002).

viii) Swelling and Erosion Studies

Swelling and eroding behavior was determined by a method similar to that reported by Avachat and Vikram (Avachat and Vikram, 2007).The dissolution jars were marked with the time points of 0- 12 hours. One medication was kept in each dissolution jar containing 900 ml of phosphate buffer pH 6.8 at 37 °C ± 0.5 °C, and the apparatus was run at 50 rpm using paddle. The pills were taken out after completion of the respected stipulated time span as mentioned above and weighed after the excess of water at the surface had been removed with filter paper. The wetted samples were then dried in an oven at 40 °C up to constant weight. The increase of the weight onthe pills reflects the weight of the liquid uptake. It was estimated according to following equation

$$Q = 100(W_w - W_i) / W_i$$

Q is the percentage swelling, and Ww and Wi are the masses of the hydrated samples before drying and the initial starting dry weight, respectively (Lopes et al., 2006).

Fourier Transform Infrared Spectroscopy

(FTIR) Studies

FTIR studies were performed on pills and the optimized preparation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wavenumbers 4000 and 400 cm^{-1}.

5.RESULT & DISCUSSION

PRE-FORMULATION STUDIES

Characterization of active pharmaceutical ingredient:

In pre formulation studies, characterization of API (appearance, identification check by FTIR, assay) was performed and it had been found that everywhere within the rangelied down in the collection of the material.

Calibration Curve of medication:

Graph of medication was victimization using 6.8 pH scale phosphate buffer. Numerous concentrations 2 to 10 µg/mL was prepared. The absorbance of ready concentrations was measured at 237(0.1N HCl) nm by adjusting to zero with blank sample. A graph was premeditated by taking concentration on coordinate axis and absorbance on y-axis and best fit line was drawn and regression value and equation was calculated represented.

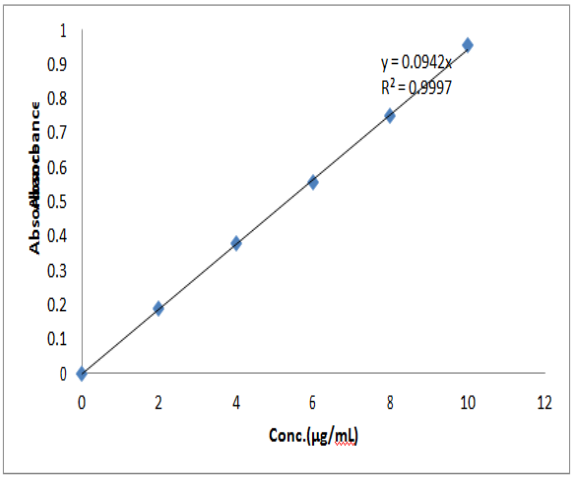


Fig no 3: Calibration Curve of Repaglinide

Calibration Curve of medication in 6.8pH:

Standard graph of Repaglinide was constructed using 6.8 pH phosphate buffer. Numerous concentrations 2 to 10 µg/mL were prepared. The absorbance of ready concentrations was measured at 237(6.8 pH) nm by adjusting to zero with blank sample. A graph was premeditated by taking concentration on coordinate axis and absorbance on y-axis and best fit line was drawn and regression value and equation was calculated represented.

Precompression parameters

Before preparation of floating medication of drug, the powder mass is evaluated for flow properties. The results of flow properties is shown in below Tables. All the prepared formulations showed good flow properties.

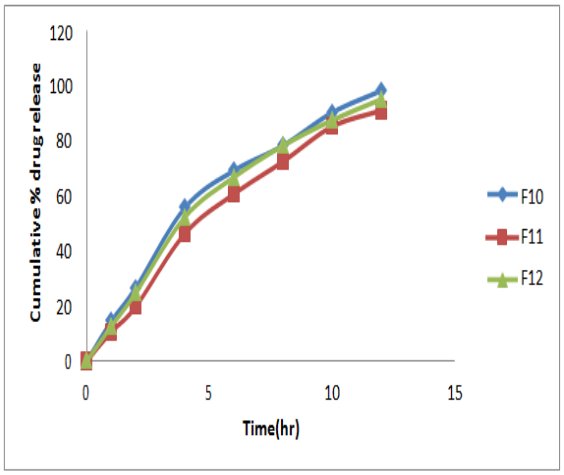


Fig no 4: In vitro release profile of medication with various polymers containing ratio 1:4

KINETIC ANALYSIS OF DISSOLUTION DATA:

To analyses the medication deliver mechanism the in-vitro ransom data was fitted into various ransom equations and kinetic models zero order, first order, and

Higuchi and Korsmeyer Peppas model. The deliver kinetics of Optimized formulation is shown in table.

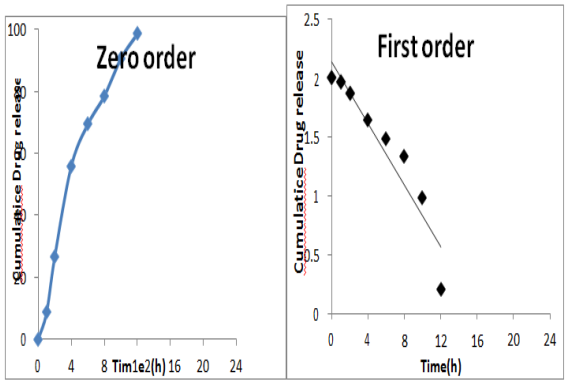


Fig no 5: Mathematical models (Kinetics)

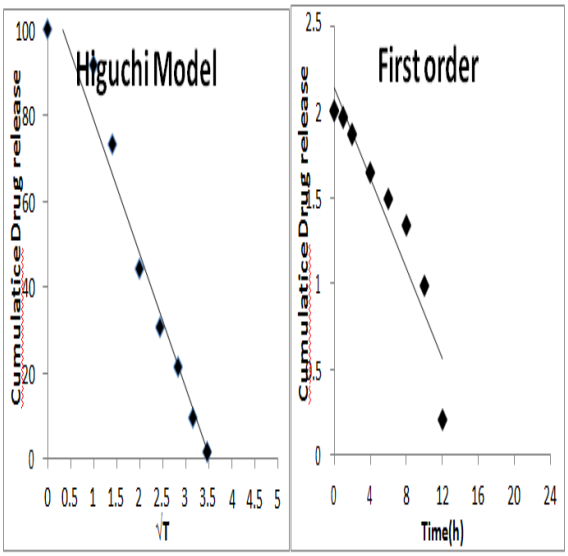


Fig no 6. Mathematical models (Kinetics)

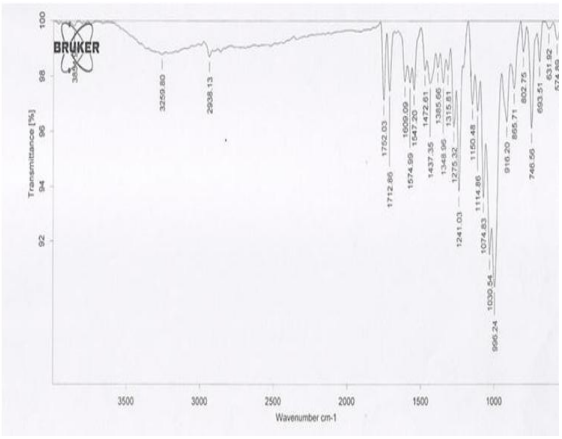


Fig no 7: FTIR Spectra for Repaglinide.

Summary & conclusion

The present investigation was under taken to formulate and Sustained deliver medication of Repaglinide.

Sustain deliver pills:

Using various compounds like HPMC K100, Xanthum gum and Locust bean gum pills were prepared along with other additives. Wet granulation process was used for the preparation of pills. A total 12 preparations were prepared and tested.

To retain pills for long period, most of the excipients selected must be water soluble by nature. This excipient was used a bulking agent to achieve the desired pills weight. Talc was employed as a lubricant and magnesium stearate used as Glidant.

Pre compressional studies:

The results obtained by evaluating the powders blends of medication and excipients are shown in pills Bulk density and tapped density were found in the range 0.52-0.56 g/cc and 0.62-0.69 g/cc respectively. The value of Hauser"s ratio was in between 1.16-1.25 (< 1.3) indicating that all batches of powder blends were having good compressibility. Values of angle of repose(θ) was found in the range of 19.65-25.8 showing that blend of powder mass was Good flowing. **Weight variation and Thickness:**

The average weight in all the nine formulations was found to be 96.7mg to 101.3 mg. In all 15 preparations numbers of pills were outside the ±10%of pills weight in weight variation test. The thickness varies between 2.4 to 2.72mm. In all preparation pills thickness of all formulations was within ±5% of standard

value. Fragile values were less than 1% in all cases. Hardness of all the pills was maintained at 5 to 6 kg/cm^2 for all the formulations. Assay was done and percent pills content of all the pills were seen to be between 96.5 % and 100.38% of Repaglinide, which was within the acceptable limits

***In vitro* dissolution:**

In vitro cassation studies are checked for Sustained pills of Repaglinide mixture of solvent 0.1N HCl using USP dissolution equipment type 2. The cassation speed was found to increase linearly with increasing concentration of chemicals compounds. The optimized preparation is HPMC K15M with HPMC 100 combination containing pills (F10).Formulation have recorded drug 98.6 respectively in 12 hrs.

Drug delivers Kinetics:

In vitro drug deliver data of all the Sustained formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi‟s and Korsmeyer–Peppas models to ascertain the mechanism of pills deliver r. The results of linearregression analysis including regression coefficients are summarized in table and plots shown in figures-6 to 25. From the above data, it can be seen that all the preparation have displayed first order release kinetics („r‟ values in the range of 0.900 to 0.965). From Higuchi and Pappas data, it is evident that the medication is released by non-fickian diffusion mechanism (n<0.5). From the kinetic data of factorial formulations (table-29), it is evident that F10 formulation has shown medication deliver by zero order kinetics. The values of „r‟ for Higuchi‟s equation of formulation F60.965 „n‟ values of Peppas equation 0.94. This data reveals that drug release follows non- Fickian diffusion mechanism Higuchi model

CONCLUSION

Success of the In vitro medication deliver studies recommends the product for further in vivo studies, which may improve patient compliance. From the results, formulationF6 containing Repaglinide 200mg, HPMC K100 100mg and Xanthum gum100mg evolved as the optimized formulation and it deliver more than 98% medication in 12hrs.

IR spectroscopic studies indicated that there is no medication -excipient interaction in the optimized formulation. The optimized formulation F10 can be considered as a promising Sustained Medication delivery system of Repaglinide providing nearly zero order drug release over a periodof 12 hrs.

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