(J I D P T S)
ISSN(O):2581-6934

FORMULATION AND EVALUATION OF EXTENDED RELEASE REPAGLINIDE TABLETS

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ABSTRACT: The aim of present investigation was to formulate and evaluate the sustained release matrix tablets of Repaglinide (RPGN). These matrix tablets were prepared by wet granulation method using synthetic and natural polymers like HPMC K4M, HPMC 100M and Guar gum (GG), Carrageen an (CG), respectively. Invitro drug release studies were performed by USP dissolution apparatus type-II (paddle method) using 0.1 N HCl buffer and pH 6.8 phosphate buffer for 12 h. amongst all the 12 formulations, formulation F12 showed maximum drug release of 97.9% for 12 h study. It was observed from the kinetic studies that all the formulations followed first order kinetics and particularly the drug release from its dosage form was fickian diffusion (F9, F12), non-fickian diffusion (F1-F8, F10-F11). Formulation F12 was subjected to stability studies and confirmed that formulation F12 was stable up to the period of 1 month.

KEYWORDS: Repaglinide, Natural polymers, Formulation, Evaluation.

INTRODUCTION:

Repaglinide is an oral ant hyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It belongs to the meglitinide class of short-acting insulin secretagogues, which act by binding to β cells of the pancreas to stimulate insulin release. Repaglinide induces an early insulin response to meals decreasing postprandial blood glucose levels. It should only be taken with meals and meal-time doses should be skipped with any skipped meal. Approximately one month of therapy is required before a decrease in fasting blood glucose is seen. Meglitnides may have a neutral effect on weight or cause a slight increase in weight. The average weight gain caused by meglitinides appears to be lower than that caused by sulfonylureas and insulin and appears to occur only in those naïve to oral anti diabetic agents. Due to their mechanism of action, meglitinides may cause hypoglycemia although the risk is thought to be lower than that of sulfonylureas since their action is dependent on the presence of glucose. In addition to reducing postprandial and fasting blood glucose, meglitnides have been shown to decrease glycosylated hemoglobin (HbA1c) levels, which are reflective of the last 8-10 weeks of glucose control. Meglitinides appear to be more effective at lowering postprandial blood glucose than metformin, sulfonylureas and thiazolidinediones. Repaglinide is extensively metabolized in the liver and excreted in bile.

Methodology:

Construction of Standard Graph of Repaglinide

Accurately weighed amount of 100 mg of Repaglinidewas transferred into a 100 ml volumetric flask. Methanol was added to dissolve the drug and the primary stock solution was made by adding 100 ml of methanol. This gives a solution having concentration of 1 mg/ml of Repaglinidestock solution. From this 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 separately and made up to 10 ml with 0.1N HCl and 6.8 pH phosphate buffer separately. The absorbance was measured at 237 nm using a UV spectrophotometer (Systronic, Hyderabad, India).

Preparation of 0.1N HCl

A 8.65 ml of Conc. HCl was placed in a 1000 ml volumetric flask and the volume was made up with water and pH was adjusted to 1.2.

Preparation of Standard Solution Repaglinide

Accurately weighed 100mg of Repaglinide was placed in a 100mL volumetric flask and 50mL of 0.1 N HCl was added to dissolve the drug. The volume was made up to 100mL HCl to give 1000 µg/mL of solution (stock solution -I).

A 10mL aliquot from stock solution -I was taken and diluted to 100mL with in a 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 obtain concentrations from 2 to 10µg/mL with 0.1 N HCl. The absorbances of solutions were determined at 237nm against respective media solutions as blank and a standard curve was plotted.

Preparation of pH 6.8 phosphate buffer: Accurately measured 50 ml of 0.2 M potassium dihydrogen orthophosphate was transferred 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 27.218 g of monobasic potassium dihydrogen phosphate was dissolved in 1000 ml of distilled water and mixed.

Preparation of 0.2M 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 prepared by direct compression method and also to study the effect of various ratios of different types of polymers on the drug release.

Formulations

In formulations prepared, the release retardants included were Hydroxypropylmethylcellulose (HPMCK100M), xanthum gum and locust bean gum. Drug polymer ratios were 1:1, 1:2 and combination for all batches. Microcrystalline cellulose (MCC) was used as diluents. Magnesium stearate (MS) 1% and talc 2% were used as lubricants. Compositions of different formulations were given in the following Tables.

Table 1: Composition of Matrix Tablets

Ingredient	Formulation Code											
	F1	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	1	1	1	1	1	1	1	1	1	1	1	1
Total	500	500	500	500	500	500	500	500	500	500	500	500

RESULTS:

PRE-FORMULATION STUDIES

Characterization of active pharmaceutical ingredient:

In preformulation studies, characterization of API (appearance, identification test by FTIR, assay) was performed and it was found that all are within the range specified in the pharmacopoeia.

Description	Specifications	Observations
Appearance	White Crystalline powder	White
Identification	FTIR	Complies
Assay	Not less than 90.0% w/w and not more than 110.0% w/w of Repaglinide	99.98%w/w

Table 2: Physical and chemical characteristics

Calibration Curve of Repaglinide:

Standard graph of Repaglinide was constructed using 6.8 pH phosphate buffer. Various concentrations 2 to 10 µg/mL were prepared. The absorbance of prepared concentrations was measured at 237(0.1N HCl) nm by adjusting to zero with blank sample. A graph was plotted by taking concentration on x-axis and absorbance on y-axis and best fit line was drawn and regression value and equation was calculated represented.

Concentration(µg/mL)	Absorbance
0	0
1	0.133
2	0.242
4	0.452
6	0.683
8	0.923

Table 3: Results of calibration curve

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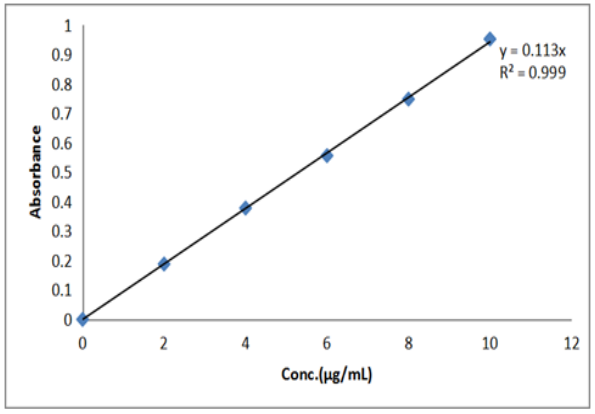

Fig. 1: Calibration Curve of Repaglinide in 6.8pH:

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

Pre compression parameters

Before preparation of floting tablets of Repaglinide, 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.

Formulation Code	Bulk Density	Tapped Density	Carr's Index	Hausner Ratio	Angle of Repose
F1	0.51	0.68	1.13	0.17	21.52
F2	0.50	0.61	1.21	0.18	21.42
F3	0.52	0.66	1.19	0.17	20.84
F4	0.56	0.67	1.17	0.17	22.08
F5	0.57	0.62	1.14	0.19	21.84
F6	0.53	0.66	1.19	0.15	22.63
F7	0.55	0.68	1.14	0.18	23.51
F8	0.54	0.61	1.19	0.19	20.86
F9	0.51	0.63	1.12	0.19	23.97
F10	0.53	0.67	1.19	0.14	21.83
F11	0.54	0.66	1.12	0.16	22.37
F12	0.54	0.67	1.17	0.17	23.81

Table 4: Results of precompression parameters

Post compression parameters:

The results of the weight variation, hardness, thickness, friability, and drug content of the Tablets are given in table

Table 5: Results of post compression parameters

Formulation Code	Thickness (mm)	Weight Variation(mg)	Friability (%)	Hardness	%Drug content
F1	2.36	499.81	0.24	5.17	98.67
F2	2.72	498.97	0.29	5.51	99.16
F3	2.37	499.52	0.33	5.72	99.82
F4	2.44	499.07	0.27	5.32	99.54
F5	2.61	500.15	0.29	5.21	100.08
F6	2.52	498.77	0.24	5.27	98.13
F7	2.58	499.31	0.24	5.44	99.49
F8	2.53	499.74	0.25	5.32	99.51
F9	2.47	499.22	0.26	5.75	98.16
F10	2.35	500.17	0.28	5.32	101.37
F11	2.38	499.63	0.22	5.21	97.54
F12	2.67	498.96	0.27	5.33	100.37

Discussion:

The present investigation was under taken to formulate and Sustained release tablets of Repaglinide.

Sustain release Tablets:

Using various polymers like HPMC K100, Xanthum gum and Locust bean gum tablets were prepared along with other additives. Wet granulation method was used for the preparation of tablets. A total number of 12 formulations were prepared and evaluated.

To retain tablet 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 tablet weight. Talc was employed as a lubricant and megnisium stearate used as glidant.

Pre compressional studies:

The results obtained by evaluating the powder blends of drug and excipients, Bulk density and tapped density were found in the range 0.50-0.57 g/cc and 0.61-0.68 g/cc respectively. The value of hausner's ratio was in between 1.12-1.19 (< 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 20.86-23.97 showing that blend of powder mass was Good flowing.

Weight variation and Thickness:

The average weight in all the 12 formulations was found to be 498.77mg to 500.17 mg. In all 12 formulations no tablets were outside the ±10%of tablet weight in weight variation test. The thickness varies between 2.35 to 2.72mm. In all formulations

ISSN:-2581-6934 |Available at :www.jidps.com | pp :(4-8)

tablet thickness of all formulations was within ±5% of standard value. Friability values were less than 1% in all cases. Hardness of all the tablets was maintained at 5.17 to 5.44 kg/cm2 for all the formulations. Assay was performed and percent drug content of all the tablets were found to be between 98.16 % and 101.37% of Repaglinide, which was within the acceptable limits

In vitro dissolution:

In vitro dissolution studies are performed for Sustained tablets of Repaglinide mixture of solvent 0.1N HCl using USP dissolution apparatus type 2. The dissolution rate was found to increase linearly with increasing concentration of polymer. The optimized formulations are HPMC K15M with HPMC 100 combination containing tablets (F10).Formulation have recorded drug 98.78 respectively in 12 hrs.

Drug Release Kinetics:

In vitro drug release 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 drug release. The results of linear regression analysis including regression coefficients are summarized and plots. From the above data, it can be seen that all the formulations have displayed first order release kinetics ('r' values in the range of 0.937 to 0.967). From Higuchi and Peppas data, it is evident that the drug is released by non-fickian diffusion mechanism (n<0.5). From the kinetic data of factorial formulations, it is evident that F10 formulation has shown drug release by zero order kinetics. The values of 'r' for Higuchi's equation of formulation F6 0.950 'n' values of Peppas equation 0.949. This data reveals that drug release follows non-Fickian diffusion mechanism Higuchi model

CONCLUSION:

Success of the Invitro drug release studies recommends the product for further in vivo studies, which may improve patient compliance. From the results, formulation F10 containing Repaglinide 200mg, HPMC K100 100mg and Xanthum gum100mg evolved as the optimized formulation and it releases more than 98.78% drug in 12hrs. IR spectroscopic studies indicated that there is no drug-excipient interaction in the optimized formulation. The optimized formulation F10 can be considered as a promising Extended drug delivery system of Repaglinide providing nearly zero order drug release over a period of 12 hrs.

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