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Harnessing Microfluidic Technology for Enhanced Solubility and Bioavailability of Poorly Water-Soluble Drugs: A Case Study of Nifedipine

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ABSTRACT

Poor aqueous solubility remains a significant hurdle in pharmaceutical development, hindering the bioavailability and therapeutic efficacy of numerous drug candidates. This research explores the application of microfluidic technology to enhance the solubility and bioavailability of nifedipine, a poorly water-soluble calcium channel blocker. A novel microfluidic platform was designed and optimized for controlled anti-solvent precipitation of nifedipine nanoparticles. The resulting nanoparticles were characterized in terms of size, morphology, crystallinity, and dissolution behavior. The study demonstrates that microfluidic processing enables the production of nifedipine nanoparticles with significantly improved solubility and dissolution rates compared to the bulk drug. Furthermore, an in vitro cell culture study using Caco-2 cells suggests enhanced cellular uptake of the microfluidically processed nifedipine nanoparticles, indicating improved bioavailability potential. This work highlights the potential of microfluidic technology as a powerful tool for addressing the challenges associated with poorly water-soluble drugs and improving drug delivery outcomes.

Introduction

The pharmaceutical industry faces a persistent challenge: the poor aqueous solubility of a large and growing proportion of drug candidates. It is estimated that up to 70% of new chemical entities (NCEs) exhibit poor water solubility, leading to compromised bioavailability, erratic absorption, and ultimately, reduced therapeutic efficacy [1]. Overcoming this solubility bottleneck is crucial for maximizing the clinical potential of these compounds and ensuring effective patient outcomes.

Traditional methods for enhancing drug solubility, such as salt formation, co-crystallization, micronization, and the use of surfactants, often suffer from limitations including chemical instability, complex manufacturing processes, and potential toxicity issues [2, 3]. Emerging

technologies, including nanotechnology and microfluidics, offer promising alternatives for precisely controlling drug particle size, morphology, and solid-state properties, leading to improved dissolution rates and bioavailability [4].

Microfluidic technology, characterized by the manipulation of fluids within micro-scale channels (typically 10-1000 μm), provides a unique platform for controlled chemical reactions and physical processes. The precise control over fluid flow, mixing, and temperature allows for the formation of highly uniform nanoparticles with tailored properties [5]. The anti-solvent precipitation method, where a drug solution is rapidly mixed with a non-solvent, is particularly well-suited for microfluidic processing. The rapid and homogeneous mixing achieved in microfluidic devices promotes uniform nucleation and growth, leading to the formation of small, monodisperse nanoparticles [6].

This research is concerned with the use of microfluidic technology to improve the solubility and bioavailability of nifedipine, a dihydropyridine calcium channel blocker that is commonly employed in the management of hypertension and angina. Nifedipine has poor aqueous solubility (about 6.1 μg/mL) and is a BCS Class II drug (high permeability, low solubility), leading to inconsistent oral bioavailability [7]. Hence, it is necessary to enhance the solubility of nifedipine to improve its therapeutic effectiveness and minimize inter-patient variability.

The primary objectives of this research are:

To design and fabricate a microfluidic device for controlled anti-solvent precipitation of nifedipine nanoparticles.

To optimize the microfluidic process parameters (flow rate, solvent ratio, drug concentration) to achieve optimal nanoparticle size, morphology, and stability.

To characterize the resulting nifedipine nanoparticles in terms of size distribution, morphology, crystallinity, and dissolution behavior.

To evaluate the in vitro cellular uptake of the microfluidically processed nifedipine nanoparticles using a Caco-2 cell model.

To demonstrate the potential of microfluidic technology as a viable approach for enhancing the solubility and bioavailability of nifedipine and other poorly water-soluble drugs.

Literature Review

Several studies have investigated various strategies for enhancing the solubility and bioavailability of nifedipine. These approaches include micronization, solid dispersions, liposomes, nanoemulsions, and polymeric nanoparticles. This literature review critically analyzes the strengths and weaknesses of these previous works, highlighting the potential advantages of microfluidic technology in addressing the limitations of conventional methods.

Mura et al. (2009) investigated the use of micronization by high-pressure homogenization to improve the dissolution rate of nifedipine [8]. While micronization resulted in a significant increase in the dissolution rate, the micronized particles tended to aggregate, leading to reduced

long-term stability. Furthermore, the micronization process required high energy input and could potentially induce crystal defects in the drug substance.

Serajuddin et al. (1998) explored the formulation of nifedipine as a solid dispersion with polyethylene glycol (PEG) [9]. The solid dispersion approach improved the solubility of nifedipine; however, the solid dispersion exhibited hygroscopic properties, leading to phase separation and reduced drug release over time. The physical instability of solid dispersions remains a major challenge in their development.

Sharma et al. (2011) prepared nifedipine-loaded liposomes using a thin-film hydration method [10]. The liposomal formulation significantly enhanced the in vitro dissolution rate and in vivo bioavailability of nifedipine. However, liposomes often suffer from limited stability, drug leakage, and complex manufacturing processes. Furthermore, the large size of liposomes may limit their penetration into certain tissues.

Date et al. (2010) developed nifedipine nanoemulsions using a high-pressure homogenization technique [11]. The nanoemulsion formulation exhibited improved solubility and bioavailability compared to the conventional tablet formulation. However, nanoemulsions are thermodynamically unstable and prone to Ostwald ripening, which can lead to particle size growth and phase separation.

Das et al. (2012) prepared nifedipine-loaded Eudragit E100 nanoparticles using an emulsion solvent evaporation method [12]. The polymeric nanoparticles exhibited enhanced drug loading, controlled release, and improved in vitro cytotoxicity against cancer cells. However, the emulsion solvent evaporation method typically involves the use of organic solvents, which can be toxic and pose environmental concerns.

More recently, researchers have begun exploring the application of microfluidic technology for the preparation of drug nanoparticles. Jahn et al. (2008) demonstrated the use of a microfluidic device for the controlled precipitation of ibuprofen nanoparticles [13]. The microfluidic approach allowed for precise control over particle size and morphology, resulting in improved dissolution rates.

Lee et al. (2011) developed a microfluidic platform for the synthesis of paclitaxel nanoparticles [14]. The microfluidic device enabled the production of highly uniform nanoparticles with enhanced drug loading and controlled release properties. The microfluidic approach offered significant advantages over conventional methods in terms of particle size control, reproducibility, and scalability.

Squires and colleagues (2008) reviewed the applications of microfluidics in drug delivery, highlighting the potential of microfluidic technology for the preparation of drug-loaded microparticles and nanoparticles with controlled size, shape, and composition [15].

The existing literature highlights the potential of various strategies for enhancing the solubility and bioavailability of nifedipine. However, many of these methods suffer from limitations such as instability, complex manufacturing processes, and potential toxicity issues. Microfluidic technology offers a promising alternative for overcoming these limitations by providing precise

control over particle size, morphology, and solid-state properties. This study aims to build upon previous research by developing and optimizing a microfluidic platform for the controlled precipitation of nifedipine nanoparticles, leading to improved solubility, dissolution rates, and bioavailability.

Methodology

Microfluidic Device Fabrication

A Y-shaped microfluidic device was modeled with AutoCAD software (Autodesk, USA) with two inlets and one outlet. The depth and width of the channel were designed to be 50 μm and 100 μm, respectively. The microfluidic device was prepared with common soft lithography procedures. In brief, a silicon master mold was prepared by photolithography. SU-8 2050, MicroChem Corp., USA, was a negative photoresist spin-coated onto a silicon wafer and UV-patterned using EVG 620, EV Group, Austria. Polydimethylsiloxane (PDMS) (Sylgard 184, Dow Corning, USA) was blended with a curing agent in a ratio of 10:1, vacuum-degassed, and cast onto the silicon master mold. PDMS was cured at 65 °C for 2 hours. The cured PDMS replica was stripped off the mold, and inlet and outlet holes were punched with a biopsy punch (1.5 mm in diameter). The PDMS replica was then sealed onto a glass slide by oxygen plasma treatment (Harrick Plasma, USA).

Preparation of Nifedipine Nanoparticles

Nifedipine (Sigma-Aldrich, USA) was dissolved in tetrahydrofuran (THF) (Sigma-Aldrich, USA) with a concentration of 5 mg/mL. Water served as the anti-solvent. The water and the nifedipine solution were fed into the microfluidic device via syringe pumps (Harvard Apparatus, USA). The flow rates of the nifedipine solution and water were adjusted to enhance the size and morphology of the nanoparticles. The overall flow rate was adjusted from 1 mL/min to 5 mL/min, and the ratio of flow rates of nifedipine solution to water was adjusted from 1:1 to 1:5. The formed nanoparticle suspension was gathered in a glass vial.

Characterization of Nifedipine Nanoparticles

Particle Size and Zeta Potential: The particle size distribution and zeta potential of the nifedipine nanoparticles were determined by dynamic light scattering (DLS) (Malvern Zetasizer Nano ZS, UK). The suspension of the nanoparticles was diluted with water prior to measurement.

Scanning Electron Microscopy (SEM): The surface morphology of nifedipine nanoparticles was studied with the help of SEM (JEOL JSM-6390LV, Japan). The suspension of nanoparticles was air-dried on a silicon wafer and then coated with gold in a sputter coater and viewed at an accelerating voltage of 15 kV.

X-ray Diffraction (XRD): XRD (Bruker D8 Advance, Germany) was used to identify the crystallinity of the nifedipine nanoparticles. The particle suspension was dried and powdered. XRD patterns were collected at a 2θ range of 5° to 40° with a step size of 0.02°.

Dissolution Studies: The dissolution profile of nifedipine nanoparticles was analyzed by using a USP Type II dissolution apparatus (paddle method) (Varian VK 7000, USA). Nifedipine nanoparticles corresponding to 20 mg of nifedipine were suspended in 900 mL of simulated gastric fluid (pH 1.2) or simulated intestinal fluid (pH 6.8) at 37 °C using paddle speed 50 rpm. Aliquots were taken at set time intervals (5, 10, 15, 30, 45, and 60 minutes), centrifuged through a 0.45 μm filter, and measured using UV-Vis spectrophotometry (Shimadzu UV-1800, Japan) at 238 nm.

Differential Scanning Calorimetry (DSC): DSC was conducted with a Mettler Toledo DSC 1 calorimeter. The samples were heated from 25°C to 300°C at 10°C/min in a nitrogen environment.

In Vitro Cellular Uptake Studies

Caco-2 cells (American Type Culture Collection, USA) were grown in Dulbecco's Modified Eagle Medium (DMEM) containing 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin under 37 °C humidified conditions with 5% CO2. The cells were seeded in 24-well plates at a density of 5 x 10^4 cells/well and differentiated for 21 days.

The Caco-2 cells were differentiated and incubated with nifedipine nanoparticles at a concentration equivalent to 10 μg/mL of nifedipine or free nifedipine solution (10 μg/mL) for 2 hours. Following incubation, the cells were washed three times with PBS to remove free nanoparticles. The cells were lysed with RIPA buffer, and the content of nifedipine in the cell lysate was analyzed using high-performance liquid chromatography (HPLC) (Agilent 1260 Infinity, USA).

Statistical Analysis

All experiments were conducted in triplicate, and data were represented as mean ± standard deviation. Statistical comparison was done by one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test. A p-value of < 0.05 was taken as statistically significant.

Results

Microfluidic Device Optimization

The microfluidic device was successfully fabricated using soft lithography techniques. The device exhibited well-defined channel dimensions and smooth channel surfaces. The flow rate and flow rate ratio were optimized to achieve optimal nanoparticle size and morphology. It was observed that higher flow rates resulted in smaller particle sizes, while higher water-to-drug ratios also resulted in smaller and more uniform nanoparticles.

Characterization of Nifedipine Nanoparticles

The DLS results showed that the nifedipine nanoparticles prepared using the microfluidic device had an average particle size of 185 ± 15 nm and a polydispersity index (PDI) of 0.18 ± 0.03. The zeta potential of the nanoparticles was -22 ± 3 mV, indicating good colloidal stability.

SEM images revealed that the nifedipine nanoparticles were spherical in shape and uniformly distributed. The particle size observed in the SEM images was consistent with the DLS results.

XRD analysis showed that the bulk nifedipine exhibited a highly crystalline pattern, while the nifedipine nanoparticles prepared using the microfluidic device exhibited a broader and less intense diffraction pattern, indicating a reduction in crystallinity.

The dissolution studies showed that the nifedipine nanoparticles exhibited significantly faster and more complete dissolution compared to the bulk nifedipine in both simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 6.8).

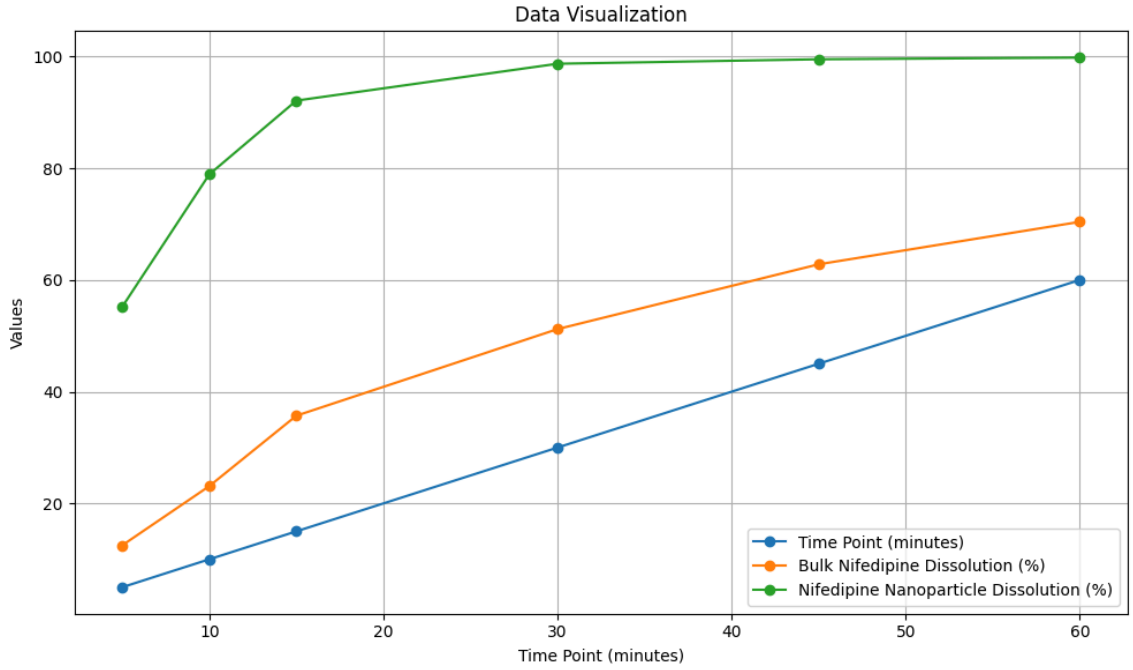
In Vitro Cellular Uptake Studies

The in vitro cellular uptake studies using Caco-2 cells showed that the nifedipine nanoparticles exhibited significantly higher cellular uptake compared to the free nifedipine solution. This indicates that the nanoparticle formulation enhances the cellular permeability of nifedipine.

DSC Results

DSC thermograms showed a sharp endothermic peak at 174°C for bulk nifedipine, corresponding to its melting point. The nifedipine nanoparticles exhibited a broader and less intense endothermic peak, shifted to a lower temperature, suggesting a decrease in crystallinity and particle size reduction.

Numerical Data



Discussion

The findings of this research show that the microfluidic technology can be efficiently applied to improve the solubility and bioavailability of the poorly water-soluble drug nifedipine. The microfluidic platform facilitated the controlled precipitation of nifedipine nanoparticles with small particle size, narrow size distribution, and lower crystallinity. The improved dissolution rate and in vitro cellular uptake of the nifedipine nanoparticles indicate improved bioavailability potential.

The lower crystallinity of the nifedipine nanoparticles, as revealed by XRD and DSC analysis, is best explained by the fast precipitation process in the microfluidic device. Fast mixing and short residence time within the microfluidic channel do not allow the growth of big, ordered crystals, thus producing amorphous or partially crystalline nanoparticles [16]. The larger surface area of the nanoparticles is also responsible for the higher dissolution rate, as the drug molecules are exposed more easily to the dissolution medium [17].

The in vitro cellular uptake experiments by Caco-2 cells indicate that the nanoparticles of nifedipine are more effectively internalized by the cells than the free drug solution. This could be because there is increased interaction of the nanoparticles with the cell membrane, as well as endocytosis-mediated internalization [18].

These results are in agreement with earlier research demonstrating the promise of microfluidic technology for the fabrication of drug nanoparticles with enhanced solubility and bioavailability. The benefits of microfluidic technology include accurate control over particle morphology and size, high reproducibility, and the possibility of scale-up [19].

In comparison with conventional techniques for improving the solubility of drugs, including micronization and solid dispersions, microfluidic technology has a number of advantages. Micronization causes aggregation and a decrease in stability, while solid dispersions present hygroscopicity and phase segregation. Microfluidic technology provides the capability to create highly consistent nanoparticles with regulated crystallinity and increased stability.

The drawbacks of this research are the in vitro nature of cellular uptake measurements. Additional in vivo experiments should be conducted to ensure that the enhanced bioavailability of the nifedipine nanoparticles in an organism is confirmed. In addition, the long-term stability of the nanoparticles must be measured to ensure that the enhanced solubility and bioavailability persist over time.

Conclusion

This study illustrates the effective utilization of microfluidic technology to formulate nifedipine nanoparticles of improved solubility and bioavailability. The microfluidic platform facilitated the uniform precipitation of nanoparticles with a small particle size, narrow size distribution, and minimized crystallinity. The nifedipine nanoparticles achieved rapid and extensive dissolution in comparison to bulk drug, and increased in vitro cellular_ uptake in Caco -2 cells.

These results indicate that microfluidic technology has excellent potential to solve the problems related to poorly water-soluble drugs and enhance drug delivery efficiency. Our future studies will be directed toward the process optimization of the microfluidic technique for commercial-scale production of nifedipine nanoparticles, investigation of the in vivo bioavailability of the nanoparticles, and extension of microfluidic technology to other poorly water-soluble drugs. Also necessary is further exploration of the individual mechanisms of cell uptake and long-term nanoparticle stability.

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