ISSN 2347-3614

UNIQUE JOURNAL OF PHARMACEUTICAL AND BIOLOGICAL SCIENCES

Available online: www.ujconline.net

Research Article

ENHANCEMENT OF THE DISSOLUTION RATE OF GLIPIZIDE CAPSULES USING FENUGREEK AS NATURAL ADDITIVE

Aly A. Abdel Rahman, Sayed H. Khidr, Eman M. Samy, Marwa, A. Sayed*

Department of Industrial Pharmacy, Faculty of Pharmacy, Assiut University, Assiut, Egypt

Received 20-11-2013; Revised 13-01-2014; Accepted 12-02-2014

*Corresponding Author: **Marwa Ahmed Sayed**
Fax: 002-0882332776 Tel:002-0882411580 Email:mmeerroo83@yahoo.com

ABSTRACT

Glipizide is an oral blood glucose lowering drug of the sulfonylurea class. It is characterized by its poor aqueous solubility. To overcome this problem in addition to improve the dissolution behaviour of glipizide, different loaded mixtures of glipizide with fenugreek or avicel PH 101 was prepared using different techniques (physical, ground mixtures, adsorbate and co-adsorbate systems). The surface solid dispersions was prepared by solvent evaporation method then formulated into capsules. The interaction between drug and the used excipients was performed using Fourier Transform Infrared (FT-IR) and Differential Scanning Calorimetry (DSC). In vitro dissolution study was performed for glipizide loaded mixtures and also for the prepared capsules in 0.1N HCl using a standard USP II dissolution apparatus. It was found that the dissolution rate of drug from solid dispersions was higher than the other prepared systems and intact drug, where release rate of glipizide from prepared capsules containing co-adsorbate system of glipizide with fenugreek at the ratio of (1:5:100, drug: tween 80: fenugreek w/w) is significantly higher than that obtained with avicel PH 101. In vivo testing of the selected prepared glipizide capsules containing glipizide solid dispersion with fenugreek was carried out on nine Newzeland rabbits. It was found that prepared glipizide capsules produce significant hypoglycaemic effect comparing with the commercial product Minidiab®. Clinical study was performed on fifteen type II diabetic human volunteers. The results showed a significant decrease in PPBGL of patients who receive capsules containing glipizide solid dispersion with fenugreek rather than those receiving glipizide commercial product Minidiab.

Keywords: Glipizide, Fenugreek, Avicel PH 101, Solid Dispersion, Capsules, Bioavailability.

INTRODUCTION

Diabetes mellitus is a heterogeneous metabolic disease characterized by altered carbohydrate, lipid and protein metabolism. According to World Health Organization the diabetes population is likely to increase up to 300 million or more by the year of 2025[1,2]. Diabetes is a group of metabolic diseases characterised by defects in insulin utilisation, either from autoimmune destruction of insulin-producing cells (Type I) or non-insulin dependent diabetes mellitus (Type II)[3]. Currently available therapies for diabetes include insulin and various oral antidiabetic agents such as sulfonylureas and biguanides. Many of them have number of serious side effects. Therefore, the search for more effective and safer hypoglycemic agents is one of the important areas of investigations[4]. Glipizide is a second generation sulfonylureas which used for the management of non-insulin dependent diabetes mellitus. It is an oral hypoglycemic agent that is 100 times more potent than tolbutamine in evoking pancreatic secretion of insulin[5]. According to biopharmaceutical classification system (BCS); glipizide is class II poorly water soluble drug that is characterized by high permeability and low solubility[6]. Therefore considerable efforts have been undertaken to enhance the dissolution rate of glipizide. These involved the inclusion of glipizide inside β-cyclodextrins[7], preparation of glipizide surface solid dispersion using PEGs and PVPs[8].

More than 400 hypoglycemic plant species have been available in literature, however, searching for new antidiabetic drugs from nature still attractive because they contain substances which demonstrate alternative and safe effects on diabetes mellitus. plants which contain glycosides, alkaloids, terpenoids, flavonoids and carotenoids have antidiabetic activity[9]. Trigonella foenum graceum is one of oldest medicinal plants, originated in India and North Africa. extracts, powders and gum of fenugreek seeds and leaves have been reported to have antidiabetic and hypocholesterolemic properties in both model animals and humans[10]. Antidiabetic activity has been attributed largely to fenugreek's saponins[11], high fiber content[12], free amino acid 4- hydroxyisoleucine[13] and the major alkaloid trigoneilline[14]. Antihyperglycemic effect was linked to delayed gastric empting caused by high

fiber content, inhibiting of carbohydrate digestive enzymes[12] and also stimulating insulin secretion[13]. 4-hydroxyisoleucine play an insulinotropic property in vitro, stimulated insulin secretion in vivo and improve glucose tolerance in normal rats of type II diabetes mellitus[3]. Fenugreek in this study is checked to improve the bioavailability of glipizide through preparation of capsules containing solid dispersion of glipizide with fenugreek (1:5:100, drug: tween: fenugreek w/w), where solid dispersion technique was used to enhance the dissolution of a variety of poorly soluble drugs[15-17].

The aim of the present study is to enhance glipizide dissolution and bioavailability by using natural additive (fenugreek) and comparing the results with synthetic excipient (avicel PH 101). Moreover, the in-vitro studies were carried out to show the effect of fenugreek and avicel PH 101 on release rate of glipizide. An in-vivo study was performed on streptozotacin diabetic rabbits and also on type II diabetic human volunteers to study the synergistic hypoglycemic effect of glipizide with fenugreek.

MATERIALS AND METHODS

Glipizide, kindly gifted from Pharco Pharmaceutical Co., Cairo, Egypt. Fenugreek was obtained from local market. Commercial glipizide tablets, Minidiab®, were obtained from Chemical Industrial Development, CID, Cairo, Egypt. Microcrystalline cellulose (avicel PH 101) was obtained from FMC Co. Ireland. HPLC grade acetonitrile and methanol was purchased from BDH, Poole, U.K. Streptozotocin was obtained from Sigma Chemicals Co., St. Louis, MO, USA. All other chemicals and reagents used were of analytical grade.

Preparation of glipizide from prepared physical and ground mixtures*:* Physical mixtures (PM) of glipizide with fenugreek or avicel PH 101 (in ratio 1:10 and 1:100 drug: excipient w/w) were prepared by gentle mixing with a spatula in a porcelain mortar for 5 min. These mixtures were stored in a desiccator for 24 hours. While, the ground mixtures (GM) were prepared through grinding of glipizide with the carriers (in the same previous ratios) using vibration ball mill for 15 min.

Preparation of glipizide from prepared solid dispersions: Solid dispersions of glipizide with the investigated carriers were prepared by solvent evaporation method using surfactant (co-adsorbate) or without using surfactant (adsorbate). In adsorbate system, the specified amount of glipizide with fenugreek or avicel PH 101 (1:10 and 1:100 drug: carrier w/w) were dissolved in the least amount of methanol with stirring for 3 minutes at room temperature. Then, the solvent was evaporated under vacuum at 40 ºC until constant weight was obtained. The obtained coprecipitate was powdered in a mortar, passed through 250- 300 µg sieve, and stored in a desiccator contains calcium chloride for 24 hour. The co-adsorbate matrix formulae were prepared using the same above procedures, except that tween 80 was added (1:5:100 drug: tween 80: fenugreek w/w).

Characterization of the Prepared Glipizide Mixtures

Fourier Transform Infrared (FT-IR): To identify drug excipients interactions, about 2-3 mg of the intact drug and selected prepared samples was mixed with potassium bromide and compressed into a disc at 4 ton pressure. IR absorption spectra were recorded using FT-IR spectrophotometer over a range of 200-4000 cm^{-1} to evaluate the molecular states of the raw material of glipizide, individual excipients as well as different prepared systems.

Differential Scanning Calorimetry (DSC): To study the solid state interaction of drug with excipients, samples were placed in sealed aluminium pans and heated from 30-300 ºC at a scanning rate of 10 ºC/min and under Nitrogen atmosphere (flow rate of nitrogen is 40 ml/min). Indium was used as standard.

Preparation of Glipizide Capsules

Glipizide capsules were prepared using manual filling for hard gelatine capsules (no. 0). The weight of each capsule was adjusted to 505 mg for capsules contain physical, ground mixture and adsorbate system of glipizide with fenugreek or avicel PH 101 in ratio of (1:100 drug: carrier w/w) and 530 mg for capsules contain co-adsorbate system of glipizide with fenugreek or avicel PH 101 in ratio of (1:5:100 drug: tween 80: carrier w/w) (Table 1).

Dissolution Studies

Dissolution studies of glipizide from the prepared loaded mixtures: The dissolution test was performed using USP no. II rotating paddle apparatus at 37 ± 0.1 °C and rotating speed of 100 rpm in 900 ml of 0.1 N HC1. Equivalent to 5 mg glipizide of the prepared physical, ground mixtures and solid dispersion samples or the intact drug were dispersed in the dissolution medium. 5 ml sample was withdrawn at each time interval and replaced with the same volume of fresh media after each withdrawal. The withdrawn samples were filtered, and measured spectrophtometrically at λmax 276 nm against a suitable blank treated similarly. The cumulative percentage released of glipizide was calculated at each time interval.

Dissolution studies of glipizide from the prepared capsules: The dissolution rates of glipizide from the prepared capsules and the commercial tablets Minidiab® were determined. Where, one capsule from each formula (contains 5 mg of glipizide) was placed in each vessel and subjected to the dissolution test and treated similarly as previous.

In Vivo Studies Glipizide on Streptozotacin Diabetic Rabbits

The study was carried out on nine Newzeland rabbits (1.5-2.0 kg). Diabetes was induced in the tested rabbits by the intraperitoneal injection of streptozotacin (STZ) at a dose of 65 mg/kg. Calculated amount of STZ was dissolved in cold 0.01 M citrate buffer (pH 4.5). Seven days after the injection, the blood glucose levels were measured using Glucometer[18]. Each animal with a blood glucose level above 200 mg/dl was considered to be diabetic[19]. The diabetic rabbits were starved overnight before the drug administration with water free access. A single dose of 0.1 mg/kg of the prepared and selected glipizide capsule C4 or commercial tablets of Minidiab® was given through gastrointestinal tube to diabetic rabbits. Blood samples were collected via an indwelling catheter in the eye vein into a 5 ml screw-capped centrifuge tubes at different time intervals (0.5, 1, 2, 4, 6, 12 and 24 hours) following the drug administration. The collected samples were centrifuged at 5000 rpm for 15 min. The supernatant was separated and transferred into a new screw-

capped centrifuge tube. This separated plasma was stored at -20 °C in a deep freezer until analysis [18]. HPLC technique was used for the determination of glipizide in plasma of the tested rabbits[20].

Clinical Studies Prepared Glipizide Capsules on Type II Diabetic Human Volunteers

The study will be a randomized, placebo-controlled, double-blinded, clinical trial, with 3 parallel arms, consist of 15 type II diabetic human volunteers with fasting blood glucose level equal to or greater than 140 mg/dl[21]. These patients will be randomly divided into 3 groups each consists of 5 patients. The patients were of either sex (male or female) between the ages of 35-60 years. Group I: control group; Group II: received glipizide commercial tablets (Minidiab®); Group III: received the prepared glipizide capsule (C4) which contains drug co-adsorbate (1:5:100 of glipizide: tween 80: fenugreek w/w). Patients received drug before breakfast and dinner at 8 am and 8 pm, respectively. One-touch glucometer was used to measure postprandial blood glucose levels (PPBGL) of diabetic human volunteers[21]. Initial PPBGL was estimated at the time of enrolment in the study and then at the end of the study period (one week). The initial and final readings were compared. The results of the current study were analyzed using Student's t-test and the significance was detected if $P < 0.05$. The study was approved by the ethical review board of Faculty of medicine, Assiut University.

RESULTS AND DISCUSSION

Fourier Transform Infrared (FT-IR) Spectroscopy Study: FT-IR spectroscopy was performed in order to identify any possible interaction between the drug and the used excipients in proposed formulations. Figures. 1& 2 demonstrate the FT-IR spectra of pure glipizide, fenugreek or avicel PH 101 alone or in their physical, ground mixture or solid dispersion systems. The major characteristic peaks of glipizide were observed at 3328 cm^{-1} for N-H stretching, 3252 cm^{-1} for aromatic C-H stretching, 1689 cm^{-1} for amide, 1650 cm^{-1} for C=O stretching, 1528 cm^{-1} for C=C stretching and 1159 cm^{-1} for $-SO_2$ stretching[22]. Also the main characteristic bands of fenugreek appear at 3297 cm^{-1} assigned as N–H stretching (amide of protein) and 2927 cm^{-1} for the secondary amide. While, 1746, 1654 and 1541 cm^{-1} represent the characteristic bands of C=O stretching of lipids, C=O of amide and N–H bending of secondary amide, respectively[23]. The FT-IR spectra of these physical , ground mixtures adsorbate and co-adsorbate system of glipizide with fenugreek or avicel PH 101 show the same characteristic bands of pure glipizide superimposed with the bands of the corresponding excipients. This indicates the absence of any chemical interaction between glipizide and investigated excipients.

Differential Scanning Calorimetry (DSC): DSC study was performed on pure glipizide, each excipient alone and the prepared physical mixtures, ground mixtures and solid dispersion systems; in order to study the interaction between glipizide and the used excipients in the solid state. Glipizide exhibited a single sharp melting endothermic peak at 215 °C (Figure 3 & 4)[22]. The DSC thermogram of fenugreek did not show any endothermic peaks except one broad endothermic peak at temperature range of 80-160 ºC which may be due to the presence of moisture[16] (Figure 3). The melting endothermic peak of the drug co-adsorbate with fenugreek using tween 80 was greatly reduced and appears as broad peak with little shifting, this may be due to transformation of drug to amorphous state[24]. While, avicel PH 101 DSC thermogram characterized by the absence of any characteristic peaks within the temperature range employed (30-300°C) (Figure 4). In general, the DSC thermograms of glipizide in different loaded mixtures using fenugreek or avicel PH 101 showed evidence of reduced crystallinity of the drug[25,26]. The extent of reduction in crystallinity was more pronounced in case of co-adsorbate mixtures. Fenugreek showed significant reduction in crystallinity of the drug in comparison to avicel PH 101. The dilution of drug in prepared mixtures may be the causative of such reduction.

Dissolution studies

Dissolution studies of different prepared glipizide loaded mixtures: It was noted that the used additives did not interfere with the absorption of glipizide at λ_{max} 276 nm in dilution range used. It was found that the solid dispersion systems containing natural additive (fenugreek) shows higher release rate of glipizide than the synthetic excipient (avicel PH 101) (Figure5). Moreover, the co-adsorbate system was superior as it showed the higher dissolution rates of glipizide than those of physical, ground mixture and adsorbate system (Table 2). Where, the order of drug dissolution from various systems is co- adsorbate > adsorbate > ground mixture > physical mixture. This may be due to the lower value of critical micellar concentration (CMC) of tween 80 (non-ionic surfactants, 0.001% w/v) that present in the co-adsorbate system[27]. It was noted that % release of glipizide from adsorbate system of fenugreek and avicel PH 101 (1:100 drug: carrier w/w) were 88 and 40.5 % w/w, respectively (Table 2). While 90 and 41.5 % w/w were released from co-adsorbate system of fenugreek and avicel PH 101 (1: 5: 100 drug: tween 80: carrier % w/w), respectively, (Tables 2). These results confirm that the rate of drug released can be much increased by the presence of surfactant at the solid surfaces as a third component. Moreover, increasing the ratio of natural additives or synthetic excipients from (1:10 to 1:100 % w/w) resulted in considerable improvement in drug dissolution. This may be a result from the increase in surface available for adsorption .

Dissolution study of prepared glipizide capsules: In concordance to the pervious results, it was found that the prepared capsules contain co-adsorbate system of glipizide with fenugreek using tween 80 still achieves the best dissolution rate (Figure6). Moreover, the dissolution results indicate that the release rate of glipizide from prepared capsules contain fenugreek (94.5 %) was higher than those capsules containing avicel PH 101 (52.5 %) (Table 3, Figure6). By studying the different kinetic models, it was found that the best fit with the highest correlation coefficient for prepared glipizide capsules was achieved with Higuchi kinetic model.

In Vivo Evaluation of Formulated Glipizide Capsules on Streptozotacin Diabetic Rabbits

According to all previous results, C4 capsule was selected for the in vivo studies, the results indicate that there was marked

decrease in blood glucose level after the oral administration of the selected formula to the rabbits. This formula showed a higher hypoglycaemic activity compared to glipizide commercial tablets Minidiab® (Table4).

The pharmacokinetic study demonstrated that formula C4 when administered to rabbits achieved higher C_{max} and shorter T_{max} compared to that of the commercially available tablets Minidiab® (Table 5). This reflects that the selected capsule C4 achieved higher rate of absorption more than commercial glipizide tablets (Minidiab®) (Figure7). Statistical analysis of pharmacokinetic parameters showed that there was a significant difference (P<0.05) between the values of AUC_{0-24} of C4 when compared to (Minidiab®) tablets. This indicates that the prepared formulae improve glipizide bioavailability more than commercial glipizide tablets Minidiab® (Table 5).

Comparative Clinical Study of Prepared Glipizide Capsule With Commercial Product on Type II Diabetic Volunteers

A significant decrease was noted in PPBGL of 15 NIDDM patients after daily administration of glipizide prepared capsule C4 and commercial product Minidiab® (Figure8). Moreover, the fall in PPBGL was marked in group III with patients received C4 than group II who received commercial glipizide tablet Minidiab® (Table 6).

CONCLUSION

The present study indicates that the natural additive (fenugreek) is more suitable for improvement of glipizide release than the synthetic excipient (avicel PH 101). Moreover, the co-adsorbate has been shown as a successful approach to improve the dissolution rate of glipizide more than other used techniques. Therefore, the preparation of glipizide co-adsorbate with fenugreek using tween 80 (1:5:100, drug: tween 80: fenugreek w/w/w) using the co-adsorbate system, significantly improved the dissolution rate of glipizide. The prepared capsules containing glipizide co-adsorbate with fenugreek using tween 80 improve drug bioavailability in streptozotacin diabetic rabbits and type II diabetic human volunteers compared to the commercial glipizide tablets (Minidiab®). Moreover, the in vivo study confirmed significant hypoglycaemic activity with rapid onset of action for the prepared and selected formulations. Thus, this study can opened up a new approach for future clinical research to find an alternative and inexpensive formulation for the NIDDM by using safe natural additives.

REFERENCES

1. World Health Organization DG., The World Health Report: Report of the Director-General (World Health Organization, 2003).
2. Sy GY., Cisse A., Nongonierma RB., Sarr M., Mbodj NA., and Faye B., Hypoglycaemic and antidiabetic activity of acetonic extract of Vernonia colorata leaves in normoglycaemic and alloxan-induced diabetic rats, J.Ethnopharmacol. 2005; 98(1): 171-175.
3. Al-Habori M. and Raman A., Antidiabetic and hypocholesterolaemic effects of fenugreek, Phytother.Res., 1998; 12(4): 233-242.
4. Saxena A. and Vikram NK. Role of selected Indian plants in management of type 2 diabetes: a review, The Journal of Alternative & Complementary Medicine, 2004; 10(2): 369-378.
5. Kumari K. and Augusti KT., Antidiabetic and antioxidant effects of S-methyl cysteine sulfoxide isolated from onions (Allium cepa Linn) as compared to standard drugs in alloxan diabetic rats, Indian J.Exp.Biol. 2002; 40(9): 1005.
6. Brown CK., Chokshi HP., Nickerson B., Reed R. A., Rohrs BR., and Shah PA., Dissolution testing of poorly soluble compounds, Pharm. Tech. 2004.
7. Aly AM., Qato MK., and Ahmed MO., Enhancement of the dissolution rate and bioavailability of glipizide through cyclodextrin inclusion complex, Pharm. Tech. 2003.
8. Hitendra Mahajan S., Manoj Dhamne R., Surendra Gattani G., Ashwini Rasal D., and Hannan Shaikh T., Enhanced dissolution rate of glipizide by a liquisolid technique, Int. J. Pharm. Sci. Nanotech 2011; 3(4): 4-8.
9. Malviya N., Jain S., and Malviya S., Antidiabetic potential of medicinal plants, Acta Pol Pharm 67**;** 2: 113-118.
10. Vats V., Grover JK., and Rathi SS., Evaluation of anti-hyperglycemic and hypoglycemic effect of Trigonella foenum-graecum Linn, Ocimum sanctum Linn and Pterocarpus marsupium Linn in normal and alloxanized diabetic rats, J.Ethnopharmacol. 2002; 79(1): 95-100.
11. Petit PR., Sauvaire YD., Hillaire-Buys DM., Leconte OM., Baissac YG., Ponsin GR., and Ribes GR., Steroid saponins from fenugreek seeds: extraction, purification, and pharmacological investigation on feeding behavior and plasma cholesterol, Steroids, 1995; 60(10): 674-680.
12. Ali L., Khan AKA., Hassan Z., Mosihuzzaman M., Nahar N., Nasreen T., Nur-e-Alam M., and Rokeya B., Characterization of the hypoglycemic effects of Trigonella foenum graecum seed, Planta Medica-Natural Products and Medicinal Plant Research 1995; 61(4): 358-359.
13. Sauvaire Y., Petit P., Broca C., Manteghetti M., Baissac Y., Fernandez-Alvarez J., Gross R., Roye M., Leconte A., and Gomis R., 4-Hydroxyisoleucine: a novel amino acid potentiator of insulin secretion, Diabetes, 1998; 47(2): 206-210.
14. Mishkinsky JS., Goldschmied A., Joseph B., Ahronson Z., and Sulman FG., Hypoglycaemic effect of Trigonella foenum graecum and Lupinus termis (leguminosae) seeds and their major alkaloids in alloxan-diabetic and normal rats, Arch. Int.de Pharmacol. et de Therapy, 1974; 210**:** 1 27.
15. Chutimaworapan S., Ritthidej GC., Yonemochi E., Oguchi T., and Yamamoto K., Effect of water-soluble carriers on dissolution characteristics of nifedipine solid dispersions, Drug Dev. Ind. Pharm. 2000; 26(11): 1141-1150.

16. Kumar R., Patil S., Patil MB., Patil SR., and Paschapur MS., Isolation and evaluation of disintegrant properties of Fenugreek seed mucilage, Int.J.Pharm.Tech.Res. 2009; 1(4): 982-996.
17. Pelavin PI., Abramson E., Pon S and Vogiatzi M. G., Extended-release glipizide overdose presenting with delayed hypoglycemia and treated with subcutaneous octreotide, J. Pediatr. Endocrinol. Metab. 2009; 22(2): 171-176.
18. Aly AM. and Ali AS., Research paper preparation and evaluation of glipizide tablets containing both enhanced and sustained release solid dispersions, Int. J Pharm. Sci. Nanotech. 2010; 2**:** 4.
19. Alam SA., Khan AH., Sirhindi GA., and Khan S., Alloxan induced diabetes in rabbits, Pakistan J Pharmacol., 2005; 22(2): 41-45.
20. Emilsson HK., High-performance liquid chromatographic determination of glipizide in human plasma and urine, J Chromatogar. B: Biomed. Sci. Appl. 1987; 421: 319-326.
21. Ismail MY, Clinical evaluation of antidiabetic activity of Trigonella seeds and Aegle marmelos leaves, World Appl. Sci. J. 2009; 7(10): 1231-1234.
22. Verma RK. and Garg S., Selection of excipients for extended release formulations of glipizide through drug-excipient compatibility testing, J. Pharm. Biomed. Anal. (2005; 38(4): 633-644.
23. El-Bahy GMS., FTIR and Raman spectroscopic study of Fenugreek (Trigonella foenum graecum L.) seeds, J.Appl.Spec. 2005; 72(1): 111-116.
24. Ismail A., Saleh K. I., and Khalaf S., Preparation and evaluation of naproxen as an attempt to improve drug dissolution characteristics, drugs 2004; 9: 12.
25. Madar Z, Abel R, Samish S, and Arad J, Glucose-lowering effect of fenugreek in non-insulin dependent diabetics, Eur. J. Clin. Nutr. 1988; 42**(**1): 51.
26. Mura P., Manderioli A., Bramanti G., Furlanetto S., and Pinzauti S., Utilization of differential scanning calorimetry as a screening technique to determine the compatibility of ketoprofen with excipients, Int. J. Pharm. (1995) 119**,** 1 71-79.
27. Rosoff M., New York, Marcel Dekker, 198.

Table (1): Composition of the prepared glipizide capsules containing physical mixture, ground mixture and adsorbate of drug with fenugreek or avicel PH 101 (1:100, % w/w)

Formula No. / Ingredients (mg)	Amount of ingredients in each capsule formula (mg)							
	C1 P.M.	C2 G.M.	C3 Ad.	C4 Co-ad	C5 P.M.	C6 G.M.	C7 Ad.	C8 Co-ad
Glipizide	5	5	5	5	5	5	5	5
Fenugreek	500	500	500	500	---	---	---	---
Avicel PH 101	---	---	---	---	500	500	500	500
Tween 80	---	---	---	15	---	---	---	15
Total weight	505	505	505	530	505	505	505	530

P.M. = Physical mixture. G.M. = Ground mixture.
Ad. = Adsorbate. Co- ad. = Co-adsorbate.

Table (2): Percentage release of glipizide from physical , ground mixtures, adsorbate and co-adsorbate systems containing different ratios of drug to fenugreek or avicel PH 101

% Cumulative release of glipizide from the prepared systems*				
Drug alone	Composition of prepared systems		Fenugreek	Avicel PH 101
10.20	Physical mixture Drug: carrier %w/w	1:10	66.94	19.63
		1:100	75.38	31.69
	Ground mixture Drug: carrier %w/w	1:10	72.25	20.54
		1:100	80.75	35.66
	Adsorbate system Drug: carrier %w/w	1:10	74.38	25.83
		1:100	88.00	40.5
	Co-adsorbate system Drug: tween 80: carrier % w/w	1:10	57.38	21.76
		1:100	90.47	41.5

***Results are the mean of three determinations.**

Table 3: Cumulative percentage release of glipizide from capsules containing drug with fenugreek or avicel PH 101 (1:100 % w/w) prepared by different techniques in 0.1 N HCl

Capsule code	Composition of prepared capsules		% Cumulative release of glipizide from the prepared capsules *
C1	Glipizide: fenugreek %w/w	Physical mixture	55.38
C2		Ground mixture	55.44
C3		Adsorbate system	79.00
C4		Co-adsorbate system	94.50
C5	Glipizide: avicel PH 101 %w/w	Physical mixture	25.50
C6		Ground mixture	28.69
C7		Adsorbate system	35.87
C8		Co-adsorbate system	52.53

*Results are the mean of three determinations.

Table 4: Effect of prepared glipizide capsules (C4) in comparison with commercial glipizide tablets Minidiab® (5 mg) on blood glucose level of STZ induced diabetic rabbits

Time (hr.)	Blood glucose level (mg/dl)*		
	placebo	Minidiab®	C4
0.5	180±5.25	193±4.89	193±2.33
1	190±6.00	150±5.78	155±5.33
2	197±5.33	145±3.56	145±1.23
4	200±3.33	130±3.33	120±2.43
6	230±7.33	128±1.78	108±2.55
12	235±4.44	123±5.55	91±6.22
24	240±5.23	120±6.22	88±1.54

*Results represent mean SD of three observations.

Table 5: Pharmacokinetic parameters of glipizide following oral administration of the prepared glipizide capsule formula (C4) in comparison with the commercial tablets (Minidiab®) to streptozotacin diabetic rabbits

Pharmacokinetic Parameters	Minidiab®	Capsule Formula C4	Significance of the difference*
C_{max} (µg/ml)	13.15±0.9	15.63±1.0	S.
T_{max} (hr)	4.00±0.0	1.00±1.2	S.
K_{abs} (hr^{-1})	0.55±1.2	1.78 ±1.1	S.
$t½_{abs.}$ (hr)	1.25±2.0	0.39 ±0.22	S.
K_{el} (hr^{-1})	0.19±0.3	0.07 ±0.08	S.
$t½_{el.}$ (hr)	3.65±0.8	9.72 ±0.7	S.
$AUC_{(0-24)}$ (µg.hr/ml)	3347.49 ±0.5	4488.32 ±1.6	S.
$AUC_{(0-\infty)}$ (µg.hr/ml)	3349.43±0.8	4518.21 ±1.4	S.
$AUMC_{(0-24)}$ hr (µg.hr^2/ml)	1186.41±1.0	1788.91 ±2.2	S.
$AUMC_{(0-\infty)}$ hr (µg.hr_2/ml)	1232.95±1.2	1788.91±2.3	S.
MRT(hr)	0.37±2.0	0.39 ±1.0	S.
Cl_T (ml/min)	0.01 ±0.6	0.01 ±0.5	N.S.

*S. = statistically significant ($p < 0.05$)

Table 6: Statistical analysis of mean postprandial blood glucose level of studied 3 groups of Type II diabetic human volunteers. (The values are given as mean ± SD)

Groups	Initial PPBGL	Final PPBGL	Significance
I-Placebo	190 ± 0.3	199± 1.2	N.S.
II- receive Minidiab®	191 ± 0.5	172±0.9	S.
III- receive formula C4	185±0.2	148±0.3	S.

S. = statistically significant ($p < 0.05$).
N.S. = Non significant ($P > 0.05$)

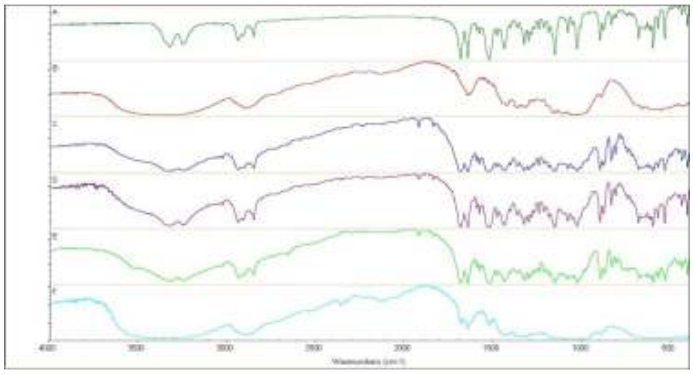

Figure 1: IR absorption spectra of glipizide powder (A), fenugreek alone (B) and their physical mixture (C), ground mixture (D), adsorbate (E) and co-adsorbate (F) systems in ratio 1:1 w/w.

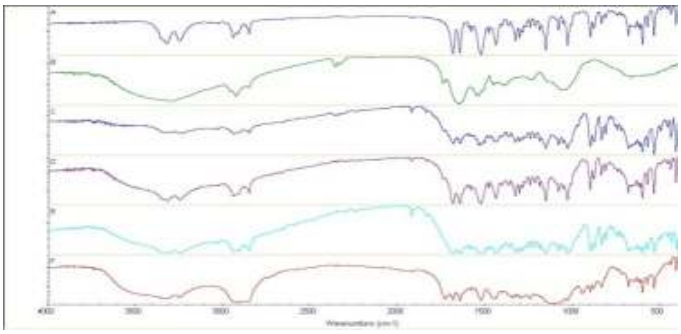

Figure 2: IR absorption spectra of glipizide powder (A), avicel PH 101 (B), their physical mixture (C), ground mixture (D), adsorbate (E) and co-adsorbate (F) systems in ratio (1:1 w/w).

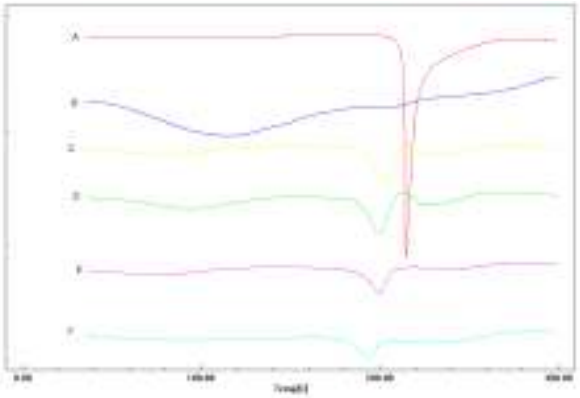

Figure 3: DSC thermograms of glipizide powder (A), fenugreek alone (B), their physical mixture (C), ground mixture (D), adsorbate (E) and co-adsorbate (F) systems in ratio (1:1 w/w).

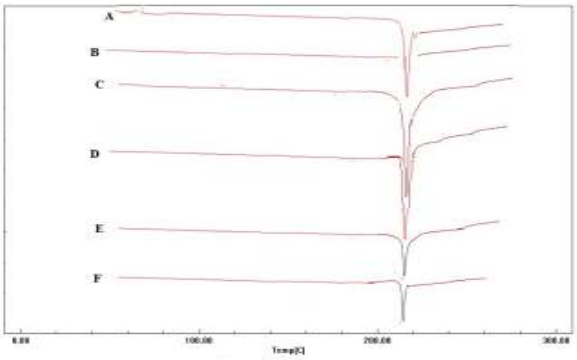

Figure 4: DSC thermograms of glipizide powder (A), avicel PH 101 (B) and their physical mixture (C), ground mixture (D), adsorbate (E) and co-adsorbate (F) systems in ratio (1:1 w/w).

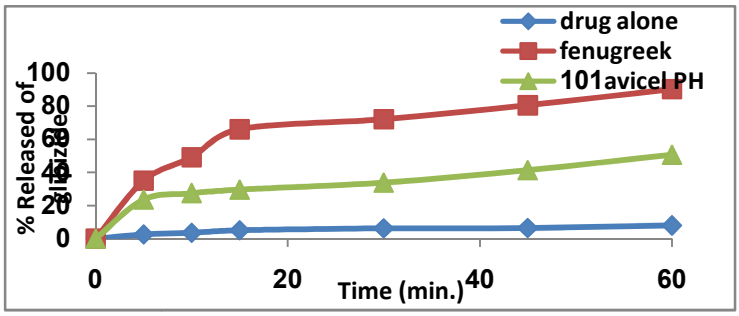

Figure 5: Dissolution profiles of glipizide released from co- adsorbate systems of drug with fenugreek or Avicel PH 101 using tween 80 (1:5:100 w/w).

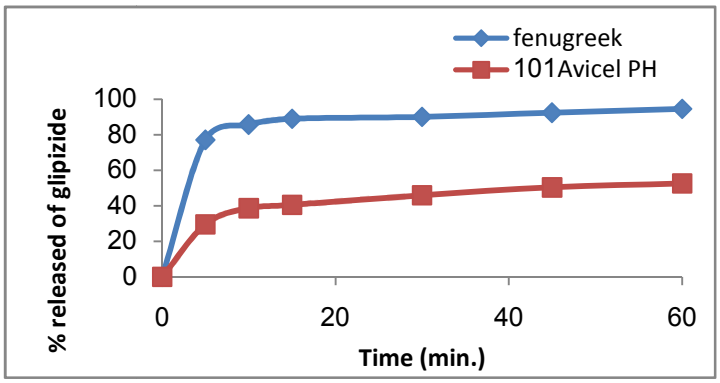

Figure 6: Dissolution profiles of glipizide released from capsules containing co- adsorbate system of drug: fenugreek or avicel PH 101 using tween 80 at a ratio (1:5:100 % w/w) in 0.1 N HCl.

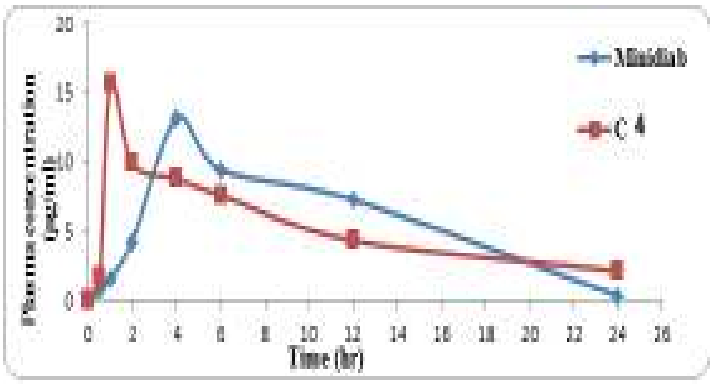

Figure 7: Plasma concentrations of glipizide after oral administration of the commercial tablets Minidiab® (5 mg) and the prepared glipizide capsule C4 to streptozotacin diabetic rabbits.

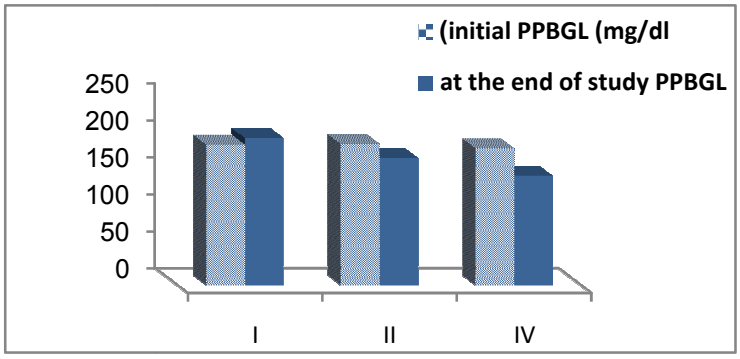

Figure 8: Comparison of antidiabetic effect of glipizide capsule C4 containing fenugreek co-adsorbate and commercial glipizide tablet Minidiab® (5 mg) on PPBGL of type II diabetic human volunteers.

Source of support: Nil, Conflict of interest: None Declared