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RESEARCH ARTICLE

DESIGN AND EVALUATION OF FAST DISSOLVING TABLETS OF SITAGLIPTIN PHOSPHATE MONOHYDRATE

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ABSTRACT

The core objective of the study was to design and evaluate fast dissolving tablets of Sitagliptin Phosphate Monohydrate. Fast dissolving or disintegrating tablets were prepared by the wet granulation method by using Sodium Starch Glycolate, Microcrystalline Cellulose, Crosscarmellose Sodium as superdisintegrants. The prepared tablets were evaluated for pre-compression and post compression parameters. The *in-vitro* release studies were carried out by using USP Type-II dissolution apparatus. The selected optimized batches were kept for stability studies at 40° c ±2 °c/75%± 5%RH for a period of three months. All the results obtained were found to be satisfactory and within the limits. The results of *in-vitro* drug release study showed that formulation F6 exhibited good and fast disintegrating time within 12 seconds.

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INTRODUCTION

Orally disintegrating tablets are unit solid dosage form containing drugs that disintegrate fastly and dissolved in mouth. The Fast dissolving delivery system has much more advantages than conventional oral dosage form such as tablets and capsules due to their convenient use. The orally dissolving formulations are suitable for pediatric geriatric, bedridden, disabled patients and also for who may have difficulty in swallowing conventional tablets. Sitagliptin Phosphate Monohydrate is an oral antidiabetic drug of the dipeptidyl peptidase-4 inhibitor class, mainly used for Type-II diabetes mellitus. The drug has more merits in efficiency and safety purpose (less weight gain, less hypoglycemic) also works by its effect on the incretin system. Sitagliptin Phosphate Monohydrate decreases the blood glucose level by inhibiting the enzyme Dipeptidyl Peptidase-4, so the blood glucose level decreases to normal (Abbaraju Prasanna Lakshmi *et al*., 2012; Ahsok Kumar and Agarwal, 2009; Uddhav Bagul *et al*., 2012; Chang *et al*., 2000; Bi *et al*., 1996; Anupama *et al*., 2009).

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So the present study was aimed to design the Fast Dissolving Tablets and to control of blood glucose values. The rationale behind the work is, the correct proportion of the super disintegrants showed fastest disintegration.

MAERIALS AND METHODS

Materials

Sitagliptin phosphate monohydrate, and other excipients were obtained as gift sample from Quliteck Pharma, (Jeedimetla). All the chemicals used in the formulation were of analytical grade.

Methods

Precompression parameters

Angle of repose (Wale *et al*., 2014) The angle of repose of powder will be carried out by funnel method. Accurately weighed powder blend is taken in a funnel. Height of the funnel is adjusted in such ways that the tip of the funnel just touches the apex of the powder blend. The powder blend is allowed to flow through the funnel freely onto the surface. The diameter

of the powder cone is measured and angle of repose will be calculated using the following equation;

tanθ = h / r where, **θ -** is the angle of repose; **h**- height of the powder cone; **r**- radius of the powder cone

Bulk Density

Accurately weigh 20 gm of the powder, which is previously passed through 20# sieve and transferred in 100ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume. Calculate the apparent bulk density in gm/ml by the following formula.

Bulk Density = Weight of powder/ Bulk volume

Tapped bulk density

Accurately weigh 20 gm of the drug, which is previously passed through 20# sieve and transferred in 100 ml graduated cylinder. Initial volume is observed. The cylinder will be tapped initially 100 times and measure the tapped volume to the nearest graduated units. The tapping can be repeated additional 750 times. Again the tap volume is measured to the nearest graduated unit.

Calculate the tapped bulk density in gm/ml by the following formula:

Tapped density = weight of the powder/ Tapped volume

Compressibility index and Hausner's Ratio

The Compressibility Index of the powder blend is determined by the Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The Hauser's ratio is a number that is correlated to the flow ability of a powder or granular material.

Drug-excipient compatibility studies

Compatibility studies were performed at 20°C, 30°C and 40°C by physical observation.

Fourier Transform Infrared Spectroscopy (FTIR) Study

Sitagliptin phosphate monohydrate, excipient and their combination were analyzed by Fourier Transform Infrared Spectroscopy studies with the potassium bromide pellet method and the spectrums were recorded in the wavelength region of 4000 to 400 cm^{-1}. The peaks of pure drug and excipient combination were analyzed by software supplied by shimadzu.

Formulation Development

The fast dissolving tablets of Sitagliptin Phosphate Monohydrate were prepared by wet granulation method. Sitagliptin Phosphate Monohydrate, Dicalcium Phosphate, Crosscarmellose Sodium, and Sodium Starch Glycolate were passed through sieve 40 and mix with other ingredients (shown in Table 1). The wet mass was prepared by adding the liquid binder and mix thoroughly. Then the damp mass was passed through a mesh to form the granules. The granules were dried and passed through No.16 sieve then it was lubricated with magnesium stearate and compressed into tablets (F_1-F_6) each weighed 230mg.

Post compression parameters of Sitagliptin Phosphate Monohydrate Fast Dissolving Tablets

General appearance

The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance.

Thickness and Diameter

The diameter of the tablet is determined with a Vernier Caliper or Screw Gauage.

Weight Variation

For Weight Variation test, twenty tablets are selected randomly from each batch and weighed individually to check for weight variation thereafter average weight and standard deviation of 20 tablets will be calculated

Hardness

The hardness of the tablet will be carried out using a Monsanto type hardness tester. The hardness of the tablet kg/cm^2 is measured

Table 1. It shows that the composition of Formulation of Fast Dissolving Tablets of Sitagliptin Phosphate monohydrate

S.No	Ingredients	F1	F2	F3	F4	F5	F6
1	Sitagliptin phosphate mono hydrate	128.5	128.5	128.5	128.5	128.5	128.5
2	Di calcium Phosphate	51.5	41.5	36.5	41.5	31.5	21.5
3	Crosscarmellose sodium	15	25	20	---	30	30
4	Sodium starch glycolate	---	---	10	25	15	25
5	PVP-30	---	10	---	20	---	10
6	Microcrystalline cellulose	30	20	30	10	20	10
7	Magnesium stearate	2	2	2	2	2	2
8	Polyvinyl alcohol	3	3	3	3	3	3
9	Mint flavor	q.s	q.s	q.s	q.s	q.s	q.s
	Total	230	230	230	230	230	230

(All the ingredients are in mg)

Friability (Khan *et al*., 2011)

Friability will be measured by taking randomly 10 tablets which are weighed and placed in a friabilator and rotated at 25

rpm for a period of 4 min. After the revolution the tablets can be dusted and weighed.

Friability is calculated by following formula.

$$\text{Friability} = \frac{(W1-W2)}{W1} \times 100$$

Where, W1 = Weight of the tablets before the test;W2 = Weight of the tablets after the test

Estimation of drug content

This is an important parameter and the efficiency can be evaluated by the assay. 10 tablets were powdered well and powder equivalent to 100mg of the drug was dissolved in 100ml of 0.1 N HCL filtered and with required dilution analyzed spectrophotometrically at 267nm. The concentration of drug was determined by using a standard calibration curve.

Disintegration test (Gohel *et al*., 2004)

The disintegration time was determined using disintegration test apparatus. A tablet was placed in each of six tubes of the USP XXII apparatus and one disc was added to each tube. The time in seconds taken for the complete disintegration of the tablet in the apparatus was measured.

Wetting time (Kuchekar *et al*., 2004; Aulton 2002)

A piece of tissue paper folded twice was placed in a small petri dish containing 6ml of water. A tablet was put on the paper and the time required for complete wetting was measured, the wetted tablet was then weighed, the results were shown in Table 6.

Water absorption ratio

Water absorption ratio 'R' was determined using the following equation.

$$R = 100 \times [\, Wb - Wa/Wa]$$

Where, Wa – is weight of the tablet before water absorption. Wb-is weight of the tablet after water absorption

***In-vitro* dissolution study (Wale *et al*., 2014)**

In-vitro dissolution study will be carried out by using the USP dissolution test apparatus (Paddle). The dissolution medium consists of 900 ml 0.1NHCL and rotation speed at 50rpm. 5ml of sample is withdrawn at regular interval upto 30 minutes and replace with same quantity of the fresh dissolution medium. And withdrawn samples are analyzed spectrophometrically at 267nm.

Stability studies (Abbaraju Prasanna Lakshmi *et al*., 2012)

Stability studies were carried out on optimized formulation as per 1CH specifications at 40°c±2 °c/75%± 5%RH for duration of three months. After an interval of one month samples were withdrawn and evaluated for percentage of drug release and moisture content.

RESULTS AND DISCUSSION

The prepared Fast Dissolving Tablets were with several merits such as release the drug immediately, increased bioavailability, no dose dumping problem, rapid dissolution and absorption of the drug which will produce quick onset of action for diabetes. In the present work, the crosscarmellose sodium, sodium starch glycolate, poly vinyl pyrrolidine, and microcrystalline cellulose were used as the superdisintegrants showed fastest disintegration.

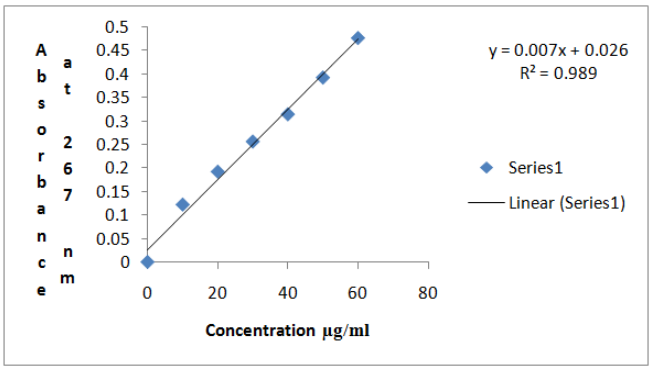

Fig.1. Calibration curve of Sitagliptin phosphate

The calibration graph of Sitagliptin Phosphate Monohydrate was plotted from the data obtained from a series of concentration ranged from 10 – 60 mg/ml at 260nm. The standard graph of Sitagliptin Phosphate Monohydrate was developed at 267nm and its equation was given as y = 0.0075x+ 0.0264 and its r^2 was given as 0. 9897.

Drug excipient compatibility studies

Compatibility studies were performed at 20°C, 30°C and 40°C by physical observation (Table 2). Fourier Transform Infrared Spectrophotometer spectra results were shown in Table 3. The results showed that there was no change in physical appearance

Table 2. It shows physical observation of Sitagliptin phosphate monohydrate - Excipient compatibility studies

S.No	API+excipient	Initial	At 20° c ±2 °c/60%± 5%RH			At 30° c ±2 °c/65%± 5%RH			At 40° c ±2 °c/75%± 5%RH		
1	Sitagliptin phosphate monohydrate(API)	Off white powder form	NC	NC	NC	NC	NC	NC	NC	NC	NC
2	(API)+DCP	Off white	NC	NC	NC	NC	NC	NC	NC	NC	NC
3	(API)+CCS	Off white	NC	NC	NC	NC	NC	NC	NC	NC	NC
4	(API)+SSG	Off white	NC	NC	NC	NC	NC	NC	NC	NC	NC
5	(API)+PVP	Off white	NC	NC	NC	NC	NC	NC	NC	NC	NC
6	(API)+MCC	Off white	NC	NC	NC	NC	NC	NC	NC	NC	NC
7	(API)+Mg.stearate	Off white	NC	NC	NC	NC	NC	NC	NC	NC	NC
8	(API)+PVA	Off white	NC	NC	NC	NC	NC	NC	NC	NC	NC

NC- indicates no change between drug and excipient.

at various temperatures (20°C - 40°C) over 30 days and there was no interaction between drug and excipients.

IR Spectra

IR spectra of Sitagliptin Phosphate Monohydrate alone and its combination with excipients are shown in Figure 2 and 3.

IR spectrum of pure Sitagliptin Phosphate Monohydrate has characteristic peaks, which are not affected along with the combination of excipients. From this, which indicate there is no interaction between drug and excipients.

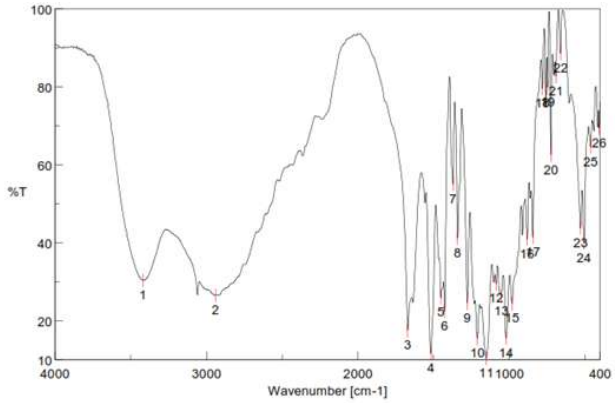

Fig.2. IR spectrum of Sitagliptin phosphate monohydrade

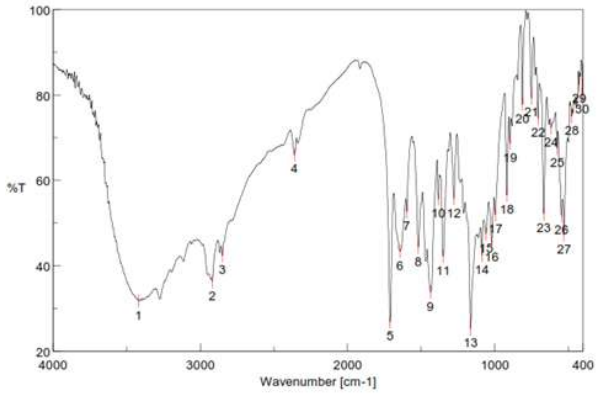

Fig.3. IR spectrum of sitagliptin phosphate and excipients

Angle of repose

The angle of repose of six batches was found to be range of 25°– 27° (θ) which indicated the blend had excellent flow property. The results were given in Table 3.

Tapped Density

The results of tapped density were found to be in the range of 0.61 to 0.82 gm/ml and the results are given in the Table.3.

Hausner's ratio and compressibility index

The compressibility index was found to be 11.84– 20.27%. And the Hausner's ratio was found to be in the range of 1.13 – 1.25. The results are given in the Table 3. From all the results the flow property of the blend was fairly good.

Post compression parameters

Weight variation (Aulton 2002)

All the formulations were ranging from 229.4 to 232.5mg, which indicates there is a uniform distribution of the drug and excipients in the formulations. The results are exhibited in Table 4.

Thickness

The thickness of the formulations are from 4.14 – 4.99mm, it assumed that the tablets shown uniformity in thickness. The results are shown in Table 4.

Hardness

The hardness of the tablets was found to 3.1 to 4.2 kg/cm^2 which desirable range of oral dissolving tablets. The results are given in Table 4.

Friability

The friability of the tablets were found to be 0.21 – 0.61% the results are shown in the Table 4

Drug content

The drug content was found to be in the range of 98.67% - 100.27%. Hence the tablets are complied with IP standards.

Disintegration time

The disintegration time of the tablets were found to be 12sec – 25sec. The results are given in the Table 5, which indicates after 25sec, there is no palpable mass remaining in the apparatus.

Table 3. It shows the evaluation of pre-compression parameters

Formulations	Angle of repose(θ)	Bulk density g/ml	Tapped density g/ml	% Compressibility	Hausner's Ratio
F1	25.31±0.02	0.50±0.02	0.61±0.02	18.03	1.2
F2	27.61±0.03	0.54±0.02	0.62±0.02	12.90	1.14
F3	26.94±0.04	0.67±0.01	0.76±0.01	11.84	1.13
F4	25.91±0.01	0.68±0.03	0.82±0.03	17.07	1.20
F5	25.72±0.02	0.59±0.04	0.74±0.02	20.27	1.25
F6	26.34±0.04	0.60±0.02	0.75±0.03	20.03	1.15

Bulk Density

The bulk density of the granules was measured by graduated cylinder. The bulk density was found to be in the range of 0.50 – 0.68 gm/ml and the results are shown in Table 3.

Wetting time

All the formulations were found to be within the limits. Wetting time of all the formulations (F_1 – F_6) shown in Table 5

Table 4. It shows the evaluation of post compression parameters

Formulation code	Average weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)
F1	232.5±0.02	3.2 ±0.02	4.14 ±0.02	0.21 ±0.02	98.7
F2	229.5±0.03	3.1±0.02	4.69 ±0.01	0.22 ±0.02	97.5
F3	2316±0.02	3.2 ±0.02	4.96 ±0.02	0.61 ±0.03	99.3
F4	230.5±0.01	3.4±0.02	4.64 ±0.03	0.51 ±0.02	98.9
F5	229.4±0.03	3.5 ±0.02	4.62 ±0.02	0.30 ±0.02	98.6
F6	229.8±0.01	4.2 ±0.02	4.99 ±0.01	0.25 ±0.02	100.2

and were found to be 18-28 sec. From this the best formulation was found to be F_6 within 18 seconds.

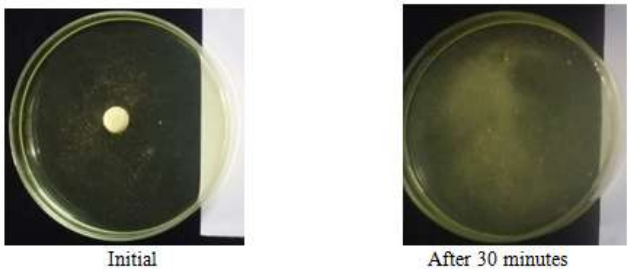

Fig.4. Different stages of tablet in wetting time

Water absorption ratio

The high water absorption capacity of the tablet was disintegrated in few seconds. Among all the formulation, F6 was selected as the best because of lesser disintegrated time which is shown in Table 5.

Table 5. It shows the evaluation of post compression parameters

Formulations	Disintegration Time (sec)	Wetting time (sec)	Water absorption ratio
F1	24 ±2.00	26	102 ± 0.93
F2	25 ±1.00	28	132 ± 0.95
F3	22 ±2.00	22	102 ± 0.29
F4	19 ±2.00	22	122 ± 0.13
F5	18±1.00	26	125 ± 0.83
F6	12±2.00	18	158 ± 0.97

In-vitro drug release

The *in-vitro* drug release profile of formulation 1 – 6 (F_1 – F_6) depicted in Table 6 and Figure 5. From the release data, F_6 shows best results in drug release. The rationale combination of PVP-30, MCC, CCM and SSG proves that these are best superdisintegrants when comparing other formulations.

Table 6. It shows the *In –Vitro* release profile of Sitagliptin phosphate

S.No	Time (sec)	Cumulative % Drug release					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	5	20	17	23	10	16	29
3	10	54	35	47	35	57	42
4	15	72	52	61	53	79	63
5	20	88	68	80	78	88	82
6	25	90	75	91	90	92	93
7	30	92	90	94	93	96	100

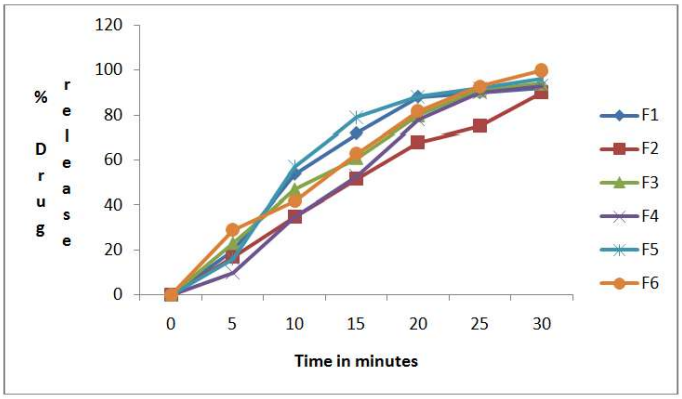

Fig. 5. In-vitro Dissolution profile of FDT of Sitagliptin Phosphate

Table 7. It shows the stability Data of optimized formulation F6 at at 40° c ±2 °c/75%± 5%RH

S.No	Time in months	Physical changes	% of Drug content* ± SD	Moisture content	% of Drug Release* ± SD
1	Initial	Round white colour uncoated tablets	99.86±0.43	0.92	99.98%
2	1 month	No changes	99.33±0.84	0.90	99.87%
3	2 month	No changes	99.06±0.56	0.83	99.80%
4	3 month	No changes	98.23±0.68	0.80	99.74%

Stability study

The best formulation F6 was subjected for stability study and drug content, moisture content and % drug release are evaluated, and the results showed (Table 7) that the formulation remained stable without any physico-chemical changes.

Conclusion

The Fast Dissolving Tablets of Sitagliptin Phosphate Monohydrate were developed successfully by Wet Granulation Method. Six formulations were prepared with different ratios of superdisintegrants. Precompression and post compression evaluation were performed. Based on the evaluations, formulation code F_6, which shown less disintegration time 12sec and 99.98% of drug release within 30minutes. The Fast Dissolving Tablets have potential advantages over conventional dosage form with their improved patient compliance and produce rapid onset of action and provide the best management for Type-II diabetes mellitus. So it can be concluded that, the combination of drug and superdisintegrants are best formulation of Fast Dissolving Tablets of Sitagliptin Phosphate Monohydrate and making it patients friendly.

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