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FORMULATION DEVELOPMENT AND IN-VITRO EVELUATION OF SUSTAINED RELEASE TABLETS OF REPAGLINIDE

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ABSTACT

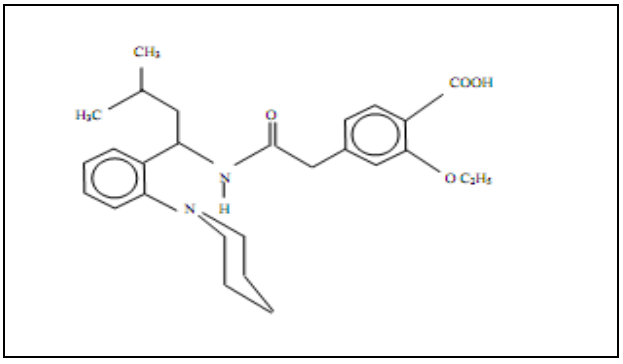
Repaglinide is an oral antihyperglycemic agent used for the treatment of non-insulin dependent diabetes mellitus (NIDDM). Repaglinide is an amino acid derivative that induces an early insulin response to meals decreasing postprandial blood glucose levels. The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility. Solid dispersions is the techniques and the most attractive processes to improve solubility of poorly soluble drugs. Here the solubility of Repaglinide is enhanced by solid dispersions with PEG 6000 and urea as carriers. Among the various solid dispersions prepared, the formulation FSDPN3 i.e., the solid dispersion of Repaglinide with PEG6000 prepared by Fusion method shows faster dissolution rate it was decided to use formulations FSDPN3 to formulate sustained release tablets using different polymers like HPMC, EC ,Guar gum and Xanthum gum by direct compression technique. Among the various sustained release tablets of Repaglinide solid dispersion prepared, the formulation F2 shows complete release of drug in 12 hrs, which is considered as best formulation for sustained release tablets of Repaglinide.

KEYWORDS: Antihyperglycemic, postprandial, xanthum gum, direct compression technique.

INTRODUCTION

Repaglinide (Prandin) is an oral insulin secretagogue of the meglitinide class. This agent is a derivative of benzoic acid & chemically it is: (S)-2-ethoxy-4-{2-[3-methyl-1- [2-(1-piperidinyl) phenyl] butyl] amino]-2-oxoethyl} benzoic acid.

Structure:



MATERIALS

Repaglinide was obtained from Chandra Labs, Hyderabad, India. Polyethylene glycol 6000 from S.D. Fine Chem. Ltd, Mumbai, India. Urea from S.D. Fine Chem. Ltd, Mumbai, India. Micro Crystalline Cellulose from S.D. Fine Chem. Ltd, Mumbai, India. Xanthum gum from S.D. Fine Chem. Ltd, Mumbai, India. Guar gum from S.D. Fine Chem. Ltd, Mumbai, India. Magnesium stearate from S.D. Fine Chem. Ltd, Mumbai, India. Talc from S.D. Fine Chem. Ltd, Mumbai, India. Ethyl cellulose from S.D. Fine Chem. Ltd, Mumbai, India. HPMC from S.D. Fine Chem. Ltd, Mumbai, India

Preparation of calibration curve for repaglinide:

A. Standard curve in 0.1N HCL by using U.V spectrophotometer

Stock Sample Preparation: Accurately weighed 100 mg of drug was first dissolved in100 mL of 0.1N HCl in 100 mL of volumetric flask to make a concentration of 1000 µg/mL (primary stock solution). 5 mL of primary stock solution was pipetted out into 50 mL of volumetric flask and volume was adjusted with 0.1N HCL to make a concentration of 100µg/mL (secondary stock solution).

Sample Preparation: From the secondary stock solution pipette out 0.2, 0.4, 0.6, 0.8, 1.0 ml in to 10ml of volumetric flask and volume made up to with 0.1N HCl to give various concentrations such as 2,4,6,8,10 µg/mL were prepared for calibration curve. Standard curve was plotted by taking absorbance of secondary stock solutions in UV double beam spectrophotometer at 292 nm.

B. Standard curve in 6.8pH phosphate buffer by using UV spectrophotometer

Stock Sample Preparation: Accurately weighed 100 mg of drug was first dissolved in100 mL of 6.8pH

phosphate buffer in 100 mL of volumetric flask to make a concentration of 1000 µg/mL (primary stock solution). 5 mL of primary stock solution was pipetted out into 50 mL of volumetric flask and volume was adjusted with 6.8pH phosphate buffer to make a concentration of 100µg/mL (secondary stock solution).

Sample Preparation: From the secondary stock solution pippet out 0.2,0.4,0.6,0.8,1.0 ml in to 10ml of volumetric flask and volume made up to with 6.8pH phosphate buffer to give various concentrations such as 2,4,6,8,10 µg/mL were prepared for calibration curve. Standard curve was plotted by taking absorbance of secondary stock solutions in UV double beam spectrophotometer at 292 nm.

METHOD

Solid dispersion of repaglinide with urea polyethylene glycol 6000 (peg 6000)

Methods of Preparation of Solid Dispersion: Solid dispersions were prepared by different methods like Solvent evaporation method and Fusion method.

1. Solvent evaporation method: Repaglinide and each of water soluble carrier PEG 6000, Urea were weighed accurately in various ratios (1:1, 1:2 and 1:3) and transferred to beaker containing sufficient quantity of acetone to dissolve. The solvent was evaporated at room temperature. The resulting solid dispersion was stored for 24 hrs in a desiccator to congeal. Finally, dispersion were passed through sieve no.85 and stored in desiccator till further use.

2.Fusion Method: Each of water soluble carrier PEG 6000, Urea were weighed accurately in various ratios (1:1, 1:2 and 1:3) and melted in a porcelain dish at 80-85ºC and to this calculated amount of Repaglinide was added with thorough mixing for 1-2 minutes followed by quick cooling. The dried mass was then pulverized by passing through sieve no.85 and stored in a dessicator until used for further studies. Solid dispersions were prepared using compositions as given in Table no.1

Table no.1: Composition of Repaglinide solid dispersions by Fusion method.

Solid dispersion composition	Method	Drug-Polymer ratio	Formulation Code
Repaglinide: Urea	**Fusion method**	1:1	**FSDUN1**
		1:2	**FSDUN2**
		1:3	**FSDUN3**
Repaglinide: PEG 6000	**Fusion method**	1:1	**FSDPN1**
		1:2	**FSDPN2**
		1:3	**FSDPN3**

Table no.2: Composition of Repaglinide solid dispersions by Solvent evaporation method

Solid dispersion composition	Method	Drug-Polymer ratio	Formulation Code
Repaglinide: Urea	**Solvent evaporation method**	1:1	**SSDUN1**
		1:2	**SSDUN2**
		1:3	**SSDUN3**
Repaglinide: PEG 6000	**Solvent evaporation method**	1:1	**SSDPN1**
		1:2	**SSDPN2**
		1:3	**SSDPN3**

Characterization of Repaglinide Solid Dispersions

1. Drug content: An accurately weighed quantity of solid dispersion equivalent to 8mg of Repaglinide was taken into a 100ml volumetric flask, dissolved in acetone and suitably diluted with 6.8 pH phosphate buffer. The content of Repaglinide was determined spectrophotometrically at 292 nm against suitable blank using UV-visible spectrophotometer (1601, Shimadzu, Kyoto, Japan).

***2. In vitro* dissolution studies**: The quantity of solid dispersion equivalent to 8mg of Repaglinide was filled in colourless hard gelatin capsule by hand filling method. The dissolution study of capsules was conducted using dissolution testing USP apparatus 1 (basket method) in 900 ml of 6.8 pH phosphate buffer at 37±0.5ºC and at a speed of 50 rpm. Aliquot of 5ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume after each sampling and analyzed spectrophotometrically at 292 nm against suitable blank using UV-visible spectrophotometer (1601, Shimadzu, Kyoto, Japan).

Preparation of sustained release tablets repaglinide solid dispersion by direct compression method: Solid dispersion of Repaglinide: PEG6000 (1:3 ratio) equivalent to 2mg of drug prepared by Fusion method were taken and mixed with directly compressible polymer, filler and lubricant and glidant in a plastic container. Powder blend were directly compressed using 9mm, round-shaped flat punch in a rotary tablet compression machine (Cadmach, Ahmedabad, India).

Table.3: Formulation Table.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Repaglinide SD	8	8	8	8	8	8	8	8
HPMC K4M	40	60	-	-	-	-	-	-
EC	-	-	40	60	-	-	-	-
Guargum	-	-	-	-	40	60	-	-
Xanthum Gum	-	-	-	-	-	-	40	60
Magnesium stearate	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10
MCC	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight	200	200	200	200	200	200	200	200

The formulations were formulated with optimized solid dispersions of PEG 6000. FSDPN3 Repaglinide solid dispersions was taken instead of Repaglinide.

Evaluation Parameters For Sustained Release Tablets Of Solid Dispersion Of Repaglinide

Precompression parameters: The powder blend was evaluated for following parameters: Bulk Density, Tapped density, Compressibility Index, Hausners ratio, Angle of repose, Drug Excipient compatibility studies

Post compression parameters[8-12]

Weight variation test: Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Thickness and diameter: The thickness and diameter of 10 tablets were recorded during the process of compression using vernier calipers..

Friability: A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

% Friability = $(W_1-W_2) / W_1 X 100$

W_1 = Weight of tablets before test
W_2 = Weight of tablets after test

***In vitro* dissolution studies**: *In-vitro* dissolution study was performed by using USP dissolution testing apparatus 2 (Paddle method). Weighed tablets from different batches were kept in a flask of the dissolution apparatus containing 900 ml of 0.1 N HCL for first 2 hrs then replaced with 6.8pH phosphate buffer dissolution medium maintained at 37 ± 0.5ºC and at a speed of 50 rpm. Aliquot of dissolution medium (5 ml) was withdrawn at specific time intervals and the samples were replaced with fresh dissolution medium. Aliquot were analyzed spectrophotometrically at 292 nm against Suitable blank using UV-visible spectrophotometer (1601, Shimadzu, Kyoto, Japan).

Dissolution parameters for SR Tablets: Apparatus -- USP-II, Paddle Method
RPM – 50 Sampling intervals (hrs) -- 1, 2, 3, 4, 5, 6, 8, 10, 12hrs.
Temperature -- 37 $\pm$ 0.5°C

RESULTS AND DISCUSSION

Table no. 4: Standard Repaglinide curve values.

S.no	Concentration	Absorbance
1	0	0
2	2	0.063
3	4	0.123
4	6	0.218
5	8	0.332
6	10	0.418

Repaglinide Standard curve in 0.1N HCL buffer

Table no.5: standard Repaglinide curve values.

S.no	Concentration	Absorbance
1	0	0
2	2	0.065
3	4	0.152
4	6	0.243
5	8	0.33
6	10	0.44

Repaglinide standard curve in 6.8pH phosphate buffer

Invitro dissolution results for solid dispersions:

Table no.6: drug release in solid dispersion by fusion method.

TIME (mins)	FSDUN1	FSDUN2	FSDUN3	FSDPN1	FSDPN2	FSDPN3
5	49.1	53.2	68.1	45.2	52.1	65.2
10	52.5	58.5	77.5	59.5	65.5	77.4
15	66.6	69.9	84.9	75.4	78.9	85.7
20	75.4	79.8	86.7	97.9	98.8	100.4

Table no7: drug release in solid dispersion by solvent evaporation method.

TIME (mins)	SSDUN1	SSDUN2	SSDUN3	SSDMN1	SSDMN2	SSDMN3	Pure drug
5	45.5	49.4	64.1	32.2	37.6	42.1	12.5
10	59.9	54.5	78.2	49.5	54.5	67.5	22.9
15	65.7	67.8	82.5	67.1	70.9	74.8	28.6
20	78.4	83.9	87.6	84.4	86.4	90.4	36.9

Analysing the release profile it was found **FSDPN3** formulation with API and PEG6000 with ratio 1:3 has shown maximum release compared with others.

Drug content results for solid dispersions

Table no.8: Percentage of drug content in Repaglinide solid dispersions.

FSDUN1	FSDUN2	FSDUN3	FSDPN1	FSDPN2	FSDPN3
97.5	97.6	98.4	98.3	98.4	98.2

The drug content in the solid dispersions was almost same and the assay was in the range and the assay did not drop in the solid dispersion the value was above 97% for all formulations.

Table no.9: Percentage of drug content in Repaglinide solid dispersions.

SSDUN1	SSDUN2	SSDUN3	SSDMN1	SSDMN2	SSDMN3
87.6	89.6	89.0	91.6	93.8	94.2

Pre-compression parameters for tablets: The flow properties of the formulations were found to be in limit and the optimized formula was in limit and has a fair flowing property. This had no effect during compression of tablet.

EVALUATION OF TABLETS

Table no: 10 In-vitro dissolution profiles for tablets.

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
0.5	15.3	9.0	18.6	16.1	14.1	19.1	21.8	21.1
1	28.3	18.4	25.2	15.2	29.2	24.3	38.1	37.9
2	37.3	29.7	41.2	22.0	38.0	35.9	59.2	46.0
3	46.9	36.9	66.4	30.8	49.8	43.9	77.2	62.3
4	58.4	44.1	72.0	39.0	60.0	56.2	90.2	71.1
5	70.9	50.3	84.3	46.4	72.6	67.0	98.2	87.0
6	82.0	62.3	90.4	51.0	85.0	74.2	-	99.1
8	94.8	74.0	97.1	60.2	98.3	78.9	-	
10	-	82.3	-	69.0	-	81.0	-	
12	-	96.0	-	78.6	-	92.2	-	

The results of release studies of formulations F1 to F8 are shown. The release of drug depends not only on the nature of polymer but also upon the drug polymer ratio. The formulation F2 was optimized because drug release was controlled up to 12hrs.

CONCLUSION

Optimized formulation F2 which includes HPMC has successfully sustained the drug release and the drug release pattern was similar to theoretical release profile. The release process involves anomalous diffusion mechanism or diffusion coupled with erosion. FTIR studies show that there is compatability between drug and excipients for the developed matrix tablets. The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility. Solid dispersions is the techniques are the most attractive processes to improve solubility of poorly soluble drugs. The concept of formulating sustained release tablets using different polymers offers a suitable and practical approach of sustained in release and dissolution characteristics. Repaglinide is an oral

antihyperglycemic 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 is an amino acid derivative that 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. Here the solubility of Repaglinide is enhanced by solid dispersions with PEG 6000 and urea as carrier. Then the formed solid dispersions is characterized and evaluated by drug content and *in vitro* dissolution studies. Among the various solid dispersions prepared, the formulation FSDPN3 i.e., the solid dispersion of Repaglinide with PEG6000 prepared by Fusion method shows faster dissolution rate it was decided to use formulations FSDPN3 to formulate sustained release tablets using different polymers like HPMC, EC ,Guar gum and Xanthum gum by direct compression technique. The prepared tablets of Repaglinide were evaluated for precompression parameters like angle of repose, bulk density, tapped density, Carr's index and postcompression parameters like the hardness, friability and weight variation and *in vitro* dissolution studies. Among the various sustained release tablets of Repaglinide solid dispersion prepared, the formulation F2 shows complete release of drug in 12 hrs, which is considered as best formulation for sustained release tablets of Repaglinide.

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