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RESEARCH ARTICLE

Studies on Improvement of Water-Solubility of Curcumin With Electrospun Nanofibers

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Studies On Improvement Of Water-Solubility Of Curcumin With Electrospun Nanofibers

SUMMARY

Curcumin has low solubility and low permeability thus classified as BCS Class 4. The aim of this study, improve the solubility of curcumin by preparing electrospun nanofibers.

Curcumin nanofibers were prepared from a final mixture (FM), which contained HPMC and PEO polymers. Before, conductivity, viscosity and surface tension values of each polymer solution and the FM were measured. Viscosity of PEO (polyethylene oxide) and HPMC (hydroxypropyl methylcellulose) solutions were found to be low compare to FM. The conductivity of FM was higher than PEO solution whereas lower than HPMC solution. The surface tension of polymer solutions were higher than FM.

Electrospinning was performed at 14 kV using a flow rate of 0.6 mL/h for 3 h. The distance of needle tip to the collector was 21 cm. The morphologies and the mean diameter of fibers were determined by SEM (138±39 nm). DSC and FT-IR studies of nanofibers were carried out. According to results, electrospinning didn't alter chemical structure of polymers and CUR during the process. Solubility studies were carried out at distilled water and pH 1.2 buffer.

FM had lowest surface tension value thus provided better electrospinning process. Drug loading was found to be 137.75 µg per cm2. Curcumin was found practically insoluble in distilled water and pH 1.2 buffer. The solubility of curcumin was increased from zero to 7.66 mg/l, 1.57 mg/l in water and pH 1.2 buffer respectively. It was concluded that electrospinning is a useful technique for the improvement of the poorly-soluble drugs such as curcumin.

Key Words: *Nanofiber, solubility, curcumin, electrospinning,*

Elektroçekim Nanolifler ile Kurkuminin Sudaki Çözünürlüğünün Arttırılması Çalışması

ÖZET

Kurkumin düşük çözünürlük ve düşük permeabiliteye sahip olmasından dolayı BCS Sınıf 4 olarak sınıflandırılmaktadır. Bu çalışmanın amacı, electroçekim nanolifler hazırlayarak kurkumin çözünürlüğünü arttırmaktır.

Kurkumin nanolifleri HPMC ve PEO polimerlerini içeren bir sonuç karışımdan hazırlandı. Önce, her bir polimer çözeltisinin ve sonuç karışımın, iletkenlik, viskozite ve yüzey gerilimi değerleri ölçüldü. PEO (polietilen oksit) ve HPMC (hidroksipropil metilselüloz) çözeltisinin viskozitesi sonuç karışımın viskozitesinden daha düşük bulunmuştur. Sonuç karışımın kondüktivite yani iletkenlik değeri PEO'nun çözeltisinden yüksek, HPMC'nin çözeltisininden daha düşük bulunmuştur. Polimer çözeltilerinin yüzey gerilimi ise sonuç karışımdan daha yüksek çıkmıştır.

Elektroçekim işlemi, 3 saat boyunca 0.6 ml/saat akış hızında 14 kV voltaj uygulanarak yapıldı, iğne ucunun toplama silindirine olan mesafesi 21 cm tutuldu. Liflerin morfolojisi ve liflerin ortalama çapı taramalı elektron mikroskobu (SEM) ile belirlenmiştir (138±39 nm). Nanoliflerde DSC ve FT-IR çalışmaları da gerçekleştirilmiştir. DSC ve FT-IR analizleri, elektroçekim işleminin polimerlerin kimyasal yapısını değiştirmediğini ve CUR'nin işlem sırasında değişmediğini düşündürmektedir. Çözünürlük çalışmaları için distile su ve pH 1.2 tampon kullanılmıştır.

Elektroçekimde kullanılan sonuç karışımın düşük yüzey gerilimi göstermesi daha iyi çekim işlemi sağlandığını göstermiştir. Liflere yüklenen ilaç miktarı 137.75 ug/cm2 olarak bulunmuştur. Kurkuminin distile su ve pH 1.2 tampon içinde pratik olarak çözünmediği bulunmuştur. Çözünürlük sırasıyla distile su ve pH 1.2 tampon içinde, sıfırdan 7.66 mg/l ve 1.57 mg/l' ye yükselmiştir.

Bu sonuç ile elektroçekim yönteminin, kurkumin gibi zayıf çözünürlüğe sahip ilaçların sudaki çözünürlüğünün arttırılması için yararlı bir teknik olduğu sonucuna varılmıştır.

Anahtar kelimeler: *Nanolif, çözünürlük, kurkumin, elektroçekim,*

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INTRODUCTION

Electrospinning has been utilized for preparing polymeric nanofibers which is simple and efficient technique. Since most synthetic and many polymers can be electrospun, there is a wide array of possible formulations (Blakney *et al.*, 2013). A number of drugs have already been loaded into electrospun fibers. This method provides high surface area to volume ratio and ensures increased solubility of poorly water soluble drugs (Yu *et al.*, 2009; Bhardwaj and Kundu, 2010). Electrospun fibers have a wide applications on pharmaceutical field including filtration, cosmetic masks, nanosensors, wound dressing, drug delivery systems, enzyme immobilization, tissue engineering scaffolds. Among these applications drug delivery is one of the most promised field for electrospinning research due to high loading capacity, encapsulation efficiency, simultaneous delivery of diverse therapies, ease of operation and low cost process (Hu *et al.*, 2014, Tort and Acartürk, 2015).

Polymeric nanofibers possess numerous structural and chemical characteristics that make them suitable for biomedical applications, such as their molecular size and potential biocompatibility. Nanofibers provide novel solutions to drug delivery (Balogh *et al.*, 2016). Hydroxypropyl methylcellulose (HPMC) is a most widespread used polymer for drug delivery. In order to improve the insufficient spinnability of HPMC another polymer should be used. Poly(ethylene oxide) (PEO) often serves as a carrier liquid (or a component) facilitating the process of electrospinning (Gatti *et al.*, 2013; Peer *et al.*, 2016, Tort and Acartürk, 2016,).

Curcumin (CUR), a polyphenol, is an active principle in turmeric (Curcuma longa L.) that imparts the yellow - orange pigmentation to the plant. It has been widely used to improve wound healing and reducing wound-healing times by increasing fibroblast and vascular density in wounds and quenching free radicals (Thangapazham *et al.*, 2007; Jurenka, 2009; Wahlang *et al.*, 2011; Bui *et al.*, 2014). CUR has also antitumor, antioxidant, anti-inflammatory, antiviral and antibacterial activities (Gupta *et al.*, 2012; Prasad *et al.*, 2014). On the other hand, CUR has low solubility and permeability thus classified as BCS Class 4 (Aggarwal *et al.*, 2007; Thangapazham *et al.*, 2007; Jurenka, 2009, Wahlang *et al.*, 2011). The results of a pharmacokinetics study conducted that oral bioavailablity is only 1% (Yang *et al.*, 2007). Therefore, the health benefits of curcumin are limited by its poor oral bioavailability (Liu *et al.*, 2016). Different formulations of CUR like nanosuspensions, microemulsions, self-microemulsions, nano-emulsions, phospolipid complexes, liposomes, polymeric micelles, solid lipid nanoparticles and polymeric nanoparticles have been prepared in order to enhance its bioavailablity (Tort and Acartürk, 2012, Liu *et al.*, 2016, Vecchione *et al.*, 2016, Anwar *et al.*, 2016, Wang *et al.*, 2017).

Solubility is one of the limiting steps for the bioavaility of drugs. Preparation of curcumin nanofibers is a new approach among the studies to increase the solubility of curcumin. The aim of this study was to enhance the solubility of CUR by preparing its nanofibers using electrospinning method. To achieve this goal, curcumin loaded HPMC/PEO nanofibers prepared and physicochemical properties of nanofibers were characterized.

MATERIALS and METHODS

Materials

Curcumin was purchased from Sigma Chemicals (Germany). Hydroxypropyl methylcellulose (HPMC K100M) and polyethylene oxide (PEO, POLYOX WSR-205, Mw 600000) were kindly donated by Colorcon, England. Methanol was purchased from Merck (Germany). pH 1.2 buffer was prepared accarding to USP. All other chemicals and reagents were of analytical grade.

Methods

Preparation of Electrospinning Solutions

Electrospinning solution (final mixture) prepared to be 10 ml which was consist of PEO 3%, HPMC 3%, methanol:water (7:3) and curcumin (10 mg). First, curcumin was dissolved in 7 ml methanol, then 3 ml distilled water was added. PEO and HPMC were added to this solution to prepare the final mixture. This mixture stirred for 2 h at room temperature to obtain homogeneous solution and was used for electrospinning.

Characterization of Polymer Mixtures

Viscosity Measurements

Rheological experiments were performed with a stres controlled cone and plate rheometer (Brookfield, DV-III Rheometer with spindle type CPE-41, USA). All the samples were measured at 25°C. Shear stress and viscosity values were obtained at different shear rates. All of the rheological measurements were repeated at least three different samples. The viscosity values of the polymer solutions obtained at 20 rpm shear rate were compared.

Conductivity Measurements

Ionic conductivity measurements of the solutions (three different samples) were carried out using a conductivity meter (Hanna Instruments, HI 9033,

USA). The values were obtained as μS/cm.

Surface Tension Measurements

Drops were formed on the tip of the needle to measure surface tensions of mixtures using pendant drop observation (Attension-Theta Lite, Biolin Scientific, Finland) and then surface tensions were calculated using Young Laplace equation.

Electrospinning

Electrospinning process was conducted using NE-100 Laboratory Scale Electrospinning Unit (Inovenso Ltd.,Turkey). First, nanofibers (blank nanofibers) from polymer solutions were produced. Each polymer solution was placed into a 10 ml plastic syringe capped with an 18-gauge blunt needle. A rectangular (20 × 10 cm) aluminium foil was used as a static collector. All parameters were tested to ensure the continuous production of nanofibers. The process parameters such as feed rate, distance of needle tip to the collector and applied voltage were same for each formulation (Table 1). The process time was kept for 3 h which was an appropriate period to collect nanofiber mats from aluminium foil without damage. After the characterization studies of nanofibers, the suitable formulation was chosen and drug was loaded to this formulation.

Table 1: Electrospinning Parameters for Nanofibers

Feed rate	0.6 ml/h
Voltage	14 kV
Tip-to-collector distance	21cm
Process time	3 h

Characterization of the nanofibers

Morphologies Studies and the Mean Diameter of the Fibers

Nanofibers were taken by scraping off from aluminum foil after the electrospinning process. The appearance of yellow fibers were recorded by photograph as a thin layer.

Images of electrospun fibers were obtained with a Quanta 400F (FEI Company, USA) field emission scanning electron microscopy. The images were taken in different parts of the nanofibers in 2000, 5000, 10000, 20000 and 50000 magnification. Average fiber diameters were determined by measuring fibers randomly selected from SEM images.

DSC Measurements

DSC (Shimadzu, DSC-60, Japan) analysis was carried out on the drug substance, polymers, and the nanofibers. The samples were heated from 25 to 250 °C at the heating rate of 10 °C/min under a nitrogen atmosphere.

FT-IR Measurements

Fourier transform infrared (FT-IR) spectroscopy analyses of the PEO, HPMC, drug and the nanofibers were performed using FT-IR (Perkin Elmer, Spectrum 400 FT-IR, USA)

Drug Content

The nanofibers were cut into a 1cm diameter pieces and dissolved in the 10 ml methanol at 37°C. The amount of curcumin-loaded nanofibers was assayed by UV/Vis-Spectrophotometer at 421 nm.

All experiments are triplicated.

Solubility studies

Solubility measurements were made in both distilled water and pH 1.2 solution. Excessive amount of curcumin powder or curcumin-nanofiber added to medium and stirred at 37°C for 3 h. Samples collected at the end of experiment and assayed by UV/Vis-Spectrophotometer (426 nm and 428 nm for distilled water and pH 1.2 buffer, respectively).

Statical analysis

The data were statistically analyzed with independent Student's t-test. A value of $p < 0.05$ was considered statistically significant. Data represent mean ± SD.

RESULTS AND DISCUSSION

In recently, nanofiber applications in the healthcare system has increased as a tool for a drug delivery system for various diseases. They have different commercial applications due to their specific properties such as small pore size and high surface area (Zhou and Gong, 2008; Sharma *et al*., 2014,).).

Drug loaded nanofibers; economic, easy to manufacture, improved drug loading capacity, stable, suitable for thermolabile drugs, available for sustained and controlled release formulations (Sharma *et al*., 2014). In addition, electrospinning is a useful technique to improve the water solubility and dissolution rate of poorly-water soluble drugs (Vigh *et al*., 2013; Bruni *et al*., 2016,).

Curcumin loaded nano-sized drug delivery systems prepared by different methods have been reported. In these studies, curcumin formulations were prepared for various routes of administration (El-Sherbiny and Smyth, 2011; Bhawana *et al*., 2011; Tort and Acartürk, 2012). In the present work, curcumin loaded into nanofibers and whose water solubility was increased.

Nanofiber production was unsuccessful with

HPMC before blending of PEO at different process parameters. The addition of PEO to the HPMC solutions facilitated the production of fibers.

Viscosity, conductivity and the surface tension values of the polymer solutions used in the electrospinning are the most criticial parameters for production.

The polymer solutions must have a certain viscosity value for electrospinning. Viscosity of PEO and HPMC solutions were found to be low compare to final mixture (Fig 1) ($p<0.05$). The low viscosity of the aqueous polymer solutions is the most apparent reason for the unsuccessful aqueous electrospinning of those polymers alone. The viscosity of the final mixture increased for the electrospinning process. It was reported that after blending of the polymers with PEO or PVA, the viscosity can be increased to the appropriate values, making electrospinning successful (Lu *et al*., 2006). The conductivity of final mixture was higher than that of PEO solution whereas lower than that of HPMC solution (Fig 2) ($p<0.05$). The charge carrying capacity of polymer solutions with high conductivity is greater than those with low conductivity. The fiber jet produced from a solution of high conductivity is subjected to a greater tensile force when exposed to an applied voltage (Pillay *et al*., 2013).

In the electrospinning process, a polymer solution held by its surface tension at the end of a capillary tube is subjected to an electric field. When the electric field reaches a critical value at which the repulsive electric force overcomes the surface tension force, a charged jet of the solution is ejected from the tip of the Taylor cone (Lu *et al*., 2006).This demonstrated that lower surface tension better for electrospinning process. In our study the surface tension of PEO and HPMC solutions were higher than final mixture (Fig 3) ($p<0.05$). Therefore, the final mixture was easily electrospun due to the lowest surface tension value.

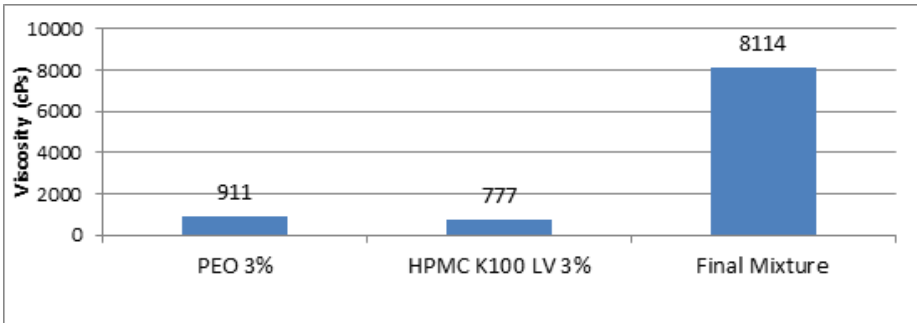

Figure 1: The viscosity (cPs) measurement results of PEO, HPMC solutions and final mixture.

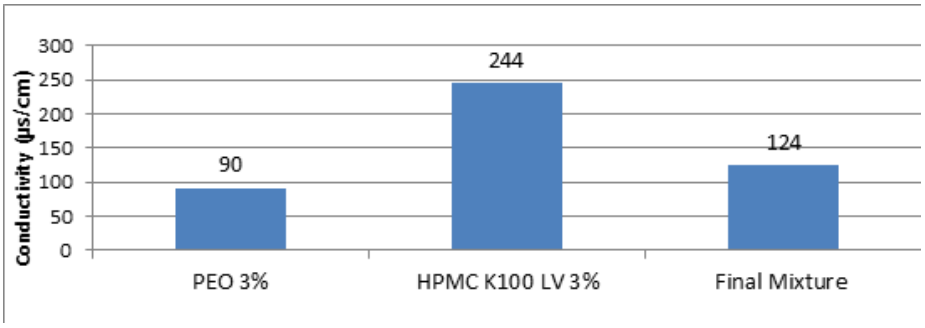

Figure 2: The conductivity **(µs/cm)**values of PEO, HPMC solutions and final mixture

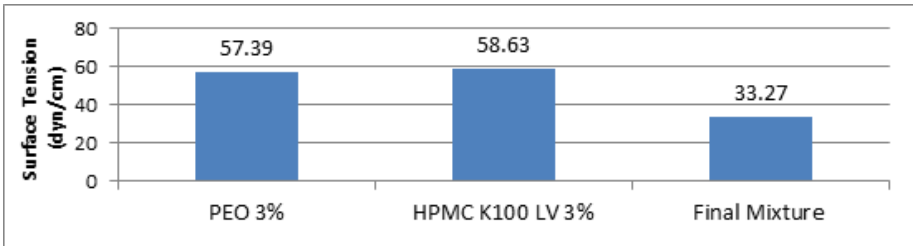

Figure 3: The surface tension (dyn/cm) values of PEO, HPMC solutions and final mixture

Curcumin nanofibers were prepared successfully by electrospinning and mean diameter of nanofibers were found to be 138±39 nm (Fig 4). This demonstrated that nano-sized drug delivery system could be prepared. In a previous study Sun et. al. (Sun *et al.*, 2013) used PVA (polyvinyl alcohol) for preparing curcumin nanofiber and mean diameter of the nanofibers was measured as 250-350nm.

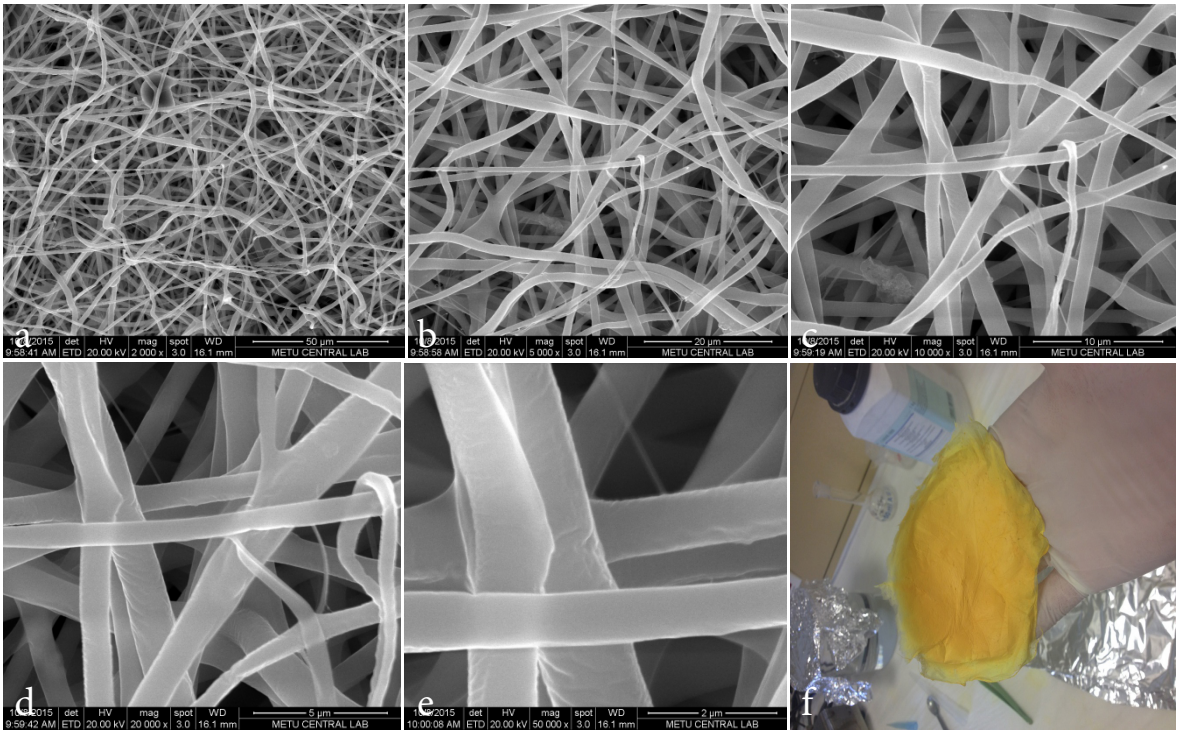

Figure 4: Appearance and SEM images of one of the nanofibers. 2000x (a), 5000x (b), 10000x (c), 20000x (d), 50000x (d), and image of fiber (f).

In Fig 5, characteristic FT-IR peak of HPMC, PEO and curcumin are shown. All major bands of both curcumin, PEO and HPMC are shifted to higher frequencies in nanofiber indicating that curcumin and polymers are bound together to form more stable nanofibers. In a similar study, the FTIR spectrum of curcumin shows the characteristic peak at 3500 cm−1 which can be attributed to phenolic O–H stretching vibration and this band was observed at 3661 cm−1 in curcumin loaded PLGA nanofiber (Sampatha *et al.*, 2014).

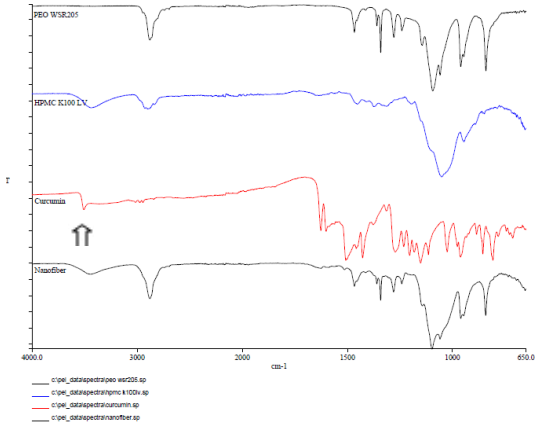

Figure5 : FT-IR peaks of HPMC, PEO, Curcumin and Nanofiber

Fig 6 shows that, DSC thermograms of PEO, HPMC and curcumin. DSC thermograms were analyzed by examining whether there was any incompatability between the polymers and the drug. Peaks of the substances were observed on nanofiber thermogram.

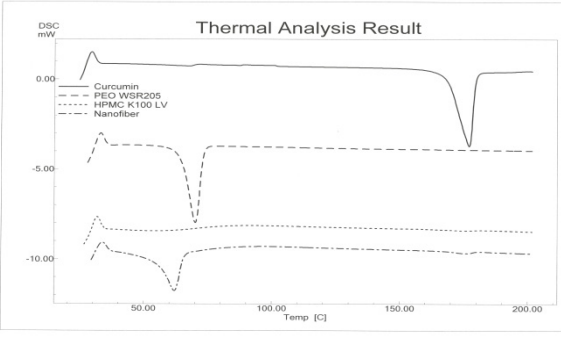

Figure 6 : DSC thermograms of HPMC, PEO, Curcumin and Nanofiber

Drug content was found to be 137.75 µg/cm2 in the nanofibers. The results showed that the solubility of curcumin powder was zero in both water and pH 1.2 buffer. The solubility of curcumin was increased from zero to 7.66 mg/l and 1.57 mg/l by the producing of the curcumin nanofibers, in water and pH 1.2

buffer, respectively (Fig 7). This result showed that the preparation of nanofiber was successful in terms of increasing the solubility of curcumin.

In a previous study, Wang *et al* used another polymer (PVP-polyvinylpyrrolidone) and they reported that the solubility and oral bioavailability of curcumin was increased with PVP nanofibers (Wang *et al*., 2015).

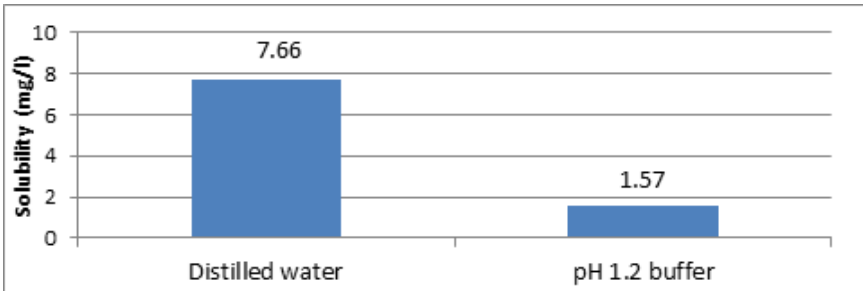

Figure 7: Solubility (mg/l) results of nanofibers in different media.

CONCLUSION

Preparation of nanofibers by electrospinning is an alternative for drug with low solubility which are not suitable for oral administration. PEO/HPMC nanofibers containing CUR have been successfully prepared by electrospinning. SEM analysis showed that surface of the nanofibers was obtained as smooth. Additionaly, no physical incompatibility was observed in the DSC thermograms. As a result of DSC and FT-IR analyses, it was thougt that electrospinning process did not alter the chemical structure of polymers and CUR during the formation of nanofibers.

In vitro solubility tests showed that the drug-loaded nanofibers dissolved in both distilled water and pH 1.2 buffer. It was concluded that HPMC-curcumin nanofibers may be a promising system for oral delivery of curcumin.

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