ORIGINAL ARTICLE

In vitro-in vivo performance evaluation of treated *Plantago ovata* husk based fast dissolving tablets of glipizide: Flashtab technology

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Physicians suggest premeal administration of glipizide (30 min before a meal) because of longer disintegration time (approximately 15 min) of conventional tablet. Hence, the dosage form was developed, called as fast dissolving tablet (FDT), which disintegrates rapidly within a minute. FDTs by Flashtab technology is based on a swellable agent and a superdisintegrant. In the current study, treated *Plantago ovata* husk (TPOH), and microcrystalline cellulose were utilized as natural superdisintegrant and swellable agent, respectively. FDT formulations were prepared by direct compression and evaluated for *in vitro* tablet performance, such as disintegration time, wetting time, hardness, friability, swelling and percent drug release. On the basis of finding, formulation with 15% TPOH concentration (TPOH 7) was selected as optimized formulation. To evaluate the *in vitro* performance, the formulation TPOH 7 and the marketed tablets (glynase) were administered to rabbits. In the case of marketed tablet, the peak plasma-concentration of glipizide was obtained in 2.83 h of administration whereas it was 2 h for TPOH 7 indicating immediate absorption and therefore faster onset of action of the prepared FDT formulation than the marketed one. Drug interaction studies, performed by using FTIR spectroscopy, X-ray diffractometry and differential scanning calorimetric methods, indicate that the glipizide is compatible with the formulation components. The accelerated stability study (40°C ± 2°C/75% ±5% relative humidity) for the optimized formulation showed a negligible change over time for the *in vitro* parameters. The results suggest that TPOH has promising potential for faster disintegration and fulfills the requirement of FDTs.

Key words: *Direct compression, fast dissolving tablets, flashtab technology, glipizide, Plantago ovata husk, superdisintegrant*

INTRODUCTION

Fast dissolving tablets (FDTs) usually dissolve within 15 s to 2 min when comes in contact with water. It not only reduces the premeal administration time of glipizide, but also minimize swallowing problem of conventional tablets and ultimately improve patient compliance.[1] The different formulation processes for making FDTs are freeze drying, molding and compression methods.[2] The compression method is the most widely used method for producing fast dissolving dosage forms. Some researchers have focused on unique conventional and novel granulation methods, such as wet granulation,[3,4] dry granulation,[5] melt granulation[6] and spray drying.[7] However, the direct compression method outshines all other compression methods. Direct compression is the easiest and cost effective method[8] which can be applied by choosing appropriate combinations of excipients that can provide fast disintegration and good physical resistance.[9] Glipizide is a sulfonylurea antidiabetic drug given orally in the treatment of type 2 diabetes mellitus and has a duration of action of up to 24 h. It 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. The usual initial dose is 2.5-5 mg daily given as a single dose

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about 30 min before breakfast.[10] On the basis of methods of making, several patented technologies, such as Zydis, Lyoc, Orasolv, Durasolv, Wow tab and Flashtab, are available for FDTs. In Flashtab technology, tablet matrix consists of a swellable agent and a superdisintegrant.[2] In the present study, microcrystalline cellulose was selected as swellable agent and treated *Plantago ovata* husk (TPOH) as a natural superdisintegrant. Disintegrants are agents added to tablet to promote the breakup of the tablet into smaller fragments in an aqtueous environment, thereby increasing the available surface area and promoting a more rapid release of the drug substance. They promote moisture penetration and dispersion of the tablet matrix. Tablet disintegration has received considerable attention as an essential step in obtaining fast drug release.[11]

METHODS

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

Treatment of *Plantago ovata* husk

The *P. ovata* husk was powdered and passed through no. 80 screens. The powdered material (2% w/v) was allowed to soak in distilled water for 24 h and dried in a Tray Drier (NSW, India) at 75°C temperature. After drying the dried material was size reduced and sieved to get free flowing powder, here in after referred as TPOH.

Powder evaluation

Bulk swelling capacity

The powdered material (2.0 g) was carefully poured into a 25 ml volumetric cylinder, and the bulk volume was measured ($V1$).[12-14] 10 ml of distilled water was added to it. The suspension was well shaken for 5 min and volume is made up to 25 ml with distilled water. The sample was allowed to stand for 24 h, and the sedimentation volume was read off ($V2$). Three parallel measurements were carried out. The process was repeated with 0.1 M HCL and phosphate buffer system, pH 7.4 (PBS 7.4). The bulk swelling capacity was calculated as:

$$\text{Bulk swelling capacity} = V2/V1$$

Capillary action

For capillary water uptake study,[15] samples were prepared by mixing different concentrations of TPOH in glipizide (1.0%, 3.0%, 5.0%, 7.0%, 9.0%, 12%, and 15% w/w in glipizide). Samples were filled with capillary tubes, and each tube was tapped 20 times on the tile in order to obtain a constant height of 7 cm of the powder column. Bottom ends were plugged with an absorbent paper and dipped in distilled water by means of supports. Water uptake by column in the tube was observed and measured up to 30 min after the start of the experiment.

Flow properties determination

Flow properties, such as angle of repose, Carr's index and Hausner ratio, were determined by making powder blends as per the formulation composition given in Table 1 without adding talc and magnesium stearate. Powder blends were mixed for 5 min in a resealable plastic bag and processed for angle of repose, Carr's index and Hausner ratio. For the determination of the angle of repose, accurately weighed powder blend (2 g) was 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 mix was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured, and angle of repose (θ) was calculated using the following equation.[16]

$$\theta = \tan^{-1}(h/r)$$

Where, h and r are the height and radius of the powder cone.

For the determination of loose bulk density (LBD) and tapped bulk density (TBD), a quantity of 2 g of powder blend 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

Table 1: Formulation composition

Ingredients (%)	Formulation code						
	TPOH 1	TPOH 2	TPOH 3	TPOH 4	TPOH 5	TPOH 6	TPOH 7
Glipizide	2	2	2	2	2	2	2
TPOH	1	3	5	7	9	12	15
Microcrystalline cellulose	35	35	35	35	35	35	35
Talc	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1
Starch soluble q.s. (mg)	250	250	250	250	250	250	250

TPOH: Treated *Plantago ovata* husk, SD: Standard deviation

no further change in volume was noted. LBD and TBD were calculated as:[17]

LBD = Weight of the powder/volume of the packing
TBD = Weight of the powder/tapped volume of the packing

The compressibility index[18] of the powder mix was determined by the Carr's compressibility index (or Carr's index)

Carr's index (%) = [(TBD − LBD) ×100]/TBD.

Hausner ratio[19] of the powder mix was determined by the formula:

Hausner ratio = Tapped density/bulk density

Preparation of fast dissolving tablets

Screened TPOH passed through a no. 100 screens were selected as superdisintegrant. Glipizide, microcrystalline cellulose, superdisintegrant and soluble starch were weighed and mixed together for 5 min in a resealable plastic bag. The powder blend was lubricated to make flow property excellent and transformed into tablets using a tablet punching machine (Cadmach, India).

***In vitro* evaluation**

Drug content study

A randomly selected tablet was crushed in a glass mortar and pestle, and the powdered tablet was suspended in 100 ml of PBS 7.4 with stirring on a magnetic stirrer (Remi, India). After 24 h, the solution was filtered, and the filtrate was analyzed by UV-1800 spectrophotometer (Shimadzu, Japan) at 225 nm. The drug content was calculated using the formula:[20]

Drug content = (Practical drug content/theoretical drug content) ×100.

Content uniformity study

For the content uniformity test[21] 10 tablets were randomly selected and assayed, individually, by UV-1800 spectrophotometer (Shimadzu, Japan) at 225 nm. The required specification for this test is that uniformity of the dosage units should be within the range of 85-115% with a relative standard deviation of ≤ 6%.

Hardness and friability study

For hardness test,[21] 6 tablets were randomly selected from each batch. Monsanto hardness tester (Cadmach, India) was used to perform hardness test. The friability test was performed using a Roche friabilator (Campbell Electronics, India). A randomly selected sample of 20 tablets from each batch was tested at a time. After 100 turns, the tablet samples were evaluated by weighing.

Disintegration study

In vitro disintegration time study for FDTs was determined using a modified disintegration test apparatus[22] with distilled water, 0.1 M HCL, and PBS 7.4 as the disintegrating media. 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 tablet placed in the basket just dipped in it. A magnetic bead, at a stirring speed of 25 rpm, was placed at the bottom of the beaker maintained at 37°C ± 2°C.

Wetting time study

Wetting time study of each tablet was carried out in wetting media such as distilled water, 0.1 M HCL and PBS 7.4 using the method reported by Bi *et al*. with slight modification.[23] A piece of tissue paper folded twice was kept in a culture dish containing 10 ml of the wetting medium. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required developing a red color on the upper surface of the tablet was recorded as the wetting time.

Swelling study

In swelling study,[24] the initial weight of the tablet was determined (*W*1). After that, each tablet was placed separately in 25 ml beaker containing tissue paper soaked in swelling media such as distilled water, 0.1 M HCL, and PBS 7.4. Tablets were removed after 2 min, wiped with filter paper, and reweighed (*W*2). The swelling index was calculated as follows:

Swelling index = [(*W*2–*W*1)/W1] 100

Dissolution study

For the FDT formulation, glipizide release was evaluated according to the procedure published in the USP monograph.[25] The test was performed with paddles operating at 50 rpm, and the dissolution medium consisted of 900 ml of PBS 7.4 and 0.1 M HCL maintained at 37°C temperature. Two milliliter dissolution medium was withdrawn at 0.25, 0.5, 0.75, 1, 1.5, 2 and 2.5 h, filtered through membrane filter and analyzed using a UV-1800 spectrophotometer (Shimadzu, Japan). Fresh medium was replaced after sample withdrawal. For the marketed formulation, the dissolution apparatus and medium were similar to the FDTs.

***In vivo* evaluation**

Preparation of stock solutions, calibration samples

A stock solution was prepared by dissolving 5 mg of glipizide in 100 ml of methanol (50% v/v) to achieve a concentration 50 µg/ml. A series of working solutions of glipizide were prepared (150-8000 ng/ml) by diluting the stock solution with methanol (50% v/v). 50 µl of the appropriate working solution of glipizide was added to 450 µl of drug-free rabbit plasma to prepare the calibration standards. The plasma calibration standards were made at the following concentrations: 15,

50, 100, 200, 400, 600 and 800 ng/ml. 500 µl of plasma calibration standards and 850 µl of 0.05 M HCL were added to the glass tube. After mixing, 5 ml of diethyl ether was added, and the mixture was stirred for 30 s. Each sample was centrifuged at 2,500 rpm for 10 min. The organic layer was transferred to a new tube and evaporated to dryness under a nitrogen stream at 50°C. The residue was reconstituted with 500 µl of 50% methanol, and a 20 µl aliquot was injected for high-performance liquid chromatography (HPLC) (Waters 600, Millipore Corporation, Milford) analysis.[26]

Pharmacokinetic study

Pharmacokinetic study[26] of FDTs was based on a single dose, randomized, two-period crossover study. The washout period between administrations was 1-week. Six male rabbits (weighing 2.0-2.5 kg) were used in this study. The rabbits were fed standard laboratory chew diet with water and fasted overnight before the experiment, although free access to water was allowed. Water was not given until 2 h after the test preparation was administered during the course of the experiment. After oral administration of the test preparation, 2 ml blood samples were collected at predetermined time intervals. Plasma was immediately separated by centrifugation of the blood samples at 8000 rpm for 10 min. All plasma samples were immediately frozen at −200°C until analysis.

For the determination of glipizide plasma-concentration, 500 µl of plasma sample and 850 µl of 0.05 M HCL were added to the glass tube. After mixing, 5 ml of diethyl ether was added, and the mixture was stirred for 30 s. Each sample was centrifuged at 2,500 rpm for 10 min. The organic layer was transferred to a new tube and evaporated to dryness under a nitrogen stream at 50°C. The residue was reconstituted with 500 µl of 50% methanol and a 20 µl aliquot was injected for HPLC analysis.

Drug interaction and stability evaluation

Drug interaction evaluation

The samples were prepared by mixing 1:1 weight ratio of glipizide and excipient. It was chosen because it maximizes the likelihood of observing any interaction.[27] Glipizide and all the excipients were passed through sieve number 100 before preparation of the samples. Physical mixture of glipizide and excipient was prepared by gently mixing for 5 min in a resealable plastic bag. Fourier transform infrared (FTIR)-spectra of glipizide and glipizide-excipient systems of the sample were recorded in the FTIR equipment (Alfa Bruker). Samples were scanned in the range of 4000-650 cm^{-1}. X-ray diffraction experiments were performed in a Seifert XRD 3003 TT (GE Inspection Technologies, Japan) by using Cu K-α radiation with a nickel filter, a voltage of 40 kV, and a current of 30 mA. The scanning rate employed was 10 min^{-1} over the 10°–80° diffraction angle (2θ) range. Diffraction patterns of glipizide and physical mixture of glipizide-excipient (1:1 w/w) were obtained.

Drug accelerated stability study

The formulations were packed in an amber colored containers, each containing 25 tablets, and subjected to accelerated stability studies as per International Conference on Harmonization (ICH) guidelines (40°C ± 2°C/75% relative humidity [RH] ±5% RH). The samples were withdrawn periodically (0, 90 and 180 days) and evaluated for the drug content, disintegration time, percentage friability, hardness, wetting time and percentage swelling.

RESULTS AND DISCUSSION

Powder evaluation

Bulk swelling and capillary water uptake studies were done to determine the swelling as well as disintegrant potential of free flowing powder, whereas derived properties, such as angle of repose, Carr's index and Hausner ratio, were utilized to know the flow ability of the powder blend. Bulk swelling study of TPOH was done in three different media, such as distilled water, 0.1 M HCL and PBS 7.4, and the results were shown in Figure 1. TPOH showed a better bulk swelling capacity in distilled water and PBS 7.4 than in 0.1 M HCL. Almost equal bulk swelling was found in the case of both distilled water and PBS 7.4. For capillary water uptake study, powder blends were prepared by using different concentrations of TPOH (1%, 3%, 5%, 7%, 9%, 12% and 15% w/w) in glipizide. Figure 2 shows capillary water uptake by TPOH-glipizide powder mix. Distilled water was used as the study medium. Capillary water uptake was increased with increasing concentration of TPOH. At low concentration of TPOH, capillary water uptake was minimal. Maximum capillary water uptake was found in the mixture containing 15% TPOH. Almost similar results were obtained when capillary water uptake study of TPOH-glipizide powder mix was performed in 0.1 M HCL and PBS 7.4.

For the determination of derived properties, the powder blends were prepared as per the composition given in Table 1 without adding lubricants. The derived properties of powder blend were obtained using the angle of repose, loose bulk and tapped bulk densities and the obtained values of loose bulk and tapped bulk densities were subjected to the calculation of Carr's index and Hausner ratio.

Table 2 shows the results of the angle of repose (θ), Carr's index and Hausner ratio. The values of the angle of repose of the powder blend were ranged from 29.46° ±01.27° to 33.63° ±1.94° suggested good flow property. The average bulk density of the powder blend containing different concentrations of TPOH was found to be 0.28 g/cm^2 and that of the powder blend without TPOH was found to be 0.42 g/cm^2. Around 40-44% reduction in bulk density values of powder blends containing TPOH indicated a higher bulk volume and thereby higher porosity when compared to powder blend without TPOH, which is desirable to support rapid disintegration. The Carr's compressibility index (%) and

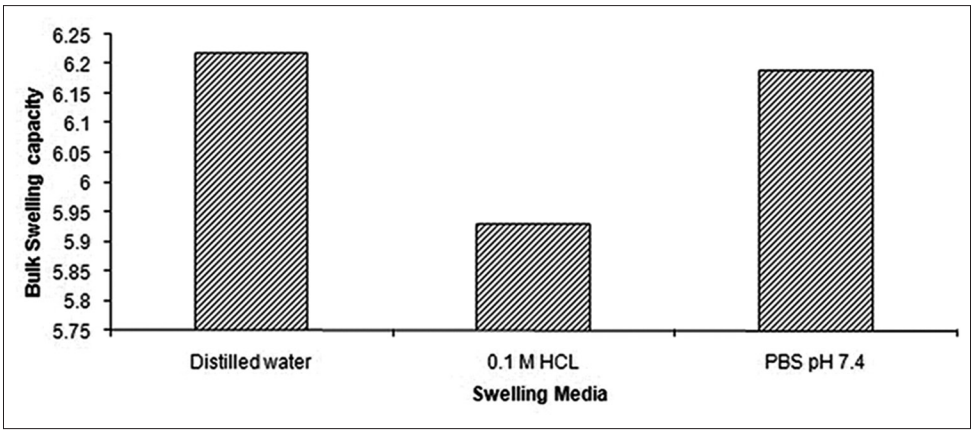

Figure 1: Bulk swelling capacity of treated Plantago ovata husk in distilled water, 0.1 M HCL and PBS 7.4

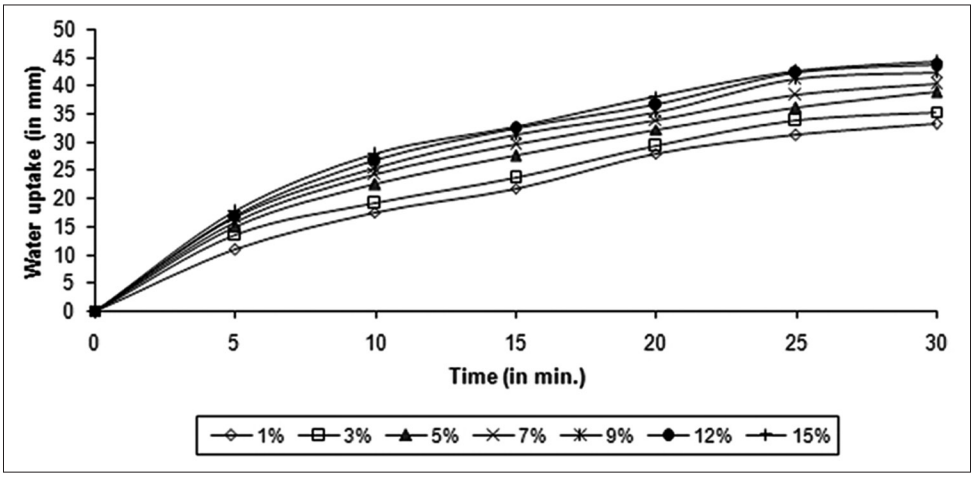

Figure 2: Capillary water uptake study of glipizide: Treated Plantago ovata husk mixture in distilled water

Table 2: Flow properties of powder blend

Formulation code	*n*=3, ±SD		
	Angle of repose (θ)	Carr index (%)	Hausner ratio
TPOH 1	33.63±1.94	18.13±2.19	1.20±0.01
TPOH 2	32.57±1.49	18.47±1.66	1.20±0.01
TPOH 3	30.17±2.16	18.51±3.01	1.18±0.05
TPOH 4	31.04±1.59	19.68±2.79	1.19±0.02
TPOH 5	30.98±2.40	19.81±1.52	1.21±0.04
TPOH 6	30.57±1.82	18.14±1.70	1.19±0.03
TPOH 7	29.46±1.27	17.63±1.29	1.18±0.03

TPOH: Treated *Plantago ovata* husk, SD: Standard deviation

Hausner ratio were ranged from 17.63% ±1.29% to 19.81% ±1.52% and 1.18 ± 0.03–1.21 ± 0.04 respectively.The values of the angle of repose, Carr's compressibility index (%) and Hausner ratio suggested fairly good flow properties. All these results showed that the powder blend didn't possess excellent flow properties and hence, lubricants were added.

In vitro evaluation

The tablets of different powder blend, as given in Table 1, were subjected to *in vitro* evaluation tests, such as a disintegration test, friability test, hardness test, drug content analysis, content uniformity test, wetting time test, swelling study and drug release study. The results of the evaluation tests were shown in Table 3. The average drug content of the formulations was rangedfrom 99.19% ±2.61% to 100.62% ±1.77% and was found to meet the pharmacopoeial requirements. For the content uniformity test, the required specification is that uniformity of the dosage units should be within the range of 85-115% with a relative standard deviation of less than or equal to 6%.[21] The average percentage deviation of all the prepared tablets was found within the above limit, and hence, all formulations passed the content uniformity test as per the official requirements. Hardness of formulations was ranged from 4.06 ± 0.23 kg to 8.56 ± 0.25 kg. Maximum hardness was found in the formulation containing 1% of TPOH. An insignificant relationship ($P > 0.05$), with negative correlation ($R^2 = 0.9812$), was found between the concentration of TPOH and tablet hardness which indicated that as the concentration of TPOH increased, tablet hardness decreased. Percentage friability of all the prepared formulations was within the range of 0.31% ±0.03%. A highly significant relationship ($P = 0.008$), with a positive correlation ($R^2 = 0.9688$), was found between

the concentration of TPOH and percentage friability, which showed that as the concentration of TPOH increased, percentage friability increased. At the 1% level of TPOH concentration, percentage variability was found to be zero. As the concentration of TPOH increased from 1% to 15% w/w, percentage friability increased from 0% to 0.14%. In the present study, the percentage friability for all the formulations was below 1%, indicating that the friability is within the prescribed limits.[28]

Disintegration time of all the prepared formulations ranged from 32.99 ± 2.51 s to 84.33 ± 4.35 s. A highly significant relationship (P = 0.0001), with negative correlation (R^2 = 0.9854) was found between the concentration of TPOH and disintegration time which indicated that as the concentration of TPOH increased, the disintegration time decreased. A highest disintegration time was found in the formulation containing 1% TPOH whereas, minimum disintegration time was found in the formulation containing 15% of TPOH. The snapshots of tablet disintegration test were shown in Figure 3. Wetting time of all the prepared formulations was ranged from 48.99 ± 4.04 s to 104.32 ± 3.05 s. A highly significant relationship (P = 0.0001), with negative correlation (R^2 = 0.9950) was found between the concentration of TPOH and wetting time which indicated that as the concentration of TPOH increased, the wetting time decreased. A very high wetting time was found in the formulation containing 1% TPOH whereas, minimum wetting time was found in the formulation containing 15% of TPOH. Percentage swelling of formulation was ranged from 204.03% ±5.50% to 303.31% ±9.15%. A highly significant relationship (P = 0.0001), with a positive correlation coefficient (R^2 = 0.9881), was found between the concentration of TPOH and percentage swelling which indicated that as the concentration of TPOH increased, the percentage swelling increased. Maximum percentage swelling was found in the formulation containing 15% of TPOH. Similar results were found when the disintegration test, wetting time test and swelling studies were performed in 0.1 M HCL and PBS 7.4.

The dissolution study of all the prepared formulation was carried out using PBS 7.4 and 0.1 M HCL. The percentage drug release of glipizide in the two media is illustrated in Figures 4 and 5, respectively. It was found that all the formulations released > 80% of glipizide within 15 min and almost 100% in an hour when PBS 7.4 was used as the dissolution medium. On the other hand, <15% glipizide release was found up to an hour when 0.1 M HCL was used as the dissolution medium. Due to the lowest disintegration time, TPOH 7 was selected optimized formulation for comparative study with a marketed product (glynase). The disintegration time of TPOH 7 was found below 40 s, whereas marketed formulation taken around 18 min to disintegrate. The dissolution study of the formulation TPOH 7 revealed the rapid release of the drug (t_{90} is approximately 60 s) in PBS 7.4 compared to marketed formulation, which has a t_{90} of 150 s. The relative standard deviation at each time point was below 10%, which indicates the reproducibility of the results. The release profile of TPOH 7 was compared with a marketed product by calculating a statistically derived mathematical parameter, "similarity factor" (f_2),[29,30] using marketed product (glynase) as a reference. Fraction released data was used for this purpose to standardize the percent drug release values for the labeled amount of glipizide

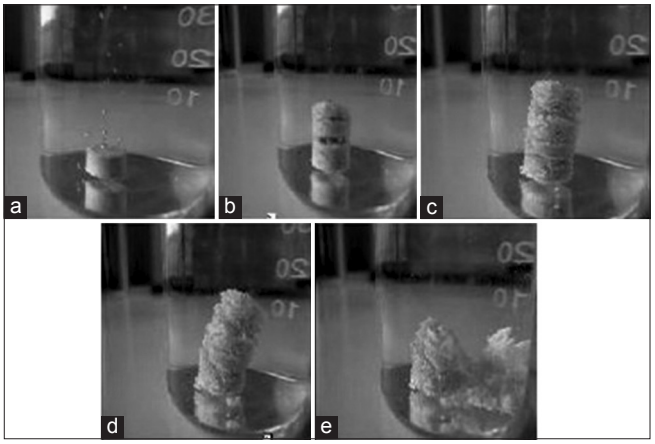

Figure 3: Snapshots of tablet disintegration test (a) at start, (b) at 5 s, (c) at 10 s, (d) at 15 s, and (e) at 20 s

Table 3: Tablet evaluation parameters

Formulation code	Drug content (%) (n=3, ±SD)	Content uniformity (%) (n=10, ±SD)	Hardness (kg) (n=6, ±SD)	Friability (%) (n=3, ±SD)	Disintegration time (s) (n=3, ±SD)	Wetting time (s) (n=3, ±SD)	Swelling (%) (n=3, ±SD)
TPOH 1	100.62±1.77	99.23±1.83	8.56±0.25	0	84.33±4.35	104.32±3.05	204.03±5.50
TPOH 2	99.19±2.61	100.31±1.93	8.33±0.11	0.03±0.03	75.99±3.51	98.84±0.98	227.03±2.96
TPOH 3	99.87±1.41	99.23±2.23	7.96±0.25	0.04±0.01	62.32±3.78	87.33±1.73	244.48±6.84
TPOH 4	99.62±0.98	99.48±1.22	6.56±0.11	0.06±0.01	56.66±2.51	80.99±4.04	256.25±1.18
TPOH 5	99.33±1.70	100.40±1.57	6.30±0.43	0.14±0.04	51.32±2.08	70.66±3.05	267.10±3.96
TPOH 6	100.31±0.74	99.97±1.58	5.66±0.30	0.26±0.03	44.33±3.60	55.66±3.51	279.73±4.50
TPOH 7	100.13±0.77	99.23±1.32	4.06±0.23	0.31±0.03	32.33±2.51	48.99±4.04	303.31±9.15
			P >0.05, NS	P =0.008, S	P =0.0001, HS	P =0.0001,HS	P =0.0001, HS
			R^2 =−0.9812	R^2 =0.9688	R^2 =−0.9854	R^2 =−0.9950	R^2 =0.9881

TPOH: Treated *Plantago ovata* husk, SD: Standard deviation, S: Significant, NS: Nonsignificant, HS: Highly significant

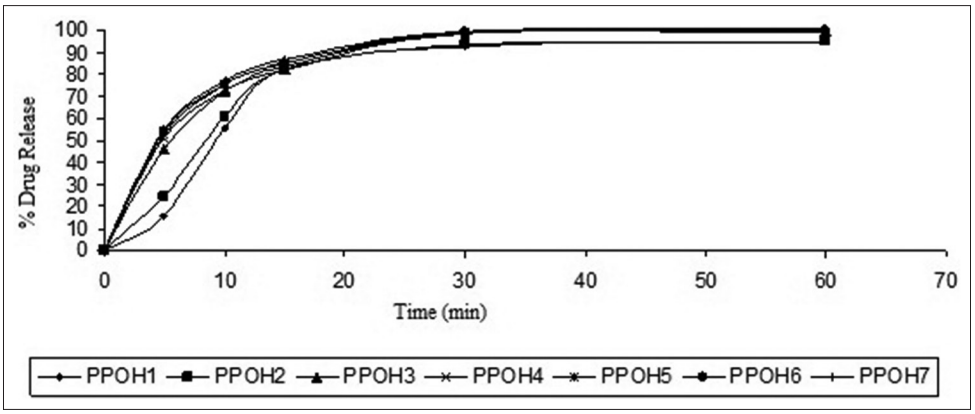

Figure 4: Percentage drug release of glipizide in PBS pH 7.4

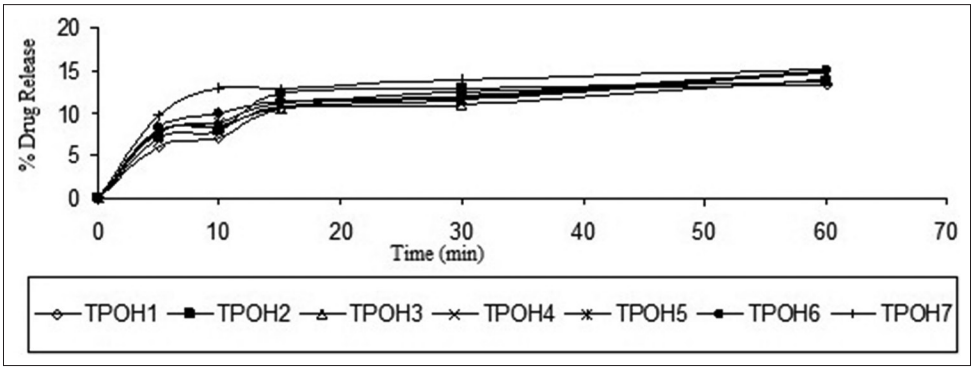

Figure 5: Percentage drug release of glipizide in 0.1 M HCL

Table 4: Pharmacokinetic parameters of marketed product (Glynase) and TPOH7

Pharmacokinetic parameters	(*n*=3, ± SD)	
	Optimized formulation (F_9)	Marketed formulation
Tmax (h)	2±1.38	2.83±0.28
Cmax (ng/ml)	417.56±3.36	438.10±7.31
$AUC_{0-\infty}$ (ng/ml*h)	4232.96±19.67	4628.03±34.27
$AUMC_{0-\infty}$ (ng/ml*h^2)	33452.63±545.32	36362.73±436.45
MRT (h)	7.90±0.23	7.85±0.31
Relative bioavailability	95.31	100

TPOH: Treated *Plantago ovata* husk, SD: Standard deviation, AUC: Area under the curve, AUMC: Area under the first moment curve, MRT: Mean residence time

present in the tablets. The value of $f_2 < 50$ indicates the dissimilarity of two dissolution profiles.

In vivo evaluation

The pharmacokinetic parameters, as shown in table 4, were calculated by noncompartmental analysis based on statistical moment theory using PK Solver. The pharmacokinetic parameters such as maximum plasma-concentration (Cmax) and time of maximum plasma-concentration (Tmax), were obtained directly from plasma-concentration-time plots. The area under the plasma-concentration-time curve up to the last time (t) (area under the curve $[AUC]_{0-t}$), area under curve extrapolated to infinity ($AUC_{0-\infty}$) and area under the first moment curve extrapolated to infinity ($AUMC_{0-\infty}$) were calculated using the linear trapezoidal rule. To evaluate the *in vitro* performance, the formulation TPOH 7 and the marketed tablets (glynase) were administered to rabbits. In the case of marketed tablet, the peak plasma-concentration of glipizide was obtained in 2.83 h of administration whereas it was 2 h for TPOH 7 indicating immediate absorption and therefore faster onset of action of the prepared formulations than the marketed one. The mean plasma level (Cmax) of glipizide following oral administration of TPOH 7 and marketed tablets was found to be 417.56 ng/ml and 438.10 ng/ml, respectively. The marketed tablets showed a slightly higher value of Cmax than the FDTs. The parameters $AUC_{0-\infty}$, of the FDTs and the marketed tablets, was 4232.96 and 4628.03 ng/ml*h. The relative bioavailability of glipizide calculated from the ratio of AUC ([testing product/reference product] $\times 100$) was 95.31.

Drug interaction and stability evaluation

Fourier transform infrared spectral analysis

The infrared (IR) spectrum of pure drug glipizide and physical mixture of glipizide and excipients were studied and are shown in Figure 6. The two IR absorption bands at 3322 cm^{-1} and 3248 cm^{-1} are assigned to the stretching vibration of N-H bonds in acylamino and carbamido groups. The band at 2943.2 cm^{-1} corresponds to the asymmetric stretching vibration of C-H bond in the methyl group, the band at 2916.2 cm^{-1} corresponds to

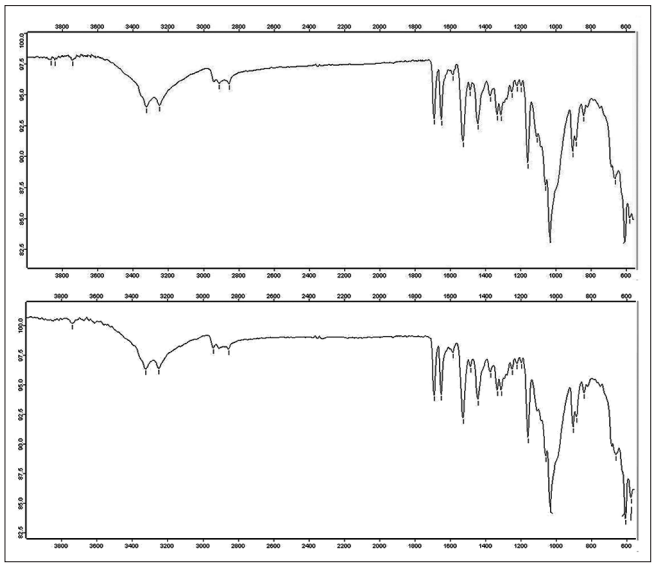

Figure 6: Fourier transform infrared spectra of glipizide and glipizide-excipient (1:1) mixture

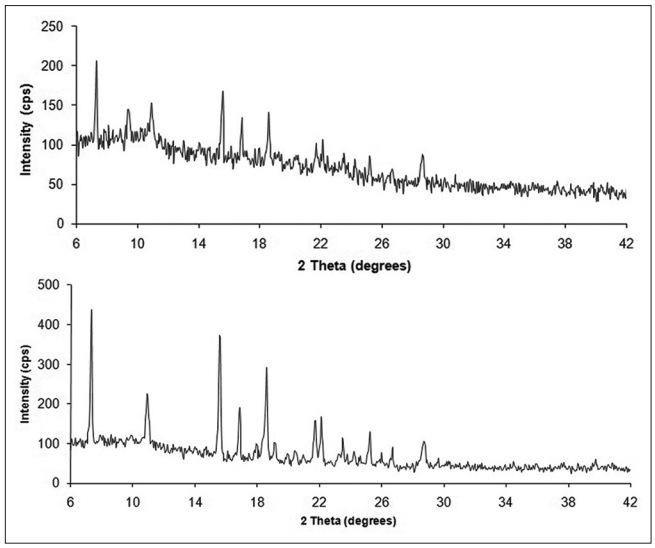

Figure 7: X-ray diffractogram of glipizide and glipizide-excipient (1:1) mixture

the asymmetric stretching vibration of C-H bond in cyclohexane and methylene, while the band at 2854.8 cm^{-1} corresponds with symmetric stretching vibration of the saturated C-H bond. The bands at 1688.8 cm^{-1} and 1650.2 cm^{-1} are interpreted as the stretching vibration of two carbonyl groups in acylamino and carbamido groups. Because the C = O bond in acylamino conjugated with pyrazine ring, it vibrated in higher absorption frequency (1688.8 cm^{-1}) than carbamido (1650.2 cm^{-1}). The bands at 1528.4 cm^{-1} and 1444.1 cm^{-1} are attributed to the stretching and deformation skeleton vibration of the benzene ring, respectively. The IR absorption bands at 1333.0 cm^{-1} and 1160.1 cm^{-1} corresponds to asymmetric and symmetric stretching vibration, respectively, of S = O in sulfone. The band at 1308.5 cm^{-1} is the characteristic absorption band of secondary amide, which contained N-H stretching and bending vibration. The band at 1034.1 cm^{-1} is assigned to the skeleton vibration of cyclohexane. The bands obtained in the spectra of formulation correlates with the bands of the drug spectrum. This indicates that the drug is compatible with the formulation components.

Powder X-ray diffraction analysis

Powder X-ray diffractograms of glipizide and physical mixture (1:1 w/w) of glipizide-excipients are shown in Figure 7. The presence of numerous distinct peaks in the XRD spectrum indicates that the glipizide was present as a crystalline material with major characteristic diffraction peaks appearing at 7.35, 10.9, 15.55, 16.85, 18.6, 21.75, 22.1, 25.25 and 28.7. The presence of distinct peaks in the XRD spectrum of glipizide-excipients mixture indicates that there is no chemical interaction in the solid state between the two entities.

Accelerated stability study

The study carried out according to ICH guidelines (Q1E step 4). The 6 months accelerated stability study (40°C ± 2°C/75% ±5% RH) for the optimized formulation showed a negligible change over time for the parameters like drug content, disintegration time, friability (%), hardness, wetting time and swelling (%).

CONCLUSION

From the findings, it is concluded that TPOH fulfills the requirement of disintegrants of FDTs. Therefore, these formulations can be explored further in clinical studies and thereafter for commercialization as it may be better substitutes for existing conventional products available in the market.

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