

Introducing of Fusidic Acid Electrospun Nanofibers Based Biopolymer for Wound Dressing

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Abstract

Electrospun nanofibers is one of the new techniques that used recently in the treatment of skin wounds and diabetic foot ulcer, through the combination of biopolymer with synthetic polymer and formulated as nanofibers mat loaded antibacterial agent by using Electrospinning process, biopolymer and synthetic polymer such as Chitosan and PVA respectively. Loading of fusidic acid with various ratios of PVA/Chitosan to produce fusidic acid nanofibers that prepared in three dimensional structures to exert antibacterial activity against skin infections; the uniformity of drug/polymer ratio is important in production of nanofibers with acceptable diameter range. The characterization studies have been performed for morphology analysis, drug content, thermal analysis and in-vitro drug release profile from nanofibers to estimate the antibacterial activity of nanofibers on the wound site to assist in the skin healing process.

Keywords: Electrospinning, biopolymer, nanofibers loaded fusidic acid, wound dressing

INTRODUCTION

Skin is a vital barrier with various functions in the human body; naturally it isolates the interior parts and tissues from external influences such as chemical agents, physical changes and biological factors. It has a crucial role during any damage in the structure of the skin such as wounds, ulcers, infections and any structural and functional changes that may alter the integrity of the skin [1]. In the current time there is a great interest in designing of biopolymer that manufactured by using a new strategy such as electrospun nanofibers drug delivery system by using Electrospinning technique which characterized by low cost, easy production of Nano-size fibers and fewer compositions which is used in the wound dressing and improving skin healing mechanism [2].

Wounds dressing history has started since Sumerian and Greek time where they used various remedies to treat wounds and burns such as plants leaves, animal leather, honey bee, milk and many other natural materials to cover the affected skin site to ensure isolating it from external factors [3]. At the current time the researches are continued to develop the conventional technique and replaced with new methods and materials to be used topically such as creams, gel, pastes, lotion and ointments with traditional dressing medical supplies such as cotton gauzes and bandage to protect the wounds and reduce the chances of bacterial infection [4];

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these methods guide into a new challenge in the treatment of severe and chronic wounds which require patent technique and special pharmaceutical materials to manufacture a novel product far from traditional methods with different dosage forms rely on many factors, which aim to acquire rapid treatment and short period of healing; such modern strategy is Electrospinning process which suitable for treatment of topical wounds and skin ulcers through the combination of biopolymer with synthetic polymer to improve the quality of the products [5]

Bioactive Dressing

Bioactive materials are also used in wound dressing and improving the skin healing mechanism, bioactive materials such as Chitosan, Gelatin and Alginate; these biopolymers are formulated and applied in the form of foam, film, transdermal patches and nanofibers mat [6]. The principle of this technique is to load the active agent within the biopolymers and apply on the affected area of skin to perform the action by isolating the wound from environmental factors and releasing of antibacterial agent [7].

Electrospinning Nanofibers Technology

Electrospinning is commonly used in production of nanofibers. The principle of Electrospinning process is applying of high voltage current to a liquid polymer that ejected from nozzle of syringe at a constant flow rate toward collector [8]. The applied voltage overcomes on the surface tension and causes to elongate the droplet of the polymer to form Taylor-cone which is considered as the beginning point of formation nanofibers. Electrospun polymer is a mixture of biopolymer and synthetic polymer at various ratios according to the purpose of manufacturing and the amount of drug require being loaded. In this study Chitosan and PVA are used in the preparation of fusidic acid nanofibers [9]. Chitosan is derived from deacetylation of Chitin; it is a polysaccharide structure with good solubility in aqueous solutions such as acetic acid and formic acid which turns them more viscous and suitable for electrospun process, due to the presence of active amino and hydroxyl groups in the Chitosan structure which have potential application in the pharmaceutical, biopharmaceutical and food industry [10]. PVA is a human made synthetic polymer [11]. It is made of alcohol and vinyl functional group, non-toxic, odorless, colorless; soluble in water, it has good physical, mechanical and thermal property. The biocompatibility and biodegradability make these polymers suitable in wide range of applications whether in pharmaceutical and industrial area [12]

Fusidic Acid

Fusidic acid is a steroidal-like structure antimicrobial agent, but does not show any steroidal activity, it is derived from *Fusidium coccineum* fungus and brought to light and synthesized about more than 45 years ago, it does not well-

known that time as an antimicrobial drug, but when the antibiotics resistance increases against classical groups due to the mutational or cellular evolution of the bacteria; it becomes as an alternative to other antimicrobial drugs formulations [13]. The mechanism of action involves inhibition of two main elongating factor (EF-G and EF-Tu) which blocked by fusidic acid through binding to these factors on the ribosome then inhibit the formation and release EF-G complex and halting the translation. Basically the bacteriostatic action is become bactericidal at high concentration [14]. External dosage form of fusidic acid is used for skin wounds owing antibacterial activity against gram negative *Staphylococcus aureus* and for the management of soft tissue infection due to the good skin permeability and diffusion efficacy [15].

METHODS

Materials

Fusidic acid is purchased from Xa-Bc-Biotech (China), Poly Vinyl Alcohol (96% hydrolyzed typical average molecular weight 120,000) is purchased from Hainan Huarong (China), Chitosan (80% deacetylated of Chitin moderate molecular weight of 88,000) is purchased from Anand Agro Care (India). Glutaraldehyde (GA) 25% is purchased from Acuro Organics Limited (India).

Process of Electrospun Nanofibers

Electrospinning uses high DC voltage current of low (mAmp) for creating ultrafine fibers. Electrospun technique is carried out at room temperature and controlled humidity inside the chamber of Electrospinning device. The applied voltage current is about 15-30kv according to the manufacturing method, the needle of 23G and 1.1mm diameter, the distance from the nozzle to the collector is 8cm and polymer flow rate is 0.3-0.5mL/h [16]. The induced charge is able to stretch the pendant drop by changing the surface tension. Once the electrostatic repulsion of the charged polymer liquid becomes higher than the surface tension, a conical shape known as Taylor's cone is formed at the end of jet tip. Remarkably, the two forces that control the formation of Taylor's cone are controlled by flow rate and applied voltage. Therefore a good balance between them favors the formation of a stable Taylor-cone jet. If enough cohesive force exist in the polymer liquid allows the polymer chains to stretch and obtain uniform fibers [17].

Characterization of Fusidic Acid

Determination of λ_{max} of Pure Fusidic Acid

The preparation of 0.1mg/mL fusidic acid in methanol and PBS pH5.5 solution are scanned by using UV spectroscopy to detect the λ_{max} of the solutions between 200-400nm [18].

Obtaining the Calibration Curve of Fusidic Acid

Calibration curve is determined by using a solution of 0.1mg/mL fusidic acid in PBS pH5.5. Taking different

concentrations of solution and recording the data (n=3) of UV absorbance at different concentration with mean value of \pm S.D [19].

Preparation Electrospun Polymer Solution

Preparation of PVA Solution

The preparation of 10% PVA is performed by dissolving 10gm of PVA (96% hydrolyzed typical average molecular weight is 120,000) in 100mL of DW in volumetric flask. Mixing continues with gradual increasing in temperature to about 80°C; until the PVA is fully solubilized [20].

Preparation of Chitosan Solution

Chitosan powder (80% deacetylated of Chitin moderate molecular weight of 88.000), is used in the preparation of

2%, 4% and 6% solution by dissolving 2gm, 4gm, and 6gm respectively in 100mL of 0.1M acetic acid with continues stirring for 2 hours at 80°C, filtration is necessary to remove high molecular weight of Chitosan particles [21].

Preparation of PVA/Chitosan Electrospun Solution

The prepared solution of 10% PVA is mixed with 2%, 4% and 6% Chitosan respectively; in a beaker inside ultra-sonication bath for 1 hour at different ratios (8/2, 7/3 and 6/4 v/v). The mixture is stored in refrigerator for 1-hour to ensure the consistency between them. Prior to the addition of fusidic acid, the mixture is placed on magnetic stirrer for 1hour [22]. The prepared formula is containing PVA/Chitosan with 2% fusidic acid of polymer weight to be mixed at different v/v ratio and produce nanofibers loaded fusidic acid Table 1 shows the nanofibers formulas loaded fusidic acid [23]

Table 1: Nanofibers formulation of PVA/Chitosan/Fusidic acid

<i>Formula</i>	<i>PVA 10%(mL)</i>	<i>Chitosan 2%(mL)</i>	<i>Fusidic acid 2% (mL)</i>	<i>Total volume(mL)</i>
F1	8	2	1.7	11.7 mL
F2	7	3	1.6	11.6 mL
F3	6	4	1.4	11.4 mL
Formula	PVA 10%(mL)	Chitosan 4%(mL)	Fusidic acid 2% (mL)	Total volume(mL)
F4	8	2	1.8	11.8 mL
F5	7	3	1.7	11.7 mL
F6	6	4	1.6	11.6 mL
Formula	PVA 10%(mL)	Chitosan 6%(mL)	Fusidic acid 2% (mL)	Total volume(mL)
F7	8	2	1.9	11.9 mL
F8	7	3	1.8	11.8 mL
F9	6	4	1.8	11.8 mL

Optimization of Nanofibers Content

Drug Content

To determine the amount of drug in each formula by dissolving a piece of nanofibers mat in 100ml PBS pH5.5 separately on magnetic stirrer for 24-hour to ensure the complete dissolving of drug in the media, the test is triplicated in the mean value of \pm S.D. The sample of 5mL is analyzed at 205nm UV spectroscopy to obtain the drug content [24].

Morphological and Topological Analysis

Thermo Fisher Scientific Electron Microscopy China is used to evaluate the morphology and nanostructure of electrospun nanofibers which is coated with a thin layer of gold by

sputtering; the morphology is observed under a scanning electron microscope that operated at the acceleration voltage of 10kV. Image analysis program ImageJ is used gray scale level processing based on image structure to characterize the SEM graphs in the original magnification. The average diameters of nanofibers are calculated by software package using different thresholds level; the diameters are measured with mean value of \pm S.D of about 100 fibers chosen randomly from each image sample to obtain the average diameter for each formula that assists in the selection of the suitable drug/polymer ratio to produce high quality nanofibers [25].

Thermal Analysis (Differential Scanning Calorimetry)

DSC- SKZ China is a thermal analyzer used to study the thermal behavior of the free drug, polymers separately,

physical mixture and the nanofibers mat. The sample of 5mg is tested at temperature range of 30-300°C and flow rate of Nitrogen is 35mL/min at 10°C/min. The data is collected for the polymers and fusidic acid to study the physicochemical properties for the materials [26].

In-vitro Drug Release Profile from the Nanofibers

Dissolution Apparatus Basket Type II RC-3 China is used to determine the drug release from nanofibers and taking the absorbance by using L7 Double Beam UV/VIS spectroscopy China, the average cumulative concentration of each sample has been tested three times (n=3) with mean value of \pm S.D during 7-hour to obtain the average percent drug release at 205nm UV absorbance. The nanofibers contains 2% fusidic acid of polymer weight according to the ratio of formula, the piece of nanofibers is placed inside the basket and immersed in 900mL PBS pH5.5 vessel at 37°C and rotates at 50rpm [27].

Release Kinetics

The drug release profile can follow kinetics approaches according to the obtained data of parentage drug release to fit with zero order, first order, Higuchi, Korsmeyer-Peppas and Hixson kinetics model to study the mechanism of drug release from nanofibers [28].

Best Formula Selection

The selection of best formula relies on the comparison of the detected results of average percent cumulative drug release, drug content, and obtained nanofibers diameter using morphology study to assist in the selection of best formula [29].

Stability Study

Short term stability test is to confirm the activity and safety of nanofibers at different conditions, by taking two pieces of selected nanofibers formula (F1); batch 1 is kept inside sealed nylon carry bag in refrigerator at 8°C and batch 2 is placed in oven at 40°C without sealing and incubated for 1-month; they estimated by short term drug release from nanofibers [30].

RESULTS AND DISCUSSION

Characterization of Fusidic acid

Determination of λ_{max} of Pure Fusidic Acid

The UV absorbance of fusidic acid in PBS pH5.5 is detected at 205nm, which agrees with pervious data of fusidic acid in methanol which is scanned with UV at 205nm and proved that the fusidic acid is in pure form, as shown in figure 1 the absorbance of fusidic acid [31].

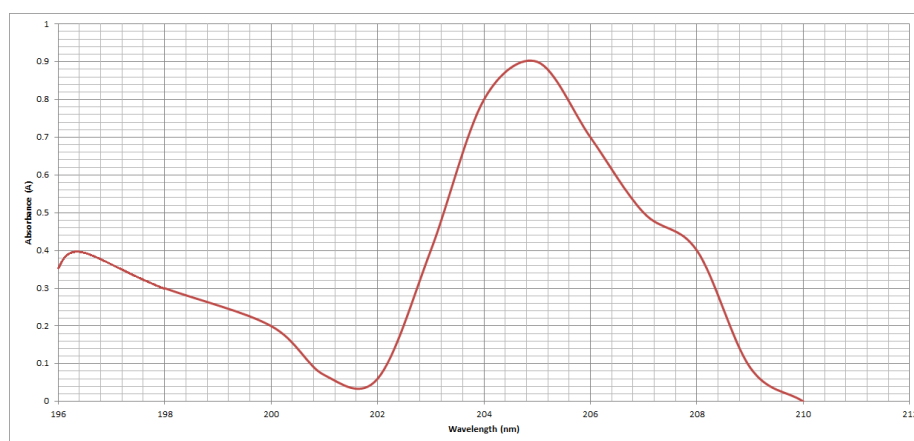


Fig. 1: UV absorbance of fusidic acid in PBS pH5.5

Calibration Curve of Fusidic acid

The calibration curve of fusidic acid is determine by preparing solution of 0.1mg/mL fusidic acid in PBS pH5.5, to take UV absorbance at 205nm of different fusidic acid concentration to draw the calibration curve, figure 2 shows

the straight line of correlation coefficient ($R^2=0.9981$) that fits the equation of Beer-Lambert at λ_{max} where the absorbance increases with concentration of the sample [32]. Table 2 shows the absorbance of different concentration of fusidic acid at 205nm.

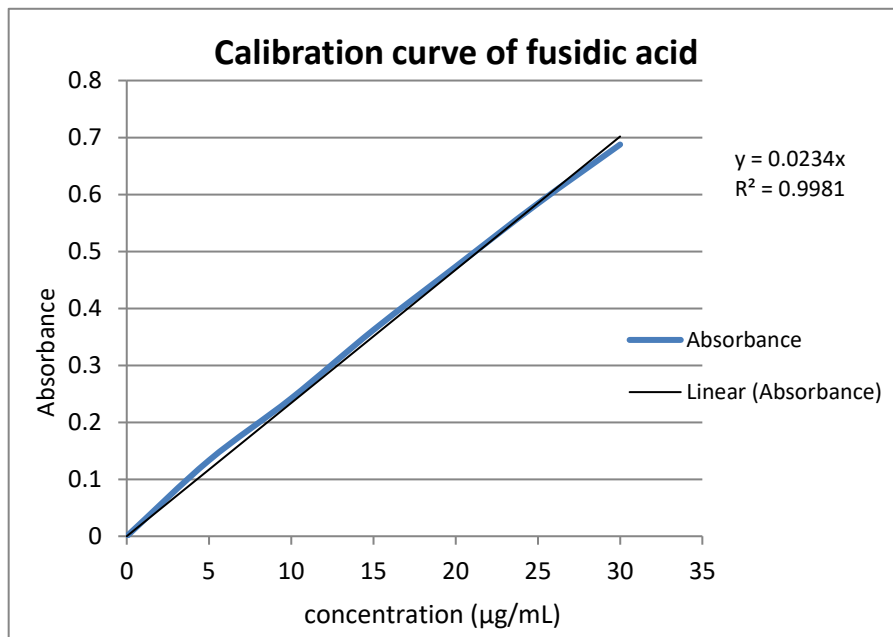


Fig.2: Calibration curve of fusidic acid

Table 2: Calibration curve data of fusidic acid in PBS pH5.5

Absorbance	0.1332 ±0.04	0.2420 ±0.06	0.3621 ±0.03	0.4733 ±0.06	0.5842 ±0.05	0.6877 ±0.06
Concentration (µg/ml)	5 µg/ml	10 µg/ml	15 µg/ml	20 µg/ml	25 µg/ml	30 µg/ml

Fusidic Acid Nanofibers Formulation

The amount of fusidic acid to be added to the polymer solution at a particular ratio to achieve 2% fusidic acid in nanofibers of polymer weight is obtained by preparing 1% fusidic acid in PBS pH5.5 that equals to 10mg/1mL; the ratio of PVA/Chitosan (8/2), (7/3) and (6/4) v/v is equivalent (20:1), (12:1) and (7.5:1) w/w to mix with 2% fusidic acid of polymer weigh, according to the ratio of polymer which represents 1.7mL, 1.6mL and 1.4mL of 1% fusidic acid solution respectively to prepare nanofibers loaded fusidic acid to study the properties of the products through the estimation of nanofibers [33].

Optimization of Fusidic Acid Electrospun Nanofibers Drug Content in Nanofibers

The amount of fusidic acid available in the formula is obtained after 24-hour immersion of each formula separately in PBS pH5.5; and the content of drug is detected by UV absorbance at 205nm which reflects the quantity of drug in the nanofibers. The study of drug content is to estimate the factors affecting the amount of drug in the final product whether polymer factors or process factors. Figure 3 illustrates the drug content in nanofibers for 9-formula, where the highest percent represents F1 (94.31%) and agrees with previous studies regarding the ratio of PVA/Chitosan [34]; as the concentration of Chitosan increases, the amount of drug release from the formula decreases due to the reducing in the wettability of the PVA and delay the release of fusidic acid from nanofibers [35].

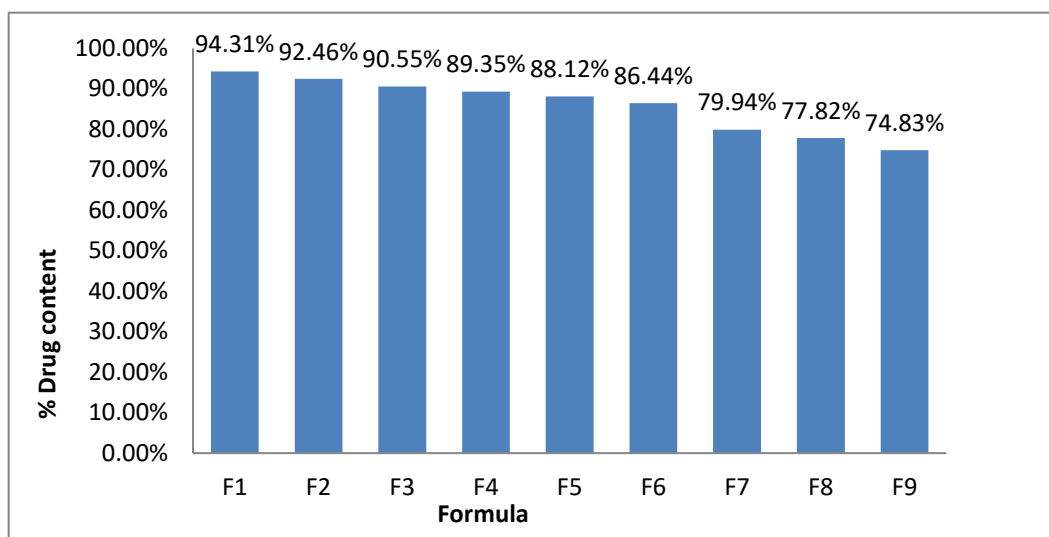


Fig.3: Fusidic acid content in nanofibers

Morphology and Topology Analysis of Nanofibers Loaded Fusidic Acid

The prepared nanofibers is investigated by SEM to study the morphology of the products, almost the ratio of PVA/Chitosan is affecting the diameter of nanofibers and their properties. Basically a nanofibers average diameters reduces with increases Chitosan concentration due to improve the charge density of the droplet surface, but at the same time reduces the wettability and drug release profile

[36]. The collected data of SEM analysis in figure 4 shows the low ratio of PVA/Chitosan has small fibers diameters; the average diameter is ranged between 430 ± 37 nm and 301 ± 22 nm of F1 to F9 respectively. In figure 5 shows F1 nanofibers which have a clear bead-free and within the acceptable range of fibers size that used in wound dressing. The diameter of nanofibers plays a crucial role in stopping the bacterial invasion at wound site, hydration of the skin and controlling the drug release during a particular time [37].

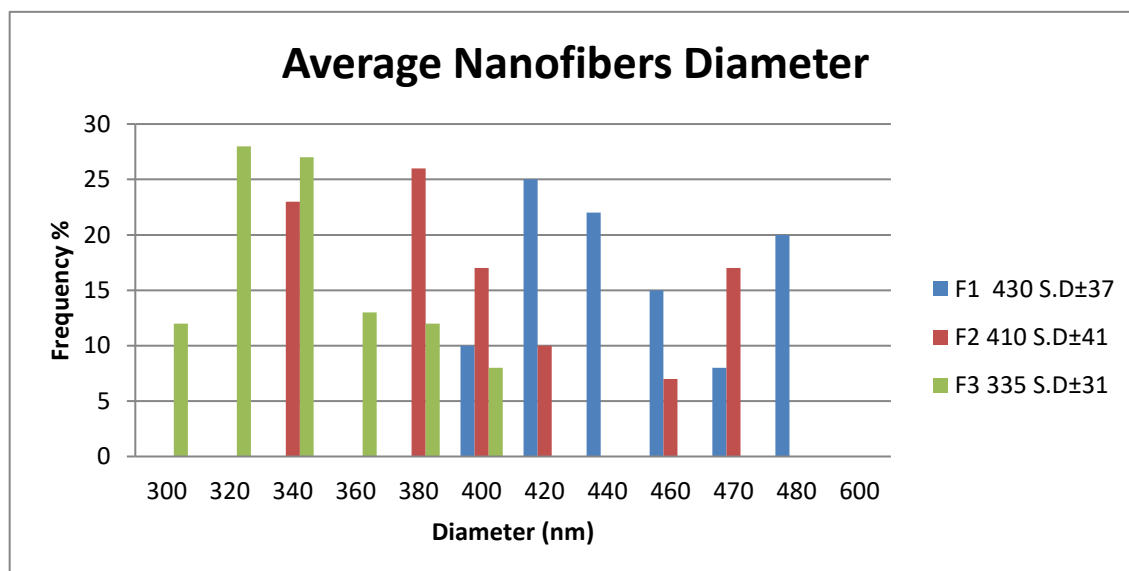


Fig.4: Average nanofibers diameter of F1, F2 and F3

The data reveal that F1 has bead like structure, due to the low concentration of Chitosan means (high PVA/Chitosan ratio), while with increasing the Chitosan concentration the

diameter decreases to 301 ± 22 nm in F9. Polymers ratio of 10% PVA to 2% Chitosan shows reliable results to load the drug in polymer solution and modify the drug release from nanofibers [38].

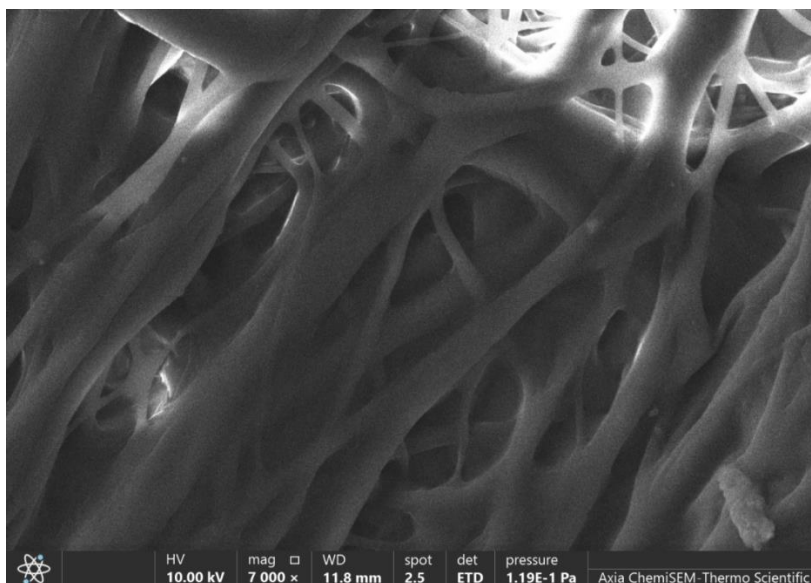


Fig. 5: Nanofibers image of F1 by SEM

Differential Scanning Calorimetric Analysis

The thermogram of differential scanning calorimetric for fusidic acid nanofibers studies the physical property of nanofibers at different temperatures as a function of time as shown in figure 6 DSC of fusidic acid nanofibers [39]. Chitosan thermogram shows an endothermic peak at 94.39°C which is also called dehydration temperature due to the loss of water owing to the hydrophilic group and an exothermic peak at 270°C. The thermogram curve of PVA shows the dehydration of water below 100°C which is

related to the amorphous part of PVA and endothermic melting point at 191.96°C. While for fusidic acid exothermic peak represents the loss of water from carboxyl group starting at 40°C to 180°C and an endothermic melting point at 191.25°C. Above these points is related to the nanofibers decomposition at 260°C due to the breakdown of H-bonds interaction between PVA and Chitosan, the data indicates a good compatibility of the component in the nanofibers form due to the stability of the drug in a soluble form in the final product [40].

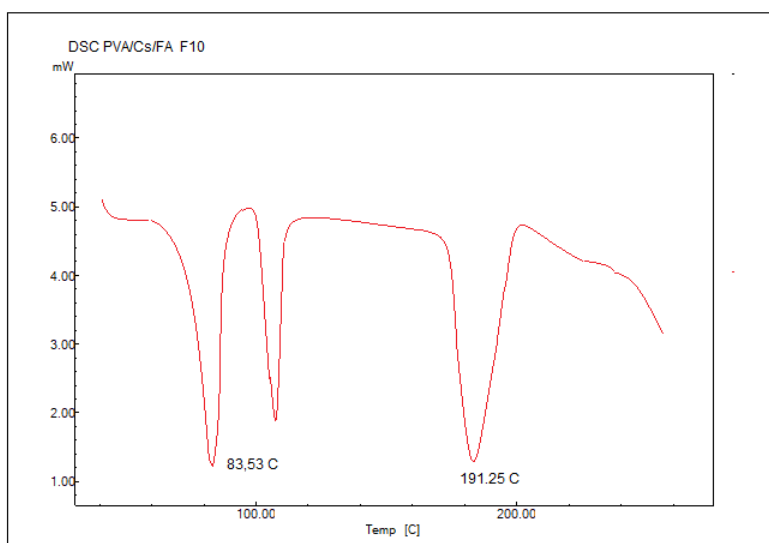


Fig.6: Differential scanning calorimetric analysis of fusidic acid nanofibers

In-vitro Percent Drug Release Profile From Nanofibers

The data of average percent cumulative drug release from nanofibers is shown in table 3 by taking the absorbance at 205nm UV during 7-hour, the test is triplicated with mean value of \pm S.D. The samples of selected nanofibers formulas F1, F2, F3, F4, F5 and F6 are tested for drug release and plotted in chart which shows that F1 has the highest percent 75.83% and the lowest is F6 58.48% at the end of 7-hour [41]. It is clearly observed that the effects of Chitosan concentration on the drug release from nanofibers, high

concentration turns the fibers into rigid net due to the difficulty in the swelling of PVA, which is responsible for the dissolution of the drug because of H-bonds formation between PVA/Chitosan and delay the release of fusidic acid from the nanofibers; and that is the reason of excluding F7, F8 and F9 from dissolution test. The remaining formulas show lowest percent due to the increasing in Chitosan concentration which prevents the access of solvent into internal layers and reduces the solubility and release of drug. Figure 7 shows the average cumulative drug release from nanofibers loaded fusidic acid during 7-hour [42].

Table 3: The average percent of cumulative drug release during 7 hours from nanofibers

Time (Hours)	F1 Average %CDR \pm SD	F2 Average %CDR \pm SD	F3 Average %CDR \pm SD	F4 Average %CDR \pm SD	F5 Average %CDR \pm SD	F6 Average %CDR \pm SD
0	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
1	15.11%	18.32%	22.60%	12.43%	16.37%	19.43%
2	20.51%	25.84%	30.57%	18.45%	20.42%	27.37%
3	36.17%	33.12%	39.69%	27.73%	30.55%	33.47%
4	57.63%	38.44%	42.52%	45.41%	39.63%	37.92%
5	65.12%	45.07%	47.45%	53.63%	47.24%	42.26%
6	74.24%	52.54%	53.74%	59.84%	56.49%	49.33%
7	75.83%	64.29%	61.07%	64.22%	60.66%	58.48%

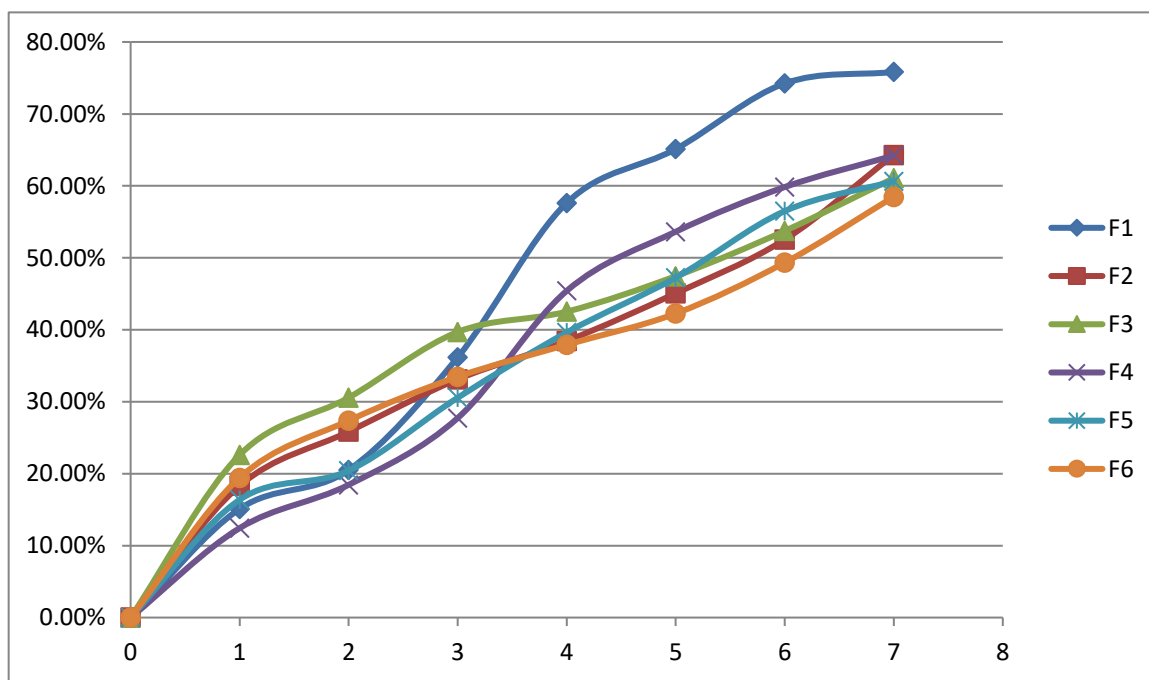


Fig.7: In-vitro Average percent of cumulative drug release during 7-hour of F1, F2, F3, F4, F5 and F6

Release Kinetics

The study of release kinetics is important to understand the mechanism of drug release from nanofibers and fit a specific kinetic model [43]. The average percent of drug release has applies in the equation of each model to obtain the regression coefficient (R²) of F1, F2, F3, F4, F4 and F6 fit with Higuchi kinetics model. The determined data are plotted as average cumulative percentage drug release against square root of time ($M_t/M_0 = kt^{0.5}$). The slope of the plot represents Higuchi dissolution constant KH [43].

Selection of Best Formula

Best formula selection is depended on the resultant data of drug content, scanning electron microscope and average percentage drug release profile; the data revealed that F1 represents the highest percent of drug content, nanofibers diameter within the acceptable range of fibers that are used in the wound dressing and finally the average percentage cumulative drug release is the highest value among the 6-formula that tested for the drug release during 7-hour. However the average percentage of drug release does not show perfect value due to the small amount of fusidic acid

loaded into nanofibers, but it is possible to increase the percent of fusidic acid to the polymer weight to obtain better release behavior [44].

Short Term Stability Test

Stability study is performed to investigate the factors affecting the drug release from nanofibers under different conditions to compare the drug release during 7-hour. F1 is tested for short term stability through determining the average drug release from nanofibers after 1-month of storage at high temperature [45]. The results revealed that, the average percent drug release from batch 1 does not have wide difference with original tested formula (F1) in-vitro release study which performed previously because it has been stored at low temperature, while the batch 2 shows a little delay in the initial burst release of the drug during first 2-hour, it may relate to the loss of water molecules from PVA portion when incubated under elevated temperature for 1-month, in this case to maintain the stability of product for longer period of time; nanofibers should be sealed with foil to prevent the loss of water and to prevent structural changes. Figure 8 shows the average percentage of drug release from F1 for both batches [46].

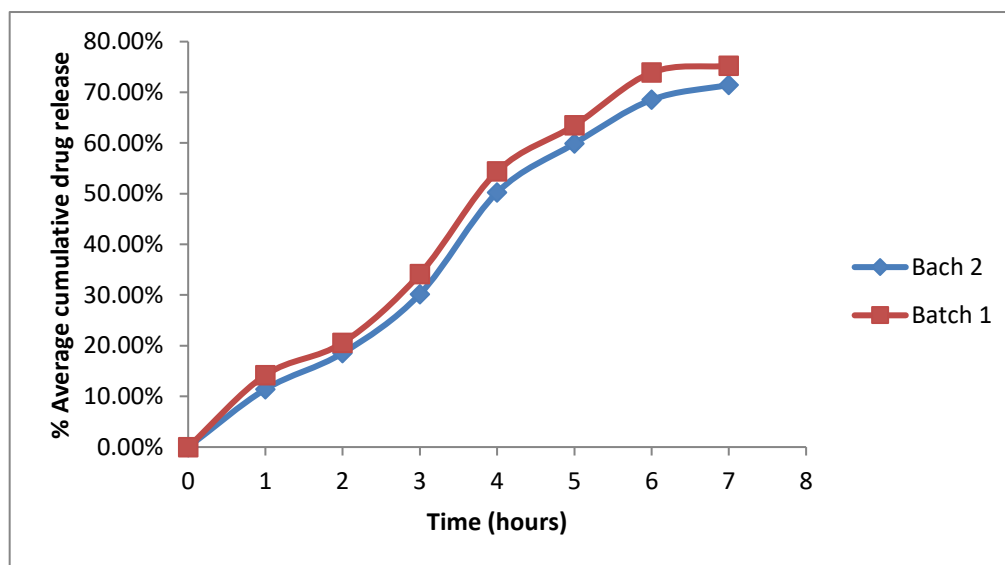


Fig.8: Percent drug release of F1 as (Batch 1 and Batch 2) for stability study

CONCLUSION

Fusidic acid nanofibers is successfully prepared by Electrospinning technique which evaluated for drug content, morphology, compatibility with excipient and in-vitro drug release from nanofibers. The obtained data revealed good results of acceptable nanofibers diameter within the range of fibers that used for wound dressing and the amount of fusidic acid could be increased to enhance the amount of drug releases with time at PVA/Chitosan ratio of (8/2) which is suitable for loading large quantity of fusidic acid and

prolonged drug release from nanofibers to be used in the treatment of skin infection as nanofibers wound dressing.

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