Formulation and evaluation of physical characteristics of matrix tablet of anti-diabetic drug Repaglinide

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ABSTRACT

The aim of this study was to formulate and develop a sustained-release tablet of repaglinide using natural occurring binders to enhance its therapeutic efficacy and improve patient compliance. The selected antidiabetic drug **repaglinide** was used for preformulation study. In preformulation study of antidiabetic **repaglinide** drug was studied by using Physical appearance, Melting point method, solubility, pH and Flow properties. The developed matrix tablets were evaluated with number of parameters.The results of evaluation parameters such as weight variation, hardness, friability, disintegration test for tablets, in vitro dissolution study indicated that prepared matrix tablets under the acceptable range. These results also confirmed that the Starch, Hydroxypropyl methyl cellulose, Sodium carboxymethyl cellulose, polyvinyl acetate was suitable for the development of matrix tablet but need to investigation for establishment of natural gum as pharmaceutical excipient.

Keywords:Repaglinide, Starch, Hydroxypropyl methyl cellulose, Sodium carboxymethyl cellulose, Polyvinyl acetate , Preformulation, Matrix tablet, sustained release.

DOI: 10.48047/ecb/2023.12.Si11.036

INTRODUCTION

Sustained release dosage forms are made to release a medicine at a set rate while keeping the drug level constant for a set amount of time with the fewest adverse effects possible. The fundamental idea behind sustained release drug delivery systems is to maximise a drug's biopharmaceutical, pharmacokinetic, and pharmacodynamic qualities in order to lessen its side effects, increase its effectiveness, and treat an illness. The most prominent technique among the numerous techniques used to create continuous release formulations is matrix systems. Since they make it simpler to produce a desired drug release profile, are affordable, and have broad FDA acceptance, hydrophilic polymeric matrix systems are frequently employed in controlled drug delivery.

Repaglinide is a non-sulfonylurea oral hypoglycaemic agent of the meglitinide class, is mainly used in the management of type II diabetes mellitus. Chemically it is (S)-2-ethoxy-4-{2-[3-methyl-1-[2-(1-piperidinyl) phenyl] butyl] amino]-2-oxoethyl} benzoic acid. It has short biological half-life of less than one hour and rapidly eliminated from body. Repaglinide is a BCS class II compound and the bioavailability of Repaglinide following oral administration is low (60%), BCS class II compounds are poorly soluble but highly permeable, and they exhibit bioavailability that is limited by dissolution rate. The dissolution rate of BCS class II drug substances may be accelerated by improvement of the wetting characteristics of the bulk powder. The poor solubility and slow dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability especially for class-II substances according to BCS. Repaglinide is well absorbed following oral administration and shows low oral bioavailability due to extensive first pass metabolism[4-6].

MATERIALS AND METHOD

Repaglinide, HPMC K100, Magnesium stearate, and Aerosil (200) were obtained as gift sample from Optimus drugs Pvt. Ltd. Hyderabad, Signet chemical corporation Pvt. Ltd., Mumbai, Diamond corporation, Mumbai, S. Kant healthcare Ltd., Mumbai and Evonic industries, Mumbai, respectively

Instruments used:

Tablet punching machine: Cadmatch (Accura), Friabilator (Electrolab, Roche type), Hardness tester (Electrilab, Pfizer type), Vernier calliper (Contech, Aerospace), HPLC (Shimadzu, LC 2010 HT), Dissolution Apparatus (Electrolab), FTIR (Shimadzu-IR Affinity-1)

Ultraviolet spectrum

The same solvent mixture was used to create 100 ml of the solution after the medication, 10 mg, was dissolved in 1 ml of 1M hydrochloric acid and 9 ml of methanol R. Then, 10 ml of this solution were collected and volume up to 100 ml with a combination of 1 ml of 1M hydrochloric acid and 9 ml of methanol R. This resulted in a solution concentration of 10 g/ml. A UV-Visible spectrophotometer (UV-1800, Shimadzu, Tokyo, Japan) was then used to scan the resultant solution between 300 and 350 nm. The UV spectra of the medication were obtained and contrasted with the maximum stated absorption (318 nm).

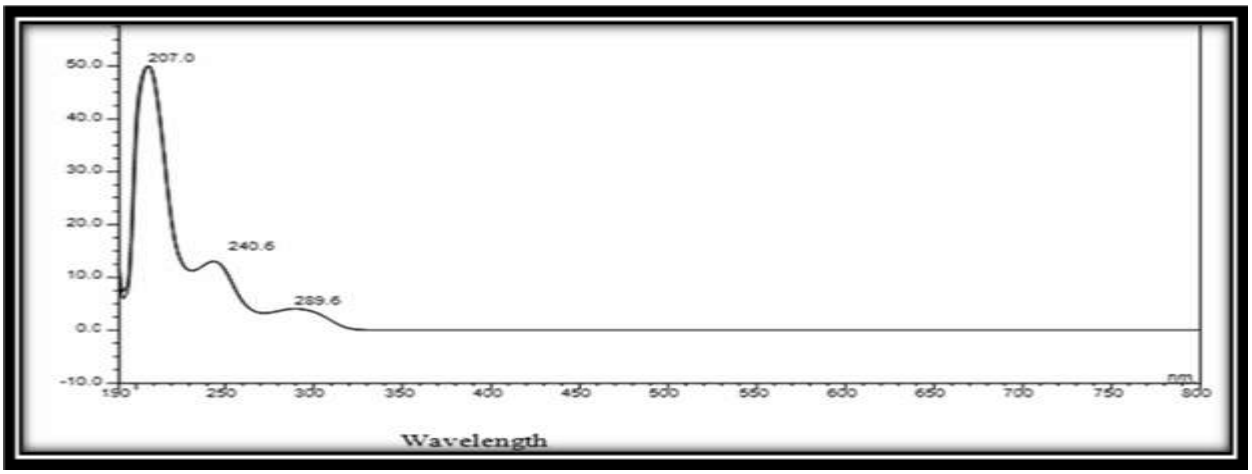


Figure 1: UV specturum of Repaglinide at 243nm in 7.4 pH phosphate buffer

IR Spectrum of Pure Drug:

The drug compatibility study was performed by using FTIR analysis. The FTIR instruments used Agilent technology. In Agilent technology drug and blends mixture was tested using direct placed technology no KBr method need to used.

Extraction of gum from fruit

Fruits were cleaned, sliced and were mashed in 2% v/v glacial acetic acid solution to form a slurry and gum was extracted in distilled water in 1000ml beaker with 1:1 ratio of water to raw material, 65 W ultrasonic power and 45 minutes extraction time at 65°C. After extraction, the slurry was filtered through muslin cloth to remove debris. Excess acetone was added for precipitating the gum. Finally, the precipitates were dried in vacuum oven at 50°C. The gum particles obtained and were collected and stored for further use.

MATRIX TABLETS PREPARATION

Wet granulation methodology was used for the preparation of the Repaglinide matrix tablets. The excipients used in the formulation are:

Procedure

The procedure for preparing matrix tablets can vary depending on the specific formulation and the active pharmaceutical ingredient (API) involved. However, here is a general outline of the steps involved in the preparation of matrix tablets:

1. **Weighing and Blending:** Weigh the required quantities of the API, excipients and other additives based on the desired formulation. Thoroughly blend these ingredients using a suitable blender or mixer to ensure uniform distribution.
2. **Granulation:** If the formulation requires granulation, add a granulating agent to the powder mixture and blend until it forms granules. This step helps improve the flow and compressibility of the powder.
3. **Lubrication:** Add a lubricant (magnesium stearate) to the powder mixture to prevent sticking to the tablet punches during compression. Blend the mixture again to ensure even distribution.
4. **Compression:** Transfer the blended or granulated mixture to a tablet compression machine. Adjust the machine settings to achieve the desired tablet size, shape, and hardness. The mixture is compressed under high pressure into tablets using suitable punches and dies.
5. **Drying (if necessary):** If the granulation process or any other step introduced moisture into the formulation, the tablets may require drying to remove excess moisture. This step helps ensure the stability and quality of the tablets.

6. **Quality Control:** Perform quality control tests on the prepared tablets, including tests for weight variation, hardness, thickness, friability, and disintegration time, among others. These tests ensure that the tablets meet the desired specifications and comply with regulatory standards.

Table No.1: Formulation table for matrix tablets

S.no	Ingredients	Batch-1	Batch-2	Batch-3	Batch-4
1.	Repaglinide	250	250	250	250
2.	Starch	20	20	15	25
3.	Hydroxypropyl methyl cellulose	105	115	105	110
4.	Sodium carboxymethyl cellulose	20	50	55	35
5.	Polyvinyl acetate	55	50	60	65
6.	Magnesium stearate	05	10	05	10
7.	Talc	05	05	10	05

EVALUATION OF MATRIX TABLETS

Matrix tablets were evaluated for uniformity of weight, hardness, friability, Assay and in vitro drug release studies.

Weight variation:

Uniformity of weight is an important evaluation parameter for matrix tablets. It ensures that each tablet in a batch has a consistent weight, which is crucial for accurate dosing and ensures that patients receive the intended amount of medication. Here's an overview of the procedure for evaluating the uniformity of weight:

Sample Selection: Randomly select a specified number of tablets from the batch. The number of tablets selected depends on the sampling plan specified in the applicable pharmacopeia or internal quality control procedures.

Weighing: Weigh each individual tablet using a calibrated analytical balance. Record the weight of each tablet accurately.

Calculation: Calculate the average weight of the tablets by summing the individual tablet weights and dividing by the number of tablets weighed.

Weight Variation: Calculate the percentage deviation of each tablet's weight from the average weight using the following formula:

Percentage Deviation = (Individual Tablet Weight - Average Tablet Weight) / Average Tablet Weight * 100

Determine the range of percentage deviations by finding the difference between the highest and lowest percentage deviations.

Figure 2: Weight Variation testing

Hardness:

Hardness is an essential parameter to evaluate the mechanical strength and integrity of matrix tablets. It indicates the tablet's ability to withstand handling, transportation, and subsequent processing without breaking or crumbling. Here's an overview of the procedure for evaluating tablet hardness:

- **Selection of Tablets:** Randomly select a specified number of tablets from the batch. The number of tablets chosen should comply with the sampling plan specified in the relevant pharmacopeia or internal quality control procedures.
- **Hardness Testing:** Use a tablet hardness tester (also known as a tablet hardness tester or tablet hardness analyzer) to measure the force required to break the tablet. The instrument consists of a load cell and a plunger or probe. Place the tablet on the testing platform and align the plunger/probe with the tablet.
- **Application of Force:** Apply a downward force gradually to the tablet until it breaks. The force required to break the tablet is recorded by the hardness tester, usually in kilopond or Newton.
- **Repeat Testing:** Perform hardness testing on multiple tablets from the sample to obtain a representative measurement of the tablet batch's hardness.

- **Calculation and Evaluation:** Calculate the average hardness value by summing the individual hardness measurements and dividing by the number of tablets tested. Compare the average hardness value against the acceptance criteria specified in the pharmacopeia or internal quality control standards.

Figure 3: Hardness testing

Friability:

Friability testing is performed to assess the resistance of tablets to abrasion and impact during handling and transportation. It measures the tendency of tablets to crumble or break under mechanical stress. Here's an overview of the procedure for evaluating tablet friability:

- **Sample Selection:** Randomly select a specified number of tablets from the batch. The number of tablets chosen should comply with the sampling plan specified in the relevant pharmacopeia or internal quality control procedures.
- **Pre-Conditioning:** If required, pre-condition the tablets by subjecting them to specific environmental conditions such as controlled temperature and humidity, as specified in the relevant guidelines. Pre-conditioning may help simulate the expected storage and transportation conditions.
- **Weighing:** Weigh the initial weight of the tablets collectively or individually. Accurate measurement of the initial weight is important for calculating the percentage of weight loss during the friability test.
- **Friability Apparatus:** Use a friability apparatus, such as a friabilator, that consists of a rotating drum or a rotating paddle. The drum or paddle is designed to rotate at a specified speed and drop the tablets repeatedly during the test.
- **Testing:** Place the pre-weighed tablets into the friability apparatus and rotate the drum or paddle for a specified number of rotations or a defined duration. The tablets are subjected to impacts and abrasion as they collide with each other and the apparatus walls.

- **Dust Removal:** After the specified number of rotations, remove the tablets from the apparatus and gently brush off any loose dust or debris from the tablets without causing any additional weight loss.
- **Weighing After Friability:** Weigh the tablets collectively or individually after the friability test. The weight measurement should be conducted carefully to avoid errors.
- **Calculation and Evaluation:** Calculate the percentage of weight loss using the following formula:

  Percentage Friability = [(Initial Weight - Final Weight) / Initial Weight] x 100

  Compare the percentage of weight loss against the acceptance criteria specified in the relevant pharmacopeia or internal quality control standards. Typically, the acceptable friability limit is below a certain percentage, such as 1%.

Figure 4: Friability Apparatus

Disintegration Test for Tablets[16-20]

The disintegration test was performed using Electrolab disintegrating apparatus. One tablet was placed in each of the six tubes of the basket and the apparatus was maintained at 37 ± 0.50°C of the immersion liquid. The time required for complete disintegration of tablet was noted. The tablets are disintegrated when no particles remain above the gauge, which readily has passed through 10# mesh screen.

In vitro dissolution Study[16-20]

In vitro drug release studies evaluate the release profile of the active ingredient from the matrix tablets. This test helps determine the drug's release kinetics and the suitability of the formulation for its intended purpose. The tablets are placed in a dissolution apparatus, and the drug release is measured at specific time intervals using a validated method. The results are often presented as a dissolution profile or as the percentage of drug released over time.

Physico-chemical properties of Repaglinide

The physico-chemical characteristics of repaglinide are a group of characteristics pertaining to its chemical make-up, physical state, and behaviour under various conditions. With regard to Repaglinide's possible interactions with other substances and systems, as well as its potential uses and downsides, these properties provide essential information.

The physical characteristics of the medicine Repaglinide were described, and it was discovered to be a pale-yellow, odourless powder with fluffy texture. Table 1 had a tally of it. Repaglinide's melting point is listed in table 5.1:

Table No.4: Physico-chemical Properties of Repaglinide

S.No	Parameter	Observed
1.	Physical appearance	white to off-white
2.	Melting point	130-134°C
3.	PKa	Approximately 4.9 and 6.3
5.	Octanol/Water Partition Coefficient	Approximately 2.4

The FTIR peaks of Repaglinide

The Repaglinide FTIR peaks responsible for the distinctive functional group were located, analysed, and compared to previously published data. Repaglinide's FTIR peaks and spectra are shown in table 5.2 and picture 5.1:

Table 5: Interpretation of FTIR Spectra of Repaglinide

S.No	Wavelength (cm-1)	Responsible Functional group
1.	1690-1710 cm^-1	C=O
2.	2950-2850 cm^-1	C-H
3.	1510-1550 cm^-1	N-H
4.	1280-1320 cm^-1	C-N
5.	1050-1150 cm^-1	C-O

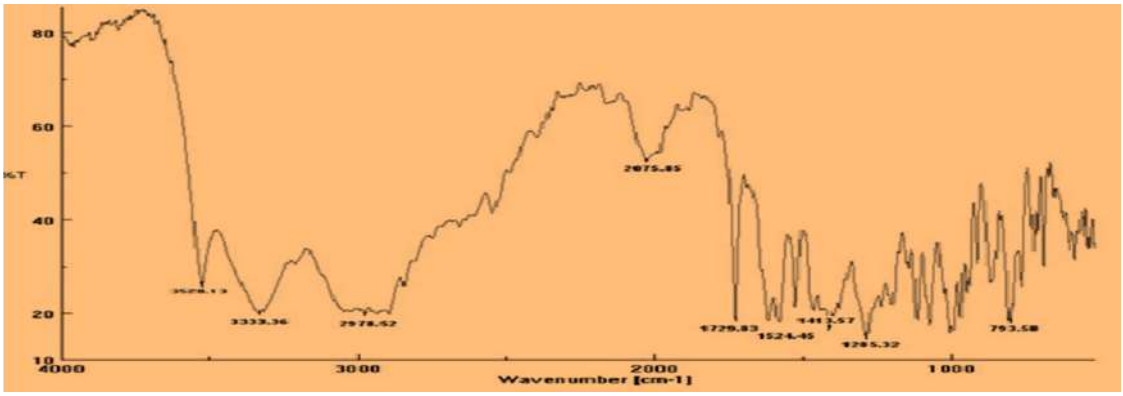


Figure 9: FTIR Spectra of Repaglinide

Table 6: The solubility of Repaglinide

S.No	Solvent system	Solubility of Repaglinide (mg/mL) at 35 ºC
1.	Water	0.1 mg/Ml
2.	0.1 (N) HCL	5-10 mg/Ml
3.	Methanol	10-20 mg/Ml
4.	Acetone	10-20 mg/Ml

Figure 10: Solubility studies of Repaglinide in various solvent systems

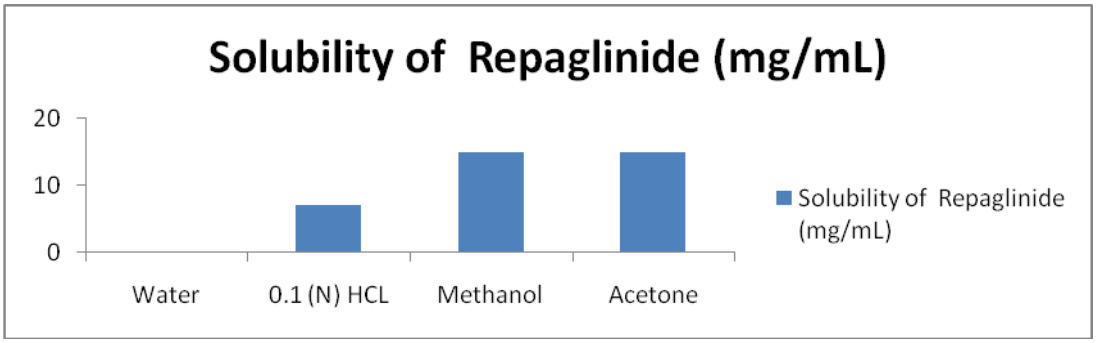


Table 7: The of Flow properties of pure drug was calculated and reported in Table.

S.No	Flow Properties	Repaglinide

1.	Bulk Density	0.62 gm/ml
2.	Tapped Density	0.73 gm/ml
3.	% Carr's Index	15.07 %
4.	Husnar's Ratio	1.25
5.	Angle of Repose	32.85°

Pre compression parameters of formulated tablets

All the compressible excipients for various batches were evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner's Ratio.

Table 8: Pre compression parameters of formulated tablets

S.No	Pre compression Properties	Batch - 1	Batch - 2	Batch - 3	Batch - 4
1.	Bulk Density	0.61	0.63	0.62	0.60
2.	Tapped Density	0.72	0.71	0.73	0.71
3.	% Carr's Index	15.28%	11.27%	15.07%	15.49%
4.	Husnar's Ratio	1.18	1.127	1.177	1.183
5.	Angle of Repose	23.5	24.5	25.5	26.90

Post compression parameters

All the post compression parameters for various batches evaluated accordingly such as thickness, coat thickness, hardness, friability, weight variation and diameter of tablet etc.

Table 10: Post compression parameters

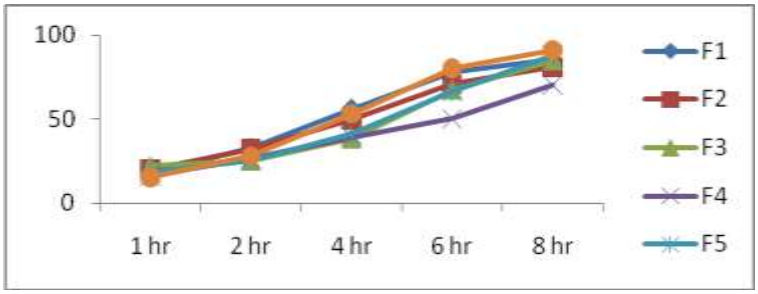
S.No	Post compression Properties	Batch -1	Batch -2	Batch -3	Batch -4
1.	Thickness(mm)	3.5	3.6	3.5	3.45
2.	Hardness (kg/cm^2)	7.2	7.4	7.3	7.5
3.	Friability %	0.30	0.35	0.28	0.32
4.	Average weight of tablet (mg)	502.5	503.10	502.15	501.32
5.	Diameter (mm)	10.15	10.23	11.16	11.05

Table No.11: Cumulative % drug released v/s. time for formulations

Time	F1	F2	F3	F4	F5	F6

1 hr	18.03	20.32	22.02	16.12	18.2	15.52
2 hr	32.90	32.57	25.23	27.11	25.34	28.32
4 hr	56.22	49.65	38.45	39.42	41.02	53.25
6 hr	78.15	70.95	67.65	50.25	66.45	80.65
8 hr	85.60	80.75	85.12	70.51	88.16	91.25

Figure 20: Cumulative % drug released v/s. time for formulations



RESULTS AND DISCUSSION

An oral medicine called repaglinide is used to treat type 2 diabetes mellitus. It is a member of the meglitinide drug class. By encouraging the pancreas to secrete insulin, repaglinide lowers blood sugar levels, especially after meals. In those with type 2 diabetes, this helps regulate blood glucose levels and improve glycemic control.

Repaglinide pills come in a variety of strengths, usually from 0.5 mg to 2 mg. The precise dosage that is recommended for a patient will vary based on their unique circumstances, including their blood glucose levels, treatment response, and other drugs they are taking.

High blood sugar levels are a recurring metabolic condition known as type 2 diabetes. It happens when the body stops producing enough insulin or when it becomes resistant to the effects of insulin. A hormone called insulin aids in controlling blood sugar levels. For those with type 2 diabetes, repaglinide is used to assist regulate blood glucose levels.

Repaglinide is a member of the meglitinide drug class. It functions by causing the pancreatic beta cells to produce more insulin. These cells' ATP-sensitive potassium channels bind to repaglinide, which causes the release of insulin. especially after meals, this lowers blood sugar levels.

Repaglinide aids in the control of blood sugar levels in people with type 2 diabetes by boosting insulin release. It works very well to control postprandial (after-meal) glucose increases. Blood

sugar regulation is essential for avoiding diabetic consequences including cardiovascular disease, renal issues, and nerve damage.

Repaglinide is frequently taken together with other anti-diabetic drugs such metformin, sulfonylureas, or thiazolidinediones.

CONCLUSION

From the current study authors team concluded that the developed SRMT formulation with release retardant polymer. The optimized F3 drug natural gum rations of SRMRT formulation retarded the drug release up-to desired time period. The hydrophilic matrix tablets containing polymer blend of polymer retard the drug release rate of drug since both are swell-able natural polymer. From the results of in-vitro release experiment found that as increases the concentration of polymer decreased the release rate of drug. These studies confirm that this is possible due to slower erosion of gum higher viscosity. The higher viscosity of natural gum might have helped to keep the hydrated gel intact thus releasing the drug for extended period 10 hrs. Among all developed SRMRT especially F3 exhibited best 91.25% released at 8 hours.

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