Engineering Universe for Scientific Research and Management
ISSN (Online): 2319-3069
Vol. XVII Issue VI
June 2025

Development of Multiunit Particulate System for Anti-Diabetic and Anti-Hypertensive management

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Abstract

Multiple Unit Pellet Systems (MUPS) for diabetes and high blood pressure drugs, focusing on drug delivery. The MUPS included immediate-release Bepridil pellets, sustained-release Glyburide/ immediate-release Bepridil pellets, the natural polymer used in the preparation included gum ghatti, guar gum, and locust bean gum. The drugs and excipients were characterized for their identity and purity, and their compatibility was tested. The drug-loaded, immediate-release Bepridil pellets and delayed-release Glyburide pellets showed good flow properties and high drug entrapment. The sustained-release Glyburide formulation continued drug release for a full day, while the Bepridil formulation for immediate release showed quick disintegration. The optimized Bepridil immediate release pellets were chosen for their stability. The MUPS solved the challenge of dose dumping associated with conventional formulations, reducing fluctuations and reducing repeated administration. The pharmacodynamic activity of the developed MUPS was found to retain drug activity, passing stability testing as per ICH guidelines. The study demonstrates the effectiveness of multiunit particle systems (MUPS) in treating long-term illnesses like diabetes and high blood pressure. The fixed-dose combination systems, developed using multiple unit pellet systems (MUPS), are better at treating metabolic illnesses. These systems can be used to address problems with current drug delivery methods, providing patients with tailored treatment choices. The research is useful for researchers, doctors, and companies in the pharmaceutical industry, as it could lead to more successful, safer, and economical therapies.

Keywords: ***Multi Unit Pellet Systems (MUPS), ICH guidelines, Glyburide pellets, sustained-release, Immediate-Release.***

1. Introduction

Innovative drug delivery techniques are critical given the prevalence of chronic and difficult-to-treat conditions like diabetes and hypertension that affect millions of people's lives and put a load on healthcare systems [1]. One notable development in the treatment of these intricate medical disorders is the use of Multi Unit Pellet Systems (MUPS)[2,3]. It provides a useful method for handling the complexities of controlling hypertension and diabetes[4,5]. By offering a more regulated and prolonged delivery of drugs, these systems seek to maximize treatment results, improving patient quality of life and illness managemen[6].

The hallmark of diabetes mellitus is high blood glucose levels brought on by the pancreas's inadequate synthesis of insulin [7]. Affected individuals may experience a variety of vascular issues as a result of this illness. In order to properly control blood sugar levels in people with type 1 diabetes, insulin is usually given parenterally[8]. On the other hand, seven distinct oral anti-diabetic drugs that help the pancreas cells produce insulin are used to treat type 2 diabetes[9,10]. The dosage of these drugs can be adjusted gradually to provide optimal blood sugar management while minimizing gastrointestinal side effects such nausea, diarrhea, and stomach pain[11]. Detrimental consequences of type 2 diabetes include anxiety, depression, early morbidity, and higher death rates from poor health, which can lead to lower productivity, higher medical costs, and unemployment[12,].

Hypertension, often referred to as the "silent killer," presents a considerable health challenge as it can go unnoticed while causing damage internally[13]. Hypertension typically shows no obvious symptoms, allowing it to cause harm silently until serious consequences arise. Glyburide may directly affect intracellular calcium transport and also promote insulin production via the beta-cell sulphonylurea receptor[14]. The medication's capacity to enhance glycemic control in Type 2 diabetes makes it popular. Doctors prefer certain pharmacological categories for managing diabetes. Glyburide was thus chosen as an antidiabetic medication for this investigation.

Bepridil, a calcium channel blocker, may lessen intracellular calcium ion transit, lowering the hypertension linked to diabetes. The BCS Class I medication bepridil is seen to be the best option for treating hypertension in those who need antidiabetic treatment. A mixture of gum ghatti with MCC, locust bean gum, and guar gum was chosen for formulations with prolonged release.

The physicochemical properties and biological behavior, such as the half-life and pharmacokinetics of Glyburide, and Bepridil, make them ideal candidates for delivery through Multiple Unit Pellet Systems (MUPS). These properties ensure controlled drug release, enhanced bioavailability, and improved therapeutic outcomes, making MUPS a suitable and efficient drug delivery strategy for these medications.[15].

2. Material And Method

Materials:

Gliburide and Bepridil was obtained as a gift sample from Cipla Ltd, dewa MP, oother all excipients used analytical grade like Locust Bean Gum, Gum Ghatti, Guar Gum, Microcrystalline Cellulose (Avicel PH 101),, Sodium Lauryl Sulfate, Croscarmellose Sodium, Polyethylene Glycol, Tween 80, Sodium Starch Glycolate, Polyethylene Glycol, Magnesium Stearate etc. From Research-Lab Fine Chem Industries, Mumbai, and Loba Chemie Pvt Ltd, Mumbai.

Methods:

1.1 Preparation of drug-loaded Drug pellets

1.1.1.1 Preparation of drug-loaded sustained-release Glyburide pellets[16]

For the formulation of sustained-release Glyburide pellets, locust bean gum (1 to 3% w/w) in combination with gum ghatti (0.5 to 1.5% w/w) along with microcrystalline cellulose (MCC) were used to create batches labeled GPSR-1 to GPSR-9. In another series, locust bean gum (1 to 3% w/w) was used in combination with guar gum and gum ghatti (0.5 to 1.5% w/w), along with MCC, to produce batches GPSR-10 to GPSR-15. A homogenous dry powder blend (batch size 50 g) was prepared by thoroughly mixing the ingredients for 10 to 15 minutes in a polyethylene bag.

The resulting dry mixture was then granulated using a solution of water and isopropyl alcohol in a 5:2 ratio as the granulating fluid. The wet granulation was extruded, and the extrudates were immediately spheroidized to form spherical pellets. The pellets were then dried in an oven at 40 ±2°C for 10 hours. Once dried, the pellets were stored in high-density polyethylene bottles with screw caps.

Table 1: Formulation of sustained-release Glyburide pellets

Formulation code	Ingredient concentration (% w/w)					Wetting agent volume
	Glyburide	MCC	Locust bean gum	Gum ghatti	Guar gum	(Water: IPA) (5:2) (mL/g)
GPSR-1	33.5	64	1	0.5	-	0.8
GPSR-2	33.5	62	2	0.5	-	0.77
GPSR-3	33.5	63	3	0.5	-	0.77
GPSR-4	33.5	62	1	1.0	-	0.7
GPSR-5	33.5	64	2	1.0	-	0.77
GPSR-6	33.5	64	3	1.0	-	0.84
GPSR-7	33.5	62	1	1.5	-	0.84
GPSR-8	33.5	63	2	1.5	-	0.8
GPSR-9	33.5	63	3	1.5		0.74
GPSR-10	33.5	64	1	-	1.0	0.74
GPSR-11	33.5	62	2	-	1.0	0.8
GPSR-12	33.5	63	3	-	1.0	0.74
GPSR-13	33.5	62	1	-	1.5	0.7
GPSR-14	33.5	63	2	-	1.5	0.8
GPSR-15	33.5	64	3	-	1.5	0.74

MCC: Microcrystalline cellulose; IPA: Isopropyl alcohol

Preparation of Sustained-Release Glyburide and Immediate-Release Bepridil Pellets into a Fixed Dose Combination Bilayer Tablet [17]

A mixture was prepared consisting of Aerosil 200 (100 mg), Crospovidone (2000 mg), Starch (50000 mg), Magnesium Stearate (350 mg), Talc (1000 mg), and Sorbitol (3000 mg) for a tablet batch size of 100 (each tablet weighing 650 mg). Various batches labeled GBT-1 to GBT-14 were prepared by using different concentrations of Croscarmellose Sodium (CCS) (5 to 20 mg/tablet), Sodium Starch Glycolate (SSG) (5 to 20 mg/tablet), and Polyethylene Glycol 2000 (PEG 2000) (10 to 20 mg/tablet) as variables to optimize the formulation.

Table 2: Formulation of Bilayer Tablet of Sustained-Release Glyburide and Immediate-Release Bepridil Pellets

S. No	Ingredients (mg/tablet)	GD-1	GD-2	GD-3	GD-4	GD-5	GD-6	GD-7	GD-8	GD-9	GD-10	GD-11	GD-12	GD-13	GD-14	GD-15	GD-16
1	Bepridil Pellet DPIR14	191.1	191.1	191.1	191.1	191.1	191.1	191.1	191.1	191.1	191.1	191.1	191.1	191.1	191.1	191.1	191.1
2	Glyburide Pellet (GPSR 6)	187.5	187.5	187.5	187.5	187.5	187.5	187.5	187.5	187.5	187.5	187.5	187.5	187.5	187.5	187.5	187.5
3	Aerosil 200	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
4	Crosspovidone	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
5	MCC Spheres	49	49	49	49	49	49	49	49	49	49	49	49	49	49	49	49
6	Starch	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
7	Magnesium Stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
8	PEG 2000	10	10	10	10	20	20	20	20	10	10	10	10	20	20	20	20
9	CCS	5	10	15	20	5	10	15	20								
10	SSG									5	10	15	20	5	10	15	20
11	Talc	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
12	Sorbitol	31	31	31	31	31	31	31	31	31	31	31	31	31	31	31	31
13	HPMC K4M	91.9	86.9	81.9	76.9	81.9	76.9	71.9	66.9	91.9	86.9	81.9	76.9	81.9	76.9	71.9	66.9
Total weight		650	650	650	650	650	650	650	650	650	650	650	650	650	650	650	650

CHARACTERIZATION AND EVALUATION

Characterization of pellets [18]

Bulk density

A 250 mL graduated cylinder was used to measure the volume (V_0) after a specified quantity of product (W) was poured into it to calculate the bulk density of pellets. The bulk density was determined using equation

$$BD = \frac{W}{V_0}$$

The results presented are the mean of three replicates determinations.

Tapped density

A graduated cylinder with a known mass of pellets was placed on a mechanical tapping fixture to calculate the tap density. The samples were tapped repeatedly until

no more sample volume loss could be seen. The tap density was carried out three times to increase the validity of the observations [19]. The degree of volume reduction (C) is calculated from the initial volume 'V_o' and tapped volume 'V' as:

$$C = \frac{V_0 - V}{V}$$

Angle of repose

The solid funnel method was used to calculate the angle of repose in order to assess the pellets' flowability. The hopper was filled with drug-filled pellets until the top of the conical pile was barely above the hopper's rim. The pile's height (h) and the radius's height (r) were then calculated.

$$\text{Angle of repose} = \tan^{-1}\frac{h}{r}$$

Compressibility

Carr's compressibility index was determined by using the values of bulk and tapped density to measure the flowability of the developed pellets. The main objective was to get an idea related tocompressibility of the pellet. The Carr's compressibility index calculated using the following equation

$$\textbf{Carr's Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

Pellet shape
An image analysis method was used to estimate the pellet's form. A Motic microscope was used to take the photomicrographs. The images revealed the surface morphology and helped in deciding the formulation parameters. The formulation batch passing the minimum shape criteria was further subjected to SEM analysis.
Pellet Size distribution
Sieve analysis was used to determine the distribution of particle sizes. A vibrating sieve machine was used to filter a 50 g sample for 10 min. at amplitude of 10. The fraction retained on each sieve 1400, 1000, and 710 µm was weighed and represented as a percentage of the total weight. [20**]**
Surface Morphology
The final formulation from the study mentioned above was analyzed using SEM at Diya Lab in Thane, Mumbai. A scanning electron microscope was used to get the necessary magnification and room temperature SEM pictures. The photographs were evaluated for morphological traits and to verify the pellets' spherical shape.
Drug Excipients interactions
The produced formulations were analyzed using a Fourier transform infrared (FT-IR) spectrophotometer (Shimadzu, FTIR 8400S, Japan) utilizing the KBr pellet method ..
Melting behavior
DSC is a method that measures the variation in heat flow as a function of temperature between a sample and a reference. Several milligrams of the sample were hermetically packed in aluminium pan sand, which was heated at a rate of 10°C/min while being in a nitrogen atmosphere.
Evaluation of pellets
Friability
The Roche Friabilator tester was used to determine friability. 10 g of pellets were put through a 4-minute, 25 rpm impact test. The attrited samples were sieved, and the pellets that remained on the sieve were weighed. From the weight difference between the pellets before and after friability, the percent friability was computed [20].
Drug loading and entrapment efficiency
A weighed powder (500 mg) from the crushed pellets was suspended in 100 mL of freshly prepared phosphate buffer pH 6.8 and 0.5% w/v sodium lauryl sulfate (SLS) with constant stirring at room temperature for 24 Hrs. Using a pH phosphate buffer of 6.8 and 0.5% w/v SLS as a blank, the solution was then filtered through Whatman filter paper. The drug content for each pellet formulation was then independently determined using a spectrophotometric method at a wavelength of 217 nm for Glyburide formulations, and 237 nm for Bepridil formulations**.** . The entrapment efficiency was calculated by using the equation;

$$\% \text{ Drug Entrapment} = \left[\frac{\text{Calculated drug content}}{\text{Theoretical drug content}}\right] \times 100$$

Percent drug loading was calculated by using the following equation;

$$\% \text{ Drug Loading} = \left[\frac{\text{Amount of drug in the sampled spheroids}}{\text{Weight of spheroids}}\right] \times 100$$

Pellet disintegration test
Using a typical tablet disintegrator, Unique transparent tubes with a diameter of 10 mm and a length of 15 mm were used. At the top and bottom of this pipe there were sieves with a mesh size of 710 mm. The conventional tablet disintegration tester was used to test the equivalent dose pellets for each drug in separate experiments, which were then filled into each tube. Six dried samples were dissolved in purified water at a rate of 25 immersions per minute for a period of 37 ± 2 °C[21]**.**

Evaluation of formulated fixed dose combination Bilayer tablets
The Bilayer tablets were evaluated for the following parameters
Weight variation
Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation. The tablet weight range was from 690-710 mg. The pharmacopoeia **[29]** limits varies from 5-10 %, depending on the weight of the tablets.
Thickness
The thickness of each layer tablet was measured using a screw gauge (Mitutoyo Manufacturing Corporation Ltd., Japan). Data are represented as average of six determinations for each layer tablet batch**[30].**
Hardness Test
Hardness or tablet crushing strength, the force required to break a tablet in diametric compression was measured using a digital Inweka hardness tester iHT100**.**
Friability
Twenty tablets were weighed and placed in a Roche friabilator and the equipment was rotated at 25 rpm for 4 min. The tablets were taken out dedusted and reweighed. The percentage friability of the tablets was calculated using below equation;

$$\% \text{ Friability} = \left[\frac{\text{Initial Weight - Final Weight}}{\text{Initial Weight}}\right] \times 100$$

Percentage Drug content
Ten tablets were powdered, a 10 mg drug equivalent powder (Glyburide/ Bepridil) equivalent of physical mixture was taken and transferred to 100 mL volumetric flask, dissolved and diluted with pH 1.2 HCl buffer containing 0.1% SLS. The 0.1% SLS was added to solubilize the drug completely from

the tablet as some excipient may not release drug completely. The concentration was determined by spectroscopic and chromatographic method

In vitro dissolution study

Drug release tests were performed using the USP Dissolution Tester I at 100 rpm, 37 ± 0.5 °C, and pH 1.2 (900 mL) buffer (i.e., 0. 1 N HCl) for two hrs. The experiment was extended for 10 Hrs. by replacing the dissolution medium with phosphate buffer (900 mL) with a pH of 6.8. Five milliliters of the samples were removed and replaced at various intervals with five milliliters of drug-free dissolution medium. The previously mentioned HPLC method was used to quantify the amount of drug administered[22].

In-Vivo Studies:

Plasma Drug Concentrations study

Animals were given fixed dose combination tablets made from the combinations of pellets, and blood samples were taken at 5, 10, 15, 20, 25, and 30 min. to measure the drug's plasma levels. To determine the dosage dumping with traditional formulations, a comparison between the novel formulation and commercial formulations was conducted. This was done to verify that the medication was being released and absorbed from the bilayer tablet. Drug concentration was measured using the protocols outlined under "bio-analytical methods" in plasma samples (test and control) extracted at different interval**[33].** Directly from the concentration–time data, the maximum plasma concentration (C_{max}) and the time required to attain peak plasma concentration (T_{max}) were determined.

Pharmacodynamic studies

Animals

The experiment employed albino Wistar rats of both sexes, weighing between 230 and 260 g, that were kept in a room with a 12-Hr. light/dark cycle at 23 ± 2 °C and free access to food and water. [23]

Antidiabetic Activity:

Glyburide pellets were screened for antidiabetic activity (As per approved IAEC protocol from College of Pharmacy, SSSUTMS, Sehore MP). Healthy adult albino wistar male and female rats weighing 150-200g procured. Diabetes was induced in animals by injecting alloxan 150mg/kg/body weight intraperitoneally (i.p.) freshly prepared in normal saline. The animals were tested for evidence of diabetes by estimating their glucose levels using glucometer. After treatment, blood samples from the rats were collected from the retro orbital plexus method. Blood glucose level was estimated at 0, 2, 4, 6, 8, 10, 12 and 24 Hrs. to understand the release of the drug from polymer matrix. The activity was compared to the marketed formulations[24]

Table 3: Animal groups for antidiabetic activity

S. no	Group	No .of Animals (mice/rat)*	Drug Treatments
1	Group I	6	Vehicle (5 mL distilled water orally)
2	Group II	6	Alloxan 150 mg/kg one time to induce diabetes subcutaneously
3	Group III	6	Alloxan 150 mg/kg one time to induce diabetes subcutaneously as in Gr II and then treated with (GPSR 6)
4	Group IV	6	Alloxan 150 mg/kg one time to induce diabetes subcutaneously as in Gr II and then treated with (VPIR 8)
5	Group V	6	Alloxan 150 mg/kg one time to induce diabetes subcutaneously as in Gr II and then treated with Metformin (25 mg/animal/d)

Data was expressed as mean ±SEM (n =6). Statistical significances were determined using one way analysis of variance (ANOVA) followed by Dunnett's post hoc test.#p<0.05, ##p<0.001, ### p<0.001 as compared to normal, *p<0.05, ***p<0.001 as compared to ENA (0.5). Ena: Enalapril. The figures in parenthesis shows the dose in mg/kg i.m. except STD which is in mg/kg oral (n=6)

Antihypertensive Activity

The bepridil pellets were screened for antihypertensive activity (As per approved IAEC protocol). Healthy adult male and female Sprague-Dawley rats weighing 200-250 g procured[36]. Hypertension was induced in animals by injection of dexamethasone (10 µg/kg/d) subcutaneously in the evening. The animals were tested for evidence of hypertension by measuring the systolic and diastolic blood pressure[37]. Animals were divided into three groups. Negative control (Placebo), positive control (Bepridil) and treatment group (Pellet fed). Systolic blood pressure (SBP) readings were taken every week between 10 and 11 a.m. during the course of treatment by the same researcher utilizing the integrated BIOPAC, a blood pressure measuring device, and the NIBP, or Non-Invasive Blood Pressure 200A system. The animal is put in the animal holder, or restrainer, with its tail left out and adjusted so that its range of motion is restricted. After being inserted into the heating chamber, the restrainer is heated to 32°C. The produced pellets had a strong antihypertensive effect[25].

Table 4: Animal groups for antihypertensive activity

S.No	Group	No. of Animals	Drug Treatments
1	Group I	6	Vehicle (0.5 mL distilled water)
2	Group II	6	Dexamethasone 10 µg/kg/d
3	Group III	6	Dexamethasone 10 µg/kg/d as in gr II and treated with Bepridl pellets 2 mg/kg/day p.o
4	Group IV	6	Dexamethasone 10 µg/kg/d as in gr II and treated with bepridil tablet 2 mg/kg/day p.o.

Data was expressed as mean ±SEM (n =6). Statistical significances were determined using one way analysis of variance (ANOVA) followed by Dunnett's post hoc test.#p<0.05, ##p<0.001, ### p<0.001 as compared to normal, *p<0.05, ***p<0.001 as compared to ENA (0.5). Ena: Enalapril. The figures in parenthesis shows the dose in mg/kg i.m. except STD which is in mg/kg oral (n=6).

Stability studies

Stability studies of optimized formulation of sustained release Glyburide (GPSR-8), immediate release Bepridil (DPIR-14), and the fixed dose combination bilayer tablets (GDT 14 and SDT 04) were carried out at 25 ± 2°C / 60 ± 5% RH, 30 ± 2°C / 65 ±5% RH and 40±2 °C / 75±5% RH. The formulations were subjected to various evaluation parameters like physical appearance, friability (%)

3. Results And Discussion

Drug and excipients characterization

Solubility

The solubility of Glyburide was found to be 0.20, 0.55, and 1.05 mg/mL in pH 1.2, 6.8, and 7.2 phosphate buffers, respectively. Similarly, the solubility of Bepridil was found to be 0.35, 0.75, and 1.10 mg/mL in pH 1.2, 6.8, and 7.2 phosphate buffers,

Viscosity

The viscosity of a 1% w/v solution of locust bean gum, guar gum, and ghatti gum was measured as 169 cP, 124 cP, and 31 cP, respectively, in distilled water, and 181 cP, 137 cP, and 36 cP, respectively, in pH 6.5 phosphate buffers. These results indicate that the polymers exhibit suitable viscosity profiles, making them effective binding agents for pelletization [26]

Melting points

The melting range of Glyburide, Bepridil hydrochloride, and these values were compared with the Certificate of Analysis (CoA) and literature values, and no deviations were observed[27]..pH determination of gums

The pH of a solution containing locust bean gum, guar gum, and gum ghatti was determined to be 5.64±0.34, 5.7±0.48, and 4.9±0.52, respectively. These pH values are within an acceptable range for the production of pharmacological dosage forms . They are suitable for ensuring compatibility with the gastrointestinal tract, as they are unlikely to cause irritation to the mucous membrane or epithelium, thereby supporting safe and effective drug delivery.

FTIR Studies

The results of the drug and excipients FTIR analysis are as follows. The drug and excipients showed the characteristic peaks for the stretching and bending of the different bonds.

Figure 1: FTIR spectra of Glyburide

1. 1597.09cm-1 C=C Aromatic Stretching 3113.16cm-1 =CH Stretching Secondary Amine N-H Stretching 3270 to 3275.19 cm-1 SO2NH Stretching 1354.05 cm-1 Sulphonyl S=O Stretching 1164.06 cm-1 Acyclic ketone carbonyl C=O Stretching 1709.92 cm-1. Oxygen-Hydrogen stretching vibrations are represented by a broad peak in the 3200–3600 cm^{-1} range. Something like the hydroxyl group on the benzene ring in Glyburide might be connected to this. In the aliphatic and aromatic regions of the molecule, the stretching vibrations of carbon-hydrogen (C-H) bonds correspond to the peaks in the 2800–3000 cm^{-1} range. An intense peak centered between 1680 and 1750 cm^{-1} signifies the stretching vibrations of carbonyl (C=O) groups. The carbonyl group in the sulfonylurea molecule of Glyburide is usually linked to this peak. Vibrations of carbon-nitrogen (C-N) bonds stretching and bending are linked to the peaks in the 1000–1500 cm^{-1} range. The stretching vibrations of the sulfonyl (S=O) group are indicated by a prominent peak found at around 1100–1200 cm^{-}

[1]. In heterocyclic compounds like Glyburide, these vibrations are frequently seen. The aromatic carbon-hydrogen (C-H) bond in-plane bending vibrations, characteristic of the benzene ring in Glyburide, are linked to the peaks in the 650–900 cm^{-1} range.

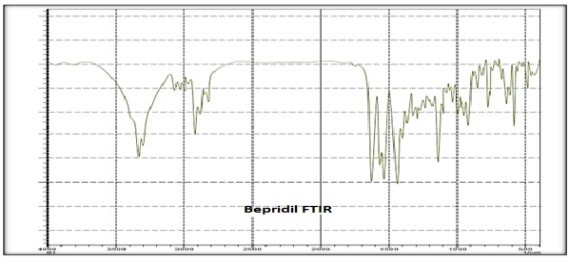


Figure.2: FTIR spectra of Bepridil

2. The peaks in the 2800-3000 cm^{-1} range correspond to the stretching vibrations of the carbon–hydrogen (C–H) bonds in the aliphatic and aromatic portions of the monolayer. At roughly 1650-1750 cm^{-1}, a significant peak indicates the stretching vibrations of carbonyl (C=O) groups. Bepridil's peak is associated with either the carbonyl group in the benzene ring or the carbonyl groups in other functional moieties. Peaks in the range of 1000-1500 cm^{-1} are associated with stretching and bending vibrations of carbon-nitrogen (C-N). These vibrations are commonly observed in the heterocyclic structures of Bepridil. Phenomena in the range of 650-900 cm^{-1} are associated with the in-plane bending vibrations of aromatic carbon-hydrogen (C-H) bonds, typical of the benzene rings in Bepridil. Thiol (S-H) group stretching vibrations are indicated by a strong peak in the 2550-2650 cm^{-1} range. The carbon-sulfur (C-S) bond stretching vibrations are characterized by peaks in the 600-900 cm^{-1} range.

Swelling studies

The swelling index of locust bean gum, gum ghatti, and guar gum was found to be 11.2±1.06 mL, 6.9±1.75 mL, and 14.7±1.30 mL, respectively, reflecting their water retention capacities, which are crucial for their role in pharmaceutical formulations[28].

Drug Excipients Compatibility

FT-IR studies of Glyburide and their formulation excipients

The size and placement of peak in FT-IR spectrum of pure Glyburide is compared using FT-IR spectrum data of Glyburide with excipients as per shown in Fig 5.10.

Table 5: Characteristic IR absorption peaks of: (A) Glyburide pure drug; (B) Glyburide + locust bean gum; (C) Glyburide + gum ghatti; (D)Glyburide + guar gum; (E) Glyburide + microcrystalline cellulose

Wave number of drug (A)	Wave number (cm^{-1}) of the physical mixture			
	(B)	(C)	(D)	(E)
1150.12 $^{cm-1}$ (S=0 symmetric stretching)	1157.5	1153.4	1154.6	1159.6
1353.41 $^{cm-1}$ (S=0 asymmetric stretching)	1352.3	1358.2	1350.7	1353.3
1705.04 $^{cm-1}$ (C=0 stretching)	1713.6	1712.1	1719.5	1717.2
3274.71 $^{cm-1}$ (-NH stretching)	3278.1	3279.2	3275.2	3273.3

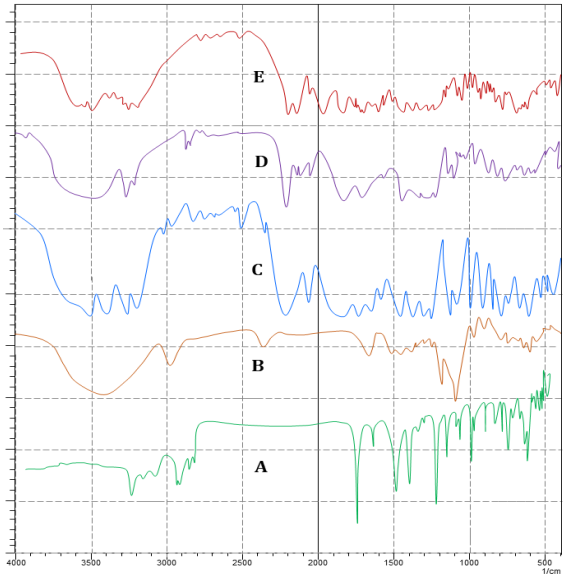


Figure 3 : FT-IR spectra of: (A) Glyburide pure drug; (B) Glyburide + locust bean gum; (C) Glyburide + gum ghatti; (D) Glyburide + guar gum; (E) Glyburide + microcrystalline cellulose

Table 5 shows that the physical mixes of the polymers (locust bean gum/ghatti gum/guar gum/microcrystalline cellulose) had the same substantial absorption peaks as the active component Glyburide. Drug-polymer compatibility did not change peaks. Thus, the drug can be used with the chosen polymer without affecting formulation stability. The Glyburide Fourier Transform Infrared (FT-IR) spectra showed a concave curve at 1705 cm^{-1}, indicating a carbonyl group. Sulfonyl group bands stretched at 1150 cm^{-1} and 1353 cm^{-1} in the spectrum. An amino group peak at 3274 cm^{-1} was also present. Table 5 shows that the physical mixtures of the polymers used (locust bean gum/ghatti gum/guar gum/microcrystalline cellulose) Because the polymer and drug are compatible. It appears that the drug and polymer can

be used together without causing formulation stability concerns[29].

FT-IR studies of Bepridil and their formulation excipients

The size and placement of peak in FT-IR spectrum of pure Bepridil is compared using FT-IR spectrum data of Bepridil with excipients as per shown in Fig 5.3.

Table 6: Characteristic IR absorption peaks of: (A) Bepridil pure drug; (B) Bepridil + microcrystalline cellulose; (C) Bepridil + sodium starch glycolate; (D) Bepridil + croscarmellose sodium; (E) Bepridil + sodium lauryl sulfate; (F) Bepridil + locust bean gum; (G) Bepridil + sodium bicarbonate; (H) Bepridil + PVP K-30

Wave number of drug	Wave number (cm-1) of the physical mixture						
(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)
3357.90 cm-1 (N-H stretching)	3364 .2	3363 .5	3365 .2	3365 .4	3364 .3	3365 .3	3364 .2
2963.25 cm-1 (Aliphatic C- H stretching)	2960 .1	2961 .1	2922 .3	2963	2962 .3	2962 .2	2962 .2
1651.12 cm-1 (C=O stretching)	1651 .4	1650 .1	1650 .2	1649 .4	1650 .5	1650 .9	1651 .1
1052.82 cm-1 (C=C bending)	1077 .2	1076 .5	1077	1076 .9	1077 .6	1077 .2	1077 .8

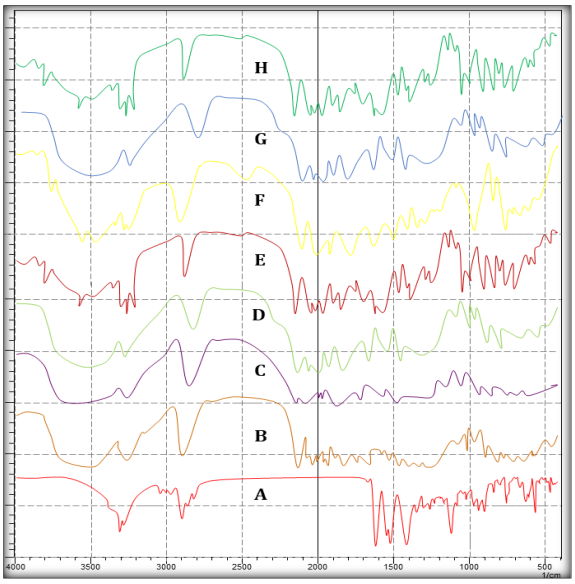


Figure 4: FT-IR spectra of: (A) Bepridil pure drug; (B) Bepridil + microcrystalline cellulose; (C) Bepridil + sodium starch glycolate; (D) Bepridil + croscarmellose sodium; (E) Bepridil + sodium lauryl sulfate; (F) Bepridil + locust bean gum; (G) Bepridil + sodium bicarbonate; (H) Bepridil + PVP K-30.

The examination of the FT-IR spectra, as shown in Table 6, revealed that the Bepridil API substance displayed distinct absorption peaks that remained present in the physical mixtures containing the excipients (microcrystalline cellulose/locust bean gum/sodium starch glycolate/croscarmellose sodium/sodium lauryl sulfate/sodium bicarbonate/PVP K-30). The absorption peaks exhibited minimal positional changes[30], indicating compatibility between the excipients, drug and polymer. Therefore, it may be inferred that the drug and the selected polymer can be used in conjunction without causing any formulation instability. The FT-IR spectra of Bepridil showed a clearly defined concave curve at 1052 cm^{-1}, which corresponds to the carbonyl group. The FT-IR spectrum of Bepridil displayed clear peaks at 1651 cm^{-1} and 1743 cm^{-1}, which corresponded to the stretching vibrations of the C=O bonds in the lactam and acetic acid derivative, respectively. The band at 2963 cm^{-1} is indicative of aliphatic C-H stretching. The presence of the amino group was identified by a peak seen at 3274 cm^{-1} (168, 169).

Analytical Method development

Determination of Absorption maxima (λ_{max})

The λmax values for Glyburide, Bepridil, and Vildagliptin were determined using the UV-Visible Spectrophotometric method. Methanol was used as the solvent, and the solutions of each drug were scanned using a Shimadzu UV-Vis Spectrophotometer (Model 1800) across the wavelength range of 200 nm to 450 nm.

Preparation of standard solution

An accurately weighed quantity of Glyburide, Vildagliptin, or Bepridil (10 mg) was transferred to a 10 mL volumetric flask and dissolved in methanol as the solvent to prepare a stock solution with a concentration of 1 mg/mL (1000 ppm).

Preparation of calibration curve of Glyburide, Bepridil

The calibration curve was plotted using aliquots of various concentrations prepared from stock solutions of Glyburide, Bepridil, The aliquots were diluted with methanol to achieve concentrations of 2, 4, 6, 8, and 10 µg/mL for each drug. The absorbance of these solutions was measured using a Shimadzu UV-Vis Spectrophotometer (Model 1800) at λmax values of 300 nm for Glyburide, 220 nm for Bepridil,

Table 7: Data for Calibration graph for Glyburide and Bepridil by UV spectrophotometer

Concentration (µg/mL)	Absorbance λ (300 nm)	Concentration (µg/mL)	Absorbance λ (220 nm)
2	0.198	2	0.188
4	0.364	4	0.374
6	0.601	6	0.621
8	0.789	8	0.799
10	0.933	10	0.932

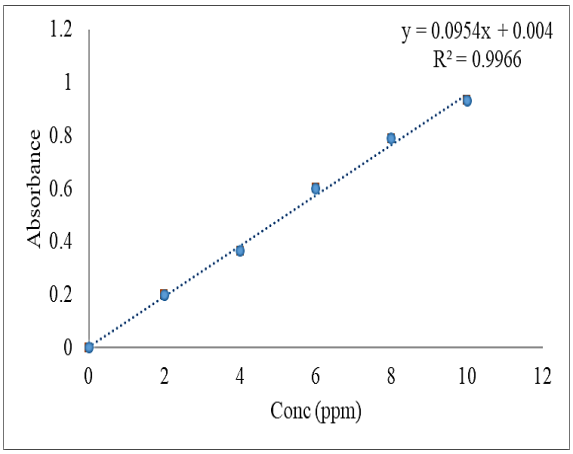


Figure 5: Calibration graph of Glyburide

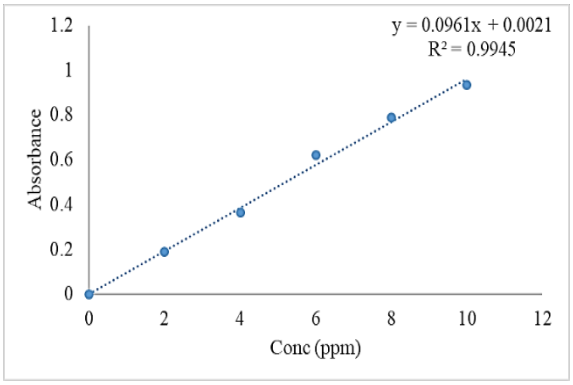
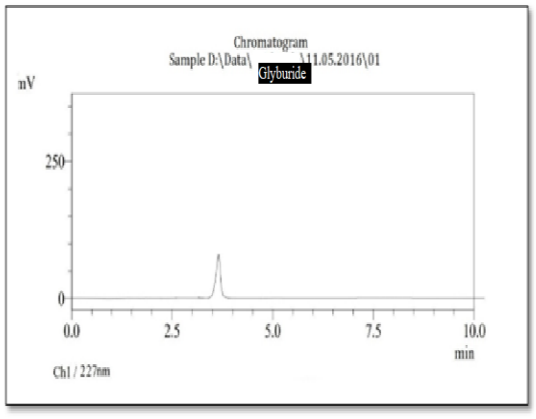


Figure 6: Calibration graph of Bepridil

Representative chromatograms of the API (Glyburide, Bepridil)



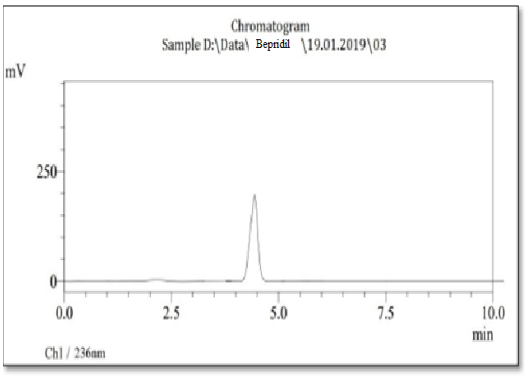


Figure 7: Representative chromatograms of the API (Glyburide, Bepridil)

Scanning electron microscopic (SEM) studies

The SEM images reveal a broad distribution of particle sizes in gum ghatti powder (Fig. 8 B) and locust bean gum powder (Fig. 8 A). Similarly, the SEM image of guar gum (Fig. 8 C) shows particles with a long, stretched tube-like shape and a smooth surface. The presence of predominantly small particles allows them to fill the spaces between larger particles, facilitating compact packing during the pelletization process. [46].

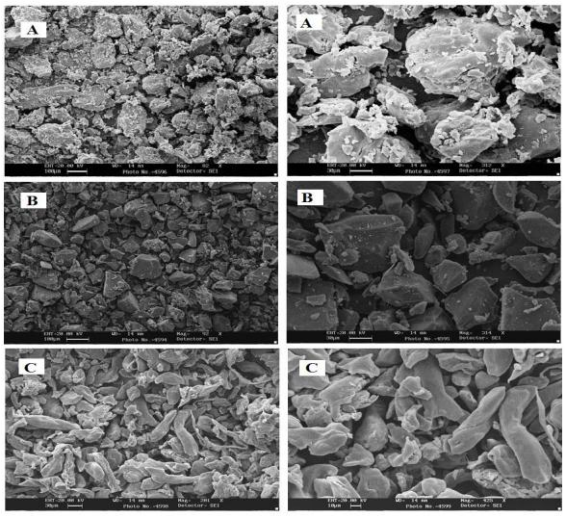


Figure 8: SEM of: (A) Locust bean gum powder; (b) Gum ghatti powder; and (c) Guar gum powder at different magnifications

Table 8: Results for compressibility behavior determined through Carr's compressibility of sustained release Glyburide pellets

Formulation Code	Weight of the pellets	Bulk Volume	Tapped Volume	Bulk Density	Tapped Density	Carr's Index
GPSR1	20 g	21	19	0.94±0.08	1.05±0.03	10.48
GPSR2		21	19	0.94±0.05	1.03±0.04	8.74
GPSR3		22	19	0.9±0.04	1.08±0.03	16.67
GPSR4		22	19	0.93±0.08	1.05±0.02	11.43
GPSR5		22	18	0.93±0.06	1.12±0.06	16.96
GPSR6		22	19	0.92±0.04	1.04±0.08	11.54
GPSR7		21	19	0.94±0.06	1.06±0.07	11.32
GPSR8		22	18	0.9±0.04	1.09±0.05	17.43
GPSR9		22	19	0.89±0.03	1.08±0.06	17.59
GPSR10		22	17	0.93±0.04	1.16±0.04	19.83
GPSR11		22	20	0.93±0.08	1.02±0.03	8.82
GPSR12		21	19	0.94±0.06	1.07±0.04	12.15
GPSR13		22	19	0.9±0.08	1.05±0.02	14.29
GPSR14		22	19	0.93±0.04	1.04±0.06	10.58
GPSR15		22	19	0.93±0.05	1.03±0.05	9.71

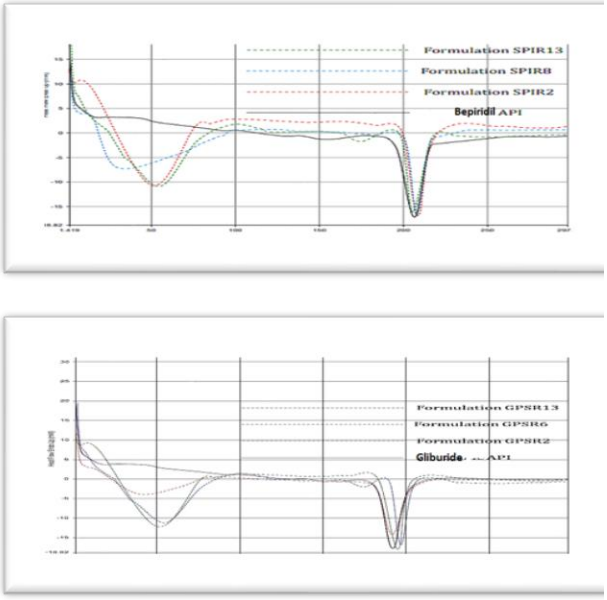


Figure 9: DSC thermogram of Glyburide API, pellets of Glyburide, n and Bepridil

The friability, yield percentage, drug loading, and entrapment efficiency of the pellets were evaluated. Results for Glyburide, Bepridil, and pellets are shown in Tables 9, and10, and respectively. Figures 5.22, 5.23 and 5.24 show the drug release profiles for Glyburide, Bepridil, respectively. Research found that pellets containing sodium starch glycolate as a superdisintegrant had a longer disintegration time compared to croscarmellose sodium. The mechanism of disintegration time of pellets containing sodium starch glycolate, which occurs through swelling upon contact with aqueous medium, may be the cause of the significant increase in disintegration time. Gel formation can then occur, potentially clogging the pores of the pellet and delaying further disintegration. Unlike sodium starch glycolate, which is the rate-limiting step for drug dissolution, croscarmellose sodium has two functional mechanisms of disintegration: water transport and rapid swelling. This results in a higher decay property[31].

Evaluation of Pellets

Table 9: Results for evaluation of Glyburide Pellets

Formulation code	Friability (%)*	Disintegration Time (min)	Yield (%)*	Drug loading (%)*	Entrapment efficiency (%)*	Drug Content
GPSR-1	0.51±0.07	11±0.47	76.9±2.31	32.37±0.12	88.76±1.54	96.32±1.85
GPSR-2	0.51±0.04	14±0.81	79.5±2.68	32.28±0.23	85.40±1.21	97.16±1.32
GPSR-3	0.41±0.08	21±0.94	74.2±3.83	32.41±0.17	90.26±1.02	97.47±0.59
GPSR-4	0.46±0.06	17±0.47	80.6±2.40	32.50±0.22	93.64±1.44	97.10±1.58
GPSR-5	0.37±0.08	17±0.81	78.3±2.21	32.34±0.24	87.65±1.38	96.18±1.7
GPSR-6	0.40±0.09	17±0.81	83.3±3.16	32.55±0.15	95.51±1.23	97.33±0.68
GPSR-7	0.35±0.01	29±0.81	79.1±2.73	32.31±0.28	86.51±1.51	95.68±0.84
GPSR-8	0.36±0.04	09±0.94	81.5±2.37	32.35±0.16	88.02±0.87	96.48±2.10
GPSR-9	0.40±0.07	10±0.94	78.7±3.21	32.46±0.26	92.14±1.91	97.55±1.16
GPSR-10	0.35±0.06	15±0.81	81.6±3.07	32.33±0.21	87.26±1.07	96.63±1.17
GPSR-	0.37±	17±0.47	77.8±	32.47±	92.51±1	96.74±

11	0.05		4.12	0.31	.82	0.39
GPSR-12	0.31± 0.08	20±0.47	78.2± 2.45	32.40± 0.26	89.89±1 .17	98.09± 0.92
GPSR-13	0.33± 0.05	22±0.81	81.6± 3.19	32.36± 0.27	88.39±1 .79	97.54± 0.64
GPSR-14	0.32± 0.05	21±0.47	71.6± 3.09	32.16± 0.27	86.39±1 .70	96.38± 1.46
GPSR-15	0.32± 0.05	23±0.47	71.6± 0.19	30.36± 0.27	87.39±1 .12	97.55± 34
*mean ± SD n = 3						

Results for evaluation of Glyburide Pellets

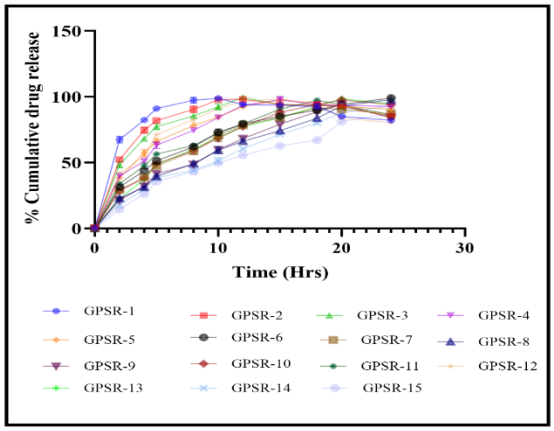


Fig. 10: In-vitro dissolution profile of sustained release Glyburide pellets prepared with different concentration of locust bean gum (formulations GPSR-1 to GPSR-15)

The preliminary studies performed related to friability, % yield, drug Loading and entrapment revealed that almost all batches passed the minimum criteria in the batches selected from initial characterization however there was drastic difference in the release profile. The **GPSR -6** was considered the best formulation and used for the development of bilayer tablet [32].

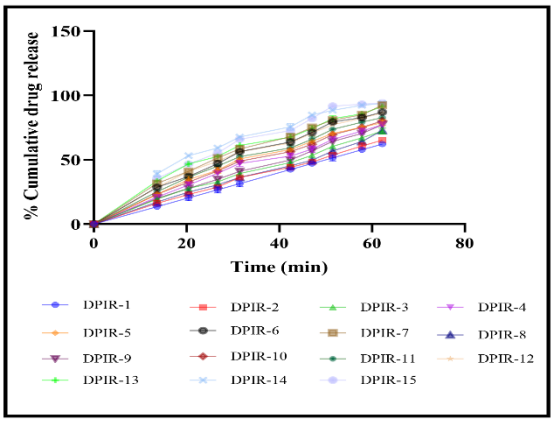


Fig 11: In-vitro dissolution profile of Immediate release Bepridil pellets prepared with different concentration of sodium starch glycolate (formulations DPIR1 – DPIR-15)

Results for evaluation of Bepridil Pellets

Table 10: Results for evaluation of Bepridil Pellets

Formulation code	Friability (%)*	Disintegration Time (min)	Yield (%)*	Drug loading (%) *	Entrapment efficiency (%) *	Drug Content
DPIR-1	0.52±0.02	1±0.47	74.8±1.21	23.06±0.18	92.21±1.24	97.02±0.64
DPIR-2	0.54±0.04	2±0.81	79.1±1.57	23.48±0.24	87.00±0.96	96.35±1.54
DPIR-3	0.47±0.02	2±0.47	81.4±1.83	23.54±0.15	88.51±1.88	95.62±0.69
DPIR-4	0.51±0.05	3±0.81	80.5±1.17	23.78±0.26	94.24±1.23	95.27±0.72
DPIR-5	0.44±0.03	4±0.81	76.8±1.34	23.59±0.25	89.67±1.84	96.65±0.23
DPIR-6	0.49±0.04	5±0.81	78.4±1.92	23.49±0.18	87.15±1.62	96.09±0.22
DPIR-7	0.54±0.05	7±0.47	75.9±1.51	23.62±0.24	90.46±1.48	97.56±1.12
DPIR-8	0.44±0.02	1±0.81	80.2±1.66	23.77±0.25	94.08±1.12	96.49±1.95
DPIR-9	0.49±0.02	1±0.47	79.7±1.77	23.80±0.31	95.19±1.76	97.35±0.83
DPIR-10	0.48±0.04	1±0.47	78.3±1.54	23.68±0.24	91.93±1.83	96.03±0.65
DPIR-11	0.54±0.03	1±0.81	79.1±1.80	23.57±0.20	89.34±1.52	97.43±1.16
DPIR-12	0.54±0.02	1±0.81	80.8±1.68	23.72±0.24	92.81±1.40	96.22±1.57
DPIR-13	0.48±0.05	1±0.81	82.4±1.49	23.63±0.26	90.54±1.07	98.04±1.34
DPIR-14	0.51±0.02	2±0.81	78.6±1.57	23.75±0.21	93.70±1.61	99.65±0.28
DPIR-15	0.45±0.04	2±0.47	77.1±1.61	23.66±0.29	91.38±1.93	98.35±1.34
*mean ± SD n = 3						

The preliminary studies performed related to friability, % yield, drug Loading and entrapment revealed that almost all batches passed the minimum criteria in the selected batches from the initial characterization however there was drastic difference in the release profile. The DPIR-14 was considered the best formulation and used for the development of bilayer tablet.

In-vitro dissolution profile of Immediate release Bepridil pellets prepared with different concentration of sodium starch glycolate (formulations DPIR1 – DPIR-15)

The preliminary studies performed related to friability, % yield, drug Loading and entrapment revealed that almost all batches passed the minimum criteria in the selected batches from the initial characterization however there was drastic difference in the release profile. The DPIR-14 was considered the best formulation and used for the development of bilayer tablet.

Evaluation of Bilayer tablets

GDT1 to GDT 16 bilayer tablet batches of Glyburide and Bepridil Pellets.

Tablet size, thickness, hardness, and friability were all within acceptable parameters, showing high reproducibility and homogeneity in the production process. The drug content analysis of GDT1 to GDT16 batches revealed that Glyburide and Bepridil Pellets were distributed uniformly in the bilayer tablets. The drug content was confirmed to be constant and meet the acceptable standards as shown in Table 11. Dissolution profiles were analyzed to determine the release behavior of Glyburide and Bepridil from the bilayer tablets as shown in Fig 12 and 13 respectively. The results showed that the formulations had the intended drug release patterns and suitable dissolving rates for both active medicinal components. The thickness value varied from 3.8 to 4.3 mm but was within the acceptable range and not posing much variation in the drug contents of both the drugs. The friability was within acceptable limit of ≤ 1 %. The hardness achieved by pellets revealed their alignment with the shape depicting good compressibility. The Weight range for the tablet sample was from 638 to 648 mg having drug content more than 95 % for both the drugs.

The formulation GDT-14 is considered as the best formulation based upon the *in- vitro* drug release studies and desired characteristics. The best model fit for Glyburide layer in tablet formulation is Korsmeyer-peppas and the 'n' value in Korsmeyer-peppas model was found to be between 0.5-1 indicating Anomalous transport as the release mechanism.

The *in- vitro* drug release studies for Bepridil layer in formulation GDT-14 is Higuchi model and the 'n' value in Korsmeyer- peppas model was found to be < 0.5 indicating less Fickian diffusion transport as the release mechanism.

Table 11: Results for evaluation of GDT1 to GDT 16 bilayer tablet batches of Glyburide and Bepridil Pellets

Formulation code	Thickness (mm)*n=20	Friability (%)*n=3	Disintegration time (min)	Hardness (N)* n=10	Weight variation (mg)* n=20	Drug content (%)*n =3	
						Glyburide	Bepridil
GDT1	3.9±0.09	0.42±0.03	12±0.47	4.1±2	642.3±1.5	97.24±2.1	97.11±1.8
GDT2	4.1±0.07	0.59±0.07	15±0.81	5.1±2	645.1±0.9	98.46±2.3	98.56±2.2
GDT3	4.3±0.10	0.53±0.04	20±0.94	5.6±3	638.6±1.2	96.01±1.8	96.90±1.6
GDT4	4.2±0.07	0.40±0.06	16±0.47	4.0±2	645.1±1.6	98.31±1.5	96.15±1.9
GDT5	4.1±0.08	0.67±0.05	18±0.81	5.5±3	646.8±1.0	95.97±1.7	95.07±1.7
GDT6	4.2±0.09	0.51±0.03	16±0.81	5.2±2	641.9±1.2	97.83±1.9	97.66±1.9
GDT7	4.0±0.06	0.46±0.04	30±0.81	4.4±2	645.0±0.8	96.08±2.1	98.27±2.6
GDT8	4.0±0.05	0.49±0.04	10±0.94	4.1±3	648.2±1.4	95.22±2.4	97.93±2.0
GDT9	4.2±0.08	0.53±0.06	10±0.94	5.1±4	642.3±1.7	96.83±1.6	98.07±1.7
GDT10	4.1±0.07	0.41±0.05	16±0.81	5.5±2	636.8±1.1	97.55±1.9	98.14±1.9
GDT11	4.0±0.05	0.55±0.07	16±0.47	5.2±2	646.1±1.3	97.60±1.4	96.07±2.1
GDT12	3.8±0.10	0.39±0.03	21±0.47	5.4±3	639.2±1.4	98.11±1.8	97.92±1.6
GDT13	4.2±0.06	0.58±0.04	21±0.81	5.3±3	643.9±1.2	96.09±2.4	98.80±1.8
GDT14	4.0±0.08	0.60±0.05	22±0.47	5.6±4	645.6±0.9	98.38±1.9	97.15±2.0
GDT15	4.1±0.08	0.46±0.03	22±0.47	5.4±2	647.5±1.5	97.55±2.3	97.68±1.6
GDT16	4.3±0.07	0.48±0.06	10±0.47	5.2±2	640.1±1.3	96.80±2.0	98.53±2.2

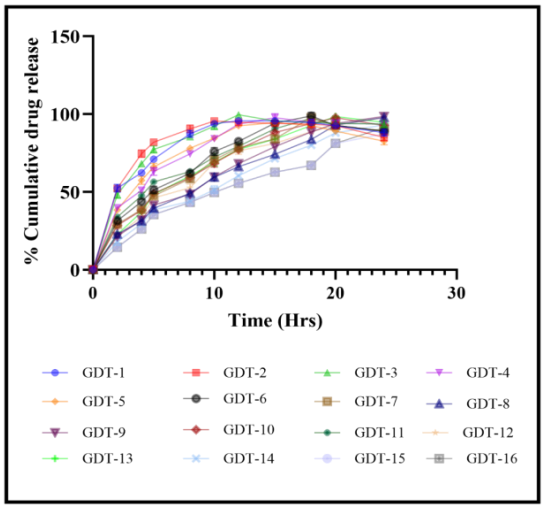


Figure 12: In vitro Glyburide release from GDT Bilayer tablet formulation

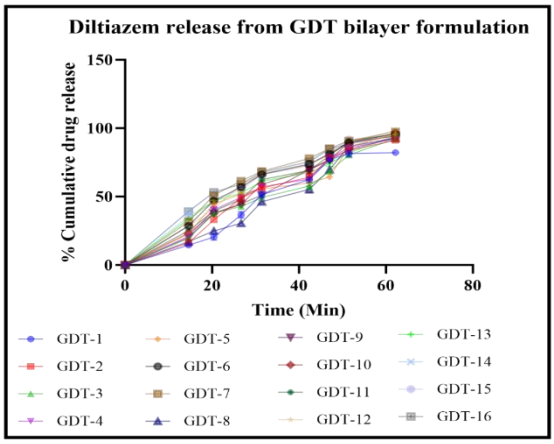


Figure 13: In vitro Bepridil release from GDT bilayer tablet formulation

Plasma Concentration Studies

The plasma drug concentration studies revealed that a Cmax of 872 ng/mL in 7 hr and 875 ng/mL in 12 hrs for Marketed Glyburide tablet and GPSR-6 respectively which indicated there is dose dumping of the Glyburide from marketed formulation however pellets achieved a sustained release with less plasma drug level fluctuation as shown in Table 12 and Fig 14.

The plasma drug concentration studies revealed that a Cmax of 178.78 ng/mL in 3 hr and 172.25 ng/mL in 8 hrs for Marketed Bepridil tablet and DPIR-14 respectively which indicated there is constant drug release from the prepared MUPS whereas the marketed formulation showed quick release achieving higher conc. in short time.

Table 12: Drug Plasma Concentrations from the mixture of Pellets (GPSR-6 and DPIR 14)

Time (Hrs)	Plasma drug concentration (ng/mL)*			
	Glyburide SR tablet (Cyblex 60 XR)	Formulation GPSR-6	Bepridil Tablet (Channel 60)	Formulation DPIR-14
0.6	187.2	119.21	38.21	43.17
1.0	223.1	133.32	85.02	65.03
1.6	536.7	263.68	97.33	73.88
2.0	658.2	378.3	119.28	95.9
3.0	738.8	487.38	173.78	107.78
5.0	828.62	563.63	128.39	135.21
7.0	872.78	683.2	107.2	149.01
8.0	772.21	735.19	89.17	172.25
10.0	593.06	853.11	72.63	151.37
12.0	427.55	875.36	55.3	90.21
24.0	9.13	378.65	37.09	78.78

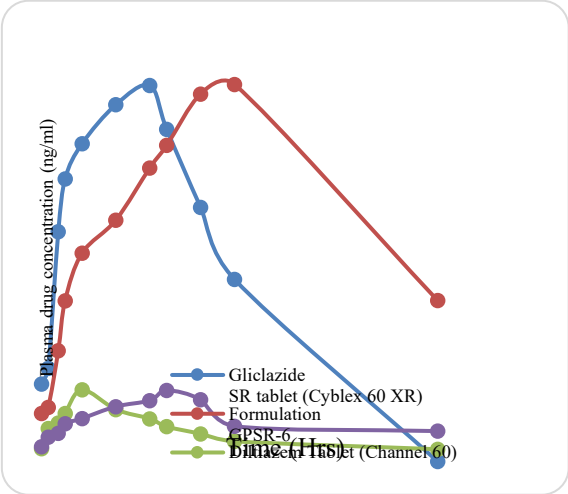


Figure 14: Drug Plasma Concentrations from the mixture of Pellets (GPSR-6 and DPIR 14)

Table 13: Pharmacokinetic parameters achieved for optimized GPSR-6 and DPIR-14 administered together and for marketed formulations of both drugs

Parameters*	C_{max} (ng/mL)	T_{max} (h)	Kel (h^{-1})	$t_{1/2}$ (h)	AUC_{0-24h} (ng h/mL)	$AUC_{0 \text{ to } \infty}$ (ng h/mL)
Glyburide SR tablet	872.78	7	-0.31	2.27	10344.76	10314.91
Glib Formulation	875.36	12	-0.06	11.15	14578.71	8485.35
Bepridil Tablet	173.78	3	-0.04	16.17	1749.22	884.01
Bepri Formulation	172.25	8	-0.03	20.2	2466.09	170.21
*mean ± SD n = 3						

Stability studies:

Physicochemical properties of the fixed-dose combination tablets (GDT and SDT), immediate-release Bepridil pellets (DPIR-14), and delayed-release Glyburide Release (GPSR-6) did not vary significantly.

Table 14: Results of stability samples subjected to 25 ±2°C and 60 ± 5% RH conditions

Parameters	GPSR-6		DPIR-14		VPIR-8	
	Untreated	Treated	Untreated	Treated	Untreated	Treated
Physical Appearance	Round	Round	Round	Round	Round	Round
% Friability	0.37±0.04	0.35±0.04	0.44±0.02	0.46±0.12	0.34±0.07	0.35±0.19
Drug content	96.22±2.4	93.92±2.1	98.93±2.0	96.53±1.6	98.18±1.90	97.08±0.10

Table 15: Results of stability samples subjected to 30 ±2°C and 65 % ± 5% RH conditions

Parameters	**GPSR-6**		**DPIR-14**		**VPIR-8**	
	Untreated	**Treated**	**Untreated**	**Treated**	**Untreated**	**Treated**
Physical Appearance	Round	Round	Round	Round	Round	Round
% Friability	0.37±0.04	0.34±0.04	0.44±0.02	0.38±0.8	0.34±0.07	0.35±0.19
Drug content	95.22±2.4	94.0±1.4	97.93±2.0	96.93±2.2	98.18±1.90	97.18±0.70

Table 16: Results of stability samples subjected to 40 ±2°C and 75 ± 5% RH conditions

Parameters	**GPSR-6**		**DPIR-14**		**VPIR-8**	
	Untreated	**Treated**	**Untreated**	**Treated**	**Untreated**	**Treated**
Physical Appearance	Round	Round	Round	Round	Round	Round
% Friability	0.37±0.04	0.30±0.54	0.44±0.02	0.30±0.72	0.34±0.07	0.30±1.02
Drug content	95.22±2.4	92.32 ±2.4	97.93±2.0	95.03 ±2.0	98.18±1.90	96.28±0.20

Among the other types of combinations developed for the FDC therapy previously described were Multiple Unit Pellet Systems (MUPS), which comprised a layer of sustained-release Glyburide and immediate-release Bepridil pellets. The gum ghatti, guar gum, and locust bean gum were among the natural polymers used to create MUPS. Following characterization to verify identity and purity, the medications and excipients were evaluated for compatibility.

According to their SEM micrographs, the drug-loaded, immediate-release Bepridil and drug-loaded, delayed-release Glyburide pellets demonstrated good flow characteristics and a high level of drug entrapment with a spherical form. The sustained-release Glyburide formulation, which was created using a combination of 2.5% ghatti gum and 2% locust bean gum, was found to be able to sustain the medication release for a whole day in an in vitro study. Likewise, the immediate-release formulation of Bepridil, which included a 1% by weight locust bean gum suspension as a binder and a 7% by weight croscarmellose sodium as a binder, demonstrated rapid pellet disintegration, which resulted in a rapid dissolution of the drug with favourable physical characteristics in the same way.

The dissolving data from the GPSR-6 formulation's kinetic study showed that the drug released at zero order using the proper model. The optimized Bepridil immediate release pellets (DPIR-14) batch passed the evaluation parameters and found stable. In the same manner.

Bilayer tablets were prepared by compressing Glyburide sustained release pellets (GPSR-6) with Bepridil pellets (DPIR 14). In bilayer tablets created by compressing pellets of immediate-release Bepridil and sustained-release Glyburide, the polymer/Superdisintegrants ratio defined/controlled tablet disintegration and further dispersion of the pellets. The bioavailability of the drugs was significantly increased in the in vivo trials on albino Wistar rats when compared to the marketed formulations. The plasma drug concentration studies for the combination of pellets and compared with marketed formulation revealed that the MUPS are able to solve the challenge of dose dumping associated with conventional formulation. The MUPS reduced even the fluctuations and could deliver the drug for longer duration thereby reducing the repeated administration.

According to the stability tests' findings, neither the prepared delayed release Glyburide pellet formulations nor the prepared rapid release Bepridil/ pellet formulations saw any appreciable changes in their friability, drug content or outward appearance. The pharmacodynamic activity of the developed MUPS was able retain the drug activity and resulted in significant activity as compared to the control and model drugs. The developed formulations passed the stability testing at the conditions of stability testing as per ICH guidelines.

4. Conclusion

The effectiveness of multiunit particle systems (MUPS) in treating long-term illnesses like diabetes and high blood pressure. The fixed-dose

combination systems, developed using multiple unit pellet systems (MUPS), are better at treating metabolic illnesses. These systems can be used to address problems with current drug delivery methods, providing patients with tailored treatment choices. The research is useful for researchers, doctors, and companies in the pharmaceutical industry, as it could lead to more successful, safer, and economical therapies.

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