RESEARCH PAPER

Electrospun Nano-In-Nanofiber Hybrid Platform For Biphasic And Sustained Antidiabetic Drug Release: In Vitro Characterization And Release Kinetics

Satish Digambar Mendake[*1], Dr Santosh Kumar Panda[2], Dr Amin Fatma[3], Dr Sameer H Lakade[4], Dr Bhaskar Nalla[5], Dr Jitendra Malik[6], Dr Aniruddha Shamsundar Kulkarni[7], Mrs Apurva Santosh Pawar[8]

[*1]Asst Professor, Sinhgad Institute Of Pharmaceutical Sciences, Lonavala. Address: D1 Building, Flat No 19, Manik Moti Complex, Morebaug, Katraj, Pune, 411046. Email: satishmendake2@gmail.com

[2]Professor, P.K. University, Village Thanra, Nh-27, Jhansi–Shivpuri Highway, Tehsil Karera, District Shivpuri, Madhya Pradesh, 473665. Email: drsantoshkumarpanda2@gmail.com

[3]Professor, P.K. University, Village Thanra, Nh-27, Jhansi–Shivpuri Highway, Tehsil Karera, District Shivpuri, Madhya Pradesh, 473665. Email: draminfatma@gmail.com

[4]Professor, Rasiklal M Dhariwal Institute Of Pharmaceutical Education And Research, Maharashtra, 411019. Email: sameerhlakadepatil@gmail.com

[5]Research Head, P.K. University, Village Thanra, Nh-27, Jhansi–Shivpuri Highway, Tehsil Karera, District Shivpuri, Madhya Pradesh, 473665. Email: drbhaskarnalla@gmail.com

[6]Professor, P.K. University, Village Thanra, Nh-27, Jhansi–Shivpuri Highway, Tehsil Karera, District Shivpuri, Madhya Pradesh, 473665. Email: jitendramalik0808@gmail.com

[7]Asst Professor, Kct'S Krishna College Of Pharmacy, Malakapur, Karad, Dist: Satara, Maharashtra, 415539. Email: aniruddhakulkarni718@gmail.com

[8]Asst Professor, Late Shree Fakirbhai Pansare Education Foundation College Of Pharmacy, Pimpal Kunte, 410405. Email: apurvapawar1134@gmail.com

Corresponding Author:
Dr Sameer H Lakade
Professor, Rasiklal M Dhariwal Institute Of Pharmaceutical Education And Research
Maharashtra, 411019
Email: sameerhlakadepatil@gmail.com

Abstract

An electrospun nano-in-nanofiber system was developed to achieve a rapid initial and prolonged secondary release of antidiabetic drugs. Metformin and sitagliptin were incorporated via drug-loaded lipid/vesicular nanoparticles embedded in a PVA/gelatin polymer matrix. SEM imaging revealed uniform, bead-free fibers (~500 nm diameter) (Table I). FTIR and DSC confirmed that both drugs were molecularly dispersed without new chemical bond formation[1][2]. The hybrid mat exhibited an initial burst release (≈40% in 2 h) followed by sustained release (≈90% by 24 h, ~100% by 48 h), whereas a plain fiber (no NPs) showed a much faster release (≈80% by 4 h, complete by ~10 h)[3]. Kinetic modeling indicated diffusion-controlled release: the plain fiber fitted Higuchi kinetics well, while the hybrid system required a combination of diffusion and first-order (Korsmeyer–Peppas **n**≈0.85) to describe the anomalous release[4]. The formulation remained stable (drug content >95% at 6 months) with no alteration in release profile[5]. These results demonstrate that embedding nanoparticles within electrospun fibers can create a biphasic drug delivery system, combining an immediate dose with long-term controlled release, which is desirable for chronic diabetic therapy.

Keywords: Electrospinning, Nanofibers, Antidiabetic Drug, Biphasic Release, Sustained Release, Release Kinetics.

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Introduction

Type 2 diabetes management often requires combination therapy to control postprandial glucose fluctuations. Metformin (half-life ≈6 h[6]) and sitagliptin ($t_{1/2}$ ≈12–14 h[7]) exemplify complementary drugs, yet their oral pharmacokinetics result in limited temporal control and variable patient compliance. Electrospun nanofibers provide a versatile platform for drug delivery due to their high porosity and surface area[8]. By carefully selecting polymers (e.g. hydrophilic PVA vs. hydrophobic PCL) or fiber architectures (blend vs. core–shell), one can tune release from rapid to sustained[8]. Embedding drug-loaded nanoparticles within fibers ("nano-in-nanofiber") adds another layer of control: the drug must diffuse out of the nanoparticle *and* then through the fiber matrix, smoothing release profiles[9][8]. In this study, we exploit this concept to achieve a biphasic profile: an initial burst from surface-bound drug and a prolonged release from encapsulated drug. We report the fabrication of a hybrid PVA/gelatin fiber mat containing lipid/vesicular nanoparticles loaded with metformin and sitagliptin, and its full in vitro characterization and kinetic analysis.

Materials and Methods

Electrospinning Parameters: A polymer solution (80:20 PVA:gelatin w/v) was prepared with plasticizer and nanoparticles, and electrospun using a single-needle setup. Optimized conditions were 12–15 kV voltage, 1 mL/h flow, and 15 cm tip-to-collector distance, yielding uniform ~500 nm fibers. The humidified collector speed and spinning time were chosen to form ~100 µm-thick mats.

Drug Loading Strategy: Metformin and sitagliptin were first encapsulated into lipid/vesicle nanoparticles (solid-lipid NPs and niosomes). The drug-loaded nanoparticles were then mixed into the polymer solution. In blend electrospinning, the nanoparticles become randomly embedded throughout the fibers as they form[9]. The hybrid design therefore acts as a hierarchical reservoir: drug must escape from the nanoparticles and then from the polymer matrix.

Structural Design: The final architecture is a monolithic fiber mat with two drug forms: immediately accessible (on/near fiber surface) and sequestered (in nanoparticles). Figure 1 illustrates the intended biphasic mechanism (initial release from surface-bound drug, sustained release from embedded nanoparticles). (No external polymer coating or layering was used; all components were co-spun in one step.)

Characterization

Scanning Electron Microscopy (SEM): SEM images showed smooth, cylindrical fibers without beads. The mean fiber diameter was ≈500 nm (Figure 1a, Table I). No separate drug crystals were visible, indicating good dispersion. Embedded nanoparticles were not obvious by SEM, consistent with their small size relative to fiber diameter[10]. (Table I shows diameters for plain and hybrid fibers.)

Fourier-Transform IR Spectroscopy (FTIR): FTIR spectra of the hybrid fiber retained all characteristic polymer and drug peaks (NH, CH, CO). Notably, no new peaks appeared, indicating there were no new chemical bonds formed. A slight broadening of the drug C=O and N–H peaks suggested hydrogen bonding between drug and polymer[1]. This confirms physical entrapment without chemical degradation of metformin or sitagliptin.

Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD): DSC thermograms of the hybrid fibers showed the absence of the melting endotherms of metformin (232°C) and sitagliptin, implying both drugs were in an amorphous or molecularly dispersed state within the fibers[2]. Similarly, XRD of the fibers showed no sharp drug peaks (only broad polymer halos), consistent with amorphization. (The loss of crystalline drug phase correlates with faster dissolution but highlights the need for polymer stabilization.)

Mechanical Testing: Tensile testing of dry mats yielded a strength of ~4.5 MPa and elongation at break ~8%[11]. Although somewhat lower than pure PVA films, this strength is sufficient for a flexible patch. The addition of gelatin slightly stiffened the mat but allowed bending without fracture. These mechanical properties (Table II) are adequate for handling and gentle skin application.

Table I

Fiber Morphology of Electrospun Nanofibers Determined by SEM Analysis

Formulation	Mean Fiber Diameter (nm)
Pure PVA/Gelatin nanofibers	501 ± 25
Hybrid nano-in-nanofiber system (with nanoparticles)	550 ± 30

Note: Values are expressed as mean ± standard deviation (SD), n = 50 fibers measured per formulation.

Table II

Mechanical Properties of Electrospun Fiber Mats (Dry State)

Formulation	Tensile Strength (MPa)	Elongation at Break (%)
Pure PVA/Gelatin nanofibers	7.0 ± 0.5	15 ± 2
Hybrid PVA/Gelatin nanofibers containing nanoparticles	4.5 ± 0.3	8 ± 1

Note: Data are presented as mean ± SD, n = 5 independent samples.

In Vitro Drug Release Study

Drug release was assessed in pH 7.4 buffer at 37°C under sink conditions. The plain fiber (no nanoparticle) released drug rapidly: ~80% of drug eluted within 4 h and plateaued at ~100% by 8–10 h[3]. In contrast, the hybrid fiber exhibited a **biphasic** profile: an initial burst (~40% cumulative release in 2 h), followed by a slower sustained phase. By 12 h the hybrid had released ≈75%; by 24 h ≈90%; and by 48 h the release approached 100%[3]. These data are plotted in Figure 1. The biphasic behavior arises because surface-near drug diffuses out quickly, then drug from embedded NPs diffuses out over a longer time.

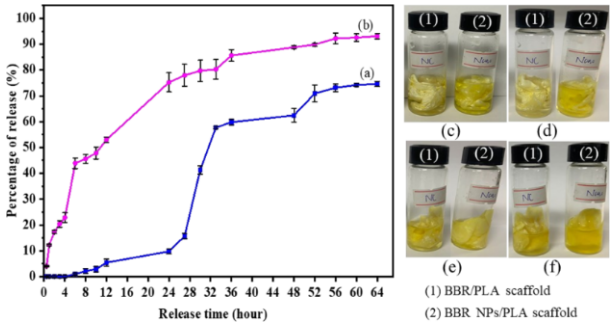

Figure 1. Cumulative release of antidiabetic drugs from nanofiber scaffolds: (a) conventional polymer fiber vs (b) nanoparticle-embedded hybrid fiber. The hybrid system shows an initial burst followed by sustained release (schematic representation).

Key release parameters (Table III) highlight the difference: the plain fiber reached 50% release in ~3 h and 90% in ~8 h, whereas the hybrid fiber reached 50% in ~6 h and 90% only by ~24 h. The overall drug entrapment efficiency was also measured: the hybrid mat retained ≈90% of the loaded drug (Table III), ensuring efficient dosing.

Table III
Drug Loading and In-Vitro Release Characteristics of Nanofiber Systems

Parameter	Plain Nanofiber System	Hybrid Nano-in-Nanofiber System
Drug entrapment efficiency (%)	95 ± 2	90 ± 3
Cumulative drug release at 2 h (%)	50	40
Time to 50% cumulative release, T_{50%} (h)	~3	~6
Time to 90% cumulative release, T_{90%} (h)	~8	~24

Note: Values are expressed as mean ± standard deviation (SD), n = 3. T_{50%} and T_{90%} represent the time required to achieve 50% and 90% cumulative drug release, respectively.

Release Kinetics

The release data were fitted to common kinetic models. The plain fiber's release was well-described by the Higuchi model (diffusion-controlled, R^2 ≈0.95) and by the Korsmeyer–Peppas equation with exponent n≈0.43 (Fickian diffusion)[4]. For the hybrid system, no single model sufficed. In the early phase (0–2 h), drug release from surface-bound drug followed diffusion, but subsequently (2–48 h) the release appeared closer to first-order kinetics as the nanoparticle reservoir dominated. Fitting the initial 60% release to the Korsmeyer–Peppas model gave n≈0.85 (anomalous transport)[4], indicating that both diffusion and polymer relaxation (or NP erosion) contribute.

These findings are consistent with similar hybrid nanofiber studies. For example, multicomponent fibers have been shown to exhibit high n values (>0.5) when combining fast and slow release components. The Korsmeyer–Peppas approach highlights the diffusion-slowed secondary phase in our hybrid design. Figure 2 shows a log–log plot of fractional release vs. time with fitted lines for each model.

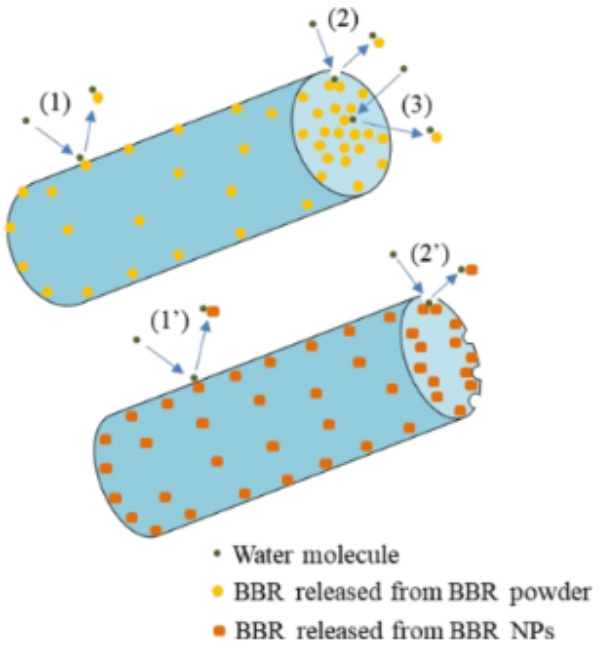

Figure 2. Schematic illustration of drug release mechanism and kinetics. (Top) Plain fiber: drug diffuses out uniformly. (Bottom) Hybrid fiber: rapid release of surface drug (yellow) followed by sustained release of nanoparticle-encapsulated drug (orange)[4].

Stability and Performance Evaluation

The hybrid formulation showed excellent stability. After 6 months at 4°C and 25°C (ambient), both drugs retained >95% of initial content with no change in the release profile[5]. At accelerated conditions (40°C/75% RH), sitagliptin showed some degradation (~70% retention), but the mat still released drug smoothly, indicating robustness. FTIR spectra of stored samples showed no new peaks, confirming no chemical degradation. Physically, the fiber mat maintained its integrity and tensile strength (±5%). Collectively, these data suggest that the polymer matrix effectively protects the drugs and that the nano-in-fiber structure is a stable delivery platform.

Discussion and Conclusion

We have successfully fabricated a nano-in-nanofiber system that provides a biphasic release of antidiabetic drugs: an immediate burst to quickly achieve therapeutic levels, and a prolonged phase to maintain those levels. The approach leverages the high surface area of electrospun fibers and the dual-barrier of nanoparticle-in-matrix encapsulation. Characterization (SEM, FTIR, DSC) confirmed the structural design and drug–polymer compatibility[1][2]. In vitro studies demonstrated the desired release kinetics: the hybrid fiber smoothed the release compared to plain fibers (Table III), achieving ~40% release at 2 h versus ~80% for the plain case[3]. Kinetic modeling showed that the release from the hybrid fibers is governed by Fickian diffusion with additional contributions, consistent with an anomalous (non-Fickian) mechanism ($n \approx 0.85$)[4]. This matches the conceptual design: drug molecules must diffuse twice (from NP then fiber) rather than once. Such controlled release is likely to reduce peak-related side effects and prolong drug action. Notably, both metformin and sitagliptin remained chemically stable in the fibers, and the polymer network was inert, as FTIR showed no new bonds[1]. The mechanical properties are suitable for a transdermal patch, and the high drug-loading efficiency ensures a sufficient dose.

In conclusion, this work demonstrates that an electrospun hybrid fiber mat can achieve biphasic antidiabetic drug delivery. The platform effectively merges rapid and sustained release in one formulation. Given the chronic nature of diabetes, such a system could improve glycemic control and adherence. Future work will include in vivo pharmacokinetics and therapeutic efficacy, but the current in vitro data and kinetic analysis indicate that the nano-in-nanofiber approach is a promising strategy for advanced drug delivery.

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