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Formulation and Evaluation of Gliclazide Solid Dispersion for Solubility and Dissolution Enhancement

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ABSTARCT

Gliclazide is a type of medication used to treat non-insulin-dependent diabetes. It belongs to a group of drugs called sulfonylureas. Gliclazide isn't very well absorbed by the body because it doesn't dissolve easily in water. In this study, scientists made a special mix called solid dispersions of gliclazide using a solvent method. They used different ratios of the drug to the mixers, which were 1:9, 2:8, 3:7, 4:6, and 5:5. The mixers used were polyvinyl pyrrolidone K-30 and polyethylene glycol 6000, and they were used in a 1:1 ratio. The properties of the mix were checked using various tests like DSC, FTIR, XRD and tests for how well the drug dissolves and how soluble it is. The SEM results showed that gliclazide was spread out well and existed in an amorphous form in the mix. The FTIR results showed that there was no chemical bonding between gliclazide and the mixers. The DSC test showed that the melting point of gliclazide was lower in the mix. The XRD test showed that the mix had less crystalline structure than pure gliclazide. The mix also made the drug dissolve and become more soluble than pure gliclazide, and this difference was statistically significant ($F < 0.05$).

KEYWORDS: Solid dispersion, solvent method, PEG 6000, Gliclazide, PVP K-30.

INTRODUCTION

The way a drug works when taken by mouth depends on how well it dissolves and how soluble it is. The speed at which a drug dissolves affects how well it works. To make a drug more soluble, certain methods are used. Some common ways to improve solubility include making salts, reducing the size of the drug particles, and adding solvents or surfactants. One method is solid dispersion, where one or more active ingredients are mixed with an inert material in a solid form. This can be made using heat, a liquid, or a mix of both. Gliclazide is a type of oral medicine used to treat type 2 diabetes. It is a second-generation sulfonylurea drug known for being well-tolerated and less likely to cause low blood sugar. Because of these qualities, gliclazide is often the preferred choice for long-term treatment of type 2 diabetes. Gliclazide is classified as a substance with low water solubility but high absorption ability, based on the Biopharmaceutics Classification System. This means it dissolves slowly in water but can pass through the body's lining easily. Improving the oral absorption of drugs that don't dissolve well in water is a challenge in developing new formulations. Using a solid dispersion of a poorly soluble drug with a water-soluble polymer can increase both solubility and absorption. The solid dispersion method helps a drug dissolve faster because it reduces the size of the drug particles, improves how well the drug mixes with liquid, and forms a temporary, unstable mix that breaks down more easily. Some studies have used surfactants to help the drug dissolve better. Surfactants work by reducing the surface tension between the drug and the liquid, making it easier for the drug to mix with the liquid. This helps the drug dissolve more quickly. When a solid dispersion has more than one component, adding a third ingredient can help improve how fast the drug dissolves or make the manufacturing process and product more stable. Researchers have tested using polyethylene glycol 6000 to speed up the dissolution of gliclazide. PEG 6000 helps the drug particles stay apart, increases how well the drug mixes with liquid, and creates smaller, more easily dissolved crystals of the drug. The purpose of this study was to examine how PEG 6000 and PVP K-30 affect the properties of solid dispersions made with gliclazide. Both PEG 6000 and PVP K-30 dissolve well in many organic solvents, which makes them useful for making solid dispersions. In addition to helping disperse the drug, PEG 6000 also helps prevent gliclazide from forming crystals again.

MATERIAL

The materials used in this study include gliclazide which is obtained as free gift sample JB Chemical Thane. PVP K-30, PEG 6000 was purchased from Dipa chemicals, Sambhajinagar. All other chemicals and reagents used were of analytical grade.

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Solid dispersion preparation

Gliclazide solid dispersion system, PEG 6000 and PVP K-30, were made using the comparison in [Table 1], with a final total weight of 20 grams. Solvent method is used to prepare dispersions. Gliclazide, PVP K-30, and PEG 6000 were each dissolved separately in 96% ethanol. Then, the solutions were mixed and stirred using a magnetic stirrer. The resulting solution was evaporated and dried using a water bath to get the dried dispersion. The solid dispersion was collected and stored in desiccators before being used. For comparison, physical mixtures of gliclazide with the carriers were also made in a ratio of 1:1.

Ingredients	F1	F2	F3	F4	F5
Gliclazide	10	20	30	40	50
PEG 6000	45	40	35	30	25
PVP K 30	45	40	35	30	25

Scanning electron microscopy analysis

The Gliclazide powder, physical mixtures, and solid dispersions were placed on an aluminum sample holder and coated with gold to a thickness of 10 nanometers. Then, they were examined under different magnifications using a scanning electron microscope. The SEM instrument (JEOL) was operated at 20 kilovolts and 12 milliamps. [3]

Fourier-transform infrared spectroscopy analysis

About 1 to 2 milligrams of gliclazide powder, physical mixtures, and solid dispersions were put into a mortar and crushed until they were evenly mixed. Then, pellets were made using a pressure of 800 mPa under vacuum. These pellets were analyzed using a Fourier-transform infrared (FTIR) spectrophotometer. The absorption spectra were taken between wave numbers 500 and 4000 cm^{-1}. [11]

X-ray diffraction analysis

Some gliclazide powders, physical mixtures, and solid dispersions were placed on glass slides, spread out evenly to avoid particle alignment during sample preparation, and then put into the diffractometer. X-ray diffraction (XRD) was performed with a scan speed of 2° per mm and a chart speed of 2° per 2 cm for each 2θ measurement. [3]

Differential scanning calorimetry analysis

About 5 milligrams of the sample was put on an aluminum cylinder and then placed into the DSC machine. The sample was heated with dry nitrogen gas flowing at 20 mL per minute, and the temperature was increased by 10 degrees Celsius every minute. The heating happened between 10°C and 250°C. An empty aluminum plate was used as a reference. The machine recorded both endothermic and exothermic changes in the sample. The melting temperature and the heat energy involved for each particle were noted. [10]

Recovery of gliclazide in solid dispersions

The wavelength where gliclazide absorbs the most light was found using a solution of gliclazide at 250 µg/mL in phosphate buffer with a pH of 7. 4. A calibration curve was made using different amounts of gliclazide: 6, 8, 10, 12, and 14 mg/mL. Both the physical mix and solid dispersion samples were weighed so they contained 80 mg of gliclazide each. Then, each sample was dissolved in 10 mL of methanol and phosphate buffer pH 7. 4 to make a total volume of 100 mL. The absorbance was measured at the wavelength where gliclazide absorbs the most. The amount of gliclazide in each sample was found by using the calibration curve. [12]

Solubility study

Samples that contained 50 mg of gliclazide were weighed and dissolved in 25 mL of phosphate buffer with a pH of 7. 4 in flask. The samples were placed in an orbital shaker and allowed to shake for 24 hours. After shaking, the samples were filtered using filter paper (Whatman, 0.45 µm). The absorbance of the filtered liquid was then measured using a UV spectrophotometer at the wavelength where the absorbance is highest. [10]

Dissolution study

A dissolution test was conducted using a type 1 dissolution apparatus, which is a basket setup, rotating at 100 revolutions per minute for a total of 2 hours. The liquid used in the test was 900 milliliters of phosphate buffer with a pH of 7. 4, and the temperature of this liquid was kept at 37 degrees Celsius plus or minus 0.5 ^{0}C. The test used a sample that was equal to 80 milligrams of gliclazide. At specific times 5, 10, 15, 30, 45, 60, 90, and 120 minutes about 5 ml of the liquid was collected. To keep the volume constant, 5 ml of the dissolution medium at the same temperature was added each time. The amount of drug in each sample was measured using a UV spectrophotometer at its maximum wavelength. [13]

FTIR results

FTIR spectroscopy was used to compare the spectrum of solid mixtures made from gliclazide and carriers like PVP K-30 and PEG 6000 with the spectrum of pure gliclazide. In every compound, different chemical bonds absorb infrared light in specific ways. In gliclazide, there is a peak at 1707. 53cm−1, which means there is a carbonyl group (C = O). There are also peaks at 1162. 02cm−1 and 1345. 90cm−1, which show the presence of a sulfonyl group. A peak at 3270. 26cm−1 indicates the amino group. These results are shown in Figure 2.

Physical mixtures and solid dispersions of all the formulas still show absorption in the same area and have a similar fingerprint region compared to the spectrum of gliclazide. This means no chemical reactions happened during the making of the solid dispersions. The small change in wave numbers shows there is a physical interaction between gliclazide and the polymers when they are in a solid form. This interaction is due to hydrogen bonds between the amine group on gliclazide and an oxygen atom–ion pair in PEG 6000 or between the sulfonyl group on gliclazide and a hydrogen atom in PVP K-30 or PEG 6000.

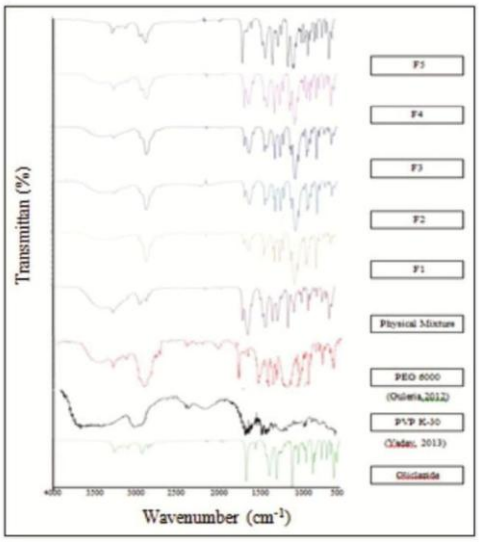

Figure 2: FTIR spectrum of Drug, Polymer and all formulation batches

XRD results

Analysis using XRD was done to study the diffraction pattern of gliclazide, physical mixtures, and solid dispersion formulas. The position of the peaks, which is the angle of diffraction, shows the crystal structure, and the height of the peaks indicates how crystalline the material is. The results are shown in Figure 3.

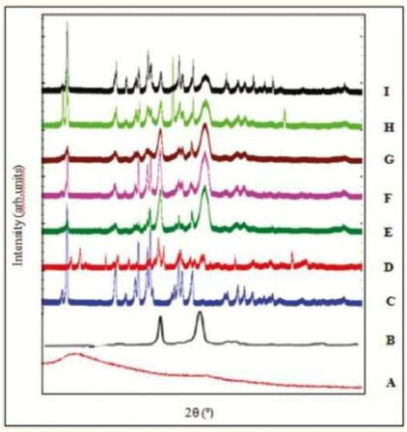

Figure 3: XR Diffractogram of Drug, Polymer and all formulation batches.

The X-ray diffraction pattern of gliclazide shows typical diffraction peaks with high intensity, which means the drug is in a crystalline form. The 2θ angles of the peaks are at 10°, 14 °, 17 °, 18 °, 20°, 213°, 21°, and 26°. The level of crystalline affects how quickly the drug dissolves. Amorphous or metastable forms dissolve faster because they have more internal energy and larger molecules move more easily. [18] In the solid dispersion formulas, there is a change or shift in the peak positions of gliclazide. A sharp peak in pure gliclazide is still visible at the same position in the solid dispersion formulas, but the overall intensity is lower. This means that the drug is still crystalline but with reduced intensity. [19] The change in the position of the diffraction peaks in the solid dispersion formula is likely due to the physical interaction between gliclazide and the polymer, such as polymorphic transformation or a change from one form to another during the evaporation of the solvent in the production of the solid dispersion system.

DSC results

Thermal analysis using a DSC was done to check the melting point and the interactions between gliclazide and the carriers, which are PVP K-30 and PEG 6000. The thermo gram showed a change in temperature at the endothermic peak of the gliclazide solid dispersion when compared to pure gliclazide. The thermo gram of pure gliclazide showed an endothermic reaction, which showed the melting process. A sharp peak at 166. 4°C represents the melting point of gliclazide. These results can be seen in Figure 4. There are two endothermic peaks in the thermogram of the physical

mixture and the solid dispersion systems F2, F4, and F5. These peaks correspond to the melting points of PEG 6000 and gliclazide. The endothermic peak of PEG 6000, which has a melting point of 65°C, has become smaller in the thermogram of the solid dispersion system. The endothermic peak of gliclazide is also broader and smaller, suggesting a decrease in the drug's crystallinity. In the DSC thermogram of solid dispersion F1, there is no peak for gliclazide. This is probably because gliclazide completely dissolved in the melted polymer during the DSC measurement. Overall, the DSC data shows that the components of the PVP K-30 and PEG 6000 solid dispersion systems affect the position and sharpness of the endothermic peak. This suggests a physical interaction between the drug (gliclazide) and the carriers. These findings support the earlier XRD results.

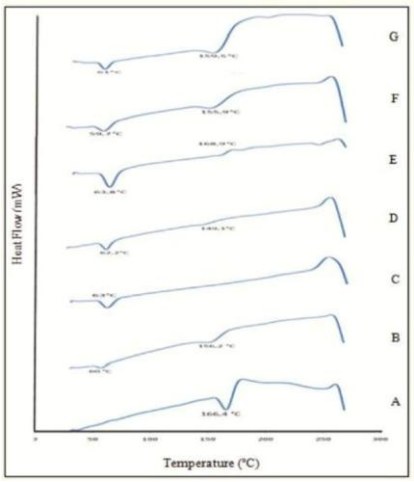

Figure 4: DSC thermogram of Drug, Polymers and all formulation batches.

Recovery results

The peak absorption happens at a wavelength of 223nm. The equation for the calibration curve is y = 0. 041 xs + 0. 064 and the regression value is 0. 999. The recovery of gliclazide in the solid dispersions F1, F2, F3, F4, and F5 are 97%, 102%, 103%, 105%, and 99%, respectively. These results are very close to the British Pharmacopoeia 2009 requirement of 95%–105%. This shows the solid dispersion system was made with care and precision to ensure the gliclazide can be retrieved as required.

Solubility study results

The study on solubility showed that gliclazide dissolved better in physical mixtures and solid dispersions. Formula F4 had the highest solubility, at 1. 478 mg per mL [Table 2]. This improvement happened because PVP K-30 and PEG 6000 helped the gliclazide dissolve more easily in the solid dispersion system.

Sample	Solubility (mg/ml)
Gliclazide	0.90
PM	1.40
F1	1.410
F2	1.31
F3	1.35
F4	1.36
F5	1.432

Dissolution study results

The solid dispersion method may help gliclazide dissolve well than when it is used on its own. Among the different samples, F4 showed the highest level of dissolving. This is shown in Figure 5. After 120 minutes, the amounts of gliclazide dissolved from F1, F2, F3, F4, and F5 were 44%, 47%, 43%, 60%, and 453%, respectively. These results
Suggest that using PEG 6000 and PVP K-30 helps improve how well the solid dispersions dissolve.

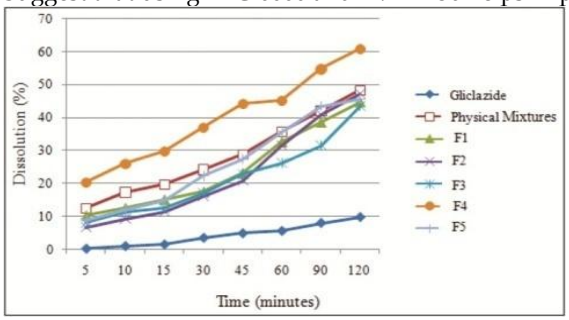

Figure 1: Dissolution profile of Drug, PM and all formulation batches.

There are physical interactions between gliclazide and carriers in solid dispersion system. There are hydrogen bonds between the amine group on gliclazide with one oxygen atom–ion pair in PEG 6000 or oxygen atom on gliclazide sulfonyl group with a hydrogen atom in PVP K-30. Solid dispersion system of gliclazide and carriers used could improve the solubility and dissolution rate of gliclazide.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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