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**Research Paper**

# Solubility Enhancement of Glibenclamide – Bougainvillea Nanosuspension for Anti-Diabetic Activity

**Balaji M, Keerthika J, Krishnan K, Narmathavalli R, Abirami M***

*Tagore College of Pharmacy, Rathinamangalam, Chennai, Tamilnadu, India.*

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## ABSTRACT

This research sought to improve the solubility and therapeutic effectiveness of Glibenclamide, an anti-diabetic medication with poor water solubility, by creating a nanosuspension formulation that included Bougainvillea spectabilis extract. Glibenclamide, classified as a BCS Class II drug, has limited aqueous solubility, which consequently restricts its dissolution rate and oral bioavailability. The inclusion of Bougainvillea spectabilis, a medicinal plant known for its D-pinitol content and demonstrated anti-diabetic properties, was intended to achieve a combined hypoglycemic effect. The nanosuspension was developed using appropriate stabilizers and excipients to decrease particle size and enhance dispersion stability. The formulation's physicochemical properties, such as particle size, stability, and solubility, were assessed. Phytochemical analysis of the plant extract revealed the presence of active compounds, including flavonoids, phenolics, tannins, alkaloids, glycosides, and other secondary metabolites associated with therapeutic effects. The nanosizing technique enlarged the drug particle surface area, leading to better dissolution and increased drug absorption. The developed Glibenclamide–Bougainvillea nanosuspension exhibited enhanced solubility and is anticipated to improve oral absorption and anti-diabetic effectiveness over the standard formulation. D-pinitol's presence may aid in better glucose control via insulin-sensitizing and insulin-mimetic mechanisms.

## INTRODUCTION

Oral drug delivery is the most widely accepted route due to its convenience and patient compliance. However, poor solubility of drugs like Glibenclamide leads to reduced bioavailability. Nanosuspension technology offers a promising solution by reducing particle size and enhancing dissolution rate. [1,2]

***Corresponding Author:** Abirami M
**Address:** *Assistant Professor, Department of Pharmaceutics*, *Tagore College of Pharmacy, Rathinamangalam, Chennai, Tamilnadu, India.*
**Email** : m.k.abirami21@gmail.com

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Bougainvillea spectabilis is a medicinal plant known for its antidiabetic, antioxidant, and anti-inflammatory properties. The presence of D-pinitol contributes significantly to its hypoglycemic activity. Combining herbal extract with synthetic drug in nanosuspension form can provide synergistic therapeutic benefits. [3-5]

Diabetes mellitus (DM) is a metabolic disorder marked by excessively high blood sugar levels. This condition encompasses various forms, such as type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and secondary diabetes caused by endocrinopathies and steroid use. The primary types of diabetes mellitus are type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), which are traditionally linked to impaired insulin secretion (T1DM) and/or function (T2DM). T1DM typically appears in children or teenagers, while T2DM is generally associated with adults in middle age or older, often due to extended periods of high blood sugar resulting from unhealthy lifestyle and dietary habits. The development mechanisms of T1DM and T2DM differ significantly, leading to distinct causes, symptoms, and treatment methods for each. Management of diabetes involves lifestyle changes, monitoring of blood glucose levels, insulin therapy, oral medications, advanced treatments like islet cell transplantation, and supportive care.[6-9]

Nanosuspension consists of the pure poorly water-soluble drug without any matrix material suspended in dispersion medium. It is one of the promising forms of drug delivery. Preparation of nanosuspension is simple and applicable to all drugs which are poorly water soluble and it has high drug loading capacity. A nanosuspension not only solves the problems of poor solubility and bioavailability, but also alters the pharmacokinetics of drug and thus improves drug safety and efficacy. Sometimes sedimentation and compaction can cause problems. [10]

**RATIONALE BEHIND NANOSUSPENSION:**

1. **Improves solubility of poorly water-soluble drugs:** Many drugs such as BCS class II & class IV (low solubility). Reducing particle size can increase surface area, leading to better interaction with dissolution media.
2. **Enhances dissolution rate:** According to the Noyes–Whitney equation, decreased particle size, increases surface area which leads to faster dissolution results in faster onset of action.
3. **Improves bioavailability:** Both faster dissolution and better solubility improves absorption, which results in higher and more consistent bioavailability.
4. **Enables versatile drug delivery system:** Nanosuspensions can be used for Oral, Parenteral (IV, IM), Pulmonary, Ocular, Topical delivery.
5. **Suitable for drugs insoluble in both water and organic solvents:** Some drugs cannot be formulated as solutions or emulsions. Nanosuspension allows formulation without the need for harsh solvents with wider formulation possibilities.
6. **Improves physical and chemical stability:** Avoids instability associated with drug solutions, which longer shelf life. [11]

**Methods of Preparation of nanosuspension:**

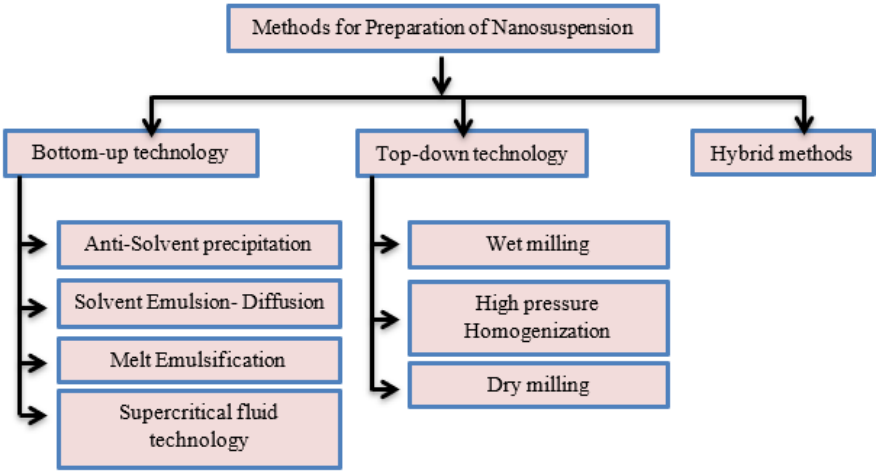


**Fig. 1: Schematic diagram for methods for preparation of Nanosuspension**

## MATERIALS AND METHODS

### Materials

Glibenclamide, Carbopol 934, Tween 80, Propylene glycol, Sodium Lauryl Sulphate, Glycerin, Mannitol, and Benzoic acid were used.

### Preparation of Plant Extract

Bougainvillea leaves were dried in shade, dried leaves were powdered, and extracted using 70% ethanol by triple maceration for 72 hours, followed by filtration and evaporation. [12,13]

water-soluble drug and shows improved solubility in organic solvents or alkaline pH conditions.

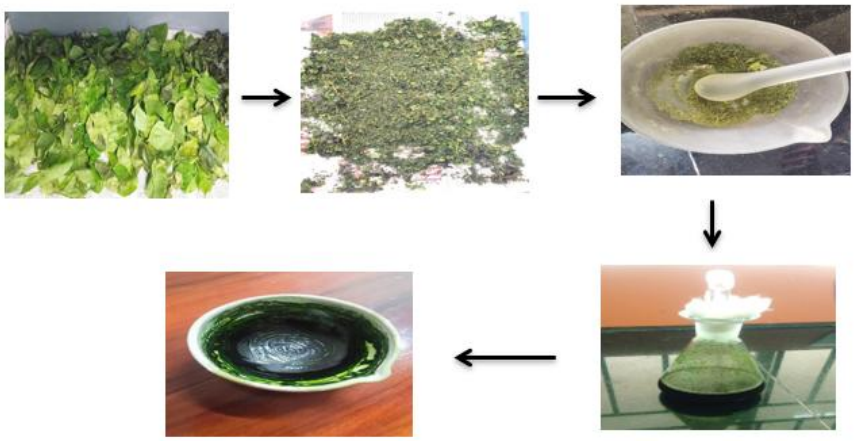

**Fig. 2: Workflow of the extraction Process**

### Preformulation studies:

The scope of Preformulation studies is to maximize the chance of formulating safe, efficacious, acceptable and safe products. The Preformulation studies were performed to identify solubility of drug, to confirm the physical appearance, to determine the melting point of the drug, and to study compatibility between the drug and other excipients.

### Solubility studies:

The solubility of Glibenclamide can be determined by the shake flask method. An excess amount of Glibenclamide API is added to a known volume (10 - 25 ml) of selected solvent such as distilled

water, 0.1 N HCl, phosphate buffer (pH 6.8), or other suitable media in a stoppered conical flask to obtain a saturated solution. The mixture is placed in a mechanical shaker and agitated continuously for 24 - 48 hours at a controlled temperature of 25 ± 2°C (or 37°C, if required). After equilibration, the solution is allowed to stand and then filtered through Whattman filter paper or a 0.45 µm membrane filter to remove undissolved particles. The filtrate is suitably diluted, and the concentration of dissolved drug is determined using a UV spectrophotometer at the 300 nm. The solubility is calculated and expressed in mg / ml or µg / ml. Glibenclamide is a poorly water-soluble drug and shows improved solubility in organic solvents or alkaline pH conditions.

**Determination of Melting Point:**

The drug's melting point was assessed using the capillary glass technique. A small quantity of the drug was placed in a capillary tube sealed at one end. This tube was then inserted into a melting point apparatus, and the temperature at which the drug began to melt was recorded. These observed melting points were then compared to the values reported in the literature. [14]

**Compatibility studies:**

This study was mainly used for detection of compatibility between API and excipients by studying the IR stretching regions of API. The occurrence of any change in IR stretching regions of specific functional groups of API due to incorporation of excipients can be identified and it will directly indicate if there was an existence of incompatibility between API and excipients used. FTIR spectra were recorded using the potassium bromide disc method. Spectra were obtained for Glibenclamide individually, as well as in combination.

**Construction of standard curve:**

**Preparation of Calibration Curve for Glibenclamide:** Before measuring the drug content, you need a calibration curve to determine the unknown concentration of Glibenclamide in the sample.

**Preparation of stock solution:** Dissolve 10 mg of Glibenclamide in 100 ml of phosphate buffer pH 6.8 to make a 100 µg/ml stock solution.

**Preparation of Standard Solution:** Pipette out 1, 2, 4, 6, 8, and 10 ml of stock solution into separate 10 ml volumetric flasks and dilute with solvent to obtain 1, 2, 4, 6, 8, and 10 µg/ml solutions. An absorbance maximum is determined by using UV-Vis spectrophotometer. Plot concentration Vs absorbance to get the calibration curve.

**Formulation of Nanosuspension**

**Table. 1: Formulation of Nanosuspension**

| S.NO | INGREDIENTS | QTY (For 100 ml) |
|---|---|---|
| 1. | Glibenclamide | 1.25 mg |
| 2. | Bougainvillea leaf extract | 2.5 mg |
| 3. | Ethanol | 5 ml |
| 4. | Carbapol 934 | 100 mg |
| 5. | Sodium Lauryl Sulphate | 0.25 ml |
| 6. | Tween 80 | 0.25 ml |
| 7. | Mannitol | 1.25 mg |
| 8. | Glycerin | 1 ml |
| 9. | Benzoic acid | 0.025 mg |
| 10. | Distilled water | 100 ml |

Nanosuspension was prepared by anti-solvent nanoprecipitation method. Drug was dissolved in ethanol (organic phase) and injected into aqueous phase containing polymer and surfactants under continuous stirring at 1500 rpm for 8 hours. [15]

## EVALUATION PARAMETERS

### Physical appearance

The nanosuspension's appearance was visually evaluated for its clarity, color, phase separation, and uniformity. To identify any particulate matter or signs of instability, the formulation was examined against a black-and-white background.

### pH Measurement

The pH level of the nanosuspension was measured at room temperature using a calibrated digital pH meter.

### Viscosity Assessment

The viscosity of lipid-based formulations with different compositions was measured at various shear rates and temperatures using a Brookfield-type rotational viscometer.

### Scanning Electron Microscope

A Scanning Electron Microscope (SEM) was employed to investigate and analyze the microstructure morphology and chemical composition. This technique involves scanning a high electron beam over the surface and observing the backscattering of electrons. The sample is mounted on a metal stub with adhesive and coated with 40-60 nm of metal, such as gold and palladium. The signals include secondary electrons (which produce SEM images), back-scattered electrons (BSE), diffracted back-scattered electrons (EBSD used to determine crystal structures and orientations of minerals), photons (characteristic X-rays for elemental analysis and continuum X-rays), visible light, and heat. Secondary electrons and back-scattered electrons are commonly used for imaging samples; secondary electrons are most useful for displaying morphology and topography, while back-scattered electrons are valuable for illustrating compositional contrasts in multiphase samples.

### Zeta Potential

The zeta potential was utilized to assess the stability and surface charge of the nanosuspension. The sample was diluted with deionized water before being analyzed with a zeta potential analyzer. Zeta potential value greater than ± 30 mV indicates strong stability due to particle electrostatic repulsion.

### Rate of sedimentation

To assess the sedimentation rate of nanosuspension containing glibenclamide and bougainvillea extract, the initial height (H0) of a 25 ml sample was recorded after agitation in a 50 ml graduated cylinder. After allowing the mixture to stand for 3 hours, the sedimentation height (H) was measured in the same cylinder. [16]

### Particle size distribution

The Polydispersity Index (PDI) can range from 0.01, indicating monodispersed particles, to between 0.5 and 0.7, while a PDI value exceeding 0.7 suggests a wide particle size distribution in the formulation. The size and distribution of particles are crucial for evaluating the performance of nanoparticles.

### Invitro drug release

Invitro drug release experiments were conducted using a Franz diffusion cell. The receptor

compartment was filled with 20 mL of phosphate buffer at pH 7.4, maintained at a temperature of 37 ± 0.5°C. A magnetic stirrer was placed in the receptor compartment, ensuring continuous stirring at 500–600 rpm throughout the experiment. A pre-treated membrane was positioned between the donor and receptor compartments, ensuring no air bubbles were present and that proper contact with the receptor medium was maintained. A measured amount of nanosuspension was evenly distributed in the donor compartment. The donor compartment was sealed to prevent evaporation, and the diffusion study commenced. At specific time intervals (10, 20, 30, 40, and 50 minutes; 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 5 hours; and every hour up to 24 hours), 2 mL samples were extracted from the receptor compartment. After each extraction, an equal volume (2 mL) of fresh, pre-warmed receptor medium was added to maintain a constant volume and sink conditions. The samples taken were analyzed using a UV–Visible spectrophotometer at designated wavelengths.

## RESULTS

### Preformulation Studies

FT-IR studies confirmed compatibility between drug and excipients with no significant peak shifts.

### Calibration Curve

Glibenclamide showed linearity with $R^2 = 0.998$ at 245 nm.

### Evaluation Parameters

### Physical appearance

The formulation shows acceptable physical characteristics with brownish green colour, Characteristic odour, slightly bitter taste, good clarity and no particulate matter.

### pH determination

The pH value of the formulation was found to be 5.45, which is slightly acidic and falls within an acceptable range for nanosuspension, indicating its suitability and stability.

### Viscosity

Since the optimum viscosity range for a nanosuspension is 4.5 to 6.5 cP, the viscosity of the prepared formulations was found to be 5.72 cP.

### Scanning Electron Microscope

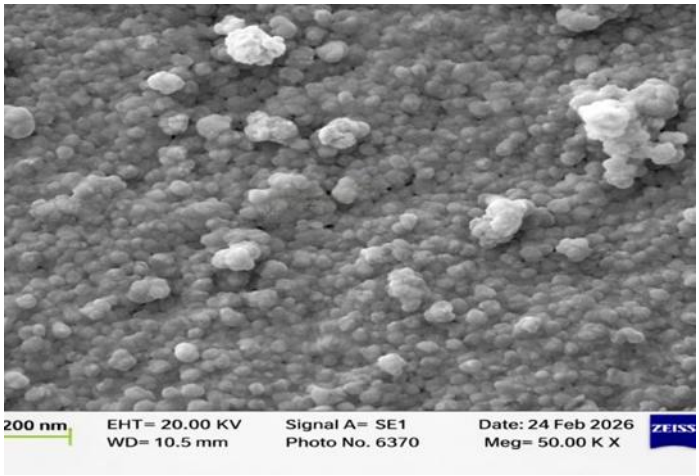


**Fig. 2: SEM Image of nanosuspension**

SEM analysis revealed nearly spherical nanoparticles with a size range of approximately 30-200 nm. Some degree of agglomeration was observed, which may be attributed to high surface energy of nano sized particles. The surface morphology appeared smooth to slightly rough, indicating possible polymeric stabilization.

**Zeta potential**

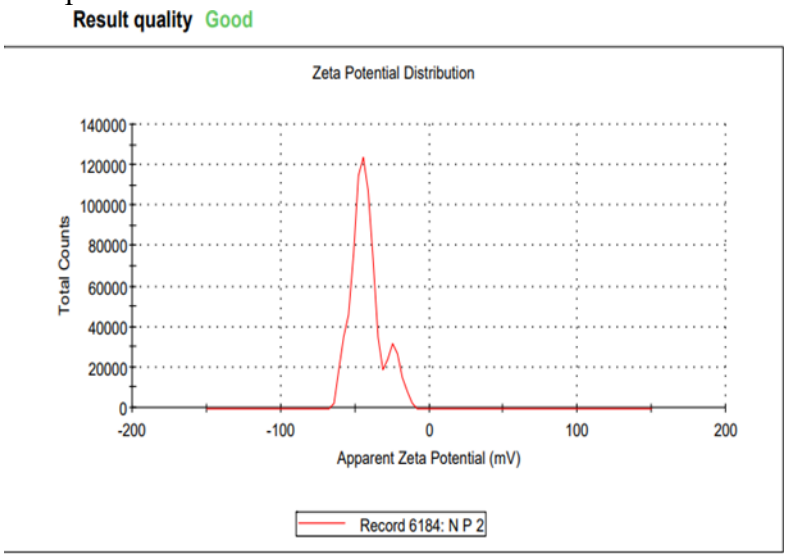


**Fig. 3: Zeta potential of nanosuspension**

The value appears around -25 mV, the nanosuspension has moderate physical stability and good electrostatic repulsion between particles.

**Sedimentation rate**

The sedimentation rate was found to be 0.725 mm which indicates good reproducibility, physical stability and consistency of formulation with minimal particles settling.

**Particle size distribution:**

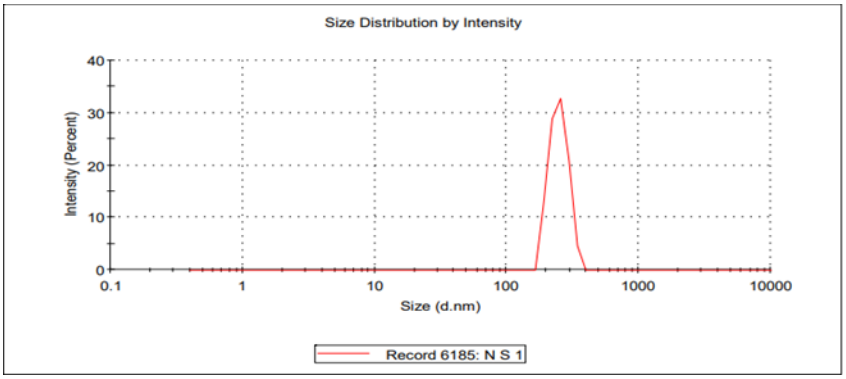


**Fig. 4: Particle size distribution**

The narrow peak indicates uniform particle size distribution, the single peak indicates monodispersed system and nano range (< 200nm).

Sustained release observed up to 24 hours with cumulative release ~46%.

**In-vitro drug release:**

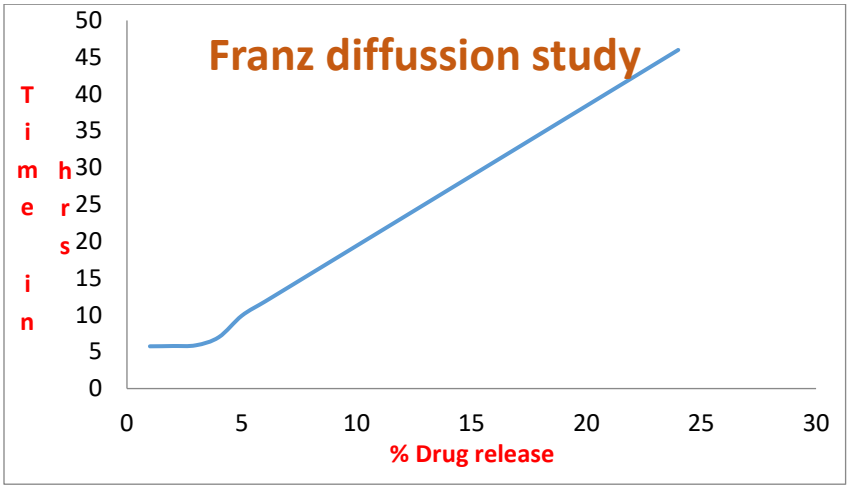


**Fig. 5: In-vitro drug release studies**

## DISCUSSION

In the present study, Glibenclamide - bougainvillea leaf extract nanosuspension were successfully formulated by the Anti-solvent precipitation method. The, Glibenclamide-bougainvillea leaf extract nanosuspension formulation were assessed based on key physicochemical and performance parameters, including pH, viscosity, zeta potential, drug content, sedimentation rate, SEM analysis, Franz diffusion cell and visual appearance.

## CONCLUSION

The study successfully formulated a stable Glibenclamide–Bougainvillea nanosuspension with improved physicochemical properties. It can be concluded that nanosuspension particle size, pH, viscosity, zeta potential, SEM values are in specified range but diffusion study does not shows promising drug release may be due to strong drug polymer interaction, dense nanoparticle matrix, high encapsulation efficiency, poor drug solubility in release medium, pH-dependent drug solubility, limited surface drug availability. Therefore, further optimization of the formulation is required. Modifying polymer/lipid concentration, incorporating release-enhancing surfactants, optimizing drug-polymer ratio, adjusting the dissolution medium pH and reducing matrix density may help to improve the drug release behaviour of the nanosuspension.

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