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RESEARCH PAPER

In Vitro and In Vivo Evaluation of Glibenclamide in Solid Dispersion Systems

Bassam M. Tashtoush,[1,*] Zubaida S. Al-Qashi,[1] and Naji M. Najib[1,2]

[1]Department of Pharmaceutical Technology, Faculty of Pharmacy, Jordan University of Science and Technology, Irbid, Jordan
[2]International Pharmaceutical Research Center (IPRC), Amman, Jordan

ABSTRACT

The purpose of this work is to improve the dissolution and bioavailability characteristics of glibenclamide as compared to Daonil® tablets (Hoechst). Solid dispersions of glibenclamide in Gelucire 44/14 (Formula 1) and in polyethylene glycol 6000 (PEG 6000) (Formula 2) were prepared by fusion method. In vitro dissolution studies showed that the dispersing systems containing glibenclamide and Gelucire 44/14 or PEG 6000 gave faster dissolution rates than the reference product Daonil. The in vivo bioavailability study was assessed in six healthy male volunteers in crossover design with a 1-week washout period. Both formulas were found to be significantly different from Daonil with regard to the extent of absorption as indicated by the area under serum concentration-time curve. Both formulas are not significantly different from Daonil with respect to time of peak plasma concentration (T_{max}). It is concluded from this pilot study that the ranking of the in vitro dissolution is similar to the ranking of in vivo availability. The ranking of the three preparations in term of dissolution rate and extent of absorption is as follows: Formula 2>Formula 1>Daonil.

Key Words: Glibenclamide; In vitro dissolution; In vivo bioavailability; Solid dispersion; Gelucire®; Polyethylene glycol 6000 (PEG 6000).

*Correspondence: Bassam M. Tashtoush, Department of Pharmaceutical Technology, Faculty of Pharmacy, Jordan University of Science and Technology, Irbid, Jordan; Fax: +962-7095019; E-mail: bmtash@just.edu.jo.

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INTRODUCTION

Glibenclamide is a second generation sulphonylureas oral hypoglycemic agent used for the management of diabetes mellitus. It causes hypoglycemia by stimulating release of insulin from pancreatic β cells and by increasing the sensitivity of peripheral tissue to insulin.[1] It is rapidly and well absorbed but may have wide inter- and intra-individual variability. Micronized glibenclamide is better absorbed and more effective at a lower dose than nonmicronized glibenclamide.[2] Glibenclamide is partially soluble in water. The formation of amorphous forms to increase drug solubility and the reduction of particle size to expand surface area for dissolution and decrease the interfacial tension with the aid of a water-soluble carrier are among the possible mechanisms for increasing dissolution rates and improving bioavailability of poor water-soluble drugs.[3] Several methods can be employed to obtain a solid dispersion to improve solubility and bioavailability, such as fusion,[4–6] fusion–dissolution,[7] dissolution/solvent removal,[8] and spray drying,[9] depending on the characteristics of the drug and carrier.

Gelucire products are inert, semi-solid waxy materials with amphiphilic character. They are identified by their melting point and their hydrophilic–lipophilic balance (HLB) value. For example, Gelucire 44/14®, which is one of most popular grades, has a nominal melting point of 44°C and an HLB of 14.[10] Most Gelucire grades are saturated, polyglycolyzed glycerides that are obtained by glycolysis from natural hydrogenated vegetable oils with polyethylene glycols (PEG).[10] Gelucire 44/14 is characterized by a unique balance of short, medium, and long chain fatty acids, which provide exceptionally fine dispersion upon contact with gastrointestinal (GIT) fluids at body temperature. It was shown that Gelucire increases the water solubility of temazepam compared with various PEGs.[9] Also, the dissolution of triametrene was increased by the addition of Gelucire 44/14. The bioavailability of poorly water-soluble drug (REV 5901) was enhanced using solid dispersion of Gelucire 44/14 and PEG 400.[11] Also, Gelucire was found to reduce the effect of food on bioavailability of (REV 5901); therefore, the Gelucire semisolid preparation can reduce the erratic nature of bioavailability of poorly water-soluble drugs.[11]

Polyethylene glycols (PEG) or macrogels are condensation polymers of ethylene oxide and water. They are liquid or solids, depending on the average molecular weight.[12] They are soluble in water and alcohol. PEG 6000 has been used as a carrier to increase the dissolution rate of various poorly water-soluble drug such as Diazepam,[13] Fenofibrate,[14] and Oxazepam.[15]

In vitro dissolution testing can provide useful information regarding development of new products and quality control of candidate formulations. The value of dissolution as a quality control tool for predicting in vivo performance of the drug product is significantly enhanced if the in vitro in vivo correlation (IVIVC) is established.[16] The variability of dissolution testing was studied with calibrator tablets by Qureshi and McGilveray.[17] It was concluded that all apparatus, both paddle and basket, had similar characteristics and the variability in dissolution testing was independent of variability due to dissolution apparatus. A multinational, postmarket comparative study of pharmaceutical quality of glibenclamide was also performed.[18] It was found that products, which are markedly differentiated in their vitro dissolution properties, exhibit also therapeutic differences in bioavailability.

The objective of this work was to study the effect of dispersing glibenclamide in Gelucire 44/14 and PEG 6000 on the in vitro dissolution and in vivo bioavailability of glibenclamide compare to Daonil® tablet (Hochest).

MATERIALS AND METHODS

The following chemicals were obtained from commercial suppliers and used as received: Glibenclamide (Chinion Chemicals, Budapest, Hungary), Gelucire® 44/14 (Gattefosse Company, Bracknell, UK), PEG 6000 (Janssen Chemica, Geel, Belgium), potassium dihydrogen phosphate (SDS Company, Mumbai, India), sodium hydroxide (GCC Company, Deeside, UK), ammonium acetate (C.B.H Lab Chemicals, Shandong, China), ammonium dihydrogen phosphate (GCC Company, Deeside, UK), Phosphoric acid (Fischer Scientific, NJ, USA), diazepam (BUFA, Uitgeest, The Netherlands), hard gelatin capsule was obtained from Arab Pharmaceutical Manufacturing Company (Salt, Jordan). All solvents were of high-performance liquid chromatography (HPLC) grade.

METHODS

Preparation of Solid Dispersion of Glibenclamide

The solid dispersions were prepared according to the fusion method.[4] To prepare 50 capsules each

containing 5 mg glibenclamide, the required amount of either Gelucire 44/14, or polyethylene glycol 6000 was weighed into a suitable glass beaker and heated to 50–55°C for Gelucire and 65–70°C for PEG 6000 using a hot plate until melted. The required amount of glibenclamide powder is added to the molten vehicle with continuous stirring using a small magnetic bar. After complete dispersion of glibenclamide, the molten system was filled using Pasteur Pipettes in a hard gelatin capsule according to weight to obtain the required weight ± 10 mg. The capsule containing Gelucire 44/14 (Formula 1) weighed 150 mg and the capsule containing PEG 6000 (Formula 2) weighed 200 mg. Then the capsules were kept upright for 24 hours until solidified. The proportions of the carriers used in this pilot study were chosen from many formulas, according to a preliminary study in which these proportions showed a fast release rate of glibenclamide.

Differential Scanning Calorimetry Studies

All solid dispersions were carried out on a Mettler TC 11 differential scanning calorimeter (DSC) to obtain thermograms at a heating rate of 10°C/min, over the temperature range from 20–250°C under nitrogen gas flow of 20 mL/min.

Content Uniformity Studies

The content uniformity of glibenclamide in Formula 1, Formula 2, and Daonil was tested according to the monograph of glibenclamide tablet of United States Pharmacopoeia (USP) 2000. One capsule was placed in a 25-mL volumetric flask containing methanol and heated to 55°C for 15 minutes with continuous stirring using a magnetic stirrer. The solution was left to cool to room temperature and the volume was completed by methanol to its actual volume two mL of this solution was diluted to 100 mL using 0.1 M phosphate buffer pH 7.4. A sample (5 mL) was taken and filtered using a 0.45-μm syringe filter and analyzed using HPLC. The content of glibenclamide was calculated according to calibration curve.

In Vitro Dissolution Studies

The dissolution of glibenclamide from Daonil® tablet, Formula 1, and Formula 2 was performed under sink conditions using Erweka DT6 dissolution test (USP XXIII Apparatus I) in 1000 mL of 0.1 M phosphate buffer of pH 7.4. The temperature was set at 37°C ± 0.5°C. The rotational speed was performed at 100 rpm. At specified time intervals up to 120 minutes, 5-mL samples were withdrawn and replaced with 5 mL fresh phosphate buffer. Samples were then filtered through a 0.45 μm syringe filter. Analysis of Glibenclamide was performed using an HPLC method and UV/VIS (Jasco UV-975) with a mobile phase of 0.02 M ammonium acetate in [methanol (30):acetonitrile (30):water (40)] at a flow rate of 1.0 mL/minute.[19] The column used was Lichrosphere RP-100, 5 μm, 12.5 cm × 4 mm ID, C18 and the detection wavelength was 240 nm.

The effect of aging on the release of glibenclamide from solid dispersions of PEG 6000 or Gelucire 44/14 was studied for a period of 2 months at room temperature.

In Vivo Studies

A pilot study was carried out under fasting conditions following a single dose (5 mg Daonil® tablet or 5 mg capsule of Formula 1 or Formula 2) according to a three-way crossover design on six healthy male volunteers whose age ranged between 18–40 years. A one-week washout interval was allowed between the three phases of the study. Subjects were randomly assigned to the treatment group. A blood sample was collected at 0, 1, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, and 12.0 hours. Plasma was separated promptly and immediately frozen until assayed. The in vivo availability of Formula 1 and Formula 2 compared to Daonil® was assessed by comparing the plasma concentration-time profile of the three products as well as the pharmacokinetic parameters derived from these profiles, such as maximum glibenclamide plasma concentration (C_{max}), the time needed to reach this peak concentration (T_{max}), elimination rate constants (K_e), half-life of elimination ($T_{1/2}$), and area under plasma concentration-time curve (AUC) for 12 hours and for infinity.

Analysis of Glibenclamide in Plasma

One mL of plasma was transferred to a 15-mL stopper glass tube. fifty μL of internal standard (Diazepam 2 μg/mL) was then added, followed by the addition of 8 mL dichloromethane. The tube was closed, vortex-mixed for 1 minute, and centrifuged for 10 minutes at 6000 rpm. The organic phase was then transferred to another tube and evaporated to dryness under a stream of nitrogen gas at 50°C. The residue

was reconstituted with 300 μL of mobile phase, transferred to a 1.5-mL Eppendorf tube, and centrifuged for 2 minutes at 12000 rpm in a micro centrifuge. Then, 100 μL was injected into the HPLC. Glibenclamide was analyzed in plasma using the above HPLC system except the mobile was 0.05 M ammonium dihydrogen phosphate: methanol (40:60) adjusted to pH 4 by phosphoric acid and the flow rate was 1.2 mL/minute.[20] The retention times for glibenclamide and internal standard were 9.5 and 5.3, respectively. The method of analysis was validated for sensitivity, stability, accuracy, precision, recovery, selectivity, and specificity.

RESULTS AND DISCUSSION

Differential Scanning Calorimetry Studies

Differential Scanning calorimetry scans were done for the PEG 6000 and Gelucire 44/14 solid dispersions prepared by fusion method. The endothermic peak of each solid dispersion occurred at about around the melting point of the corresponding polymeric carriers, which indicates complete formation of solid solution system in both.

Content Uniformity

The content uniformities of glibenclamide were found to be in the range of 95.6–99.4%, 96.4–100.6%, and 96.0–101.4%, for Formula 1, Formula 2, and Daonil, respectively. These values are within the acceptable range set in the USP. This test will eliminate the effect of overloading the capsule with more than 5 mg glibenclamide, which would give false results later in either an in vitro or in vivo study of the capsules as compared with the 5 mg Daonil® tablet.

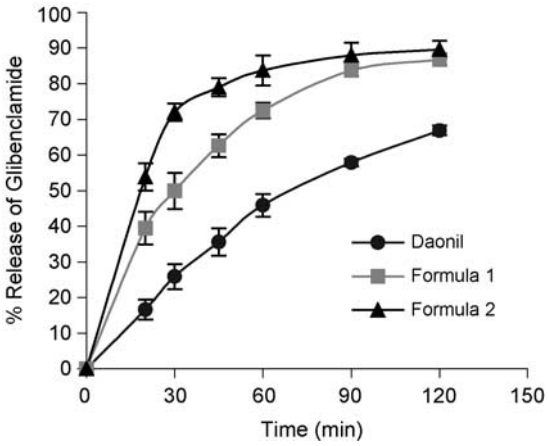

Figure 1. % Release of Glibenclamide from Daonil®, Formula 1, and Formula 2 in phosphate buffer pH 7.4. (*View this art in color at www.dekker.com.*)

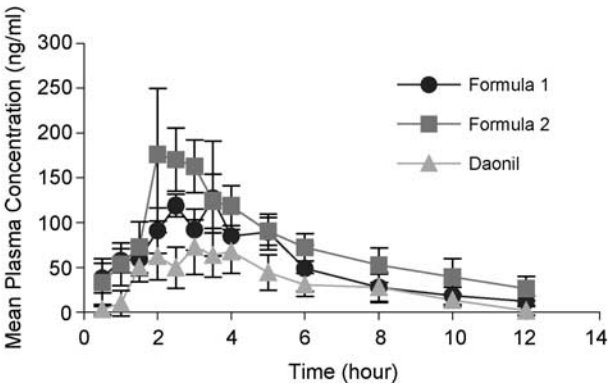

Figure 2. Mean plasma concentration of Glibenclamide after oral administration of Formula 1, Formula 2, and Daonil® tablet to six healthy volunteers. (*View this art in color at www.dekker.com.*)

In Vitro Release Studies

The releases of glibenclamide from the three products were plotted as percent amount glibenclamide released vs. time in minutes as shown in Fig. 1. Each value of the presented curve is the mean of six experiments. As shown in Fig. 1, more than 50% of glibenclamide was dissolved out of Formula 2 in the first 20 minutes, and more than 35% was dissolved out of Formula 1, while only 16.6 % was dissolved out of Daonil® tablet. These results showed that both Formula 1 and Formula 2 have faster dissolution than the Daonil® tablet. Also, after 120 minutes both Formula 1 and Formula 2 showed more amount dissolved of glibenclamide than the Daonil® tablet. The rank of dissolution of the three products is as follows: Formula 2 >Formula 1 >Daonil®. The rate of release of glibenclamide from solid dispersion made of PEG 6000 or Gelucire system is higher than the Daonil tablet. This may be due to the emulsifying effect of the carrier, its prevention of aggregation and agglomeration effect, and its improvement of wetability and dispersibility of drug from solid dispersion, which can result in increasing the dissolution rate of glibenclamide.[7,21]

The effect of aging from PEG 6000 or Gelucire 44/14 on the release of glibenclamide was analyzed weekly for 2 months. There was no significant change

Table 1. Pharmacokinetic parameters (average, SD) of glibenclamide (5 mg) following oral administration of Daonil® tablet, Formula 1, and Formula 2 to six healthy volunteers.

	Daonil®		Formula 1		Formula 2	
Parameter	Average	SD	Average	SD	Average	SD
T_{max} (hour)	3.42	0.93	3.17	0.69	2.67	0.69
C_{max} ng/mL	103.6	30.5	209.0	63.8	237.6	73.9
$T_{1/2}$ (hour)	2.60	0.92	3.19	1.45	4.78	1.77
K_e ($hour^{-1}$)	0.30	0.11	0.270	0.130	0.170	0.08
AUC_{0-12hr} (ng.hr/mL)	381.2	64.6	608.5	105.0	895.4	248.1
$AUC_{0-infinity}$ (ng.hr/mL)	432.1	67.8	680.8	94.4	1035.7	317.0

in the release of drug from the two formulas during this period.

In Vivo Studies

Analysis of glibenclamide using HPLC was validated. The minimum limit of quantitation of glibenclamide in plasma sample was 10 ng/mL. Glibenclamide in plasma when stored in a freezer was stable for at least 3 weeks. The intra-day precision was determined and the coefficient of variance ranged from 1.45–11.25%. The inter-day precision was evaluated over 21 days, yielding a coefficient of variance ranging from 3.84–13.62%. Absolute recovery ranged from 90.30% to 95.94% and relative recovery ranged from 99.35–105.28%. These values reflect the suitability of the analytical method for the analysis of glibenclamide.

The plasma concentration of glibenclamide in ng/mL after oral administration of Daonil®, Formula 1, and Formula 2 were plotted vs. time in hours. Figure 2 shows the mean plasma concentration of glibenclamide-time profile for six healthy volunteers. It is clear that both Formula 1 and Formula 2 achieved higher bioavailability than Daonil® tablets. These results were supported clinically because of signs of hypoglycemia, as dizziness and headache are more apparent and have higher intensity upon taking Formula 1 and Formula 2. Table 1 summarizes the pharamacokinetic parameters of glibenclamide after oral administration of the three products. The pharmacokinetic methods used were standard noncompartmental analysis and linear trapezoidal rule for AUC calculations. The average half-lives of elimination of Formula 1, Formula 2, and Daonil® were 3.19, 4.78, and 2.6 hours, respectively, which is within the range reported in different references.[20–24] With regard to T_{max} and C_{max} they are ranked as follows: Formula 2 > Formula 1 > Daonil®. The differences in T_{max} between the three products were found statistically not significant according to analysis of variance (ANOVA) analysis. None of the experimental parameters (phase, subject, and treatment) have an effect on T_{max} with $P > 0.05$ at $\alpha = 0.05$. With regard to C_{max}, Formula 1 was not significantly different from Daonil® ($P > 0.05$), but Formula 2 was significantly different from Daonil® ($P < 0.05$). With regard to $AUC_{0-infinity}$, Daonil® (432.05 ng.hr/mL) showed lower bioavailability than either Formula 1 (680.805 ng.hr/mL) or Formula 2 (1035.6705 ng.hr/mL). All the results were analyzed statistically by a two-way analysis of variance using Systat with $P < 0.05$ at $\alpha = 0.05$ being taken as the

Table 2. Fisher's least-significant-differences test of (C_{max}, $AUC_{0-infinity}$) matrix of pair wise comparison probabilities.

	Daonil	Formula 1	Formula 2
Daonil	(1.00, 1.00)		
Formula 1	(0.259, 0.026)	(1.00, 1.00)	
Formula 2	(0.002, 0.002)	(0.00, 0.093)	(1.00, 1.00)

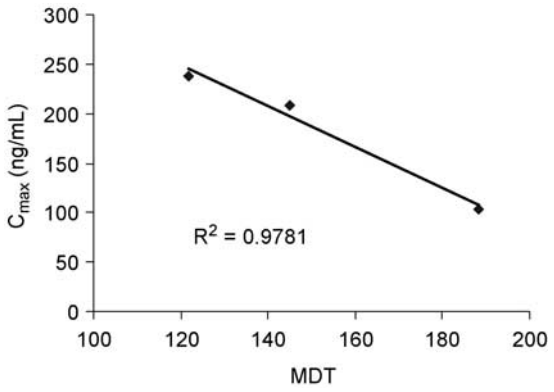

Figure 3. Single-point relationship between mean dissolution time (MDT) and maximum plasma concentration (C_{max}). (*View this art in color at www.dekker.com.*)

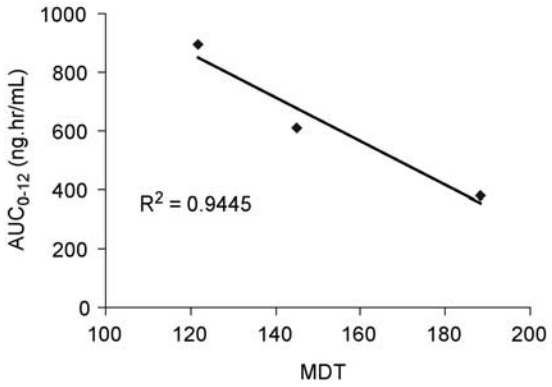

Figure 4. Single-point relationship between mean dissolution time (MDT) and AUC_{0-12}. (*View this art in color at www.dekker.com.*)

minimal level of significance to determine subject, treatment, and phase variation on the parameters C_{max} and $AUC_{0-infinity}$. Statistically, both Formula 1 and Formula 2 were significantly different from Daonil® with regards to $AUC_{0-infinity}$, but Formula 1 and Formula 2 were similar. Also, statistical analysis between the different treatments using Fisher's Least-Significant-Difference Test based on matrix of pair-wise comparison was conducted using Systat (Table 2). The ranking of Formula 1, Formula 2, and Daonil® based on in vitro dissolution and in vivo bioavailability terms (C_{max} and $AUC_{0-infinity}$) was as follows: Formula 2 > Formula 1 > Daonil®.

In order to define the performance of the two formulas in vivo with the change in dissolution, a single-point Level C correlation between the means dissolution time (MDT) and the pharmacokinetic parameters (C_{max} and AUC_{0-12}) has been performed. The mean dissolution time in vitro $(MDT)_{vitro}$ was calculated from the Equation:[25,26]

$$MDT_{vitro} = \frac{AUMC}{AUC}$$

where AUMC = area under the moment vs. time curve from t = 0 to 120 minutes; and AUC = area under plasma time vs. concentration curve from t = 0 to 120 minutes, Fig. 3 shows a single-point relationship between MDT and C_{max}. The R^2 value is 0.9781, which indicates good correlation. On the other hand, Fig. 4 shows good correlation with $R^2 = 0.9445$ between MDT and $AUC_{0-infinity}$. This pilot study makes it clear that glibenclamide, when dispersed in PEG 6000 or Gelucire 44/14, has improved solubility when as compared to the Daonil® tablet, which correlates well with the pharmacokinetic parameters. This suggests that less than 5 mg of glibenclamide can be dispersed in Gelucire® 44/14 or PEG 6000 and still attain similar bioavailability to Daonil® tablet.

CONCLUSIONS

This pilot study showed that when glibenclamide was dispersed in a suitable water-soluble carrier such as Gelucire® 44/14 or PEG 6000, its dissolution was enhanced compared with Daonil tablets. The water-soluble carrier may operate in the microenvironment (diffusion layer) immediately surrounding the drug particles in the early stage of dissolution, since the carrier completely dissolves in short time, enhancing the dissolution of drug. It is concluded that the in vitro dissolution study of glibenclamide formulation correlates with the in vivo bioavailability. Therefore, in vitro release experiments can be utilized to predict the in vivo performance of drug products.

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