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FORMULATION DEVELOPMENT AND EVALUATION OF IMMEDIATE DRUG RELEASE TABLET DOSAGE FORM OF SITAGLIPTIN PHOSPHATE

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ABSTRACT

The purpose of this research was to formulate and evaluate immediate drug release tablets of sitagliptin phosphate by direct compression method. Sitagliptin phosphate is as antidiabetic drug in type-II diabetes mellitus. Immediate release tablets were prepared by addition of different superdisintegrants. These superdisintegrants are crospovidone, sodium starch glycolate, croscarmellose sodium. All the powder blends and tablets were subjected to Pre-compression parameters, hardness, friability, weight variation, water absorption ratio, wetting time, disintegration time, drug content, in-vitro dissolution and short-term stability studies. Their results found satisfactory. Friability and weight variation of tablets were found in limits as per Indian Pharmacopoeia. Disintegration time of all batches was found near one minute. Percentage drug content of formulations was found in the range 98-102%. In-vitro dissolution studies in 0.1N HCl show the release 95-99% in the following order of superdisintegrants Croscarmellose > Sodium starch glycolate > Crospovidone. Maximum in-vitro dissolution was found with formulation batch F6 which having Croscarmellose as superdisintegrants. Short-term stability studies of optimized formulation F6 indicated that there were no significant changes in dosage form when changing temperature, humidity in three months. The optimum concentration of superdisintegrants used in various combinations results in the rapid swelling of tablet in dissolution medium, rapid disintegration and release drug release.

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INTRODUCTION

In the present study and research novel drug delivery systems are developed for better drug release and absorption. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain avoidance, versatility and most importantly patient compliance. The oral route remains the perfect route for the

administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance. Many patients require quick onset of action in particular therapeutic condition and consequently immediate release of medicament is required. It is estimated that50% of the population is affected by this problem, which results in a high incidence of ineffective therapy. Faster disintegration of tablet administered orally minimizes absorption time and improves its bioavailability in less time.

Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. In the formulation of immediate release tablets superdisintegrants are used enhance rapid disintegration and drug release. Because they are effective in lower concentrations, less effect on compressibility and flowability, more effective intragranularly. Some super disintegrants are Sodium Starch Glycolate (Explotab, Primogel), Cross-linked Povidone or crospovidone (Kollidon), Low-substituted hydroxyl propyl cellulose, Cross linked carboxy methyl cellulose sodium or Croscarmellose sodium (Ac-Di-sol). Superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction which causes the tablet to burst or the accelerated absorption of water leading to promote disintegration. Sitagliptin phosphate is a oral hypoglycemic drug used to treat diabetes mellitus type-2. Sitagliptin phosphate works to competitively inhibit the enzyme dipeptidyl peptidase 4 (DPP-4) so known as DPP-4 Inhibitor. Some other dipeptidyl peptidase-4 inhibitors are vildagliptin, Saxagliptin, Linagliptin. Its pharmacokinetic properties are dose: 100mg (adult dose daily), half life ($t_{1/2}$): 12.4 hours, bioavailability: 87%, plasma protein binding: 38%, excreted in urine (87%), T_{max}: 1-4hrs, C_{max}: 950 nM.

MATERIALS AND METHOD:

Materials used in this study were obtained from various sources. Gift sample of Sitagliptin phosphate was obtained from Aurobindo pharma, Hyderabad. Superdisintegrants crospovidone, sodium starch glycolate, croscarmellose sodium were obtained from Crystal Polymers & Additives Pvt. Ltd, Penderghast Road, Hyderabad. Mannitol, magnesium stearate, talc, aspartame were obtained from Hychem Resources, Ameerpet, Hyderabad. Direct compression is the simplest and most cost-effective tablet manufacturing method. The advantages of the direct compression are primary reduced production cost, better product stability and faster dissolution of API when compare to process of granulation. The preparation of immediate drug release tablet by this method involves same processing steps as that of conventional solid dosage forms such as weighing, screening, mixing and compression. Hence, most of the pharmaceutical companies adopt this method for preparing IR tablets, FDTs, MDTs. Addition of superdisintegrants in IR tablets, leads to quick disintegration of tablets and hence improves dissolution. So that all ingredients passed through sieve 20# and weighed according to formula table 1. After that as per formula weighed ingredients mixed in poly bag by weight decreasing order. Drug sitagliptin phosphate mixed with superdisintegrants (Crospovidone, Sodium starch glycolate, Croscarmellose sodium), mannitol (sweetener, mouth feel enhancer), magnesium stearate (lubricant), talc (glidant), and aspartame (sweetener) as per master formula. Then the entire powder blend batch passed through sieve 20#. Powder blend compressed to get tablets of all batches after adjusting thickness, weight and hardness in 10stations rotary punch machine (MINI PRESS, RIMEK).

Table 1: Master Formula for Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
Sitagliptin Phosphate	100	100	100	100	100	100	100
Crosspovidone	30	40	-	-	-	-	10
Sodium Starch Glycolate	-	-	30	40	-	-	10

Croscarmellose Sodium	-	-	-	-	30	40	10
Mannitol	112	102	112	102	112	102	112
Magnesium Stearate	3	3	3	3	3	3	3
Talc	1	1	1	1	1	1	1
Aspartame	5	5	5	5	5	5	5
Total	**250**	**250**	**250**	**250**	**250**	**250**	**250**

EVALUATION OF POWDER BLEND:

The prepared blend is evaluated by following tests.

- Angle of repose
- Bulk density
- Tapped density
- Hauser's ratio
- Carr's index

Angle of repose:

Angle of repose was determined by using fixed funnel method. The fixed funnel method employ a funnel that was secured with its tip at a given height (2cm), above the graph paper that was placed on a flat horizontal surface. Granules or tablet blend were carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. Thus, with r being the radius of the base of the conical pile. Angle of repose was calculated using the following equation.

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

Here **h** = Height of pile

r = Radius of pile

θ = Angle of repose

Bulk density:

Bulk density was determined by pouring a weighed quantity of tablet blend into graduated cylinder and measuring the height. Bulk density is the ratio of mass of tablet blend to bulk volume.

$$\textbf{Bulk Density} = \frac{m}{v} = \frac{m}{\pi r^2 h}$$

Here; **m** = weight of powder or granules (gm.)

v = Bulk Volume ($cm.^3$)

π = 22/7 = 3.14

r = Radius of Cylinder (cm.)

h = Height reached by powder in cylinder (cm.)

Tapped Density:

Tapped density is ratio of mass of tablet blend to tapped volume of tablet blend. Accurately weighed amount of tablet blend poured in graduated cylinder and height is measured. Then cylinder was allowed to 100tap under its own weight onto a hard surface. The tapping was continued until no further change in height was noted.

$$\textbf{Tapped Density} = \frac{m}{v} = \frac{m}{\pi r^2 h}$$

Here; **m** = weight of powder or granules (gm.)

v = Tapped Volume ($cm.^3$)

π = 22/7 = 3.14

r = Radius of Cylinder (cm.)

h = Height reached by powder in cylinder after tapping (cm.)

Hausner's Ratio:

Hausner's ratio indicates the flow properties of powder and measured by the ratio of tapped density to bulk density. Hausner's ratio was determined by the given formula

$$\textbf{Hausner's ratio} = \frac{\textbf{Tapped density}}{\textbf{Bulk density}}$$

Carr's Index (Compressibility Index):

Compressibility is the ability of powder to decrease in volume under pressure using bulk density and tapped density the percentage compressibility of powder were determined, which is given as carr's compressibility index. It is indirectly related to the relative flow rate. Carr's compressibility index was determined by the given formula

$$\textbf{Carr's Index} = \left(1 - \frac{\textbf{Bulk Density}}{\textbf{Tapped Density}}\right) \times 100$$

EVALUATION OF TABLETS

These tests are as following:-

- Appearance
- Thickness
- Hardness
- Weight variation
- Friability
- Disintegration
- Uniformity of dispersion

- Wetting Time
- Water absorption ratio
- Drug content
- *In vitro* Dissolution
- Stability studies

Appearance:

The general appearance of tablet is its visual identity and all over elegance, shape, color, surface textures. These all parameters are essential for consumer acceptance. Tablets have smooth, clean surface, round concave shaped, white color tablet with pleasant taste.

Thickness:

The thickness of the tablets was determined by using vernier calipers. Randomly 10 tablets selected were used for determination of thickness that expressed in Mean± SD and unit is mm.

Hardness:

The hardness of tablet is an indication of its strength against resistance of tablets to **capping,** abrasion or breakage under conditions of storage, transportation and handling before usage. Measuring the force required to break the tablet across tests it. Hardness of 10 tablets (randomly) from whole tablet batch was determined by Monsanto hardness tester. Hardness measured in kg/cm^2.

Weight variation:

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets randomly from whole batch was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

Friability test:

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface during transportation or handling. Roche friabilator was employed for finding the friability of the tablets. For tablets with an average weight of 0.65 g or less take a sample of whole tablets corresponding to about 6.5 g and for tablets with an average weight of more than 0.65 g take a sample of 10 whole tablets. Roche friabilator is rotated at 25rpm for 4 minutes for 100rounds. The tablets were dedusted and weighed again. The percentage of weight loss was calculated using the formula

$$\%f = \frac{W_0 - W_1}{W_0} \times 100$$

Here, %f = Percentage friability

W_0 = Initial weight (Before test)

W_1 = Final weight (After test)

Disintegration test:

The USP device to rest disintegration was six glass tubes that are "3 long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of distilled water at 37± 2^oC, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

Wetting Time:

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10cm diameter were placed in a petridish containing 0.2% w/v solution of amaranth (10ml). One tablet was carefully placed on the surface of the tissue paper. The time required for develop blue color due to amaranth water soluble dye on the upper surface of the tablets was noted as the wetting time.

Water Absorption Ratio:

A small piece of tissue paper folded twice was placed in a small petridish containing 6ml of water. A tablet was put on the paper. The wetted tablet was then weighed. Water absorption ratio, R was determined by using following formula

$$R = \frac{W_a - W_b}{W_b} \times 100$$

Here, R = Water absorption ratio

W_b = Weight of tablet before water absorption

W_a = Weight of tablet after water absorption

Drug content:

10 tablets were powdered and 100mg drug equivalent powder dissolved in suitable media buffer or 0.1N HCl. Volume of the solution made up to 100ml by that media. Solution was filtered and diluted 100times and analyzed spectrophotometrically and further calculation

carried out to determine drug content in one tablet.

***In-vitro* drug release studies:**

The immediate release tablets are subjected to *in-vitro* drug release studies in 0.1N HCl for 30 minutes to access the ability of the formulation for providing immediate drug delivery. Drug release studies were carried out in dissolution test apparatus USP type II using specified volume 900ml of dissolution media maintained at 37±0.5^{o}C. The tablets are directly placed in medium with paddle then rotated at 50 rpm. 5ml of the sample from the dissolution medium are withdrawn at each time interval (5, 10, 15, 20 & 30 minutes) and 5ml of fresh medium was replaced each time. The samples were filtered and from the filtrate 1ml was taken and diluted to 10ml with 0.1N HCl. These samples were analyzed spectrophotometrically and further calculation was carried out to get drug release. The drug released data were plotted as cumulative % drug release Vs time.

Stability study:

Stability is defined as the ability of a particular drug or dosage form in a specific container to remain within its physical, chemical, therapeutic, and toxicological specifications. Drug decomposition or degradation occurs during storage, because of chemical alteration of the active ingredients or due to product instability, lowering the concentration of the drug in the dosage form. The stability study indicates that the formulation is quite stable at different conditions of storage. Accelerated stability studies carried out at 40°C ± 2°C/75% RH ± 5% RH for 3 months.

From the evaluation of dosage form batch F6 optimized so that this formulation was now processed from beginning to ensure reproducibility of this formulation and then stability study were carried out for three months on new batch formed of F6. Stability studies were carried out as per ICH stability testing guidelines (ICH guidelines). The optimized formulation F6 was stored in aluminium capped clear glass vials and were subjected to a storage condition of 40°C±2^{o}C**/** 75%±5% RH for 3 months in humidity chamber. The samples were withdrawn at time intervals of 0, 1, 2, 3 months and evaluated for hardness, friability, disintegration time, drug content and *in-vitro* dissolution study.

RESULT AND DISCUSSION:

Pre-compression parameters of powder blend-

The formulation was undertaken with the aim to formulate and evaluate sitagliptin phosphate immediate release tablet. Formulation of tablet was done by direct compression technique because the flow properties of the powder blend (table.2) have good powder flow. Values of angle of repose have found in the range of 31^{o}-35^{o} (good powder flow).

Table 2: Pre-compression parameters of powder blend

Formulation	Angle of repose	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Hausner's ratio	Carr's Index (%)
F1	31.22^{o}	0.495	0.578	1.167	14.286
F2	31.61^{o}	0.473	0.547	1.158	13.636
F3	31.51^{o}	0.473	0.547	1.158	13.636
F4	31.41^{o}	0.452	0.520	1.150	13.043
F5	31.31^{o}	0.452	0.520	1.150	13.043
F6	31.22^{o}	0.473	0.547	1.158	13.636
F7	31.41^{o}	0.452	0.520	1.150	13.043

Hausner's ratio and Carr's index have in the range of 1.12-1.18 and 11-15 respectively (table.2). Hence the prepared powder blend has good flow property and can be used for tablet manufacture.

Post-compression parameters-

The powder blend was compressed using direct compression technique. Tablets prepared by direct compression method have found to be good without any chipping, capping and sticking. Various physical parameters like thickness, hardness, weight variation, friability, hardness, disintegration time were measured to evaluate tablets. It is found that the average thickness of the tablets also ranged between 3.22-3.28 mm; however, the variations have not alarming and remained within the acceptable range. Hardness of tablets of the different formulations varied widely ranging from 3.1 - 4.3 kg/cm^2 (Table 3), all the formulations have therefore thought to show the acceptable hardness.

Table 3: Post-compression parameters

Parameters	F1	F2	F3	F4	F5	F6	F7
Thickness (mm)	3.25±0.05	3.22±0.04	3.27±0.05	3.20±0.06	3.22±0.04	3.23±0.05	3.23±0.05
Hardness (Kg /cm^2)	4.07±0.19	4.22±0.23	3.83±0.27	3.45±0.15	3.52±0.21	3.17±0.25	3.62±0.40
Weight Variation (mg)	250.7±2.43	250.25±2.24	250.4±2.21	250.4±2.06	250.5±1.57	250.45±1.7	250.7±1.59
Friability (%)	0.446	0.415	0.645	0.599	0.661	0.584	0.553
Disintegration Time (Sec.)	64	67	56	53	49	46	54
Wetting Time (Sec.)	142	148	139	135	137	132	141
% Water Absorption	26.29	29.88	26.69	25.50	29.08	27.89	24.30
%Drug Content	99.22	98.56	100.52	99.87	101.18	99.87	98.56

Theoretically, the average weight of tablets of the different formulations should be 250 mg (Table1). It was seen that the average weight of the tablets was particularly found to be remarkably consistent and somewhat uniform, which was approximately 250 mg. from table 3. Friability of the tablets of different formulations varied greatly range from 0.41-0.67%. The friability has found to be the greatest for formulation F6 but as per IP limit it should be below 1%. Disintegration time of the tablets has found to be less than 3.0 mins. Tablets containing crospovidone (F1, F2) showed highest disintegration time. Disintegration time of all batches found satisfactory which nearly about 1 min. Wetting time of all batches has found in the range 130-150sec. % water absorption ratio found in the range of 24-30%. Drug content of all batches has found in the range of 98-102%.

***In-Vitro* dissolution profile:**

Table 4: *In-Vitro* dissolution profile of IR tablet of Sitagliptin Phosphate in 0.1N HCl

Time (Min.)	Cumulative % Drug Release (Zero Order Kinetics)						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
5	24.59	29.88	27.53	34.00	29.29	45.76	32.82

10	59.29	62.82	57.53	65.76	60.47	67.53	64.59
15	71.65	74.59	73.41	78.12	75.18	79.88	76.94
20	85.76	90.47	86.94	91.06	88.12	89.88	89.29
30	95.18	96.94	96.35	97.53	96.94	98.12	96.94

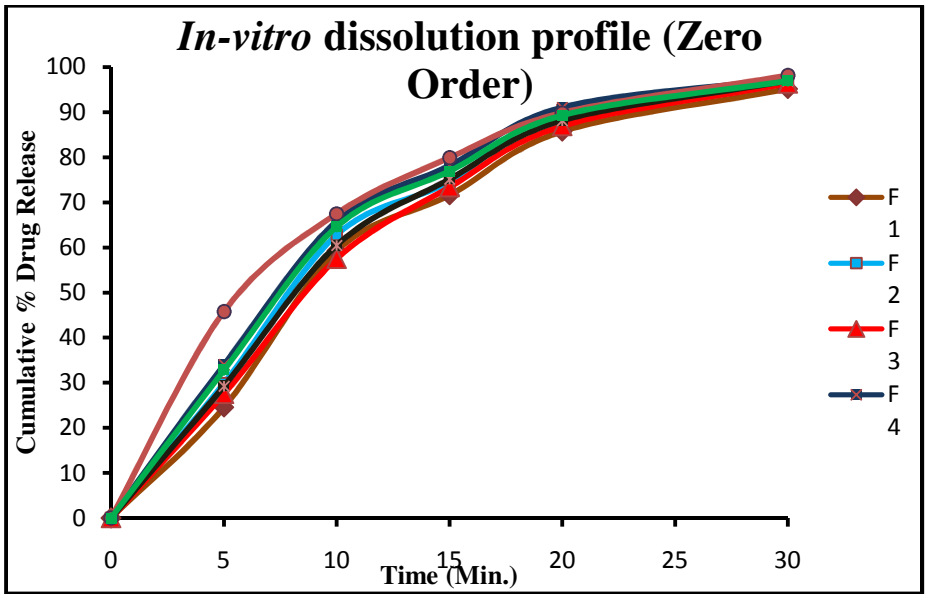

Figure 1: *In-Vitro* dissolution profile of IR tablet of Sitagliptin Phosphate in 0.1N HCl

Above dissolution profile shows highest drug release with optimum level of superdisintegrants in batches F2, F4, F6 and drug release has found 96.94%, 97.53% and 98.12% respectively in 30 minutes. Drug release curve shows the fast drug release from all batches of IR tablet of sitagliptin phosphate due to presence of superdisintegrants. Amongst all batches F6 has showed optimum and rapid drug release with 98.12%. Hence, batch F6 has selected as optimized batch for immediate drug release tablet of sitagliptin phosphate.

Stability studies:

Table 5: Stability data for optimized formulation F6

Formulation	**Parameters Evaluated**	**Time interval (months)**			
		0	1	2	3
F6	**Hardness (kg/cm^2)**	3.14	3.17	3.15	3.18
	Friability (%)	0.584	0.554	0.584	0.538
	Disintegration time (sec)	47	48	45	49
	Drug content (%)	99.22	100.22	99.87	98.56
	Cumulative % drug release	98.71	98.12	96.94	97.53

The stability study revealed that the formulation was physically stable when stored at 40±2^{0}C and 75±5 % RH till 3 months and there has no significant difference in dissolution for optimized formulation.

CONCLUSION:

This study discusses the preparation of immediate release tablets of sitagliptin phosphate. Pre-compression parameters have shown that powder blend having good powder flow properties which has desirable to make immediate release tablets by

direct compression technique. Tablets prepared by direct compression method have found to be good without any chipping, capping and sticking. All the formulated tablets met the pharmacopoeial standard of thickness, hardness, weight variation, percentage friability, disintegration time. During the optimization of formulation it was observed in dissolution that increasing the concentration of superdisintegrant increased release profile could be achieved. It was also observed that dissolution is highly dependent on the disintegrant and disintegration. The *in-vitro* dissolution study of formulations (F1-F6) of sitagliptin phosphate have compared with F7 (Innovator) formulation. Formulation F6 showed good results than rest of the 6 formulations in pre and post-compression studies. This formulation also displayed faster and better immediate drug release in 0.1N HCl medium. So that F6 has optimized formulation in this study. Short-term stability studies of optimized formulation F6 indicate that there are no significant changes in dosage form when changing temperature, humidity in three months. The optimum concentration of superdisintegrants used in various combinations results in the rapid swelling of tablet in dissolution medium, rapid disintegration of tablets and release of drug from the formulation. With reference to the type of superdisintegrant, the better release rate has found to follow the order Crosscarmellose sodium > Sodium starch glycolate > Crospovidone. The *In vitro* drug release profile of all formulations has evaluated and the release studies demonstrated that the release of sitagliptin phosphate from all formulations has generally immediate. High concentration of superdisintegrants have used in the formulations caused high percent release of drug, while lower concentration caused low release. Thus, the release characteristics were significantly influenced by the type and concentration of superdisintegrants used. Disintegration time has also governed by type and quantity of superdisintegrants. Thus, the granules and tablets were found satisfactory in terms of physical parameters, drug release profiles from the immediate release tablets.

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