RESEARCH PAPER

Formulation Development of Fast Dissolving Oral Nanofiber Mats of Quercetin: A BCS Class II Drug

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Received: 24th Feb, 2026; Revised: 11th April 2026; Accepted: 17th June, 2026; Available Online: 20st June, 2026

ABSTRACT

The poor water solubility of drugs belonging to BCS Class II continues to be a significant obstacle to obtaining the best oral bioavailability. The current study used electrospinning to fabricate and evaluate fast-dissolving oral nanofiber mats of quercetin, a BCS Class II flavonoid with low aqueous solubility. The physicochemical characteristics of quercetin and its compatibility with particular excipients were described. The hydrophilic polymer polyvinyl alcohol (PVA) was used to improve wettability and dissolution. SEM was used to assess the morphological features of the electrospun nanofiber mats. Thickness, drug content homogeneity, tensile strength, pH, folding endurance, disintegration time, and in vitro drug release were evaluated. In comparison to plain quercetin, the produced nanofibers showed uniform thickness, good mechanical strength, rapid disintegration (≈1 s), and dramatically improved drug solubility. Smooth, bead-free nanofibers with uniform medication distribution were verified by SEM examination. The findings suggest that fast-dissolving oral nanofiber mats are a viable method for enhancing the oral bioavailability and dissolution of quercetin and other BCS Class II medications.

Keywords: Quercetin, Oral nanofibers, Electrospinning, Fast dissolving patches, BCS Class II drugs
How to cite this article: Bashir R, Raza SN, Rehman R, Kawoosa S, Khan NA. Formulation Development of Fast Dissolving Oral Nanofiber Mats of Quercetin: A BCS Class II Drug. Int J Drug Deliv Technol. 2026;16(64s):1762-1767.
DOI: 10.25258/ijddt.16.64s.196

INTRODUCTION:

The most preferred route of drug administration is still the oral route owing to its ease, safety, cost-effectiveness and patient compliance. However, poor aqueous solubility continues to be a major limitation for many orally administered drugs, particularly those classified under the BCS Class II, which exhibit high permeability but low solubility. For such drugs, dissolution is the rate-limiting step for absorption, resulting in low and variable oral bioavailability [1].

Quercetin is a naturally occurring flavonoid widely reported for its antioxidant, anti-inflammatory, anticancer, and cardioprotective properties [16, 17]. Despite its promising therapeutic potential, quercetin suffers from extremely poor water solubility and limited oral bioavailability, which restricts its clinical application [14]. Various formulation strategies such as solid dispersions, inclusion complexes, nanosponges, and polymeric nanoparticles have been explored to overcome these limitations and enhance its dissolution and bioavailability [14, 15].

In modern times, drug delivery systems based on nanotechnology have gained considerable attention for the improvement of the solubility of the poorly water-soluble drugs. Among these, electrospun nanofibers have emerged as useful and efficient carrier systems for drug delivery owing to their nanoscale diameter, porosity, high surface-to-volume ratio and capability to encapsulate drugs in an amorphous or molecularly dispersed state [2, 3, 6, 10]. The electrospinning technique is a simple and scalable process capable of producing continuous polymeric nanofibers with controlled morphology and drug distribution [4,5]. Electrospun nanofibers have been extensively investigated

for biomedical uses with controlled drug delivery, tissue engineering and wound healing [13, 20]. Their application in oral drug delivery has shown particular promise due to rapid wetting, fast disintegration, and improved dissolution characteristics [6, 7]. Fast-dissolving oral nanofiber mats and films dissolve quickly in saliva without the need for water, offering advantages such as quick action onset, bioavailability enhancement and better patient compliance, especially for pediatric and geriatric populations [7, 9, 19]. Hydrophilic polymers such as polyvinyl alcohol (PVA) are commonly used in electrospinning due to their excellent film-forming ability, biocompatibility, and capacity to enhance wettability and dissolution of poorly soluble drugs [3,8,12]. Incorporation of drugs into PVA-based nanofibers can significantly improve drug dispersion, reduce crystallinity, and enhance dissolution performance.

Based on these considerations, the current study aimed to develop and assess fast-dissolving oral nanofiber mats of quercetin using the electrospinning technique. The study focuses on improving the dissolution behaviour and physicochemical properties of quercetin by formulating it into PVA-based nanofibers, thereby offering a favourable approach for enhancing the bioavailability of BCS Class II drugs through the oral route.

2. Materials and Methods

2.1 Materials

The selected drug Quercetin was procured from Merck, and the polymer PVA was purchased from Sigma-Aldrich. The remaining reagents and solvents were all analytical grade.

2.2 Pre-formulation Studies

The physical characteristics of quercetin, including its colour, taste, odour, melting point, and solubility, were described. FTIR spectroscopy was used to confirm the identification.

2.3 Selection of Polymer and Excipients

PVA was chosen as the polymer based on wettability, solubility improvement, and electrospinning capability. To increase mechanical strength and consistent medication dispersion, excipients were selected.

2.4 Drug–Excipient Compatibility Studies

Physical observation was used to assess the compatibility of quercetin with specific excipients under accelerated stability settings (40 °C/75% RH) for a maximum of four weeks. Colour and flow characteristics were tracked**.**

2.5 Preparation of Nanofiber Mats

The electrospinning method was used to create quercetin-loaded nanofibers. Voltage is supplied by a high-power source during the electrospinning process. The solutions to be electrospun are filled into a disposable syringe of 5ml fitted with a needle to prevent air bubbles. The needle tip is attached to the high-voltage power supply's positive electrode. An aluminium foil-wrapped metal collector is attached to the earthed electrode. Fibres are collected at a specific distance from the syringe tip during electrospinning, which is done in ambient conditions. A syringe pump is used to regulate the feed rate of the solutions, and before being used again, the processed samples are vacuum-dried to eliminate any remaining organic solvents [21].

2.6 Characterisation of nanofibres

2.6.1 Per cent Yield

The fibre mat weight obtained after spinning the PVP-Quercetin spinning solution was used to calculate the yield of the nanofiber formulation in percentage, which establishes the process efficiency. The optimised nanofiber formulation's mean ± standard deviation of triplicates was used to record the results.

$$Percentage\ Yeild = \frac{Nanofiber\ formulation\ weight}{Polymer\ weight + drug} \times 100$$

2.6.2 Drug encapsulation efficiency

One of the crucial factors is the drug's trapping in the nanofiber composition. The formulation's maximum entrapment indicates that drug loss has been prevented. The entrapment efficiency was determined by below formula:

$$Drug\ entrapment\ (\%) = \frac{Loading\ drug}{Theoretical\ drug} \times 100$$

2.6.3 Thickness of the nanofiber formulations

Using a 6mm biopsy puncher, four circular discs (15 × 15 cm) were pierced at random from four different sites (one from the centre) in the nanofiber composition. The aluminium foil was removed from the circular section and by using a digital calliper, the thickness was measured and reported as Mean ± SD.

2.6.4 pH

Circular discs of 6 mm diameter were punched from the nanofiber formulation using a biopsy puncher and dispersed in 10 millilitres of distilled water. Three circular discs that were randomly pierced were measured for pH using a benchtop digital pH meter (Orion420A+, Thermo Electron Corporation). The results were displayed as Mean ± SD.

2.6.5 Folding endurance

Folding endurance was to determine the brittleness of nanofibres by counting the number of folds a film or fibre mat can sustain when folded repeatedly along the same axis until it fractures or breaks [22]. To determine the parameter, 6 cm circular discs were punched using a biopsy puncher from the electrospun nanofiber formulation and manually folded at their diameter until they cracked. The number of foldings needed to break the nanofiber formulation diametrically was determined as the folding endurance.

2.6.6 Tensile strength

Tensile strength is used to determine the mechanical strength of the nanofiber formulation and was measured by an in-house laboratory device. Two clamps are built within the apparatus for holding the sample. The lower clamp is movable to support the weight, while the upper clamp is fixed to hold the sample. Tensile strength was measured by attaching 3 × 3 cm fibres to the clamp, which is fixed, and 2 gm of weight was added to the movable clamp until the nanofiber mat cracked or broke. The tensile strength was measured by using below formula. The findings were expressed as Mean ± SD in Newton.mm-2 (N.mm-2).

$$Tensile\ strength\ = \frac{W \times g}{l \times T}$$

Where W is the sample's weight (kg), g is the acceleration caused by gravity (9.81N.Kg-1), l is the sample's breadth (mm), and T is its thickness (mm).

2.7 *In-Vitro* Drug Release Studies

In vitro drug release study was done by using a Franz diffusion cell. Each sample was cut into a circular disk in order to conduct this investigation. The disc was placed over the membrane in a donor compartment and wrapped in parafilm. All through the experiment, the receptor compartment holding the phosphate buffer was kept at 37 ± 2^0C. In order to maintain sink conditions throughout the experiment, 1 ml of buffer was removed from the receptor compartment at regular intervals and replaced with an equivalent volume of buffer to quantify the amount of drug diffused over the membrane. After passing the samples via Whatman filter paper, their drug content was determined using spectrophotometry [23].

2.8 Morphological Characterisation

By using scanning electron microscopy (SEM), the surface morphology and fibre structure were determined.

3. Results and Discussion

3.1 Pre-formulation and Compatibility Studies

Quercetin was identified as a yellow, crystalline, odourless powder with a bitter taste and was found to be practically insoluble in water. The melting point was observed at 316°C, confirming purity. FTIR spectra confirmed the identity of quercetin. Compatibility studies showed no significant physical changes, indicating stability and compatibility with PVA.

Table 1: Physical characteristics of quercetin

Nature	Crystalline powder
Colour	Yellow
Taste	Bitter
Odour	odourless
Solubility	Almost insoluble in water but soluble in ethanol, methanol and aqueous alkaline solutions
Melting point	316^0C (As found by melting point apparatus).

FTIR spectrum observed

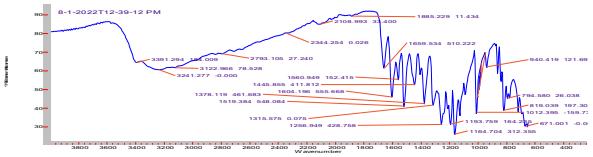

Figure 1: Observed FTIR spectrum of pure quercetin

Reference FTIR spectrum

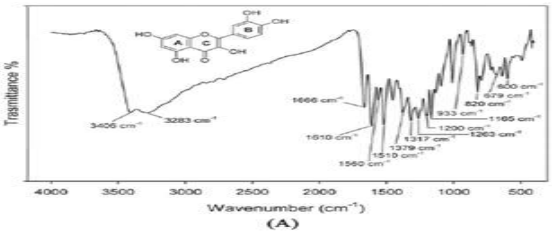

Figure 2: Reference FTIR spectrum of quercetin

Compatibility studies indicated no significant interaction between quercetin and formulation components.

Table 2: Results of compatibility studies

Sample	**Ratio**	**Initial color and flow**	**Observation after 2 weeks (40 °C/75 RH)**	**Observation after 4 weeks 40 °C/75 RH**
Nepafenac	-	Yellow crystalline powder, good flow	No change	No change
PVP	-	White fluffy powder ,good flow	No change	No change

Table 3: Results of compatibility studies

Sample	**Ratio**	**Initial color and flow**	**Observation after 2 weeks (40 °C/75 RH)**	**Observation after 4 weeks 40 °C/75 RH**

Nepafenac +PVP	1:1	Off white mixture	No change	No change

3.2 Formulation of Nanofiber Mats

Quercetin-loaded nanofibers were successfully prepared using electrospinning technique. Preliminary screening was done to find out the best concentration of selected polymer polyvinyl alcohol. Nanofibres were made by using different concentrations of PVA ranging from 3% w/w, 5%w/w, 7%w/w and 10%w/w with fixed dose of the drug which was designed based on the collector dimensions and dose to be incorporated in each unit dose of 3×2 cm. After SEM analysis of the prepared nanofibres it was found out that the nanofibres which were prepared by using 5%w.w polymer concentration, voltage 20kv, flow rate of 0.5ml/hr and tip to collecter distance 10 cm resulted in smooth, uniform, bead-free nanofibers also suggesting efficient drug incorporation and was selected as the optimised formulation for further evaluation,

3.3 Characterisation of nanofibres

Table 4: Results of pharmaceutical characterisation of nanofibre formulation

Formulation Code	**% Yield**	**% Drug encapsulation**	**Tensile strength (N.mm^{-2}) (N=3)**	**Thickness (mm) Mean ±SD (N=3)**	**Fiber pH in SSF Mean ±SD (N=3)**	**Folding endurance (N=3)**
F1	98	95	0.125 ± 0.004	0.392 ± 0.002	6.93 ± 0.02	44 ± 3
F2	99	96	0.129 ± 0.001	0.384 ±0.005	6.90 ± 0.09	45 ± 1
F3	97	97	0.124 ± 0.009	0.395 ± 0.004	6.88 ± 0.09	47 ± 2

These kinds of formulations can be prepared using electrospun nanofibers, which are known to generate better yields due to the process's high efficiency. Dripping of the spinning solution typically results in minor losses. High drug encapsulation is the outcome of minimal losses during the manufacturing process.

The tensile strength of nanofibers is intended to be within an appropriate range. It should be neither too high to prevent the fibre mat from disintegrating nor too low to prevent proper handling and packing. This kind of formulation should have enough mechanical strength to be applied to the mucosal membrane. Additionally, the observed values match other published data.

An essential feature of oromucosal films is their mucoadhesive qualities. It was not possible to conduct a test to determine the fibre mats' adhesive capacity because our formulation is intended to quickly break down upon contact with oral fluids or moist mucosa. The test calculates the force required to remove the film from the mucosal surface. As a result, when the fibers were placed to the moist mucosal surface in our instance, they quickly stuck to the mucosa and broke down so quickly that it appeared as though they had disappeared. This is also connected to the disintegration test, in which a high-speed camera shows the fibers breaking apart in milliseconds. Since these FDDS devices adhere to the mucosal surface as if they were a part of the mucosa, they do not require supporting material. Regardless of whether the medication in the fiber forms a molecular solution in the oral fluids, it quickly penetrates the mucosa. The nanofiber sticky mats' special feature stops medication loss in the mouth cavity.

The thickness of nanofibres was suitable for applying to mucosal tissue. Most significantly, the thickness values are within the ranges established for orodispersible films and are similar to those found in earlier investigations. Depending on the volume of spinning solution, the fiber mat's thickness can be changed.

The formulation in the SSF should have a pH that is sufficiently near to the pH of the mucosal surfaces, which ranges from 6.28 to 7.34.It is anticipated that the improved nanofiber formulation in SSF (Table 7) will not harm the mucosal lining where it is delivered because its pH values were within acceptable bounds.

Folding endurance ratings reveal information on the fiber mat's brittleness. Brittle films cannot be placed to the intended surface since they are prone to breaking. In terms of the fiber mats' packaging, this is also a determining aspect. All of the mats had folding endurances greater than 40, indicating that they were not fragile.

3.4 In-vitro Drug Release

When compared to plain medication, quercetin dissolved far more readily in nanofiber mats. Nanoscale fiber diameter, higher surface area, amorphous drug dispersion, and PVA's enhanced wettability are all responsible for the enhanced release profile. Several electrospun nanofiber characteristics can be responsible for quick release from the optimized nanofiber formulation. These formulations' large effective surface area helps the nanoform of drug particles to be uniformly distributed over the fiber surface, improving the dissolving medium's ability to interact with the drug particles deposited. The nanosizing of drug also improves solubility by increasing their effective surface

area. Due to electrospinning the amorphization of the extremely crystalline substance is the main cause of this exceptional solubilization.

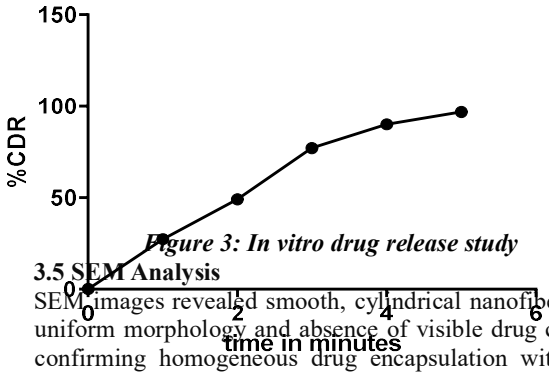

Figure 3: In vitro drug release study

3.5 SEM Analysis

SEM images revealed smooth, cylindrical nanofibers with uniform morphology and absence of visible drug crystals, confirming homogeneous drug encapsulation within the polymer matrix.

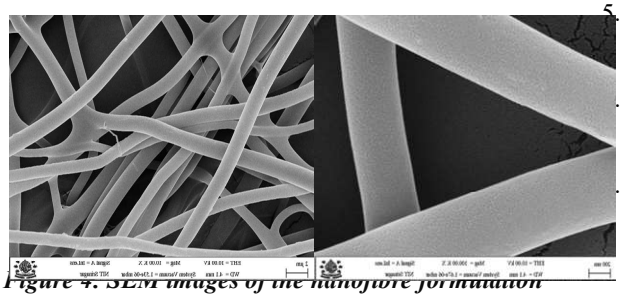

Figure 4: SEM images of the nanofibre formulation

4. Conclusion

Fast dissolving oral nanofiber mats of quercetin were successfully formulated using the electrospinning technique. The developed system exhibited rapid disintegration, enhanced dissolution, and satisfactory physicochemical properties. This approach offers a favourable approach to increase the oral delivery and bioavailability of BCS Class II drugs like quercetin having poor solubility in aqueous media.

Acknowledgement

The authors are highly grateful to the JK Science Technology and Innovation Council, Department of Science and Technology. Govt. of UT of J&K for funding the project under grant number JKST&IC/SRE 1150-54.

Declaration of Competing Interest:

The authors affirm that they have no known financial or interpersonal conflicts that would have appeared to have an impact on the research presented in this study.

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