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Preparation of solid dispersions of glibenclamide for in-vitro dissolution enhancement

Khalid Bashir Mir, Nisar Ahmad Khan*

Department of Pharmaceutical Sciences, University of Kashmir, Srinagar, J&K, India

ABSTRACT

The purpose of this study was to prepare solid dispersions (SD) of Glibenclamide (GLB) and evaluate them for in-vitro drug release enhancement. Glibenclamide is a second generation sulfonylurea antidiabetic drug used to control blood glucose in type 2 diabetic patients, but poor-water solubility is responsible for its low oral bioavailability which has severely restricted it in the clinical application for diabetic control. Therefore, to increase the aqueous solubility and thereby, in-vitro dissolution of glibenclamide, solid dispersions were prepared with poloxamer-188in the ratio of 1:1, 1:2; 1:4 & 1:6 by solvent evaporation method in ethanol after conducting preliminary screening for the selection of best carrier and ratio for the development of solid dispersion of glibenclamide . Among the prepared SD formulations, GLB-SD_4 (1:6 Drug: Carrier ratio) showed highest enhancement in solubility and in-vitro dissolution rate in phosphate buffer (pH 6.8). In-vitro drug release profiles revealed that the drug release (%) of glibenclamide from GLB-SD_4 was achieved 6-fold higher than pure drug after 180 mins. It is worth noting that GLB-SD_4 provided the highest solubility and in-vitro dissolution rate compared to rest of the SD formulations, pure glibenclamide, market formulation and physical mixtures of glibenclamide in the same medium (Phosphate Buffer pH 6.8) as per the following manner: GLB-SD_4 > GLB-PM_4 > GLB-MF>Pure GLB. This may be due to more reduction in particle size at molecular level, enhanced wetting properties and better solubilization of P-188 and use of ethanol. The hydrogen bonding interactions between the drug and carrier in the final solid dispersion formulation (GLB-SD_4) was detected by Fourier Transform Infrared (FTIR) spectroscopy. These results demonstrated that the carrier (P-188) proved effective in improving the solubility of a poorly soluble glibenclamide, thereby endorsing the application of solid dispersion technology for the enhancement of solubility and thereby, in-vitro dissolution rate of glibenclamide.

Keywords: Glibenclamide, Solid dispersion, Solubility, In-vitro dissolution, Fourier Transform Infrared.

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***Address for Correspondence:**

Nisar Ahmad Khan, Department of Pharmaceutical Sciences, University of Kashmir, Srinagar, J&K, India

1. INTRODUCTION

Glibenclamide, also known as glyburide belongs to the second generation of oral anti-diabetic class of sulphonylurea. The chemical name of glibenclamide is 5-Chloro-N-(2-{4-[(cyclohexylcarbamoyl) sulfamoyl] phenyl} ethyl)-2-methoxybenzamide and chemical formula is $C_{23}H_{28}ClN_3O_5S$ (Figure 1).

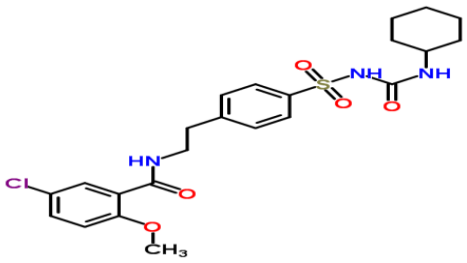

Figure 1 Chemical Structure of Glibenclamide

The aqueous solubility of glibenclamide is 0.0025 mg/ml. [1] There are two types of diabetes mellitus i.e. type 1 diabetes mellitus (T_1DM) and type 2 diabetes mellitus (T_2DM). T_1DM is known as insulin-dependent diabetes mellitus, in which there is usually the autoimmune destruction of β-cells of pancreatic islets due to which the production of insulin is impaired. T_2DM is known as non-insulin dependent diabetes mellitus in which there is either resistance to insulin and/or abnormal insulin secretion from β-cells of pancreatic islets. [2-4] Glibenclamide is most frequently used as a drug of choice for the treatment of T_2DM. Glibenclamide works by inhibiting the sulphonylurea receptor in β-cells of the pancreatic islets that ultimately leads to the opening of voltage-dependent calcium channel. This results in the increased concentration of intracellular calcium in β-cells that subsequently leads to the stimulation of insulin release. [5]

The present study was aimed to develop a formulation, which efficiently enhanced the aqueous solubility and in-vitro dissolution rate of glibenclamide. The various approaches investigated till date includes particle size reduction, complexation and solid dispersion. [6] Among all these, solid dispersion is one of the most applicable formulation strategies extensively studied to improve the aqueous solubility and thereby, enhancement of in-vitro dissolution rate. [7] The methods of preparation include melting, solvent evaporation, etc. Poloxamer-188 had been previously shown to enhance drug solubilization in phosphate buffer. [8] The solid dispersion could improve solubility and in-vitro dissolution rate of a poorly water-soluble drug by dispersing it at the molecular level in a biologically inert solid carrier.

2. MATERIALS & METHODS

Materials

Glibenclamide was obtained from Lark Laboratories, Delhi and the purity was >99%. Poloxamer-188 was obtained from cadila healthcare, Ahmedabad. Glibenclamide Tablets (Daonil, 10mg) were purchased from Sanofi Ltd. Ethanol was purchased from the supplier. All the other reagents and chemicals were of analytical grade.

Methods

2.1 Preliminary Screening of Carriers [9]

Various hydrophilic carriers (PEG-4000, PEG-6000, and Poloxamer-188) in different drug:polymer ratios (1:1, 1:2, 1:4, 1:6) were analysed for their solubility enhancing potential of glibenclamide in phosphate buffer (pH 6.8). The excess amount of pure drug (10 mg) was taken in separate 25 ml conical flasks and 15 ml of buffer was added to each flask. Then, the carriers were added as per the plan discussed in the Table 1. Both, weight of drug and volume of buffer were kept constant in each flask. The conical flasks were put in an orbital shaker (Remi orbital shaking incubator RIS-224BL) for 48 hours at 100 rpm at 37±0.5˚ C. Then, the solutions were kept for equilibration for 6 hours and then filtered through 0.45 µm filter. Each filtrate was suitably diluted with buffer and the amount of drug dissolved in buffer was estimated by UV Spectrophotometric (Labomed UVD 2950) method at λmax 300 nm.

2.2 Preparation of solid dispersions (SDs) [10]

The solid dispersions of glibenclamide with poloxamer-188 were prepared by a conventional solvent evaporation method. The weight ratios (1:1, 1:2, 1:4, 1:6) of drug to carrier were taken in different beakers containing ethanol. The beakers were placed in a water bath held at 40˚ C, till the solvent got evaporated completely from the solution in each beaker. Then the preparations were cooled immediately and kept overnight for solidification at room temperature. The solidified mass was pulverized by a pestle and the powder was passed through a 250 µm sieve to get uniformly sized particles and then the collected mass was stored in separate glass vials with tight lid and put in a dessicator till further analysis.

2.3 Percent Practical yield (%PY) [11, 12]

Solid dispersions were collected and weighed to determine percent practical yield from the following equation. (Table 2 & Figure 2)

$$\%PY = \frac{\text{Mass of Solid Dispersions (Practical)}}{\text{Mass of drug \& } carrier\ used \text{ (Theoretical)}} \text{ x100}$$

2.4 Percent Drug Content (%DC) [11, 13]

Solid dispersions equivalent to 10 mg of glibenclamide were weighed accurately and dissolved in 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 275 nm by UV spectrophotometrically. The drug content (%) was calculated using the following equation: (Table 3& Figure 3)

$$\%DC = \frac{\text{Amount of Solid Dispersions (Practical)}}{\text{Amount of Solid Dispersions (Theoretical)}} \text{ x100}$$

2.5 Preparation of physical mixtures (PMs) [14]

Physical mixtures were prepared with glibenclamide and poloxamer-188 at the same weight ratios as discussed in the preparation of solid dispersions. In this, each component (drug and carrier) were accurately weighed out and simply triturated in the mortar with pestle for 15 minutes. The powder was passed through 250 µm sieve and the mass collected was stored in glass vial with tight lid and kept in a dessicator till further analysis.

2.6 Saturation Solubility Studies [14, 15]

Saturation solubility studies of solid dispersions and physical mixture were conducted according to the method reported by Hecq et al. The solid dispersion and physical mixture formulations containing equivalent amount of drug (10 mg) were placed in a 25 ml conical flask with glass stopper containing 15 ml of buffer. The samples were placed in orbital shaker, agitated for 48 hours at 37±0.5 C until equilibrium was achieved and the aliquots were filtered through 0.45 µm filter. The filtered samples were suitably diluted with buffer and amount of glibenclamide estimated by UV-Spectrophotometrically at λmax 300 nm. (Table 4 & Figure 4)

2.7 Fourier Transform Infra-Red Spectroscopy (FTIR) [16, 17]

FTIR Spectroscopic analysis was carried using FTIR (Nicolet™ iS5, ART module, Thermo Fisher Scientific, USA) by the potassium bromide pressed pellet technique. The samples, pure glibenclamide, poloxamer-188 and solid dispersion were dried at 35˚ C for half an hour to ensure complete removal of moisture. The sample was scanned in 4000–400 cm^{-1} region with the resolution of 4 cm^{-1} (Figure 5.a, b, c)

2.8 In vitro dissolution rate [18, 19, 20]

The in-vitro dissolution study was carried in USP Type II dissolution rate test apparatus (Bells India) using the paddle method. The release of glibenclamide was estimated by putting 10 mg pure glibenclamide and 10 mg equivalent of glibenclamide of solid dispersions, physical mixtures and market formulation (Daonil, 10mg). The in-vitro dissolution conditions maintained during the evaluation were, stirring rate of 100 rpm, temperature of 37±0.5 ˚ C, 900 mL of phosphate buffer (pH 6.8) as dissolution medium and 5 ml of the dissolution samples were withdrawn from the dissolution vessel at predetermined time intervals at 15, 30, 60, 90, 120, and 180 minutes and simultaneously replenished with the addition of an equal volume of fresh dissolution medium maintained at the same temperature to keep the volume of dissolution medium constant and to maintain the sink conditions. The withdrawn samples were immediately filtered through 0.45 µm filter and the filtrate was suitably diluted and amount of glibenclamide was estimated UV Spectrophotometrically at 300 nm at each time interval. (Table 5, 6 & Figure 6, 7)

3. RESULTS & DISCUSSION

3.1Preliminary Screening of Carriers

The preliminary screening of carriers was carried out as per the method discussed in section 2.1. It was observed that out of the three carriers, poloxamer-188 potentially enhanced the solubility more than PEG-4000 & PEG-6000 in the same medium and it was also found that the solubility of glibenclamide increased with increasing amount of the carrier and within the poloxamer-188 ratios, 1:6 recorded highest solubility of glibenclamide. So, on the basis of this screening, the poloxamer-188 was selected for further experimentation.

Table1 Preliminary Screening of Carriers

Drug	Polymer	D:P Ratio	Drug (mg)	Carrier (mg)	Solvent	Solvent (ml)	Solubility (mg/ml) (±SD) n=3
GLB Pure							0.0025±0.0008
GLB	PEG-4000	1:1	10	10	Phosphate Buffer pH 6.8	15	0.042 ± 0.004
		1:2		20			0.057±0.001
		1:4		40			0.066±0.006
		1:6		60			0.071±0.003
	PEG-6000	1:1	10	10	Phosphate Buffer pH 6.8	15	0.044±0.006
		1:2		20			0.061±0.002
		1:4		40			0.077±0.004
		1:6		60			0.089±0.002
	P-188	1:1	10	10	Phosphate Buffer pH 6.8	15	0.122±0.005
		1:2		20			0.213±0.007
		1:4		40			0.248±0.005
		1:6		60			0.488±0.006

3.2 Percent Practical yield

The practical yield of solid dispersions was found to be between 91.66 % to 92.84 %. This reveals the efficiency of the method of preparation.

Table 2: Percent Practical Yield of SDs of GLB (±SD); n=3

Formulation Code	Drug	Carrier	Drug-Carrier Ratio	Drug Content (%)
GLB-SD_1	GLB	P-188	1:1	92.66±0.04
GLB-SD_2			1:2	92.64±0.02
GLB-SD_3			1:4	92.67±0.06
GLB-SD_4			1:6	92.66±0.05

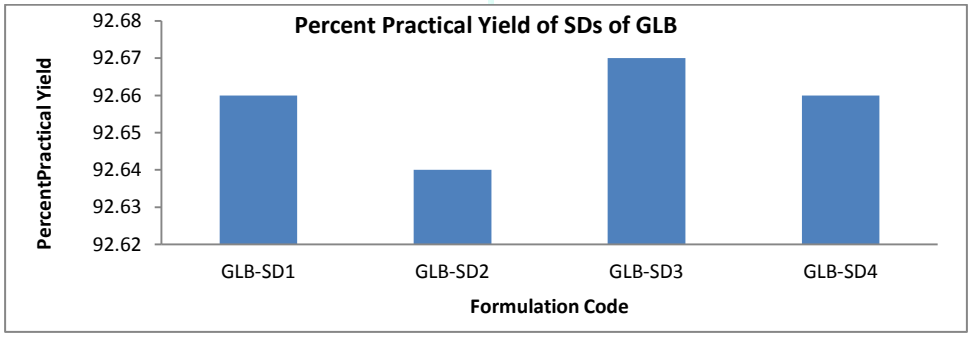

Figure 2 Percent Practical Yield of SDs of GLB

3.3 Percent Drug Content

The drug content of solid dispersions was found to be between 99.76% to 99.78%.

Table 3Percent Drug Content of SDs of GLB (±SD); n=3

Formulation Code	Drug	Carrier	Drug-Carrier Ratio	Drug Content (%)
GLB-SD_1	GLB	P-188	1:1	99.76±0.002
GLB-SD_2			1:2	99.76±0.003
GLB-SD_3			1:4	99.78±0.003
GLB-SD_4			1:6	99.76±0.001

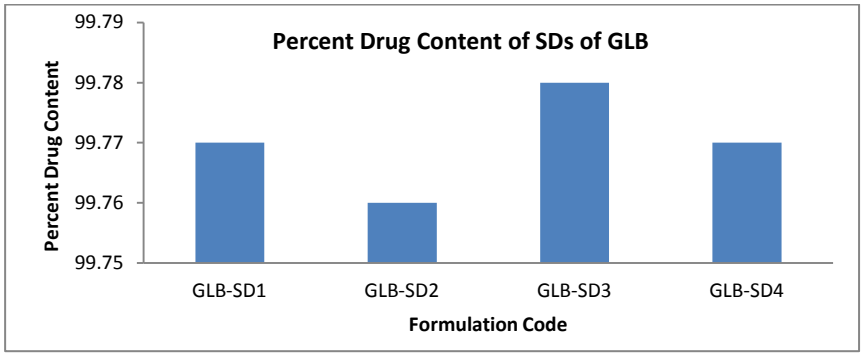

Figure 3 Percent Drug Content of SDs of GLB

3.4 Saturation Solubility Studies

Table 4 Saturation Solubility Studies of SDS & PMs of GLB

Formulation Code	Drug	Carrier	D:C Ratio	Solubility (mg/ml) (±SD); n=3
GLB Pure				0.0025±0.02
GLB-SD$_1$	GLB	P-188	1:1	0.255±0.01
GLB-SD$_2$			1:2	0.345±0.05
GLB-SD$_3$			1:4	0.531±0.03
GLB-SD$_4$			1:6	0.643±0.02
GLB-PM$_1$			1:1	0.052±0.05
GLB-PM$_2$			1:2	0.083±0.03
GLB-PM$_3$			1:4	0.132±0.02
GLB-PM$_4$			1:6	0.199±0.01

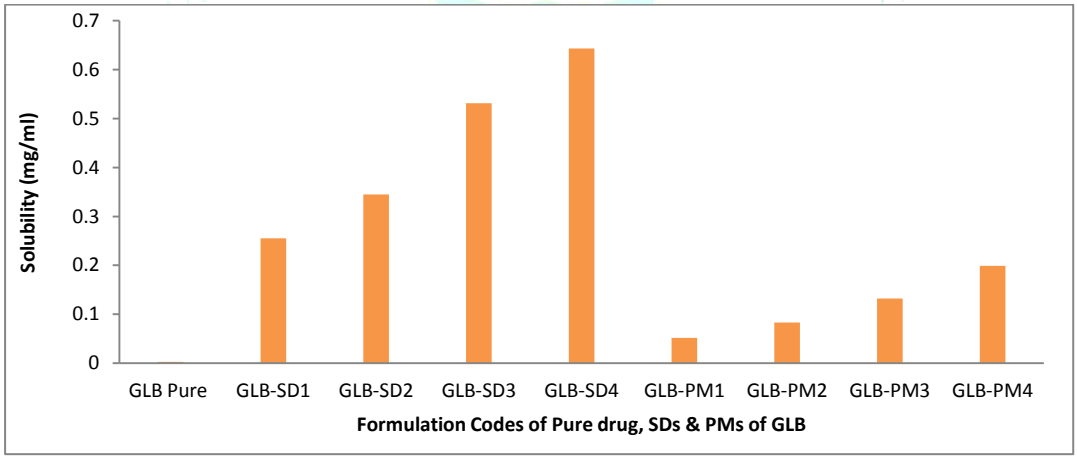

Figure 4: Saturation Solubility Studies of SDs and PMs of GLB

3.5 Fourier Transform Infra-Red Spectroscopy (FTIR)

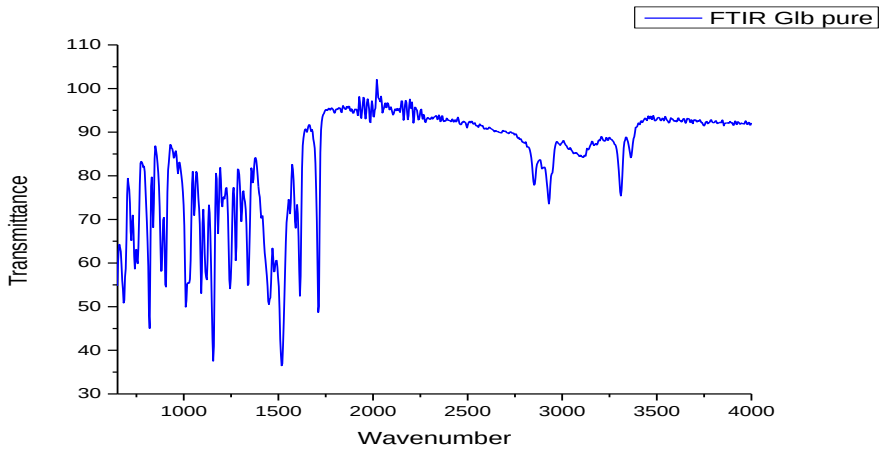

Figure 5.a FTIR of GLB Pure

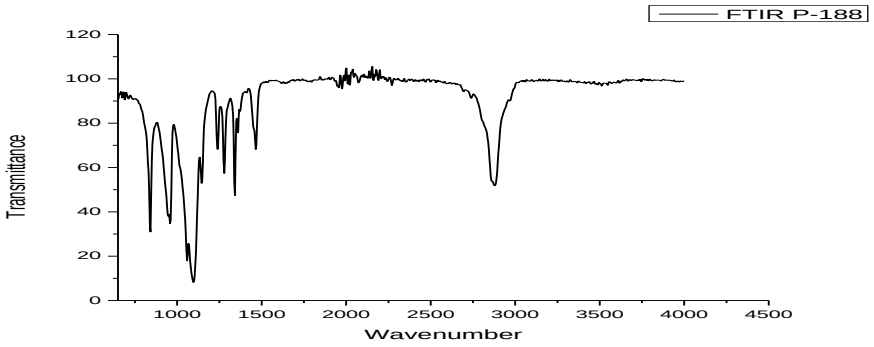

Figure 5.b FTIR of P-188

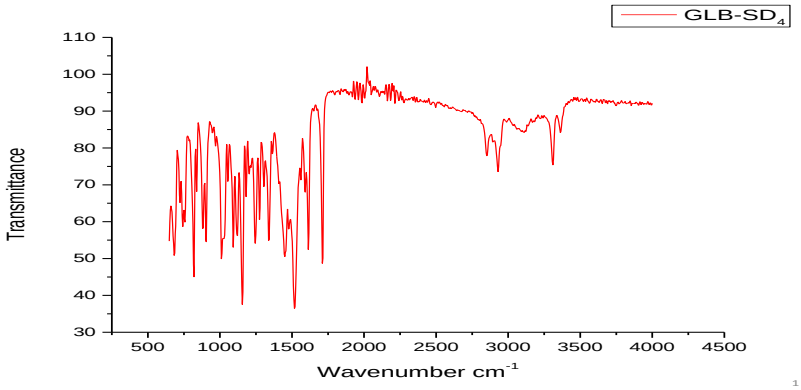

Figure 5.c FTIR of GLB-SD4

3.6 In-vitro dissolution studies

The solid dispersion formulation (GLB-SD4) having 1: 6 glibenclamide and poloxamer-188 ratio showed highest in vitro dissolution in the phosphate buffer than the rest of the solid dispersion formulations. The enhancement was approximately recorded as 6 fold higher than the pure glibenclamide in the same buffer conducted under same conditions as in dissolution of GLB-SD4. It was also, observed that the GLB-SD4 showed higher in-vitro dissolution than the physical mixtures prepared and market formulation.

Table 5 in-vitro drug release of pure drug, SDs and MF of GLB in PB (pH 6.8) (± SD); n = 3

Time (mins)	Drug Released (%)					
	GLB-Pure	GLB-SD1	GLB-SD2	GLB-SD3	GLB-SD4	GLB-MF
15	01.58	09.07	18.77	29.44	36.67	06.96
30	03.87	19.67	27.78	37.33	43.49	15.89
60	06.45	28.88	36.68	41.99	53.65	21.67
90	09.76	39.65	43.79	51.01	64.88	28.54
120	11.57	45.89	54.77	64.67	77.17	37.78
180	15.66	51.76	64.89	72.76	90.12	41.97

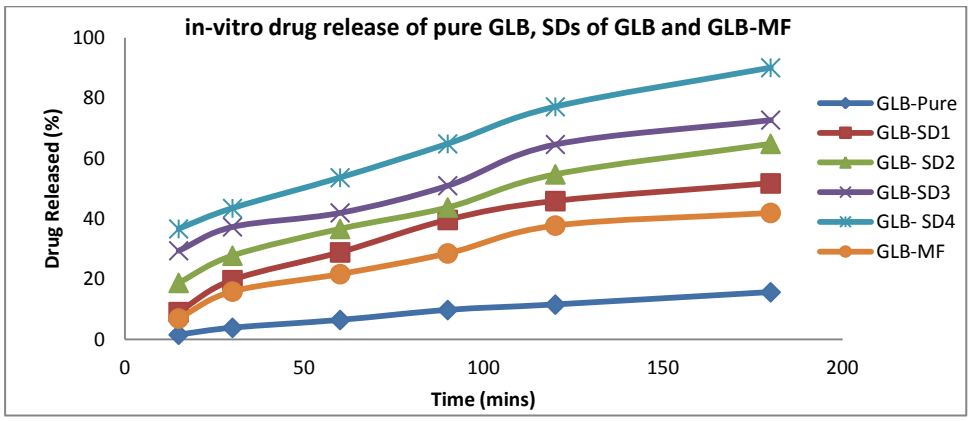

Figure 6 in-vitro release of Pure drug, SDs and MF of GLB in PB (pH 6.8) (± SD); n = 3

Table 6 in-vitro drug release of pure drug and PMs of GLB in PB (pH 6.8) (± SD); n = 3

Time (mins)	Drug Released (%)				
	GLB-Pure	GLB-PM1	GLB-PM2	GLB-PM3	GLB-PM4
15	01.58	04.12	06.11	08.98	07.34
30	03.87	08.11	10.71	13.12	15.45
60	06.45	12.87	14.99	17.89	22.78
90	09.76	15.34	18.11	22.78	30.87
120	11.57	17.99	22.89	28.76	36.67
180	15.66	22.34	27.67	33.45	43.87

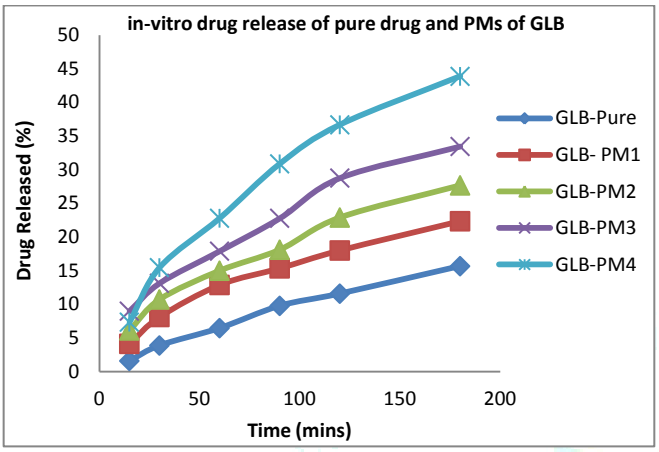

Figure 7 in-vitro release of Pure drug, SDs and MFT of GLB in PB (pH 6.8) (± SD); n = 3

4 CONCLUSIONS

SDs of glibenclamide in poloxamer-188 were successfully prepared by the solvent evaporation method with excellent yield and the drug: polymer ratio significantly influenced GLB dissolution rate, as higher amounts of hydrophilic carrier led to enhanced drug dissolution i.e., 1:6 GLB: P-188 ratio showed highest dissolution than rest of the SDs of glibenclamide, pure glibenclamide, market formulation and physical mixtures in phosphate buffer pH 6.8. The FTIR characterization revealed that there is hydrogen bonding interactions between drug and carrier. Thus, the present study demonstrated that SDs of GLB in P-188 prepared by the solvent evaporation method showed to be an effective way to overcome problems related to the poor aqueous solubility of this drug, improving its dissolution and thereby serving as a good release system for use in pharmaceutical formulations.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

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