RESEARCH ARTICLE

Formulation and evaluation of glipizide-loaded fast-dissolving tablets using husk of *Plantago ovata* as a superdisintegrant

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The objective of the present study was to develop fast-dissolving tablets (FDTs) of glipizide, a sulfonylurea antidiabetic drug. The husk of *Plantago ovata* and pregelatinized husk of *P. ovata* were used as disintegrating agents. Microcrystalline cellulose was used as binder and starch (soluble) was used as bulk-forming agent. The powder blends were evaluated for angle of repose, compressibility index and Hausner ratio. The results of angle of repose, compressibility index (%) and Hausner ratio ranged from 24.23±0.57 to 29.34±0.78, 15.76±0.82 to 20.12±1.25 and 1.18±0.011 to 1.25±0.019, respectively. The tablet blends were converted into tablets by using direct compression method. The tablets were evaluated for disintegration test, hardness test, friability test, drug entrapment efficiency, content uniformity tests and drug release study. Formulations, which contained pregelatinized husk of *P. ovata* as a superdisintegrant, showed faster disintegration, higher percentage friability and lesser hardness than formulations containing husk of *P. ovata* as a superdisintegrant. Drug entrapment efficiency was found to be uniform among different batches of the tablets and ranged from 97.53±0.52 to 99.72±0.45. The results of content uniformity test of all the batches were found in the official range. The batches containing husk of *P. ovata* as a superdisintegrant released 15%–27% of glipizide per minute and those containing pregelatinized husk of *P. ovata* as a superdisintegrant released more than 95% of the drug within a minute. These results revealed that pregelatinized husk of *P. ovata* can be used as a superdisintegrant for obtaining FDTs.

Key words: *Fast-dissolving tablets, glipizide, Plantago ovata husk*

INTRODUCTION

Oral fast-dissolving dosage forms, also known as "fast-melt" and "fast-disintegrating," are a relatively novel dosage technology that involves the rapid disintegration or dissolution of the dosage form, be it a tablet (the most common form) or a capsule,[1-3] into a solution or suspension in the mouth without the need for water.[4] The dosage form begins to disintegrate immediately after coming into contact with saliva, with complete disintegration normally occurring within 30–50 s after administration.[5] The solution containing the active ingredients is swallowed, and the active ingredients are then absorbed through the gastrointestinal epithelium to reach the target and produce the desired effect. Target groups for oral fast-dissolving tablets (FDTs) are wide-ranging as people of all ages can experience difficulty in swallowing conventional tablets. This includes children and the elderly who either experience difficulty and cannot swallow or have not learnt to swallow the conventional tablets. In addition, it institutionalized psychiatric patients as well as hospitalized or bedridden patients suffering from a variety of disorders, such as stroke, thyroid disorders, Parkinson's disease, and other neurologic disorders, such as multiple sclerosis and cerebral palsy[4] also find difficulty in swallowing and require FDTs because of their physical condition. The convenience and ease of using FDTs is more important to normal consumers, with some adults preferring this dosage forms as they are easy to handle and swallow, can be taken without water, and have a rapid onset of action.[1,6] Patients with a limited access to water would also find such FDTs extremely beneficial.[2,4]

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Clinically, glipizide is a sulfonylurea antidiabetic drug. It is given orally in the treatment of type-2 diabetes mellitus and has the duration of action of up to 24 h. Glipizide is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring 1–3 h after a single dose. It is extensively bound to plasma proteins and has a half-life of about 2–4 h. It is metabolized mainly in the liver and excreted chiefly in the urine, largely as inactive metabolites.[7]

This study aims to fabricate and optimize FDTs prepared by direct compression to not only have sufficient mechanical strength/hardness to withstand manual handling, but also have a rapid disintegration time. Various techniques can be used to formulate fast-disintegrating or -dissolving tablets.[8,9] Direct compression, by one of these techniques, requires the incorporation of a superdisintegrant into the formulation, or the use of highly water-soluble excipients to achieve fast tablet disintegration. Direct compression does not require the use of water or heat during the formulation procedure and is the ideal method for moisture- and heat-labile medications.[10]

Mucilage and gums have been known since ancient times for their medicinal uses. Mucilage of natural origin is preferred over semi-synthetic and synthetic substances because they are comparatively cheaper, abundantly available, nonirritating and nontoxic in nature. In the modern era also they are widely used in the pharmaceutic industries as thickeners, water retention agents, emulsion stabilizers, suspending agents, binders, and film formers.[11,12] Mucilage of *Plantago ovata* (Ispaghula) has various characteristics, such as binding, disintegrating, and sustaining properties.[13] Hence, in the present study, the husk of *P. ovata* was used to develop FDTs of the selected model drug glipizide.

MATERIALS AND METHODS

Materials

Glipizide was obtained as a gift sample from Supra Chemical Pvt. Ltd. (Mumbai, India). *P. ovata* husk was purchased from Sidhpur Sat-Ishabgol Factory (Gujarat, India). Magnesium stearate, talc, and microcrystalline cellulose were purchased from Loba Chemie Pvt. Ltd. (Mumbai, India). Microcrystalline cellulose and starch (soluble) were purchased from Merk Speciality Pvt. Ltd. (Mumbai, India). All the other chemicals used were of high analytic grade.

Preparation of fast-dissolving tablets

The husk of *P. ovata* was powdered and passed through a no. 80 screen. The powder was soaked in distilled water for 24 h and boiled for a few minutes, so that complete gelatinization takes place and dried in an oven at a temperature less than 60°C. After drying gelatinized material was collected, and size reduced. FDTs of glipizide were prepared by direct compression method. The raw materials were passed through a no. 100 screen before mixing and mixed using a glass mortar and pestle. The powder blends was lubricated with 1% wt/wt talc and 1% wt/wt magnesium stearate. The powder blends ready for compression was converted into tablets using a tablet punching machine (Cadmach, India).

Evaluation of powder blends

Angle of repose

The angle of repose of powder blends was determined by the funnel method. Accurately weighed powder blends were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder blends. The powder blends were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:[14]

$$\tan \theta = h/r$$

Where, h and r are the height and radius of the powder cone (1)

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-s intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas:[15]

$$\text{LBD} = \text{weight of the powder/volume of the packing} \quad (2)$$

$$\text{TBD} = \text{weight of the powder/tapped volume of the packing} \quad (3)$$

Compressibility index[16] and Hausner ratio[17]

The compressibility index of the powder blends was determined by Carr's compressibility index (or Carr's index).

$$\text{Carr's index (\%)} = [(\text{TBD} - \text{LBD}) \times 100]/\text{TBD} \quad (4)$$

$$\text{Hausner ratio} = \text{tapped density/bulk density} \quad (5)$$

Analytic method

A total of 100 mg of glipizide was accurately weighed, placed in l00 mL volumetric flask and dissolved in the phosphate buffer (pH 7.4). A 5 mL of this solution was taken in a 100 mL volumetric flask. To generate a calibration curve, 5–50 µg/mL of primary standard was prepared and the calibration curve was obtained by measuring their absorbance at predetermined UV-1800 spectrophotometer (Shimadzu, Japan) at 275 nm. The concentration of glipizide was calculated using the linear regression equation of the calibration curve.

$$(\text{absorbance} = 0.0234 \times \text{concentration} + 0.0031, r^2 = 0.9993) \quad (6)$$

Evaluation of tablets

Content uniformity test

The content uniformity test is used for tablets with <50 mg of the active ingredients and/or representing <50% total mass of the tablets. For this test, representative samples of 10 tablets were selected and assayed individually. The required specification for this test is that uniformity of the dosage units should be within a range of 85%–115% with a relative standard deviation of ≤6%.[18]

Drug entrapment efficiency

A tablet was crushed in a glass mortar and pestle, and the powdered tablet was suspended in 100 mL of phosphate buffer (pH 7.4). After 24 h, the solution was filtered and the filtrate was analyzed by UV-1800 spectrophotometer (Shimadzu, Japan) at 275 nm. The drug entrapment efficiency was calculated using the formula:

Drug entrapment efficiency = [practical drug content/theoretical drug content] × 100.[19] (7)

Hardness and friability

The hardness test was performed using the Monsanto hardness tester (Cadmach, Ahmedabad, India). For each formulation, the hardness of 6 tablets was determined. The friability test was performed using the Roche friabilator (Campbell Electronics, Mumbai, India). Samples of 20 tablets were tested at a time. After 100 turns, the tablet samples were evaluated by weighing.[18]

Disintegration time

In vitro disintegration time for FDTs was determined using modified disintegration test apparatus with simulated salivary fluid (pH 6.2) as the disintegrating medium.[20] A more suitable apparatus was developed because many reports[21-24] indicated the unsuitability of the conventional disintegration test apparatus for FDT. Briefly, the apparatus consisted of a glass beaker of 1000 mL capacity with the wire basket positioned in the beaker with the help of a support in a way that when the beaker contained 900 mL of disintegrating medium, the basket had only 6 mL of it. A magnetic bead was placed at the bottom of the beaker and maintained at 37°C±2°C. Disintegration time was determined at 25 rpm.[20]

Drug release study

Release of glipizide from the FDTs was studied in the phosphate buffer of pH 7.4 (900 mL) using a United States Pharmacopeia (USP) XXIII 3-station Dissolution Rate Test Apparatus (Campbell Electronics, Mumbai, India) with a rotating paddle stirrer at 50 rpm and 37°C±1°C as prescribed for glipizide tablets in USP. A tablet was used in each test. Samples of dissolution fluid were withdrawn through a filter (0.45 μm) at different time intervals and were assayed at 275 nm for glipizide content using a UV-1800 spectrophotometer (Shimadzu, Japan). The drug release experiments were conducted in triplicate ($n = 3$).

RESULTS

Formulation scientists generally use superdisintegrant for developing FDTs or for improving dissolution of active pharmaceutical ingredients from solid dosage forms. The superdisintegrants are used from as low as 4% to as high as 66% in fast-dissolving formulations.[25] The compositions of all the formulations were shown in Table 1.

Formulation A1, which was prepared without using superdisintegrant, contained highest disintegration time, lowest percentage friability, and highest hardness. Formulations A2, A3 and A4 were prepared using HPO (5%, 10%, and 15% of the total weight) as a superdisintegrant. Similarly, formulations A5, A6, A7, and A8 were prepared using PHPO (5%, 10%, 15%, and 20% of the total weight) as a superdisintegrant. The powder blends of all the batches were evaluated for angle of repose, compressibility index, and Hausner ratio. The results of angle of repose, compressibility index (%), and Hausner ratio, shown in Table 2, ranged from 24.23±0.57 to 29.34±0.78, 15.76±0.82 to 20.12±1.25, and 1.18±0.011 to 1.25±0.019, respectively.

The results of the disintegration test, friability test, hardness test, drug entrapment efficiency, and content uniformity test were shown in Table 3. Disintegration time (s), friability (%), and hardness (kg) ranged from 17±0.08 to 225±0.09, 0.09±0.08 to 0.77±0.13, and 4.0±1.93 to 7.5±0.98, respectively.

Because of the results obtained in the studies, formulations containing PHPO showed the faster disintegration, higher percentage friability, and lesser hardness. Drug entrapment efficiency was found to be uniform among different formulations of the tablets and ranged from 97.53±0.52 to 99.72±0.45%. The results of content uniformity test of all the formulations were found in the official range. The percentage drug release of all the formulations was conducted in the phosphate buffer (pH 7.4). Figures 1 and 2 depict the dissolution profile of all the batches.

Table 1: Formulation table

Ingredients	Formulation code							
	A1	A2	A3	A4	A5	A6	A7	A8
Glipizide (mg)	5	5	5	5	5	5	5	5
HPO (mg)	–	10	20	30	–	–	–	–
PHPO (mg)	–	–	–	–	10	20	30	40
Talc (mg)	2	2	2	2	2	2	2	2
Magnesium stearate (mg)	2	2	2	2	2	2	2	2
Microcrystalline cellulose (mg)	175	165	155	145	165	155	145	135
Starch (soluble) (mg) q.s.	200	200	200	200	200	200	200	200

HPO: Husk of *Plantago ovata*; PHPO: Pregelatinized husk of *P. ovata*.

Table 2: Evaluation of powder blends

Formulation code	Angle of repose (degree) (*n*=5, ± SD)	LBD (mL) (*n*=5, ± SD)	TBD (mL) (*n*=5, ± SD)	Carr's index (%) (*n*=5, ± SD)	Hausner ratio (*n*=5, ± SD)
A1	29.34±0.78	0.33±0.002	0.413±0.004	20.12±1.25	1.25±0.019
A2	24.23±0.57	0.33±0.003	0.398±0.003	15.76±0.82	1.18±0.011
A3	24.65±1.00	0.33±0.002	0.396±0.004	16.82±1.27	1.20±0.018
A4	24.85±0.84	0.32±0.002	0.395±0.003	17.57±1.62	1.21±0.024
A5	25.57±1.80	0.33±0.003	0.398±0.003	15.76±0.82	1.18±0.011
A6	24.59±0.57	0.33±0.002	0.396±0.004	16.82±1.27	1.20±0.018
A7	24.55±0.49	0.32±0.002	0.395±0.004	17.84±1.48	1.21±0.021
A8	24.47±0.60	0.32±0.002	0.392±0.005	17.20±1.35	1.20±0.020

SD: Standard deviation; LBD: Loose bulk density; TBD: Tapped bulk density

Table 3: Evaluation of tablets

Formulation code	Disintegration time (s) (*n*=5, ± SD)	Friability (%) (*n*=5, ± SD)	Hardness (kg) (*n*=5, ± SD)	Entrapment efficiency (%) (*n*=5, ± SD)	Content uniformity (*n*=10, ±SD)
A1	225±0.09	0.09±0.08	7.5±0.98	98.53±0.43	98.55±0.63
A2	189±0.02	0.32±0.13	5.2±1.44	98.49±0.89	98.64±0.69
A3	170±0.03	0.52±0.22	4.5±1.78	98.24±0.67	98.31±0.47
A4	145±0.01	0.77±0.13	4.0±1.93	99.20±0.94	98.52±0.76
A5	53±0.03	0.18±0.12	5.2±0.93	98.79±0.51	98.65±0.40
A6	35±0.07	0.31±0.31	5.0±1.43	99.72±0.45	98.83±0.52
A7	24±0.04	0.39±0.13	4.6±1.76	98.04±0.29	98.92±0.25
A8	17±0.08	0.53±0.19	4.1±2.03	97.53±0.52	98.36±0.45

SD: Standard deviation

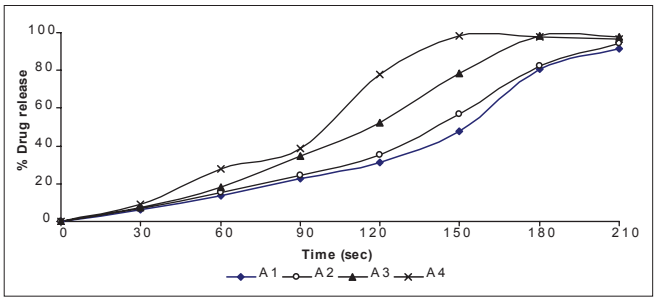

Figure 1: Drug release profile of fast-dissolving tablets with and without the husk of *Plantago ovata*

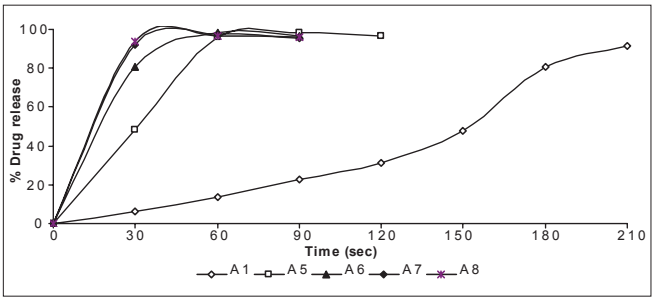

Figure 2: Drug release profile of fast-dissolving tablets with and without pregelatinized husk of *Plantago ovate*

DISCUSSION

The powder blends were prepared according to the formula given in Table 1. The powder blends of different formulations were evaluated for angle of repose, compressibility index, and Hausner ratio. The results of angle of repose (<30) showed good flow properties of the powder blends.[16,26] All these results showed that the powder blends possessed satisfactory flow properties, compressibility, and Hausner ratio. The tablets of different formulations were subjected to various evaluation tests, such as a disintegration test, friability test, hardness test, drug entrapment efficiency, content uniformity test, and *in vitro* dissolution test. The disintegration times for formulations, which contained HPO as a superdisintegrant, ranged from 145±0.01 to 189±0.02 s. Similarly, disintegration times for formulations, which contained PHPO as a superdisintegrant, ranged from 17±0.08 to 53±0.03 s. These results showed a concentration-dependent relationship in formulations prepared using HPO and PHPO as superdisintegrant where disintegration time was decreased on increasing concentration of the superdisintegration.

A tablet requires a certain amount of mechanical strength to withstand the shocks of handling in its manufacturing, packing, shipping, and dispensing. Hardness and friability are most common tests used to evaluate tablet strength. If a tablet is more fragile than expected, then the friability test will detect its substandard quality. Conventional compressed tablets that loose less than 1% of their weight are generally considered acceptable. In the present study, the percentage friability for all the formulations was below 1%, indicating that the friability is within the prescribed limits.[27] The required specification for content uniformity test is that uniformity of

the dosage units should be within a range of 85%–115% with a relative standard deviation of ≤6%. The average percentage deviation of all the prepared tablets was found to be within the above limit, and hence all formulations passed the content uniformity test as per the official requirements.[18] The percentage of drug content was found to be >97% in all the formulations. The percentage drug release for formulations containing HPO and PHPO as a superdisintegrant was shown in Figures 1 and 2. Batch A1 containing no superdisintegrant released about 13% of glipizide in a minute. The bathes A2, A3, and A5 containing HPO as a superdisintegrant, released 15%, 18%, and 27% approximately, of glipizide per minute. Formulations containing PHPO as a superdisintegrant, released more than 95% of drug within a minute. Among eight batches, Batch F8 is selected as optimized batch because of its lowest disintegration time, acceptable percentage, and hardness.

CONCLUSION

The results of the various evaluation tests revealed that pregelatinized husk of *P. ovata* significantly affects the tablet properties, and thus it is concluded that by using pregelatinized husk of *P. ovata* as a superdisintegrant, direct compression may be an effective alternative approach for the formulation of FDTs.

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