Journal of Molecular Science

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Volume 35 Issue 2, Year of Publication 2025, Page 233-237
DoI-17.4687/1000-9035.2025.032

Journal of Molecular Science

www.jmolecularsci.com ISSN:1000-9035

Formulation and Evaluation of Gliclazide Nanosuspension for Solubility and Dissolution Enhancement

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Article Information
Received: 08-06-2025
Revised: 20-06-2025
Accepted: 09-07-2025
Published: 30-07-2025

Keywords
Nanosuspension, Gliclazide, Solubility, poloxamer, Dissolution.

ABSTRACT

In this study, we tried to make a nanosuspension of Gliclazide, which is a medicine used to treat non-insulin-dependent diabetes mellitus. The nanosuspension was made using the precipitation method with a mix of polymers like PVP K-30, poloxamer (407), sodium lauryl sulphate and acetone. To measure the amount of Gliclazide, we used a spectrophotometer at a wavelength of 232nm. The oral nanosuspension was checked for several physical and biological properties, including drug content uniformity, particle size, zeta potential, in-vitro drug release, short-term stability, and drug-excipients interactions using FTIR. The infrared studies showed there were no interactions between the drug and the excipients. The formulations F1 to F9, which included different ratios of PVP K-30, Eudragit S 100, poloxamer (407), and acetone, were found to be effective. Among them, formulation F9, which had Eudragit S 100 and PVP K-30, released 99% of the drug within 20 minutes and followed first-order drug release kinetics. These formulations showed good nanosuspension stability.

1. INTRODUCTION

Nanotechnology is getting a lot of attention from researchers and the pharmaceutical industry. In the pharmaceutical world, the word Nanoparticle refers to very small particles that are smaller than a micron. The medicine being studied is dissolved, trapped, or wrapped inside these particles. Nanoparticle technology is used as a key method to deliver medicines, such as peptides, proteins, vaccines, and new types of nucleotides. In the field of pharmaceuticals nanosuspension, nanoemulsion, self-nanoemulsifying drug delivery systems, and solid lipid Nanoparticle are all considered parts of nanotechnology. Nanosuspension is made up of tiny drug particles, stabilizers like surfactants or polymers, and a liquid medium. The drug particles are solid and have an average size smaller than 1 micrometer, usually between 200 -500 nanometers. [6] Even though the term nanocrystals sounds like it means the particles are crystal-like, they can be crystal, partially crystal, or completely amorphous.

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The liquid can be water, a mix of water and other liquids, or just non-water-based liquids. Nanosuspension helps in delivering medicines that don't dissolve well in water or break down in the body. Nanosuspension is a type of colloid that contains very small drug particles that are kept stable by surfactants. It can also be seen as a two-phase system where pure drug particles are spread in a liquid and the size of the particles is less than 1 micrometer. Making drug particles as small as nanometers increases their dissolution speed. This happens because the surface area is larger and the solubility is higher. The increased solubility and faster dissolving of Nanoparticle is also because of the higher vapor pressure of the small particles.[1-2]

MATERIALS AND METHODOLOGY:

1. Materials:

Excipients and Chemicals:

Glipizide was obtained as gift sample from JB Chemical Thane. All the materials used in the formulations, evaluation and other experiments are of analytical grade. The double distilled water was used in all experimental work.

2. Methods:

Pre-formulation studies:

Before making a nanosuspension, it's important to know the basic physical and chemical features of the drug by itself and when it's mixed with other ingredients. This first step is called pre-formulation. The main aim of pre-formulation is to gather useful information that helps the formulator create stable and effective drug forms that can be made in large amounts. The main goals of pre-formulation studies are: i) to check the drug substance carefully and find out its important features, ii) to see if it works well with different helper ingredients, iii) to do spectroscopic studies, and iv) to identify the pure drug.

3. Organoleptic properties:

The colour, odour and taste of the drug were recorded using descriptive terminology.[10]

4. Determination of Melting Point:

The temperature at which the first particle of the substance completely melts is regarded as melting point of the substance. The temperature at which the first particle starts to melt and last particle completely melts is regarded as the range of melting point. Melting point of the drug was determined by capillary tube method.

5. Solubility studies of Gliclazide:

Solubility of Gliclazide was carried out in different buffers as follows:

1) Purified water
2) 0.1 N hydrochloric acid (HCl), (pH 1.2) USP
3) Phosphate buffer pH 6.8, USP

6. Preparation of different buffer media:

pH 6.8 Phosphate Buffer: Placed 50.0 ml of 0.2 M potassium dehydrogenate phosphate in a 200-ml volumetric flask and 22.4 ml 0.2 M sodium hydroxide was added, then made up the volume with water.

0.2M Potassium Dihydrogen Phosphate: Dissolved 27.218 g of potassium dehydrogenate phosphate in water and dilute with water to 1000 ml.

0.2M Sodium Hydroxide: Dissolved 8.0 g of sodium hydroxide in 1000 ml. Saturated solutions were made by adding more than enough drug to the liquid medium and shaking it on a shaker for 24 hours at 25°C with constant shaking. The solubility of Gliclazide was checked at a temperature of 25°C plus or minus 10°C. To find out how much Gliclazide dissolves in distilled water and different buffers, the shake flask method was used. In this method, more drug than needed was added to different water-based solutions like distilled water, 0. 1N hydrochloric acid, and pH 6.8 phosphate buffer. The flasks were covered with aluminum foil and shaken continuously at room temperature (25°C ± 10°C) for 24 hours using a mechanical shaker. After 24 hours, the mixture was filtered through a 0. 45 µm membrane filter. The filtered liquid was then diluted as needed, and the amount of drug that had dissolved was measured by checking how much light it absorbed at 232 nm using a UV-VIS spectrophotometer, compared to the absorbance of the blank solution.[14-15]

7. Preparation of Nanosuspension:

Nanosuspension was made using the nanoprecipitation method described by Fessi et al with a small change. ERLPO polymer and the right amount of drug were mixed in acetone at 40°C to create a smooth organic solution. This organic solution was then slowly added drop by drop with a syringe into an aqueous solution that had 2% (w/v) P-188, while the mixture was stirred quickly at 8,000 rpm to form the desired nanodispersion. The nanosuspension was then stirred using a magnetic stirrer at 500 rpm at room temperature for 12 hours to remove the organic solvent. The complete removal of acetone was checked using the vanillin method. After that, the volume was adjusted by adding triple distilled water to make up for any loss in volume. All samples were made in three copies. The ratio of drug to polymer and the stirring time were changed, while all other conditions stayed the same.[12]

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8. Evaluation of Nanosuspension:

Organoleptic properties:

The color, odor and taste of the drug were recorded using descriptive terminology and found to be yellow crystalline powder, bitter taste and odourless.

Determination of Melting Point:

The melting point of Gliclazide was found to be between 168°C. This was determined using the capillary method. A fine powder of Gliclazide was placed into a glass capillary tube that had one end already sealed. The tube was attached to a thermometer, and the whole setup was placed in a fire. The temperature at which the powder started to melt was then observed.

Saturation Solubility:

Saturation solubility was done at 25^0C using three different solution pH 6.8 phosphate buffer, 0.1 N HCl and purified water. Gliclazide has shown highest solubility in pH 6.8 phosphate buffer, as well as in 0.1N HCl (Table 6.1 and Figure 6.1). It is practically insoluble in water**.** The solubility of Gliclazide in pH 6.8 phosphate buffer was almost similar which is in the range of 5-20 mg/ml, indicating the high solubility of the drug was in acidic pH. From the above conducted solubility studies in various buffers we can say that pH 6.8 phosphate buffer has more solubility when compared to other buffer solutions due to reason gliclazide is a weak acid with good lipophilicity. Results show that gliclazide has poor solubility in the acidic media and its solubility increases as the ph becomes more alkaline. This confirms the selection of pH 6.8 phosphate buffer as dissolution medium.

Table 1: Solubility determination of gliclazide in different medium

Media	**Solubility(mg/ml)**
0.1 N HCL	7.50
6.8 Phosphate buffer	12.30
Purified water	1.08

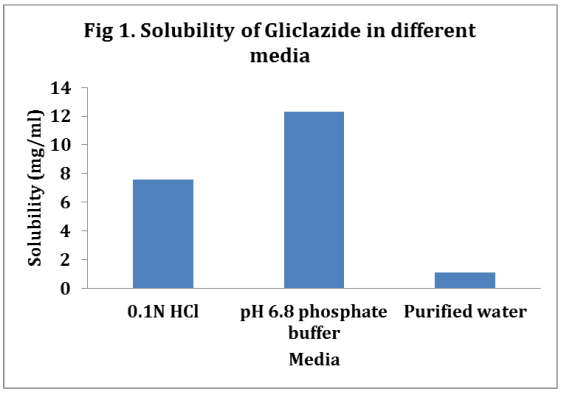

Figure 1: Solubility of Gliclazide in Different Media

Compatibility Studies:

Compatibility study is important because it help to understand the how drug is interacted with polymers. It saves costs and it makes easier to choose a few excipients from the long list of excipients for a better formula. Drug- excipients interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. In the present study, it has been observed that there is no chemical interaction between drug and the polymers used. No prominent difference was observed in the principal IR peaks of Gliclazide, Optimized stabilisers, physical mixture formulations upon comparison with the peaks of drug and stabiliser alone, which may considered that Gliclazide, Eudragit S100, Poloxamer and PVP are compatible enough without any interactions.

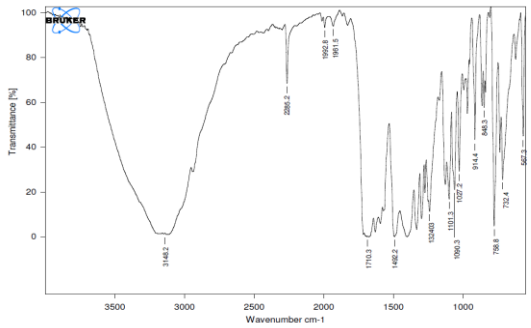

Figure 2: FTIR spectra of drug and polymers

Spectrum curve of Gliclazide:

The maximum absorbance of the Gliclazide in 6.8 phosphate buffer was found to be 232nm. Hence the wavelength of 232nm was selected for analysis of drug in dissolution media.

Calibration Curve Determination:

The standard calibration curve shown linearity, through that the drug obeys Beers and Lamberts law in the concentration range of 5 to 30µg/mL. A standard graph was plotted by keeping the known concentration on X – axis and obtained absorbance on Y – axis. The values of calibration curve of Gliclazide with 6.8 phosphate buffer were given below

Table 2: standard graph of gliclazide

concentration	absorbance
0	0
5	0.1322
10	0.2740
15	0.4323
20	0.5877
25	0.7411
30	0.8891

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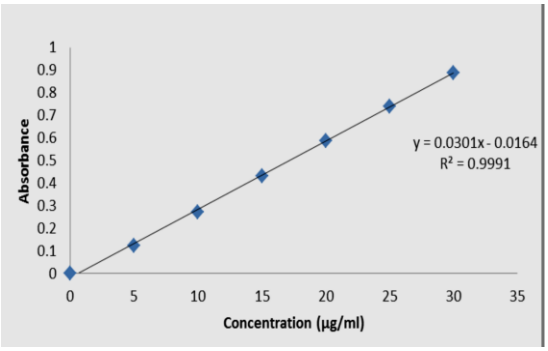

Figure 3: Calibration curve of gliclazide

Linear relationship was observed between concentration of drug solution (5-30µg/ml) and absorbance in 6.8 phosphate buffer The coefficient of correlation (R2)was found to be 0.999, indicating that drug solution obeys Beer's- Lambert law in the concentration range of 5-30µg/ml. Hence it was concluded that dissolution samples can be analyzed in 6.8 phosphate by measuring absorbance at 232 nm using UV-Visible Spectrophotometer.

Drug content: The drug content of the formulated Nanosuspension was found in the range of 93.26 to 99.87% respectively.

Nanosuspension of Drug content.
The amount of drug in formulation F1 was 93%, in F2 it was 94%, in F3 it was 93%, in F4 it was 94%, in F5 it was 95%, in F6 it was 96%, in F7 it was 95%, in F8 it was 96%, and in F9 it was 99%.
Entrapment efficacy: - The entrapment efficacy of the formulated Nanosuspension was found to be in the range of 72.55% to 96.30% respectively.

Table 3: Entrapment Efficiency of Gliclazide Nanosuspension

Formulation Code	Entrapment
F1	72.55±0.07
F2	73.10±0.64
F3	72.99±0.46
F4	78.62±0.29
F5	80.21±0.60
F6	82.19±0.47

The entrapment efficacy of formulation F1 was found to be 72.55%, formulation F2 was found to be 73.10%, formulation F3 was found to be 72.99%, formulation F4 was found to be 78.62%, formulation F5 was found to be 80.21%, formulation F6 was found to be 82.19%, formulation F7 was found to be 88.54 %, formulation F8 was found to be 94.63 %, and finally formulation F9 was found to be 96.30%.

Zeta potential: The test uses a method called particle electrophoresis. It measures how fast particles move when a electric field is applied. This movement is detected by looking at the change in the color of light scattered by the moving particles, which is called the Doppler shift. A voltage of 20 volts per centimeter was used. The speed of the particles is then used to find the zeta potential in millivolts. To do this, the electrophoretic mobility is multiplied by a factor of -12. 8, based on the Helmholtz-Smoluchowski equation. This equation works well under standard conditions, which include a room temperature of 25^0C

Stability study:
The stability of the optimized formulation F12 was tested under three temperature conditions: 4-8°C (refrigerator), room temperature (25±2°C), and 45±2°C (stability chamber). The drug content and in vitro drug release were measured and shown in table 6. 7. From the data, it is clear that the prepared nanosuspension F9 remained stable for three months when stored under these different temperature conditions.

Drug content of optimized formulation

Sr. No	Formulation code	1 st day	30 th day	60 th day	90 th day
1	F9	99 %	98%	98%	98%

DISCUSSION:

During FTIR study it was cleared that there was no any chemical interaction between the drug and various excipients was found. Gliclazide drug is from poorly water-soluble drug category and this nanoprecipitation method was used for the preparation of nanosuspension was able to increase the solubility and dissolution rate of the formulation. Particle size of drug can be obtained in nano range, by changing various surfactant and polymer concentration and agitated at 6000 rpm and the time was 12 hours keep constant. The optimum concentration of different polymers and surfactant was successfully showed effect on particle size reduction. Formulation F9 showed greatest drug release and drug content due to optimal concentration of different polymers used in the study. For all the formulations various evaluation parameters was done like particle size, dissolution rate which shows rapid dissolution. Showed value of optimized formulation was desirable and it indicates that prepared formulation was stable. Surface morphology was also studied which showed that prepared nanosuspension were spherical with smooth surface. For all formulation batches drug release study was carried out and among them F9 formulation selected which showed highest % release of nanosuspension than other batches. Cumulative percentage drug release of nanosuspension with increase optimal concentration of the polymers.

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CONCLUSION:

The study found that Gliclazide nanosuspension can be made using different types of polymers and surfactants. The results showed that F5 released the drug slowly, mainly because the drug was in very small particles. This means the goal of making the nanosuspension using the nanoprecipitation method was successfully achieved. The new liquid form of the medicine works well for patients and is especially useful for adjusting doses in diabetes treatment. In the future, scientists should focus on developing this type of medicine for traditional dosage forms and also use it in industrial production.

ACKNOWLEDGEMENT:

The authors express their gratitude to JB Pharma Thane for the complimentary drug sample. They also express their sincere gratitude to MIT College, Valmik Naik College of Pharmacy Kannad, Teerthanker Mahaveer University, Moradabad, for providing the facilities needed to carry out the research.

AUTHOR CONTRIBUTION:

All authors have contributed to design the study as well as to analysis and interpretation of data. Each of played active roles in drafting, evaluation of data and revision of manuscript. All authors have consented to the submission of the manuscript to the journal, and given final approval for the publication.

FINANCIAL SUPPORT:

This research study has no fund from any government or private recourses.

CONFLICT OF INTERST:

No financial conflicts of interest are disclosed by the authors of this study.

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