

## ***In vitro* and *in vivo* Evaluation of Glibenclamide using Surface Solid Dispersion (SSD) Approach**

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**Abstract:** The aim of this study is to enhance the solubility of poorly water soluble drugs via the Surface Solid Dispersion (SSD) strategy using glibenclamide as a model drug. The drug was solubilized by surfactants and/or polymers then adsorbed onto the surface of extremely fine carriers to increase its surface area and to form the SSD. Characterization of SSD was carried out using differential scanning calorimetry, X-ray diffraction, infrared spectroscopy, scanning electron microscopy and *in vitro* drug release. F5 showed the highest drug release with  $r^2 > 0.99$ . Furthermore, both DSC and X-ray diffraction showed a decrease in the melting enthalpy and reduced drug crystallinity consequently in SSDs. However, infrared spectroscopy revealed no drug interactions with the carriers. A bioequivalence study using six male volunteers showed a significant difference ( $p = 0.006$ ) between the mean  $C_{max}$  estimates from F5 tablets ( $391.21 \pm 2.36$  ng/mL) and Daonil tablets ( $296.3 \pm 3.18$  ng/mL). The  $t_{max}$  was  $2 \pm 0.173$  h for the experimental group and  $2.5 \pm 0.2$  h for the control group, which suggests that enhanced solubility accelerates the absorption of the drug. The two formulas were shown to be bioequivalent due to lack of significant difference between their mean  $AUC_{0-24}$ . The results indicate that surface solid dispersion may serve as a successful strategy for enhancing solubility of poorly water soluble drugs.

**Key words:** Glibenclamide, poor water soluble, surface solid dispersion

### **INTRODUCTION**

The formulation of poorly water soluble drugs for oral delivery is an ongoing challenge for scientists (Emara *et al.*, 2002). The oral bioavailability of a drug depends on its solubility and dissolution rate which is the rate determining step for the onset of therapeutic activity. There are many techniques that are used to improve the solubility of poorly water soluble drugs. Some examples of these techniques include particle size reduction (micronization and nanonization) (Aguilar *et al.*, 1967), modification of the crystal habit by manipulating the crystalline state of the drug, formulation of drug dispersion within different carriers by formation of eutectic mixtures, solid dispersions or solid solutions (Ginés *et al.*, 1996), complexation using complexing agents (Brewster *et al.*, 1997) and finally, solubilization using surfactants to form micro/nano emulsions and self emulsified drug delivery systems (Akkar and Müller, 2003; Kim *et al.*, 2001).

Formation of surface solid dispersions is a strategy that is used to reduce the agglomeration of the drug by increasing its surface area in a way that can help in increasing its dissolution rate. Solid dispersion may be achieved by the incorporation of the drug into hydrophilic carriers then and the subsequent deposition of the drug solution onto adsorbent materials (Bauer *et al.*, 1975; Kneuer *et al.*, 2000; Rupprecht *et al.*, 1981).

The surface solid dispersion (SSD) technique has been used to increase the solubility, dissolution and consequently the bioavailability of many practically insoluble or poorly water soluble drugs such as ibuprofen (Williams *et al.*, 2005), piroxicam (Barzegar-Jalali *et al.*, 2002), meloxicam (Sharma *et al.*, 2005), itraconazole (Chowdary and Rao, 2000), and aceclofenac (Derle Dilip *et al.*, 2010).

Many materials reported to perform as carriers in surface solid dispersion are non- biodegradable, porous materials and hydrophilic in nature and include such compounds as microcrystalline cellulose, silicon dioxide, sodium starch glycolate, potato starch and croscarmellose (Babu *et al.*, 2008; Dhamane *et al.*, 2005; kakkar *et al.*, 1993).

The release of drug from the carrier material depends on the hydrophilic nature, particle size, porosity and surface area of the carrier, (Westerberg *et al.*, 1986) which means the larger the surface area available for surface adsorption of the drug, the better the release rate. For carriers with a large surface area such as silicon dioxide, a smaller amount of the carrier can increase the dissolution rate significantly.

Glibenclamide (GBM) is an oral hypoglycemic agent belonging to the second generation of sulfonylurea's commonly employed in the treatment of type II non insulin-dependent diabetes (Fig. 1). Its hypoglycemic effect is mainly due to stimulation of insulin release from

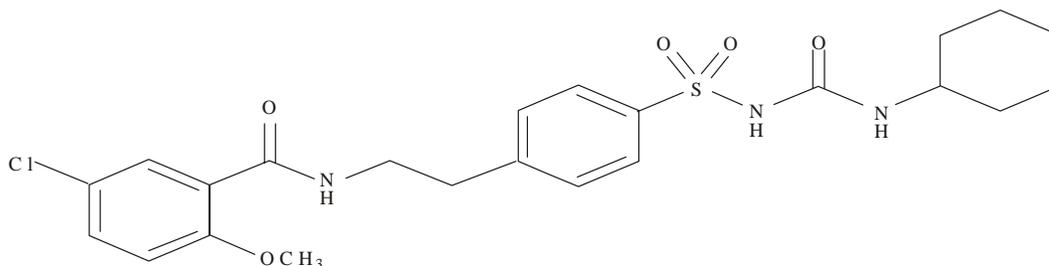


Fig. 1: The chemical structure of glibenclamide

pancreatic beta cells and sensitization of the peripheral tissues to insulin (Ashcroft and Ashcroft, 1992; Edwards and Weston, 1993). GBM is highly lipophilic and minimally soluble in aqueous media. According to the Biopharmaceutical Classification Scheme, GBM can be classified as a Class II drug: poorly soluble but able to permeate gastrointestinal mucosa. For class II drugs, the rate of drug dissolution is almost certainly the principal limitation to its oral absorption. In this case, the enhancement of the apparent aqueous solubility of the drug can improve its clinical performance, and eventually decrease the dose (Wei *et al.*, 2006). Over the last few years, various approaches aimed to enhance glibenclamide include dissolution properties using amorphization (Cordes and Müller, 1996), complexation with cyclodextrins (Sanghavi *et al.*, 1994; Zerrouk *et al.*, 2006), solid dispersion (Betageri and Makarla, 1995; Tashtoush *et al.*, 2004; Varma and Singh, 1992) and lyophilization (Betageri and Makarla, 1995).

In the present work, solvent deposition (SD) technique was modified by loading the drug onto the surface of the carrier to form agglomerates then further dispersion of the agglomerates was achieved using either hydrophilic polymers or surfactants. To the best of our knowledge, there are no known reports of further dispersion of the drug carrier agglomerates using either surfactants or polymers for glibenclamide (Siavoush Dastmalchi *et al.*, 2005). The aim of the present study is to enhance the solubility of glibenclamide using surface solid dispersion technique and to study the effect of different polymers and/or surfactants at different ratios on the dissolution rate of the poorly water soluble acidic drug glibenclamide.

## MATERIALS AND METHODS

**Materials:** Glibenclamide: Boots Company, Nottingham, U.K (Kindly supplied by pharco Pharmaceutical Co. Cairo, Egypt); Polyethylene glycols 4000, 6000, and 10000 (Fluka AG Buchs SG, Switzerland); Polyvinylpyrrolidones K25 & K90 (BHD chemicals Ltd. Poole, England); Polysorbate 80, Brij35 (Atlas Chemical

Table 1a: Formulation and dissolution parameters of glibenclamide SSDs

Formula no.	Drug: carrier (1:19)	Dissolution parameters	
		DE% <sup>a</sup> ± SD <sup>b</sup>	MDT <sup>c</sup> ± SD
Pure GBM <sup>d</sup>	-	14.58±0.07	28.28±1.42
F1	Avicel PH 102	55.12±1.26	9.09±1.25
F2	Aerosil 200	49.94±1.73	11.19±1.31
F3	Lactose	45.07±0.86	11.68±1.27
F4	Starch	48.49±0.48	13.82±0.96

a: Percent of Dissolution efficiency; b: Standard deviation; c: Mean dissolution time; d: Pure glibenclamide

industries, Inc. Wilmington, USA); Pluronic F68 and F127 (Fluka AG Buchs SG, Switzerland); Maize starch, Lactose monohydrate and calcium chloride (through El Gomhoria CO. Cairo, Egypt); Avicel PH 102: Microcrystalline cellulose, FMC Corporation, Pennsylvania, USA; Aerosil 200: Colloidal silicon dioxide (Degussa-Huls Ltd., Frankfurt, Germany); Explotab: sodium starch glycolate (FMC corporation, Philadelphia, USA); Magnesium stearate, (Prolabo, France); Chloroform (analytical grade), Adwic CO., Cairo, Egypt.

## Methods:

**Preparation of solid dispersions:** The SSDs of glibenclamide and the different carriers Avicel PH102, Aerosil200, lactose, starch other carriers were prepared in a 1:19 drug to carrier ratio using solvent deposition technique (Kiran *et al.*, 2009) (Table 1a): The calculated amount of drug (5 mg) was dissolved into an amount of chloroform (5 mL). This solution was added to each carrier while mixing until a homogenous mixture was attained. The obtained slurry was stirred using a magnetic stirrer at room temperature until the solvent (chloroform) evaporated completely. The resulting mass was transferred to desiccators containing CaCl<sub>2</sub> and stored until completely dry. The resulting solid mass was then pulverized in a mortar to get dry free-flowing powder. The powder was passed through a no. 60 sieve (50 μm), and the particles retained on a no 80 sieve (180 μm) then they were compressed into tablets and used in the in vivo studies.

Table 1b: Formulation and dissolution parameters of glibenclamide SSDs containing different surfactant and polymers

Formula No.	Carrier	Additives		Dissolution parameters	
				DE% <sup>a</sup> ± SD <sup>b</sup>	MDT <sup>c</sup> ± SD
F5	GBM/Avicel Ph 102 (1:19)	Brij 35	1:1	92.50±0.62	3.55±1.43
F6			1:2	81.92±0.54	5.37±1.52
F7		1:4	70.98±1.62	6.84±0.91	
F8		Polysorbate 80	1:1	84.15±1.95	5.04 ±1.67
F9	1:2		75.82 ±1.93	4.24±1.59	
F10			1:4	72.67±0.95	6.46±1.48
F11			Pluronic F-68	1:1	71.49±1.05
F12		1:2		76.90±0.75	11.5±1.36
F13		1:4	89.90±1.91	4.78±0.94	
F14	Pluronic F-127		1:1	73.74±0.24	6.74±1.21
F15			1:2	84.20±2.12	1.25±1.53
F16			1:4	81.30±0.61	1.90±1.41
F17			PVP K-25	1:1	70.32±1.86
F18		1:2		74.70±1.55	5.20±1.08
F19		1:4	83.20±0.68	4.03±0.89	
F20	PVP K-90		1:1	74.28±0.50	5.42±1.24
F21			1:2	81.5±0.63	1.69±0.98
F22			1:4	76.44±2.03	4.83±1.52
F23			PEG 4000	1:1	57.70±1.01
F24		1:2		53.90±0.6	14.40±0.81
F25		1:4	47.30±1.13	9.59±1.52	
F26	PEG 6000		1:1	57.40±1.62	4.50±1.08
F27			1:2	68.00±0.93	11.20±0.86
F28			1:4	59.80±0.55	13.30±1.08
F29			PEG 10000	1:1	74.00±1.81
F30		1:2		82.10±0.41	10.10±1.23
F31			1:4	71.83±0.27	7.12±0.94

a = Percent of Dissolution efficiency; b = Standard Deviation; c = Mean Dissolution Time; d = Pure glibenclamide

### Preparation of surface solid dispersions of glibenclamide:

This experiment was conducted in the Faculty of pharmacy the University of Beni Suef and was carried out to evaluate the efficiency of various polymers and/or surfactants in the solubilization of the drug carrier composite whose preparation was described in the previous experiment. Based on the dissolution parameters measured, superiority of Avicel PH 102 as a carrier in enhancing the dissolution rate of glibenclamide was clearly seen. So it was selected as the carrier of choice to complete the study. Various additives were then added to the carrier composites (Table 1b). The additives used were mainly polyethylene glycols (PEG4000, PEG 6000, and PEG 10000), polyvinylpyrrolidones (PVPK25 and PVPK90), pluronic (F68 and F127), polysorbate 80 and Brij35. Each additive was firstly mixed with the drug at ratios of (1:1, 1:2, and 1:4 w/w) and then dissolved in chloroform (5 mL). The drug was incorporated into this solution. Each solution was poured directly onto the carrier while mixing until homogenous slurry was obtained. The method of preparation was preceded similarly to the previous section.

### Physicochemical characterization of the Surface solid dispersions:

**Differential Scanning Calorimetry (DSC):** DSC analysis of the free drug, drug with carrier and the drug with carrier and additives were carried out using DSC

(TA-60WSI, Shimadzu, Japan). The instrument was calibrated using purified Indium (99.99%). Samples (5 mg) were sealed in a flat bottomed aluminum pan (Shimadzu DSC-60, Japan). The pan was placed in the DSC instrument and scanned between 30 and 300°C at a rate of 10°C/min. Dry nitrogen was used as a carrier gas to eliminate the oxidative and pyrolytic effects with a flow rate of 10 mL/min. The melting and transition point measurements were performed using the software provided with the device.

**Dissolution studies:** *In-vitro* dissolution studies of the formulas were carried out using USP apparatus II paddle (TDT-08L, Electrolab, USA). One tablet was chosen from each formula and placed in a dissolution vessel. Borate buffer (0.05 M, 500 mL) was used as a dissolution medium at pH 9.5. The experimental conditions were maintained at 37±0.5°C and at 75±1 rpm. An aliquot (5 mL) was withdrawn at predetermined time intervals and filtered through 0.45mm membrane filter. An equal volume of fresh dissolution medium was immediately replaced. The concentration of glibenclamide at each sampling time was analyzed spectrophotometrically at 226 nm (Jasco V530, Japan).

**FTIR spectroscopy:** FTIR spectra of the drug, the drug and carriers and the drug carriers and the additives were all carried out. Each formula (5 mg) was mixed with

about 100 mg. potassium bromide and compressed into discs under pressure of 10,000 to 15,000 pounds per square inch. The IR spectra were recorded using Infra-red Spectrophotometer (IR435-U-04, Shimadzu, Kyoto, Japan).

**X-ray diffraction studies (XRD):** XRD was used to trace any change in the crystalline state of the drug that may affect its solubility. X-ray powder diffraction patterns of the drug, and SSD were plotted using X-ray diffractometer (XRD-610, Shimadzu, Japan). Samples were exposed to Cu K $\alpha$  radiation at a scan rate of 5°/min over the 2 $\theta$  range of 4° to 70°. Operating voltage and current were 40 kV and 55 mA, respectively. The receiving beam slit was 0.2 mm. The results were then obtained as the peak height (intensity) versus 2 $\theta$ .

**Scanning electron microscopy (SEM):** The free drug, free avicel, F1 and F5 were all mounted and onto copper stubs with double-sided adhesive tape and coated with gold using the coated sputter (S150A Edward, England). The sample was examined under a JXA-840A electron probe microanalyzer (Jeol, Japan).

**Saturated solubility:** Saturated solubility measurements of F1, F5 and F13 in comparison to the drug were carried out using known excess amount of each formula. Each formula was added to the dissolution medium (10 mL) and was kept in a shaking water bath (37°C) for 24 h. The samples were left for 12 h to equilibrate then were filtrated using membrane filter (0.45 $\mu$ m, Millipore®, USA). The filtrate was analyzed spectrophotometrically at 226 nm.

**Effect of ageing:** Different formulas were stored for 3 months at 30°C at 65% relative humidity. The effect of ageing was studied by measuring both the *in vitro* drug release and the change in the crystalline state. The change of the crystalline state was evaluated by comparing the DSC, IR and XRD of the stored formulas to those freshly.

**Preparation and evaluation of tablets:** From each formula, an amount equivalent to 5 mg glibenclamide was accurately weighed; other ingredients were incorporated in the tablets such as sodium starch glycolate (10% w/w), microcrystalline cellulose (9% w/w), and magnesium stearate (1% w/w). Tablets were formulated using the wet granulation method using starch paste (10% w/w) and compressed into tablets using a single punch machine set at 8 mm concave punch and die set. The tablets prepared were evaluated for parameters such as hardness, friability, disintegration time, content uniformity, drug release.

#### **In vivo studies:**

**Study design:** The studies were carried out to compare the pharmacokinetics of GBM from a SSD tablet

formulation (F5, treatment A) to the conventional, marketed immediate-release tablet formulation (Daonil, Sanofi Aventis, treatment B) following administration of a single dose (5 mg) using randomized crossover design. Six healthy male volunteers participated in the study after giving informed written consent and were randomly assigned to one of two groups of equal size. The subjects' mean age was 32 $\pm$ 6, the mean height was 170 $\pm$ 8 cm, and the mean of their weights was 70  $\pm$ 5 Kg. The study was approved by the Ethical Committee of the University of Beni-Suef. The drug was administered orally after overnight fasting and washout period of 1 week. Venous blood samples (5 mL) were collected into heparinized tubes at the following time intervals: 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 h after administration of a treatment. Plasma was obtained by centrifugation at 2000 rpm for 10 min and stored at -20°C until the time of analysis.

**Chromatographic conditions:** GBM concentrations were determined using a validated HPLC (Emilsson *et al.*, 1986). The mobile phase was 0.01M phosphate buffer (pH 3.9): acetonitrile (50:50, v: v). Glipizide (Sigma, St. Louis, MO, USA) was used as the internal standard (IS). HPLC apparatus (Shimadzu, LC-10AS liquid chromatography connected to UV-visible detector (SPD-10A) with C-R6A chromatopack, column: (NOVA-Pack C18 60A, 4U, 3.9 X 300 mm cartridge column, Waters, USA). The UV detector was set at a wavelength of 225 nm. The flow rate was 1.5 mL/min. Peak areas were determined with a C-R6A chromatopack Shimadzu integrator.

**Plasma analysis:** The plasma obtained from the six subjects after receiving treatment A and treatment B was assayed as follows: 1 mL of the plasma sample was mixed with 1 mL acetonitrile and 1 mL of stock solution of the internal standard. The mixture was vortexed for 1 min and then centrifuged for 10 min at 3000 rpm. The upper layer was separated and transferred to another tube then filtered through 0.45  $\mu$ m Millipore filter for analysis with HPLC. 20  $\mu$ L were injected to the column for analysis. The GBM recovery (10-600 ng/mL) varied between 91.55 and 100.86%. The calibration line was linear between 10-600 ng/mL ( $r^2 = 0.9996$ ) ( $n = 8$ ).

**Pharmacokinetic analysis:** Pharmacokinetic characteristics from plasma data following administration of the two treatments were estimated for each subject using, WinNonlin® (version 1.5, Scientific consulting, Inc., Cary, NC, USA). Non-compartmental analysis was used.  $C_{max}$  (ng/mL) and  $t_{max}$  (h) were the observed maximal drug concentration and the time needed to reach this concentration respectively. The area under the curve,  $AUC_{(0-24)}$  (ng.h/mL) was calculated using the trapezoidal rule from zero time to the last time of the blood sample. The area under the curve from zero to infinity,  $AUC_{(0-\infty)}$

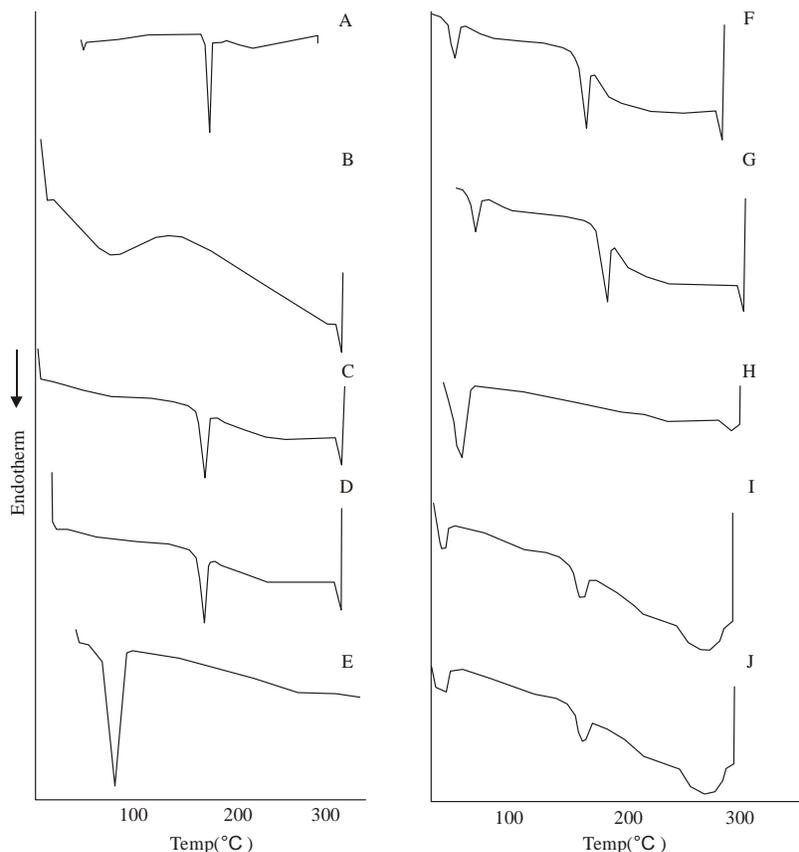


Fig. 2: DSC thermogram of (A) pure glibenclamide; (B) pure Avicel PH102; (C) F1 (fresh); (D) F1(stored); (E) Pure Pluronic F-68; (F) F13(fresh); (G) F13 (stored); (H) Pure Brij 35; (I) F5 (fresh); (J) F5(stored)

(ng.h/mL), was calculated as  $AUC_{(0-\infty)} = AUC_{(0-24)} + C_t/k$ , where  $C_t$  is the last measured concentration at time t, and k is the terminal elimination rate constant estimated by log-linear regression analysis on data visually assessed to be at terminal log-linear phase. Apparent terminal elimination half-life ( $t_{1/2}$ ) was calculated as  $t_{1/2} = 0.693/k$ .

**Statistical analysis:** An analysis of variance (ANOVA) was performed for untransformed data for the pharmacokinetic parameters  $C_{max}$ ,  $t_{max}$ ,  $AUC_{0-24}$ , and  $t_{1/2}$  using the software SPSS 11.0 (SPSS Inc., Chicago, USA). The level of significance was  $\alpha = 0.05$ . A p-value  $<0.05$  was considered statistically significant.

## RESULTS AND DISCUSSION

All SSD were found to be fine and free flowing powders. The tablets complied with the official specifications. The mean results of various quality control parameters evaluated for the prepared tablets were, disintegration time ( $1.39 \text{ min} \pm 1.91$ ), hardness ( $5-8 \text{ kg/cm}^2$ ), friability ( $0.4 \pm 1.24\%$ ), and drug content ( $100.4 \pm 1.68\%$ ). The dissolution studies will be discussed in detail.

Table 2: DSC parameters of glibenclamide and prepared SSDs systems

Drug-excipient mixture	Drug		Excipient	
	Peak temp (°C)	Enthalpy (J/g)	Peak temp (°C)	Enthalpy (J/g)
GBM <sup>a</sup>	175.69	- 87.69	-	-
Avicel PH 102	-	-	86.73 299.34	- 220.54 - 310.72
Brij 35	-	-	44.44	- 1.95
Pluronic F-68	-	291.31	-	101.26
F1 (fresh)	175.59	- 336.76	296.84	- 332.89
F1 (stored)	173.77	- 0.13	289.49	- 0.13
F5 (fresh)	172.87	- 166. 89	40.14 272.51	- 91.98 - 379.60
F5 (stored)	164.32	- 0.03	38.71 280.49	- 0.00 - 0.17
F13 (fresh)	172.56	- 249.34	53.42 278.83	- 180.68 - 451.6
F13 (stored)	169.05	- 0.09	48.73 281.74	- 0.06 - 1.28

a = Glibenclamide

**Differential scanning calorimetry (DSC):** DSC was used to assess the thermal behavior of the drug, carrier, additives, and SSD systems prepared. DSC thermograms of the drug and SSD systems are shown in Fig. 2 and Table 2. It is clear from the figure that the thermogram of

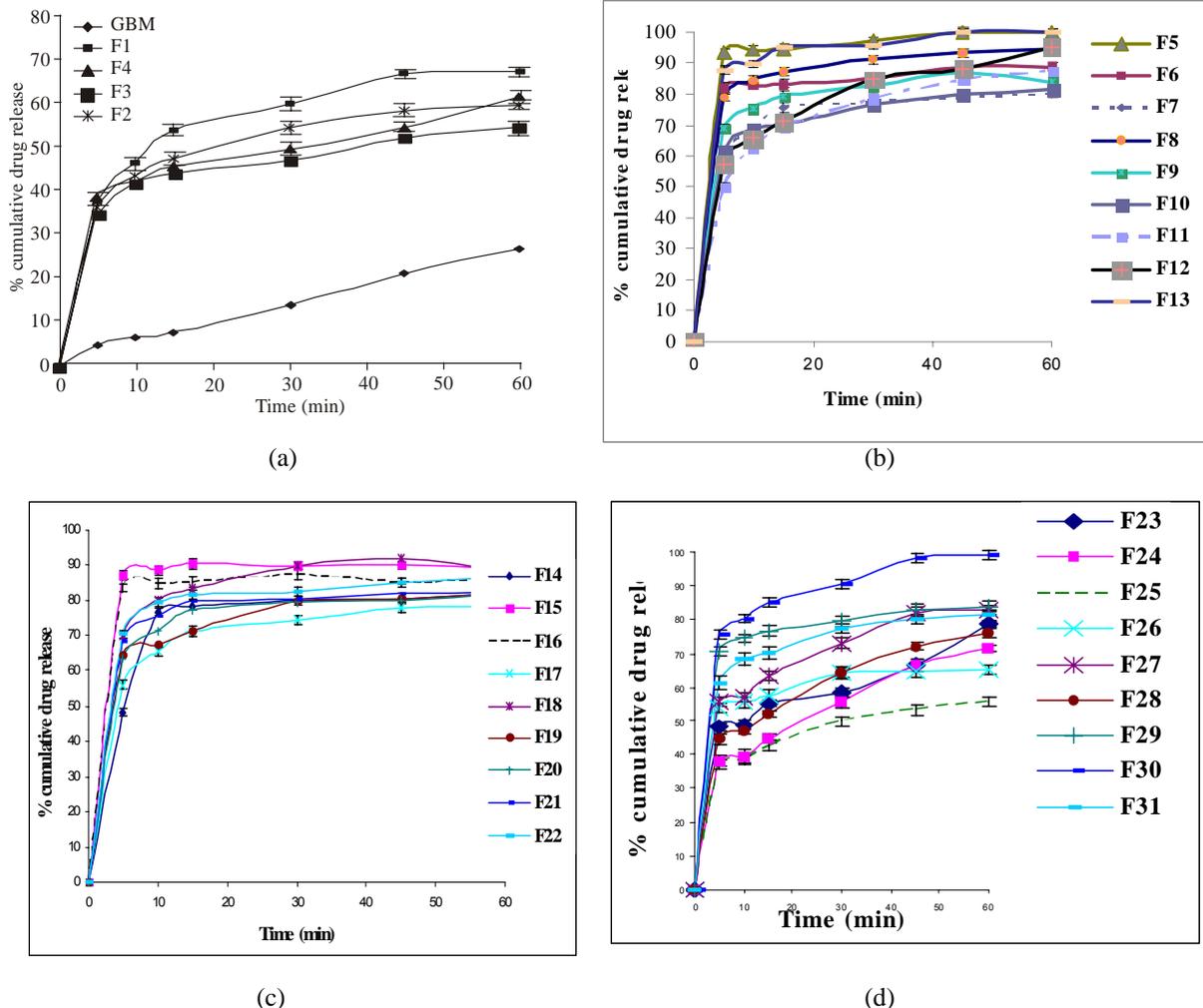


Fig. 3: Dissolution profiles of GBM in SSD tablets, and GBM alone in borate buffer at 37°C (n = 3± S.D.)

the drug was that of a highly crystalline drug with a sharp endothermic peak at 175.69°C ( $\Delta H = 87.69 \text{ J/g}$ ) corresponding to its melting point. Formation of SSD did not show any significant change in the crystalline state of the drug with a minor shift in the endothermic peak of both the carrier and the additives used. Upon storage for three months, the DSC of the stored F1, F5 and F13 formulations did not significantly change from that of fresh one, indicating the stability of the prepared solvent deposition formulae during the period of the study.

**Dissolution of different SSD:** The aqueous dissolution profile of the SSDs of glibenclamide on different carriers diluted to the ratio of 1:19 is shown in (Fig. 3a). From the results, it is clear that the initial dissolution efficiency of pure glibenclamide was very low (14.13%). However, an increase in the dissolution rates was recognized with SSDs of the glibenclamide. Analysis of the dissolution rate of the drugs and the SSD was carried out using

model-independent approaches. This model is based on calculating the ratio between the area under the dissolution curve (dissolution efficiency) and the mean dissolution time (Arias *et al.*, 1996). The percent dissolution efficiency (% DE) and mean dissolution time (MDT) were also calculated to compare the performance of various concentrations of carrier in SSDs. The % DE of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain time (t). The % DE can be calculated as a percentage of the area of the rectangle described by 100% dissolution at the same time. The % DE can be calculated from Eq. (1):

$$DE = \left( \frac{\int_0^L Y \times dt}{Y_{100} \times t} \right) \times 100\% \quad (1)$$

where, Y is the percent drug dissolved at a time t.

The Mean Dissolution Time (MDT) was calculated using the dissolution data of both glibenclamide and SSD. The mean dissolution time can be calculated by using Eq. (2) (Costa and Sousa Lobo 2001):

$$MDT_{in\ vitro} = \frac{\sum_{i=1}^n T_{mid} \Delta M}{\sum_{i=1}^n \Delta M} \quad (2)$$

Here,  $i$  is the sample number,  $n$  is the sampling times,  $T_{mid}$  is the midpoint between times  $T_i$  and  $T_{i-1}$ , and  $\Delta M$  is the amount of the drug dissolved ( $\mu\text{g}$ ) between times  $T_i$  and  $T_{i-1}$ . MDT reflects the time for the drug to dissolve. It is the first statistical moment for the cumulative dissolution process that provides an accurate drug release rate (Reppas and Nicolaidis, 2000). A low MDT value indicates greater drug solubility. The % DE was increased in the following order:  $F1 > F2 > F4 > F3 > \text{GBM}$ . The values of % DE are consistent with the dissolution data.

The previous articles showed the efficiency of Avicel PH102 to act as a carrier and to enhance the dissolution rate of glibenclamide. (Siavoush Dastmalchi *et al.*, 2005). On the other hand, the mean dissolution time data MDT showed that the order of the drug release was as follows  $\text{drug} > F4 > F3 > F2 > F1$ .

All of the prepared SSD containing either polymers or surfactants had a much higher % DE and a much lower MDT than either of the pure GBM or the mixture of the drug and the carrier as shown in (Table 1b) and (Fig. 3b). F5 showed the highest % DE (92.5%) and lowest MDT (3.5 min).

The release mechanism of glibenclamide from various preparations of SSDs was studied. The data was used to study the best linear fit. The results indicate that the mechanism of the release of the drug, F5 and F13 followed first order kinetics and that the formula F1 showed diffusion kinetics.

It should be noted that there was a significant increase in the average percent of glibenclamide dissolved

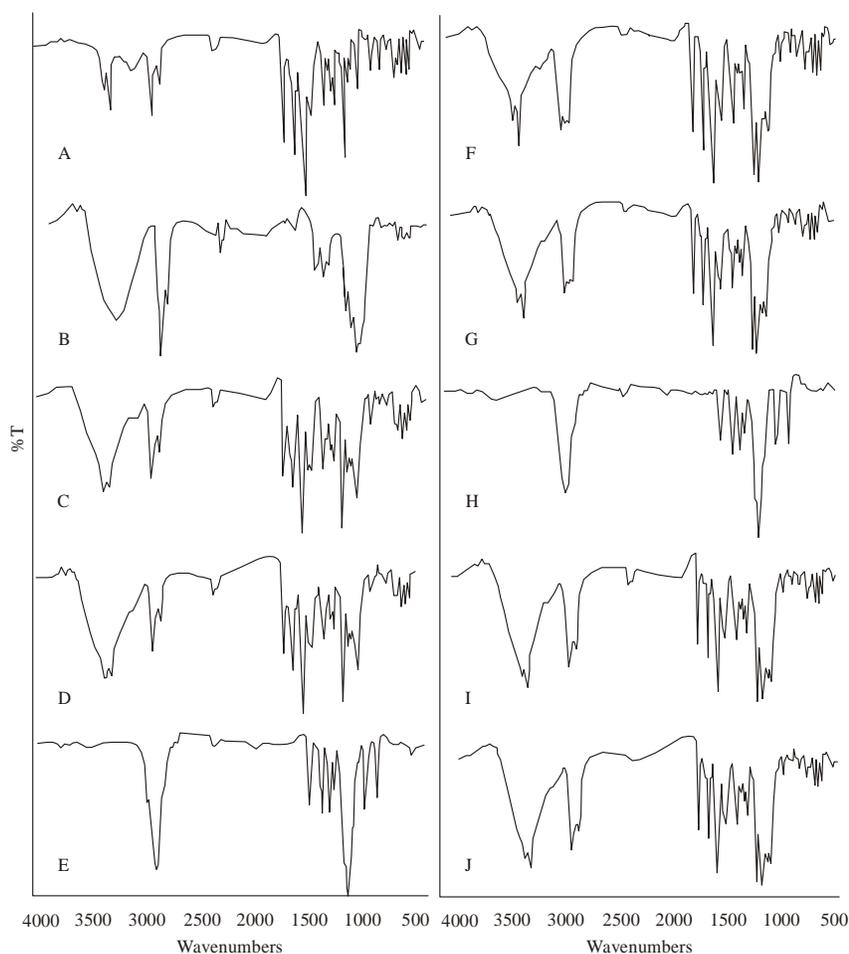


Fig. 4: FTIR spectra of (A) pure glibenclamide, (B) pure Avicel PH102, (C) F1 (fresh) (D) F1(stored), (E) Pure Pluronic F-68, (F) F13 (fresh), (G) F13 (stored), (H) Pure Brij 35, (I) F5 (fresh), (J) F5 (stored). 4000

from the SSD on carriers compared to the plain drug ( $p < 0.05$ ). This might be attributed to the assumption that the carriers sterically stabilized the surface of the hydrophobic drug. The drug is then adsorbed on the surface of carriers in an extremely fine state of subdivision. The resulting decrease in particle size and the concomitant increase in the surface area served to increase the thermodynamic activity of the drug, which in turn greatly enhanced the dissolution of the drug compared to the drug alone. These results are concurrent to those obtained by Barzegar-Jalali *et al.* (2002) who reported that the increase in the dissolution rate and consequent enhancement of anti-inflammatory effect of piroxicam in solvent deposition system on microcrystalline cellulose were attributed to the reduced particle size of drug deposited on the carrier and enhanced wettability of the particles brought about by the carrier. (Broman *et al.*, 2001; Dordunoo *et al.*, 1991; Leuner and Dressman 2000; Passerini *et al.*, 2002).

**IR spectroscopy:** The IR study was conducted to examine if an interaction between GBM and the carriers in the solid state could occur. The FTIR spectrum of pure GBM (Fig. 4) showed characteristic amide peaks at 3367.5, 3314.3, 1713.5 per cm, urea carbonyl stretching (urea N-H stretching) vibrations at 1618.4 and 1526.5 per cm,  $\text{SO}_2$  stretching vibration at 1158, 1341.5 per cm (Bhaskar *et al.*, 2005). Figure 4 illustrates the IR spectra of fresh and stored solvent depositions of F1, F5, and F13. The characteristic bands of the drug were also apparent in the excipients albeit with decreased intensity. This may be attributed to the dilution factor of the mixture by the carrier. There were no new bands observed in the spectrum, which confirms that no new chemical bonds were formed between the drug and the excipients.

**X-ray diffraction studies (XRD):** Figure 5 illustrates the X-ray diffraction of glibenclamide, Avicel PH 102, pluronic F-68, brij 35, fresh and stored SSD of F1, F5

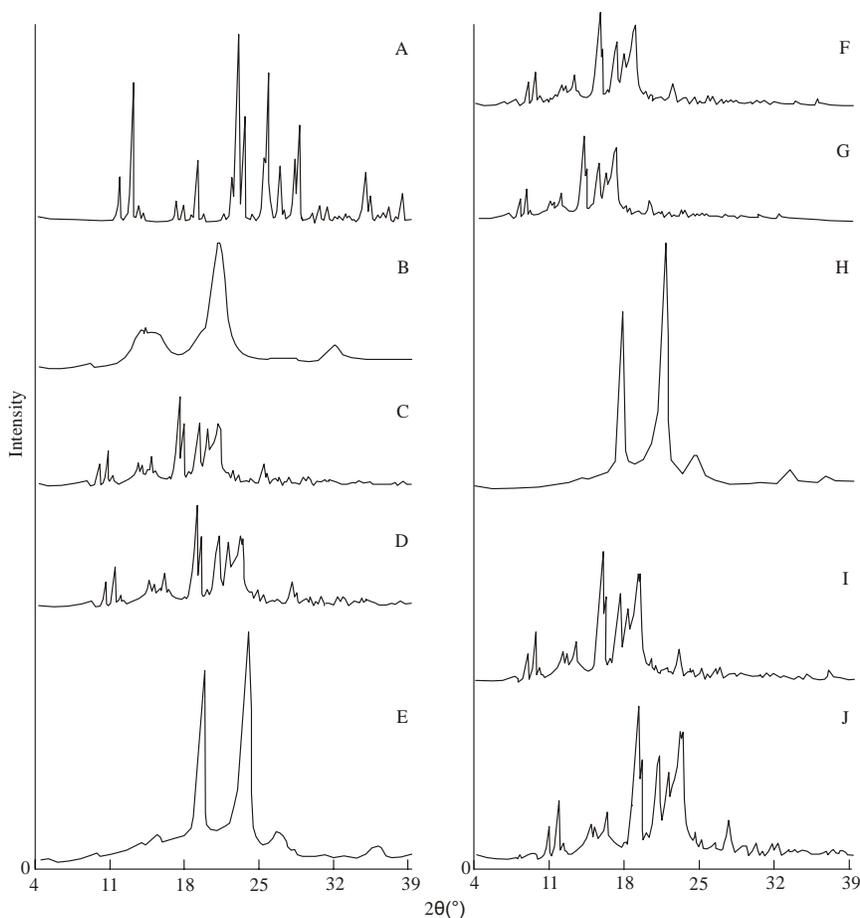


Fig. 5: X-ray diffractograms of (A) pure glibenclamide, (B) pure Avicel PH102, (C) F1 (fresh) (D) F1(stored), (E) Pure Pluronic F-68, (F) F13 (fresh), (G) F13 (stored), (H) Pure Brij 35, (I) F5 (fresh) and (J) F5(stored)

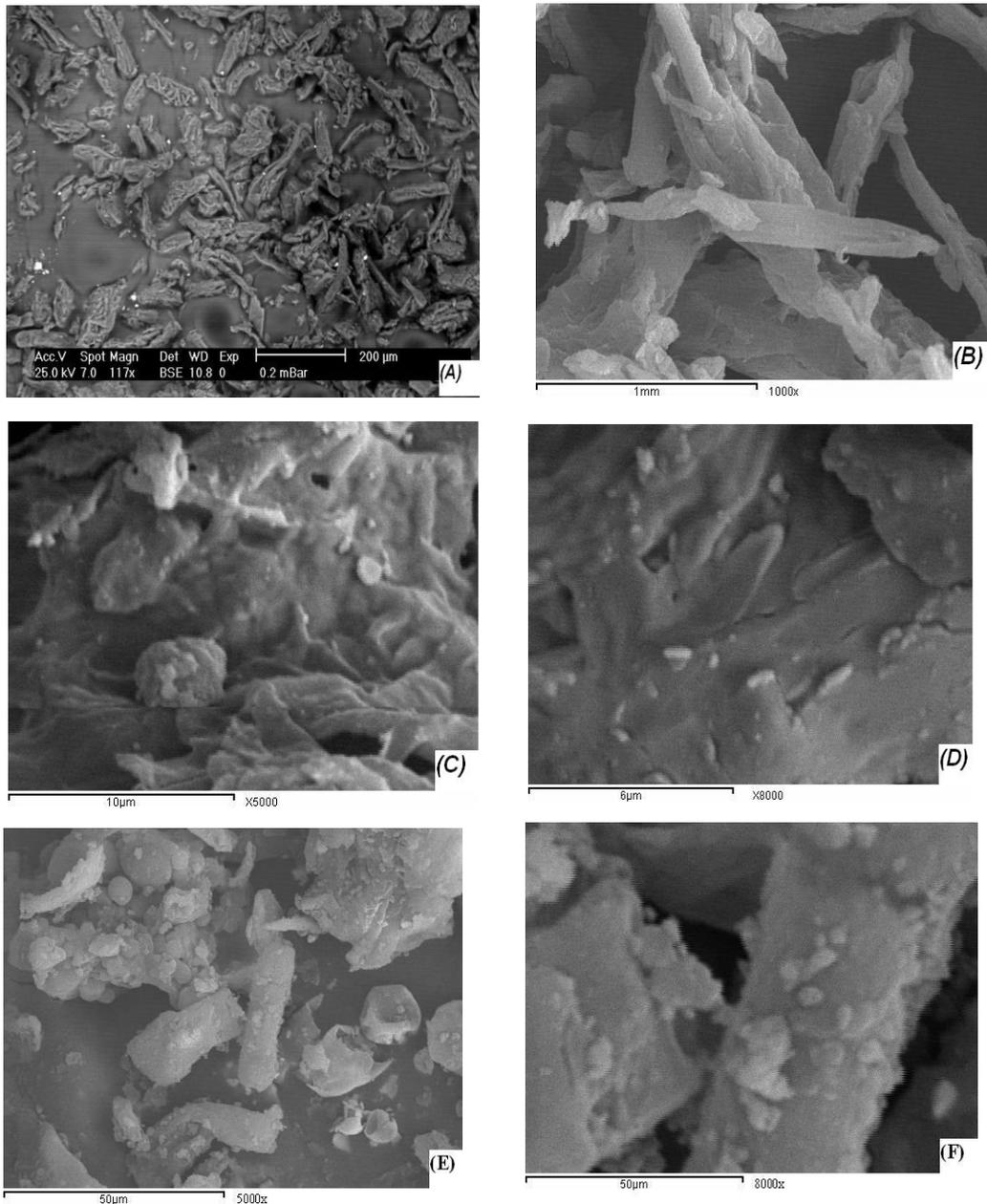


Fig. 6: SEM microphotographs of (A) pure glibenclamide (B) pure Avicel PH 102 as received (C) Surface solid dispersion (F1) (d) Close up of surface solid dispersion(F1) (E) Surface solid dispersion (F5) and (F) Close up of (F5)

and F13. The diffraction spectrum of pure glibenclamide shows that the drug was crystalline in nature as demonstrated by numerous peaks observed at  $2\theta$  of  $11.698^\circ$ ,  $14.755^\circ$ ,  $16.196^\circ$ ,  $18.919^\circ$ ,  $20.96^\circ$ ,  $23.15^\circ$ ,  $27.66^\circ$ , and  $30.278^\circ$ .

However, Avicel PH 102 shows major peaks at  $2\theta$  of  $14.57^\circ$ ,  $22.41^\circ$ , and  $34.485^\circ$ , while, pluronic F-68 shows major peaks at  $2\theta$  of  $19.515^\circ$ ,  $23.695^\circ$ ,  $26.535^\circ$  and  $36.46^\circ$  and brij 35 shows its major peaks at  $2\theta$  of

$19.455^\circ$ ,  $23.720^\circ$ ,  $26.935^\circ$  and  $36.53^\circ$ . The prominent peaks from pure glibenclamide were clearly seen at the same positions in the SSDs, but with decreased intensities. The relative reduction in diffraction intensity at these angles suggest that the size of the crystals was reduced to a microcrystal form (Valizadeh *et al.*, 2004).

Upon analysis of the SSDs, it was clear that the positions of Avicel PH 102, brij 35 and pluronic F-68 peaks patterns in the SSDs were still the same and

Table 3: Saturated solubilities of different glibenclamide formulations

Type of formulation	Saturated solubility ( $\mu\text{g/mL}$ )
Pure GBM <sup>a</sup>	24.83 $\pm$ 1.05
F1	44.28 $\pm$ 1.83
F5	57.92 $\pm$ 1.41
F13	51.34 $\pm$ 1.52

a = Glibenclamide

superimposable, but with decreased intensities. This, again, rules out the possibility of any chemical interaction among the additives and the drug that can affect its physical form. It also rules out the formation of any new compound among the drug and the additives. No new peaks were detected, hence the possibility of any change in the crystals pattern to a polymorphic form was ruled out. The diffractogram of the stored SSD did not show any change from that of the fresh one, indicating stability of the prepared solid dispersion.

**Scanning Electron Microscopy (SEM):** The electromicrophotographs of pure GBM, Avicel PH10 and SSDs are shown in (Fig. 6a, b, c, and d). Figure 6a shows the large crystals of pure GBM with average diameters of 50  $\mu\text{m}$ . Figure 6b shows the large particle size of Avicel needles with a diameter approaching 200  $\mu\text{m}$ . SSDs (Fig. 6c and d) are shown as irregular matrices due to the porous nature of the carrier with the fine particles of the drug deposited on it. Therefore, it is possible that the reduced particle size, increased surface area and the close contact between the hydrophilic carrier and the drug may be the reason for the enhanced drug solubility of the SDs.

**Saturated solubility:** All the test samples showed an increase in drug solubility over crystalline GBM (Table 3). It might be due to either the reduction of the crystallinity of drug or the improved wetting of the drug particles. This phenomenon was corroborated by previous reports with similar results with other drugs such as the mixture of nifedipine and mixture of pluronic F68 and gelucire 50/13. Pluronic F68 and gelucire 50/13 may enhance the solubility of the poorly water-soluble drug (nifedipine) in solid dispersions either by micellar solubilization or by increasing the steric hinderance among the particles or by both mechanisms (Vippagunta *et al.*, 2002). Improving the wettability of the hydrophobic drug crystals might also occur.

**Aging study:** During the aging study, almost no decrease of *in vitro* drug dissolution was observed between the freshly prepared SSDs and the 3 month old preparation (Fig. 3). The results obtained from the DSC, IR and XRPD indicated stability of the prepared systems (Fig. 2, 4 and 5, respectively). Based on the results of ageing study SDs, F5 was selected to carry out the bioequivalence studies.

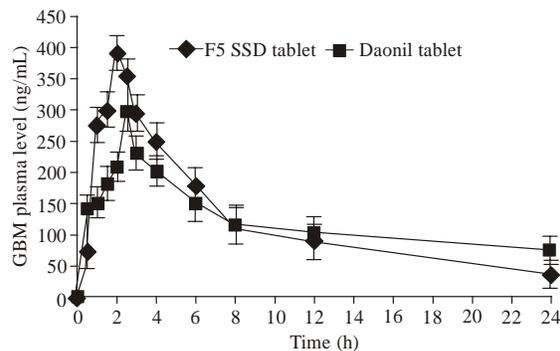


Fig. 7: Pharmacokinetic parameters and mean plasma concentrations (ng/mL) following administration of F5 in comparison to Daonil<sup>®</sup> tablets in six male subjects

**In vivo study:** The mean plasma concentration time profile for GBM following oral administration of F5 tablets and Daonil tablets are shown in Fig. 7. Remarkable differences in the shape of the concentration time profile between the two treatments were found, expressed by higher  $C_{\text{max}}$  and earlier  $t_{\text{max}}$  for the SSD tablet. The mean  $C_{\text{max}}$  and  $t_{\text{max}}$  estimates for the F5 tablets were 391.21 $\pm$ 2.36 and 2h respectively. The mean  $C_{\text{max}}$  and  $t_{\text{max}}$  for the Daonil tablets were 296.3 $\pm$  3.18 ng/mL and 2.5 h respectively. The differences between the two treatments for  $C_{\text{max}}$  ( $p = 0.006$ ) and  $t_{\text{max}}$  ( $p = 0.03$ ) were statistically significant. The mean area under the curve  $\text{AUC}_{(0-t)}$  estimate from F5 was 2954.597 $\pm$ 283 (ng.h/mL), which reflects the total amount of drug absorbed over the 24 h time period. The AUC of F5 was not significantly different ( $p = 0.75$ ) from the mean AUC of the Daonil tablets (2896.37 $\pm$ 222 ng.h/mL). The comparison of the half-life did not show a significant difference ( $p = 0.59$ ) between the F5 tablets (9.817 $\pm$ 1.69 h) and Daonil tablets (8.826 $\pm$ 2.16 h).

Based on these results, it can be concluded that the rapid and enhanced absorption of GBM obtained from the F5 SSD tablet, with higher  $C_{\text{max}}$  and shortened  $t_{\text{max}}$ , could be due to improved dissolution resulting from reduced particle size, increased surface area, the close contact between the hydrophilic carrier and the drug, and enhanced wettability. These results are in agreement with what was reported in literature regarding the enhanced solubility of poorly soluble drugs. Kiran *et al.* (2009) reported superiority of croscarmellose as a carrier in enhancing the dissolution rate of glibenclamide. Improving solubility of aceclofenac by adsorbing it on lactose employing solvent deposition technique is also reported by Derle Dilip *et al.* (2010). Similar observations have been reported for solid dispersions of naproxen in PEG 4000, 6000 and 20,000 (Mura *et al.*, 1996).

## CONCLUSION

From the dissolution data of all formulations developed, solubility of glibenclamide, a poorly water-soluble drug was enhanced by the surface solid dispersion technique using Avicel PH 102 as a carrier. This effect may be due to fine particle size of glibenclamide adsorbed over Avicel resulting in a higher surface area of drug exposed to the dissolution media and improved wettability of the drug particles (Broman *et al.*, 2001; Leuner and Dressman 2000). The significant reduction in particle size during the formation of SSDs and the inherently higher rate of dissolution of the soluble component of SDs may also contribute to the increased solubility of glibenclamide (Dordunoo *et al.*, 1991; Passerini *et al.*, 2002).

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