# Macromolecular Materials and Engineering

## A Comparison of Electric-Field-driven and Pressure-driven Fiber Generation Methods for Drug Delivery

--Manuscript Draft--

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| **Manuscript Number:** | mame.201700577R1 |
| **Full Title:** | A Comparison of Electric-Field-driven and Pressure-driven Fiber Generation Methods for Drug Delivery |
| **Article Type:** | Full Paper |
| **Section/Category:** | |
| **Keywords:** | pressure; gyration; electrospinning; fibers; drug delivery |
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# A Comparison of Electric-Field-driven and Pressure-driven Fiber Generation Methods for Drug Delivery.

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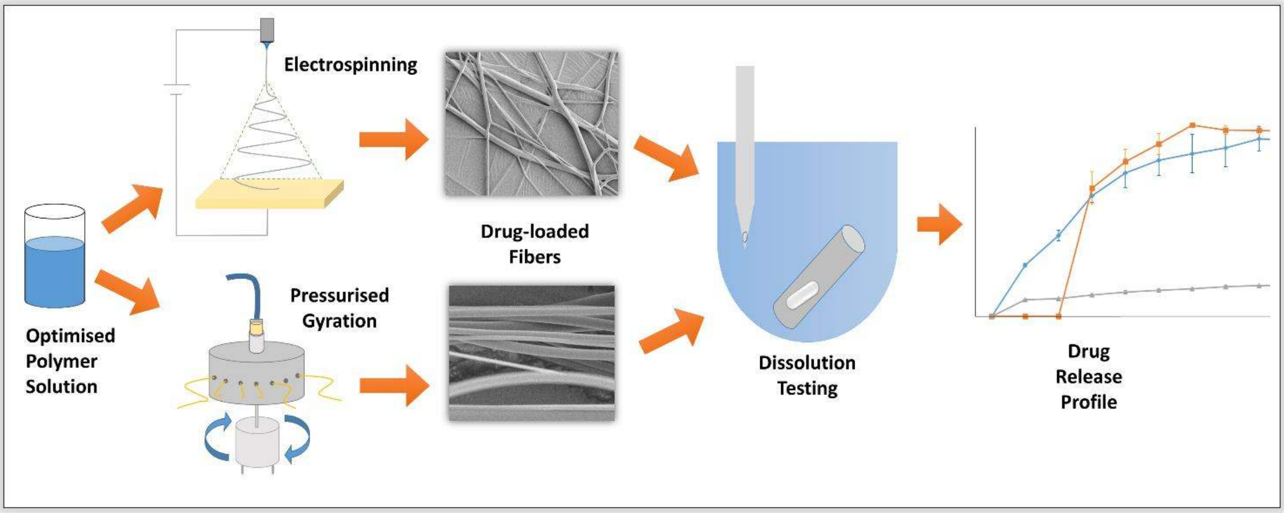
Keywords: (pressure; gyration; electrospinning; fibers; drug delivery)


Electrospinning
Drug-loaded
Fibers
Pressurised
Gyration
Optimised
Polymer
Solution
Dissolution
Testing
Drug
Release
Profile

# 1. Introduction

Interest in fibers, at both the micro and nano-scale has not conveyed any slowdown in recent years. Fiber production continues to be an area of soaring interest in both the academic and industrial fields. The global market for nanofibers reached a staggering $383.7 million in 2015 and is projected to approach $2 billion by 2020 [1].

The sheer versatility of such fibers, allows them to be exploited in a multitude of applications including: biomaterials, tissue engineering, textiles, sensors, wound healing and moreover drug delivery [2-4]. It is the inherent compact nature of these small diameter fibers that unravels many astonishing and undeniably beneficial characteristics. As the diameters of these fibers are reduced below the micrometre scale (1-100 μm): features corresponding to enormously high surface area to volume ratio, superior mechanical properties and tailorable surface functionalization become increasingly apparent [5]. For these reasons and many others to be explored, small diameter fibers are remarkably suited for the range of functional applications that they are exploited in.

The production of small-diameter fibers is thus a key area for research and development. Improving upon the yield, efficiency, and control in manufacturing will inevitably speed the advancement of these valuable materials. Until only recently, there has been a single tried and tested method for laboratory fiber production. The exploration and comparison with novel methods of fiber production serves to evolve the field of fiber production as there are several shortcomings and downfalls that exist for the current "gold standard", electrospinning (ES), which has been widely recognised as a simple, versatile and facile method for the fabrication of polymeric fibers with a wide range of uses including drug delivery [5, 6]. However, there are inherent limitations to this technology that impede its ability to upscale production to meet the ever-increasing demand on micro- and nano-scaled materials. Furthermore, the use of fine tubing produces problems of solution and needle clogging, which reduces production yield and increases maintenance costs [7].

A novel pressure driven route for the production of fibers was reported in 2013 and has been improved further incorporate simultaneous use of pressure, flow and rotation [8,9]. The process known as pressurised gyration (PG), marries centrifugal spinning with solution blow spinning. Pressure-driven nanofiber production methods such as pressurised gyration, offer a compelling alternative to electric-field driven technologies such as electrospinning. This comes with the ability to spin charge-absent polymers and potentially improve production yield. In essence, centrifugal spinning involves a perforated spinneret to which a polymer solution is fed into and then rotated at high speeds. Upon reaching a critical rotational speed, the solution is forced out of the perforations and deposited as dry nanofibers following solvent evaporation [9, 10]. Conversely, solution blow spinning is an alternative nanofiber production route which implicates a high velocity gas flow to a polymer solution. The pressurised gas extrudes and drives the polymer solution to cause rapid solvent evaporation, generating dried fibers in a simple one-step process [11].

Polyvinylpyrrolidone (PVP), is a hydrophilic polymer of N-vinylpyrrolidone[12]. In their history spanning over 70 years, vinylpyrrolidone polymers have seen extensive use in technical applications, food packaging, cosmetics and especially in pharmaceuticals where it is used as a disintegrant or tablet binder [13]. Furthermore, due to its profound ability to readily dissolve in water and oil; PVP has been used as a vehicle for suspending and dispersing drugs [14]. Polyvinylidene fluoride (PVDF), is a non-reactive thermoplastic commonly used as insulation material for electrical wires but has promising use in biomedical applications such as hemodialysis filtration [15]. Poly (methyl methacrylate) (PMMA), is a biodegradable transparent thermoplastic which sees frequent use as bone cement in joint replacement surgeries [16]. Poly(N-isopropylacrylamide) (PNIPAm), is a temperature-responsive polymer with a wide range of applications ranging from biosensors, tissue engineering and drug delivery [17]. Thermo-responsive core-sheath nanofibres have been prepared by electrospinning but literature with other fibre-production methods is scarce [18].

A comparison in the fiber morphology, accessibility and final product performance (drug delivery) has yet to be completed. The importance of this study is to assess the formation of fibres from two fundamentally different techniques to determine any differences in product performance in terms of drug delivery. As pressuirised gyration offers the advantage of potential scale up: the proposition of this study was to compare the fiber production of electrospinning and pressurised gyration on the product morphology, production efficiency and drug release capability. For this purpose, four different polymers were selected: namely Polyvinylpyrrolidone (PVP), Polyvinylidene fluoride (PVDF), Poly(methyl methacrylate) (PMMA) and Poly(*N*-isopropylacrylamide) (PINIPAAM). Production of fine diameter fibers are beneficial towards drug release as finer fibers afford a higher surface area to volume ratio, which can improve drug dissolution [19]. Therefore, PVP Fibers are compared in their ability to improve the oral dissolution of a poorly soluble drug, amphotericin B (AMB) and itraconazole (ITZ).

## 2. Materials and Methods

PVP (Mw 1,300,000 g mol$^{-1}$), PVDF (Mw 275,000 g mol$^{-1}$), PMMA solution (Mw 120,000 g mol$^{-1}$), PNIPAm (Mw 300,000 g mol$^{-1}$), itraconazole (CAS: 84625-61-6; ITZ) and amphotericin B (CAS: 1397.89.3; AMB) were obtained from Sigma-Aldrich (Gillingham, UK). Solvents used are summarised in **Table 1:** Ethanol (CAS: 64-17-5), Dimethylformamide (CAS: 68-12-2), Acetone (CAS: 67-64-1) and Chloroform (CAS: 67-66-3), all of which were aquired from Sigma-Aldrich (Gillingham, UK).

### 2.1. Preparation of spinning solutions and spinning conditions

The polymer solutions used in this study are listed in **Table 1**. Each polymer solution was prepared by adding the specific amount of polymer to the solvent and mechanically stirred for 24 hours at 24° C ± 3 ° C to obtain a homogeneous polymer solution.

### 2.1.1. Solution Characterisation

Surface tension of the prepared solutions were characterised via a tensiometer (Tensiometer K9, Kruss GmbH, Germany) and were repeated 5 times to find the average surface tension. Viscosity was characterised using a programmable rheometer (DV-III Ultra, Brookfield Engineering Laboratories INC, Massachusetts, USA), readings were taken at a shear stress of ~ 5 Pa, measurements were repeated 3 times to find the average value.

### 2.1.2. Electrospinning

A schematic diagram of the electrospinning setup is shown in **Figure 1 (a)** and the spinning solutions were carefully placed into a plastic syringe (10 mL, (BD Plastic™, VWR, Lutterworth, UK), great care taken to avoid any air bubbles. A metal dispensing tip (spinneret; inner diameter: 2.03 mm, outer diameter: 1.52mm Stainless Tube & Needle Co Ltd., Tamworth, UK) was attached to the syringe. The polymer solution was dispensed from the syringe at a feed rate of 1.2 mL/h using a syringe pump (PHD 4400, Harvard Apparatus, Edenbridge, UK). The positive electrode of a high voltage power DC supply (Glassman Europe Ltd., Tadley, UK) was then connected to the spinneret. The grounded electrode was connected to a metal collector wrapped with aluminium foil. Electrospinning was carried out under ambient conditions (23 ± 3 ˚C and relative humidity 48 ±5 %). The electrospinning process parameters for each polymer solution are given in **Table 2**.

### 2.1.3. Pressurised Gyration

A schematic diagram of the gyration apparatus is shown in **Figure 1 (b)**. The rotary aluminium cylindrical vessel (with a diameter of ~60 mm and a height of ~35 mm) contains 24 orifices on its face, each having a diameter of 0.5 mm.

For the purposes of this testing, 5 ml of each polymer solution was placed in the vessel and spun at 36, 000 rpm using 0.1 MPa applied pressure. The fibers were collected using a rod collector placed 100 mm away from the vessel. All the spinning experiments were carried out under ambient conditions (22 ± 3°C and relative humidity of 40 ± 3%). The gyration parameters for each polymer solution are given in **Table 2**.

A range of applied gas pressures where trialled using PVP polymer solution to discover the optimal pressure at which subsequent tests would be carried out. 5ml of PVP solution was spun under at pressures ranging from 0.0 MPa to 0.3 MPa, tests where repeated 5 times at ambient conditions. It was decided that 0.1 MPa produced fibers which has the highest yield in terms of mass of fiber produced.

### 2.2. Production of PVP Drug-loaded Fibers

PVP was selected as the polymer to prepare drug loaded fibers. Appropriate amount of AMB was dissolved in ethanol and added to PVP polymer solution to prepare AMB loaded PVP fibers. Similarly, ITZ was dissolved in dichloromethane and was added to the PVP polymer solution to prepare ITZ loaded PVP fibers. Both polymer solutions were stirred overnight with a magnetic stirrer to form a homogenous solution of drug molecules dispersed into the polymer solution. These polymer solutions were used to prepare 5 % w/w AMB loaded PVP fibers and 2.5% w/w ITZ loaded PVP fibers.

### 2.3. Fiber Characterisation

Fibers formed from both techniques were examined by Scanning Electron Microscopy (SEM). The fiber samples were gold sputter-coated (Q150R ES, Quorum Technologies) for 3 minutes preceding SEM imaging (Hitachi S-3400n). The SEM images were then surveyed using Image J software, 100 fibers were measured at random and the mean diameter was calculated. The frequency distribution of the fiber diameters was modelled using OriginPro software. Fourier Transform Infrared Spectrometry (FTIR) (Spectrum 100, PerkinElmer Inc, Beaconsfield, UK) was used to compare the chemical composition of itraconazole-loaded PVP fibers produced by electrospinning and pressurised gyration. A summary of the average diameters of the tested polymers spun by the two techniques are presented in **Table 3.**

### 2.4. Dissolution Studies

Dissolution tests were carried out in a controlled water bath at 37°C using PBS at pH 7.4. The tests consisted of dropping a metal sinker with 30mg of PG or ES drug-loaded fibers, encapsulated within a gelatine capsule. Drug content by weight was consistent in all samples including AMB and ITZ virgin powders. The timer started immediately following the sinking of the capsules, and 4 mL of the sample was taken and volume replaced with PBS at 37°C. The absorbance was measured at 408 nm for AMB and 254 nm for ITZ using an UV spectrometer (Jenway Instruments, 7305). All fiber samples and pure drug were tested in over a three-hour period in triplicate.

## 3. Results and Discussion

### 3.1. Fiber morphology and analysis

Fundamentally, pressurised gyration manipulates the Rayleigh-Taylor instability of the polymer solution, which explains its production mechanism. The solution is overwhelmed by centrifugal force and is forced out through the apertures, remerging as a droplet [20]. A surface tension gradient occurs along the liquid-air interface which creates a separation of the solution from the surrounding air which also focuses the jet. The surface tension gradient prompts a Gibbs–Marangoni stress tangential to the liquid-gas interface, which instigates flow to the tip of the polymer droplet [21]. The tip of the exiting droplet undergoes additional stretching and thus elongates due to the pressure differential between the collection atmosphere and the drum.

One striking convenience of PG, is its non-electric-field driven nature thus permitting the spinning of an almost-limitless number of polymers. This is also in contrast to ES, where the electric field limits the choice of polymer. ES has been widely recognised as a simple, versatile and facile method for fabrication of polymeric fibers with a wide range of uses including drug delivery. Pressure-driven nanofiber production methods such as pressurised gyration offer a compelling alternative to electric-field driven technologies such as electrospinning. This comes with the ability to spin charge-absent polymers and potentially improve production yield. However, a comparison in the fiber morphology, accessibility and final product performance (drug delivery) has yet to be completed.

The magnitude of applied gas pressure had a consequence on the production yield of pressurised gyration PVP fibers. **Figure 2** shows the effect of gas pressure on the mass of fibers produced by pressurised gyration. We can see from the graph that the effective yield reduces as gas pressure increases. During the spin-up time of the motor in which the motor accelerates to maximum velocity, higher pressures cause a scattering effect on the polymer solution which causes the solvent to be lost through the orifices. At these lower rotation speeds, the centrifugal force does not surpass the surface tension of the polymer solution and thus a polymer jet is not formed. It can be observed during initial rotation that higher pressures result in more solvent being displaced on the collection surfaces. Higher pressure gas streams have higher kinetic energy thus increasing its velocity. The high velocity of the gas creates a driving force for the acceleration of the solvent out through the orifices [22]. At 0 MPa pressure, the average yield was greatest at 81mg (±4). No overlap in the error bars and the presence of linear regression with a $R^2$ value of 0.99 suggests that yield in terms of fiber mass decreases with increasing gas pressure. This inherent disadvantage can however be overcome by applying the gas pressure after critical rotation speed has been reached. The delay in applying the gas pressure will ensure that solution and solvent are not forced out of the orifices which will lead in maximum yields being obtained. Thus, most experiments in this work were carried out at 0.1 MPa to minimise human error in judging when critical rotation speeds were met.

### 3.2. Fiber Characterisation

Surface topography of the PVP fibers formed via ES and PG (**Figure 3**) both showed a smooth and pore-less surface. Fibers produced by ES exhibited a cross-woven profile with overlapping fibers, due to the agitated motion of the whipping instability onto the grounded collector [23]. PG fibers were found to be more aligned due to the unidirectional rotation of the drum and outward force of the applied gas pressure [24]. Cross-woven fibers could however attribute to a superior drug-release profile as there is increased steric hindrance of the drug molecules in their amorphous state [25]. The fiber diameter distribution of ES fibers demonstrated a smaller variation, proving that ES created more uniform fibers with a smaller diameter. ES provided greater control over fiber diameter due to having more processing parameters, capable of fine-tuning fiber diameter, however in more recent processes like pressure-coupled infusion gyration, this limitation can be overcome [26]. In pressure-driven fiber formation, the minimum achievable diameter is limited by the orifice area and the compactability of the polymer [27]. Increasing the rotational speed would result in a higher centrifugal force which could result in finer diameter fibers for PG [9].

Centrifugal dispersion affects fiber diameter, uniformity and alignment [28]. At higher rotational speeds, the centrifugal force overcomes the surface tension of the solution, increasing fiber uniformity. From the SEM images, PG-formed PVDF fibers displayed a more aligned configuration especially when compared to ES fibers (**Figure 4**), this is predominantly due to unidirectional high speed rotation of the pressurised gyration drum. Fiber uniformity was noticeably greater with PG fibers; this is possibly due to the rotational speed being matched with the surface tension of the 30% w/w solution (28.1 ± 0.5 $mNm^{-1}$). The bending instability of the polymer jet is corrected for by the centrifugal force, in ES the instability sees no modification and fibers are deposited as a cross-woven mat [29]. Fiber diameters were also observed to be significantly finer with PG with a smaller spread about the mean. This further supports that an optimal rotational speed was created for the polymer system in PG. The ES PVDF solution required a flow rate of 50 μL/min and a voltage of 18.0 kV, indicating a higher surface tension than PVP (21.6 ± 0.9 $mNm^{-1}$) which had to be overcome with a higher voltage [30]. Physical characteristics of the polymer solvents used are summarised in **Table 4**.

The occurrence of "bead-on-string" morphology has been a point of interest in electrospinning studies, with many attributing this behaviour to instabilities resulting from low charge density or surface tension of the solution (PMMA surface tension: 26.8 ± 0.4 $mNm^{-1}$) [31-33]. ES PMMA fibers showed a beaded morphology whilst PG did not (**Figure 5**). This interesting outcome could be the result of having a low charge density in ES, whilst centrifugal-lead spinning in PG does not require the exploitation of charge. Both PG and ES produced fibers with a porous topography. Formation of pores requires a highly volatile solvent such as chloroform which creates a temperature drop resulting in formation of water droplets, these droplets then evaporate forming pores [10], The average pore size was 390 nm (± 68) for ES fibres and 70 nm (± 18) for PG fibres. Pores found on ES fibers had a significantly larger average diameter, which could be explained by the necessary use of high flow rate to overcome solution stagnation [34]. Average fiber diameter of PG fibers were again notably smaller and less dispersed than ES fibers. This shows that PG is capable of producing finer diameter fibers on some polymer systems that would otherwise be very difficult to spin with ES. It must be noted that PMMA fiber production were very high in PG and in ES. However, prolonged electrospinning was not possible because the solution would eventually clog the needle causing blockages.

PNIPAm ES fibers exhibited an average fiber diameter of 3.0 µm (± 0.5), displaying high uniformity. PG fibers produced a larger average fiber diameter at 6.3 µm (± 3.6) with a high spread of diameters as shown in **Figure 6**. A high flow rate typically produces electrospun fibers with a thicker diameter owing to the shorter drying time of the solvent before reaching the collector and the reduced stretching forces [35]. However even at a high flow rate of 150 µL/min, ES PNIPAm fibers produced smaller diameter fibers with a tighter size distribution compared to PG fibers. At high viscosities in PG, fiber stretching becomes more difficult and as a consequence, thicker fibers are produced with a wider diameter distribution [36]. Although not a particularly high molecular weight polymer (300,000 g $mol^{-1}$), PNIPAm has a high viscosity (654.1 mPa. s) due to its polar ester group promoting stronger interactions in its inter-chains [37]. Electrospun PNIPAm fibers displayed a very uniform diameter distribution with very little spread. The surface was smooth in fibers produced by both technologies. It must be noted that there was difficulty with electrospinning the PNIPAm solution due to its high viscosity. A large flow rate was required to overcome solution stagnation and tube blocking. Even at a high flow rate (150 µL/min) the solution would not allow prolonged spinning sessions. In comparing simplicity and processability, pressurised gyration did not pose any difficulties when spinning PNIPAm, providing feasibility which was not shown by electrospinning.

Comparing pressure-driven fiber forming techniques with electric field driven techniques, there are notable differences in the production mechanism. One key element contributing to fiber thinning is solvent evaporation [38]. Pressurised gyration is capable of forming finer diameter fibers such as in the case of PMMA and PINIPAm. When dimethylformamide, acetone and chloroform were used as solvents, they produced lower diameter fibers using pressurised gyration than electrospinning. The high volatility of these solvents ensures rapid evaporation from the emerging polymer jets. The rotation of the spinning vessel also accelerates solvent evaporation by increasing the kinetic energy of the solvents in the emerging droplets.

Electrospinning produced fibers with finer diameters for PVP and PNIPAm, coincidently both polymers were dissolved in ethanol. The principle of electro spray Ionisation (ESI) can be used to explain the ionisation of the ethanol in a polymer solution. Given sufficient polymer chain entanglement, the polymer is not atomised. However, the solvent undergoes ionisation in the same way as it would under ESI. Solvent evaporation occurs when the droplets traverses between the opening of the nozzle and the open environment [39]. As solvent evaporation ensues, the size of the droplets decreases until reaching the Rayleigh limit. Coulomb fission occurs when the droplets reach the Rayleigh limit and are unable to withstand the Coulomb force of repulsion [40]. Initial droplets disintegrate creating smaller "offspring" droplets. Coulomb fission and solvent evaporation occur repeatedly generating increasingly smaller droplets which finally become charged nano-droplets from which the gas-phase charged molecules form [41]. Due to the presence of an electric field in electrospinning, solvent evaporation rates are accelerated by Coulomb fission. Ethanol is readily atomised which potentially explains the difference in fiber diameter between ES and PG, as the atomisation increases solvent evaporation rate in electrospinning but not pressurised gyration.

### 3.3. Drug-loaded Fibers and dissolution studies

Poorly water soluble drugs ITZ (water solubility 1-4 ng/mL) and AMB (water solubility 0.08 mg/mL) where selected to prepare drug loaded fibers [42, 43]. AMB-loaded and ITZ-loaded PVP fibers were successfully produced using both ES and PG. SEM analysis revealed all the fibers were cylindrical in shape, with smooth surfaces and no visible particles. This indicates that AMB and ITZ were successfully encapsulated homogenously within the polymeric fibers. The

SEM images of the drug loaded fiber are given in **Figure 7.** and fiber diameters are tabulated in **Table 3**. Smaller fiber diameters are highly desirable in drug delivery applications, as this drastically improves their contact surface area: volume ratio, thus also improving the drug dissolution rate. Electrospinning produced drug loaded PVP fibers with finer diameters as compared with pressurised gyration.

The drug dissolution profile (**Figure 8**) evidently illustrates that drug-loaded PVP fibers significantly improve the dissolution of AMB and ITZ. The dissolution enhancement of AMB and ITZ can be attributed to several factors. Essential factors for dissolution rate improvement include amorphisation, particle size reduction, improved dispersibility and wettability [44]. It can be eluded from the dissolution data of drug-loaded fibers that improvement in dissolution is ascribed to the increased wettability and dispersibility that PVP provides. The mixing of AMB and ITZ with the hydrophilic PVP resulted in superior wetting, this increased the contact surface area for dissolution as it reduced the interfacial tension between the hydrophobic AMB and ITZ and the dissolution media [45]. It is expected that the drug molecules were uniformly distributed within the polymer in a highly dispersed state. When in contact with the dissolution media, the hydrophilic PVP readily dissolved and this resulted in the precipitation of the embedded drug into fine colloidal particles. The absence of drug molecule aggregation due to steric hindrance of the polymer chains and the amorphisation of the drug could have also attributed to the enhanced dissolution profile of the PG and ES drug-loaded fibers [46].

There is an observable difference between the dissolution rates of the PG fibers compared with the ES fibers. The distribution of AMB and ITZ drug molecules within the polymer chain would have been influenced by the electric field of electrospinning, where the pressure and centrifugal force of pressurised gyration would not have. Alternatively, the cross-woven conformation of ES fibers may have reduced the available surface area via a "barrier effect" of the interlaced fiber branches. Via the close overlapping of fiber branches, effective surface area is reduced as the fibers aggregate creating a "barrier" of fibers which act as larger diameter branches. A reduced surface area yields fewer electrostatic interactions between the polar molecules of the dissolution media and the polymer surface [47]. PG fibers consistently displayed absence of release within the first 10 minutes, this could be due to the dispersion of drug molecules within the centre of the fibers due to the rotation of the gyration vessel. Structure of the fibers produced by the two techniques seem to play a role in the release kinetics. ES fibers were finer in diameter and also revealed earlier release when these came in contact with the dissolution media. The finer diameter afforded for greater surface area as the hydrogen bonds of the PVP chain were being broken. PG fibers had a slightly larger diameter which could explain the delay in drug release.

The FTIR absorption spectra of the itraconazole-loaded PVP fibers are shown in **Figure 9.** The peak at 3430 cm$^{-1}$ corresponds to the O-H stretching vibration of PVP, peak at 1018 cm$^{-1}$ matches the C-N vibrations [48]. Characteristic peaks observed at 2824 - 3128 cm$^{-1}$ were due to C-H vibrations, showing itraconazole was present [49]. Peaks at 1660 cm$^{-1}$ show the C=O stretching vibrations of PVP. The two fibers types show superimposability suggesting they have almost identical chemical properties. The FTIR spectrum corroborated that the itraconazole-loaded PVP fibers produced by ES and PG contained itraconazole. Characteristic peaks at 2824 - 3128 cm$^{-1}$ and 3069 cm$^{-1}$ were observed in all samples, N-H stretching of amides were detected at 3430 cm$^{-1}$ [50]. Superimposability of the spectrum demonstrations that the two ITZ drug-loaded fibers were closely related in terms of their chemical characteristics. There are minor peak shifts at 1755 and 1045 cm$^{-1}$ and this is merely due to the delocalisation of $\pi$-electrons. The FTIR spectrum thus demonstrations that the ITZ fibers produced by ES and PG do not differ in their chemical makeup, as expected. Any differences in the drug-release profile is more likely due to structural differences in the fibers such as the aforementioned "cross woven" conformation of fibers produced by pressurised gyration and the differences in fiber morphology,

When comparing the drug release profiles between AMB and ITZ, it can be seen that there is a general pattern. Both AMB and ITZ drug loaded PVP fibers showed extensive increase in dissolution when compared to the dissolution of drug powder. The increase in dissolution rate of AMB drug compared with ITZ drug is merely due to its greater solubility. Fibers spun by PG displayed consistent maximum release whilst ES fibers showed inconsistent release. Pressurised gyration fibers are thus able to release the active pharmaceutical ingredient in a more precise and predictable manner which is highly desired in drug delivery. Itraconazole loaded fibers produced by PG show accelerated release in contrast to a slightly delayed maximum release with electrospun fibers. The difference in release profile for itraconazole fibers is likely due to the difference in fiber morphology. Furthermore, it can be seen that PG drug loaded fibers do not express any release within the first 10 minutes of testing, whereas ITZ ES fibers show release within the first 5 minutes. Slight differences between the dissolution profile of AMB and ITZ loaded fibers can be ascribed to PVP's tendency to bind differently to different drugs via hydrogen bonding, where the two drugs differed in their chemical structure. The difference in drug loading between AMB (5%) and ITZ (2.5%) fibers showed a predictable shift in the maximum release times with PG fibers releasing at 55 minutes for AMB and 30 minutes for ITZ. The drug release profile can thus be tailored by multiple parameters. The working parameters of electrospinning and pressurised gyration allow configuration of drug loaded fibers that can vary in fiber diameter, structure and drug to polymer ratio. Pressurised gyration alongside electrospinning has proven to be a dependable method of producing fibers for drug delivery, pressurised gyration allows for additional reliability in controlled drug delivery of poorly water-soluble drugs.

## 4. Conclusions

Several types of polymeric fibers were prepared with two different fiber making techniques: electrospinning and pressurised gyration. PVP, PVDF, PMMA and PINIPAm were selected as the polymers. Pressurised gyration produced finer diameter fibers with polyvinylidene fluoride and Poly(methyl methacrylate) as compared with electrospinning. On the other hand, fiber diameter of gyrospun poly(*N*-isopropylacrylamide) was larger than electrospun fibers and fiber diameter of both electrospun and gyrospun Poly(vinylpyrrolidone) fibers have roughly similar fiber diameters. Needle clogging and polymer solution flowing difficulties were observed during electrospinning. Such difficulties were not observed with pressurised gyration and fiber production rate was higher in this technique compare to electrospinning. Amphotericin B and itraconazole loaded PVP fibers were prepared using both techniques. In-vitro dissolution studies showed a more rapid release with electrospun fibers than gyrospun fibers at the beginning, for 15 minutes. Gyrospun fibers showed accelerated dissolution following 15 minutes and were able to reach 100% release due to their structure and morphology. Both ES and PG fibers are suitable for improving the dissolution of poorly water soluble drugs, pressurised gyration offers promising potential in producing controlled and specific-release pharmacokinetics.

## References

[1] M. Gagliardi, "Global Markets and Technologies for Nanofibers", USA, 2016.

[2] M. C. Wang, G. D. Pins, F. H. Silver, *Biomaterials* **1994**, *15*, 507.

[3] P. X. Ma, R. Zhang, *Journal of Biomedical Materials Research* **1999**, *46*, 60.

[4] G. M. Whitesides, B. Grzybowski, *Science* **2002**, *295*, 2418.

[5] Z.-M. Huang, Y. Z. Zhang, M. Kotaki, S. Ramakrishna, *Composites Science and Technology* **2003**, *63*, 2223.

[6] Y. Márquez, L. Franco, P. Turon, L. J. del Valle, J. Puiggalí, *Macromolecular Materials and Engineering* ***2017***, 1700401.

[7] L. Persano, A. Camposeo, C. Tekmen, D. Pisignano, *Macromolecular Materials and Engineering* **2013**, *298*, 504.

[8] X. Hong, S. Mahalingam, M. Edirisinghe, *Macromolecular Materials and Engineering* **2017**, *302*, 1600564.

[9] Y. Lu, Y. Li, S. Zhang, G. Xu, K. Fu, H. Lee, X. Zhang, *European Polymer Journal* **2013**, *49*, 3834.

[10] U. Illangakoon, S. Mahalingam, R. Matharu, M. Edirisinghe, *Polymers* **2017**, *9*, 508.

[11] J. L. Daristotle, A. M. Behrens, A. D. Sandler, P. Kofinas, *ACS Applied Materials & Interfaces* **2016**, *8*, 34951.

[12] W. Reppe, *Angewandte Chemie* **1953**, *65*, 577.

[13] F. Haaf, A. Sanner, F. Straub, *Polymer Journal* **1985**, *17*, 143.

[14] T. R. Bates, *Journal of Pharmacy and Pharmacology* **1969**, *21*, 710.

[15] L. P. Zhu, J. Z. Yu, Y. Y. Xu, Z. Y. Xi, B. K. Zhu, *Colloids and surfaces. B, Biointerfaces* **2009**, *69*, 152.

[16] G. Lewis, *Journal of Biomedical Materials Research* **1997**, *38*, 155.

[17] J. Zhang, N. A. Peppas, *Macromolecules* **2000**, *33*, 102.

[18] M. Chen, M. Dong, R. Havelund, V. R. Regina, R. L. Meyer, F. Besenbacher, P. Kingshott, *Chemistry of Materials* **2010**, *22*, 4214.

[19] H. Friedrich, B. Fussnegger, K. Kolter, R. Bodmeier, *European Journal of Pharmaceutics and Biopharmaceutics* **2006**, *62*, 171.

[20] S. Mahalingam, B. T. Raimi-Abraham, D. Q. M. Craig, M. Edirisinghe, *Chemical Engineering Journal* **2015**, *280*, 344.

[21] X. Xu, J. Luo, *Applied Physics Letters* **2007**, *91*, 124102.

[22] E. S. Medeiros, G. M. Glenn, A. P. Klamczynski, W. J. Orts, L. H. C. Mattoso, *Journal of Applied Polymer Science* **2009**, *113*, 2322.

[23] R. Jalili, M. Morshed, S. A. H. Ravandi, *Journal of Applied Polymer Science* **2006**, *101*, 4350.

[24] J. Pal, S. Singh, S. Sharma, R. Kulshreshtha, B. Nandan, R. K. Srivastava, *Materials Letters* **2016**, *167*, 288.

[25] B. Rambali, G. Verreck, L. Baert, D. L. Massart, *Drug development and Industrial Pharmacy* **2003**, *29*, 641.

[26] J. Du, S. Shintay, X. Zhang, *Journal of Polymer Science Part B: Polymer Physics* **2008**, *46*, 1611.

[27] J. Dudowicz, K. F. Freed, *Macromolecules* **1991**, 5112.

[28] D. Edmondson, A. Cooper, S. Jana, D. Wood, M. Zhang, *Journal of Materials Chemistry* **2012**, *22*, 18646.

[29] F. Dabirian, S. A. Hosseini Ravandi, A. R. Pishevar, R. A. Abuzade, *Journal of Electrostatics* **2011**, *69*, 540.

[30] X. Zong, K. Kim, D. Fang, S. Ran, B. S. Hsiao, B. Chu, *Polymer* **2002**, *43*, 4403.

[31] Y. Liu, J.-H. He, J.-y. Yu, H.-m. Zeng, *Polymer International* **2008**, *57*, 632.

[32] W. Zuo, M. Zhu, W. Yang, H. Yu, Y. Chen, Y. Zhang, *Polymer Engineering & Science* **2005**, *45*, 704.

[33] T. Lin, H. Wang, H. Wang, X. Wang, "*The charge effect of cationic surfactants on the elimination of fibre beads in the electrospinning of polystyrene*", 2004, p. 1375.

[34] J. Rnjak-Kovacina, S. G. Wise, Z. Li, P. K. Maitz, C. J. Young, Y. Wang, A. S. Weiss, *Biomaterials* **2011**, *32*, 6729.

[35] C. J. Buchko, L. C. Chen, Y. Shen, D. C. Martin, *Polymer* **1999**, *40*, 7397.

[36] J. E. Oliveira, L. H. C. Mattoso, W. J. Orts, E. S. Medeiros, *Advances in Materials Science and Engineering* **2013**, *2013*, 14.

[37] D. E. Bergbreiter, B. L. Case, Y.-S. Liu, J. W. Caraway, *Macromolecules* **1998**, *31*, 6053.

[38] Y. Dzenis, *Science* **2004**, *304*, 1917.

[39] S. Banerjee, S. Mazumdar, *International Journal of Analytical Chemistry* **2012**, *2012*, 1.

[40] P. Kebarle, L. Tang, *Analytical Chemistry* **1993**, *65*, 972A.

[41] J. V. Iribarne, B. A. Thomson, *The Journal of Chemical Physics* **1976**, *64*, 2287.

[42] J. C. DiNunzio, C. Brough, D. A. Miller, R. O. Williams, J. W. McGinity, *Journal of Pharmaceutical Sciences* **2010**, *99*, 1239.

[43] R. Mannhold, G. I. Poda, C. Ostermann, I. V. Tetko, *J Pharm Sci* **2009**, *98*, 861.

[44] J. L. Ford, *Pharmaceutica acta Helvetiae* **1986**, *61*, 69.

[45] A. Modi, P. Tayade, *AAPS PharmSciTech* **2006**, *7*, E87.

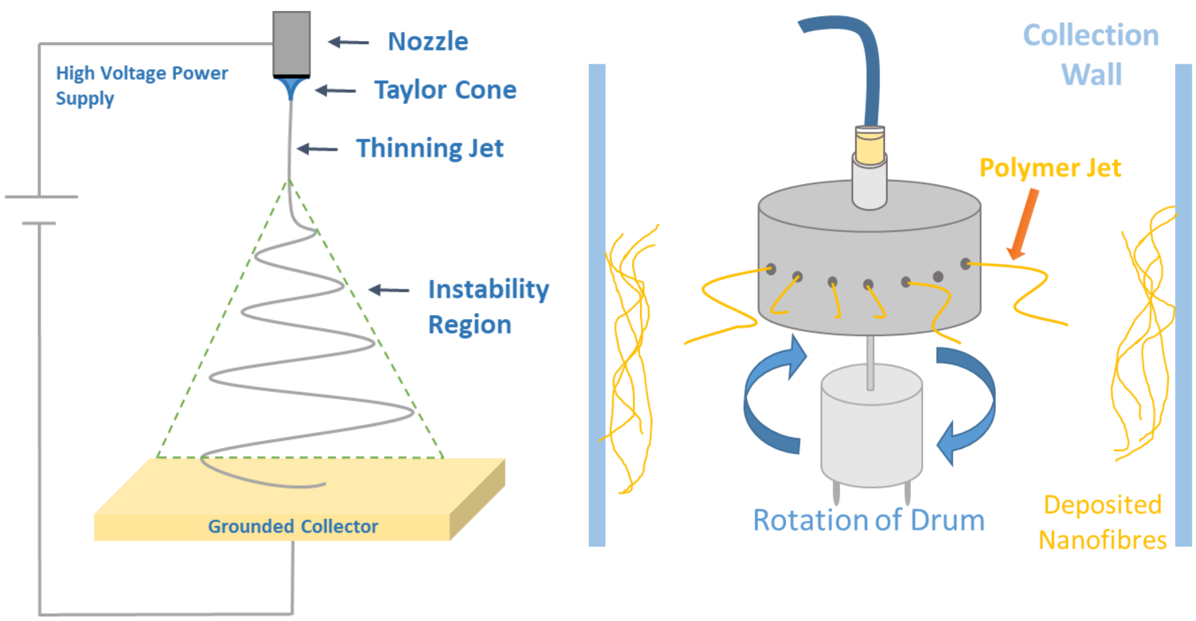
[46] P. Mura, A. Manderioli, G. Bramanti, L. Ceccarelli, *Drug Development and Industrial Pharmacy* **1996**, *22*, 909.

[47] M. L. Sanchez, M. A. Aguilar, F. J. O. delValle, *Journal of Computational Chemistry* **1997**, *18*, 313.

[48] L. S. Taylor, G. Zografi, *Pharmaceutical Research* **1997**, *14*, 1691.

[49] K. Malarvizhi, D. Ramya, A. Raymond, D. B. N. V. Hari, "*Engineered Nanoparticle Aerosol Foam Formulation for Skin Diseases*", 2014, p. 109.

[50] T. Tao, Y. Zhao, J. Wu, B. Zhou, *International Journal of Pharmaceutics* **2009**, *367*, 109.




(a) (b)

*Figure 1*. (Schamatic diagrams illustrating (a) electrospinning (b) presurised gyration setups used)

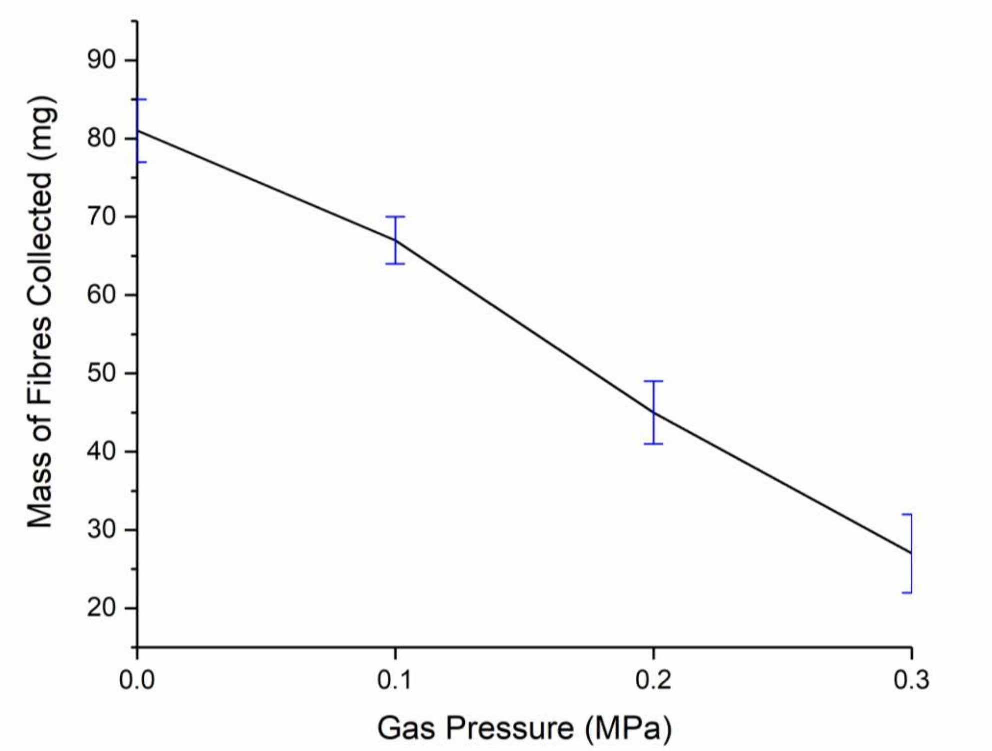



*Figure 2*. Shows the effect of increasing gas pressure on the of fibre yield, spun for 15 seconds at a speed of 36,00 rpm. The standard deviation of the repeated tests is represented by error bars (n = 5).

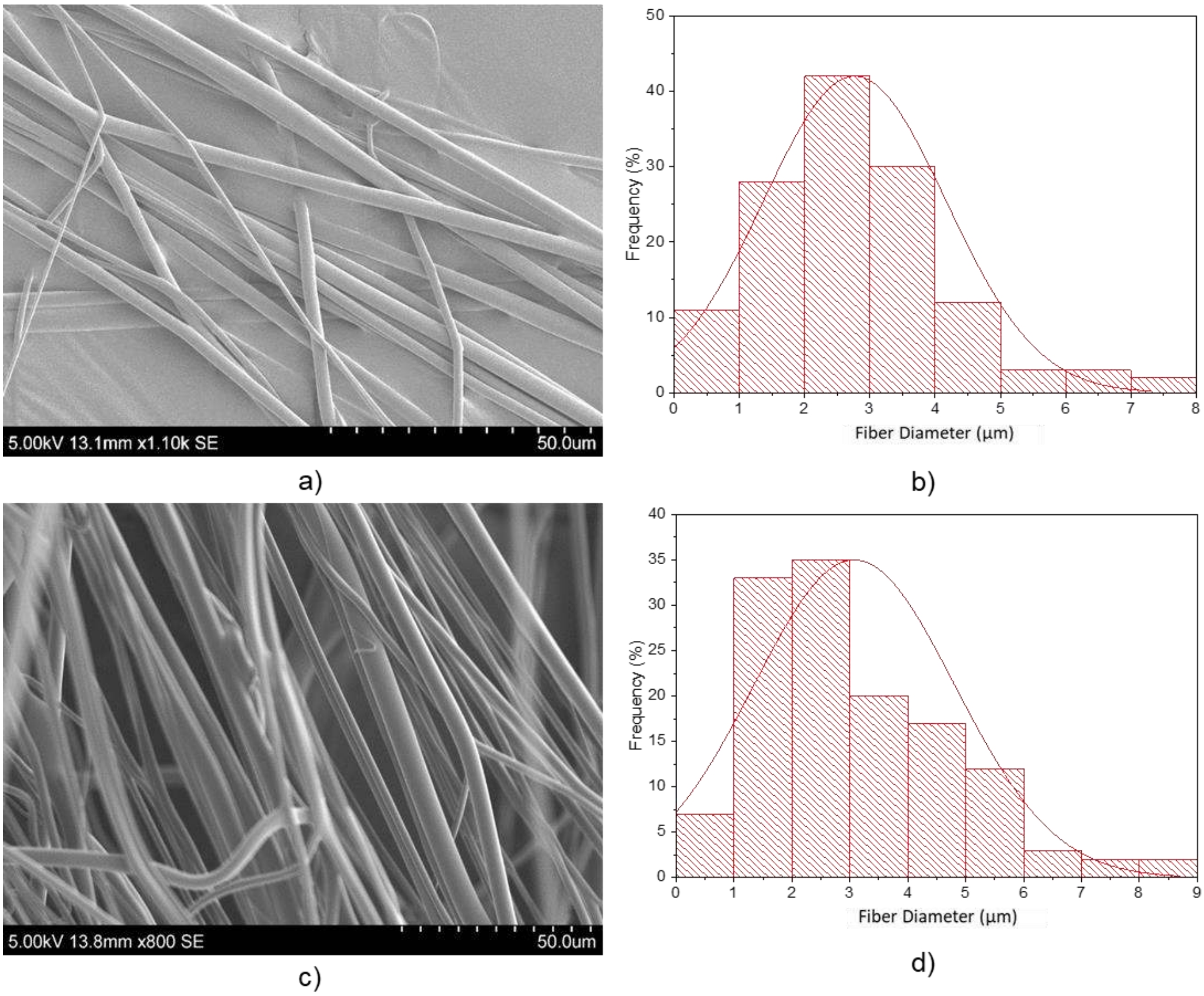



*Figure 3*. SEM images and fibre diameter distribution of PVP fibres prepared by electrospinning (a, b) and pressurised gyration (c, d).

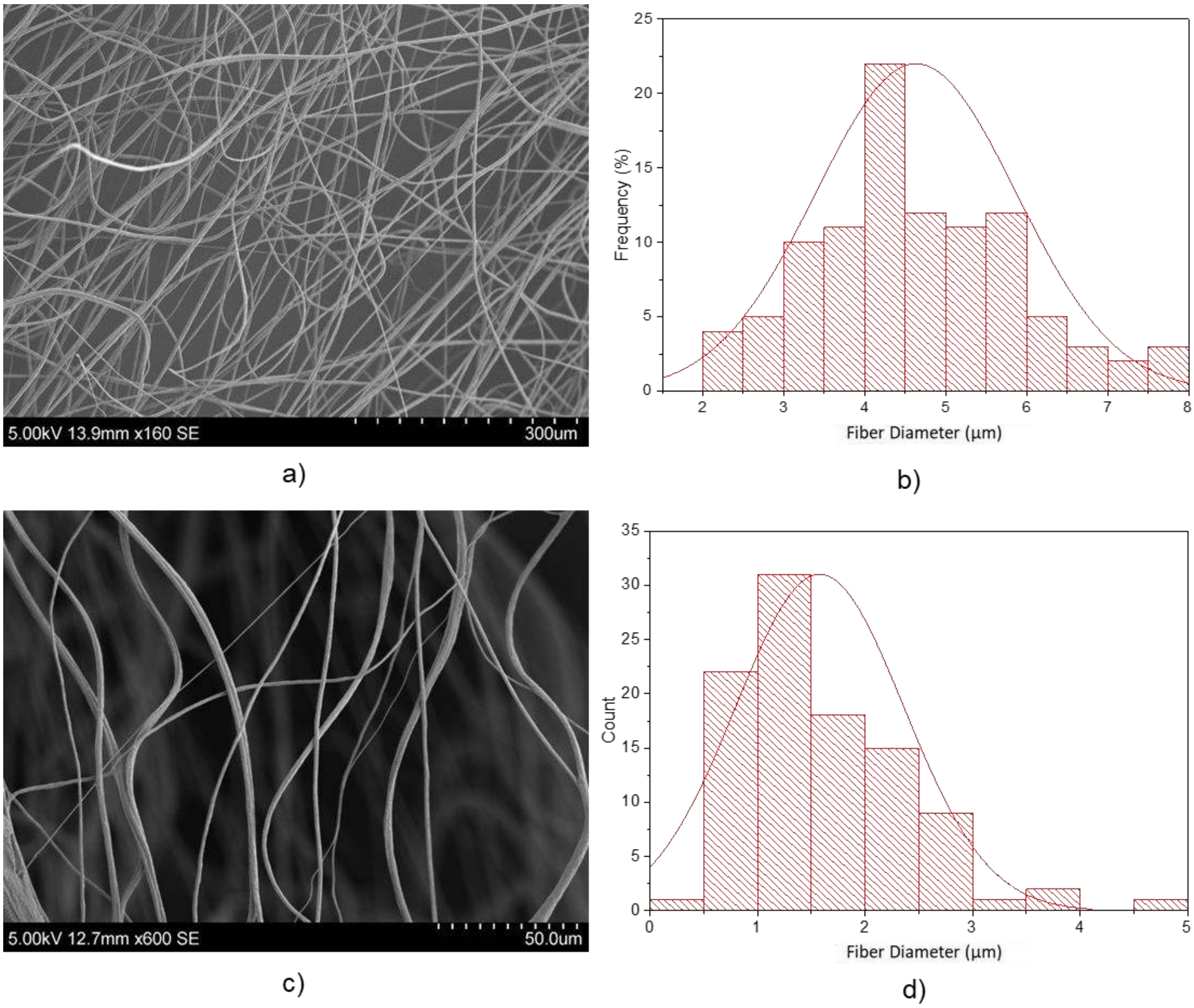



*Figure 4*. SEM images and fibre diameter distribution of PVDF fibres prepared by (a,b) electrospinning and (c,d) pressurised gyration.

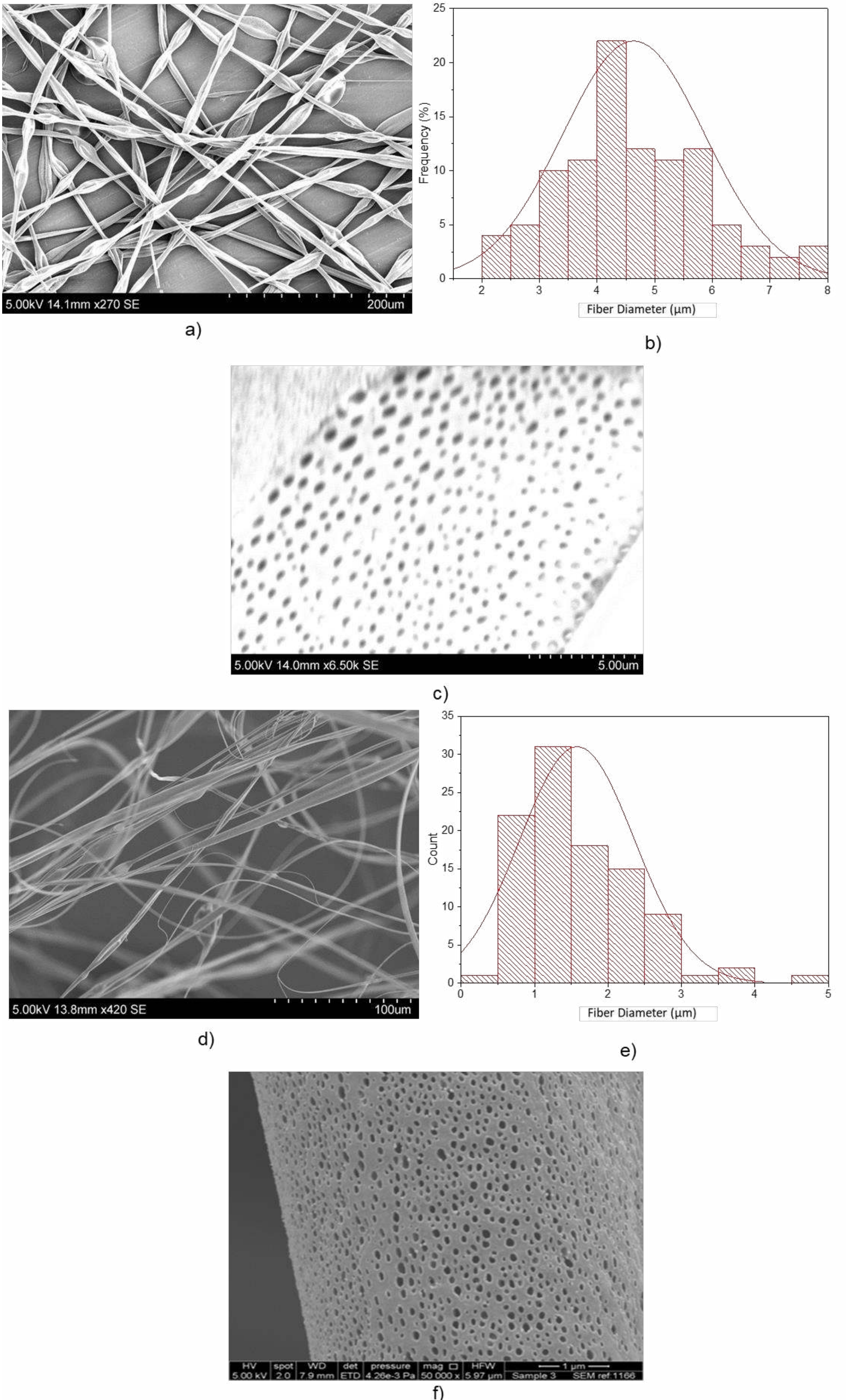

5.00kV 14.1mm x270 SE
200um
a)
Frequency (%)
Fiber Diameter (µm)
b)
5.00kV 14.0mm x6.50k SE
5.00um
c)
5.00kV 13.8mm x420 SE
100um
d)
Count
Fiber Diameter (µm)
e)
HV spot WD det pressure mag HFW
5.00 kV 2.0 7.9 mm ETD 4.26e-3 Pa 50 000 x 5.97 µm
1 µm
Sample 3 SEM ref:1166
f)

*Figure 5*. SEM images and fiber diameter distribution of PMMA fibres prepared by electrospinning (a, b, c) and pressurised gyration (d, e, f).

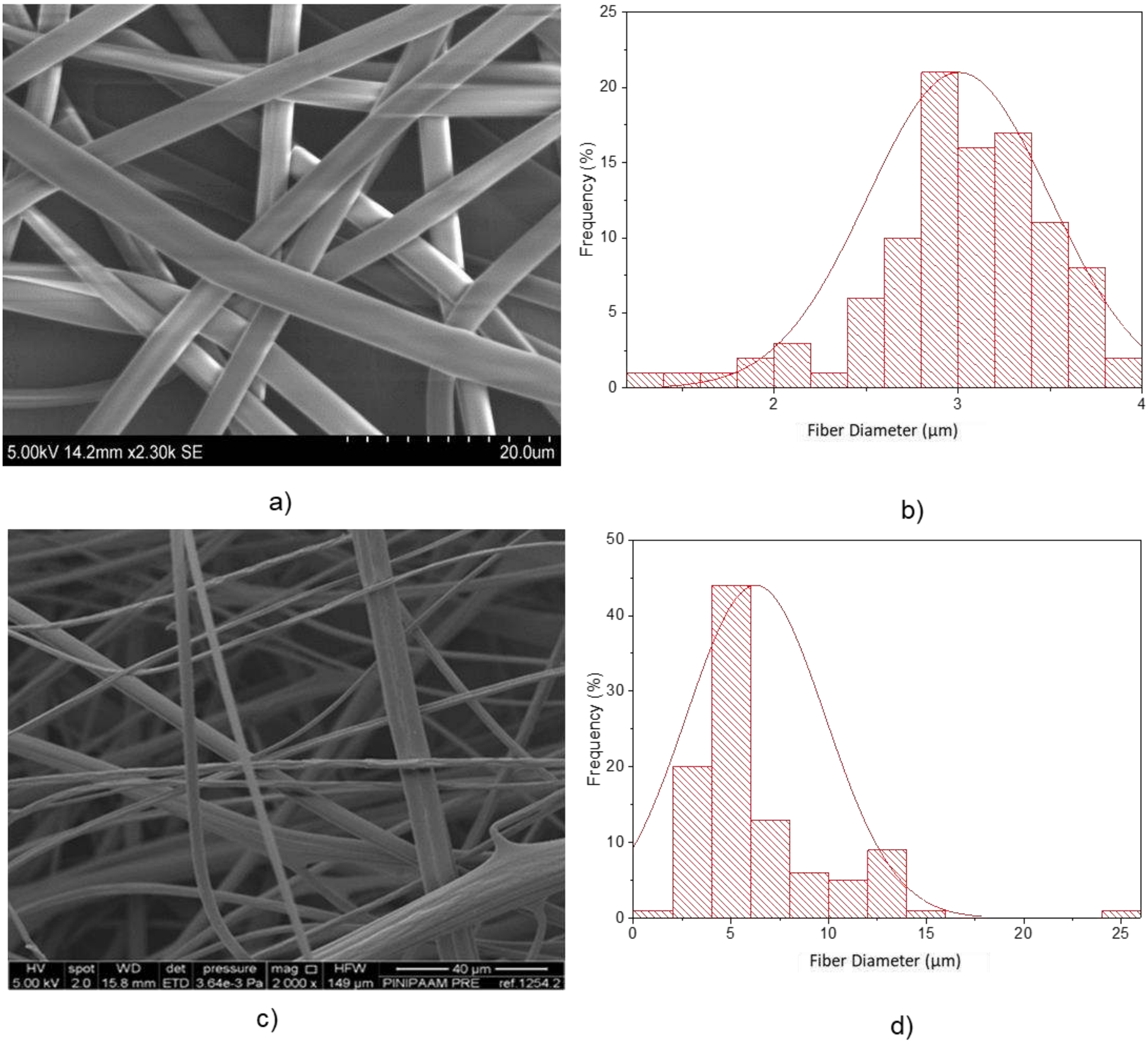



*Figure 6*. SEM images and fiber diameter distribution of PINIPAM fibres prepared by electrospinning (a, b) and pressurised gyration (c, d).

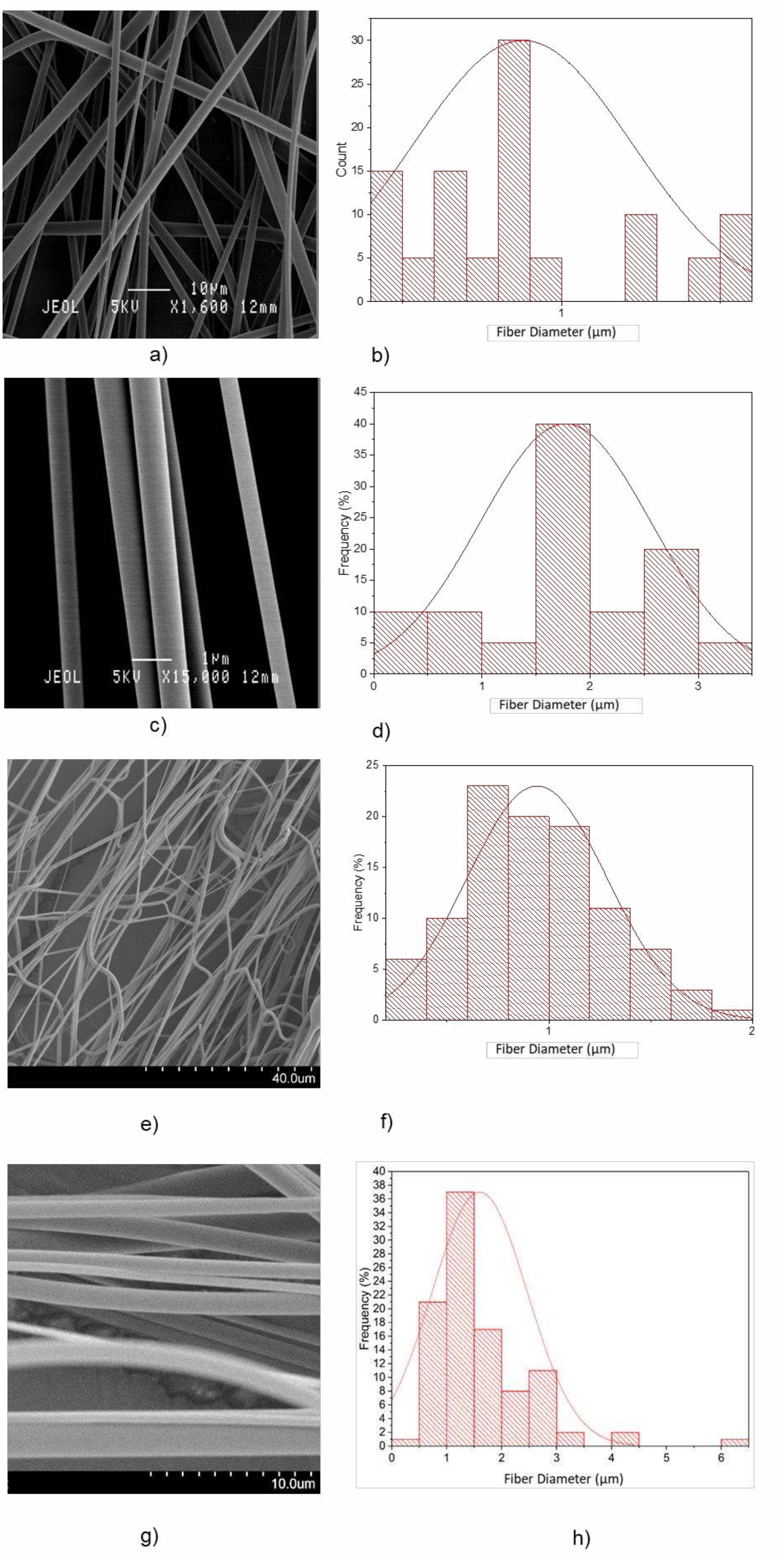
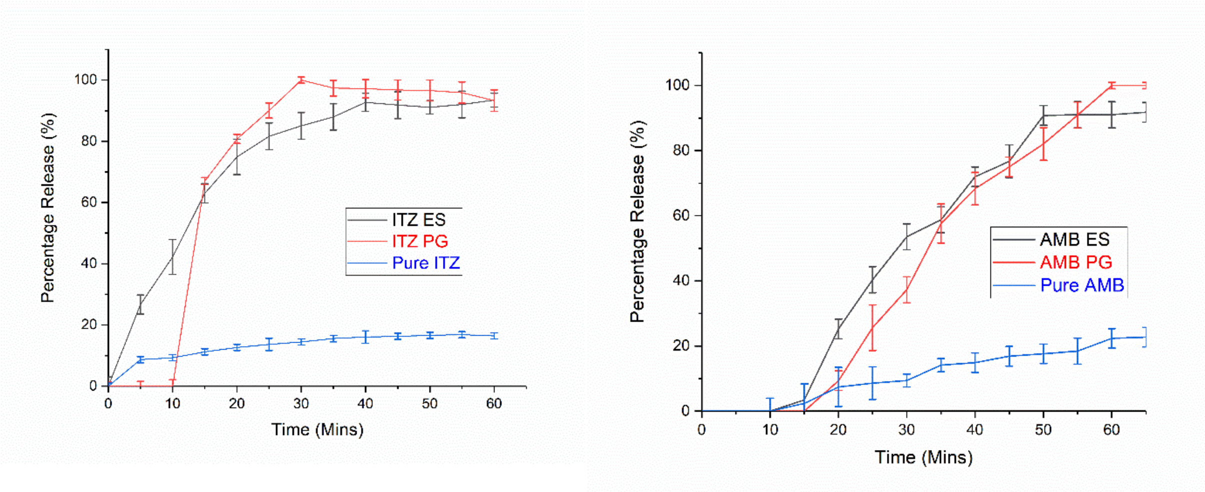

10µm
JEOL 5KV X1,600 12mm
Count
Fiber Diameter (µm)
1µm
JEOL 5KV X15,000 12mm
Frequency (%)
Fiber Diameter (µm)
40.0um
Frequency (%)
Fiber Diameter (µm)
10.0um
Frequency (%)
Fiber Diameter (µm)
a)
b)
c)
d)
e)
f)
g)
h)

*Figure 7*. SEM images and fibre diameter distribution of: Amphotericin B loaded PVP fibres prepared by electrospinning (a) and pressurised gyration (c), Itraconazole loaded PVP fibres produced by (e) electrospinning and (g) pressurised gyration. Figures (b,d,f,h) show the fibre diameter distribution for the corresponding fibre type.




(a) (b)

*Figure 8*. (Drug dissolution profiles (a) Itraconazole-loaded fibers (b) amphotericin B fibers.)

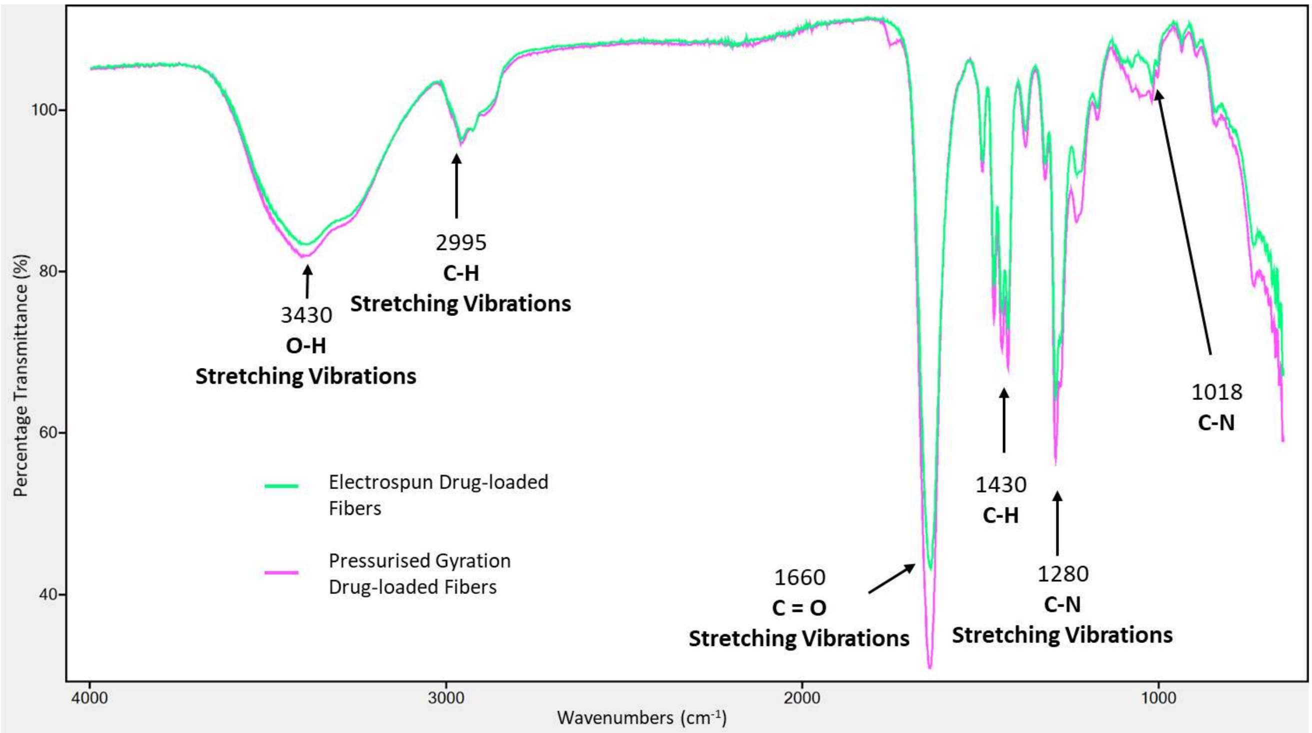



*Figure 9*. FTIR spectra for ES and PG itraconazole-loaded PVP fibres.

Table 1. Polymer solutions used in this work

| Polymer | % (w/v) | Solvent system |
|---|---|---|
| PVP | 10 | Ethanol |
| PVDF | 25 | 1:1 Dimethylformamide : Acetone |
| PMMA | 20 | Dichloromethane |
| PINIPAm | 20 | 2:1 Chloroform : Ethanol |

Table 2. Electrospinning and Gyration spinning conditions

| Polymer | Electrospinning | | | Pressurised Gyration | | |
|---|---|---|---|---|---|---|
| | kV | Flow rate (µl/min) | Collecting distance (mm) | Pressure (MPa) | Rotation speed (rpm) | Collecting distance (mm) |
| PVP | 16.0 | 100 | 150 | 0.1 | 36000 | 120 |
| PVDF | 18.0 | 50 | 150 | 0.1 | 36000 | 120 |
| PMMA | 16.0 | 150 | 150 | 0.1 | 36000 | 120 |
| PINIPAm | 17.0 | 150 | 150 | 0.1 | 36000 | 120 |

Table 3: Average fibre diameters achieved

| Polymer System | Average Fibre Diameter (± µm) | |
|---|---|---|
| | Electrospinning | Pressuirised Gyration |
| PVP (Pure) | 3.13 ± 1.34 | 3.53 ± 1.70 |
| PVDF | 4.63 ± 1.22 | 1.58 ± 0.76 |
| PMMA | 5.57 ± 2.11 | 1.97 ± 1.75 |
| PNIPAm | 3.00 ± 0.50 | 6.30 ± 3.60 |
| PVP (Itraconazole) | 0.94 ± 0.34 | 1.60 ± 0.87 |
| PVP (AMP B) | 0.88 ± 0.35 | 1.78 ± 0.81 |

Table 4: Polymer solutions used

| Polymer Solution | Surface Tension ($mNm^{-1}$) | Viscosity (mPa. s) |
|---|---|---|
| **PVP** (Ethanol) | 21.6 ± 0.9 | 476.3 |
| **PVDF** (1:1 Dimethylformamide : Acetone) | 28.1 ± 0.5 | 475.4 |

| | | |
|---|---|---|
| **PMMA** (Dichloromethane**)** | 26.8 ± 0.4 | 27.6 |
| **PINIPAm (**2:1 Chloroform: Ethanol**)** | 83.0 ± 1.5 | 654.1 |

Graphical Abstract Image

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Abstract.tif

Figure 1a Image

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Fig 1a.tif

Figure 1b Image

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Figure 8a Image

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Figure 8b Image

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Fig 8b.tif

Figure 9 Image

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