RESEARCH ARTICLE

Formulation Development and Evaluation of Sitagliptin Phosphate Monohydrate and Metformin HCl Tablets

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ABSTRACT

Insulin resistance is actively treated with metformin. This drug improves insulin sensitivity and is essential for managing type 2 diabetes. Glucose can treat diabetes alone if there are no safety concerns, such as renal or liver disease, gastrointestinal difficulties, or lactic acidosis. Metformin is safe and effective. Metformin is the only oral diabetes medicine that does not cause weight gain. Additionally, many diabetics only take this medicine. Treatment for type 2 diabetes usually begins with metformin and sitagliptin. This helps manage blood sugar when diet and exercise fail. When administered alone, sitagliptin plus metformin may not regulate blood glucose well. This aims to manufacture film-coated metformin phosphate monohydrate and hydrochloride tablets in various dosages. This study seeks to create a fixed dose pharmaceutical combination for non-insulin-dependent diabetic mellitus. Metformin HCl with Sitagliptin may improve blood sugar management and HbA1c levels. This combination causes minimal weight gain and fewer adverse effects. This study created and tested sitagliptin-metformin HCl film coated tablets. Wet granulation was used to make the tablets with the requisite excipients. The tablet's parameters before and after compression were evaluated according to the standard. The pre-compression factors, including overall and tapped density, showed good flow characteristics. The weight, hardness, thickness, friability, disintegration, drug concentration, and drug release % were assessed after compression. Results showed these parameters were within acceptable ranges.

Keywords: Insulin resistance, type 2 diabetes, Metformin HCl, Sitagliptin, film coated tablets.

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INTRODUCTION

Definition of Diabetes

People with diabetes type 2, which is another name for diabetes, have a constellation of metabolic ailments that cause their blood sugar levels to stay high. Either the pancreas doesn't make enough hormone or the cells don't react well enough to the insulin that it does make. Either of those events can lead to diabetes. A hormone known as insulin is responsible for facilitating the movement of glucose from meals into cells for the purpose of energy use. There are several types of diabetes mellitus, each of which is classified according to the treatment or origin of the condition[1,2].

Type 1 (IDDM)

Insufficient production of insulin due to beta cell loss in the islets of Langerhans characterizes Type I (or) Insulin-dependent diabetes mellitus (IDDM). It was previously named "insulin-dependent diabetes mellitus" or "juvenile diabetes". Autoimmune reactions destroy beta cells. Unknown autoimmune cause. Adults can get type 1 diabetes, although children and adolescents are most likely[3].

Type II (NIDDM)

Characterized by insulin resistance, cells fail to respond to insulin appropriately. As the situation gets worse, there might not be enough insulin. "Non-insulin-dependent diabetes II " or "adult-onset diabetes" were the first names for this. Diabetes of the type 2 type is particularly prevalent in people over 60. But childhood obesity has increased its prevalence. Insufficient exercise and obesity are the main causes[4].

GDM

Diabetes during pregnancy, also known as gestational diabetes mellitus (GDM), usually goes away after the baby is born. During pregnancy, more hormones are released by the placenta, which helps nutrients move from the pregnant woman to the baby. Placental hormones aid development. Hormones also inhibit the mother's insulin, causing insulin resistance. Insulin resistance makes insulin use difficult for mothers. She may need three times more insulin[5].

Studies suggest that 285 million persons (20-79 years old) had diabetes in 2010, and by 2030, 438 million (7.8%) of the adult population would have it.

Development-dominated regions will see the biggest rises. Diabetes is rising worldwide due to population expansion, ageing, urbanization, obesity, and inactivity. India, China,

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Table 1: Formulation of sitagliptin and metformin tablets 50/500mg; 50/1000

S. No.	Materials	50/50mg	50/1000mg
1	Sitagliptin phosphate monohydrate	135	64.25
2	Metformin hydrochloride	1000	1000
3	Microcrystalline cellulose	27	141.50
4	Povidone k-30	27	30
5	Sodium lauryl sulphate	3	3
6	Croscarmellose sodium	40	40
7	Magnesium stearate	14	14
8	Talc	14	14
9	Colloidal silica	7	7
10	LHPC lh11	46	47
11	Mccp (102)	47	-
Total weight		1360	1360

and the U.S. have the most diabetics. (50.8, 43.2, and 26.8 million)[6].

Metformin- The Preeminent Oral Antidiabetic Agent

Metformin is a biguanide which directly fights insulin resistance. It is also known as an insulin-sensitizing drug and is an important part of managing the condition called type 2 diabetes syndrome (T2DM). As long as there aren't any concerns regarding safety, like kidney or liver disease, stomach problems, or the chance of getting lactic acidosis, glucose can be used as a sole treatment for diabetes.

Metformin works well and is safe. Metformin is the exclusively diabetes medicine that can be taken by mouth that does not help people gain weight. Also, a lot of people with diabetes only take this one drug to treat it. People with diabetes with type 2 mellitus are first treated with a combination of metformin and sitagliptin. It's meant to help control blood sugar levels better when changes to the food and exercise aren't enough. Insufficient regulation of blood glucose levels can be achieved by sitagliptin and metformin on their own[7].

Aim

The study's goal is to create film-coated tablets with this medication phosphate monohydrate and hydrochloride of metformin in a range of dosage sizes.

Objective of the Study

The primary focus of this study is to create a dosage form that delivers fixed-dose combination medicine for the management of NIDDM.

The conjunction of Metformin HCl with Sitagliptin demonstrates a synergistic and perhaps additive impact on glycaemic regulation and minimized glycosylated haemoglobin (HbA(1c)) levels, accompanied by minimal weight gain and fewer adverse effects.

MATERIALS AND METHODS

Method of Preparation of Sitagliptin/ Metformin Granules 50/500mg

Sitagliptin/metformin tablets were prepared by the wet granulation method.

Step 1: Sifting

Metformin HCL, sitagliptin phosphate monohydrate, and additional excipients such as microcrystalline cellulose, sodium lauryl sulfate, and croscarmellose sodium were passed through a #30 sieve.

Table 2: Formulation of coating material

S. No.	Ingredients	Quantity	
		50/500mg	50/1000mg
1	Protectab hp2 transparent	50gm	43.6
2	Talc	15gm	-
3	Titanium dioxide	5gm	5.12
4	Iron oxide red	5gm	5.12
5	Iron oxide yellow	5gm	5.12
6	Purified water	450ml	0.392l

Table 3: Specifications for Weight Changes Based on IP

The average weight of tablet	% deviation
80 mg or lower	± 10
More than 80 mg but not exceeding 250 mg	± 7.5
250mg or accelerating	± 5

Table 4: bulk density of formulations

S. No.	formulations	Bulk density
1	50/500	0.6030
3	50/1000	0.542

Table 5: tapped density of formulations

S. No.	formulations	Tapped density
1	50/500	0.7321
3	50/1000	0.687

Step 2: Dry Mixing

The previously sorted materials were combined for five minutes and thereafter passed through filter number 30.

Step 3: Granulation

Appropriate volumes of povidone K30 (27g) and isopropyl alcohol (260g) were mixed in 60ml of water to create the binding solution, which was subsequently included into the mixture from step 2 and kneaded for 10 minutes in a ribbon mixer at 30 rpm. The travailed mixture was air-dried for one hour and then sifted through a #14 sieve.

Step 4: Drying of Granules

The granules acquired in step 3 were re-dried in a plate dryer at 500°Centigrade for 2 hours.

Step 5

Subsequently, 47g of microcrystalline cellulose, 46g of LHPC, and 7g of water were combined and sifted through sieve #14.

Step 6: Lubrication

Volumes of magnesium stearate, talc, and colloidal silicon dioxide were weighed and subsequently passed through a #30 sieve. Overall dry granules and the sieved mixture from step 5 were uniformly lubricated with a sieved blend of magnesium stearate, talc, and colloidal silica for 10 minutes at 16 rpm[8].

Step 7: Compression

The aforementioned granules were pressed into tablets utilizing a 16D station compression machine with a 7mm punch.

Method of Preparation of Coating Solution

Talc powder, titanium dioxide, reddish iron oxide, and yellow iron oxide were measured according to the quantities specified in the table 2, then triturated and

dissolved in water. Protectab HP2 Transparent was incorporated into the aforementioned solution. The solution underwent filtration.

Method of Preparation of Sitagliptin/ Metformin Granules 50/1000mg

The tablets of sitagliptin and metformin were formulated using the wet granulation technique.

Step 1: Sifting

Microcrystalline cellulose a substance called sodium lauryl sulfate, croscarmellose sodium, metformin HCL, and sitagliptin phosphate hydrates were some of the other ingredients that were put passed by a #30 sieve.

Step 2: Dry Mixing

The previously sorted materials were combined for five minutes and thereafter passed through filter number 30.

Step 3: Granulation

Thirty grams of povidone K30 and 260 grams of isopropyl alcohol were dissolved in 60 milliliters of water, after which the binding solution was incorporated into the mixture (step 2) and kneaded for 10 minutes in a ribbon mixer at 30 rpm. The kneaded dough was air-dried for one hour and then put through a #14 sieve.

Step 4: Drying of Granules

After getting the granules in step 3, they were dried again in an oven dehydrator at 500°C for two hours.

Step 5:

Subsequently, microcrystalline cellulose, 47g of LHPC, and 7g of water were combined and passed through filter #14.

Table 6: hardness of tablet formulation

S. No.	formulations	Core tablet	Film Coated tablet
1	50/500	6	8
2	50/1000	10	15.2

Table 7: The thickness of Tablet Formulation

S. No.	formulation	Core tablet	Film coated tablet
1	50/500	5.6	5.8
2	50/1000	6.8	6.88

Table 8: friability of tablet formulations

S. No.	formulation	Core tablet	Film coated tablet
1	50/500	0.1	0.13
2	50/1000	0.3	0.3

Table 9: disintegration time of tablet formulations

S. No.	formulation	Core tablet	Film coated tablet
1	50/500	3 min 30 sec	5 min 1 sec
2	50/1000	3 min 30 sec	5 min 9 sec

Step 6: Lubrication

The amounts of magnesium ions stearate, talcum powder, and colloid silicon dioxide were weighed, and then that they were placed by means of a #30 sieve. A sieved mix of mg stearate, talc, which and colloidal clay was used to evenly coat the dry crystals as well the processed combination from Step 5. This was done for ten minutes at 16 rotations per minute.

Step 7: Compression

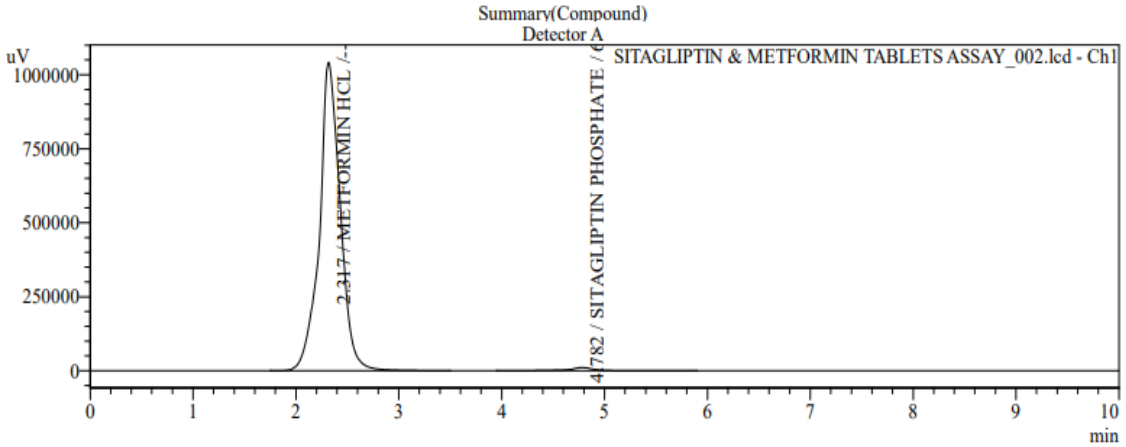

Figure 1: The Chromatogram of sitagliptin and metformin hydrochloride 50/500 mg standard

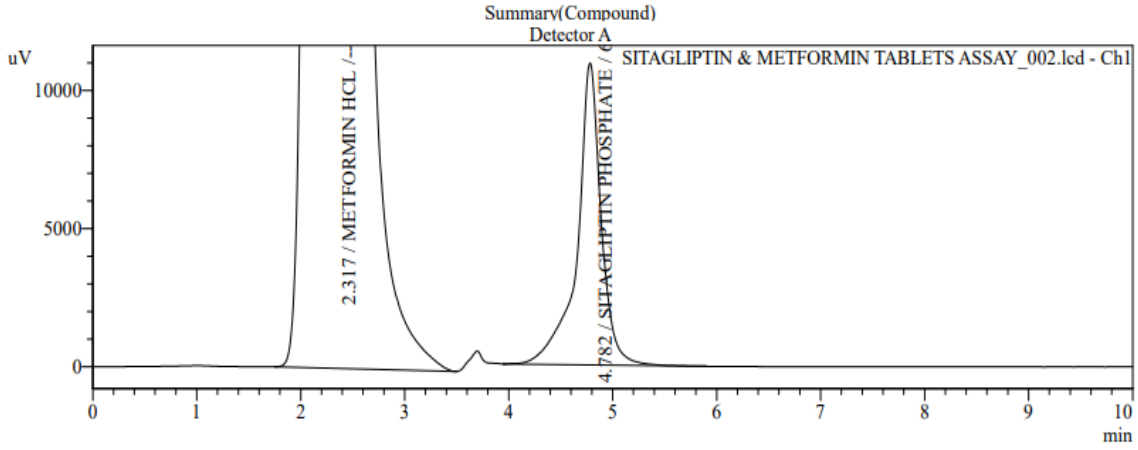

Figure 2: The Chromatogram of sitagliptin and metformin hydrochloride 50/500 mg standard (zoom)

Table 10: Assay of tablet formulations

S. No.	Formulation	Each film coated tablet contains	
		Sitagliptin phosphate monohydrate	Metformin hcl
1	50/500	99.6%	100.4%
2	50/1000	102.5%	99.3%

Table 11: Average weight of core tablet and film coated tablets

S. No.	Formulation	Avg. wt of 20 tablets	
		Core tablet	Film coated tablet
1	50/500	0.680gm	0.698gm
2	50/1000	1.387gm	1.420gm

The aforementioned granules were compressed in an individual stationary rotational compression machine utilizing a 17.5×7mm D-tooling standard somewhat biconvex capsule-shaped punch[9].

Precompression Studies

Bulk Density (Db)

This number shows how much powder there is compared to how much space it takes up. To measure, the ground substance (sieved through standard sieve #20) was put into a measuring vessel, the starting weight was written down, and the method below was used to figure out the final weight. It is written in grams per milliliter and is equal to Db times M/Vb[10].

Where M is the powder's mass and Vb is its bulk volume.

Density in Taps (Dt)

The volume was measured by pressing the powder 750 times. If there was a difference of less than 2% between the two volumes, the tapped volume was written down. If it's more than 2%, tapping is done 1250 times, and the amount that was tapped is saved[11].

Table 12: observed retention time and area for standard

S. No.	Name of sample	Dose (mg)	Retention time	area
1	sitagliptin	50	4.801	212757
		50	4.871	212567
2	Metformin Hcl	500	2.323	139647
		1000	2.322	2481594

Table 13: observed retention time and area for the sample

S. No.	Name of sample	Dose (mg)	Retention time	area
1	sitagliptin	50	4.782	175383
		50	4.889	174492
2	Metformin hcl	500	2.317	1465340
		1000	2.310	1490604

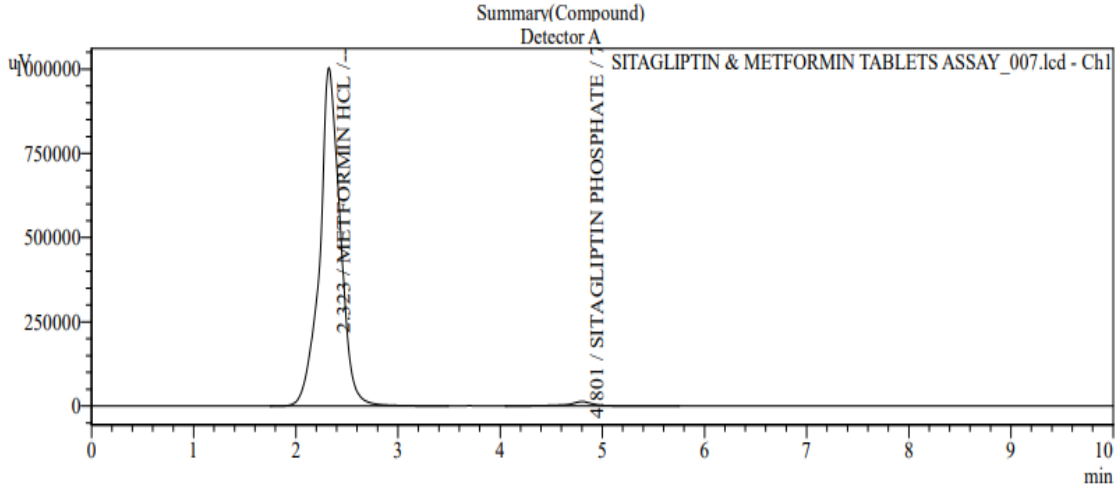

Figure 3: The Chromatogram of sitagliptin and metformin hydrochloride 50/500 mg sample

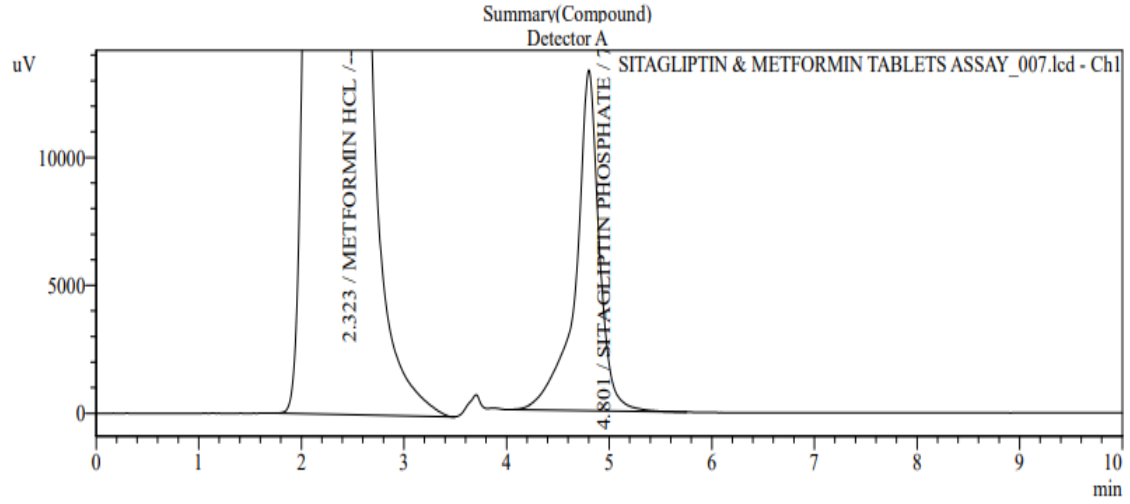

Figure 4: The Chromatogram of sitagliptin and metformin hydrochloride 50/500 mg sample(zoom)

It's written in grams per milliliter and given by
Dt = M / Vt
Where M is the powder's mass and Vt is its tapping volume.

Post Compression Studies

Weight Variation

Twenty pills were chosen at random about the batch and measured separately to see how different their weights were. A median weight was then found. The percentage variation was found by finding the difference between the weight of each tablet and the mean weight[12]. It shows the weight change specifications according to I.P. in Table 3. The medication compression machine was set up correctly so that tablets of the same weight could be made.

Measurement of Thickness

Vernier callipers were used to take individual measurements of the thickness in millimeters for ten tablets that had been pre-weighed, and the median thickness was reported following the measurements. Hardness, disintegration duration, and dissolving rate are all parameters that can be affected by thickness[13].

Hardness

An electro laboratory hardness tester was utilized in order to assess the tablet's level of hardness. Kiloponds(kp) were used to record the crushing capacity of the 10 tablets, each of which had an established weight and thickness. Additionally, the average hardness of the tablets was determined and reported. At the beginning of the compression process as well as throughout the process, the tablet's hardness was evaluated in order to ensure that it remained within an acceptable range.

Friability (F)

The weight of twenty pills were chosen at random from each batch. The battery-powered lab tablet friabilizer spun all of the different combinations of tablets at a speed of 25 spins per minute for four minutes, for a total of 100 rotations[14]. After that, some of the pills were turned into a powder, and the people were weighed again to see how much weight they had lost. After that, the amount of weight loss that was achieved with the first pills was used to figure out the friability. This method is used to find the friability, which is shown by the letter F.

$$F = \frac{initial\ weight - final\ weight}{initial\ weight} \times 100$$

HPLC

The method of high-speed liquid chromatography (HPLC), which is also known as the process of high-pressure liquid chromatography, is used in analytical chemistry to separate, name, and measure the parts that make up a mixture. Pumps are used to move a pressurized liquid solvent containing the

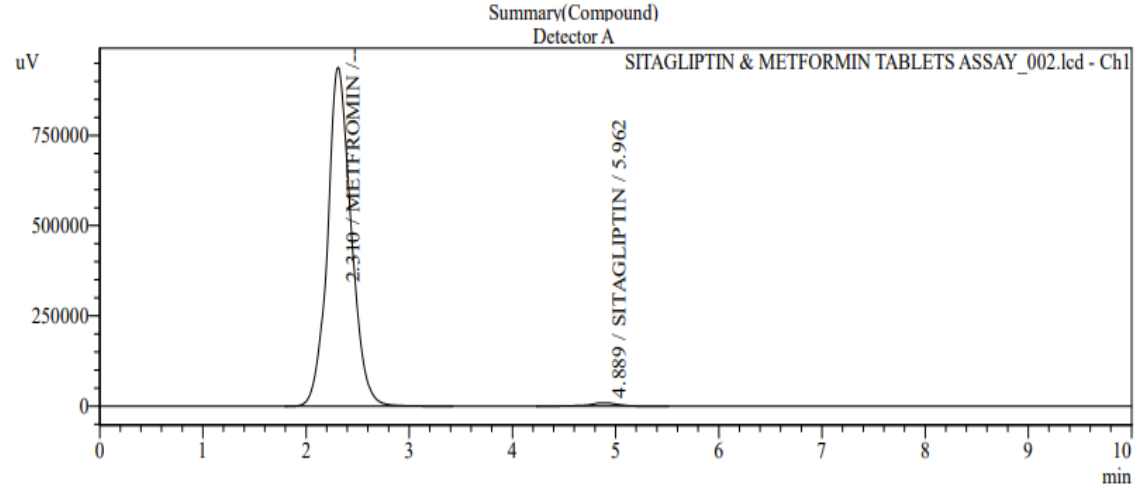

Figure 5: The Chromatogram of sitagliptin and metformin hydrochloride 50/1000 mg Standard

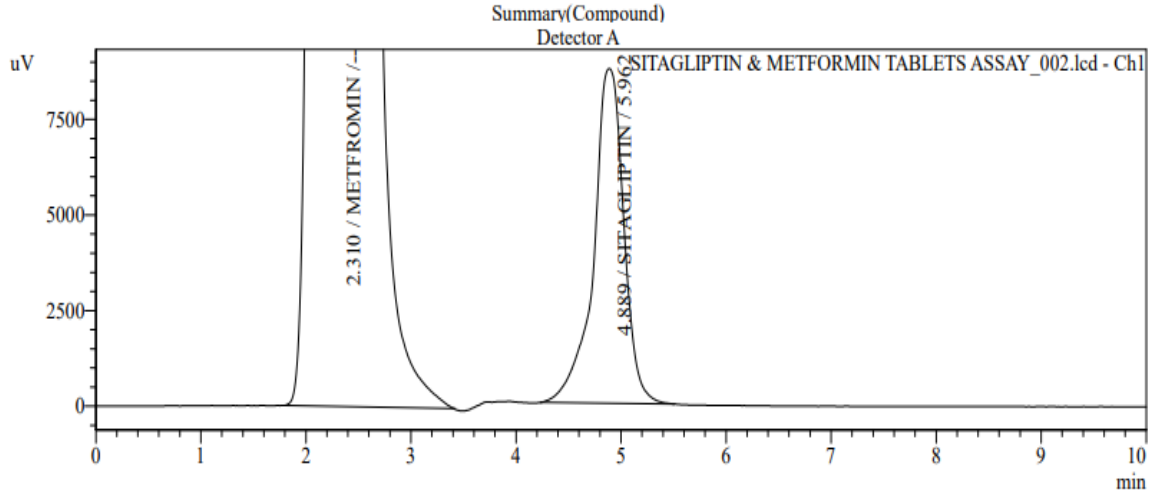

Figure 6: The Chromatogram of sitagliptin and metformin hydrochloride 50/1000 mg Standard (zoom)

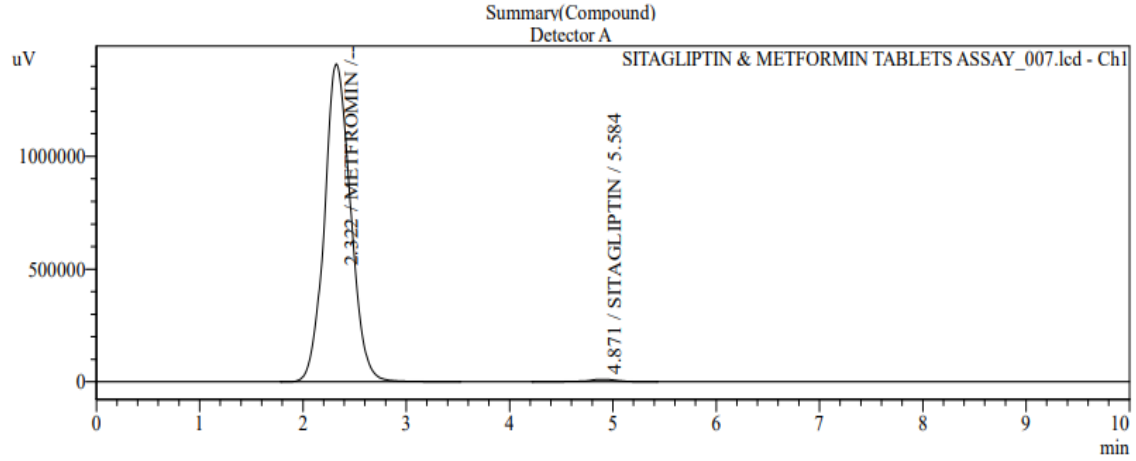

Figure 7: The Chromatogram of sitagliptin and metformin hydrochloride 50/1000 mg sample

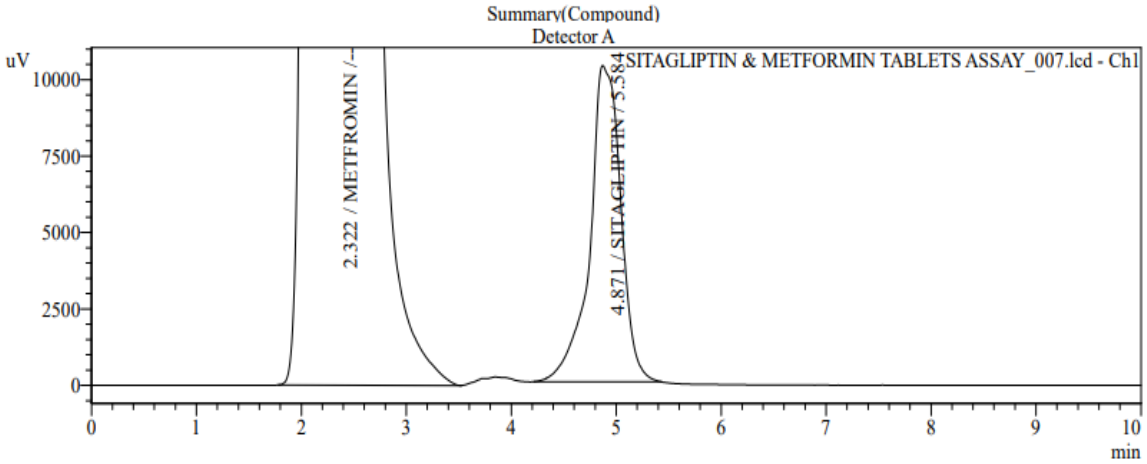

Figure 8: The Chromatogram of sitagliptin and metformin hydrochloride 50/1000 mg sample (zoom)

sample mixture through a column filled with solid absorbent material. Different flow rates are created because each part of the sample interacts with the absorbent material in a different way[15]. With these flow rates, the components can separate as they leave the column.

ASSAY

Buffer Preparation

2.72 granules of dibasic phosphate of potassium were dissolved in 1 litre of water. Orthophosphoric acid was implemented to bring the pH back to 4.01.

Mobile Phase

In a 1-litre volumetric flask, 700 millilitres of acetonitrile was combined with 300 millilitres of the buffer. The solution was sonicated for 10 minutes and subsequently filtered via nylon membrane filters.

Diluent: Water

Standard Preparation

In a 250 ml volumetric flask, 50.9 mg of sitagliptin phosphate working standard and 501.5 mg of metformin hydrochloride were combined with 100 ml of diluent, sonicated until dissolved, and the volume was adjusted with diluent. Subsequently, 25ml of the solution was diluted to a final volume of 50ml using a diluent.

Assay Sample Preparation (50/500mg)

In a 250ml volumetric flask, 611.7mg of sample was combined with 150ml of diluent and sonicated for 30 minutes with continuous shaking, followed by dilution to a final volume of 250ml using diluent. An additional 25 ml of solution was diluted to 50 ml using a diluent, centrifuged, and the clear supernatant was injected.

Assay Sample Preparation (50/1000mg)

In a 250ml volumetric flask, 1.2g of sample was combined with 150ml of diluent and sonicated for 30 minutes with continuous agitation, then the volume was adjusted to 250ml using diluent. An additional 25 ml of solution was diluted to 50 ml using a diluent, centrifuged, and the clear supernatant was injected.

RESULTS AND DISCUSSION

The study details the manufacturing process of sitagliptin and metformin HCl in several forms of administration, specifically 50/500mg and 50/1000mg, to make therapy more efficient and make things easier for patients. The tablets were made employing moist granulation and the alcohol isopropyl as a solvent. They have been tested exhaustively with different polymers to find the best release properties. The composition is being made better. Before they were made, the tablets of various formulations had been assessed for their density in bulk, tapped density. After they were made, they were tested for their compressibility measure, the weight deviations, thickness, the hardness of friability, and the amount of medication. The results are shown in a table number 6,7 & 8. All of the arrangements follow the IP rules.

Evaluation Results of Precompression Parameters
Bulk Density(gm/cm)[3]: How dense the mixture is based on the size of the particles. The bulk density data are shown in the table 4. The bulk density of formulations ranges from 0.603 to 0.542gm/cm^3.
Tapped Density(gm/cm)[3]*:* The results of tapped density are summarized in the table 5. The tapped density of formulations ranges from 0.7321 to 0.687gm/cm^3.
Evaluation Results of Post Compression Parameters
Hardness(kg/cm)[3]: The hardness of tablet formulations is summarized in table 6.
Thickness (mm): The thickness of the tablets is delineated in the table 7.
Friability (%): The friability of tablet formulations is summarized in table 8.
Disintegration Time(min): The Disintegration time of tablet formulations is summarized in table 9.
Assay (%): The drug composition of tablet forms is delineated in table 10.
Average Weight (mg): The average weight of tablet formulations are summarized in table 11.

CONCLUSION

This research was conducted with the intention of developing and evaluating film-coated tablets containing sitagliptin and metformin HCl. In order to make the tablets, the wet granulation method was utilized, and the required amount of excipients was included in the formulation. In accordance with the requirements of the standard, the tablets that had been manufactured were analyzed regarding Parameters for before and after compression. The pre-compression factors, which included the overall density and tapped density, showed that the flow properties were very good. The post-compression parameters, which included weights variation, the degree of hardness its thickness, friability, disintegration, drug concentration, and percentage drug release, have been assessed and it was concluded that they fell within acceptable levels.

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