RESEARCH ARTICLE

Formulation and evaluation of glimepiride solid dispersion tablets

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Glimepiride (GMP) is poorly water soluble drug, so solubility is the main constraint for oral its bioavailability. An attempt has been made to increase the solubility of this model drug by formulating solid dispersion (SD) using Poloxamer 188 (PXM 188) as polymer and then formulating SDs tablets of the best formulation of SDs. Tablet formulations were prepared by direct compression technique using superdisintegrant croscarmellose sodium in different concentrations. SDs were evaluated for XRD, SEM, *in vitro* dissolution profiles, and dissolution efficiency, and developed tablet formulations were evaluated for various pharmaceutical characteristics viz. hardness, % friability, weight variation, drug content, disintegration time, *in vitro* dissolution profiles, and dissolution efficiency. Among different formulations of SDs, SD containing drug is to polymer ratio 1 : 4 gives best dissolution profile and dissolution efficiency and among tablet formulations, formulations containing 5% croscarmellose sodium gives best disintegration and dissolution profiles compared with other formulations. Results showed that poloxamer is a promising polymer for enhancing the solubility of GMP.

Key words: *Glimepiride, poloxamer 188, solid dispersions, solid dispersion tablets*

INTRODUCTION

The sparingly water-soluble drugs often show an erratic dissolution profile in gastrointestinal (GI) fluids, which consequently results in variable oral bioavailability.[1] To improve the dissolution and bioavailability of sparingly soluble drugs, researchers have employed various techniques, such as micronization, solubilization, salt formation, complexation with polymers, change in physical form, use of prodrug and drug derivatization, alteration in pH, addition of surfactants, and others.[2] Chiou and Rigelman and Serajuadin *et al*. have used the solid dispersion (SD) technique for dissolution enhancement of poorly water-soluble drugs.[3,4] Among the various approaches, the SD technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble active pharmaceutical ingredients because it is simple, economic, and advantageous.[5] Sekiguchi and Obi were the first to propose the SD method using water-soluble carriers to improve the dissolution characteristics of poorly water-soluble drugs.[6] In this method, the drug is thoroughly dispersed in a water-soluble carrier by melting, solvent, or solvent-melting methods.[3] Many water-soluble carriers have been employed for preparation of SD of poorly soluble drugs. The most common are polyethylene glycols,[7,8] polyvinyl pyrrolidone,[9,10] lactose,[11] β-cyclodextrin,[12,13] and hydroxypropyl methylcellulose.[14] Recently, poloxamers, a group of block copolymer nonionic surfactants, have attracted considerable attention for application in preparation of SDs.[15-17] These polymers are widely used as emulsifiers, solubilizing agents, and suspension stabilizers in liquid, oral, topical, and parenteral dosage forms and also act as wetting agents and plasticizers, and have been reported for enhancing the solubility and bioavailability of sparingly soluble drugs in solid dosage forms.[18,19] Nine grades of poloxamers have been evaluated by Saettone *et al.*[20] as solubilizers for tropicamide, a poorly water-soluble drug. Solubility was found to increase as the oxyethylene content increased. Poloxamer 188 (PXM 188) is a nonionic block copolymer composed of two hydrophilic polyoxyethylene chains and connected by a hydrophobic polyoxypropylene chain, and has been used by researchers to increase the aqueous solubility of poorly water-soluble drugs.[21-23,24-26] PXM 188 was thus selected as a carrier for dissolution enhancement of a poorly water-soluble drug.

Glimepiride (GMP), belonging to BCS II,[27] is a third generation oral hypoglycemic drug used to treat type II diabetes mellitus.[28] It has shown high anti-diabetic activity and is very effective in type II diabetes mellitus in addition to low toxicity.[24] However, GMP is

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practically insoluble in aqueous fluids, and as such its oral absorption is dissolution rate limited. Therefore, it displays poor solubility in GI fluids, which results in low and erratic oral bioavailability.[28] It was selected as a model drug for dissolution enhancement studies in the present investigation. Attempts were made to enhance the dissolution of GMP using a SD technique. SDs of GMP-PXM 188 were prepared in different ratios using the melting method, and then tablets of best formulation of SD were formulated by using direct compression method. SDs were evaluated for XRD, SEM, *in vitro* dissolution profiles, and dissolution efficiency, and developed tablet formulations were evaluated for various pharmaceutical characteristics viz. hardness, % friability, weight variation, drug content, disintegration time, *in vitro* dissolution profiles, and dissolution efficiency.

MATERIALS AND METHODS

GMP was obtained from Nicolas Piramal India Ltd, Baddi as a gift sample; PXM 188, croscarmellose sodium, and Avicel PH 102 were obtained from Signet Chemicals Pvt. Ltd., Mumbai. Magnesium stearate and talc were obtained from Central Drug House (P) Ltd., Mumbai.

Preparation of solid dispersions, and determination of drug content

Melting method was used for the preparation of SDs. Seven different drug : carrier ratios (1 : 1, 1 : 2, 1 : 3, 1 : 4, 1 : 5, 1 : 6, 1 : 7) were used [Table 1]. GMP and PXM 188 were weighed according to these weighed ratios. PXM 188 was melted (melting point - 40°C) and GMP was added into it. It was mixed well and flashed cooled in an ice bath and then stored over night in a dessicator. The prepared SD was then grounded by using a mortar and pestle, sieved through a mesh 40, and stored over a fused calcium chloride in a dessicator for further use. Drug content was calculated by dissolving SDs equivalent to 10 mg GMP in a suitable quantity of methanol, filtering (0.45 μm, Whatman), suitably diluting with methanol, and analyzing by ultraviolet (UV) spectrophotometer at 226 nm.

Preparation of physical mixture

Physical mixture of drug : PXM 188 in 1 : 5 ratio (PM) was prepared by thoroughly mixing the accurately weighed quantity of drug and carrier for 5 minutes in glass mortal, which was then passed through mess number 40 and stored in a dessicator.

Powder X-ray diffraction

XRD patterns were recorded using Philips PW 1729 X-ray generator (computer 1710). Powder X-ray diffraction patterns were traced for GMP, various carriers, and SDs.

Electron microscopy

The external morphology of SDs was analyzed by Scanning Electron Microscopy (SEM). The samples were examined under a scanning electron microscope (JSM 6100 JEOL, Japan).

In vitro drug release

Accurately weighed preparations equivalent to 10 mg of GMP were added to 900 ml of dissolution media (6.8 phosphate buffer) in a USP dissolution apparatus II (Paddle type) and stirred at a speed of 50 rpm at 37±0.5°C. Five milliliter aliquots were withdrawn at 2, 4, 6, 8, 10, 15, 20, 25, 30 minutes and replaced by 5 ml of fresh dissolution media (37°C). The collected samples were analyzed after suitable dilution (if required) at 226 nm using UV-visible spectrophotometer against the blank. Drug release studies were carried out in triplicate. The dissolution of pure GMP was done similarly. The release profile data were analyzed for cumulative percent dissolved at different time intervals and for dissolution efficiency at 6 and 10 minutes.

Formulation of glimepiride solid dispersions tablets

GMP SD tablets of GP4 formulation were prepared by direct compression method using single punch tablet machine. GP4 formulations were chosen as they have shown high dissolution rate and maximum dissolution efficiency. Five milligram equivalent SD was taken for each formulation. Tablets were prepared with or without using Ac-Di-Sol as superdisintegrant. The concentration of superdisintegrant varies from 2 to 5% in tablet formulations. All the ingredients [Table 2] were co-grounded in a glass pestle motor (except talc and magnesium stearate) and were passed through mesh number 60. Finally, talc and magnesium stearate were added and mixed for 5 minutes. The mixed blend of drug and excipients was compressed using a single punch tablet machine to produce flat-faced tablets weighing 80 mg each, with ≈3.2 mm thickness and 5 mm in diameter.

Table 1: Composition of glimepiride-poloxamer 188 solid dispersions

Formulation number	Drug: Carrier ratio
GP1	1:1
GP2	1:2
GP3	1:3
GP4	1:4
GP5	1:5
GP6	1:6
GP7	1:7

Table 2: Composition of glimepiride solid dispersion tablets

Ingredients	T1	T2	T3	T4	T5
GP4	25	25	25	25	25
Ac-Di-Sol	–	1.6	2.4	3.2	4
Avicel PH 101	51	49.4	48.6	47.8	47
Talc	2.4	2.4	2.4	2.4	2.4
Magnesium stereate	1.6	1.6	1.6	1.6	1.6

Evaluation of blends

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing step and all these can affect the characteristics of blend produced. The various characteristics of blends tested are bulk density, tapped density, compressibility index, Hausner ratio, and angle of repose.

Evaluation of glimepiride solid dispersion tablets

All prepared tablets were evaluated for drug content, friability, hardness, thickness, and weight variation and *in vitro* disintegration time. Friability was determined using Roche friabilator. Hardness was measured using Pfizer hardness tester. Thickness was measured using Vernier Caliper.

Content uniformity

Ten randomly selected tablets of each formulation were weighed and average weight was calculated, and the tablets were powdered in a glass mortar pestle. The weight equivalent to 5 mg GMP was weighed. The weighed amount was dissolved in 5 ml of dichloromethane in separate 10 ml volumetric flask using magnetic stirrer; the volume was adjusted to 10 ml with methanol, and the solution was filtered. An aliquot of 0.2 ml from this solution was diluted to 10 ml with methanol in separate volumetric flask. The content in each formulation was determined spectrophotometrically at 226 nm.

***In vitro* disintegration test**

The *in vitro* disintegration time was determined using Disintegration Test Apparatus. This device uses six glass tubes that are three inches long, open at the top, and held against a 10-mesh screen at the bottom end of the basket rack assembly. To test for disintegration, one tablet was placed in each of the six tubes of apparatus and one disc was added to each tube. The basket rack assembly was positioned in 1 l of pH 6.8 phosphate buffer at 37± 2°C. The time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in minutes.

***In vitro* dissolution test for tablet formulations**

In vitro dissolution studies for all the fabricated tablets were carried out using USP paddle method in 900 ml of phosphate buffer (pH 6.8) as dissolution media, maintained at 37±0.5°C at 50 rpm. Five milliliter aliquots were withdrawn at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60 minutes and replaced by 5 ml of fresh dissolution media (37°C). The collected samples were analyzed after suitable dilution (if required) at 226 nm using UV-visible spectrophotometer against phosphate buffer (pH 6.8) as the blank.

The release profile data were analyzed for cumulative percent dissolved at different time intervals and for dissolution efficiency at 15, 30, and 60 minutes.

RESULTS AND DISCUSSION

GMP assay in all SDs was almost more than 99% and also the low values of standard deviation indicate that the drug was uniformly distributed in SDs. Hence, the method used to prepare SDs was found to be reproducible.

The X-ray diffractograms [Figure 1] of pure GMP (A) and pure PXM 188 (B) show that both are crystalline in nature. The XRD of SD (GP4 formulation) shows peaks corresponding to GMP and also the peaks related to PXM 188 persists (C). But, the GMP peaks with reduced peak height and area was observed, suggesting reduced crystallinity of GMP in GP4 formulation.

In scanning electron microscopy [Figure 2], GMP appeared in a crystal form (A) and PXM 188 as smooth-surfaced spherical particles (B). In SD, the crystals of GMP were dispersed between the carrier (PXM 188) in the GP4 formulation, which demonstrated that the drug was thoroughly mixed in the carriers with the loss of little crystallinity (C).

Cumulative amount of GMP dissolved from pure GMP was lower compared with SDs and physical mixtures [Figure 3]. At the end of 6 minutes, approximately 16.13, 23.66, 70.47, 77.71, 82.46, 85.54, 86.00, 86.86, and 87.84% of GMP was released from GMP physical mixture and 1 : 1, 1 : 2, 1 : 3, 1 : 4, 1 : 5, 1 : 6, and 1 : 7 (w/w) SDs, respectively. Enhanced solubility and dissolution rate of GMP from physical mixtures could be correlated to the chemical structure of highly water soluble PXM 188. Arrangement of ethylene oxide (EO) and propylene oxide (PO) blocks in PXM 188 results in an amphiphilic structure that has the property

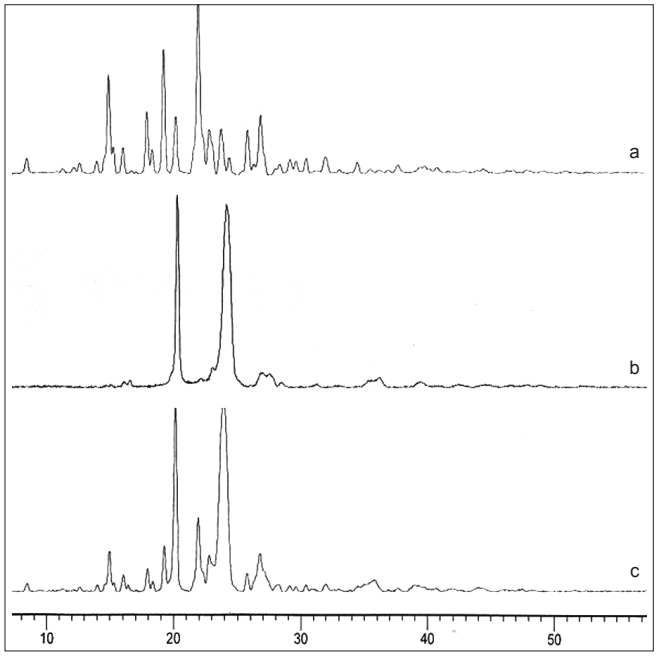

Figure 1: XRD patterns of glimepiride (a), poloxamer 188 (b) and solid dispersion (c)

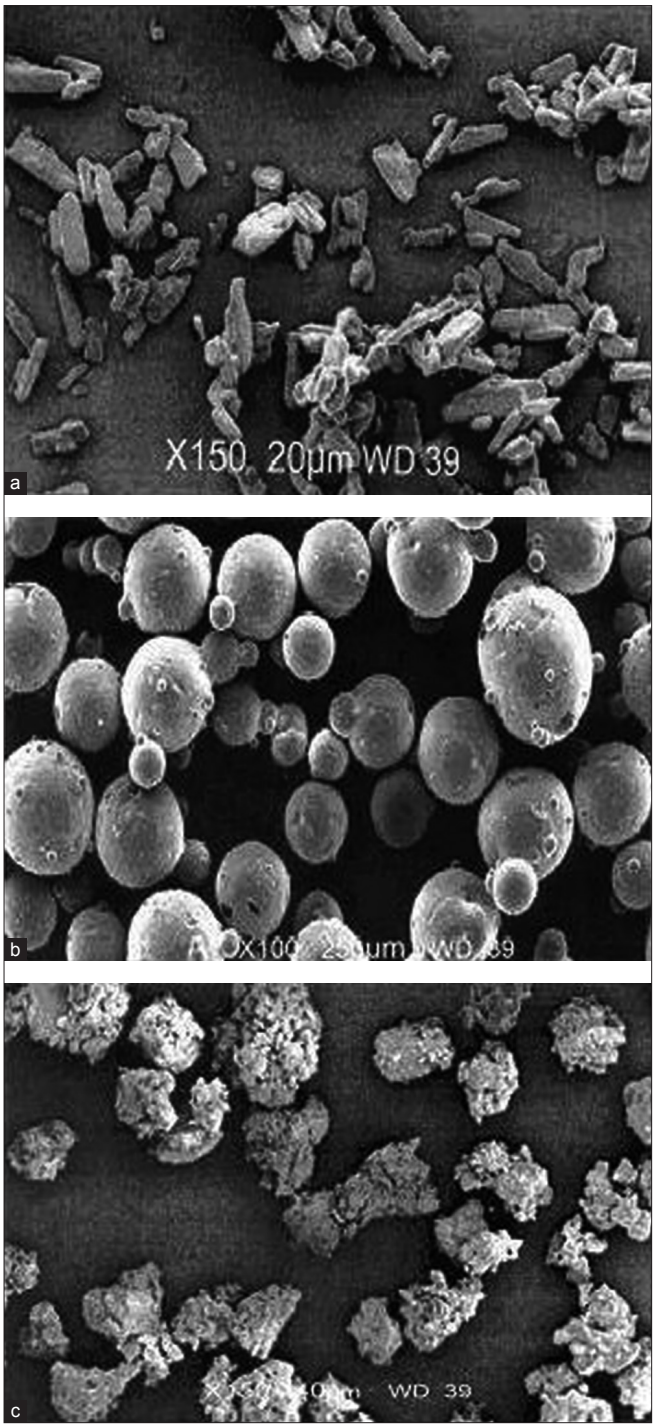

Figure 2: Scanning electron micrographs: (a) glimepiride, (b) poloxamer 188 and (c) 1:4 solid dispersions

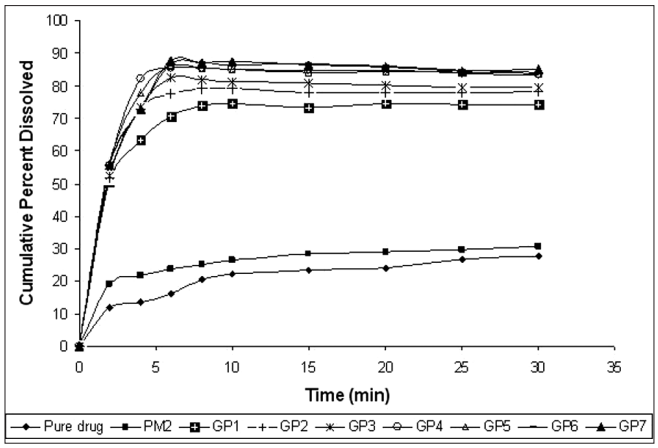

Figure 3: Cumulative percent release of glimepiride from solid dispersions and physical mixtures of glimepiride-poloxamer 188 systems

Table 3: Dissolution efficiency of glimepiride-poloxamer 188 solid dispersions

Formulation number	Dissolution efficiency (%)	
	DE_6	DE_{10}
Pure drug	9.19	13.39
PM2	14.38	18.65
GP1	41.31	54.09
GP2	46.76	59.61
GP3	47.05	60.97
GP4	50.85	64.70
GP5	49.61	63.99
GP6	47.90	63.52
GP7	48.27	62.94

to self-assemble into micelles in aqueous solution;[25] the hydrophobic core (PO block) can act as reservoir for the drug, while the hydrophilic portion (EO) acts as interface between the aqueous medium and the drug. At low concentrations, approximating those at which more conventional nonionic detergents form micelles, the poloxamer monomers are thought to form monomolecular micelles by a change in configuration in solution. At higher concentration, these monomolecular micelles associate to form aggregates of varying size, which have the ability to solubilize drugs and to increase the stability of solubilized agents.[26] Solubilization is likely to occur through the following mechanism: in the dry state, drug particles were in close contact or adhered to the polymer particles as a result of mixing (shown by SEM); when the mixture came in contact with water, the polymer particles might have hydrated rapidly into polymer solution, solubilizing the adjacent drug particles and subsequently releasing the drug into the medium. Furthermore, reduction in crystallinity of GMP crystals in SD formulation (partially amorphization) and particle size reduction of GMP crystals are the additional reasons for improving the solubility and thus dissolution rate of GMP.

Dissolution efficiency of pure GMP and all the SD formulations at 6 minutes and 10 minutes were calculated [Table 3]. As the dissolution time was increased from 6 to 10 minutes, the dissolution efficiency was increased in all the formulations. Among the formulations, GP4 has shown maximum dissolution efficiencies of 50.58 and 64.70% at 6 minutes (DE_6) and 10 minutes (DE_{10}), respectively.

The characterization of mixed blend was done for determination of mass-volume relationship parameters. The evaluated parameters are bulk density, tapped density, Hausner's ratio, compressibility index, and angle of repose [Table 4].

The bulk density of mixed blend varied between 0.379 and 0.402 gm/cm^3, indicating good packaging capacity of tablets. The tapped density was found in the range of 0.387 to 0.419 gm/cm^3. The Hausner's ratio was found between 1.021 and 1.061. The compressibility index was found between 2.067 and 5.764. The angle of repose was found to be 24.43 to 26.43°.

The diameter of the tablet was found to be 5.034 mm. The thickness of the tablet was found to be 3.14 mm. The average weight of the prepared tablet was between 78.52 and 83.06 mg. So, it was predicted that all the tablets exhibited uniform weight with low standard deviation values within the acceptable variation as per IP [Table 5].

The hardness of the prepared tablet varied from 3.2 to 3.9 kg/cm^2 [Table 5], which has satisfactory strength to withstand the applied mechanical shocks.

The friability of all the formulations was found to be less than 1.0%, which shows the durability of the prepared tablets; resistance to loss of weight indicates the tablet's ability to withstand abrasion in handling, packaging, and shipment [Table 5].

In the formulation of GMP SD tablets, Ac-Di-Sol was used as a superdisintegrant in 2 to 5% concentration. The tablets containing superdisintegrant shows better disintegration properties when compared with T1 formulation in which no superdisintegrant was added. The disintegration time of these tablets varied from 7 to 30 minutes [Table 5]. The lack of disintegration of T1 could be related to the soft and waxy nature of carrier used (PXM 188). This carrier essentially acts as strong binders within tablets. During compression, the carrier would plasticize, soften, or melt, filling the pores within tablets and thus making them nondisintegrating. The drug content of all the tablet formulations was determined spectrophotometrically at 226 nm. It varied from 4.94±0.058 to 5.00±0.028 mg per tablet. The correlation of variation was found to be less than 0.058, indicating uniformity of the drug content in the prepared tablets.

In vitro drug release experiments of GMP SD tablets were performed at 37±1°C in three Basket dissolution apparatus. The results showed that as the concentration of the superdisintegrant (Ac-Di-Sol) was increased, the dissolution rate increased and also the drug was released faster. The maximum drug release was found in formulation T5 (86.95%). The disintegrant Ac-Di-Sol shows faster disintegration as its concentration was increased from 2 to 5% [Table 6 and Figure 4]. So the order of drug release was found to be as follows:

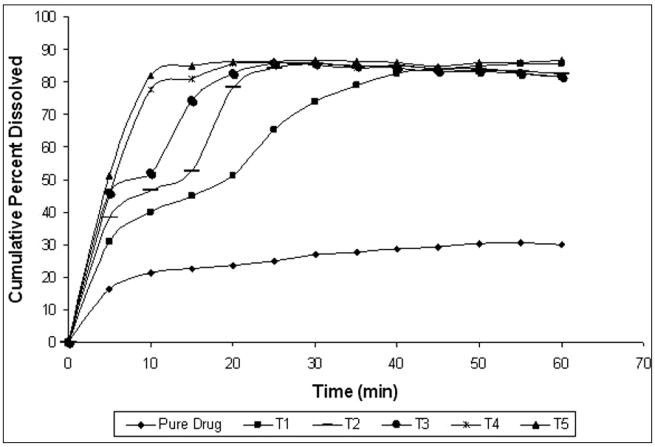

Figure 4: Cumulative percent release of glimepiride solid dispersion tablets of GP4 formulation

Table 4: Characterization of blends

Formulation number	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Compressibility index(%)	Angle of repose(°)
T1	0.391	0.405	1.035	3.456	25.32
T2	0.376	0.399	1.061	5.764	26.43
T3	0.398	0.407	1.022	2.211	25.54
T4	0.402	0.419	1.042	4.057	24.43
T5	0.379	0.387	1.021	2.067	26.13

Table 5: Characterization of glimepiride solid dispersion tablets

Formulation number	Diameter (mm)	Thickness (mm)	Weight (mg)	Hardness (Kg/cm^2)	Friability (%)	Disintegration time (Minutes)
T1	5.034	3.14	80.08±2.09	3.6±0.31	0.54±0.10	7
T2	5.034	3.14	81.64±2.04	3.2±0.14	0.79±0.09	11
T3	5.034	3.14	78.52±1.94	3.4±0.16	0.62±0.13	14
T4	5.034	3.14	80.13±1.94	3.9±0.22	0.65±0.13	19
T5	5.034	3.14	83.06±1.88	3.7±0.28	0.47±0.19	30

Table 6: Dissolution release profile of glimepiride solid dispersion tablet formulations

Time (min)	Cumulative mean percent release±standard deviation					
	Pure drug	T1	T2	T3	T4	T5
5	16.37±0.81	30.85±1.12	38.21±0.59	45.95±0.59	45.44±0.39	51.25±0.67
10	21.45±0.98	39.98±0.59	46.62±0.97	51.99±0.59	77.58±0.97	82.00±0.59
15	22.63±0.22	44.91±1.74	52.78±0.81	74.36±0.39	81.02±1.24	84.95±0.77
20	23.59±0.45	51.19±0.45	78.18±0.59	82.56±0.98	85.79±0.77	86.46±0.22
25	25.13±0.39	65.22±0.78	84.48±0.59	85.67±0.22	85.99±0.81	86.46±0.45
30	27.06±1.25	74.09±0.78	85.54±0.22	85.69±0.01	85.29±0.81	86.72±1.25
35	27.65±1.12	79.03±1.19	84.65±0.39	84.90±0.22	84.39±0.98	86.33±0.22
40	28.80±0.98	82.67±0.78	84.89±0.59	84.38±0.22	85.03±1.02	85.94±1.79
45	29.19±1.25	83.85±1.17	84.12±0.98	83.35±0.45	83.99±0.97	84.78±2.13
50	30.35±0.97	84.89±0.98	83.60±0.022	83.47±0.89	84.38±0.98	85.93±0.58
55	30.55±0.81	85.67±0.98	83.21±0.59	82.69±0.39	82.70±0.68	86.07±0.59
60	29.97±0.59	85.68±1.19	82.82±1.25	81.53±0.67	81.53±1.17	86.59±0.67

Table 7: Dissolution efficiency of glimepiride solid dispersion tablets

Formulation number	Dissolution efficiency (%)		
	DE_{15}	DE_{30}	DE_{60}
Pure drug	13.65	19.09	24.58
T1	28.95	45.62	63.72
T2	32.53	55.48	69.79
T3	40.38	61.74	72.74
T4	47.44	66.39	75.01
T5	50.36	68.47	77.21

T5 >T4 >T3 >T2 >T1

Dissolution efficiency of all the GMP SD tablets formulations at 15, 30, and 60 minutes was calculated [Table 7]. As the dissolution time was increased from 15 to 60 minutes, the dissolution efficiency was increased in all the formulations. Among the formulations, T5 has shown maximum dissolution efficiency of 50.37, 68.48, and 77.21% at 15 (DE_{15}), 30 (DE_{30}), and 60 minutes (DE_{60}), respectively.

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