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Original article

Development and Evaluation of Fast Dissolving Tablets of Poorly Soluble Drug Sitagliptin using Superdisintegrants

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ABSTRACT:
Sitagliptin is used to treat persons with type 2 diabetes and reduce blood sugar levels. The BCS classification for sitagliptin is class II. In the current study, an effort has been made to create a Sitagliptin Fast dissolving tablet using starch soluble as a disintegrant and Cross povidone as well as Crosscarmellose Sodium as superdisintegrants in order to achieve rapid disintegration, which will hasten the onset of action and increase bioavailability. For the creation of Sitagliptin fast-dissolving granules, wet granulation techniques were used, and the evaluation of all pre-compression parameters fulfilled the approval criteria, demonstrating the granules' good flow characteristics. The medication and excipients were compatible, according to FTIR analyses. Following the foregoing formulations, the drug and polymers are thermally stable, according to DSC investigations that were conducted to determine the thermal stabilities of the drug and the physical mixture of the drug and excipients employed in formulation. Different post-compression characterizations of the tablet were conducted, and the results complied with pharmacopoeia requirements. For various formulations, in vitro release tests were performed using a USP II paddle type dissolution equipment. Formulation SFDF12, which has the best initial release rate among all formulations and comprises all three super disintegrant in a concentration of 4% (2% Crosscarmellose and 2% Cross povidone), releases the medication more than 99% within 35 minutes. For the zero order and first order kinetic models, in vitro release kinetic investigations were conducted. To verify the stability of dosage forms, accelerated stability studies were conducted, and the optimised formulation was discovered to be stable to an acceptable range.

Keywords: Fast dissolving, Sitagliptin, Croscarmellose Sodium, Crosspovidone, Sodium starch glycolate.

1. INTRODUCTION

Tablets are still the most popular and widely accepted dosage form. This is because they are constantly being improved and new ideas are being used to fix the main problems with existing formulations. Rapid dissolving drug delivery systems were invented to solve the shortcomings of conventional tablets [1] fast dissolving tablets dissolve and release their medications without rate-controlling coatings or other methods. When the drug has a long half-life and no need for regular dosing, immediate release dose forms are most prevalent. This aids patient cooperation. Rapid response is another rationale for fast dissolving dosage form. Superdisintegrant, along with other excipients such diluents, binder, lubricants, and glidant, is essential for making fast dissolving tablets. Superdisintegrants such sodium starch glycolate (Primojel^{TM}), crosscarmellose (AC-Di-Sol^{TM}), and different grades of crosspovidone (Polyplasdone-XL^{TM}) are used to make fast dissolvingtablets. [2]

Inhibitors of dipeptidyl peptidase 4 (DPP-4) as sitagliptin are effective in treating type 2 diabetes. Damage to the body's ability to control and utilise sugar (glucose) as fuel leads to type 2 diabetes. Too much glucose (sugar) circulates in the blood because to this persistent (chronic) disease. In the long run, elevated blood sugar levels can cause problems with the body's nervous system, immunological system, and circulation. Type 2 diabetes is characterised by either insufficient insulin production or insulin resistance. Increased thirst, urination, hunger, weariness, and difficulty seeing are all symptoms. Symptoms aren't always present. When combined with diet, exercise, and maybe other drugs, sitagliptin can help persons with type 2 diabetes control their blood sugar levels (condition in which blood sugar is too high because the body does not produce or use insulin normally). The insulin-boosting effects of sitagliptin reduce glucose excess in the liver. The effects of GLP-1 and GIP are prolonged by sitagliptin. Sitagliptin reduces glucose excess in the liver by increasing insulin synthesis and

decreasing glucagon output from alpha cells. The scientific name for sitagliptin is (3R) -3-amino -1-[3-(trifluoromethyl) -6,8-dihydro-5H-[1,2,4] triazolo[4,3-a]pyrazin-7-yl] Hydrochloride of 4-(2,4,5-trifluorophenyl)butan-1-one. Although cytochrome p450 (CYP)3A4 and, to a lesser extent, CYP2C8 and protein binding mediate the minor metabolic pathways by which sitagliptin is metabolised, these routes account for less than 1% of the drug's total clearance. Sitagliptin is only moderately bound to plasma proteins (38 percent). In addition to the once-daily administration of 100 mg, the terminal half-life (t12) of elimination is around 8 to 14 hours. With a BCS classification of Class III/borderline Class I and a high oral bioavailability of 87%, sitagliptin is easily absorbed. Cmax is reached about 1–4 hours post oral dosing. At 24.5 degrees Celsius, sitagliptin has a PKa of 8.78 and an aqueous solubility of 69.5 mg/g [3].

Using starch soluble as a disintegrant and Cross povidone and Crosscarmellose Sodium as superdisintegrants, the primary goal of the current studies was to formulate and conduct in vitro evaluation studies of fast dissolving tablets of Sitagliptin to achieve rapid disintegration when taken via oral route, permitting a rapid onset of action and improved therapeutic efficacy.

2. MATERIALS AND METHODS

2.1. Materials

Sitagliptin was got through a free sample from Dr. Reddy's Laboratories in Hyderabad, India.

Also, Dr. Reddy's Laboratories Pvt. Ltd. generously gave gift samples of the superdisintegrantcrosscarmellose and crosspovidone. Specifically, Otto Manufacturing supplied both the micro crystalline cellulose (Avicel 101) and the mannitol employed in the formulation. S.D. fine chemicals Pvt. Ltd. in Mumbai, India provided the talc, magnesium stearate, talc, and PVP K30. Everything was of the top-notch quality needed for rigorous scientific study. Before being used in the lab's research, the water went through two distillation processes.

2.2. Determination of λ_{max} of pure Sitagliptin and preparation of calibration curve

In order to quantify the maximum wavelength absorption against a blank between 200 and 400 nm, the UV spectrophotometer was auto-zeroed and the standard solution was scanned. The absorbance maxima of the standard solution were scanned against a blank. In pH 0.1N HCl buffer, the greatest absorbance was discovered to be 267nm, which was fixed as the wavelength for drug analysis. To achieve 500 ppm, 50 mg of Sitagliptin were accurately weighed and dissolved in 250 ml of 0.1N HCl acid buffers. From this, aliquots of 5, 10, 15, 20, and 25 ppm were prepared, and the absorbance was measured at a maximum wavelength of 267 nm, in accordance with Beer Lambart's law and linearity [4].

2.3. Drug excipients compatibility studies

FTIR and DSC analyses were performed to ensure that drug excipients were compatible.

2.4. Fourier Transform Infrared (FTIR) spectroscopy:

To ensure there was no chemical or physical contact between the active ingredient and the excipients, a Fourier transform infrared (FTIR) analysis was conducted. FTIR analyses were performed on both Sitagliptin in its purest form and the drug's physical mixture with all excipients (the optimum formulation). The KBr pellet approach was used to carry it out. Using a pressure of 100 kg/cm2 for 2 minutes, we triturated the samples with KBr and made pellets. To examine the pellet, scientists used an FTIR 8400S from Shimadzu, Japan. First, a KBr history was compiled, followed by an examination of the samples themselves. Analyses of the drug, individual excipients, and the physical mixing of the drug and excipients all followed the same protocols [5].

2.5. Differential Scanning Calorimetric (DSC) analysis:

Thermal analysis using DSC or TGA techniques is another way to estimate the physical interaction between the drug and polymers employed in the formulation of various dosage forms. These experiments used a Shimadzu DSC 60, Japan, to analyse Sitagliptin and the physical mixing of drug with excipients (optimised formulation) used in the development of Sitagliptin fast-dissolving tablets in order to assess the potential for a thermal interaction between the polymer and the drug. Hermetically sealed samples of 5–6 mg were heated at a continuous rate of 10 °C/min from 40–300 °C. Purging with nitrogen gas at a rate of 50 ml/min kept the environment completely inert [6].

2.6. Formulation of Sitagliptin fast dissolving tablets

The fast dissolving tablets of Sitagliptin were made using the wet granulation process (Table 1). Before being used in formulations, all constituents were weighed and sieved through no. 80 to ensure accuracy. Sitagliptin, mannitol, MCC, crosscarmellose sodium, crosspovidone, soluble starch, and PVP K30 powders were mixed together and sieved through a #20 mesh screen to ensure uniformity and accuracy in each formulation. Binders consisting of polyvinylpyrrolidone (PVP K30) were used. Drying the aggregates for 5-10 minutes after adding the binder helped to lower the moisture content and keep them from sticking to the sieve. In order to obtain granules, the aggregates were sieved through a #20 mesh screen. Water content is reduced to 2-5% by drying the granules at 40 degrees Celsius for 20 minutes. The necessary amounts of Magnesium Stearate and talc were combined with the dry granules for two to three minutes to create a lubricant. Lubricated formulations were tested for compressibility index, Hausner's ratio, angle of repose, and bulk density before being compressed. Tablets were formed from the evaluated granules using a 10-station rotary punching machine equipped with 8mm concave punches (Saimach Pharmaceutical Pvt. Ltd.). Sitagliptin 100 mg/250 mg = 250 mg/tablet. Table 1 provides the formulas used to create the various formulations, all of which were

created using the same procedure. The post-compression characteristics of the tablets were examined, including their mean thickness, standard deviation of weight, hardness, friability, drug content, and solubility in vitro [7, 8].

Table 1: Compositions of different excipients used for Sitagliptinfast dissolving tablets

Drug and Excipients	SFD F_1	SFD F_2	SFD F_3	SFD F_4	SFD F_5	SFD F_6	SFD F_7	SFD F_8	SFD F_9	SFD F_{10}	SFD F_{11}	SFD F_{12}
Sitagliptin (mg)	100	100	100	100	100	100	100	100	100	100	100	100
Mannitol (mg)	25	25	25	25	25	25	25	25	25	25	25	25
Microcrystalline cellulose (mg)	85	80	75	85	80	75	85	80	75	80	80	80
PVP K30 (mg)	25	25	25	25	25	25	25	25	25	25	25	25
Starch soluble (mg)	5	10	15	-	-	-	-	-	-	5	5	
Cross Povidone (mg)	-	-	-	5	10	15	-	-	-	5	-	5
Cross Carmellose (mg)	-	-	-	-	-	-	5	10	15	-	5	5
Magnesium Stearate (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc (mg)	5	5	5	5	5	5	5	5	5	5	5	5
Titanium Dioxide (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total Weight	250	250	250	250	250	250	250	250	250	250	250	250

2.7. Evaluation of pre-compression parameters of Sitagliptin fast dissolving granules of all formulations

Angle of repose(θ):

The angle of repose is the highest angle that may be made between the surface of a pile of granules and the horizontal plane, and it is a crucial element in determining the flow properties of granules. Granules were dropped into a funnel that was mounted on a platform at a known height (h). Then, the angle of repose was determined by gauging the height and radius of the granules' resulting found (Equation 1).

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$ .....(Equation 1)

Whereas h and r were the height and radius of the granule heap, respectively, is the angle of repose. If the angle of repose is less than 250, the flow is considered great, and if it is between 250 and 300, the flow is considered good. If the angle is between 300 and 400, the flow is acceptable, and if it's higher than 400, the flow is quite poor [9].

Bulk density:

Sitagliptin fast dissolving granules were made in a variety of different formulations, and their LBD and TBD were measured. Two grammes of each formulation's granules were measured out and added to a 10-milliliter measuring cylinder after being gently shaken to disperse any clumps. The initial volume was recorded, and then the cylinder was dropped from a height of 2.5 cm at second interval until it hit a hard surface under its own weight. In order to ensure that no further volume fluctuations would be detected, the tapping was continued until it was no longer necessary. The following equations were used to determine the LBD and TBD of the granules after they had been produced (Equation 2 and 3) [10].

$$LBD = \frac{weight\ of\ the\ granule}{volume\ of\ the\ packing}$$ .....(Equation 2)

$$TBD = \frac{weight\ of\ the\ granule}{tapped\ volume\ of\ the\ packing}$$ .....(Equation 3)

Compressibility Index (Carr's index):

The flow ability of granules can be measured by comparing the loose bulk density (LBD) and tapped bulk density (TBD) of granules and the pace at which it packed down. Compressibility index (Carr's index) of produced Sitagliptin fast dissolving granules were computed by following formula (Equation 4)

$$Carr's\ index\ (\%) = \frac{TBD - LBD}{TBD} \times 100$$ .....(Equation 4)

For optimal flow, the standard calls for a Carr's index "between" 5 and 15, whereas a number of 12 to 16 suggests good flow. If the value is between 18 and 21, it's considered to be passable, but if it's between 23 and 25, it's considered to have poor flow. Very bad flow is between 33 and 38, while extremely poor flow is over 40 [11].

Hausner's ratio:

Formula was used to determine Hausner's ratios for finished fast-dissolving granules of Sitagliptin (Equation 5).

$$Hausner's\ ratio = \frac{TBD}{LBD}$$ .....(Equation 5)

By definition, numbers below 1.25 indicate good flow (20% of Carr's index), whereas values above 1.25 indicate bad flow (33% of Carr's index). The optimal glidant addition range is between 1.25 and 1.5, where the flow is typically improved [12].

2.8. Evaluation of post-compression parameters of Sitagliptin fast dissolving tablets of all formulations

Thickness

The thickness of ten fast-dissolving Sitagliptin tablets from each formulation was measured. Digital Vernier Calipers (Mitutoyo dial Thickness Gauge, Mitutoyo, Japan) were used to measure the thickness of each tablet, and the results were reported as the average value and standard deviation of 10 measurements. In order to meet specifications, tablets' thickness must be maintained within a range of 5% of the nominal value [13].

Tablet Hardness

The hardness of all Sitagliptin fast dissolving tablet formulations was evaluated using a Monsanto hardness tester (Cad Mach). Ten fast dissolving tablets of known

weight were crushed from each formulation, and the average crushing strength and standard deviation were recorded. The USP specifies that for uncoated tablets, a hardness value of 3-3.5 kg is the maximum that can be used safely [14].

Friability

Ten fast-dissolving Sitagliptin pills from each batch were previously weighed using a Roche friabilator (Roche friabilator, Secor India, Delhi, India). One hundred turns of the friabilatorresulted in the recovery of the tablets. Following this, the dust was cleaned off the tablets and their final weight was recorded. The following formula was used to determine friability (Equation 6).

$$\%F = \frac{(Wi - Wf)}{Wi} \times 100$$ .....(Equation 6)

Where Wi and Wf were the tablets' starting and ending weights before and after the friability test, respectively. Losses in pill weight of 0.1% to 1.0% are considered acceptable during compression [15].

Weight variation test

The weight variation of all Sitagliptin fast dissolving tablet formulations was assessed in accordance with the USP standard. Using an electronic balance, twenty pills were weighed in bulk and then separately. It was possible to determine the standard deviation and the percentage of variance in each tablet's weight. The USP standard specifies a 10% weight tolerance limit for uncoated tablets with an average weight of 130mg or less, a 7.5% weight tolerance limit for tablets with an average weight of 130mg to 324mg, and a 5% weight tolerance limit for tablets with an average weight of 324mg or more. For the tablet to be approved, its weight cannot vary by more than 7.5% from the mean value, and no individual tablet's weight can vary by more than 15% from the mean [16].

Content uniformity

Twenty Sitagliptin fast-dissolving pills were consumed, triturated to make powder, and then dissolved in 100 ml of HCl buffer pH 1.2 while being heated at 37 0C for 15 to 20 minutes while stirring. The result was powder equivalent to one tablet. The sitagliptin content was determined using a UV Spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at 267 nm after the solution had been filtered and appropriately diluted. The average medication content in the Sitagliptin fast dissolving tablets was computed after each measurement was made in triplicate [17].

Wetting time and water absorption ratio

A petri dish with an internal diameter of 6.5 cm and 10 ml of HCl buffer pH 1.2 containing methylene blue (0.1% w/v) was filled with twice-folded tissue paper. On the surface of the tissue paper in the petri dish, a tablet was carefully placed from each variety of Sitagliptin quick dissolving tablets. Wetting time was measured as the length of time it took for the dye to reach the tablet's top surface. The standard deviations were also calculated, and measurements were done in triplicate.

The weight (Wb) of the tablet before it is placed on the petri dish, followed by the observation of the wetting period, can be used to determine the water absorption ratio (R). The wetted tablet was taken out and weighed again (Wa), and the water absorption ratio (R) was calculated using the equation below [18] (Equation 7).

$$R = \frac{(Wa - Wb)}{Wb} \times 100$$ .....(Equation 7)

In-vitro disintegration time (D_t)

The disintegration apparatus is used without the covering plastic discs in the USP (United States Pharmacopoeia) disintegration test for fast-dissolving tablets, and 2 min is specified as the acceptable time limit for tablet disintegration fulfilling the official requirements (2 min) for fast-dissolving dosage form. The experiment was conducted using a tablet disintegration device (model EI D-16, Electrolab, Mumbai, India). Using a modified disintegration method, an in vitro disintegration test was performed (n = 6) with the disintegration tester kept at 37°C ± 0.5°C in HCl buffer pH 1.2. The time it took for each tablet to totally break down into smaller particles was recorded while the tablets were kept in the basket [19].

In-vitro drug release study

Using an eight station USP dissolution rate test apparatus type-II, the in vitro dissolution research for all of the formulations was carried out (LABINDIA DS 8000, Mumbai, India). As the dissolution media, a total volume of 900 ml of HCl buffer pH 1.2 was used, which was kept at 37°C 0.5°C at 50 rpm. The sample volume was periodically refilled with an equivalent volume of new dissolving medium while 5ml of aliquots were removed. The Whatmann filter paper was used to filter the samples, which were taken at 5-minute intervals. Spectrophotometric analysis was used to measure the amount of sitagliptin released from fast-dissolving tablets in samples [20, 21].

Characterization of the in vitro drug release profile

By plugging the dissolution data into the subsequent exponential equations, the rate and mechanism of Sitagliptin release from manufactured fast-dissolving tablets were examined.

Zero-order release formula (Equation 8)

$$Q = K_0 t$$ .....(Equation 8)

Where Q is the amount of drug released at time t and K_0 is the zero-order release rate constant.

The first order equation (Equation 9):

$$\log(100 - Q) = log100 - K_1 t$$ .....(Equation 9)

Where, K_1 is the first order release rate constant [22, 23].

2.9. Stability studies of optimised formulation

According to ICH requirements, stability tests of the Sitagliptin fast-dissolving tablet's optimised formulation

were conducted. The improved formulation was put under accelerated stress conditions for 90 days at 40°C ± 2 °C/ 75% ± 5% and 75 % ± 5 % relative humidity. Following that, the product's friability, hardness, weight variation, thickness, drug content, and in vitro drug release research were assessed [24].

3. RESULTS AND DISCUSSION

Compatibility studies by FTIR and DSC:

The FTIR spectra of pure drug Sitagliptin, and physical mixture (optimised formulation) of drug with all excipients used were shown in **figure 1 and 2**. By comparing the spectra of the pure Sitagliptin drug and Sitagliptin with excipients used in formulation, it can be seen that the broad peak that appeared at 3503 cm-1 also appears in Sitagliptin with excipients used in formulation at 3525 cm^{-1} due to N-H stretching and the sharp peaks that appear in spectra of Sitagliptin at 2918 cm^{-1} appear at 2920 cm^{-1} due to -CH stretching. Due to CH stretching, the broad peak that first occurred at 3184 cm^{-1} also emerges in a physical mixture of sitagliptin with formulation excipients at 3209 cm^{-1} (Alkene). The characteristic Sitagliptin IR absorption peaks at 1557 cm^{-1} (C=C stretching (Aromatic)), 1508 cm^{-1} (N-H bending), 1339 cm^{-1} (CH bending (alkane)), 1015 cm^{-1} (C-N vibration), and 853 cm^{-1} (CH bending (aromatic)) were also present in the physical mixture of Sitagliptin with excipients used for formulation. There was no shifting in the major peaks and no additional.

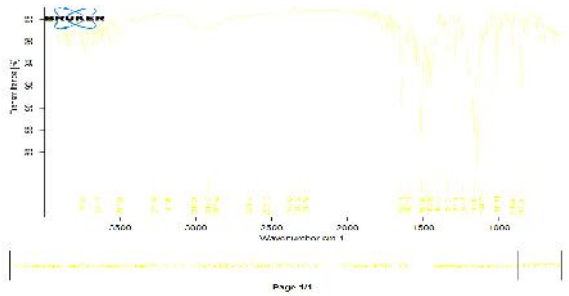

Fig 1:FTIRSpectra of Sitagliptin Pure Drug

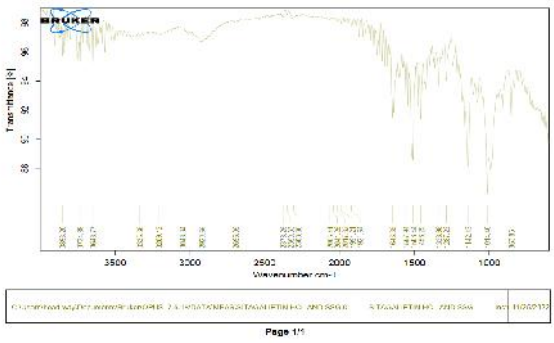

Fig 2: FTIR Spectra of Sitagliptin with excipients used in Indications

To rule out any potential drug and polymer thermal interaction, Sitagliptin's DSC thermogram and a physical mixture of Sitagliptin and excipients utilized in the formulation of fast-dissolving tablets were obtained. This study evaluated the endothermic peaks that formed in the formulations of pure medication and tablets that dissolve quickly. It was noted that the endothermic peak for sitagliptin appeared at 120.35°C and in the physical mixture at 120.15°C. When sitagliptin is physically mixed with polymers, such as crospovidone and croscarmellose sodium, endothermic peaks can be seen at 148.2 °C and 80.5 °C on the DSC thermogram, respectively. According to the aforementioned DSC investigations, the formulation is thermodynamically stable because it required approximately the same amount of heat as the pure medication and the inclusion of various excipients in the drug didn't result in any thermal changes. Additionally, no endothermic to exothermic peak shifting was observed. Figures 4.5 and 4.6 display the DSC thermograms for sitagliptin and the physical mixture of sitagliptin and excipients utilized in the manufacture of fast-dissolving tablets.

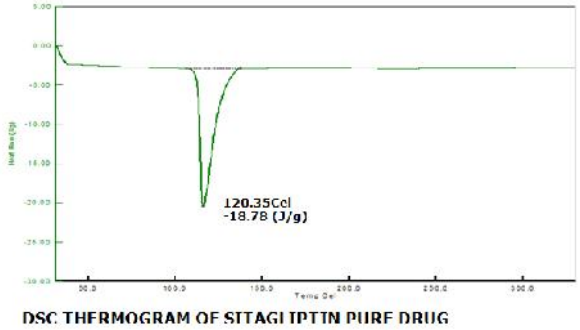

Fig 3: DSC thermogram of the pure medication Sitagliptin

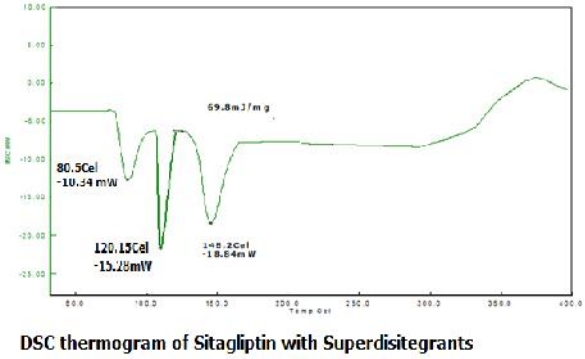

Fig 4: Sitagliptin DSC Thermogram with Excipient for Fast Dissolving Tablets

To better understand the flow characteristics of granules for the convenience of tablet formulation manufacturing, precompression parameters including bulk and tapped density, Hausner's ratio, Carr's index, and angle of repose were measured. This indicated that the granules had good packing capacity. According to measurements of bulk and tapped densities, the density of granules is dependent on particle packing and changes when the granules consolidate. The relevant phenomena to employ in estimating the flow properties of particles larger than 150 m is angle of repose. Angles of repose 25°C indicate free flowing of the material, whereas 40° indicate poor flowing of the substance The angle of repose of all formulations was less than 25°C, and

the Sitagliptin fast-dissolving tablet granules had good flow properties that were suitable for tablet compression. Table 2 provides the precompression parameter results for all Sitagliptin fast dissolving tablet formulations. When the Carr's index is less than 16%, it typically means that all of the formulations have adequate flow properties. A lack of consistency in powder size and the presence of more small particles in some formulations may be the cause of higher Carr's index readings. The Hausner's ratio is a simple method for determining the cohesiveness of a granule column and for estimating the flow parameters. All Sitagliptin fast dissolving tablet formulations showed low ranges of Hausner's ratio, indicating good granule flowability. In general, granules with a Hausner's ratio value below 1.25 have excellent flow properties, and this was the case for all of the formulations of the fast-dissolving sitagliptin granules under study.

Table 2: Evaluation of pre-compression parameters Sitagliptin fast dissolving tablets formulations $SFDF_1$ to $SFDF_{12}$

Formulation Code	Angle of repose ± SD*	Bulk density ± SD*	Tapped Density ± SD*	Compressibility Index (%)± SD*	Hausner's ratio ± SD*
$SFDF_1$	23.10±0.37	0.342±0.02	0.392±0.01	12.76±0.12	1.15±0.004
$SFDF_2$	22.34±0.62	0.301±0.01	0.352±0.02	14.49±0.14	1.17±0.005
$SFDF_3$	22.41±0.37	0.324±0.01	0.378±0.03	14.29±0.12	1.17±0.003
$SFDF_4$	21.46±0.25	0.322±0.02	0.376±-01	14.36±0.34	1.17±0.004
$SFDF_5$	21.57±0.18	0.343±0.02	0.397±0.02	13.60±0.34	1.16±0.003
$SFDF_6$	20.25±0.47	0.324±0.01	0.375±0.03	13.60±0.31	1.16±0.002
$SFDF_7$	22.51±0.26	0.343±0.01	0.388±0.02	11.60±0.24	1.13±0.005
$SFDF_8$	21.35±0.40	0.334±0.03	0.374±0.03	10.70±0.15	1.12±0.002
$SFDF_9$	22.72±0.35	0.313±0.02	0.365±0.01	14.35±0.26	1.17±0.005
$SFDF_{10}$	22.60±0.47	0.332±0.02	0.381±0.06	12.86±0.14	1.15±0.002
$SFDF_{11}$	22.46±0.28	0.323±0.04	0.379±0.04	15.34±0.15	1.17±0.004
$SFDF_{12}$	20.28±0.56	0.322±0.03	0.374±0.02	13.90±0.27	1.16±0.003

All values are expressed as average± SD; (n=3)

The uniformity of tablet thickness mostly influences the formulations' content homogeneity. Each batch had a consistent thickness, and the fluctuation fell within the acceptable range. The homogeneity of tablet thickness indicated that the depth of granule fills and applied force were both uniform during tablet punching. The weight fluctuation is a crucial variable that needs to be closely monitored because it has an immediate impact on the formulations' medication content. For several formulations, the percent weight changes were determined to be under 5%. All formulations were accepted for the test for weight uniformity in accordance with official requirements because the tolerated percentage variation for tablet formulations with weights of 250 mg is 5%, and all formulations fell within the limit.

One crucial factor that shows a tablet's resistance to damage during transportation is its hardness. For all Sitagliptin Fast dissolving tablet formulations, the hardness was between 3 and 4 kg/cm2. The hardness of the formulations typically decreased when the amount of superdisintegrant was increased, as was the case with formulations $SFDF_3$, $SFDF_6$, and $SFDF_9$.The physical characteristic of a tablet called friability is typically used to calculate the percentage of losses that occur during packing and shipping. All formulations had a percentage friability < 1%, and the percentage friability increased as the concentration of superdisintegrant rose. To keep the formulations' bioequivalency, tablets' medication contents must be consistent from one to the next. All of the Sitagliptin Fast dissolving tablet formulations $SFDF_1$ to $SFDF_{12}$ had drug content percentages that ranged from 95 to 105 percent, which was within acceptable bounds (Table 3). The value made sure that the tablet's medication content was evenly distributed.

Table 3: Sitagliptin fast-dissolving tablets were evaluated based on post compression parameters ($SFDF_1$ to $SFDF_{12}$)

Formulation Code	Weight variation ± SD*	Hardness ± SD*	Friability (%) ± SD*	%Drug content ± SD*
$SFDF_1$	3.23±0.025	4.4±0.054	0.54±0.14	99.34±1.15
$SFDF_2$	3.34±0.020	4.1±0.010	0.59±0.21	98.72±1.21
$SFDF_3$	3.26±0.037	3.2±0.011	0.63±0.23	98.85±1.16
$SFDF_4$	3.34±0.041	4.3±0.010	0.53±0.34	99.28±0.65
$SFDF_5$	3.25±0.015	4.0±0.013	0.57±0.05	98.94±0.28
$SFDF_6$	3.35±0.012	3.5±0.026	0.65±0.07	100.68±0.65
$SFDF_7$	3.26±0.023	4.6±0.015	0.55±0.05	99.47±0.47
$SFDF_8$	3.65±0.022	4.2±0.015	0.60±0.08	101.28±0.76
$SFDF_9$	3.64±0.015	3.1±0.055	0.65±0.06	99.16±1.15
$SFDF_{10}$	3.73±0.024	4.7±0.024	0.54±0.06	99.73±1.27
$SFDF_{11}$	3.27±0.015	4.2±0.077	0.61±0.08	101.37±0.54
$SFDF_{12}$	3.38±0.022	3.8±0.961	0.68±0.09	99.38±0.37

All values are expressed as average± SD; (n=3)

Another crucial factor that impacts the formulation's disintegration time is wetting time. A fast-dissolving formulation's wetting time will affect how quickly it dissolves, as will its disintegration time. All of the fast-dissolving formulations had a mean wetting time of 1-2 minutes. When it comes to wetting time, formulas for $SFDF_3$, $SFDF_6$, $SFDF_{11}$, and $SFDF_{12}$ typically saw a reduction in wetting time when the amount of superdisintegrant was increased. At equivalent

concentrations, the former showed a shorter wetting time than the latter for cross povidone, cross carmellose, and starch soluble. To accelerate dissolution, disintegration is a necessary first step. Usually, the rate of dissolution increases as the disintegration time decreases. All Sitagliptin fast dissolving tablet formulations ($SFDF_1$ to $SFDF_{12}$) were found to have disintegration times between one and three minutes. It was shown that increasing the amount of superdisintegrant decreased the disintegration time, but that increasing the concentration above 6% caused the hardness value to drop significantly. Superdisintegrants' hydrophilic nature leads it to absorb water and trigger burst effects that break larger particles into smaller ones. Fast-dissolving formulations' water absorption ratio and disintegration time are directly related. Less time is required for disintegration the higher the water absorption ratio. The range of the water absorption ratio for formulations **$SFDF_1$ to $SFDF_{12}$** was found to be 64.25±0.9 to 98.54±1.3; the rise in the water absorption ratio with an increase in superdisintegrants concentration may have something to do with the formulations becoming more porous. Table 4 lists the physicochemical characteristics of several formulations of Sitagliptin fast-dissolving tablets.

Table 4: Sitagliptin fast-dissolving tablet post-compression properties, from formulation $SFDF_1$ to $SFDF_{12}$

Formulation	Wetting time ± SD*	Water absorption ratio ± SD*	*In Vitro* dispersion time (secs) ± SD*	Dis-integration time (secs) ± SD*
$SFDF_1$	82±0.26	64.25±0.9	27.01±0.34	28.45±0.7
$SFDF_2$	66±0.36	79.36±1.4	22.55±0.42	25.02±0.2
$SFDF_3$	35±0.31	91.54±1.5	18.11±0.21	22.78±0.5
$SFDF_4$	56±0.35	85.26±1.3	19.97±0.34	29.96±0.2
$SFDF_5$	37±0.47	93.81±0.8	15.81±0.52	24.56±0.9
$SFDF_6$	22±0.25	96.22±1.2	12.23±0.56	18.22±0.4
$SFDF_7$	60±0.32	91.60±1.3	18.91±0.37	24.51±0.2
$SFDF_8$	35±0.33	94.53±0.8	16.43±0.27	17.04±0.4
$SFDF_9$	16±0.45	98.54±1.3	13.56±0.43	14.44±0.8
$SFDF_{10}$	55±0.38	89.27±1.2	19.42±0.29	19.25±0.3
$SFDF_{11}$	46±0.54	94.65±0.9	15.90±0.36	17.36±0.4
$SFDF_{12}$	20±0.38	98.28±1.3	13.03±0.50	15.72± 0.5

Every value is expressed as a mean SD; (n=3)

In a dissolve medium of HCl buffer pH 1.2, the in vitro drug release characteristics of each formulation of Sitagliptin fast dissolving tablets ($SFDF_1$-$SFDF_{12}$) were investigated. The procedure took place utilizing a USP type-II paddle type eight station dissolving device for 45 minutes.Starch soluble was used as a disintegrant in the formulations $SFDF_1$ through $SFDF_3$, cross povidone was used as a superdisintegrant in the formulations $SFDF_4$ through $SFDF_6$, and crosscarmellose sodium was used as a superdisintegrant in the formulations $SFDF_7$ through SFDF9. It was shown that the rate of dissolution increased as the concentration of superdisintegrant rose, but that 4% was the ideal concentration. No changes in the rate of dissolution were seen as the superdisintegrant concentration was increased further, up to 6%, although the hardness reduced and the friability rose, which is typically undesirable. For the $SFDF_{12}$ formulation, the drug was released up to 99.361.3% in 35 minutes, which had a superdisintegrants concentration of 4% (2% Crosscarmellose Sodium and 2% Crosspovidone). All formulations used mannitol and microcrystalline cellulose as diluents because they are hydrophilic by nature and have a better capacity to disintegrate than other diluents.The dissolution profiles of all the formulations ($SFDF_1$-$SFDF_{12}$) were shown in **figure 5 to 8**.

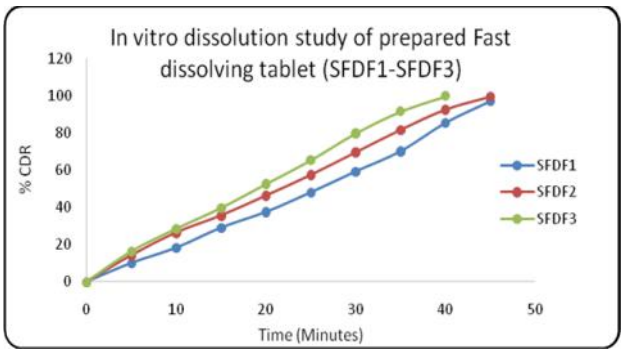

Fig 5: Formulation dissolution investigations conducted *in vitro* ($SFDF_1$-$SFDF_3$)

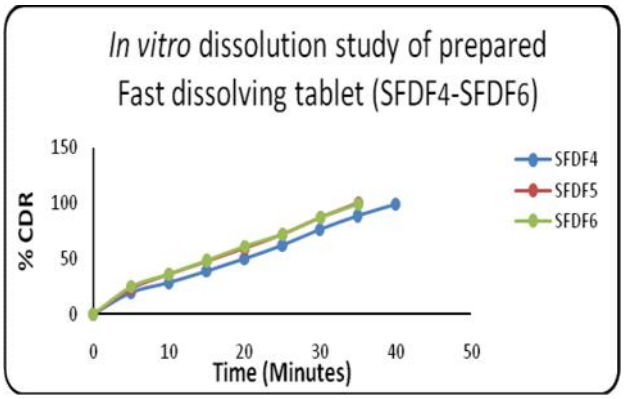

Fig 6: Formulation dissolution investigations conducted *in vitro* ($SFDF_4$-$SFDF_6$)

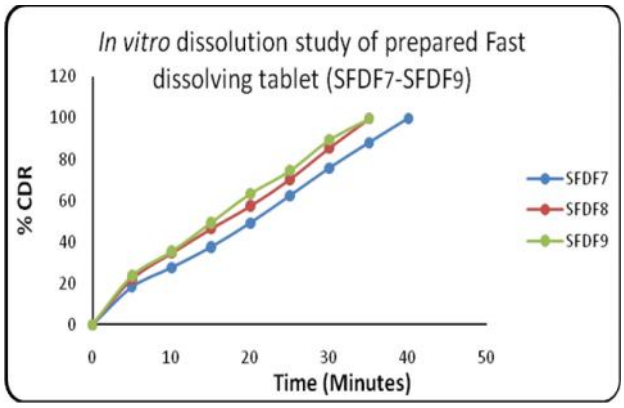

Fig 7: Formulation dissolution investigations conducted *in vitro* ($SFDF_7$-$SFDF_9$)

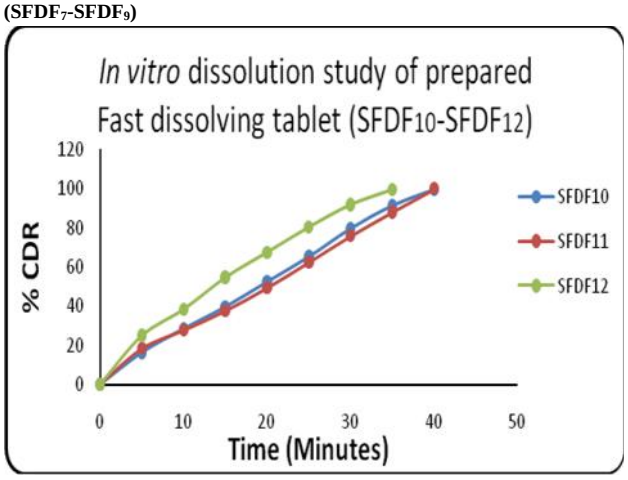

Fig 8: Formulation dissolution investigations conducted *in vitro* ($SFDF_{10}$-$SFDF_{12}$)

Using multiple kinetic models, such as zero order and first order kinetic models, the release kinetic analyses of all formulations of sitagliptin fast dissolving tablets ($SFDF_{12}$) were conducted based on the *in vitro* dissolution data. The best formulation, $SFDF_{12}$, was the subject of *in vitro* drug release kinetic investigations using zero order and first order kinetic models. Because it has the highest R^2 value, it was determined from the R^2 value that the *in vitro* release kinetics follows a zero-order kinetic model. Figures 9–10 and table 5 depict the *in vitro* drug release kinetic study.

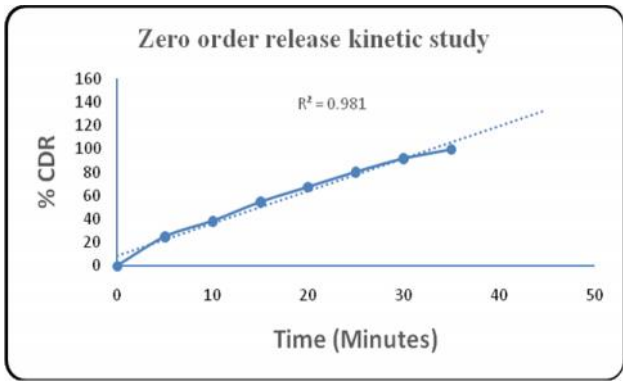

Fig 9: Shows the Zero order release percentage over time

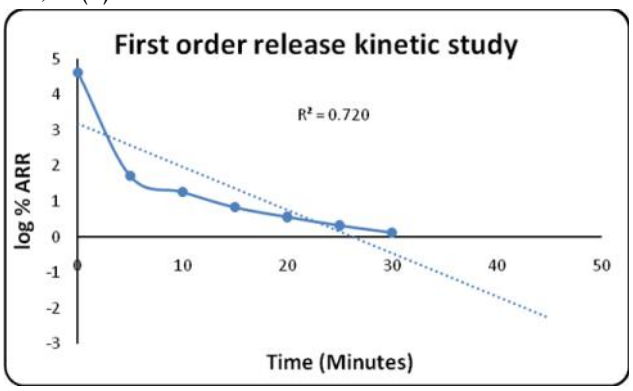

Fig 10: Shows the first order release (Time and log%ARR)

Table 5: *In vitro* release kinetic study regression values

Formulation	Regression coefficient of Zero order	Regression coefficient of 1st order	Conclusion
Best Sitagliptin fast dissolving tablets Tablet ($SFDF_{12}$)	$R^2 = 0.981$	$R^2 = 0.7201$	Release kinetics follows zero order kinetic model

The accelerated stability studies are a technique used to quickly determine the stability of the dosage form under stressful temperature and humidity conditions. The best Sitagliptin fast-dissolving tablet formulation **($SFDF_{12}$)** was exposed to an accelerated stressed condition for 90 days (**40 ° C ± 2 ° C/ 75% ± 5% RH**), after which the samples were removed and tested for various physicochemical characteristics, such as hardness, weight variation, friability, uniformity of drug content, and in vitro drug release characteristics. All tablets with adjusted formulations showed an increase in friability, hardness, floating lag time, and weight variation, but a decrease in drug content, swelling index, and floating duration value. All of the physicochemical characteristics were found to alter very little overall and within acceptable limits. Analyses of the medicine's composition and in vitro dissolution tests conducted over a 90-day period showed that more than 90% of the drug had been preserved. The formulation of Sitagliptin fast dissolving tablets under consideration was therefore found to be stable for at least two years, according to the results of stability studies.

Table 6: Comparative physicochemical analysis of the optimised batch ($SFDF_{12}$) under accelerated circumstances (40 ° C ± 2 ° C/ 75% ± 5% RH)

Physicochemical characteristics	Initial	After 30 days	After 60 days	After 90 days
Physical appearance	Cream white, circular, concave smooth surface without any cracks	No change	No change	No change

Weight variation	3.38±0.022	3.45±0.032	3.53±0.041	3.62±0.036
Hardness	3.8±0.961	3.6±0.452	3.5±0.376	3.4±0.562
Friability	0.68±0.09	0.70±0.06	0.72±0.05	0.74±0.07
Disintegration time {D_t (Sec)}	15.72± 0.5	18.36± 0.3	21.46± 0.6	23.57± 0.4
Wetting time (Sec)	20±0.38	22±0.25	25±0.34	28±0.27
Drug content	99.38±0.37	98.42±0.26	96.36±0.38	94.76±0.47

All values are expressed as mean± SD; (n=3)

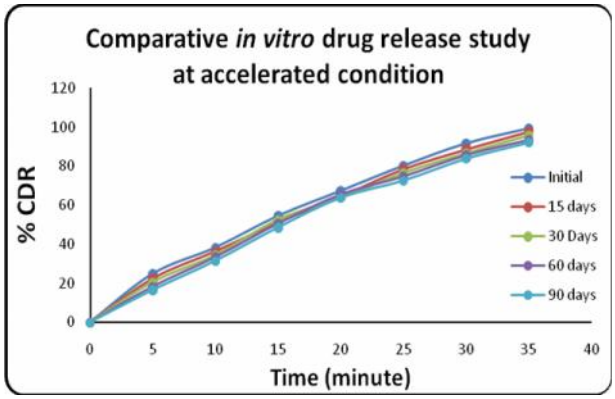

Fig 11: $SFDF_{12}$ *in vitro* release research under accelerated stressful conditions

Table 6 presents the results of various physicochemical parameters that were assessed at various time intervals while under stress for the optimal formulation of Sitagliptin fast dissolving tablets formulation **($SFDF_{12}$),** while **figure 11** shows the drug release profile plotted taking% CDR with respect to time at various time intervals in an accelerated stressed environment.

4. CONCLUSION

This study produced fast-dissolving sitagliptin pills. This study's key challenge was determining how starch soluble, Cross povidone, and Croscarmellose Sodium affected the in vitro release rate of fast-dissolving sitagliptin tablets. The quick-dissolving drug delivery device was promising for bypassing fast metabolism and lowering blood sugar in persons with type 2 diabetes.According to FTIR and DSC, the medication and excipients are compatible and the formulation is thermally stable. Wet granulation was utilised to make Sitagliptin fast-dissolving granules, which met all precompression specifications and had good flow characteristics.All post-compression metrics—average thickness, hardness, friability, weight variation, and disintegration—are satisfactory. To increase medication release, all formulations used lactose, a hydrophilic diluent. Formulation SFDF12, which contains all three super disintegrants at 4% (2% Croscarmellose and 2% Cross povidone), releases the medication at more than 99% within 35 minutes and has the best initial release rate. Combining all three super disintegrants improved medication release. Super disintegrant concentration increased drug release but decreased formulation hardness and friability. The highest dissolving formulation, $SFDF_{12}$, was chosen for drug release kinetic and mechanistic experiments. The current study's sitagliptin fast-dissolving tablet's in vitro drug release kinetics followed the zero-order release kinetic model and used anomalous diffusion and erosion. Zero-order kinetic plots showed the largest regression.ICH stability assays showed that a chosen $SFDF_{12}$ formulation was stable at 40°C/75% RH for up to 3 months with just a slight change in its physicochemical and drug release parameters. Tablet friability, hardness, weight variation, thickness, drug content, in vitro release testing of the optimum fresh formulation ($SFDF_{12}$), and post-accelerated stability testing were compared. The stability test passes. The Sitagliptin rapid dissolving tablets medication delivery method offers considerable promise for treating acute illnesses in men with type 2 diabetes since the drug is released quickly through fast pass metabolism. However, more clinical research is needed to evaluate this approach for type 2 diabetics with lower blood sugar levels.

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