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The Flow-Through Cell as an *In Vitro* Dissolution Discriminative Tool for Evaluation of Gliclazide Solid Dispersions

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ABSTRACT

Gliclazide (GLZ) is used to treat type II diabetes mellitus. It is a poorly soluble drug with variable bioavailability. The aim of this study was to improve GLZ solubility and dissolution rate by mixing or co-grinding with different polymers (PEG 4000, PEG 8000, MCC, HPMC E15 and alginates). Dissolution of two commercial products was carried out for comparison. GLZ solubility in phosphate buffer (pH 7.4) showed that grinding of GLZ considerably increased its solubility while, other polymers did not affect GLZ solubility. Flow-through cell (FTC) dissolution apparatus with two patterns of GLZ powder loading were utilized to achieve sensitive and reproducible dissolution data. Results revealed that distribution of untreated and ground GLZ powder with large volume of glass beads gave the best dissolution profiles in terms of rapid onset of dissolution (Q_{5min}) and dissolution efficiency (DE_{60min}). The best excipient among all was PEG (4000 and 8000), where GLZ physical mixture (PM) enhanced the dissolution rate without co-grinding to form solid dispersion (CSD). The highest dissolution rate and extent were obtained from GLZ:PEG 4000 (1:5) PM, where about 45.88 % was dissolved after 5 min and DE_{60min} was 74.18%.

INTRODUCTION

Dissolution of drugs is one of the major evaluation criteria during drug product development whether we are dealing with a new molecule, a modified or a generic product. It is a pre-requisite test required before carrying out bioavailability or bioequivalence studies (Wähling *et al.*, 2011). Although the Flow through cell (FTC) became an official USP method since 1995 (USP App. 4) (Wähling *et al.*, 2011), *in vitro* dissolution studies using this apparatus under different operational conditions and/or features are very few in literature (Emara *et al.*, 2014a; Emara *et al.*, 2014b; Emara *et al.*, 2013; Emara *et al.*, 2009; Krämer and Stippler, 2005; Beyssac and Lavigne, 2005; Fotaki and Reppas, 2005; Bhattachar *et al.*, 2002; Emara *et al.*, 2000). Our previous studies using the FTC proved that we should optimize the *in vitro* dissolution conditions for the finished product or during the preparation of different formulations to achieve accurate and reproducible results and to detect the effect of minor formulation changes upon storage. All these previous studies suggested that proper method of drug loading and the selection of cell design are crucial to obtain a reliable discriminating *in vitro* dissolution method otherwise, the dissolution results may become confusing or erroneous (Emara *et al.*, 2014b; Emara *et al.*, 2014a). In addition, the *in vitro* dissolution test using FTC could be modified to give a good *in vitro-in vivo* correlation (IVIVC) due to its flexibility in changing the dissolution conditions (Emara *et al.*, 2000).

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Previously, we concluded that considerably different dissolution profiles of drug(s) from the same product and/or formulation were obtained upon utilizing variable features of the FTC (Emara *et al.,* 2014a; Emara *et al.,* 2014b; Emara *et al.,* 2013; Emara *et al.,* 2009; Emara *et al.,* 2000). These variable features include, but are not limited to, type of flow (laminar, turbulent (Emara *et al.,* 2014a; Emara *et al.,* 2014b; Emara *et al.,* 2009)), rate of flow (4 to 45 ml/min (Emara *et al.,* 2009; Beyssacand Lavigne, 2005; Bhattachar *et al.,* 2002)), small and large cell (Emara *et al.,* 2014a; Emara *et al.,* 2014b; Emara *et al.,* 2009), open- or closed loop setup and pH of the dissolution medium (Emara *et al.,* 2014b; Fotaki, 2011; Brown, 2005; Emara *et al.,* 2000). Moreover, loading the test sample in different positions of the cell has also been studied (Emara *et al.,* 2014a; Fotakiand Reppas, 2005; Brown, 2005).

Optimization of the FTC operational conditions should be carried out individually for each tested drug due to the differences in the specific physicochemical properties and/or dosage form of each drug (Emara *et al.,* 2014a; Emara *et al.,* 2014b; Emara *et al.,* 2013; Emara *et al.,* 2012; Emara *et al.,* 2009; Emara *et al.,* 2000). A practical example can be seen if the drug is degradable in a certain pH (e.g. Amoxicillin in acidic medium), the release rate study of the sustained-release preparations should be carried out in an open-loop setup of the FTC (Emara *et al.,* 2013).

Enhancement of the dissolution rate of poorly soluble drugs, and hence its bioavailability, remains the major challenge during product development. Gliclazide (GLZ) is a poorly water soluble, second generation sulphonylurea oral hypoglycemic agent used in the treatment of type II diabetes mellitus. It has many added advantages such as protection of human beta-cells from apoptosis induced by intermittent high glucose, potentially slowing the progression of diabetic retinopathy, good general tolerability and low incidence of hypoglycemia (Del Guerra *et al.,* 2007; Palmerand Brogden, 1993). However, GLZ exhibits low solubility and high permeability (Biopharmaceutical classification system, class: II) (Grbic *et al.,* 2011). It also shows slow dissolution rate due to its hydrophobicity and poor wettability (Jondhale *et al.,* 2012; Grbic *et al.,* 2011; Biswal *et al.,* 2008). Therefore, GLZ exhibits slow gastrointestinal absorption rate and high inter-subject variation for its bioavailability (Biswal *et al.,* 2008; Jondhale *et al.,* 2012; Biswal *et al.,* 2009a; Palmerand Brogden, 1993).

Many approaches to enhance the dissolution rate of GLZ have been reported such as complexation with cyclodextrins, salt formation and preparation of different types of solid dispersions (El-Sabawiand Hamdan, 2014; Barzegar-Jalali *et al.,* 2010; Biswal *et al.,* 2008; Sapkal *et al.,* 2007; Moyano *et al.,* 1997b; Moyano *et al.,* 1997a). Among all of these approaches, co-grinding is the simplest and the most environmentally desirable technique because it does not require toxic solvents or complex equipment (Barzegar-Jalali *et al.,* 2010). Co-grinding of poorly soluble drugs with hydrophilic polymers lead to enhancement of their dissolution rate (Pandey *et al.,* 2013; Swamy *et al.,* 2010; Vogt *et al.,* 2008; Yamada *et al.,* 1999). This enhancement is thought to be due to particle size reduction and co-crystal formation (Jayasankar *et al.,* 2006).

GLZ co-crystals were prepared by liquid-assisted grinding. An almost 2-fold improvement in the solubility and intrinsic dissolution was observed (Chadha *et al.,* 2016). Solid dispersions obtained by co-milling of GLZ with amorphous silica or cross-linked swellable superdisintegrants like crosslinked polyvinylpyrrolidone, sodium starch glycolate and crosslinked carboxymethyl cellulose were quite effective in increasing the drug dissolution rate (Maggi *et al.,* 2015). Barzegar-Jalali *et al.* (2010) reported that the type and ratio of carrier could play a major role in controlling the dissolution rate of GLZ from the co-ground samples. In addition, they found that co-grinding decreased the crystallinity and increased amorphousness of GLZ (Barzegar-Jalali *et al.,* 2010). All these studies have evaluated the *in vitro* dissolution rates utilizing the conventional methods (USP apparatuses: I & II).

This study aimed to prepare different physical mixtures (PMs) and co-ground solid dispersions (CSDs) of GLZ with different polymers (PEG 4000, PEG 8000, MCC and HPMC E15) to enhance its dissolution behavior. Some commercial GLZ tablet products were considered as references. Moreover, the evaluation of GLZ preparations was carried out utilizing special FTC operational features which were capable of proper discrimination between the different dissolution profiles of GLZ from the tested PMs and CSDs.

MATERIALS AND METHODS

Materials

Gliclazide (GLZ) powder (particle size < 15 µm) was kindly donated from Sigma Pharma, Cairo, Egypt. GLZ market products were: Diamicron® 80 mg Tablets, Servier, Egypt (batch number: 19920) and Diamicron® 60 mg MR Tablets, Servier, Egypt (batch number: 20378).

Reagent grade chemicals were used unless otherwise indicated. Avicel PH-101(MCC, microcrystalline cellulose, particle size~50 µm, Fluka, Germany), hydroxylpropyl methyl cellulose (HPMC E15, Sigma, USA), Polyethylene glycol 4000 (WNLAB, UK), Polyethylene glycol 8000 (Fluka, Germany), Alginic acid sodium salt-high viscosity (Alg-High, Sigma, USA), Alginic acid sodium salt-medium viscosity (Alg-Med, Sigma, USA), Alginic acid sodium salt-low viscosity (Alg-Low, Sigma, USA) were used in the preparation of different CSDs and PMs. Potassium dihydrogen orthophosphate (ADWIC, Egypt), sodium hydroxide (ADWIC, Egypt) and Milli-RO purified water (Millipore Corp., Billerica, MA, USA) were used to prepare the dissolution medium.

Preparation of co-ground solid dispersions and physical mixtures

PMs as well as CSDs of GLZ with excipients in different ratios were prepared (Tables 1 – 4). For CSDs, a fixed weight of GLZ with the corresponding excipient were co-ground in a mortar

for 5 min (Emara *et al.*, 2016; Jayasankar *et al.*, 2006). PMs of GLZ with different excipients were manually mixed in a low-density polyethylene bag (Emara *et al.*, 2016; Nama *et al.*, 2008) for 5 min. Content uniformity tests were carried out and the results were found within the acceptable range.

Solubility test

Solubility measurements were performed according to Higuchi and Connors method (Higuchiand Connors, 1965). For each experiment, a specified weight, containing an excess amount of GLZ, was weighed into stoppered glass test tubes and 5 ml of distilled water or phosphate buffer of pH 7.4 was added (Tables 1 and 2). Samples were shaken at 37 °C for 48 h (Grbic *et al.*, 2011) in a temperature-controlled shaking water bath (Lab-Line, USA) at 250 rpm and then filtered through 0.45 µm filter (Mellix, USA). The filtrate was suitably diluted and analyzed spectrophotometrically at a predetermined λ_{max} 225 nm against water or phosphate buffer pH 7.4 as blank. All solubility experiments were carried out in triplicates.

Table 1: GLZ measured solubility in water and phosphate buffer (pH 7.4) after 48 h at 37 °C.

GLZ (powder)	Solubility (mg/ml) ± S.D.	
	Water	pH 7.4
Untreated	0.075 ± 0.004	1.56 ± 0.06
Ground	-	1.87 ± 0.06

Table 2: GLZ measured solubility from different physical mixtures (PMs) and co-ground solid dispersions (CSDs) in phosphate buffer (pH 7.4) after 48 h at 37 °C.

	GLZ Solubility (mg/ml) ± S.D.	
Drug carrier system	PM	CSD
GLZ:MCC (1:1)	1.64 ± 0.06	1.75 ± 0.03
GLZ:MCC (1:5)	1.47 ± 0.09	1.32 ± 0.02
GLZ:MCC (1:10)	1.37 ± 0.01	-
GLZ:Alg-Low (1:1)	-	1.64 ± 0.09
GLZ:Alg-Med (1:1)	-	1.64 ± 0.03
GLZ:Alg-High (1:1)	-	1.60 ± 0.01
GLZ:HPMC E15 (1:1)	-	1.68 ± 0.18
GLZ:PEG 8000 (1:5)	-	1.44 ± 0.04

***In vitro* dissolution test**

In vitro dissolution tests were carried out using the closed loop setup of FTC [USP Apparatus 4, a Dissotest CE-6 equipped with a CY 7-50 piston pump (Sotax, Switzerland)]. A Built-in filtration system with 0.7-µm Whatman glass micro-fiber (GF/F and GF/D) and glass wool was used throughout the study. The dissolution medium was 900 ml filtered and degassed phosphate buffer (pH 7.4) maintained at 37.0 ± 0.5 ℃ and pumped at a flow rate of 8 ± 0.2 ml/min. Samples were collected at the predetermined time intervals and replaced with fresh dissolution medium. Collected samples were analyzed UV/ spectrophotometrically at 225 nm against phosphate buffer pH 7.4 as blank.

Tablet loading into the FTC

For the evaluation of GLZ market products, tablets were loaded in the small FTC cell (Ø 12 mm), allowing for turbulent flow of the dissolution medium.

Powder sample loading:

Two FTC cell patterns (A and B), using the large cell (Ø 22.6 mm), allowing for laminar flow of the dissolution medium, were employed (Figure 1). For each preparation, a weight of powder that was equivalent to 80 mg GLZ was evaluated:

For cell pattern (A): homogeneously mixed powder (GLZ, PM or CSD) with glass beads (1:2, respectively) was loaded into the cell followed by addition of glass beads to fill the remaining space within the cell.

While for cell pattern (B): homogeneously mixed powder (GLZ, PM or CSD) with a quantity of glass beads sufficient to fill up to the score of tablet holder (Fotaki, 2011) was loaded into the cell followed by addition of a small amount of glass beads just to fill the remaining space within the cell.

Similarity of the dissolution profiles:

Dissolution profiles of some CSDs or PMs were compared by calculating the similarity factor (f_2) as proposed by Moore and Flanner (Moore and Flanner, 1996), defined as follows:

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}\Sigma w_t(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

Equation (1), (Moore and Flanner, 1996)

Where R_t is the percentage of dissolved drug for a reference batch at time point t, T_t is the percentage of dissolved drug for the test batch, n is the number of time points and w_t an optional weight factor. The weight factor can be adjusted to give high or low weightings to selected time points as required. For example, if it is important to achieve a certain dissolution level by 40 min, the 40 min time point should be given a high weighting. The present study uses w_t = 1, meaning that each time point is weighted equally. For each experiment, the calculations were made on the mean of the triplicates.

Similarity factor value(s) can be between 0 and 100. The value is 100 when the test and the reference profiles are identical and approaches zero as the dissimilarity increases, but because f_2 is a log function small differences in profile lead to a large drop in f_2 (Anderson *et al.*, 1998). The FDA suggests that two dissolution profiles are considered similar if the similarity factor f_2 is between 50 and 100 (FDA, 1997).

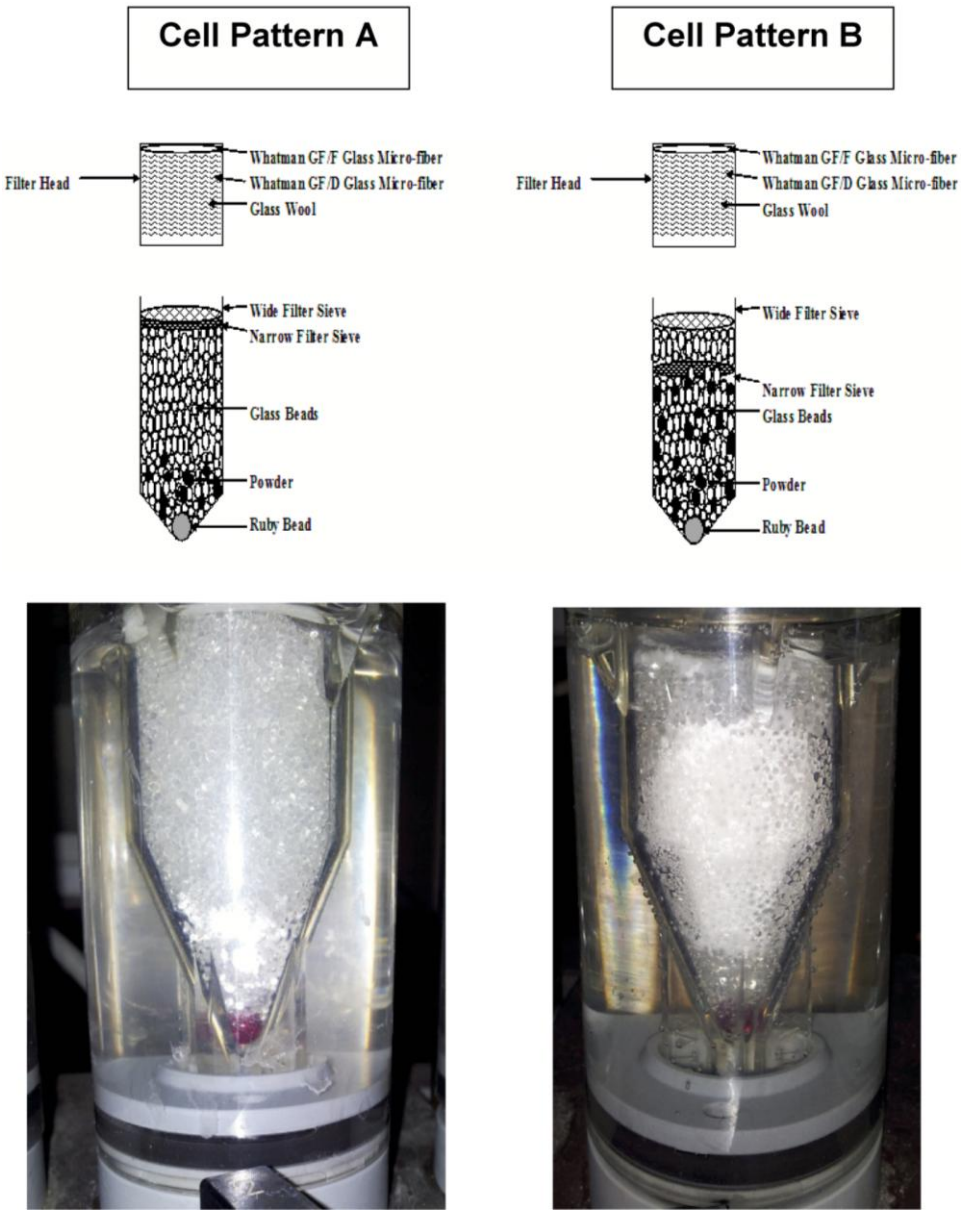

Fig. 1: Schematic diagrams and photographs showing the two FTC cell patterns (A and B) employed for sample loading.

Dissolution efficiency

Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time (t), measured using the trapezoidal rule, and expressed as percentage of the area of the rectangle described by 100% dissolution in the same time "Equation 2" (Khan, 1975).

$$DE = \frac{\int_0^t y.dt}{y_{100}.t} .100\%$$

Equation (2), (Khan, 1975)

RESULTS AND DISCUSSION

There were very few studies in literature that evaluated the solubility of GLZ in water and phosphate buffer (pH 7.4) (Maggi *et al.*, 2015; Grbic *et al.*, 2011; Biswal *et al.*, 2009a).

Table 1 showed the solubility of untreated GLZ powder, after shaking for 48 h at 37ºC in water and phosphate buffer at pH 7.4. In water, the solubility of GLZ was found to be (0.075±0.004 mg/ml). While, in a previous study of Biswal *et al*. (Biswal *et al.*, 2009a), the solubility of GLZ in water after shaking for 72 h at 37ºC was reported to be 0.8 mg/ml which was very far from our results. Also, in another study by Grbic *et al*. (Grbic *et al.*, 2011), the solubility of GLZ was 0.5 mg/ml after shaking for 48 h at 37 ºC in neutral medium. It is worthy to mention that, in our study, the particle size of GLZ was less than 15 µm, while both Biswal *et al*. (Biswal *et al.*, 2009a) and Grbic *et al*. (Grbic *et al.*, 2011) did not mention GLZ particle size. Maggi *et al*. (Maggi *et al.*, 2015) have studied the concentrations of GLZ, with a mean volume diameter of 38.41 ± 30.64 µm, (at 21°C for 24 h) in distilled water at different time intervals. They found that the amount of GLZ

dissolved after 4h was 0.0539 mg/ml and almost remained constant till 24 h (about 0.0540 mg/ml), confirming that GLZ reached a thermodynamic equilibrium in solution. Table 1 showed that the solubility of untreated and ground GLZ powder in phosphate buffer pH 7.4 was increased from 1.564±0.064 to 1.872±0.058 mg/ml, respectively (Table 1), which might be due to particle size reduction and distribution (Loh *et al.,* 2015; Khadka *et al.,* 2014). While, the study of Grbic *et al*. (Grbic *et al.,* 2011) reported GLZ solubility of 1.25 mg/ml at pH 7.4, which was slightly lower than our results.

Table 2 showed that PM of GLZ:MCC (1:1) slightly increased GLZ solubility compared to that of untreated powder (1.64±0.06 and 1.56±0.06 mg/ml, respectively). While, increasing MCC to drug ratio (1:5 and 1:10) showed a pronouncedly decreased GLZ solubility. In case of co-ground GLZ with different carriers, the measured solubility were decreased compared to ground GLZ powder as shown in Tables (1 & 2) where the highest solubility was obtained from ground GLZ without any additives.

The dissolution profiles, in phosphate buffer (pH 7.4), of two GLZ commercial products available in Egyptian market were depicted in (Figure 2). It was found that, both Diamicron® 80 mg and Diamicron® 60 mg MR showed very slow dissolution rates that failed to meet the requirements described by the British Pharmacopoeia for conventional-release and prolonged-release oral dosage forms (British Pharmacopoeia, 2011). Moreover, Diamicron® 80 mg tablets showed a dissolution profile that is similar to the modified release product Diamicron® 60 mg MR tablets (f_2=76).

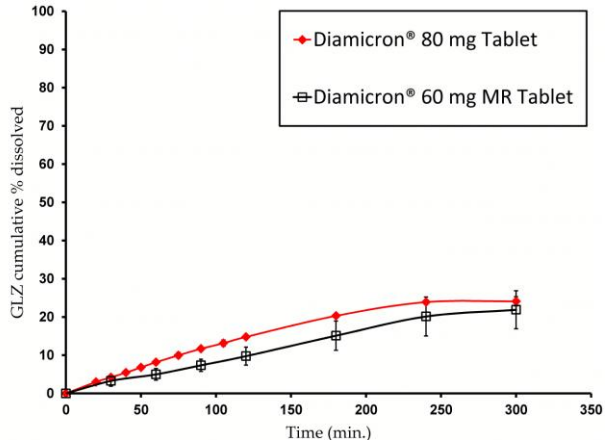

Fig. 2: Dissolution profiles of two GLZ products available in the Egyptian market (Diamicron® 80 mg and Diamicron® 60 mg MR, Servier, Egypt) in phosphate buffer (pH 7.4) employing the FTC apparatus.

Figure 3 and Table 3 showed the dissolution profiles of untreated and ground GLZ powder for two different cell loading patterns. Ground GLZ powder showed faster onset of dissolution (i.e. Q_{5min}) compared to untreated GLZ powder in both patterns A & B. Moreover, the two patterns proposed showed a considerable difference within the same test sample and this would be an important factor to consider in selecting the dissolution conditions to overcome the erratic data and poor detection of any minor formulation changes which might have its impact on product bioavailability. The calculated f_2 values were found to be 38 and 42 (Figure 3) for the untreated and ground drug, respectively, employing the two patterns (A & B) within the same test samples, indicating dissimilarity between the dissolution profiles obtained. This could be attributed to the large volume of powder dispersion and distribution within glass beads in case of pattern-B (Figure1). Distribution of the tested drug powder within the glass beads could be critical for giving reproducible *in vitro* dissolution data, with a low standard deviation of the test replicates, as previously reported (Eaton *et al.*, 2012; Stippler, 2011; Bhattachar *et al.*, 2002).

Table 3: Q_{5min} * and dissolution efficiency values ($DE_{60\ min}$) of untreated and ground GLZ powder employing different FTC cell patterns.

GLZ powder	FTC Pattern			
	A		B	
	Q_{5min} (%)	$DE_{60\ min}$ (%)	Q_{5min} (%)	$DE_{60\ min}$ (%)
Untreated	12.79 ± 0.49	38.32	26.23 ± 1.46	55.02
Ground	14.6 ± 1.19	42.77	36.50 ± 2.50	57.74

* Q_{5min} = % drug dissolved after 5 min.

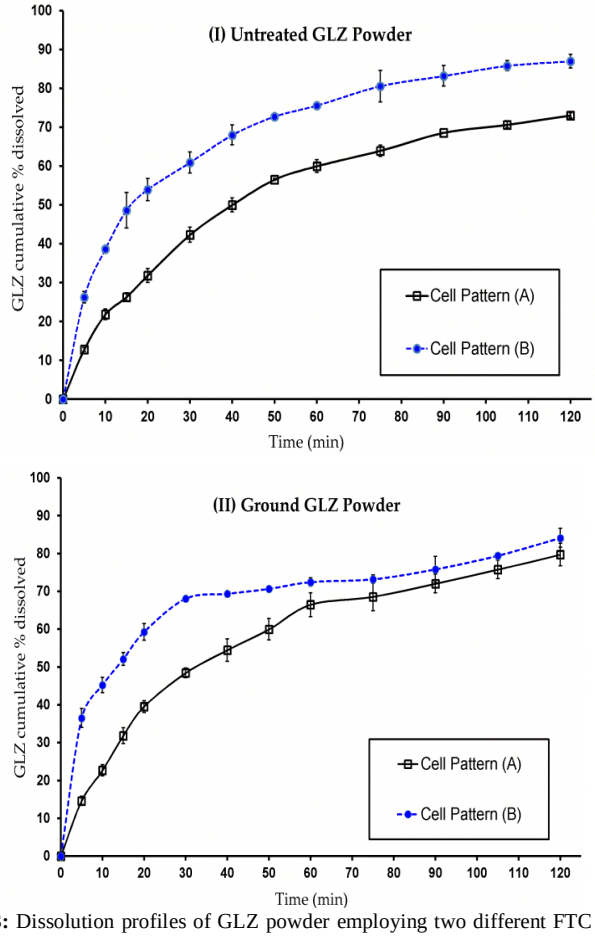

Fig. 3: Dissolution profiles of GLZ powder employing two different FTC cell patterns (A & B) in phosphate buffer (pH 7.4).

Therefore, pattern-B might solve the problems of aggregation, agglomeration and poor wettability of GLZ powder, which were suspected to be the reason of slowing down the

dissolution rate of the untreated drug powder using pattern-A. Consequently, pattern-B was selected for the *in vitro* dissolution testing of different GLZ PMs and CSDs. This provided a practical example of one of the advantages of FTC over the conventional USP I & II dissolution testers that it enabled optimization of the operational conditions and features of the dissolution test for each individual drug.

PM and CSD of GLZ with different polymers (MCC, HPMC E15, PEG 4000, PEG 8000) were prepared and their corresponding Q_{5min} and DE_{60min} values were listed in Table 4.

Table 4: Composition of different physical mixtures (PMs) and co-ground solid dispersions (CSDs) with their corresponding Q_{5min} and dissolution efficiency values ($DE_{60\ min}$).

Drug carrier system	PM		CSD	
	Q_{5min} (%)	$DE_{60\ min}$ (%)	Q_{5min} (%)	$DE_{60\ min}$ (%)
GLZ:MCC (1:5)	32.29 ± 2.40	59.63	23.76 ± 1.69	41.10
GLZ:HPMC E15 (1:1)	-	-	27.20 ± 0.05	41.74
GLZ:HPMC E15 (1:5)	-	-	7.87 ± 2.64	15.79
GLZ:HPMCE15 (1:10)	-	-	4.06 ± 1.30	8.00
GLZ:PEG 8000 (1:5)	29.43 ± 2.38	66.69	35.92 ± 1.49	67.73
GLZ:PEG 4000 (1:5)	45.88 ± 2.77	74.18	-	-

Figure (4) showed the dissolution profile of GLZ:MCC (1:5). It was found that the PM gave higher dissolution rate than the CSD. The PM (GLZ:MCC, 1:5) gave a dissolution rate similar to the ground GLZ powder (f_2 = 71), where the early initial amount of GLZ dissolved (Q_{5min}) as well as ($DE_{60\ min}$) values were 36.50 & 32.29% and 57.74 & 59.63 %, for ground GLZ and PM GLZ:MCC (1:5), respectively (Table 4). MCC might have acted as a diluent that suppresses the aggregation and agglomeration of GLZ powder, and hence increased GLZ surface to volume ratio exposed to the dissolution media. Also, this enhancement of the dissolution rate upon mixing with MCC is thought to be due to the hydrophilic nature of MCC particles that improved the wettability of the hydrophobic drug particles (Valizadeh *et al.*, 2007; Barzegar-Jalali *et al.*, 2006; Friedrich *et al.*, 2005). On the other hand, Figure (4) and Table (4) showed that CSD (GLZ:MCC, 1:5) considerably suppressed the dissolution rate of GLZ compared to the ground GLZ (f_2 = 39) and PM (GLZ:MCC, 1:5) (f_2 = 35). MCC is considered as a plastic material and a water insoluble diluent (Katdare and Chaubal, 2006), which might be the reason for decreasing the dissolution rate of GLZ from CSD. This might enforce the drug particles to be intimately incorporated in MCC upon co-grinding and form a continuous plastic-like structure with the disappearance of the characteristic fiber-like structure of MCC as previously described (Emara *et al.*, 2016).

Therefore, the dissolution of GLZ was not increased. We should address here the major influence of the exerted force during co-grinding on the fiber network structure of MCC, which was not observed with PM. This means that MCC could not be a promising excipient for preparing a CSD of GLZ, where the inherent physical properties of MCC could be dramatically altered by grinding techniques. Co-grinding of GLZ with MCC might possibly collapse the fiber network structure of MCC with reduction of pore size. Eventually, formation of tight networks around the solid drug particles occurred. This led to reduction of water uptake ability which lowered gliclazide release from GLZ:MCC CSD (Kolakovic, 2013). This result was found to be in a good agreement with a previous study of Emara *et al*. (Emara *et al.*, 2016), where, MCC meloxicam CSD drastically decreased the amount of meloxicam dissolved compared to those without MCC which might have acted as a dissolution retarding polymer after grinding.

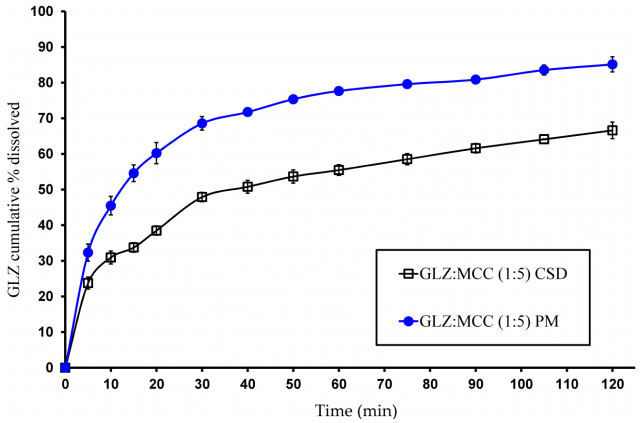

Fig. 4: Dissolution profiles of GLZ from its PM and CSD with MCC (1:5, drug to polymer ratio) in phosphate buffer pH 7.4 (FTC cell pattern B).

The dissolution rate of GLZ from the CSDs with HPMC E15 showed that increasing HPMC E15 in GLZ: polymer ratio (1:1, 1:5 and 1:10) slowed down the dissolution rate (Figure 5). Moreover, co-grinding with any ratio of HPMC E15 gave a slower dissolution rate than the untreated drug (Table 4). In contact with water, HPMC swells to form a gel, which acts as a barrier to drug diffusion. In addition, it is reported that increasing HPMC concentration or using higher viscosity grades increases the strength of the gel layer and retards the penetration of water thus delaying drug dissolution (Ghimire *et al.*, 2010). In addition, this might be attributed to the swelling behavior of HPMC E15 that leads to increasing viscosity of the dissolution medium and hence retarding drug dissolution (Colombo *et al.*, 2000).

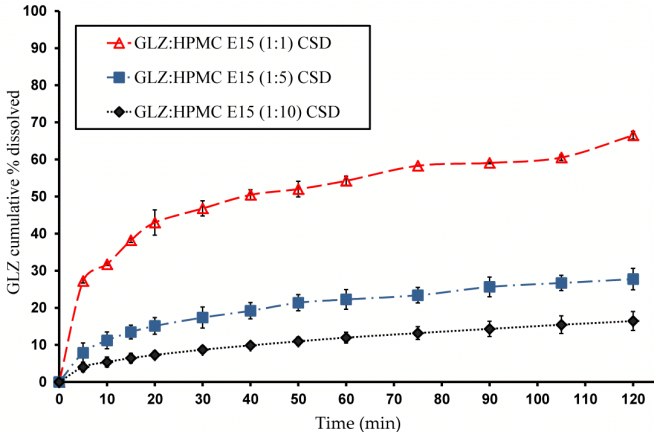

Fig. 5: Effect of HPMC E15 ratio on the dissolution profile of GLZ from different CSDs with HPMC E15 in phosphate buffer pH 7.4 (FTC cell pattern B).

Physical mixing or co-grinding of GLZ with PEG 8000 (1:5) enhanced the dissolution rate (Figure 6, Table 4), where both Q_{5min} and the DE_{60min} were almost the same for PM and CSD.. In addition, the PM and CSD with PEG 8000 showed similar dissolution rates of GLZ (f_2 = 73). This enhancement of the dissolution rate might be due to the known solubilizing capability of PEG 8000 (Koh *et al.*, 2013; Biswal *et al.*, 2009b). PEG 8000 is known to reduce particle aggregation, increase wettability and dispersibility and alter the surface properties of drug particles (Koh *et al.*, 2013; Biswal *et al.*, 2009b). Figure (6) and Table (4) showed that the dissolution profile of GLZ from the PM of GLZ:PEG 4000 (1:5) showed the fastest onset of dissolution (Q_{5min} = 45.88%) and dissolution rate (DE_{60min} =74.18%) among all of the tested preparations. Different types of PEG have the ability to enhance dissolution by increasing the wettability and solubility of different drugs (Koh *et al.*, 2013).

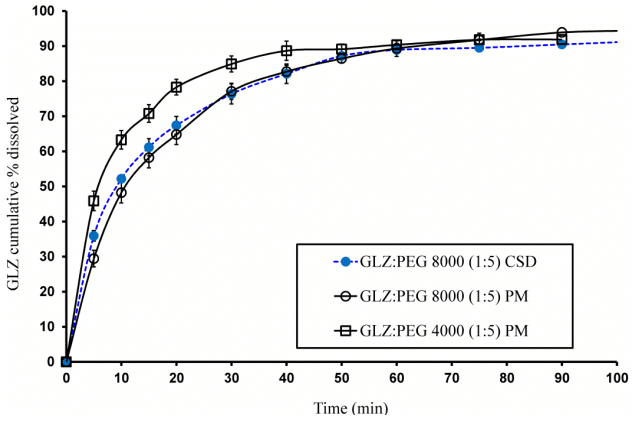

Fig. 6: Dissolution profiles of GLZ from PMs and CSD with PEG 4000 and PEG 8000 (1:5, drug to polymer ratio) in phosphate buffer pH 7.4 (FTC cell pattern B).

CONCLUSION

Testing of drug powder preparations requires proper selection of FTC operational conditions to obtain trustful and reproducible *in vitro* dissolution results with high accuracy. Improper selection of different features of FTC will give misleading dissolution data. The most promising preparation was the physical mixture with PEG 4000 (GLZ:PEG4000, 1:5). Meanwhile, all the proposed test preparations showed much faster dissolution rates compared to the commercial products: Diamicron® 80 mg and Diamicron® 60 mg MR tablets. Thanks for the presence of the FTC which could be able to optimize the dissolution conditions to solve all the problems of poor wettability, aggregation and agglomeration of hydrophobic drug particles.

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