Available Online at www.jddt.in

ISSN: 2320 - 4230

*Journal of Drug Discovery and Therapeutics* 1 (6) 2013, 38-49

RESEARCH ARTICLE

# DEVELOPMENT OF SUSTAINED RELEASE DOSAGE FORM OF GLICLAZIDE

***Asija Rajesh, Dadarwal Poonam, Asija Sangeeta**

Maharishi Arvind Institute of Pharmacy, Department of Pharmaceutics, Mansarovar, Jaipur, Rajasthan, India

**ABSTRACT**

The main aim of present work was to prepare solid dispersion of poorly water soluble drug Gliclazide to enhance its i*n-vitro* dissolution rate and aqueous solubility of drug. Gliclazide is a second generation of hypoglycemic sulfonyl urea. The major drawback in the therapeutic application and efficacy of Gliclazide as oral dosage forms is its very low aqueous solubility because of its hydrophobic nature. It has short biological half-life, small dose (30-80 mg) hence suitable for solid dispersion and sustained release formulation. In present study, polyethylene glycol 6000 and PVP K-30 were selected as carrier because of their chemical and pharmacological inertness. Polyethylene glycol 6000 and PVP K-30 by virtue of their water solubility leads to high degree of solubilization of poorly soluble drug. After comparing the solubility and dissolution profiles of various solid dispersions, it was observed that solid dispersion such as SDPEG ½ or SDPVP ½ gave desired dissolution profile of Gliclazide (more than 80% release in first 120 min). *In-vitro* dissolution studies also revealed that SDPVP K-30 ½ has shown less percentage of drug release from tablet for first two to three hours than SDPEG ½. It may due to binding effect of PVP K-30.

**KEY WORDS:** Gliclazide, Poorly water soluble, I*n-vitro* dissolution, solid dispersion, Matrix tablet

## INTRODUCTION:

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles.[1] Oral drug delivery is the simplest and easiest way of administering drugs. Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosages forms have many advantages over other types of oral dosage forms. If these drugs are not completely released in this gastrointestinal area, they will have a low bioavailability. Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs.[2]

A number of methodologies can be adapted to improve solubilization of poor water soluble drug and further to improve its bioavailability. Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. Bioavailability depends on several factors, drug solubility in an aqueous environment and drug permeability through lipophilic membranes being the important ones.[3]

Ideally a sustained release oral dosage form is designed to release rapidly some predetermined fraction of the total dose in to GI tract. This fraction (loading dose) is an amount of drug, which will produce the desired pharmacological response as promptly as possible and the remaining fraction of the total dose (maintenance dose) is then release at a constant rate. The rate of the drug absorption from the entire maintenance dose into the body should equal to the rate of the drug removal from the body by all the processes over the time for which the desired intensity of pharmacological response is required[4,5]

Gliclazide is readily absorbed from gastrointestinal tract. It is extensively bound to plasma proteins. The half-life is about 6 to 12 hour. It is extensively metabolized in liver to metabolite without significant hypoglycemic activity. Metabolite and a small amount of unchanged drug are excreted in urine. Gliclazide is a second generation sulphonylurea which acts as a hypoglycemic agent. It stimulates β cells of the islet of Langerhans in the pancreas to release insulin. It also enhances peripheral insulin sensitivity. Overall, it potentiates insulin release and improves insulin dynamics. Gliclazide is freely soluble in dichloromethane, soluble in dilute solution of alkali hydroxide, sparingly soluble in acetone, practically insoluble in water and ethanol.

## MATERIALS AND METHODS:

### PREPARATION OF CALIBRATION CURVE OF GLICLAZIDE:



*Corresponding author: Asija Rajesh / Email: asijar@gmail.com

**Table 1: calibration curve of Gliclazide**

| **Calibration curve in pH 1.3 buffer solution** | | |
|---|---|---|
| **Preparation** | **Standard stock solution** | **Working stock solution** |
| The pH 1.2 buffer solution was prepared as per IP 1966 | Gliclazide, 10 mg, was accurately weighed and transferred to 100 ml volumetric flask. It was dissolved in pH 1.2 buffer and volume was made upto 100 ml. | A series of Gliclazide solutions ranging from 2 to 20 µg/ml were prepared from standard stock solution. The absorbance of the solutions was measured spectrophotometrically at 227 nm. |
| **Calibration curve in pH 6.8 buffer solution** | | |
| The pH 6.8 buffer solution was prepared as per IP 1996. | Gliclazide, 10 mg, was accurately weighed and transferred to 100 ml volumetric flask. It was dissolved in pH 6.8 buffer and volume was made upto 100ml. | A series of Gliclazide solutions ranging from 2 to 20 µg/ml were prepared from standard stock solution. The absorbance of solutions was measured spectrophotometrically at 227 nm. |
| **Calibration curve in pH 7.4 buffer solution** | | |
| The pH 7.4 buffer solution was prepared as per IP 1996. | Gliclazide, 10 mg, was accurately weighed and transferred to 100 ml volumetric flask. It was dissolved in pH 7.4 buffer and volume was made upto 100 ml. | A series of Gliclazide solutions ranging from 2 to 20 µg/ml were prepared from standard stock solution. The absorbance of solutions was measured spectrophotometrically at 227 nm. |
| **Calibration curve in methanol** | | |
| **Standard stock solution** | | **Working stock solution** |
| Gliclazide 20 mg was accurately weighed and transferred to 100 ml volumetric flask. It was dissolved in methanol and volume was made upto 100 ml. | | A series of Gliclazide solutions ranging from 2 to 20 µg/ml were prepared from standard stock solution. The absorbance of solutions was measured spectrophotometrically at 227 nm. |

**PREPARATION OF SOLID DISPERSIONS AND PHYSICAL MIXTURES:**

**PREPARATION OF PHYSICAL MIXTURES OF GLICLAZIDE / PEG 6000 AND GLICLAZIDE / PVP K-30[6]:**

Physical mixtures of Gliclazide with PEG 6000 and PVPK-30 containing three different weight ratios (1:1, 1:2, 1:5) and denoted as PMPEG 1/1, 1/2 1/5, PMPVP 1/1, 1/2, 1/5 respectively were prepared separately as follows. Gliclazide and PEG 6000 or PVP K30 were accurately weighed, pulverized and then mixed thoroughly by light trituration for 5 min in a mortar until homogenous mixture was obtained. The mixture was passed through a sieve no. 100.

**PREPARATION OF SOLID DISPERSION OF GLICLAZIDE-PEG 6000 BY MELTING METHOD[6]:**

Solid dispersions of Gliclazide in PEG 6000 in different weight ratios (1:1, 1:2, 1:5) and denoted as $SD_m$ PEG 6000 1/1, 1/2, 1/5, respectively were prepared by melting method as follows. Gliclazide was added to the molten PEG 6000 at 72 °C with constant stirring and the resulting homogenous dispersion was rapidly cooled in a ice bath, and stored in desiccator for 34 hours. Subsequently, the dispersion was ground in a mortar.

**PREPARATION OF SOLID DISPERSIONS OF GLICLAZIDE / PEG 6000 BY MELTINGSOLVENT EVAPORATION METHOD[7]:**

Solid dispersions of Gliclazide in PEG 6000 containing three different weight ratios (1:1, 1:2, 1:5) and denoted as SDms PEG 1/1, 1/2, 1/5 respectively were prepared by melting-solvent method as follows. A solution

of Gliclazide (1gm) in chloroform (3 ml) was added to appropriate amount of molten PEG 6000 at 60 °C with constant stirring. The solvent was evaporated at ambient temperature and the resulting residue was dried in hot air oven for 3 hours and stored in desiccator for 24 hours. Subsequently, the dispersion was ground in a mortar and passed through a sieve no.100.

**PREPARATION OF SOLID DISPERSIONS OF GLICLAZIDE / PEG 6000 AND GLICLAZIDE / PVP K-30 BY CO-EVAPORATION METHOD (SOLVENT EVAPORATION METHOD):**

Solid dispersions of Gliclazide in PEG 6000 or PVPK-30 containing three different weight ratios (1:1, 1:2, 1:5) and denoted as $SD_{SE}$ PEG (1/1, 1/2, 1/5), and SDPVP (1/1, 1/2, 1/5) respectively, were prepared by the solvent evaporation method. To a solution of Gliclazide (1gm) in chloroform (20 ml), the appropriate amount of PEG 6000 or PVPK-30 was added. The solvent was then evaporated at 45 °C and resulting residue was dried in hot air oven for 3 hours and stored for 24 hours in a desiccator. Subsequently, the dispersion was ground in a mortar and passed through sieve no.100.

**PREPARATION OF SUSTAINED RELEASE TABLETS:**

**Table 2: Composition of sustained released tablets**

| Batch | SDms PEG½ (%) | SDPVP K-30 ½ (%) | HPMC K4M (%) | DCP (%) | Lactose (%) | Binder PVP K-30 (%) | Magnesium stearate (%) | Talc (%) |
|---|---|---|---|---|---|---|---|---|
| $B_1$ | 34 | -- | 34 | 39 | -- | 3 | 0.5 | 0.5 |
| $B_3$ | - | 34 | 34 | 39 | -- | 3 | 0.5 | 0.5 |
| $B_3$ | 34 | -- | 34 | -- | 31 | -- | 0.5 | 0.5 |
| $B_4$ | - | 34 | 34 | -- | 31 | -- | 0.5 | 0.5 |
| $B_5$ | 43 | -- | 34 | 31 | -- | 1 | 1 | 1 |
| $B_6$ | -- | 43 | 34 | 31 | -- | 1 | 1 | 1 |
| $B_7$ | 43 | -- | 34 | -- | 31 | 1 | 1 | 1 |
| $B_8$ | -- | 43 | 34 | -- | 31 | 1 | 1 | 1 |
| $B_9$ | 45 | -- | 30 | -- | 33 | 1 | 1 | 1 |
| $B_{10}$ | 45 | -- | 30 | -- | 33 | 1 | 1 | 1 |

SDms PEG = Solid dispersion with PEG 6000
SDPVP K-30 = Solid dispersion with PVP K-30
HMPC K4M = Hydroxy propyl methyl cellulose
DCP = Dicalcium phosphate

**EVALUATION:**

**ANALYSIS OF DRUG CONTENT IN SOLID DISPERSIONS:**

The content of Gliclazide in each physical mixtures and solid dispersions (PEG 6000/PVPK-30) was determined using UV-spectroscopy. Accurately weighed solid dispersion or physical mixture equivalent to 40 mg of Gliclazide was transferred to 100 ml of volumetric flask and diluted to 100 ml with methanol and sonicated for 15 minutes for complete solubilization of drug. Solution was filtered with membrane filter paper 0.45 µm. One ml of this solution was taken and it was diluted to 100 ml with

methanol and absorbance was noted at 227 nm, concentration of Gliclazide was determined using calibration curve of Gliclazide in methanol.[8, 9]

**EVALUATION OF SOLID DISPERSION:**

**PHASE/SATURATION SOLUBILITY STUDIES:**

The effect of concentrations of PEG 6000 or PVP K-30 on the equilibration solubilities of Gliclazide in distilled water at 37±0.5 °C was carried out by adding an excess of drug (50 mg) into a screw-capped glass vial containing 20 ml of 0.1 N hydrochloric acid solution (pH 1.2) and various amounts of the carrier (2-20% w/v). The samples were placed on a water bath shaker and agitated at 37±0.5°C for 72 hours, previously determined to be adequate time for equilibration. An aliquot of each solution was withdrawn and filtered through a 0.45 µm pore size Millipore membrane filter fitted with syringe holder. The assay of Gliclazide was determined spectrophotometrically at 227 nm, a wave length at which PEG 6000 or PVP K-30 does not interfere. Similarly, the solubility of Gliclazide from physical mixtures and the solid dispersions was determined as method described above for pure drug, but in different pH such as pH 1.2, pH 6.8, and pH 7.4 buffer solutions.

**DISSOLUTION RATE STUDIES:**

*In-vitro* dissolution studies of Gliclazide, physical mixtures (PMPEG or PMPVP) and solid dispersions (SDPEG or SDPVP) prepared by melting method and melting-solvent method in 1/1,1/2 and 1/5 weight ratios were evaluated.

Following conditions were followed to study the *in-vitro* dissolution of Gliclazide.

**Table 3: Dissolution parameters**

| | |
|---|---|
| USP dissolution apparatus | Type-II (Paddle method) |
| Dissolution medium | pH 1.2 buffer |
| Volume of dissolution fluid | 900 ml. |
| Temperature | 37 ± 0.5 $^0$C. |
| Sample size | Equivalent to 30 mg of Gliclazide |

Sample of 5 ml, was withdrawn at regular intervals of 15 minutes by using syringe filter 0.45 µm. The volume withdrawn was replaced by fresh volume of dissolution medium to maintain constant volume of medium. The filtered samples were analysed spectrophotometrically at 227nm. Analyzed using UV spectrophotometer (Shimadzu 1800, Japan). Equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percentage drug dissolved at different time intervals was calculated. Similarly, *in-vitro* dissolution studies of Gliclazide, physical mixtures (PM PEG or PMPVP) and solid dispersions (SDPEG or SDPVP) prepared by melting method and melting-solvent method in 1/1, 1/2, and 1/5 weight ratios were evaluated in phosphate buffer pH 7.4 dissolution medium.[10, 11]

**EVALUATION OF MATRIX TABLETS:**

All prepared matrix tablets were evaluated for the following parameters.

**WEIGHT VARIATION:**

It was determined as per IP 1996. Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of tablet weight was calculated.[12, 13]

**FRIABILITY:**

Twenty tablets were weighed and placed in the Roche friabilator test apparatus, the tablets were exposed to rolling and repeated shocks, resulting from free falls within the apparatus. After 100 revolutions, the tablets were dedusted and weighted again. The friability was determined as the percentage loss in weight of the tablets.[14, 15]

**HARDNESS:**

Hardness was measured using the Monsanto hardness tester.

**DRUG CONTENT:**

Twenty tablets from each formulation batch were powdered and quantity of 210 mg of powder was added to 100 ml of methanol and the mixture was sonicated to dissolve the drug from HPMC. The filtrate was suitably diluted with methanol and analyzed against blank solution for the drug content at 227 nm spectrophotometrically[16, 17]

***IN-VITRO* DRUG RELEASE STUDIES:**

*In-vitro* dissolution studies of all formulations ($B_1$ – $B_{10}$) were evaluated.

Following conditions were followed to study *in-vitro* dissolution of formulations ($B_1$-$B_{10}$)

| | |
|---|---|
| USP dissolution apparatus | Type-II (Paddle method) |
| Dissolution medium | pH 1.2 buffer for 2 hours and pH 6.8 buffer for 3 to 10 hours. |
| Volume of dissolution fluid | 900 ml |
| Temperature | 37 ± 0.5 °C |
| Sample size | Equivalent to 30 mg of Gliclazide |

In vitro release study was carried out using USP Type-II (Paddle method) dissolution apparatus. Sample of 5 ml, was withdrawn at regular intervals of 1 hour using 0.45 µm syringe filter. The volume withdrawn was replaced by fresh volume of dissolution medium to maintain constant volume of dissolution medium. The filtered samples were analyzed spectrophotometrically at 227 nm. The amount of drug released was determined using respective calibration curves (PCP dissolution software). Dissolution studies for each formulation were performed in triplicates[18-20].

**RESULTS AND DISCUSSION:**

**DETERMINATION OF ABSORPTION MAXIMA OF GLICLAZIDE:**

Figures 1-4 show the calibration curves of Gliclazide in pH 1.2 buffer, pH 6.8 buffer, pH 7.4 buffer and methanol solution with regression values of 0.9953, 0.9785, 0.9802 and 0.9959 respectively.

The calculations of drug content and *in-vitro* drug release were based on respective calibration curves. The drug concentration and absorbance is linear in the curves. The curve obeys Beer-Lambert's law within concentration range of 2 to 20 µg/ml of Gliclazide in pH 1.2, pH 6.8, pH 7.4 buffer and methanol.

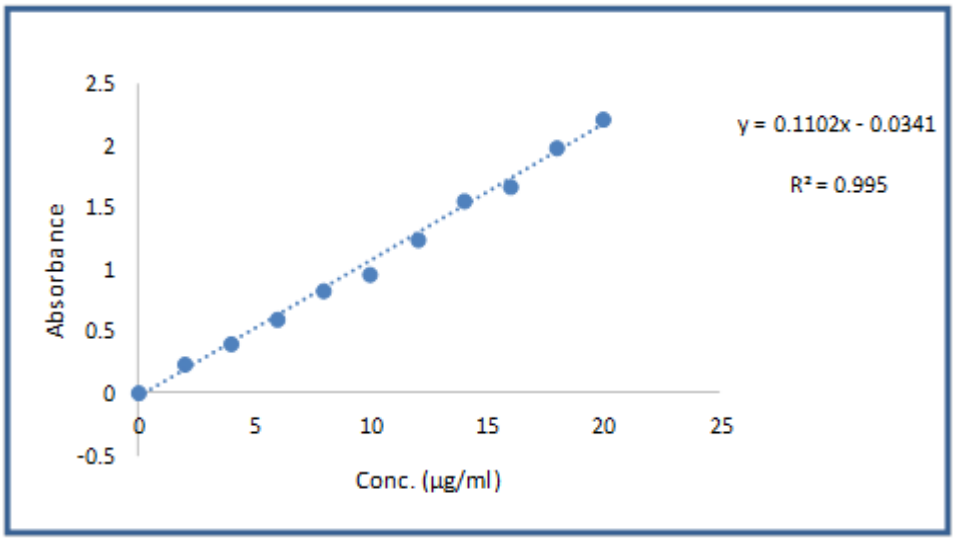


**Figure 1: calibration curve of Gliclazide in pH 1.2 buffer**

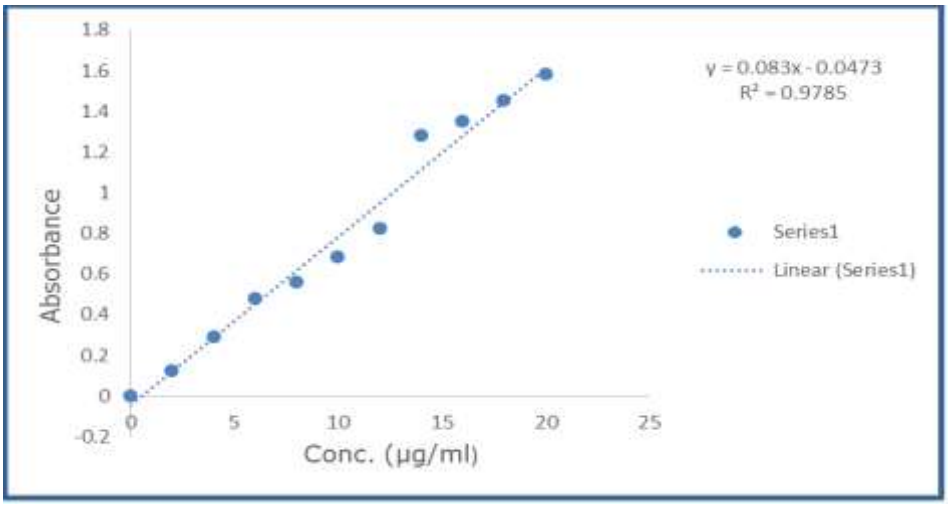


**Figure 2: calibration curve of Gliclazide in pH 6.8 buffer**

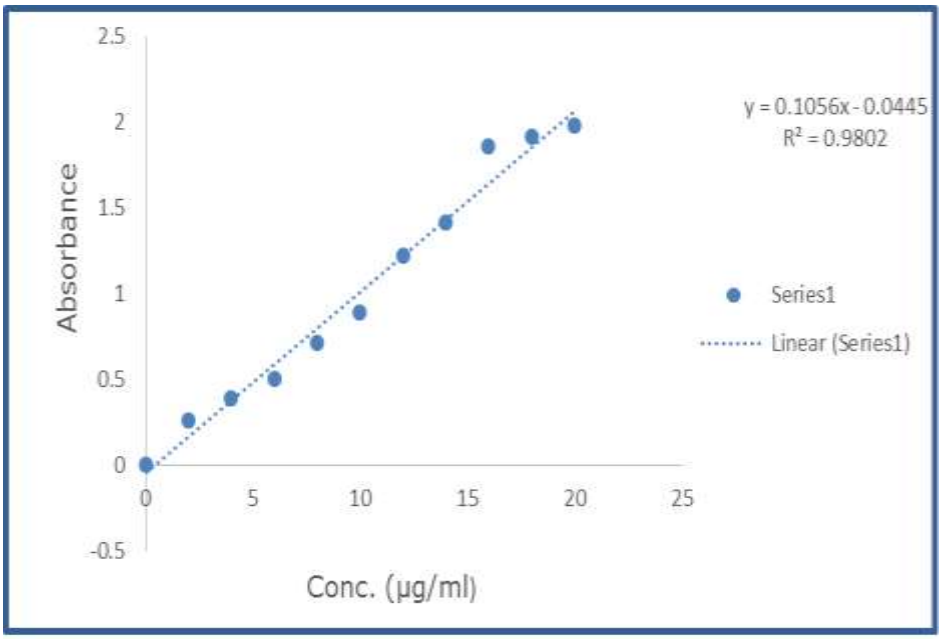


**Figure 3: Calibration curve of Gliclazide in pH 7.4 buffer**

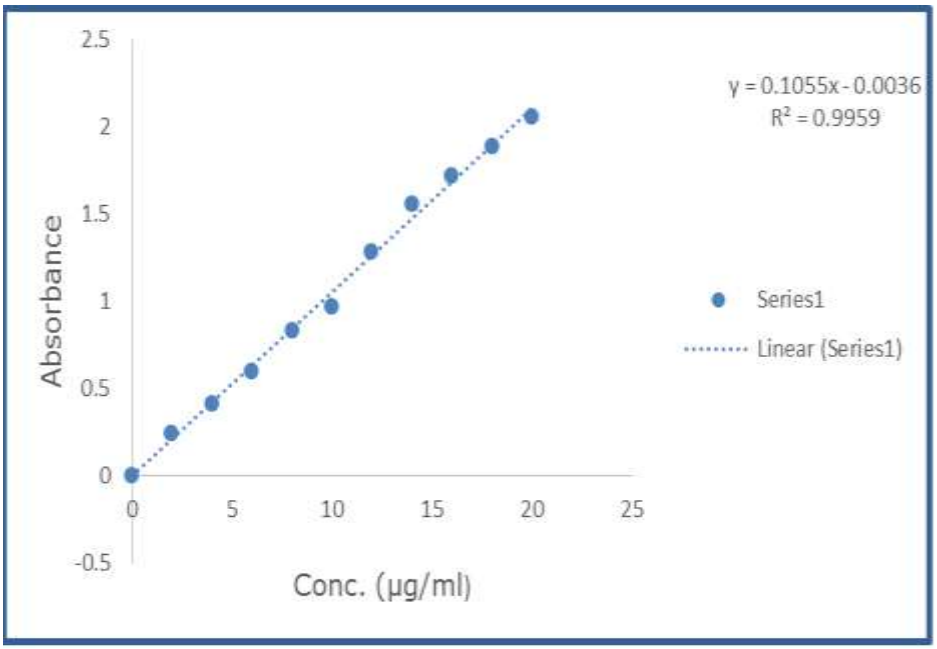


**Figure 4: Calibration curve of Gliclazide in methanol**

**PREPARATION OF SOLID DISPERSION OF GLICLAZIDE:**

Solid dispersions of Gliclazide with PEG 6000 or PVPK-30 were prepared by melting method, melting-solvent evaporation method, & solvent evaporation method. Solid dispersion of Gliclazide with PEG 6000 prepared by melting method was very sticky mass. It was difficult for processing of formulation development. But other two methods of preparations were found to be suitable for preparation of solid dispersions of Gliclazide with PEG 6000 or PVP K-30. The products of melting-solvent evaporation method and solvent evaporation method were found non-sticky and easy for processing in formulation of dosage form development.

**ANALYSIS OF DRUG CONTENT IN SOLID DISPERSIONS AND PHYSICAL MIXTURES:**

The solid dispersions or physical mixtures equivalent to 30 mg of Gliclazide were used to determined drug content. The drug content of solid dispersions and physical mixtures is shown in Table 4.

**Table 4: Drug content in solid dispersions and physical mixtures**

| Sr. No. | Solid dispersion and physical mixture | Drug content (%) (Mean ± S.D.) |
|---|---|---|
| 1 | PMPEG 1/1 | 96.13 ± 0.33 |
| 2 | PMPEG 1/2 | 97.35 ± 0.43 |
| 3 | PMPEG 1/5 | 95.55 ± 0.94 |
| 4 | PMPVP 1/1 | 97.44 ± 0.87 |
| 5 | PMPVP 1/2 | 95.16 ± 0.87 |
| 6 | PMPVP 1/5 | 94.15 ± 1.08 |
| 7 | $SD_{MS}$PEG 1/1 | 97.48 ± 0.65 |
| 8 | $SD_{MS}$PEG 1/2 | 96.55 ± 0.67 |
| 9 | $SD_{MS}$PEG 1/5 | 96.25 ± 0.56 |
| 10 | $SD_{SE}$PEG 1/1 | 97.72 ± 0.69 |
| 11 | $SD_{SE}$PEG 1/2 | 96.18 ± 1.66 |
| 12 | $SD_{SE}$PEG 1/5 | 96.50 ± 0.76 |
| 13 | SDPVP 1/1 | 97.75 ± 0.92 |
| 14 | SDPVP 1/2 | 96.84 ± 0.48 |
| 15 | SDPVP 1/5 | 95.46 ± 0.55 |

n=3

**SATURATION SOLUBILITY STUDIES:**

The saturation solubilities of drug, physical mixtures and solid dispersions in pH 1.2, 6.8 and 7.4 buffers are shown in Table 5.

**Table 5: Solubility of Gliclazide in physical mixture and solid dispersion in different pH 1.2, 6.8 and 7.4 buffer solutions**

| Sr. No. | Sample | Solubility of Gliclazide (mg/ml) | | |
|---|---|---|---|---|
| | | pH 1.2 buffer | pH 6.8 buffer | pH 7.4 buffer |
| 1 | Drug | 0.71± 0.11 | 0.34 ± 0.04 | 0.33± 0.05 |
| 2 | PMPEG 1/1 | 0.7 ± 0.02 | 0.42 ± 0.01 | 0.42 ± 0.01 |
| 3 | PMPEG 1/2 | 0.72 ± 0.03 | 0.45 ± 0.02 | 0.44 ± 0.04 |
| 4 | PMPEG 1/5 | 0.73 ± 0.02 | 0.46 ± 0.02 | 0.45 ± 0.02 |
| 5 | PMPVP 1/1 | 0.74 ± 0.02 | 0.52 ± 0.04 | 0.52 ± 0.04 |
| 6 | PMPVP 1/2 | 0.76 ± 0.01 | 0.54 ± 0.03 | 0.53 ± 0.04 |
| 7 | PMPVP 1/5 | 0.78 ± 0.03 | 0.61 ± 0.02 | 0.59 ± 0.06 |
| 8 | $SD_{MS}$PEG 1/1 | 1.33 ± 0.01 | 0.74 ± 0.03 | 0.74 ± 0.04 |
| 9 | $SD_{MS}$PEG 1/2 | 1.31 ± 0.04 | 0.73 ± 0.01 | 0.72 ± 0.05 |
| 10 | $SD_{MS}$PEG 1/5 | 1.68 ± 0.07 | 0.93 ± 0.05 | 0.92 ± 0.02 |

| | | | | |
|---|---|---|---|---|
| 11 | $SD_{SE}$PEG 1/1 | 1.64 ± 0.05 | 0.87 ± 0.03 | 0.91 ± 0.04 |
| 12 | $SD_{SE}$PEG 1/2 | 2.37 ± 0.08 | 1.47 ± 0.04 | 1.46 ± 0.03 |
| 13 | $SD_{SE}$PEG 1/5 | 2.32 ± 0.03 | 1.46 ± 0.03 | 1.45 ± 0.05 |
| 14 | SDPVP 1/1 | 1.57 ± 0.02 | 0.88 ± 0.08 | 0.87± 0.08 |
| 15 | SDPVP 1/2 | 1.89 ± 0.01 | 1.42 ± 0.07 | 1.41 ± 0.05 |
| 16 | SDPVP 1/5 | 2.67 ± 0.04 | 2.03 ± 0.06 | 2.02± 0.01 |

An increase in saturation solubility of Gliclazide explains the improved dissolution of solid dispersions, as per the Noyes-Whitney equation, since the saturation solubility of a compound is dependent on the size of the particles (If the particle size is less than 0.1µm). Since it is possible to achieve such reduction in particle size with solid dispersion systems, the saturation solubility studies were performed with all formulations using the untreated Gliclazide as a control. The solid dispersions have shown the increase in solubility by 3.76 to 6.12 folds as compared to Gliclazide. The best results have been obtained with PVPK-30 and among the PEG batches, the melt-solvent evaporation method resulted in higher increase in drug solubility than the corresponding solvent method.

**DISSOLUTION STUDIES:**

As shown in Figure 5 and 6, Gliclazide solid dispersions presented better dissolution performance over corresponding physical mixtures and the pure drug. This may be due to an improved wettability of drug particles, a significant reduction in particle size during the formation of solid dispersion, and the intrinsically higher rate of dissolution of the soluble polymer component of the solid dispersion. The dissolution profiles of Gliclazide, physical mixtures and solid dispersions in pH 1.2 and 7.4 are shown in Table 6 and 7.

**Table 6: *In-vitro* dissolution profile of Gliclazide, physical mixture of Gliclazide and solid dispersion of Gliclazide in pH 1.2 buffer**

| Sr. No. | Sample | % Cumulative gliclazide release | | | | | |
|---|---|---|---|---|---|---|---|
| | | 15 min. | 30 min. | 45 min. | 60 min. | 75 min. | 90 min. |
| 1. | Gliclazide | 21.01 ± 0.13 | 40.82 ± 0.32 | 41.24 ± 0.31 | 41.79± 0.16 | 41.72 ± 0.21 | 42.22 ± 0.18 |
| 2. | PMPEG1/1 | 24.14 ± 0.12 | 44.36 ± 0.28 | 45.25 ± 0.35 | 45.95 ± 0.12 | 46.25 ± 0.33 | 46.31 ± 0.31 |
| 3. | PMPEG1/2 | 26.18 ± 0.21 | 46.11 ± 0.24 | 46.76 ± 0.32 | 47.31 ± 0.23 | 47.73 ± 0.31 | 47.75 ± 0.19 |
| 4. | PMPEG1/5 | 26.51 ± 0.19 | 47.25 ± 0.21 | 47.29 ± 0.18 | 47.41 ± 0.12 | 47.61 ± 0.11 | 47.73 ± 0.21 |
| 5. | PMPVP1/1 | 26.15 ± 0.12 | 46.76 ± 0.18 | 46.93 ± 0.14 | 47.17 ± 0.14 | 47.51 ± 0.36 | 47.73 ± 0.14 |
| 6. | PMPVP1/2 | 27.31 ± 0.23 | 47.63 ± 0.23 | 47.57 ± 0.22 | 47.78 ± 0.41 | 47.82 ± 0.62 | 47.91 ± 0.12 |
| 7. | PMPVP1/5 | 34.64 ± 0.09 | 49.77 ± 0.05 | 50.79 ± 0.03 | 51.22 ± 0.03 | 51.62 ± 0.31 | 52.95 ± 0.17 |
| 8. | $SD_{SE}$PEG1/1 | 46.12 ± 0.12 | 54.57 ± 0.41 | 56.44 ± 0.22 | 58.83 ± 0.62 | 59.87 ± 0.33 | 60.27 ± 0.24 |
| 9. | $SD_{MS}$PEG1/1 | 46.76 ± 0.08 | 54.81 ± 0.14 | 56.89 ± 0.11 | 58.92 ± 0.14 | 59.95 ± 0.24 | 61.19 ± 0.16 |
| 10. | $SD_{SE}$PEG1/2 | 63.62 ± 0.17 | 73.79 ± 0.13 | 76.36 ± 1.81 | 79.01 ± 0.75 | 80.15 ± 0.53 | 80.78 ± 0.45 |
| 11. | $SD_{MS}$PEG1/2 | 64.38 ±0.36 | 74.41 ± 0.18 | 75.72 ± 0.24 | 80.76 ± 0.58 | 82.89 ± 0.15 | 83.98 ± 0.21 |
| 12. | $SDPEG_{SE}$1/5 | 69.19 ± 0.08 | 79.38 ± 0.11 | 80.32 ± 0.34 | 81.43 ± 0.22 | 82.39 ± 0.39 | 84.3 ± 0.24 |
| 13. | $SD_{MS}$PEG1/5 | 69.41 ± 0.14 | 79.63 ± 0.23 | 80.71 ± 0.21 | 82.22 ± 0.32 | 83.6 ± 0.22 | 85.24 ± 0.72 |
| 14. | SDPVP1/1 | 47.33 ± 0.22 | 58.39 ± 1.37 | 61.68 ± 0.12 | 63.17 ± 0.1 | 64.41± 0.12 | 65.48 ± 0.38 |
| 15. | SDPVP1/2 | 64.66 ± 0.17 | 74.12 ± 0.32 | 79.49 ± 0.12 | 82.43 ± 0.37 | 83.65 ± 0.11 | 84.55 ± 0.1 |
| 16. | SDPVP1/5 | 83.34 ± 0.23 | 86.35 ± 0.19 | 89.49 ± 0.36 | 90.69 ± 0.18 | 91.55 ± 0.33 | 92.72 ± 0.89 |

Mean ± SD (n = 3)

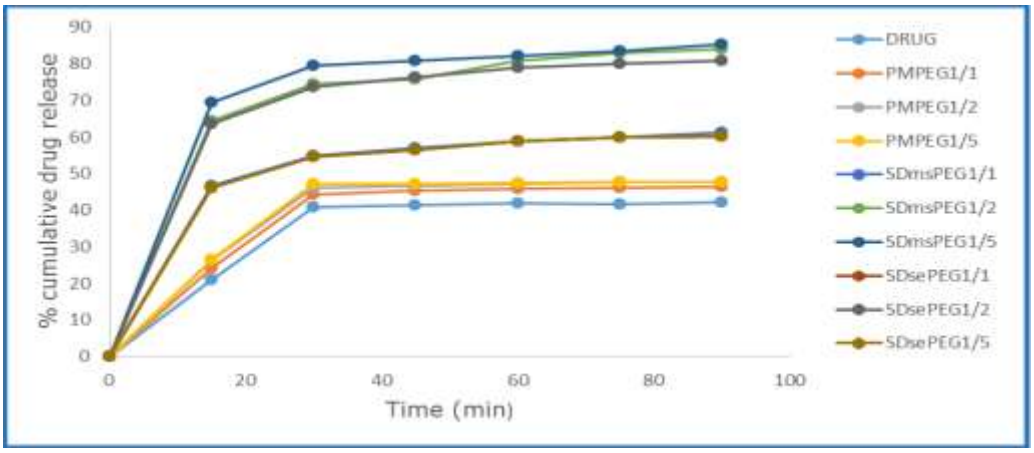


**Figure 5: *In-vitro* dissolution profile of Gliclazide, physical mixture and solid dispersion of Gliclazide with PEG 6000 in pH 1.2 buffer**

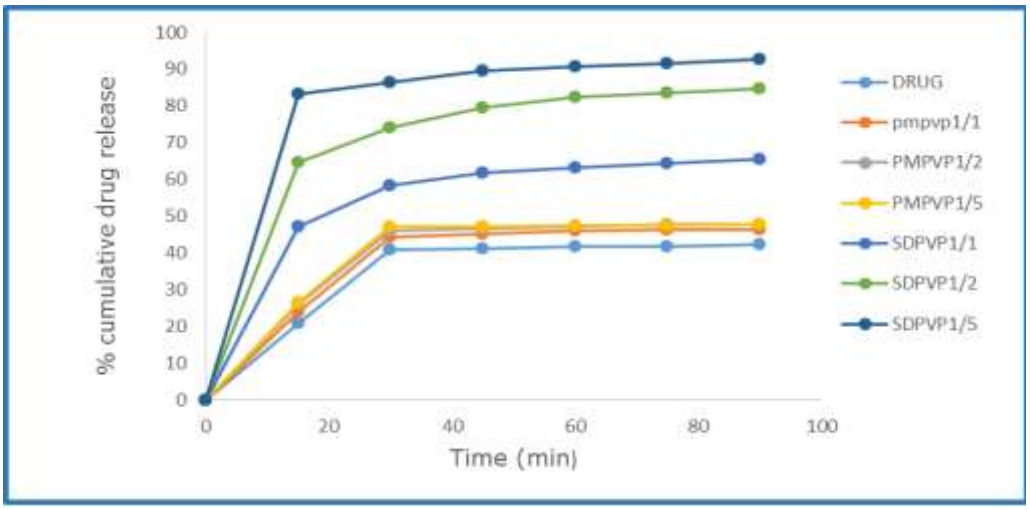


**Figure 6: *In-vitro* dissolution of Gliclazide, physical mixture and solid dispersion of Gliclazide with PVP K-30 in pH 1.2 buffer**

**Table 7: *In-vitro* dissolution of Gliclazide, physical mixture and solid dispersion of Gliclazide in pH 7.4 phosphate buffer**

| Sr. No. | Sample | % Cumulative gliclazide release | | | | | |
|---|---|---|---|---|---|---|---|
| | | 15 min. | 30 min. | 45 min. | 60 min. | 75 min. | 90 min. |
| 1. | Gliclazide | 11.17 ± 0.13 | 22.44 ± 0.24 | 23.49 ± 0.34 | 26.34± 0.12 | 27.13 ± 0.11 | 27.24 ± 0.22 |
| 2. | PMPEG1/1 | 13.73 ± 0.26 | 25.74 ± 0.25 | 26.57 ± 0.3 | 30.35 ± 0.04 | 32.34 ± 0.03 | 32.48 ± 0.04 |
| 3. | PMPEG1/2 | 14.67 ± 0.22 | 26.57 ± 0.53 | 27.76 ± 0.44 | 33.68 ± 0.43 | 33.44 ± 0.24 | 33.51 ± 0.21 |
| 4. | PMPEG1/5 | 15.69 ± 0.06 | 27.75 ± 0.16 | 31.19 ± 0.14 | 34.19 ± 0.32 | 37.16 ± 0.25 | 37.51 ± 0.33 |
| 5. | PMPVP1/1 | 16.04 ± 0.32 | 28.5 ± 0.72 | 29.76 ± 0.51 | 32.37 ± 0.22 | 35.85 ± 0.15 | 36.45 ± 0.41 |
| 6. | PMPVP1/2 | 17.24 ± 0.07 | 29.56 ± 0.5 | 30.77 ± 0.08 | 33.42 ± 0.1 | 36.74 ± 0.2 | 37.64 ± 0.48 |
| 7. | PMPVP1/5 | 19.16 ± 0.15 | 31.11 ± 0.12 | 33.2 ± 0.32 | 37.81 ± 0.14 | 40.38 ± 0.38 | 41.78 ± 0.19 |
| 8. | $SD_{SE}$PEG1/1 | 41.28 ± 0.06 | 49.33 ± 0.43 | 51.48 ± 0.24 | 54.13 ± 0.26 | 54.39 ± 0.13 | 55.24 ± 0.11 |
| 9. | $SD_{MS}$PEG1/1 | 41.82 ± 0.14 | 50.98 ± 0.22 | 54.87 ± 0.44 | 55.35 ± 0.31 | 55.91 ± 0.6 | 55.98± 0.2 |
| 10. | $SD_{SE}$PEG1/2 | 59.62 ± 0.18 | 69.62 ± 0.13 | 73.88 ± 0.04 | 75.39 ± 0.05 | 76.65 ± 0.15 | 80.67 ± 0.49 |
| 11. | $SD_{MS}$PEG1/2 | 61.63 ±0.16 | 70.34 ± 0.05 | 74.21 ± 0.15 | 75.97 ± 0.11 | 77.11 ± 0.05 | 78.91 ± 0.08 |
| 12. | $SD_{SE}$PEG1/5 | 67.62 ± 0.28 | 76.69 ± 0.14 | 78.47 ± 0.13 | 80.03 ± 0.24 | 81.54 ± 0.13 | 82.71 ± 0.21 |
| 13. | $SD_{MS}$PEG1/5 | 68.23 ± 0.15 | 77.21 ± 0.22 | 78.68 ± 0.51 | 80.23 ± 0.23 | 81.63 ± 0.16 | 83.11 ± 0.18 |
| 14. | SDPVP1/1 | 47.31 ± 0.28 | 55.34 ± 0.22 | 60.12 ± 0.16 | 61.39 ± 0.29 | 62.28 ± 0.21 | 63.22 ± 0.21 |
| 15. | SDPVP1/2 | 60.32 ± 0.22 | 74.4 ± 0.25 | 77.57 ± 0.55 | 81.84 ± 0.33 | 82.78 ± 0.26 | 83.43 ± 0.21 |
| 16. | SDPVP1/5 | 77.11 ± 0.23 | 79.71 ± 0.25 | 82.41 ± 0.34 | 84.84 ± 0.41 | 85.12 ± 1.24 | 88.79 ± 1.34 |

Mean ± SD (n = 3)

**EFFECT OF DIFFERENT METHODS OF PREPARATION:**

Solid dispersions of Gliclazide with PEG 6000 were prepared by. melting-solvent evaporation and solvent evaporation method. Solid dispersions prepared by melting-solvent method showed more rate of *in-vitro* dissolution rate than solvent evaporation method.

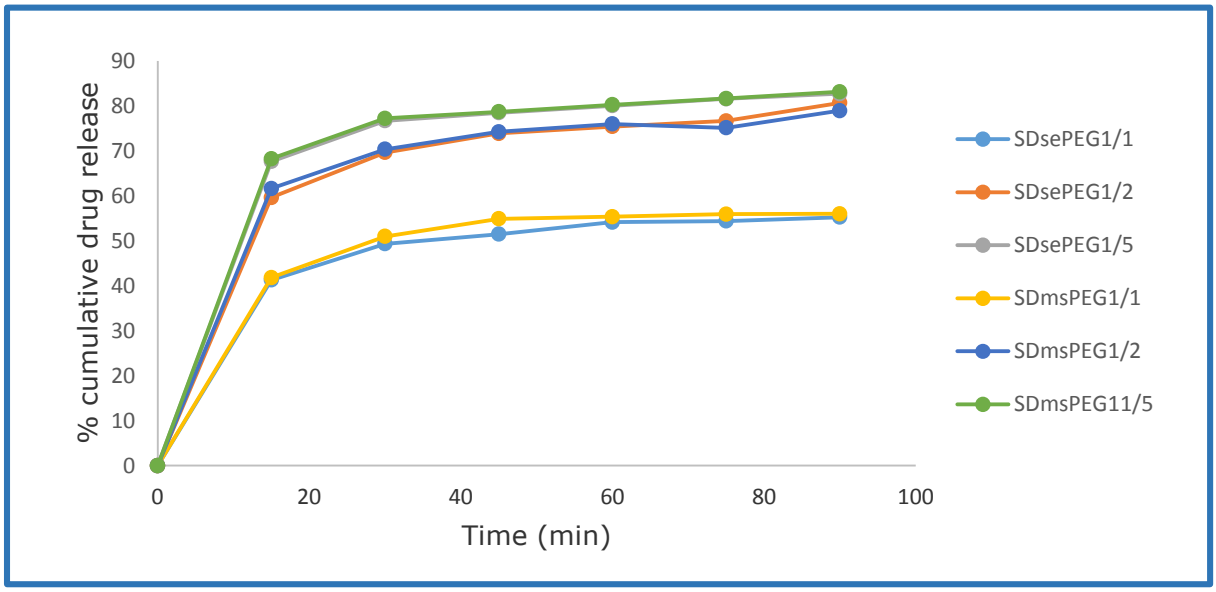


**Figure 7: Effect of method of preparation**

**EVALUATION OF MATRIX TABLETS:**

The physical parameters of sustained release tablets are shown in Table 8.

**Table 8: Physical parameters of gliclazide sustained released tablets**

| Batch | Weight Uniformity (mg)(Mean±SD) | Hardness (kg/cm$^2$) | % Friability | Drug content |
|---|---|---|---|---|
| $B_1$ | 218.5±1.5 | 5.4 | 0.32 | 97.26±1.4 |
| $B_2$ | 214.3±1.6 | 4.7 | 0.35 | 98.22±1.8 |
| $B_3$ | 212.5±1.5 | 5.2 | 0.34 | 96.99±2.2 |
| $B_4$ | 213.5±1.4 | 4.1 | 0.32 | 98.21±1.6 |
| $B_5$ | 209.6±1.4 | 4.2 | 0.39 | 97.24±1.6 |
| $B_6$ | 208.8±2.6 | 4.4 | 0.33 | 98.24±1.5 |
| $B_7$ | 215.8±1.3 | 3.9 | 0.38 | 97.15±1.6 |
| $B_8$ | 216.9±1.5 | 2.6 | 0.44 | 95.99±1.7 |
| $B_9$ | 211.8±1.4 | 2.2 | 0.41 | 98.24±2.4 |
| $B_{10}$ | 212.8±2.2 | 2.3 | 0.43 | 97.99±1.4 |

Weight variation data for all the formulations batches indicated no significant difference in the weight of individuals tablets from the average value and weight variation were found to be within IP limits. The hardness values were found to be in range of 2.2 to 5.4 kg/cm$^2$. But tablets with higher hardness have shown no release in first two hours. But tablets with hardness of 2.2 kg/cm$^2$ have shown good release profiles. The friability values were found to be within IP limits. The drug content was found to be within IP limits.

***IN-VITRO* DRUG RELEASE FROM GLICLAZIDE SUSTAINED RELEASE TABLETS FORMULATION:**

The results of evaluation of prepared sustained release tablets are shown in Table 9.

**Table 9: *In-vitro* drug release from gliclazide sustained release tablets formulation**

| Time (hour) | Me di-um pH | % cumulative Gliclazide release | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $B_1$ | $B_2$ | $B_3$ | $B_4$ | $B_5$ | $B_6$ | $B_7$ | $B_8$ | $B_9$ | $B_{10}$ |
| 1 | 1.2 | 1.1±.035 | 1.04 ±0.24 | 1.32 ±0.45 | 1.45 ±0.43 | 5.52 ±0.23 | 4.21 ±0.22 | 10.32± 0.34 | 9.32 ±0.17 | 10.33± 0.13 | 10.39± 0.19 |
| 2 | 1.2 | 1.7±0.12 | 1.63 ±0.23 | 8.23 ±0.18 | 7.81 ±0.13 | 15.27 ±0.29 | 15.65 ±0.35 | 25.53± 0.43 | 22.32 ±0.3 | 24.65± 0.89 | 25.22± 0.27 |
| 3 | 6.8 | 3.1±0.2 | 2.45 ±0.43 | 15.23 ±0.44 | 14.18 ±0.35 | 23.14 ±0.23 | 24.14 ±0.29 | 35.42± 0.28 | 32.21 ±0.15 | 36.17± 0.32 | 37.62± 0.03 |
| 4 | 6.8 | 5.2±.035 | 6.22 ±0.32 | 22.17 ±0.45 | 23.13 ±0.36 | 33.43 ±0.35 | 30.12 ±0.81 | 45.55± 0.35 | 46.32 ±0.22 | 48.41± 0.33 | 46.48± 0.09 |
| 5 | 6.8 | 16.26 ±0.43 | 18.32 ±0.56 | 29.18 ±0.37 | 28.19 ±0.58 | 39.83 ±0.82 | 35.34 ±0.24 | 55.32± 0.42 | 52.91 ±0.51 | 57.91± 0.54 | 59.44± 0.34 |
| 6 | 6.8 | 26.84 ±0.86 | 24.74 ±0.74 | 35.63 ±0.47 | 33.01 ±0.87 | 46.44 ±0.22 | 44.44 ±0.54 | 62.13± 0.64 | 58.18 ±0.99 | 62.91± 0.64 | 66.28± 0.15 |
| 7 | 6.8 | 33.45 ±0.92 | 29.84 ±0.19 | 44.19 ±0.31 | 40.18 ±0.96 | 52.83 ±0.49 | 54.19 ±0.91 | 65.43± 0.63 | 64.25 ±0.72 | 68.92± 0.83 | 68.52± 0.27 |
| 8 | 6.8 | 36.73 ±0.13 | 38.19 ±0.49 | 49.19 ±0.39 | 49.55 ±0.42 | 58.28 ±0.53 | 59.94 ±0.84 | 68.58± 0.58 | 68.29 ±0.72 | 74.28± 0.35 | 77.15± 0.94 |
| 9 | 6.8 | 44.37 ±0.79 | 46.19 ±0.89 | 58.23 ±0.99 | 56.23 ±0.24 | 69.14 ±0.68 | 68.28 ±0.98 | 78.77± 0.94 | 76.77 ±0.81 | 83.77± 0.28 | 83.56± 0.29 |
| 10 | 6.8 | 46.49 ±0.71 | 48.18 ±0.81 | 62.23 ±0.73 | 61.24 ±0.89 | 72.28 ±0.32 | 73.18 ±0.79 | 81.81± 0.87 | 80.41 ±0.91 | 90.21± 0.86 | 92.79± 0.76 |

**SUMMARY AND CONCLUSION:**

The present study has been a satisfactory attempt to formulate Solid dispersion technique for Development of sustained release dosage form of poorly water soluble drug of delivery of Gliclazide. From there producible results of the executed experiments, it can be concluded that Gliclazide is a second generation of oral hypoglycemic sulfonylurea. It is practically insoluble in water and its absorption is dissolution rate limited. Sustained release dosage forms of Gliclazide have several advantages over its conventional formulation. Therefore in order to formulate sustained release formulation of Gliclazide, matrix tablets were tried. But Gliclazide as such and it gives negligible release due to its poor aqueous solubility. Improving the dissolution characteristics of poorly water soluble drugs is important to achieve better bioavailability and reduced side effects. The solid dispersion technique is an important.

Thus, to enhance the dissolution rate of Gliclazide, solid dispersion of Gliclazide with hydrophilic carriers such PEG 6000 and PVP K-30 were first prepared using solvent-melting and solvent evaporation method. Solid dispersions were prepared using various ratio of PEG 6000, PVP K-30, and drug, physical mixtures with stated polymers also prepared in same ratios. After comparing the solubility and dissolution profiles of various solid dispersions, it was observed that solid dispersion such as SDPEG ½ or SDPVP ½ gave desired dissolution profile of Gliclazide (more than 80% release in first 120 min). From *in-vitro* release study of $B_1$-$B_{10}$ batches, it was observed that the release of drug was less than 2% in first two hrs due to use of 45% of HPMC K4M. *In-vitro* dissolution studies also revealed that SDPVP K-30 ½ has shown less percentage of drug release from tablet for first two to three hours than SDPEG ½. It may due to binding effect of PVP K-30.

**REFERENCES:**


1. Mogal, S.A., Gurjar, P.N., Yamgar, D.S., and Kamod, A.C.; 2012 Solid dispersion technique for improving solubility of some poorly soluble Drugs. Der Pharmacia Lettre, 4 (5):1574-1586.
2. Joshi, M., Tiwari, G., Tiwari, R., Pandey, S., Pandey, P., Rai, A.K.; 2012 Solid Dispersion: A Technology for the Improvement of Oral Bioavailability of Poorly Soluble Drugs. Current Pharma Research ISSN: 2230-7842 CPR 2(4), 668-677.
3. Chaudhary, A., Nagaich, U., Gulati, N., Sharma, V.K., Khosa, R.L.; 2012 Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review. Journal of Advanced Pharmacy Education & Research ISSN 2249-3379 2 (1): 32-67.
4. Ayhan, S.¸ Yalcýn, O., Askýn, I.; 2005 Preparation and in vitro evaluation of sustained release tablet formulations of diclofenac sodium., Il Farmaco; 171–177.
5. Bravo, S., Lamas, M., Salomon, M.; 2002 In-Vitro Studies of Diclofenac sodium controlled release from biopolymeric hydrophilic matrices., J Pharm Pharmaceut Sci; 5(3): 213-219.
6. Villiers, M.M., Wurster, E.D., Van der Watt, G.J., and Ketkar, A.; 1998. X−ray powder diffraction determination of the relative amount of crystalline acetaminophen in solid dispersion with polyvinyl pyrrolidone. Int. J. Pharm., 163 (1-2): 219−224.
7. Chiu, W.L. and Riegelman, S.; 1971 Pharmaceutical application of solid dispersion. J. of Pharm. Sci., 60(9):1281-1302.
8. Narang, S.A., and Srivastav, K.A.; 2002 Evaluation of solid dispersions of clofazimine. Drug Dev. Ind. Pharm. 28(8): 1001-1013.
9. Mohd, T.J.; 2002 Tensile strength and bonding in the compacts: A compression of diametrical compression and three point bending for plastically deforming material. Drug Dev. Ind. Pharm., 28, 809−813.
10. Ayhan, S.¸ Yalcýn, O., Askýn, I.; 2005 Preparation and in vitro evaluation of sustained release tablet formulations of diclofenac sodium., Il Farmaco; 171–177.
11. Costa and Sausa, J. 2001s Modeling and comparison of dissolution profiles. Euro. J. Pharm. Sci., 13. 123-133.
12. Ansel, C., Allen, V., Popovich, A.; 2000 Pharmaceutical dosage forms and drug delivery system, 7th edition 248-252.
13. Arunachalam, A.,Karthikeyan, M., Konam, K.,Prasad, P.H., Kumar, S.A.; 2010Solid Dispersions: A Review. Current Pharma Research 1(1): 82-90.
14. Prediction of drug release from HPMC matrices: effect of physicochemical properties of drug and polymer concentration. Journal of Controlled Release, 95: 209–216.
15. Abdelbary, G.A., Tadros M.I; 2008 Design and in vitro/in vivo evaluation of novel nicorandil extended release matrix tablets based on hydrophilic interpolymer complexes and a hydrophobic waxy polymer; Eur J Pharm Biopharm. 69(3): 1019-28.
16. Gubbins, R., O'Driscoll, C.,Corrigan, O.; 2003The effects of casein on diclofenac release from hydroxypropylmethylcellulose (HPMC) compacts. International Journal of Pharmaceutics; 260: 69–76.
17. Gohel, M.C., and Patel, L.D.; 2003 Processing of Nimesulide−PEG 400−PG−PVP solid dispersion: preparation, characterization, and *in-vitro* dissolution. Drug Dev. Ind. Pharm., 29 (3): 299−310.
18. Chien, Y.W.; 1982 Controlled Release Drug Admninistration: Logic, Novel Drug Delivery Systems. (James Swarbrick, Eds). Marcel Dekker Inc, New York, 1-11.
19. Brahmankar, D.M. and Jaiswal, S.B.; 1999 Controlled Release Medication, In Biopharmaceutics and Pharmacokinetics: A. Treatise, 1st Ed. (D. M. Brahmankar and S. B. Jaiswal Eds) Vallabh Prakashan: 335-371.
20. Bravo, S., Lamas, M., Salomon, M.; 2002 In-Vitro Studies of Diclofenac sodium controlled release from biopolymeric hydrophilic matrices., J Pharm Pharmaceut Sci; 5(3): 213-219.