

# **Encapsulation of Theophylline in Poly (vinyl alcohol) using Electrospaying Method**

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## **Abstract**

Controlled drug delivery retain optimize drug concentration in blood, decrease side effects, cause patient comfort and improve life quality. In order to achieve optimize particles; a PVA poly (vinyl alcohol) with different molecular weight was used. In this research, PVA samples in different concentrations from 23000(gr/mol) molecular weight and 98% degree hydrolysis were prepared. Moreover, poly (vinyl alcohol) nanoparticles loaded with theophylline as a drug model. Morphology and homogeneity of nanoparticles was investigated by scanning electron microscopy. The morphology of particles (10% concentration) was observed uniform and without fibers.

Keyword: Drug delivery, Nanoparticle, Encapsulation, Electrospay, Poly (vinyl-alcohol).

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## **1. Introduction**

Medical improvements have many advantages to increasing lifetime of human [1-4]. According to the fundamental structures, drug delivery systems divided into three main groups including microencapsulation, transdermal techniques and polymers [5]. Microencapsulation is a method which particles or droplets were prepared by coating a layer and small capsules with certain properties. In a simple definition, the microcapsule is a small spherical which covered with a uniform layer. The inside part of microcapsule is called core or filler phase, and the outer surface is shell or membrane. After the advent of this method in 1950, electrospay

has been well-studied due to their simple procedure and the potential for industrial scale-up [6]. Recently, many works have focused on electrospay, a novel technique, which can produce particles with different diameters in micrometer and nanometer dimensions [7]. In this setup, high voltage operated between syringe and collector drums as a driving force to prepare particles [8]. In addition, flow rate and the distance between needle and drum could be change as critical parameters. There are various methods to preparing nanoparticles including Chemical Vapor Deposition (CVD) [9, 10], electrostatic method [11], Chemical Vapor Condensation (CVC) [12, 13], Sol-Gel [14-18], Mechanical Attrition [19-23], and

Electrospray [24-27]. Moreover, nanoscale materials have many advantages such as increasing specific surfaces [28], improving activity of materials [29], chemical reactions and mechanical properties [30]. The electrospray has been an attractive candidate to produce nanocomposite materials due to some advantages such as easy controlling of particle precipitation rate, producing in the atmosphere condition without high temperature and low cost materials. Kostakova et al. [31] reported that using PVA nanoparticles and nanofibers to achieve to the composite material. They confirmed that nanostructure composite of electrospin and electrospray with addition of spherical fullerenes with right procedure conditions is possible. Almeria et al. [6] were produced PLGA nanoparticles via multiples electrospray system. Parhizkar et al. [32] worked on Encapsulation of amphiphilic agents such as doxorubicin, Rhoda mine B and Rhodamine B octadecyl ester. Chitosan is a hydrophilic polymer with antibacterial property and an proper natural polymer as a drug carrier [32]. In another study Gentamicin was encapsulated as a model drug on Chitosan micro particles [33]. In this research, firstly, the concentration of poly (vinyl alcohol) solvents was optimized. Then, the parameters of PVA nanoparticles electrospray such as flow rate, the distance between needle and drum and electrostatic voltage were investigated. Theophylline as a drug model was encapsulated in the polymeric particles. The formed particles and drug-loaded nanoparticles were characterized by scanning electron microscopy. To overcome the easy solubility of PVA and drug-loaded PVA in addition enhance the durability of particles during the investigation, particles were cross-linked in two different ways including exposing glutaraldehyde vapor and take them at 130°C temperature.

## 2. Materials and Method

### 2.1. Materials

Poly (vinyl-alcohol) with different molecular weights (144000-72000-23000 gr/mol) and degree of hydrolysis (89% and 98%) were provided from Sigma-Aldrich, Co. United States. Distilled water and glutaraldehyde which are used for crosslinking were purchased from Sigma-Aldrich, Co. USA.

### 2.2. Optimization of electrospray parameters

PVA (144000 gr/mol) was dissolved in a solvent and gently stirred for 30 minutes at 90 °C then samples with different concentrations were obtained. Comparatively, PVA solution with lower molecular weight was stirred for 15 minutes at 80°C. The electrospray set-up was utilized in this study which was consisted of a syringe, metal capillary and a ground electrode. The needle was connected to the high voltage supply, which could generate positive DC voltages that was optimized to achieve a stable cone jet over the duration of particle collection. PVA and PVA/drug solution were placed in syringes with metal capillaries and were fed by a syringe pump with different feeding rates. Solid particles were collected on an aluminum sheet covered on the stainless steel drum. Experiments were conducted under conditions of atmospheric pressure, humidity and ambient temperature. Influence of concentration was evaluated in different values as tables take to achieve optimize electrospray parameters (Table 1). In order to produce uniform particles, the investigation was carried out using a polymer with lower molecular weight; the effects of concentration and molecular weight parameters were determined and listed in the tables 2-4.

Table 1. Electro spray parameters of PVA samples (144000 gr/mol) molecular weight

Samples	PVA%	Flow rate(ml/h)	Voltage(kV)	Distance(cm)
1	2	30	50	22
2	1	30	50	22

Table 2. Electro spray parameters of PVA samples (72000 gr/mol) molecular weight

Samples	PVA%	Flow rate(%)	Voltage(kV)	Distance(c)
1	6	50	50	18
2	7	50	50	18

Table 3. Electro spray parameters of PVA samples (23000 gr/mol) molecular weight

samples	PVA%	Hydrolysis degree	Flow rate(%)	Voltage(kV)	Distance(c)
5	18	98	60	50	18
6	18	89	25	58	10

Table 4. Electro spray parameters of PVA samples (23000 gr/mol) molecular weight and 98% degree of hydrolysis.

Samples	PVA%	Flow rate(ml/h)	Voltage(kv)	Distance(cm)
6	50	60	50	18
7	58	25	58	10
8	10	5	50	20
9	5	20	58	20

### 2.3. Preparation of PVA drug loaded samples

Poly (vinyl-alcohol) solution (10 %wt.) was produced with molecular weight of 23000 g/mol, and Theophylline (5%wt) as a drug model was added to the polymeric solution followed by stirring. The solutions were electro sprayed with a voltage of 44kV, flow rate of 20 ml/h and distance between the needle and drum of 20 cm. Crosslinking was carried out in two different technique: (1) the samples were exposed to glutaraldehyde vapor (2) samples were maintained in an oven at 130 °C to cross-link. Morphology of

cross-linked nanoparticles of various ways was determined by SEM to optimize crosslinking method.

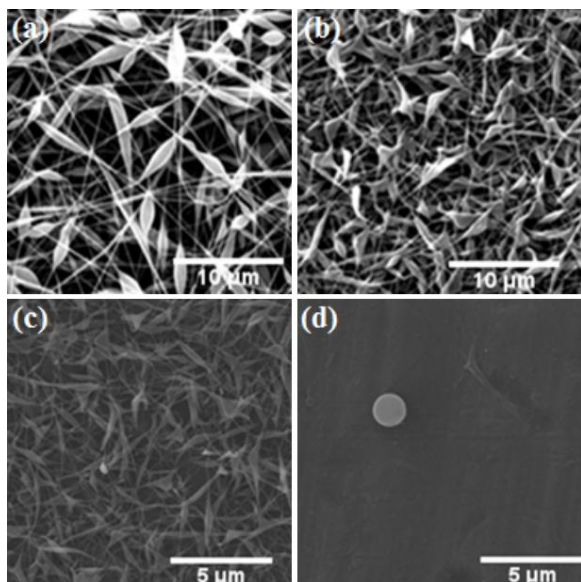
### 2.4. Scanning electron microscopy

The surface morphology of electro sprayed nanoparticles was studied by scanning electron microscopy (SEM (VEGA/TESCAN, Czech)). The samples were coated with gold to enhance their conductivity.

### 3. Results and discussion

#### 3.1. Morphology of PVA nanoparticles (molecular weight 144000 g/mol)

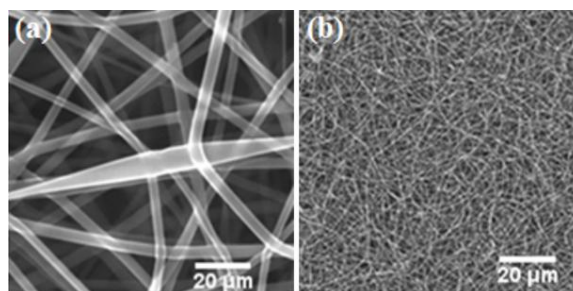
Scanning electron microscopy images of electro sprayed nanoparticles are indicated in Fig 1. However, PVA nanoparticles (Fig. 1a) which are prepared from 5 wt.% solution are uniform and particles like. In addition there are fibers incorporation with particles. Fig 1b shows PVA (4 wt.%) nanoparticles, in which nanoparticles are uniform, without fibers and are beads. The main reason for this improvement in morphology is a lower concentration of sample solution. According to the SEM images, decreasing the solution concentration, leads to more decreasing percentage of nanofibers [8]. Also, additional samples with lower concentrations were prepared to provide better comparison conditions. Because of the presence of high amounts of water in solution with concentration of 1% neither fiber nor particles were formed, however sample with 2% concentration showed a uniform morphology (Fig.1 c,d).



**Fig. 1:** Scanning electron microscopy micrographs electro sprayed nanoparticles of PVA with 144000 (gr/mol) (a) 5 wt.% (b) 4 wt.% (c) 2 wt.% and (d) 1%.

#### 3.2. Morphology of PVA nanoparticles (molecular weight 72000 gr/mol)

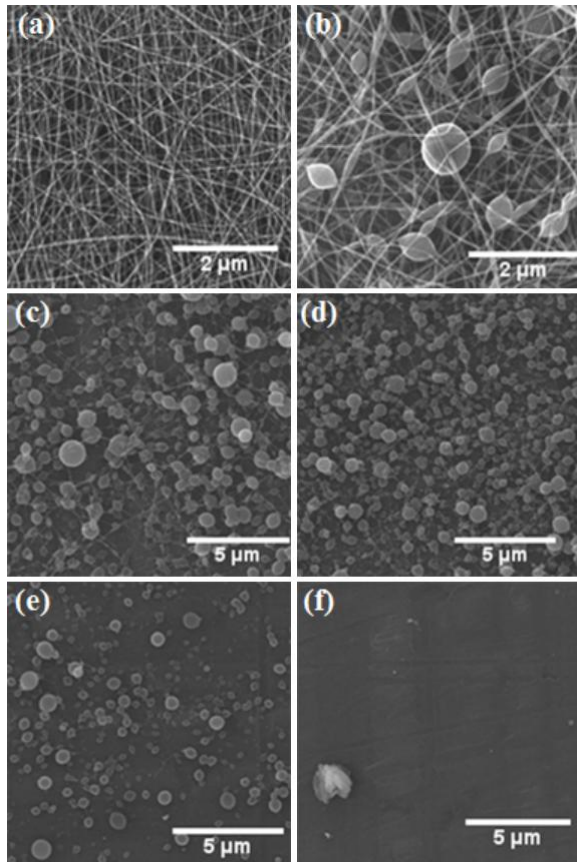
PVA sample solution with 72000 (g/mol) molecular weight at 7 % wt. was prepared and electro sprayed. SEM results show that this molecular weight is not proper for producing the particles (Fig 2).



**Fig. 2:** scanning electron microscopy of PVA with 72000 (gr/mol), concentration 7 (wt%).

#### 3.3. Morphology of PVA nanoparticles (molecular weight 23000 gr/mol)

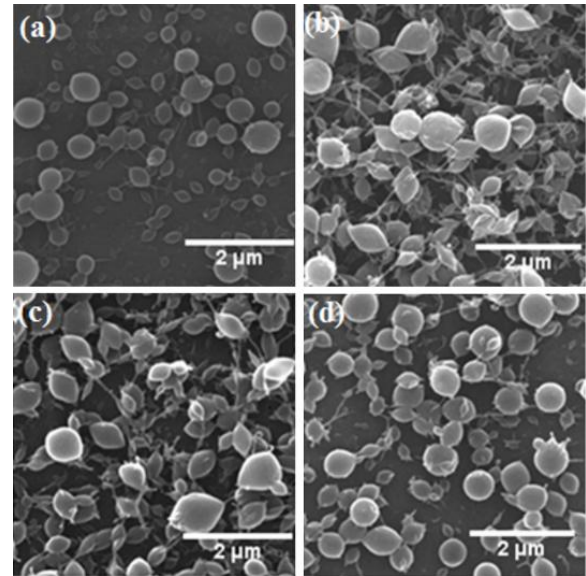
In Fig.3a it can be seen that PVA polymer with the hydrolysis degree of 89% is not suitable for spraying. However, the samples are completely nanofiber shaped. On the other hand, SEM image (Fig. 3b) with 98% hydrolysis shows particles among the fibers. Therefore, decreasing the fibers percentage and increasing particles is not impossible. Optimizing the concentration of PVA solution with a molecular weight of 23000 g/mol (98% hydrolysis) was carried out by preparing samples with 15, 13, 10 and 5 (% wt.). By decreasing concentration, the amount of fibers was decreased and the percentage of the particle was increased [34]. Fig. 3e shows a SEM image of PVA nanoparticles having optimized concentration of 10% solution. Despite, in samples with concentrations more than 10% (Fig 3 c,d) fibers are formed along with particles, because of high amounts of water and at a lower concentration of 10%, the fibers and particles were not formed (Fig. 3f).



**Fig. 3:** Scanning electron microscopy micrographs electrospayed nanoparticles of PVA with 23000 (gr/mol) and 18(wt%) (a) 89% hydrolysis (b) 98% hydrolysis. 98% hydrolysis and concentrations (c) 15 wt% (d) 13%, (e) 10 wt% and (f) 5 wt.%.

#### 3.4. Crosslinking of PVA nanoparticles

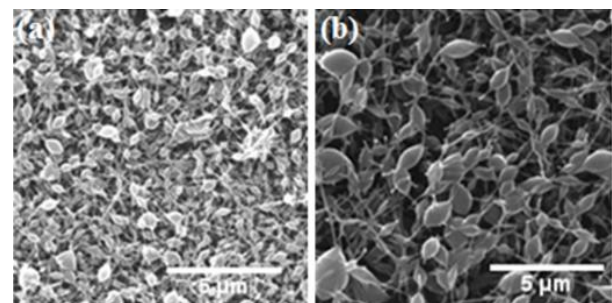
PVA nanoparticles were cross-linked in two different techniques. In the first one, the samples were exposed to the glutaraldehyde at room temperature for 24 hours and in other one, they were kept in an oven at 130 °C. Fig. 4 illustrates the obtained SEM micrographs showing the morphology of cross-linked nanoparticle with glutaraldehyde vapor that has no influence on its morphology (Fig. 4b, c). In addition, cross-linked nanoparticles with temperature sustained the particles structure and nanoparticles were more spherical (Fig. 4d).



**Fig. 4:** Scanning electron microscopy micrographs electrospayed nanoparticles of PVA cross-linked with glutaraldehyde vapor for (a) control sample (b) 24 h (c) 48 h (d) with oven at 130°C for 48 h.

#### 3.5. Theophylline loaded PVA particles

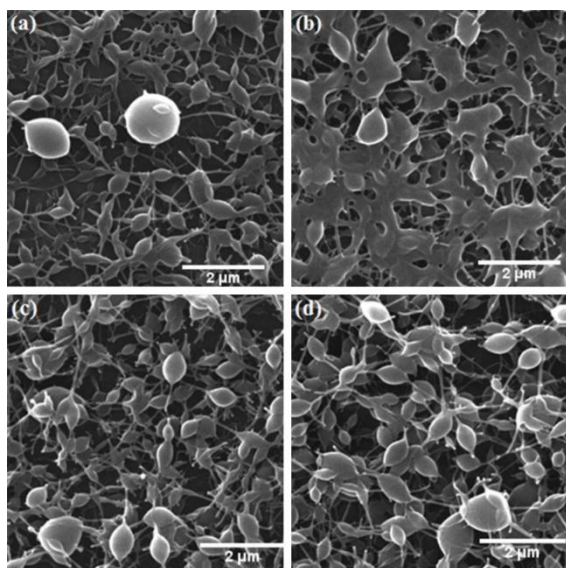
PVA solution was mixed with 5 %wt. Theophylline polymeric solution as a drug model. SEM images reveal the morphology and size of drug loaded PVA nanoparticles (Fig. 5).



**Fig. 5:** Scanning electron microscopy micrographs electrospayed nanoparticles of PVA with 23000 (gr/mol) and 10(wt%) 98% hydrolysis loaded with Theophylline.

### 3.6. Crosslinking of Drug-loaded PVA

Fig 6 illustrates SEM images of samples. The cross-linked particles using glutaraldehyde vapor for 24 hours and oven sustained structure and morphology are shown in Fig 6a, c, d. Since cross-linked nanoparticles with glutaraldehyde indicates that they would be destroyed after 48 hours, it is not a good idea to cross-link PVA samples (Fig 6,b).



**Fig. 6:** Scanning electron microscopy micrographs electrospayed nanoparticles of PVA loaded with Theophylline cross-linked with glutaraldehyde vapor for (a) 24hours (b)48 hours, cross-linked at 130°C at oven for (a) 24 hours (b)48hours.

### 4. Conclusion

In the present study, PVA and encapsulated nanoparticles of PVA with a model drug Theophylline were synthesized via electrospay method. In order to obtain optimized nanoparticles, different molecular weights of PVA were investigated and subsequently a polymer with molecular weight of 23000 g/mol and 98% hydrolysis was chosen. Furthermore, samples with different concentration were prepared. It was concluded that particles with concentration of

10 %wt. exhibit a uniform structure. However, fibers and particles were produced in samples with concentrations higher than 10 %wt. Also, samples with concentration lower than 10 %wt. did not produce any particles. Theophylline as a drug model incorporated into the solution and electro sprayed to gain drug loaded particles. Finally, cross-linking between nanoparticles was successfully performed due to prevention of dissolving polymers during drug release.

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