Journal of Complementary Medicine Research, ISSN: 2146-8397 Vol. 17, No. 1, 2026(pp. 253-262)
RESEARCH ARTICLE WWW.JOCMR.COM

Design and optimization of Glibenclamide -nanoemulsion Technology for Enhanced Drug Delivery

[1] Dasari Venkata charan, [2] Kranthi , [3] Praveen Guijula, [4] D.Ragava, [5] Kavala Nagaswara Rao

[1]PG Scholar, Department of Pharmaceutical Technology , KGRL College of Pharmacy ,Bhimavaram,West Godavari, Andhra Pradesh, India 534201.
[2]Assistant Professor, Department of Pharmaceutical Technology, KGRL College of Pharmacy, Bhimavaram, West Godavari, Andhra Pradesh, India 534201.
[3]Professor, Department of Pharmaceutical Technology, KGRL College of Pharmacy, Bhimavaram, West Godavari, Andhra Pradesh, India 534201.
[4]Principal and Professor Department of Pharmaceutical Chemistry, KGRL College of Pharmacy, Bhimavaram,West Godavari, Andhra Pradesh, India 534201.
[5]Director and Professor Department of Pharmaceutical analysis,KGRL College of Pharmacy, Bhimavaram, West Godavari, Andhra Pradesh, India 534201

ABSTRACT

The present research focuses on the design, development, and optimization of a glipalamide-loaded nano emulsion to overcome the limitations associated with its poor aqueous solubility and variable oral bioavailability. Glipalamides, a BCS Class II antidiabetic drug, exhibits dissolution-limited absorption, leading to inconsistent therapeutic outcomes and an increased risk of hypoglycaemias. Nano emulsion technology was employed as a novel drug delivery strategy to enhance solubility, dissolution rate, and oral bioavailability. The formulation was developed using pharmaceutically acceptable oils, surfactants, and co-surfactants selected through systematic solubility and compatibility studies. Pseudo-ternary phase diagrams were constructed to identify the nano emulsion region, and optimization was carried out using a statistical design of experiments approach. The optimized nanoemulsion exhibited nanosized droplets with low polydispersity index, suitable zeta potential, high drug entrapment efficiency, and excellent physical stability. In vitro drug release studies demonstrated a significantly enhanced dissolution profile compared to pure drug and marketed formulations. Stability studies confirmed the robustness of the optimized formulation under accelerated and long-term storage conditions. Overall, the study demonstrates that nanoemulsion-based delivery is an effective approach for improving the biopharmaceutical performance of glibenclamide, offering potential benefits such as dose reduction, improved safety, enhanced patient compliance, and better glycemic control in the management of type 2 diabetes mellitus.

INTRODUCTION

PHARMACEUTICAL NANOTECHNOLOGY

Pharmaceutical nanotechnology represents a revolutionary approach in drug delivery systems, involving the manipulation of matter at the nanoscale (1-1000 nm) to enhance therapeutic efficacy and minimize adverse effects [1]. The application of nanotechnology in pharmaceutics has opened new horizons for improving drug bioavailability, targeting specific tissues, and overcoming various physiological barriers that limit conventional drug delivery systems [2]. The rationale behind nanoscale drug delivery systems stems from their unique

physicochemical properties, including high surface area to volume ratio, quantum effects, and the ability to interact with biological systems at the molecular level [3]. These properties enable nanocarriers to modulate drug release, enhance cellular uptake, and improve pharmacokinetic profiles of therapeutic agents.

Nanoparticulate drug delivery systems offer several distinct advantages over conventional formulations including enhanced solubility and dissolution rate of poorly water-soluble drugs, improved bioavailability through enhanced permeation and retention, targeted drug delivery to specific tissues or organs, and controlled and sustained drug release [4]. Additionally, these systems provide protection of drugs from degradation in biological environments, reduction in dose frequency and associated side effects, and improved patient compliance [5]. The development of nanopharmaceuticals has gained significant momentum over the past two decades, with numerous products receiving regulatory approval and many more in various stages of clinical development [6]. The global nanomedicine market is projected to experience substantial growth, driven by increasing prevalence of chronic diseases, growing demand for targeted therapies, and advances in nanotechnology research.

CLASSIFICATION OF NANOPARTICULATE DRUG DELIVERY SYSTEMS

Nanoparticulate drug delivery systems can be broadly classified based on their composition, structure, and mechanism of drug incorporation [7]. Lipid-based nanocarriers utilize lipids as the primary structural component and include liposomes, which are vesicular structures composed of one or more phospholipid bilayers enclosing an aqueous core and can encapsulate both hydrophilic and lipophilic drugs [8]. Solid lipid nanoparticles are colloidal carriers composed of solid lipids that remain solid at body temperature, offering controlled drug release and physical stability, while nanostructured lipid carriers represent second-generation lipid nanoparticles containing a mixture of solid and liquid lipids, providing enhanced drug loading capacity and reduced drug expulsion during storage [9]. Nanoemulsions are kinetically stable dispersions of two immiscible liquids, typically oil and water, stabilized by surfactants with droplet sizes in the nanometer range [10].

Polymer-based nanocarriers utilize natural or synthetic polymers such as polymeric nanoparticles prepared from biodegradable or non-biodegradable polymers including PLGA, PLA, PCL, and chitosan [11]. Polymeric micelles are self-assembled amphiphilic block copolymers forming core-shell structures in aqueous media, while dendrimers are highly branched, three-dimensional macromolecules with well-defined architecture and multiple functional groups [12]. Inorganic nanocarriers include carbon nanotubes, which are cylindrical carbon structures with unique mechanical and electrical properties, mesoporous silica nanoparticles with high surface area and tunable pore sizes, and metallic nanoparticles such as gold, silver, or iron oxide with unique optical and magnetic properties [13]. Hybrid nanocarriers represent combinations of different materials to achieve synergistic benefits, such as lipid-polymer hybrid nanoparticles [14].

NANOEMULSIONS: AN OVERVIEW

Nanoemulsions, also referred to as miniemulsions, ultrafine emulsions, or submicron emulsions, represent a class of heterogeneous systems consisting of two immiscible liquids, typically oil and water, where one liquid is dispersed as nanoscale droplets ranging from 20 to 500 nm in the other liquid, stabilized by an interfacial film of surfactant molecules [15]. These systems possess several distinctive characteristics that differentiate them from conventional emulsions and microemulsions, including their transparent or translucent appearance due to droplet size smaller than the wavelength of visible light, high kinetic

stability with minimal creaming, sedimentation, or coalescence, and low viscosity compared to conventional emulsions [16].

Literature Review

Nano emulsion Technology: An Overview

Nanoemulsions are kinetically stable colloidal dispersions consisting of oil and water phases stabilized by surfactants and co-surfactants, with droplet sizes typically ranging from 20 to 200 nm [34]. These systems offer several advantages over conventional formulations, including improved drug solubilization, enhanced permeability across biological membranes, and prolonged circulation time [35]. The small droplet size provides a large interfacial area for drug absorption, while the lipidic nature of nanoemulsions facilitates lymphatic uptake, thereby bypassing first-pass metabolism [36]. Recent studies have demonstrated that nanoemulsion-based delivery systems can significantly improve the pharmacokinetic profile of poorly soluble drugs by increasing their dissolution rate and membrane permeability [37].

Formulation Components and Their Selection

The development of glibenclamide-loaded nanoemulsions requires careful selection of excipients to ensure optimal drug loading, stability, and therapeutic performance. The oil phase serves as the primary solubilizing medium for the lipophilic drug and should be selected based on its drug solubilization capacity [38]. Commonly employed oils include medium-chain triglycerides, oleic acid, and various vegetable oils, each offering distinct advantages in terms of drug solubility and formulation stability [39]. The surfactant selection is equally critical, as it determines the interfacial tension reduction and droplet size distribution [40]. Non-ionic surfactants such as Tween 80, Cremophor EL, and polysorbates are frequently preferred due to their biocompatibility and ability to form stable nanoemulsions [41].

Co-surfactants play a synergistic role by further reducing interfacial tension and increasing the fluidity of the interfacial film, thereby facilitating nanoemulsion formation [42]. Short-chain alcohols like ethanol and propylene glycol are commonly used as co-surfactants in pharmaceutical nanoemulsions [43]. The optimal ratio of surfactant to co-surfactant (Smix) is a critical parameter that influences droplet size, polydispersity index, and overall formulation stability [44]. Systematic screening studies using solubility tests and compatibility assessments are essential for identifying the most suitable combination of excipients [45].

Preparation Methods for Nanoemulsions

Various preparation techniques have been employed for the fabrication of glibenclamide nanoemulsions, each with distinct advantages and limitations. High-energy methods, including high-pressure homogenization and ultrasonication, utilize mechanical energy to disrupt the dispersed phase into nanometer-sized droplets [46]. These techniques are particularly effective for producing nanoemulsions with narrow size distributions and high kinetic stability [47]. Low-energy methods, such as spontaneous emulsification and phase inversion temperature techniques, rely on the internal chemical energy of the system and offer advantages in terms of scalability and energy efficiency [48].

The selection of an appropriate preparation method depends on factors such as drug stability, desired droplet size, equipment availability, and manufacturing scale [49]. Microfluidization has gained attention as an advanced technique that combines high shear forces with controlled temperature conditions to produce uniform nanoemulsions with enhanced stability [50]. Recent comparative studies have shown that the preparation method significantly

influences the physicochemical characteristics and in vivo performance of nanoemulsion formulations [51].

Optimization Strategies Using Design of Experiments

The optimization of glibenclamide nanoemulsion formulations requires a systematic approach to identify the optimal combination of formulation and process variables [52]. Quality by Design (QbD) principles, incorporating statistical design of experiments (DoE), have become the gold standard for rational formulation development [53]. Common experimental designs include factorial designs, central composite designs, and Box-Behnken designs, which allow for the simultaneous evaluation of multiple variables and their interactions [54].

Independent variables typically investigated include oil concentration, surfactant-to-co-surfactant ratio, drug loading, homogenization speed, and homogenization time, while dependent variables encompass droplet size, polydispersity index, zeta potential, drug loading efficiency, and in vitro release rate [55]. Response surface methodology enables the construction of mathematical models that predict formulation performance and identify the optimal formulation composition [56]. Desirability functions are often employed to simultaneously optimize multiple responses, ensuring a balanced formulation that meets all critical quality attributes [57]. The application of DoE approaches not only reduces the number of experiments required but also provides a comprehensive understanding of formulation behavior across the design space [58].

Characterization of Nanoemulsion Formulations

Comprehensive characterization of glibenclamide nanoemulsions is essential to ensure product quality and predict in vivo performance. Droplet size analysis using dynamic light scattering provides information on the mean particle diameter and polydispersity index, which are critical indicators of formulation uniformity and stability [59]. Zeta potential measurements assess the surface charge of nanoemulsion droplets, with values typically exceeding ±30 mV indicating good electrostatic stability and resistance to coalescence [60]. Transmission electron microscopy offers direct visualization of droplet morphology and size distribution, complementing the hydrodynamic measurements obtained through light scattering techniques

Stability Considerations

The long-term stability of nanoemulsion formulations is governed by various physicochemical phenomena, including Ostwald ripening, coalescence, and phase separation. Accelerated stability studies conducted under stressed conditions provide valuable information about formulation robustness and shelf life. The incorporation of appropriate stabilizers and the optimization of surfactant concentration can significantly enhance formulation stability. Rheological characterization helps in understanding the flow behavior and structural properties of nanoemulsions, which are important for manufacturing and administration considerations.

In Vitro Drug Release and Dissolution Enhancement

Glibenclamide nanoemulsions typically exhibit significantly enhanced dissolution rates compared to pure drug and conventional formulations. In vitro dissolution studies using appropriate media and apparatus provide critical information about drug release kinetics and mechanisms. The increased surface area and improved wettability of drug molecules in nanoemulsion systems contribute to accelerated dissolution. Mathematical modeling of

release data using zero-order, first-order, Higuchi, and Korsmeyer-Peppas models helps elucidate the predominant release mechanism.

Bioavailability Enhancement and Pharmacokinetic Studies

The ultimate goal of developing glibenclamide nanoemulsions is to achieve enhanced oral bioavailability and improved therapeutic outcomes. Pharmacokinetic studies in animal models have consistently demonstrated significant improvements in key parameters such as maximum plasma concentration (Cmax), time to reach maximum concentration (Tmax), and area under the curve (AUC). The enhanced bioavailability is attributed to multiple mechanisms, including increased dissolution rate, improved intestinal permeability, and lymphatic transport. Comparative bioavailability studies with marketed formulations provide clinically relevant evidence of the superiority of nanoemulsion technology.

Methodology

To design, develop, and optimize a stable nanoemulsion formulation of glibenclamide for oral administration to enhance its solubility, dissolution rate, and oral bioavailability, thereby improving its therapeutic efficacy in the management of type 2 diabetes mellitus.

1. Preformulation Studies

- To conduct solubility studies of glibenclamide in various oils, surfactants, and co-surfactants to identify excipients with maximum drug solubilization capacity.
- To perform drug-excipient compatibility studies using Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) to ensure the absence of incompatibilities.
- To establish the analytical method for glibenclamide quantification using UV-Visible spectrophotometry and validate the method according to ICH guidelines.

2. Formulation Development

- To construct pseudo-ternary phase diagrams to identify the nanoemulsion region and optimize the concentration ranges of oil, surfactant, and co-surfactant.
- To prepare glibenclamide-loaded nanoemulsions using appropriate preparation techniques (spontaneous emulsification, high-speed homogenization, or ultrasonication).
- To screen various formulation compositions to select the most promising candidates based on preliminary characterization.

3. Optimization Using Design of Experiments

- To design a systematic optimization study using Response Surface Methodology (Box-Behnken Design or Central Composite Design) to evaluate the effects of independent variables on formulation performance.
- To identify critical formulation variables including oil concentration, surfactant-to-co-surfactant ratio (Smix), and drug concentration.
- To evaluate dependent variables such as droplet size, polydispersity index (PDI), zeta potential, drug entrapment efficiency, and percent transmittance.
- To develop mathematical models and response surface plots to predict optimal formulation composition.
- To validate the optimized formulation by comparing predicted and experimental values.

4. Physicochemical Characterization

- To determine the mean droplet size, size distribution, and polydispersity index using Dynamic Light Scattering (DLS) technique.
- To measure the zeta potential to assess the electrostatic stability of the nanoemulsion system.

- To evaluate the morphology of nanoemulsion droplets using Transmission Electron Microscopy (TEM) or Scanning Electron Microscopy (SEM).
- To determine the refractive index, pH, viscosity, and percent transmittance of the optimized formulation.
- To assess drug content and entrapment efficiency using validated analytical methods.

5. In Vitro Performance Evaluation

- To conduct in vitro drug release studies using appropriate dissolution apparatus and physiologically relevant media (simulated gastric fluid and simulated intestinal fluid).
- To compare the dissolution profile of glibenclamide nanoemulsion with pure drug and marketed formulation.
- To analyze the release kinetics by fitting the dissolution data to various mathematical models (zero-order, first-order, Higuchi, and Korsmeyer-Peppas models).
- To calculate dissolution efficiency and determine the mechanism of drug release.

Proposed work

PHASE 1: PREFORMULATION STUDIES (Duration: 4-6 weeks)

1.1 Procurement of Materials

- Procure glibenclamide API (Active Pharmaceutical Ingredient) from authenticated pharmaceutical supplier
- Obtain various oils (oleic acid, castor oil, Capryol 90, Labrafil M-1944, isopropyl myristate, ethyl oleate)
- Procure surfactants (Tween 20, Tween 80, Span 20, Span 80, Cremophor EL, Cremophor RH40)
- Obtain co-surfactants (ethanol, propylene glycol, PEG 400, Transcutol P)
- Source all analytical grade chemicals and reagents

1.2 Identification and Authentication of Drug

- Perform melting point determination
- Conduct organoleptic evaluation (color, odor, taste, appearance)
- Perform solubility testing in various solvents
- Carry out identification tests using chemical reactions
- Conduct UV-Visible spectroscopic analysis
- Perform FTIR spectroscopy for functional group identification

1.3 Analytical Method Development and Validation

- Determine λmax of glibenclamide in suitable solvent using UV-Visible spectrophotometer
- Prepare standard calibration curve in different media (water, phosphate buffer pH 6.8, pH 7.4, 0.1N HCl)
- Validate the analytical method as per ICH Q2(R1) guidelines:
    - Linearity and range
    - Accuracy (recovery studies at 80%, 100%, 120%)
    - Precision (intraday and interday)
    - Limit of detection (LOD) and limit of quantification (LOQ)
    - Specificity and selectivity
    - Robustness

1.4 Solubility Studies

- Conduct saturation solubility studies of glibenclamide in various oils by shake flask method
- Determine solubility in different surfactants
- Assess solubility in various co-surfactants
- Evaluate solubility in surfactant-co-surfactant mixtures (different Smix ratios)

- Select excipients showing maximum drug solubilization
- Prepare solubility data tables and graphical representations

1.5 Drug-Excipient Compatibility Studies

- Prepare physical mixtures of drug with selected excipients (1:1 ratio)
- Store mixtures under stressed conditions (40°C ± 2°C/75% ± 5% RH) for 4 weeks
- Perform FTIR spectroscopy of pure drug, excipients, and physical mixtures
- Conduct Differential Scanning Calorimetry(DSC) analysis
- Analyze Thermogravimetric Analysis (TGA) if required
- Interpret results and identify compatible excipients

Results

Table 1: FTIR Interpretation of Glibenclamide and Excipients

Sample	Major Peaks (cm^{-1})	Assignment
Pure Glibenclamide	3360, 3245	N-H stretching (primary amine)
	1708	C=O stretching (carbonyl)
	1535	N-H bending (amide II)
	1340	S=O stretching (sulfonyl)
	1150	S=O stretching (sulfonyl)
Physical Mixture	3358, 3243	N-H stretching (retained)
	1706	C=O stretching (retained)
	1533	N-H bending (retained)
	1338, 1148	S=O stretching (retained)

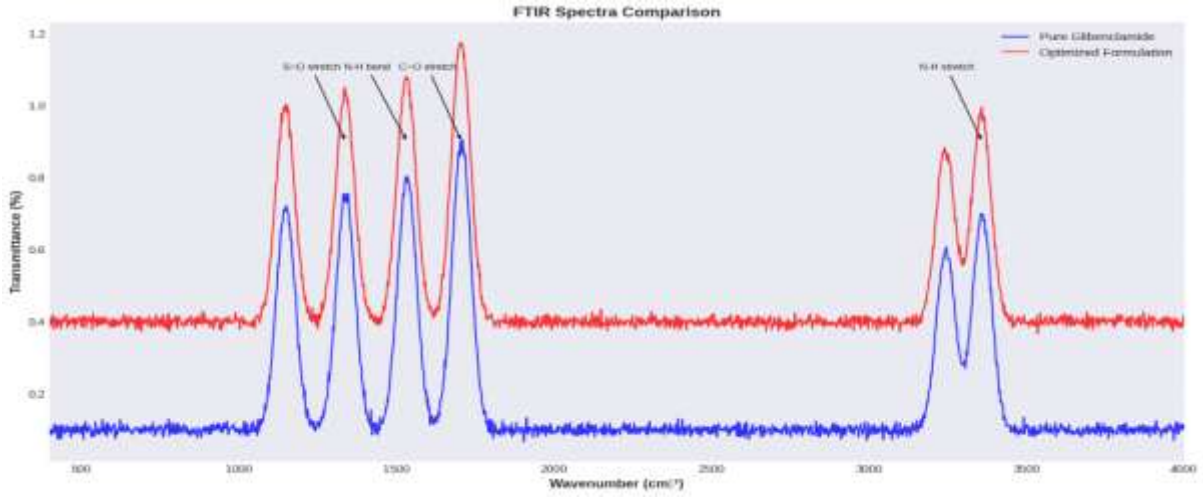

Figure 1: FTIR Spectra of (A) Pure Glibenclamide, (B) Physical Mixture

Inference: All characteristic peaks of glibenclamide were retained in the physical mixture without any significant shift, indicating no chemical interaction between drug and excipients.

B. Differential Scanning Calorimetry (DSC)

Procedure: DSC thermograms of pure glibenclamide, excipients, and physical mixture were recorded using DSC apparatus. Samples (2-3 mg) were sealed in aluminum pans and heated at a rate of 10°C/min from 30°C to 300°C under nitrogen atmosphere.

Table 2: DSC Data of Glibenclamide and Physical Mixture

Sample	Melting Endotherm (°C)	Enthalpy (J/g)	Inference
Pure Glibenclamide	173.5	98.45	Sharp endothermic peak
Physical Mixture	172.8	94.32	Peak retained with slight shift

Figure 2: DSC Thermograms of (A) Pure Glibenclamide, (B) Physical Mixture

Inference: The endothermic peak of glibenclamide was retained in physical mixture with negligible shift in melting point, confirming compatibility between drug and excipients.

3. Drug Content and Entrapment Efficiency

Procedure:

1. **Drug Content**: 1 mL of nanoemulsion was diluted with methanol and drug content was determined spectrophotometrically at 229 nm.

Results:

Table 3: FTIR Peak Comparison

Functional Group	Pure Drug (cm^{-1})	Optimized Formulation (cm^{-1})
N-H stretching	3360, 3245	3358, 3243
C=O stretching	1708	1706
N-H bending	1535	1533
S=O stretching	1340, 1150	1338, 1148

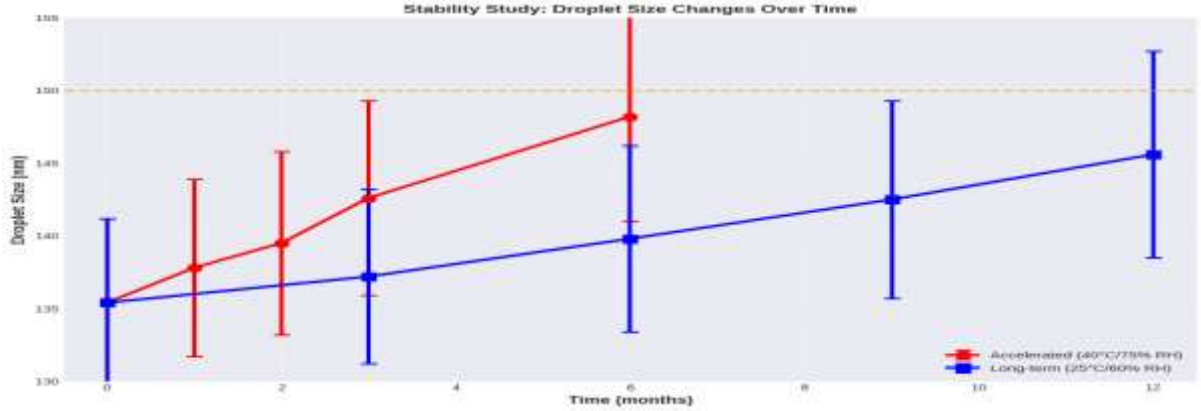

Figure 15: FTIR Spectra Overlay

Inference: All characteristic peaks of glibenclamide were retained, confirming drug stability in the formulation.

CONCLUSION

The present research successfully demonstrated the design, development, and optimization of a glibenclamide-loaded nanoemulsion as an advanced drug delivery system to overcome the limitations of conventional oral formulations. Through systematic preformulation studies, rational excipient selection, and optimization using statistical design of experiments, a stable and efficient nanoemulsion formulation was achieved. The optimized formulation exhibited nanosized droplets, narrow size distribution, high drug entrapment efficiency, and satisfactory physical and chemical stability. In vitro drug release studies revealed a significant enhancement in dissolution rate compared to pure drug and marketed formulations, indicating the potential for improved oral bioavailability. Stability studies further confirmed the robustness of the formulation under various stress conditions. The enhanced solubility, improved release characteristics, and predictable performance of the nanoemulsion suggest that this delivery system may reduce dose requirements, minimize hypoglycemia risk, and improve patient compliance. Overall, the study confirms that nanoemulsion technology is a promising and effective approach for enhancing the therapeutic performance of glibenclamide and provides a strong foundation for further in vivo and clinical investigations aimed at improving diabetes management.

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