

Formulation of fast release glibenclamide liquid and semi-solid matrix filled capsules

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The ability of liquid and semi-solid matrix (SSM) filling capsule technology to improve the dissolution rate of glibenclamide (GBD) was investigated. Semi-quantitative estimation of GBD solubility in various vehicles was carried out. Tetraglycol was found to be the most efficient solubilizer. GBD was formulated in different concentrations as solutions in tetraglycol or tetraglycol/PEG 6000 blend and as suspensions in SSM composed of Gelucire44/14 as a base. Dissolution rate studies revealed that the release profiles of GBD from capsule formulations containing the drug in concentrations up to 3.5% (*m/m*) were comparable.

Keywords: liquid matrix, semi-solid matrix, capsules, glibenclamide, dissolution

Glibenclamide (GBD) is an oral hypoglycemic of the sulphonyl urea group that is frequently prescribed for treatment of non-insulin dependent *diabetes mellitus* (1). GBD is a low dose, poorly soluble drug with possible content uniformity problems and dissolution rate-limited bioavailability (2, 3). Several techniques have been reported to enhance the dissolution rate of GBD. These include comelt dispersion in polyethylene glycol (PEG) 6000 and/or 4000 (4), sorbitol and/or mannitol (5), coprecipitate formation with poloxamer or polyvinylpyrrolidone (PVP) (6) and lyophilization (7).

Liquid or semisolid filled capsules can offer a simple and sometimes comparatively economic technique for formulation of oral dosage forms with enhanced dissolution rates. This can be achieved by formulation of the drug as a solution (8), dispersion in a hydrophilic carrier (9), emulsion or inclusion in a self-emulsifying base (10, 11).

The aim of this study was to improve the dissolution rate of GBD *via* its formulation as liquid and/or semisolid filled capsules and to investigate the *in vitro* release characteristics of the formulated capsules as compared to the commercial products.

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EXPERIMENTAL

Materials

The following materials were used as received: glibenclamide (Hochest, Egypt), tetraglycol and polyethylene glycol 400 (R. P. Scherer, Egypt), polyethylene glycol 6000 (Fluka, Switzerland), Gelucire 44/14 (G44/14) (Gattefossé Etablissement, France), propylene glycol and glycerol (El-Nasr Pharmaceutical Chemical Co., Egypt), methanol and acetonitrile for HPLC, glacial acetic acid (Fischer Chemicals, UK), four commercial brands of glibenclamide tablets, namely, tablets A: Daonil[®] (5 mg, Hochest Orient, Egypt), tablets B: Semidaonil[®] (2.5 mg, Hochest Orient, Egypt), tablets C: Euglucon[®] (5 mg, Glaxo Wellcome, Egypt) and the innovator product: Euglucon[®]N (3.5 mg, Boehringer, Germany). Hard gelatin capsules, size 3, transparent, yellow cap, colourless body (preservative free) and soft gelatin capsules, air-filled transparent colourless shell were kindly supplied by Arab-Caps. Pharmaceuticals (Egypt), and R. P. Scherer (Egypt), respectively.

Methods

Solubility study. – Semi-quantitative estimation of GBD solubility in various vehicles (tetraglycol, PEG 400, propylene glycol, glycerol, 25% and 50% PEG 6000 in tetraglycol and G44/14) was carried out. Accurately weighed amounts of GBD were added to each vehicle to give a final drug concentration ranging from 0.5–3.5% (*m/m*). Drug/vehicle mixtures were shaken in a thermostatically controlled water bath at 60 °C for 8 h and then left for equilibration at 25 °C for 24 hours. Mixtures were microscopically observed for complete drug dissolution, using an optical microscope (Olympus-35 mm, Japan). The highest concentration of GBD giving a clear solution was taken as the solubility value.

Formulation of capsule fills. – GBD was solubilized or suspended in the liquid or melted semi-solid base by stirring at 60 °C for 15 min. The composition of the prepared GBD formulations is presented in Table I. Formulations were volumetrically filled into hard gelatin capsules (HGC) using a syringe to contain the equivalent of 5 mg GBD. Some selected formulations (F2 and F5) were also filled into soft gelatin capsules (SGC) by the same method to contain the equivalent of 2.5 mg GBD. Both capsule types were sealed with a 15% (*m/m*) warm gelatin solution.

Mass uniformity of the test capsules. – The test was done according to the BP 98 procedure (12).

Content uniformity of the test capsules. – Each of 5 capsules was emptied into a 50 mL volumetric flask containing 30 mL methanol. The capsule shell was thoroughly rinsed with 10 mL methanol. The flask was sonicated for 15 min, then made up to the volume with methanol. The sample was filtered using a 0.45 µm Millipore filter and the solution was assayed for GBD by HPLC.

Dissolution rate studies. – The dissolution rate of GBD from test capsules and commercial tablets (equivalent to 5 mg GBD) was studied using the USP 24 (13) dissolution apparatus type II. The dissolution medium consisted of 900 mL of USP phosphate buffer (pH 7.4) or 500 mL of USP borate buffer (pH 9.5) kept at 37 ± 0.5 °C and stirred at 75

Table I. Composition of liquid and SSM capsule formulations

Code	Composition (% , m/m)			
	GBD	Tetraglycol	PEG 6000	G44/14
F1 ^a	1.8	98.2	–	–
F2 ^a	2.5	97.5	–	–
F3 ^a	3.5	96.5	–	–
F4 ^a	1.8	73.2	25.0	–
F5 ^a	2.5	72.5	25.0	–
F6 ^a	3.5	71.5	25.0	–
F7 ^a	5.0	70.0	25.0	–
F8 ^a	2.5	–	–	97.5
F9 ^a	5.0	–	–	95.0

^a 5 mg GBD, HGC capsule

^b 2.5 mg GBD, SGC capsule

rpm. Filtered samples were withdrawn at different time intervals up to 1 h and the concentration of GBD was assayed by HPLC. Each experiment was done in triplicate.

HPLC analysis. – GBD was assayed using the HPLC method reported by Emilsson *et al.* (14). A modular high performance liquid chromatograph was used. It consisted of a solvent delivery module (Water Model 501), a septumless injector (Waters Model U6K), a variable wavelength spectrophotometric detector (Waters Model 486) and a data module (Waters Model 746). The analytical column was a Novapack C-18, 4 ×150 mm, 5 μm, (Millipore Corp., Waters Chromatography Division, USA). The mobile phase consisting of acetonitrile/1% acetic acid (1:1, V/V) was pumped at a flow rate of 1.5 mL min⁻¹. Retention time of GBD was 3.1 min and the drug was detected at 227 nm.

RESULTS AND DISCUSSION

Solubility and formulation studies

As a low dose drug, GBD was a good candidate for being formulated in the solution form. Solubility of GBD in various vehicles commonly used in capsule formulations is shown in Table II. Tetraglycol was found to be the most efficient solubilizer for GBD in which up to 3.5% (*m/m*) GBD can be dissolved. Hence, it was chosen as a vehicle for further formulation studies. Solutions of GBD in tetraglycol were prepared in concentrations of 1.85, 2.5 and 3.5% (*m/m*).

Owing to their high moisture uptake, hydrophilic fill solutions might exhibit stability problems including crystallization of the dissolved drug as well as gelatin shell rupture due to reduction of the moisture or plasticizer content of hard or soft gelatin capsules, respectively (15). High molecular mass PEG grades have much lower moisture uptake properties than liquid polyols (16). Therefore, semi-solid matrix capsules (SSM) of GBD were prepared by replacement of 25% tetraglycol with PEG 6000.

Table II. Semi-quantitative solubility of GBD in various vehicles

Vehicle	Amount of GBD added (% m/m)							
	0.5	1	1.5	2	2.5	3	3.5	5
Tetraglycol	+	+	+	+	+	+	+	–
PEG 400	+	+	–					
Propylene glycol	+	–						
Glycerol	–	–						
25% PEG 6000 in tetraglycol ^a	+	+	+	+	+	+	+	–
50% PEG 6000 in tetraglycol ^a	+	+	+	+	–			
G44/14 ^a	–							

(+) Microscopically clear solution, indicating solubility of the drug in the indicated solvent at the specified concentration

(–) Microscopically turbid

Gelucire 44/14 is an amphiphilic base commonly used for enhanced *in vitro* dissolution of drugs *via* improved wettability and emulsification properties. The distribution of glyceride esters and mono- and di-esters of PEG in this gelucire results in unique emulsifying properties in contact with the physiological medium at 37 °C (17). In addition, rapid dispersion of G44/14 is independent of the pH of the dissolution medium. Furthermore, G44/14 have been shown to greatly enhance the bioavailability of poorly soluble drugs, *e.g.*, the HIV protease inhibitor REV 5901 (18), through micellar transport of the drug and probable absorption enhancement at the gastrointestinal wall level. Hence, the effect of this base on the dissolution rate of GBD was also studied.

Evaluation of GBD test capsules and commercial tablets

All the formulations prepared in this study complied with the specified requirements for quality control tests, namely, the uniformity of drug content (4.9 ± 0.14 mg), and mass uniformity (286 ± 3.1 mg for F1, F4; 200 ± 2.2 mg for F2, F5, F8; 143 ± 1.9 mg for F3, F6; 100 ± 2.8 mg for F7, F9).

In a multinational postmarket comparative study of the pharmaceutical quality of GBD tablets, marked differences of *in vitro* dissolution behaviour were reported (19). Two dissolution media were used to evaluate the tested products: the first was borate buffer (pH 9.5), a tentative medium recommended by FDA (20), the second was phosphate buffer (pH 7.4), a medium for which a close correlation of dissolution rate and bioavailability for several GBD products has been demonstrated (2). Dissolution results of all the tested products in borate buffer (pH 9.5) complied with the FDA requirements (20). However, their release profiles were superimposed. On the other hand, the dissolution test in phosphate buffer (pH 7.4) revealed high variability in the rate and extent of the dissolution of various products (Fig. 1). These differences are likely to be responsible for the differences in the *in vivo* availability (2). The results, therefore, raise the question about the discriminative power of borate buffer as a dissolution medium for GBD. Hence, in the present study, phosphate buffer (pH 7.4) was chosen for evaluation of the developed GBD formulations.

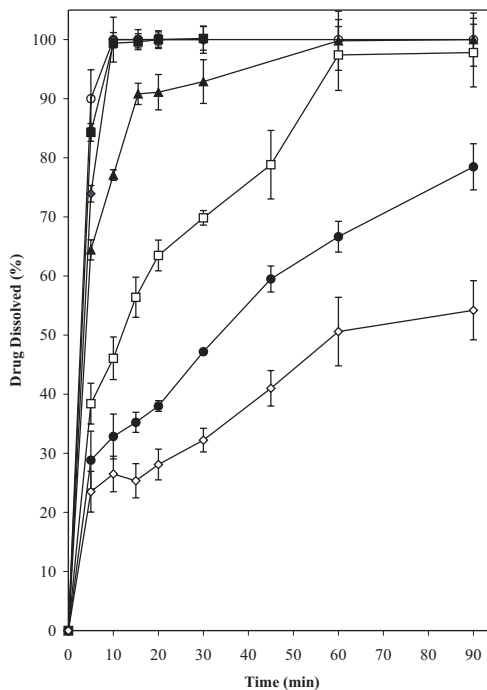


Fig. 1. Release profiles of GBD in phosphate buffer (pH 7.4) from commercial products: Euglucon N 3.5 mg tablets (O), tablets A (□), tablets B (●), tablets C (◇), and hard gelatin capsules containing different drug concentrations in tetraglycol solution: 1.75% (*m/m*) GBD (◆), 2.5% (*m/m*) GBD (■), 3.5% (*m/m*) GBD (▲). Each point represents mean \pm SD value, ($n = 3$).

Fig. 1 shows the dissolution profiles of HGC containing solutions of GBD in tetraglycol. Dissolution profiles of 1.8 and 2.5% (*m/m*) GBD solutions (F1 and F2, respectively) showed 100% drug dissolved after 10 min in both cases. Release profiles were almost identical to that of the innovator product. Initial dissolution rate from 3.5% (*m/m*) solution (F3) was slightly delayed with 75% drug released after 10 min. This may be attributed to the initial crystallization of GBD upon dilution with the dissolution medium. Analysis of the release rate data revealed that the drug release from HGC containing solutions of GBD in tetraglycol followed first-order kinetics (Table III).

Fig. 2 illustrates the release profiles of SSM composed of 1.8, 2.5, 3.5 and 5% (*m/m*) GBD in the tetraglycol vehicle containing 25% PEG 6000. The release profiles of SSM containing 1.8 or 2.5% (*m/m*) drug (F4 and F5, respectively) were nearly similar to those of liquid formulations of the same drug concentrations, but with a slightly delayed initial release. Time for 100% GBD release from F4 and F5 was 15 min compared to 10 min in cases of F1 and F2. This may be due to the time required for disintegration of the SSM. Release rate from SSM containing 3.5% (*m/m*) GBD (F6) was improved relative to that of the liquid formulation of the same concentration (F3) (the rate constants were 2.05×10^{-3} and $2.75 \times 10^{-3} \text{ s}^{-1}$ for F3 and F6, respectively). This may be attributed to the increased matrix viscosity resulting in a slower diffusion rate of dissolution medium and inhibited precipitation of the drug. Table III shows that the drug release from the above SSM formulations, containing GBD in soluble form, also followed first-order kinetics. The formulation of GBD as SSM allowed incorporation of 5% (*m/m*) GBD, which formed a sus-

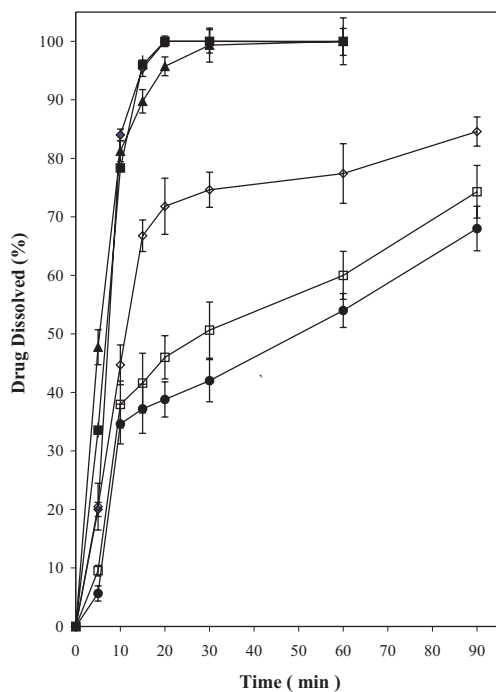


Fig. 2. Release profiles of GBD in phosphate buffer (pH 7.4) from hard gelatin capsules containing different drug concentrations in SSM composed of tetraglycol/PEG 6000 blend: 1.75% (*m/m*) GBD (◆), 2.5% (*m/m*) GBD (■), 3.5% (*m/m*) GBD (▲), 5% (*m/m*) GBD (◇), or from Gelucire 44/14: 2.5% (*m/m*) GBD (□); 5% (*m/m*) GBD (●). Each point represents mean \pm SD value, ($n = 3$).

pension in this base without sedimentation. The drug release from this formulation (F7) was biphasic (Fig. 2). The initial amount released from this matrix was 67% after 15 min, which corresponded to the amount of GBD soluble in the matrix material (3.5%). The drug release at this phase followed first-order kinetics (Table III). This rapid phase was followed by a second one, in which the suspended drug particles were slowly dissolving. Analysis of the data demonstrates that the drug release in this second phase followed zero-order kinetics (Table III).

GBD formed a suspension in G44/14 even at a 2.5% (*m/m*) concentration level. G44/14 based SSM formulations containing 2.5 and 5% (*m/m*) (F8 and F9, respectively) showed biphasic dissolution profiles (Fig. 2). In the first phase (up to 20 min), the drug release followed first-order kinetics, while in the second one (20–90 min) zero-order kinetic was predominant (Table III). The matrix containing 2.5% (*m/m*) GBD showed a higher extent of drug release than that with a 5% (*m/m*) drug concentration (Fig. 2). The higher amount released in the former case may correspond to the solubility of the drug in the matrix. In addition, the initial drug release from 5% (*m/m*) GBD suspension in tetraglycol/PEG blend (F7) was much higher than from the G44/14 matrix (F9). Percent of the drug released after 15 min was 67 and 42%, respectively. This is clearly attributed to the higher drug solubility in tetraglycol-based SSM. However, it could be noted that during the second phase of dissolution the release rate from G44/14 was higher than that from tetraglycol-based SSM (release rates constants were 7.20×10^{-5} and 2.86×10^{-5} $\text{g L}^{-1} \text{s}^{-1}$, respectively). This may be due to the solubilizing and emulsification properties of G44/14.

In the present study, the effect of the capsule shell type on the release of GBD from liquid and SSM fill formulations was also investigated. SGCs containing 2.5% (*m/m*) drug in tetraglycol solution or tetraglycol/PEG SSM showed a relatively slower initial dissolution rate within the first 15 minutes, as compared to that of the same formulations packed in HGCs. This is probably due to the observed longer disintegration time of the SGC shell.

Table III. Release kinetic parameters of glibenclamide from liquid and SSM filled capsules

Formula code	First-order kinetics		Zero-order kinetics	
	<i>r</i>	<i>k</i> (s ⁻¹)	<i>r</i>	<i>k</i> (g L ⁻¹ s ⁻¹)
F3	0.967	2.05 × 10 ⁻³	–	–
F4	0.971	4.60 × 10 ⁻³	–	–
F5	0.977	3.75 × 10 ⁻³	–	–
F6	0.997	2.75 × 10 ⁻³	–	–
	0–20 min		20–90 min	
F7	0.988	1.10 × 10 ⁻³	0.981	2.86 × 10 ⁻⁵
F8	0.953	0.55 × 10 ⁻³	0.991	6.06 × 10 ⁻⁵
F9	0.92	0.56 × 10 ⁻³	0.996	7.20 × 10 ⁻⁵

CONCLUSIONS

Based on the above results, it can be concluded that the dissolution rate of glibenclamide from hard or soft gelatin capsules containing a solution of 2.5% (*m/m*) drug in tetraglycol or tetraglycol/PEG6000 blend was highly superior to commercial tablet formulations.

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S A Ž E T A K

Kapsule s tekućim i polučvrstim matriksom za brzo oslobađanje glibenklamida

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Ispitivano je oslobađanje glibenklamida (GBD) iz kapsula s tekućim i polučvrstim matriksom (SSM). Polukvantitativno je procijenjena topljivost GBD u različitim podlogama, a najpogodniji je bio tetraglikol. Pripravljene su otopine GBD u tetraglikolu ili smjesi tetraglikola i PEG 6000, te suspenzija GBD u polučvrstom matriksu na bazi Gelucire 44/14, s različitim koncentracijama GBD. Oslobađanje GBD iz kapsula sa sadržajem ljekovite tvari u koncentracijama do 3,5% (*m/m*) bilo je slično.

Ključne riječi: tekući matriks, polučvrsti matriks, kapsule, glibenklamid, oslobađanje

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