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Pectin/poly(vinylpyrrolidone) composite sponges as wound dressings for delivery of silver sulfadiazine

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ABSTRACT: Wound dressings based on sponges with good antimicrobial performance could be suitable options to prevent wound infection and promote wound healing for exudative wounds. In the current study, silver sulfadiazine (AgSD) loaded ionically crosslinked pectin (PEC)/ polyvinylpyrrolidone (PVP) based composite sponges were fabricated by freeze-dried molding with tunable mechanical features for wound dressing application. The structure of composite sponges was confirmed by Fourier transform infrared spectroscopy (FT-IR) and they were characterized in terms of gel fraction, mechanical, swelling, degradation and drug release properties. In particular, the longer incubation of composite sponges in $CaCl_2$ solution resulted in enhanced mechanical properties. For instance, compressive moduli of PEC sponges were improved from 23.30 kPa to 37.24 kPa after 30 minutes and 120 minutes incubation in $CaCl_2$ solution, respectively. Moreover, the addition of PVP improved the mechanical property of pectin. All composite sponges exhibited higher gel fraction in distilled water compared to phosphate buffer saline (PBS, pH: 7.4). The composite sponges exhibited rapid and high swelling ability of 802.47±69.31% and 714.56±39.78% for PEC and PEC/PVP composite sponges, respectively. They degraded completely after 48 hours. AgSD entrapment efficiency was about 70% for all composite sponges. The AgSD release from PEC slightly reduced after blending PVP, and the cumulative release was 39.19% and 51.49% after 1 h, respectively. AgSD/PEC and AgSD/PEC/PVP composite sponges allowed AgSD release for six hours. In summary, AgSD/PEC/PVP composite sponges with antimicrobial activity have a favorable potential to accelerate wound healing by providing wound closure and effectively absorbing wound exudates.

KEYWORDS: Wound dressing; sponge; pectin; polyvinylpyrrolidone; silver sulfadiazine.

1. INTRODUCTION

Skin represents a fundamental role in protection, hydration, secretion, and thermal regulation. Serious skin disruption upon trauma, burn, and cut could result in increased mortality [1]. Hence, the functional management of wounds could present a great challenge to medical staffs and financial burden to healthcare system. For instance, skin traumas affect 10 million people in the United States, and $50 billion were spent annually for the treatment [2]. Since, there has been growing incidence of skin wounds upon aging population paired with chronic diseases, there is an urgent need for functional wound care materials.

Wound healing is well orchestrated and complicated biological process that requires interaction of various cells, cytokines, growth factors [3]. Thereby, wound care materials should be designed according to specific needs of wounds. An ideal wound dressing should have biocompatibility, suitable mechanical property and flexibility, favorable water vapor transmission and gaseous exchange rate, provide proper removal of excess exudate, prevent risk of infection, and enhance tissue-healing rate [4-6]. In particular, wounds (both acute and chronic) could include some exudate. In acute wounds that can heal within 8-12 weeks, the amount exudate could gradually decrease in the healing process. However, large amount of exudate generated owing to inflammatory process [7].

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Currently, plenty of novel wound dressing materials such films, foams, sponges or hydrogels have been developed by using natural or synthetic materials, or a combination of them [8]. Even though there has been a growing interest to develop effective wound dressing, wound dressings technology still cannot meet the demands of clinical needs because of the complexity of wound healing. Recently, composite sponges have presented favorable alternatives for the management of especially exudative wounds due to their superior capability of absorbing wound exudates, high porosity, high surface area and pore volume to achieve wound healing as well as enhancing hemostasis [8-10]. In this study, silver sulfadiazine incorporated ionically crosslinked pectin and polyvinylpyrrolidone (PVP) based composite sponges were developed for intended use in exudative wounds. Silver sulfadiazine is an antibacterial agent for topical treatment of wounds due to its significant broad-spectrum antimicrobial activities and enhanced patient survival [11, 12].

Pectin, a natural polysaccharide, has been widely investigated in fabrication of wound dressings thanks to its hydrophilic structure, stability in acidic conditions mucoadhesive, antimicrobial and film forming behavior as well as its favorable biocompatibility and biodegradability [13-15]. Pectin is obtained from the cell walls of most plants and is composed of linear chains of (1–4)-linked α-D-galacturonic acid residues [16, 17]. Furthermore, pectin has strong anti-inflammatory effect owing to the high level of esterified galacturonic acid residues [18]. The guluronate or galacturonate blocks of pectin can be crosslinked in the presence of divalent cations such as Ca^{2+} to form egg-box model [19, 20]. The calcium and pectin could present a hemostatic effect by providing erythrocyte and the platelet accumulation. In addition, the presence of calcium ions into wound site could provide the generation of pro-inflammatory cytokines (e.g. tumor necrosis factor, interleukins) [21].

PVP is a synthetic polymer that has been used for many years as a biomaterial, drug carrier, and excipients in owing to its biocompatibility, low chemical toxicity, and good transparency [22, 23]. It could be generally employed as main ingredient of wound dressings and temporary skin covers [24, 25]. PVP has a hydrophilic character beneficial to remove wound exudate and offer suitable moisture in wound bed to avoid scab formation and dehydration [26, 27]. PVP and Ag+ ions could strongly interact to generate a complex to accelerate formation and stabilization of Ag nanoparticles [28, 29]. Recently, Kumari and coworkers fabricated chitosan/PVP/nanocellulose composites by solution casting method. According to water vapor and oxygen permeability studies, their designed composites could allow a moist environment over wound bed [23]. Then, they coated one side of this composite by using stearic acid to obtain hydrophobic surface, while the other side revealed a hydrophilic surface. These asymmetric membranes were cytocompatible and exhibited a superior wound healing compared to symmetric dressing [30]. Archana et al. developed silver oxide nanoparticles incorporated chitosan/PVP films. These films allowed accelerated wound healing compared to cotton gauge and 100% chitosan based dressings [22].

Currently, Jung and coworkers developed alginate-pectin composite sponges through ionic crosslinking. Sponges with higher pectin concentration exhibited higher water absorption and higher bovine seum albumine release [16]. Wang *et al.* fabricated polyvinyl alcohol/alginate composite sponges by using ionic crosslinking and lyophilization process. In particular, composite sponges allowed over 20 fold volume expansion with unique shape-adaptive ability which is essential to entirely fill large, irregular, and deep wound site [31]. Ngece *et al*. developed a alginate-gum acacia sponges loaded with a combination of ampicillin and norfloxacin [8]. Tavakoli *et al*. designed a chitosan/PVP sponge containing platelet-rich fibrin for advance wound healing [10]. Ma and coworkers prepared nanocomposite sponges of sodium alginate/graphene oxide/polyvinyl alcohol for the management of exudative wounds [32].

In this initial study, silver sulfadiazine loaded pectin and PVP based composite sponges were fabricated by lyophilization method and crosslinked by the divalent cation $CaCl_2$ to form a polymeric network. Firstly, the structure of formulation ingredient and active agent and the structure of composite sponges were evaluated by using Fourier-transform infrared (FT-IR). Then, initial wound dressing features of composite sponges including the mechanical properties, swelling ability, degradation profile, and gel fraction were investigated. Finally, *in vitro* drug release profile was determined.

2. RESULTS AND DISCUSSION

2.1. Fourier Transform Infrared Spectroscopy (FTIR)

FT-IR spectroscopy was used to investigate chemical and/or structural characteristics of PEC, PVP and AgSD (Figure 1A). In the FTIR spectra of PEC, the strong and sharp absorption band at 1007 cm^{-1} may be related to C-O and Si-O bonds presented in polysaccharide structure. The peaks located at 1126 cm^{-1} and 2929 cm^{-1} were attributed to tertiary alcohol and alkane absorption, respectively, due to polysaccharide structure.

The observed peaks at 1560 cm^{-1} and 1815 cm^{-1} were correspond to stretching vibrations of carboxylate anion (COO^-) and ester stretching vibrations of carboxyl (C=O), respectively. The broad band at about 3015-3600 cm^{-1} was attributed to stretching of OH groups. The obtained results were consistent with previous findings for pectin [33]. In the FTIR spectra of PVP, the characteristic peaks were observed at 2921 cm^{-1} and 1645 cm^{-1} correspond to stretching vibrations of C–H and C=O, respectively. In addition, a very broad band at about 3000-3670 cm^1 was related to stretching vibrations of O-H owing to absorbed water in accordance with previous literature [34, 35]. The FTIR spectrum of AgSD displayed a characteristic peak at 1229 cm^{-1} for the S=O asymmetric stretching vibration. The peaks associated with vibrational stretching of $-NH_2$ were determined at 3341and 3389 cm^{-1}. The peak observed at 1596 was attributed to phenyl structure conjugated to the NH_2. In addition, the peaks presented at 1551, 1500 and 1412 cm^{-1} were assigned as pyrimidine skeletal vibrations [12, 36].

The chemical structures of PEC, PEC/PVP, PEC/AgSD and PEC/PVP/AgSD sponges were investigated using FTIR (Figure 1B). The expected peaks of all the components within the sponges were observed in the FTIR spectrum with small variations. Compared to PEC and PVP sponges, the hybridization of PEC/PVP in composite sponges resulted in the shift of carbonyl stretching vibrations (from 1644 to 1641 cm^{-1}) and hydroxyl groups (from 3276 to 3271 cm^{-1}). Since carbonyl group tasked hydrogen bonding, the shift of this group indicated stronger intermolecular interactions compared to self-associated hydrogen bonding. In addition, ester-stretching vibrations were shifted to from 1737 to 1746 cm^{-1} with the presence of PVP in the composite sponges. The displacement of ester stretching vibrations could be attributed to generation of hydrogen bonds between PVP (from carbonyl group) and pectin (from oxygen of the C-O covalent bond in methoxyl groups) [37]. As a result, the blend of pectin and PVP could provide structural interactive network to from a functional structure. In case of PEC/AgSD and PEC/PVP/AgSD, it was not observed an undesired interaction between drug and polymers.

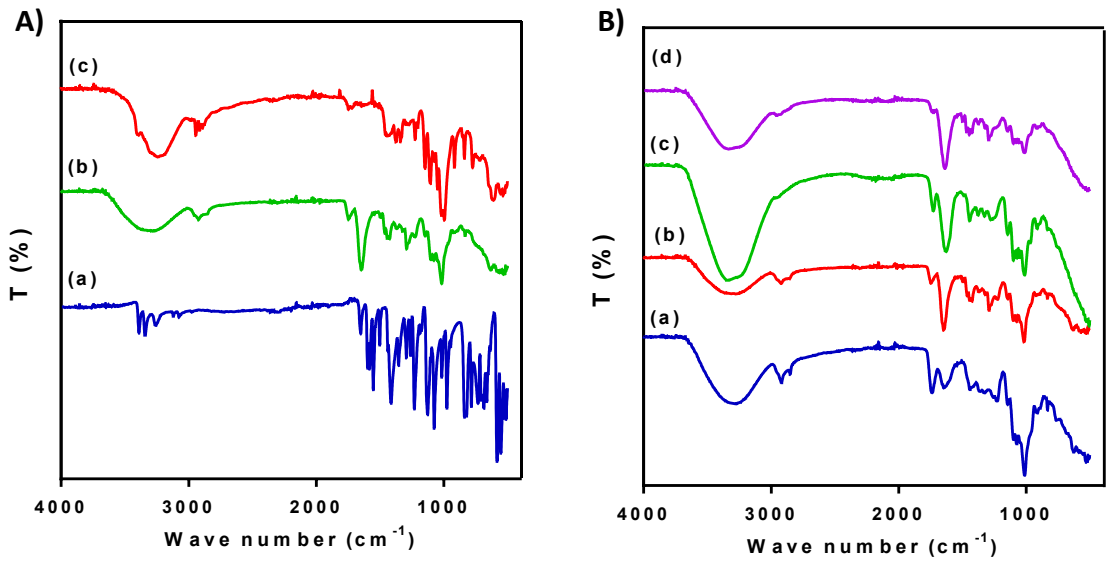

Figure 1. FTIR spectra of formulation ingredients and composite sponges **A)** FTIR spectra of AgSD (a), PVP (b), and (PEC) (c), **B)** FTIR spectra of PEC sponges (a), PEC/PVP sponges (b), AgSD/PEC sponges (c), AgSD/PEC/PVP sponges (d).

2.2. Mechanical Behavior

To obtain functional wound dressing material, the mechanical properties of material should be similar to human skin and possess high durability to adapt to wounds with different shapes [38, 39]. They could also have appropriate mechanical features not to break due to load or deformation. The contractility of myofibroblasts could lead a significant strain at wound site. The skin also could be faced with external mechanical forces. In addition, elastic properties of skin deformations and dressings should be comparable. Otherwise, high stresses and possible decohesions could occur at the applied edges [40, 41]. The compressive

moduli of designed sponges were calculated from the stress-strain curves. The compressive modulus and compressive strength were enhanced by the longer duration of crosslinking in $CaCl_2$ solution and the presence on PVP. In particular, compressive moduli were improved from 23.3 ±5.9 kPa to 37.24±3.19 kPa of PEC sponges ($p<0.01$) and from 31.48±8.13 kPa to 43.05±4.12 kPa for PVP/PEC composite sponges ($p<0.01$) after 30 minutes and 120 minutes incubation in $CaCl_2$ solution, respectively (Figure 2A). Moreover, compressive strengths were improved from 117.51±32.47 kPa to 198.29±30.23 kPa of PEC sponges ($p<0.01$) and from 134.85±29.42 kPa to 219.11±34.69 kPa for PVP/PEC composite sponges ($p<0.01$) after 30 minutes and 120 minutes incubation in $CaCl_2$ solution, respectively (Figure 2B). Since, the highest compressive strength and compressive modulus were obtained after 120 minutes of incubation in $CaCl_2$ solution, for the following studies all composite sponges were crosslinked for 120 minutes.

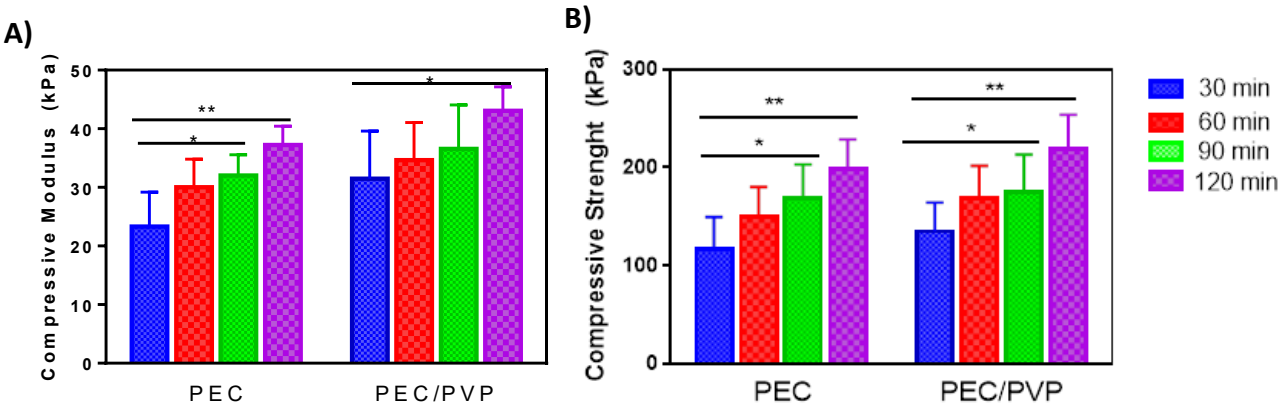

Figure 2. Mechanical properties of PEC and PEC/PVP sponges. **A)** Compressive modulus and **B)** Compressive strength of composite sponges (n=4) (ns > 0.05,*p < 0.05, **p < 0.01).

2.3. Gel Fraction Analysis

Since the strength and flexibility of hydrogels have directly affected by gel fraction, gel fraction of composite hydrogels is of particular interest [16, 42]. Figure 3 displays the gel fraction of composite sponges. All composite sponges exhibited higher gel fraction in distilled water (DW) with 54.05± 3.31% and 57.45±4.42% for PEC and PEC/PVP, respectively. After immersion in PBS, PEC and PEC/PVP composite sponges revealed 31.61±2.48% and 39.52±2.89% of gel fraction, respectively. In particular, the gel fraction decreased with the immersion in PBS, whereas increased by the presence of PVP. Herein, the composite sponges were crosslinked due to the immersion of pectin in a calcium chloride solution to form insoluble gels. The crosslinking density could be reduced by the exchange between sodium and calcium ions. Hence, composite sponges provided lower crosslinking in PBS solution, leading to a reduction of the gel fraction.

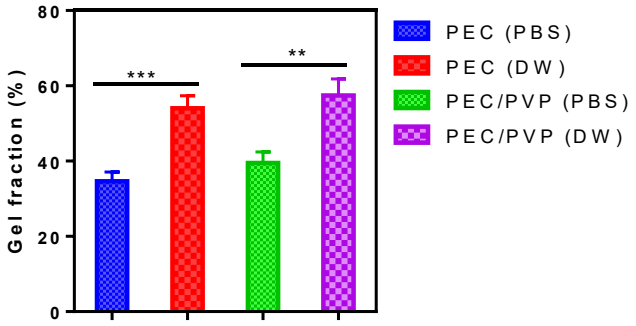

Figure 3. Gel fraction of PEC and PEC/PVP sponges in PBS or DW (n=4) (ns > 0.05,*p < 0.05, **p < 0.01; ***p < 0.001).

2.4. Swelling

For the application of wound dressings, the absorption of large volume exudates from the surface of wounds has a great importance. Hence, wound dressing materials need to have moderate swelling ability to remove exudate, maintain appropriate moisture preventing wound from drying, and further promoting healing [16, 22, 32, 43]. One of the main advantages of sponges in wound management is their ability to provide optimal moisture at the wound site due to outstanding water absorption [16, 38]. Figure 4 demonstrates the swelling ability of developed composite sponges in DW and PBS. All designed sponges exhibited a rapid and high swelling with greater than 500% swelling. All composite sponges swelled rapidly and reached swelling equilibrium in PBS after 60 minutes. However, the duration to reach swelling equilibrium has been reduced to 15 minutes in DW. The swelling capabilities of PEC sponges were higher compared to PEC/PVP composite sponges, after incubation in PBS or DW. Moreover, the swelling ability of all sponges was accelerated in PBS compared to DW. Particularly, after 2 hours, the swelling ratios (%) for PEC and PVP in PBS were 802.47±69.31% and 714.56±39.78%, respectively. The swelling ratios (%) for PEC and PVP in DW after 2 hours were 762.46±64.25% and 637.71±54.16%, respectively. It is known that pectin could exhibit lower cross-linking density because of its low calcium content, which leads higher water absorption. Additionally, degree of crosslinking could be decreased by the exchange between sodium and calcium ions. Accordingly, the exchange of calcium ions in pectin based sponges immersed in PBS could lead relaxation of polymer chains, resulting in higher water absorption [16, 44].

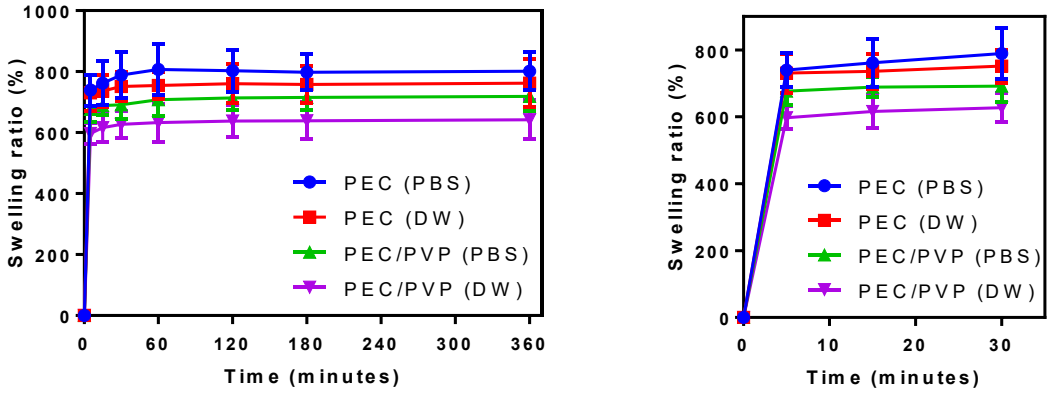

Figure 4. Swelling ratio (%) of PEC and PEC/PVP sponges in PBS or DW (n=4)

2.5. Degradation Study

The degradation profile of wound dressing is important factor for clinical application. Since rapid degradation could lead to the release of absorbed exudates, decreased hydration and finally rapid release of active agent, wound dressing material should not degrade too fast [41]. Figure 5 presents the degradation profile of composite sponges. The presence of PVP increased the weight remaining (%) of the composite sponges. After 6 hours of incubation, remaining masses of PEC and PEC/PVP were found to be 53.67±7.59% and 65.79±4.57%, respectively. The remaining mass (%) of all sponges was over 45% after 12 hours of incubation. After 24 hours of incubation, remaining masses were determined as 21.48±11.23% and 24.22±8.62% for PEC and PEC/PVP, respectively. The complete degradation of all composite sponges took about 48 hours.

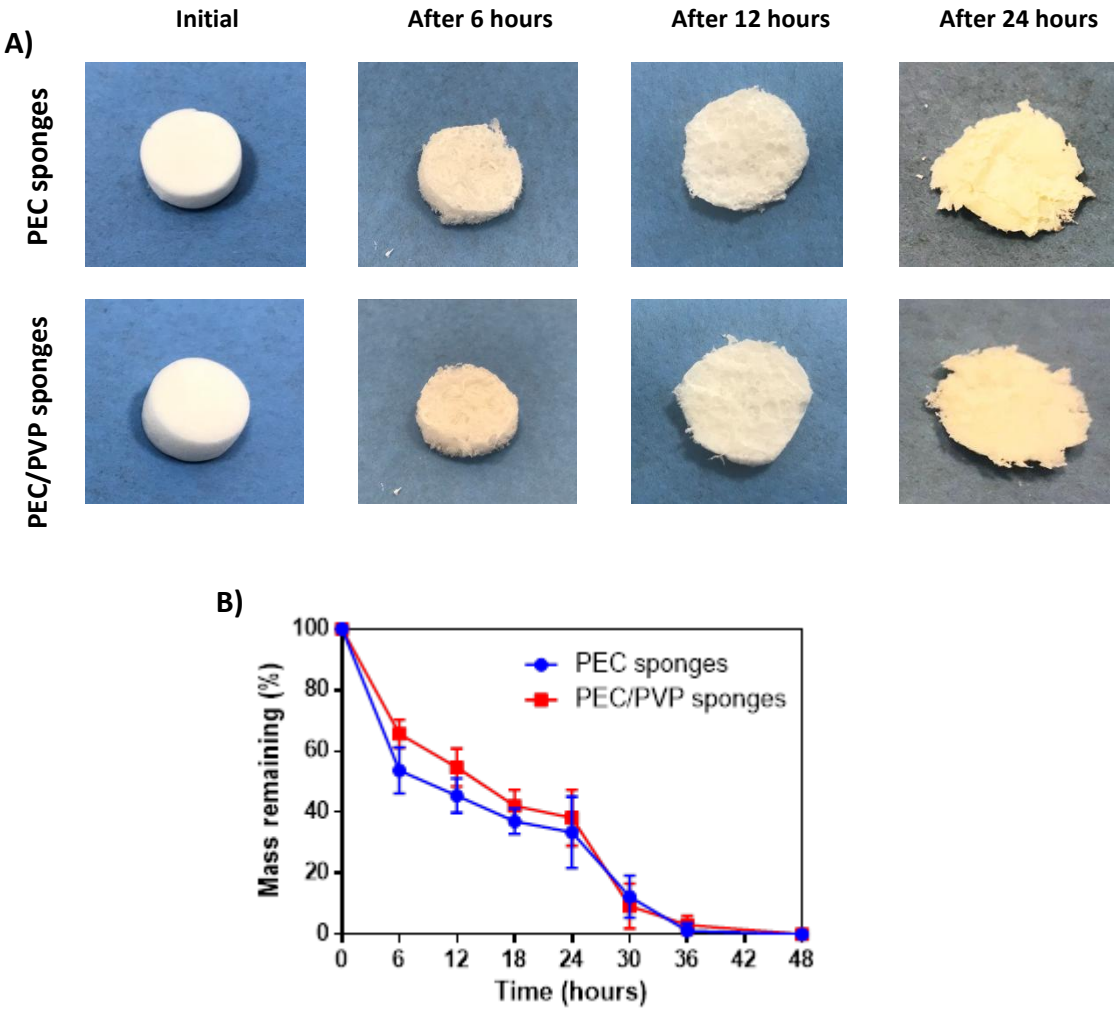

Figure 5. Degradation studies of PEC and PEC/PVP sponges. **A)** The photographs of PEC and PEC/PVP sponges before and 6, 12, and 24 h after incubation in PBS, **B)** Degradation profile of PEC and PEC/PVP sponges in PBS (n=4).

2.6. AgSD Entrapment And *In Vitro* Drug Release

AgSD, an antimicrobial drug, was selected to characterize the drug carrying capabilty and *in vitro* release properties of PEC and PEC/PVP sponges. Entrapment efficiency of AgSD was found as 70.19±8.21% and 73.27±7.94% for PEC and PEC/PVP sponges, respectively. In addition, drug loading of PEC and PEC/PVP sponges were 30.28 mg/g sponge and 28.99 mg/g composite sponge, respectively. The *in vitro* drug release result showed that drug release slightly reduced in PEC/PVP sponges compared to PEC sponges (Figure 6). After 30 minutes, 33.88±3.13% and 35.24±5.16% drug release occurred for PEC/PVP and PEC sponges, respectively. After 1 hour, drug release from PEC sponges reached 51.49±3.76%, while drug release from PEC/PVP composite sponges reached 39.14±6.74%. Drug release from the PEC and PEC/PVP sponges

reached 100.23±7.45% and 97.12±9.23% after 6 hours. The release curves of PEC and PEC/PVP sponges were applied to zero-order, first-order, Higuchi model, Korsmeyer Peppas, and Hixson Crowell. The results were shown in Table 1. In particular, Higuchi kinetic model exhibited a better fit. The release profile of silver sulfadiazine represented a linear relationship with the square root of time for PEC and PEC/PVP sponges, which indicated that the silver sulfadiazine released by diffusion.

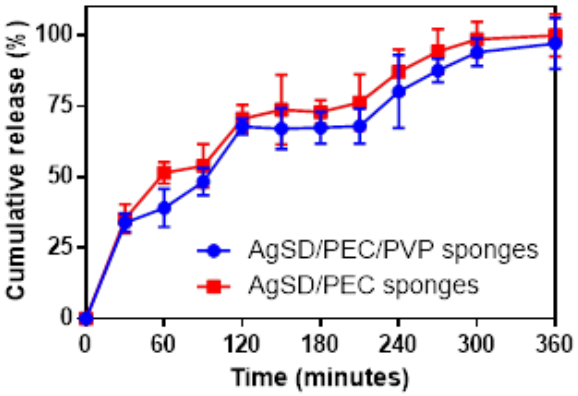

Figure 6. *In vitro* release profile of AgSD from AgSD/PEC and AgSD/PEC/PVP sponges (n=4).

Table 1. Determination coefficient (R^2) values of drug release kinetics of AgSD/PEC and AgSD/PEC/PVP sponges

Code	Zero order	First order	Higuchi	Korsmeyer-Peppas	Hixson Crowell
PEC	0.8938	0.9513	0.9851	0.9435	0.9405
PEC/PVP	0.9163	0.9344	0.9624	0.8953	0.9379

3. CONCLUSION

Sponges with highly porous structure could be favorable alternatives for the management of exuding wounds [7-9]. In this study, PEC and PEC/PVP composites sponges based wound dressings were developed through freeze-dried molding by crosslinking in the presence of divalent cation $CaCl_2$ for the delivery of AgSD. Herein, crosslinking density and the addition of PVP accelerated the mechanical properties. The PEC and PEC/PVP composite sponges showed rapid and high swelling ability as 802.47±69.31% and 714.56±39.78%, respectively. The complete degradation of all composite sponges completed after 48 hours. In addition, the entire release of AgSD from composite sponges completed after 6 hours. As a result, the developed composite sponges could be promising options to prevent wound infection and accelerate wound healing for exudative wounds.

4. MATERIALS AND METHOD

4.1. Materials

AgSD was kindly donated from Deva Pharmaceuticals (Turkey). High methoxy pectin was purchased from Herbstreith and Fox KG (Germany). Plasdone™ C-30 was purchased from Ashland (Switzerland). All other chemicals and reagents were of analytical grade and purchased from Sigma-Aldrich (Germany).

4.2. Preparation of Pectin/PVP Composite Sponges

Pectin/PVP based composite sponges were fabricated by freeze drying molding [32] and crosslinked by the $CaCl_2$. Briefly, 6% (w/v) pectin or pectin 6% (w/v) and PVP %4 (w/v) were dissolved in distilled water and stirred at 40 ^{0}C for 3 h by magnetic stirrer to obtain a homogeneous gel. Afterwards, this gel poured into a mold, frozen at −20 °C for 24 h and lyophilized for 48 h. Following lyophilization process, obtained sponges were cross-linked with 0.1 M calcium chloride for 30, 60, 90 and 120 minutes. Afterwards, obtained constructs were washed by using distilled water, frozen at −20 °C for 24 h, and lyophilized for 48 h.

4.3. Fourier-Transform Infrared (FTIR) Spectroscopy

Firstly, to investigate the structure of formulation ingredients, the FTIR spectra of pectin, PVP, silver sulfadiazine were evaluated. Then, the FTIR spectra of composite sponges were investigated. FTIR spectroscopy was conducted using a FTIR spectrometer equipped with ATR sampling accessory (Jasco FT/IR-4600) between 4000 and 400 cm−1 at a resolution of 4 cm−1[45].

4.4. Mechanical Properties

To determine the mechanical properties of composite sponges, lyophylized PEC and PEC/PVP sponges were cut in the cylindrical shapes with a diameter of about 7 mm and thickness of about 2.5 mm. Then, samples were immersed in DW for 30 minutes to equilibrate, and mechanical properties were evaluated by compression tests using a mechanical testing machine (TA Instruments) [45]. Briefly, composite PEC or PEC/PVP sponges were loacated on the platen, and compressive strength of composite sponges were determined at a cross speed of 1 mm s-1 and a 80% strain level. The compressive modulus was calculated as the slope of the linear region in the 0-10% strain.

4.5. Gel Fraction Analysis

To investigate the gel fraction of the composite sponges, the sponges were weighed following lyophilization and incubated in distilled water or phosphate buffer saline (PBS, pH = 7.4) at 37°C for 24 h to allow entirely dissolution of the ionically cross-linked polymer chains from the networks. Subsequently, the composite sponges were lyophilized for 48 h and weighed (n=4). The gel fraction percentage was determined by using following equation [46]:

$$\text{Gel fraction (\%)} = \frac{\text{The dry weight of sponges following incubation}}{\text{The dry weight of sponges before incubation}} \text{x100}$$

4.6. Swelling

The swelling capacity of the composite sponges in distilled water or PBS (pH=7.4) was evaluated by using gravimetric method. The composite sponges were lyophilized and weighed. Then, they incubated in distilled water or phosphate buffer saline (PBS, pH 7.4) at 37°C, and at predetermined time intervals, the composite materials were weighed following removing the residual surface water or PBS with a filter paper (n=4). The swelling percentage was determined by using following equation[8]:

$$\text{Swelling ratio (\%)} = \frac{\text{The weight of swollen sponges} - \text{The weight of dried sponges}}{\text{The weight of dried sponges}} \text{x100}$$

4.7. Degradation Studies

For the evaluation of *in vitro* degradation behavior of the composite sponges, formulations were incubated in PBS (pH 7.4) at 37°C and they removed from the PBS after predetermined time points. The

composite sponges were dried by lyophylization and weight loss was monitored (n=4). The percentage of degradation was calculated by using following Equation [47]:

$$\text{Mass remaining (\%)} = \frac{\text{The final weight of composite sponges}}{\text{The initial weight of sponges}} \text{x100}$$

4.8. Determination of Encapsulation Efficiency and Drug Loading

The fabricated drug loaded sponges were cut into small pieces and immersed in 10 ml of deionized water by stirring at 1000 rpm and 37 ^{0}C for 24 hours. Afterwards, obtained solution was filtered and UV absorbance was determined at 287 nm. Drug entrapment efficiency (EE) was determined by using following equation:

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Mass of drug found in sponges}}{\text{Mass of the drug initially present}} \text{x100}$$

4.9. *In vitro* Release Studies

Composite sponges were incubated in 10 mL of PBS (pH 7.4) at 37°C to investigate *in vitro* release behavior [32]. At predetermined time intervals, 1 ml solution was withdrawn, and equal volume of fresh buffer was added to provide sink condition. The concentration of drug was determined at a wave-length of 287 nm (n=4).

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REFERENCES

[1] Tottoli EM, Dorati R, Genta I, Chiesa E, Pisani S, Conti B. Skin wound healing process and new emerging technologies for skin wound care and regeneration. Pharmaceutics. 2020;12(8):735. [CrossRef]

[2] Zhu Y, Zhang J, Song J, Yang J, Xu T, Pan C, Zhang J. One-step synthesis of an antibacterial and pro-healing wound dressing that can treat wound infections. J Mater Chem B. 2017;5(43):8451-8458. [CrossRef]

[3] Mirmajidi T, Chogan F, Rezayan AH, Sharifi AM. In vitro and in vivo evaluation of a nanofiber wound dressing loaded with melatonin. Int J Pharm. 2021;596:120213. [CrossRef]

[4] Dragostin OM, Samal SK, Dash M, Lupascu F, Pânzariu A, Tuchilus C, Ghetu N, Danciu M, Dubruel P, Pieptu D, Vasile C, Tatia R, Profire L. New antimicrobial chitosan derivatives for wound dressing applications. Carbohydr Polym. 2016;141:28-40. [CrossRef]

[5] Yaşayan G, Karaca G, Akgüner ZP, Bal Öztürk A. Chitosan/collagen composite films as wound dressings encapsulating allantoin and lidocaine hydrochloride. Int J Polym Mater Polym Biomater. 2021;70(9): 623-635. [CrossRef]

[6] Bal-Öztürk A, Özkahraman B, Özbaş Z, Yaşayan G, Tamahkar E, Alarçin E. Advancements and future directions in the antibacterial wound dressings - A Review. J Biomed Mater Res B Appl Biomater. 2021; 109(5): 703-716. [CrossRef]

[7] Wojcik M, Kazimierczak P, Benko A, Palka K, Vivcharenko V, Przekora A. Superabsorbent curdlan-based foam dressings with typical hydrocolloids properties for highly exuding wound management. Mater Sci Eng C Mater Biol Appl. 2021;124:112068. [CrossRef]

[8] Ngece K, Aderibigbe BA, Ndinteh DT, Fonkui YT, Kumar P. Alginate-Gum Acacia based sponges as potential wound dressings for exuding and bleeding wounds. Int J Biol Macromol. 2021; 172: 350-359. [CrossRef]

[9] Dong R, Guo B. Smart wound dressings for wound healing. Nano Today. 2021; 41: 101290. [CrossRef]

[10] Tavakoli M, Mirhaj M, Labbaf S, Varshosaz J, Taymori S, Jafarpour F, Salahi S, Mosleh Abadi SA, Sepyani A. Fabrication and evaluation of Cs/PVP sponge containing platelet-rich fibrin as a wound healing accelerator: An in vitro and in vivo study. Int J Biol Macromol. 2022; 204: 245-257. [CrossRef]

[11] Wen X, Zheng Y, Wu J, Yue L, Wang C, Luan J, Wu Z, Wang K. In vitro and in vivo investigation of bacterial cellulose dressing containing uniform silver sulfadiazine nanoparticles for burn wound healing. Prog Nat Sci Mater Int. 2015; 25(3): 197-203. [CrossRef]

[12] Aris FAF, Fauzi FNAM, Tong WY, Abdullah SSS. Interaction of silver sulfadiazine with bacterial cellulose via ex-situ modification method as an alternative diabetic wound healing. Biocatal Agric Biotechnol. 2019; 21: 101332. [CrossRef]

[13] Bostancı NS, Büyüksungur S, Hasirci N, Tezcaner A. pH Responsive release of curcumin from photocrosslinked pectin/gelatin hydrogel wound dressings. Mater Sci Eng C Mater Biol Appl. 2022: 112717. [CrossRef]

[14] Kocaaga B, Kurkcuoglu O, Tatlier M, Dinler-Doganay G, Batirel S, Güner FS. Pectin–zeolite-based wound dressings with controlled albumin release. Polymers. 2022; 14(3): 460. [CrossRef]

[15] Rezvanian M, Ahmad N, Amin MCIM, Ng S-F. Optimization, characterization, and in vitro assessment of alginate-pectin ionic cross-linked hydrogel film for wound dressing applications. Int J Biol Macromol. 2017; 97: 131-140. [CrossRef]

[16] Özkahraman B, Özbaş Z, Yaşayan G, Akgüner ZP, Yarımcan F, Alarçin E, Bal-Öztürk A. Development of mucoadhesive modified kappa-carrageenan/pectin patches for controlled delivery of drug in the buccal cavity. J Biomed Mater Res B Appl Biomater. 2022; 110(4): 787-798. [CrossRef]

[17] Oh G-W, Nam SY, Heo S-J, Kang D-H, Jung W-K. Characterization of ionic cross-linked composite foams with different blend ratios of alginate/pectin on the synergistic effects for wound dressing application. Int J Biol Macromol. 2020; 156: 1565-1573. [CrossRef]

[18] Tummalapalli M, Berthet M, Verrier B, Deopura BL, Alam MS, Gupta B. Drug loaded composite oxidized pectin and gelatin networks for accelerated wound healing. Int J Pharm. 2016; 505(1-2): 234-245. [CrossRef]

[19] da Silva MA, Bierhalz ACK, Kieckbusch TG. Alginate and pectin composite films crosslinked with Ca^{2+} ions: Effect of the plasticizer concentration. Carbohydr Polym. 2009; 77(4): 736-742. [CrossRef]

[20] Kocaaga B, Guner FS, Kurkcuoglu O. Molecular dynamics simulations can predict the optimum drug loading amount in pectin hydrogels for controlled release. Mater Today Commun. 2022; 31: 103268. [CrossRef]

[21] Shahzad A, Khan A, Afzal Z, Umer MF, Khan J, Khan GM. Formulation development and characterization of cefazolin nanoparticles-loaded cross-linked films of sodium alginate and pectin as wound dressings. Int J Biol Macromol. 2019; 124: 255-269. [CrossRef]

[22] Archana D, Singh BK, Dutta J, Dutta PK. Chitosan-PVP-Nano Silver Oxide wound dressing: In vitro and in vivo evaluation. Int J Biol Macromol. 2015; 73: 49-57. [CrossRef]

[23] Poonguzhali R, Basha SK, Kumari VS. Synthesis and characterization of chitosan-PVP-nanocellulose composites for in-vitro wound dressing application. Int J Biol Macromol. 2017; 105: 111-120. [CrossRef]

[24] Wang M, Xu L, Hu H, Zhai M, Peng J, Nho Y, Jiuqiang J, Genshuan W. Radiation synthesis of PVP/CMC hydrogels As wound dressing. Nucl Instr and Meth in Phys Res B. 2007;265(1):385-9. [CrossRef]

[25] Archana D, Singh BK, Dutta J, Dutta PK. In vivo evaluation of chitosan–PVP–Titanium Dioxide nanocomposite as wound dressing material. Carbohydr Polym. 2013; 95(1): 530-539. [CrossRef]

[26] Aytimur A, Uslu I. Promising materials for wound dressing: PVA/PAA/PVP electrospun nanofibers. Polym Plast Technol Eng. 2014; 53(7): 655-660. [CrossRef]

[27] Yoo HJ, Kim HD. Characteristics of waterborne Polyurethane/Poly (N-Vinylpyrrolidone) composite films for wound-healing dressings. J Appl Polym Sci. 2008; 107(1): 331-338. [CrossRef]

[28] Rosa RM, Silva JC, Sanches IS, Henriques C. Simultaneous Photo-induced cross-linking and silver nanoparticle formation in a PVP electrospun wound dressing. Mater Lett. 2017; 207: 145-148. [CrossRef]

[29] Malina D, Sobczak-Kupiec A, Wzorek Z, Kowalski Z. Silver nanoparticles synthesis with different concentrations of polyvinylpyrrolidone. Dig J Nanomater Biostruct. 2012;7(4) : 1527-1534.

[30] Liang D, Lu Z, Yang H, Gao J, Chen R. Novel asymmetric wettable Agnps/chitosan wound dressing: In vitro and in vivo evaluation. ACS Appl Mater Interfaces. 2016; 8(6): 3958-3968. [CrossRef]

[31] Wang Y, Wang C, Qiao L, Feng J, Zheng Y, Chao Y, He W, Xie Y, Shuai W, Li M. Shape-adaptive composite foams with high expansion and absorption used for massive hemorrhage control and irregular wound treatment. Applied Mater Today. 2018; 13: 228-241. [CrossRef]

[32] Ma R, Wang Y, Qi H, Shi C, Wei G, Xiao L, Huang Z, Liu S, Yu H, Teng C, Liu H, Murugadoss V, Zhang J, Wang Y, Guo Z. Nanocomposite Sponges of sodium alginate/graphene oxide/polyvinyl alcohol as potential wound dressing: In vitro and in vivo evaluation. Compos B Eng. 2019; 167: 396-405. [CrossRef]

[33] Zaid RM, Mishra P, Ab Wahid Z, Sakinah AMM. *Hylocereus Polyrhizus* peel's high-methoxyl pectin: A potential source of hypolipidemic agent. Int J Biol Macromol. 2019; 134: 361-367. [CrossRef]

[34] Sethia S, Squillante E. Solid dispersion of carbamazepine in PVP K30 by conventional solvent evaporation and supercritical methods. Int J Pharm. 2004; 272(1-2): 1-10. [CrossRef]

[35] Sharma A, Jain CP. Preparation and characterization of solid dispersions of carvedilol with PVP K30. Res Pharm Sci. 2010; 5(1): 49. [CrossRef]

[36] Yasayan G. Chitosan films and chitosan/pectin polyelectrolyte complexes encapsulating silver sulfadiazine for wound healing. Istanbul J Pharm. 2020;50(3):238-45. [CrossRef]

[37] Nešić A, Ružić J, Gordić M, Ostojić S, Micić D, Onjia A. Pectin-Polyvinylpyrrolidone Films: a sustainable approach to the development of biobased packaging materials. Compos B Eng. 2017; 110: 56-61. [CrossRef]

[38] Song E-H, Jeong S-H, Park J-U, Kim S, Kim H-E, Song J. Polyurethane-silica hybrid foams from a one-step foaming reaction, coupled with a sol-gel process, for enhanced wound healing. Mater Sci Eng C Mater Biol Appl. 2017; 79: 866-874. [CrossRef]

[39] Khan TA, Peh KK, Ch'ng HS. Mechanical, bioadhesive strength and biological evaluations of chitosan films for wound dressing. J Pharm Pharm Sci. 2000; 3(3): 303-311.

[40] Sun F, Nordli HR, Pukstad B, Gamstedt EK, Chinga-Carrasco G. Mechanical characteristics of nanocellulose-PEG bionanocomposite wound dressings in wet conditions. J Mech Behav Biomed Mater. 2017; 69: 377-384. [CrossRef]

[41] Op't Veld RC, Walboomers XF, Jansen JA, Wagener FA. Design considerations for hydrogel wound dressings: Strategic and molecular advances. Tissue Eng Part B Rev. 2020; 26(3): 230-248. [CrossRef]

[42] Kim JO, Park JK, Kim JH, Jin SG, Yong CS, Li DX, Choi JY, Woo JS, Yoo BK, Lyoo WS, Kim JA, Choi HG. Development of polyvinyl alcohol–sodium alginate gel-matrix-based wound dressing system containing nitrofurazone. Int J Pharm. 2008; 359(1-2): 79-86. [CrossRef]

[43] Golafshan N, Rezahasani R, Esfahani MT, Kharaziha M, Khorasani SN. Nanohybrid hydrogels of laponite: PVA-alginate as a potential wound healing material. Carbohydr Polym. 2017; 176: 392-401. [CrossRef]

[44] Awasthi R, Kulkarni GT, Ramana MV, Pinto TdJA, Kikuchi IS, Ghisleni DDM, Braga MS, Bank P, Dua K. Dual crosslinked pectin–alginate network as sustained release hydrophilic matrix for repaglinide. Int J Biol Macromol. 2017; 97: 721-732. [CrossRef]

[45] Yuce-Erarslan E, Tutar R, Izbudak B, Alarçin E, Kocaaga B, Guner FS, Emik S, Bal-Öztürk A. Photo-Crosslinkable chitosan and gelatin-based nanohybrid bioinks for extrusion-based 3D-bioprinting. Int J Polym Mater Polym Biomater. 2021:1-12. [CrossRef]

[46] Lewandowska-Łańcucka J, Mystek K, Mignon A, Van Vlierberghe S, Łatkiewicz A, Nowakowska M. Alginate-and gelatin-based bioactive photocross-linkable hybrid materials for bone tissue engineering. Carbohydr Polym. 2017; 157: 1714-1722. [CrossRef]

[47] Alarçin E, Lee TY, Karuthedom S, Mohammadi M, Brennan MA, Lee DH, Marella A, Zhang J, Syla D, Zhang YS, Khademhosseini A, Jang HL. Injectable shear-thinning hydrogels for delivering osteogenic and angiogenic cells and growth factors. Biomater Sci. 2018; 6(6): 1604-1615. [CrossRef]