PREPARATION, CHARACTERIZATION AND PHARMACOKINETIC RELEASE OF DICLOFENAC SODIUM-DUAL LAYER POLYVINYL ALCOHOL PATCH FOR TRANSDERMAL DELIVERY

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DEDICATION

This thesis especially dedicated to: My loving and understanding husband,
whose sacrificial care for me and our daughters (Amanda, Amani & Ariana)
made it possible for me to complete this study,
My beloved mother, father and in law's family
My strong supportive and dedicated supervisors
My family members
My dearies friend,
Thanks for all the courage and spirit.

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ABSTRACT

Polyvinyl alcohol (PVA) has been broadly used in biomedical applications due to its biocompatibility, non-toxicity, nanofiber and hydrogel-forming ability. Despite these advantages, their structures are easily disrupted due to water absorption (swelling), thus resulting in the burst release of drugs due to drug leaching in transdermal delivery. Therefore, this study mainly aimed to prepare the diclofenac sodium (DS) medicated dual layer PVA patch by a combination of electrospinning and cryogelation (freeze-thaw) methods to reduce the swelling capacity and enhance the physicochemical and mechanical properties with good drug compatibility between the DS and PVA cryogel. Then, to subsequently evaluate the kinetic release mechanism using four different mathematical models. The morphological analysis of the cross-section demonstrates good polymer-polymer interaction between both layers and, fourier transform infrared (FTIR) and x-ray diffraction (XRD) also demonstrate good dispersion and entrapment of DS in the PVA matrix limited to 2% w/v. The DS loads were found to be homogeneously dispersed in the PVA matrix as no visible FTIR spectra of DS-PVA interaction was identified. The crystallinity level of the dual layer PVA patches also increased as the nanofiber thicknesses and freeze-thaw cycles increased. The hydrophilicity of the dual layer PVA patch also decreased, with increases in all other parameters. The DS-medicated dual layer PVA patch labelled as 2%DLB5C shows the lowest percentage of swelling capacity (13.49%). All formulations of the dual layer PVA patch show an enhancement in tensile strength but a decrease in elasticity as the DS percentage loading increases. The 2%DL_A5C and 2%DL_B5C exhibited good mechanical properties with the highest tensile strength (538.19 and 551.73 KPa, respectively), also a lower percentage of elongation and the highest values of elastic modulus. The Franz-diffusion assessment uncovered that the 2%DL_A5C and 2%DL_B5C have better sustainable releases of DS (~49% after 12 hours). The 2%DL_A5C and 2%DL_B5C had a flux (J_{ss}) of 0.220 and 0.231 mg/cm^2/h, respectively, and a permeability coefficient (K_p) value of 0.018 cm/h for both patches. The release of DS for both patches follows the Higuchi and Korsmeyer-Peppas models. Based on these findings, a dual layer PVA patch with thicker nanofiber, higher freeze-thaw cycles, and higher DS loading percentages has lowered the swelling capacity yet improved the physicochemical and mechanical properties and is suitable for transdermal patches. In conclusion, both medicated dual layer PVA patches can complete the release of the DS for up to 24 hours with the one-time application, hence would serve as promising transdermal drug delivery.

ABSTRAK

Polivinil alkohol (PVA) digunakan secara meluas di dalam aplikasi bioperubatan kerana ianya bioserasi, tidak toksik, mudah membentuk nanoserat dan hidrogel. Walaupun mempunyai kelebihan, oleh kerana strukturnya mudah terganggu semasa proses penyerapan air (pembengkakkan), boleh menyebabkan pelepasan mendadak kesan dari ubatan yang melesap keluar semasa penghantaran secara transdermal. Oleh itu, tujuan utama kajian ini adalah untuk menyediakan pelekap berubat natrium diklofenak (DS) dua lapisan PVA melalui gabungan kaedah putaran elektro dan kaedah pembekuan-percairan bagi mengurangkan kapasiti pembengkakan dan menambahbaik sifat fizikokimia dan mekanikal serta keserasian yang baik diantara DS dan PVA. Seterusnya menilai mekanisma kinetik pelepasan ubat menggunakan empat model matematik yang berbeza. Analisis morfologi keratan rentas menunjukkan interaksi polimer-polimer yang baik antara kedua-dua lapisan dan, Fourier transformasi inframerah (FTIR) dan difraksi sinar-x (XRD) juga menunjukkan penyebaran dan perangkap DS yang baik di dalam matriks PVA yang terhad pada muatan 2% w/v. Muatan DS tersebar secara homogen di matriks PVA kerana tiada interaksi spektrum FTIR antara DS-PVA yang dilihat. Tahap pengkristalan dua lapisan PVA juga meningkat apabila ketebalan nanoserat dan bilangan kitaran pembekuan-pencairan meningkat. Sifat hidrofilik dua lapisan PVA juga menurun, akibat dari peningkatan pada kesemua parameter. Pelekap berubat DS dua lapisan PVA yang berlabel 2%DL_B5C menunjukkan peratusan kapasiti pembengkakan terendah (13.49%). Semua formulasi pelekap berubat dua lapisan PVA menunjukkan peningkatan terhadap kekuatan tegangan, tetapi apabila peratusan muatan DS meningkat ia menunjukkan penurunan keanjalan. 2%DL_A5C dan 2%DL_B5C menunjukkan sifat mekanikal yang baik dengan kekuatan tegangan tertinggi (masing-masing 538.19 dan 551.73 KPa), juga peratusan pemanjangan yang lebih rendah dan nilai anjalan modulus yang tertinggi. Penilaian *Franz-diffusion* merungkai bahawa 2%DL_A5C dan 2%DL_B5C mempunyai pelepasan DS yang lebih lestari (~49% selepas 12 jam). 2%DL_A5C dan 2%DL_B5C mempunyai fluks (J_{ss}) masing-masing 0.220 dan 0.231 mg/cm^2/j, dan nilai pekali kebolehtelapan (K_p) 0.018 cm/j untuk kedua-dua pelekap. Pelepasan DS untuk kedua-dua pelekap itu mengikuti model *Higuchi* dan *Korsmeyer-Peppas*. Berdasarkan penemuan ini, pelekap berubat dua lapisan PVA dengan nanoserat yang lebih tebal, serta kitaran pembekuan- pencairan dan peratusan muatan DS yang lebih tinggi terbukti mengurangkan kapasiti pembengkakkan serta meningkatkan sifat fizikokimia dan mekanikal dan sesuai untuk dijadikan pelekap berubat transdermal. Kesimpulannya, kedua-dua formulasi pelekap berubat dua lapisan PVA boleh menghabiskan pelepasan DS sehingga 24 jam dengan sekali penggunaan, dan berfungsi sebagai penghantar ubat transdermal yang diyakini.

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LIST OF ABBREVIATIONS

TDDS	-	Transdermal Drug Delivery System
DS	-	Diclofenac Sodium
NSAIDs	-	Non-Steroidal Anti-Inflammatory Drugs
PVA	-	Poly-vinyl Alcohol
SEM	-	Scanning Electron Microscopy
XRD	-	X-Ray Diffraction
FTIR	-	Fourier Transform Infrared Spectroscopy
WCA	-	Water Contact Angle
UTM	-	Universal Testing Machine
FDA	-	Food and Drug Administration
SC	-	Stratum Corneum
PBS	-	Phosphate Buffered Saline
ASTM	-	American Society for Testing and Materials
UV	-	Ultra-violet
Jss	-	Steady-State Fluxes
K_p	-	Permeability Coefficients
R^2	-	Linear Regression
L	-	Lag Time
GF	-	Gel Fractions
WC	-	Water content
WL	-	Weight loss
UTS	-	Ultimate Tensile Strength
CDR	-	Cumulative Drug Release

LIST OF SYMBOLS

mg	-	Milligram
kV	-	Kilo Volt
h	-	Hour
kPa	-	Kilo Pascal
mPa	-	Mega Pascal
Pa	-	Pascal
mg/ml	-	Milligram Per Milliliter
°C	-	Degree Celsius
$gmol^{-1}$	-	Grams Per Mol
w/w	-	Weight Over Weight
w/v	-	Weight Over Volume
mm	-	Millimeter
cm	-	Centimeter
ml/h	-	Milliliter Per Hour
µm	-	micrometer
N	-	Newton
mm/min	-	Millimeter Per Minute
Å		Ångström
cm^2	-	Centimeter Square
µg/ml	-	Microgram Per Milliliter
λ	-	Lambda

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CHAPTER 1

INTRODUCTION

1.1 Background of Research

The transdermal drug delivery system (TDDS) distributes a particular therapeutic quantity of drugs systemically at locations far from the topical application site for the treatment or prevention of disorders. TDDS is classified as a self-contained with various dosage forms which, when applied to intact skin, it delivers the particular drugs through the skin at a controlled rate to the systemic circulation (Shirsand et al., 2012). Moreover, Alam et al. (2013) stated that TDDS also involves drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect while a very major fraction of drug transported into the systemic blood circulation. In the past decades, TDDS has gained interest in order to develop innovative formulation and application methods for improving drug specificity by modifying appropriate material to a therapeutic agent.

The major advantages of the transdermal route are the constant drug dosage that is available and maintained in the circulation due to its sustained release properties (Alkilani et al., 2015). According to Patel et al. (2011), TDDS compared to conventional pharmaceutical dosage forms, such as oral tablet, pills, capsule and injection, exhibits a great potential in avoiding hepatic first-pass metabolism, maintaining constant blood levels for more extended period, decreasing side effects, improved patient acceptability and compliance. As stated by Raja et al. (2017), transdermal patches have gained popularity as an effective analgesic modality, owing to advantages such as ease of application; reduced risk of dose dumping compared with cream, ointment, and gel forms of topical delivery; constant and duration of action; self-administration capability; and ease of termination. Transdermal patch has several components including liners, adherents, drug reservoirs, drug release membrane which play a vital role in the drug's release via the skin.

Diclofenac Sodium (DS) is advocated for the treatment of painful and inflammatory rheumatic and certain non-rheumatic conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendinitis, and bursitis, and in other inflammatory or painful conditions such as strains and sprains, dysmenorrhea, back pain, sciatica, and postoperative pain (Kołodziejska and Kołodziejczyk, 2018).

DS and paracetamol (acetaminophen) are either pain relievers, or analgesics, and can reduce fevers. They differ in numerous ways, however, such as in their drug classification and strength. DS also has pain-relieving and fever-reducing properties, but it belongs to a special class of drugs called non-steroidal anti-inflammatory drugs (NSAIDs). The NSAIDs patches are safer and convenient than its oral form. The side effects like stomach bleeding, increased acidity, ulcers are avoided by using transdermal patches of NSAIDs. The analgesic patch of NSAIDs may be used on the site of bruise, sprain or strain. This class of medicines is more useful in controlling swelling from injury. Such anti-inflammatory properties are not characteristic of paracetamol. A study by Malhotra et al. (2013) stated that diclofenac is considered a stronger drug than paracetamol with a lower dosage.

Polymers are the main component of TDDS and advances in polymer sciences have facilitated the design of different transdermal delivery systems with considerable flexibility using natural, synthetic and semi-synthetic polymers to control the release of drug through the intact skin (Akhtar et al., 2020). Polymer selection and design must be considered when striving to meet the diverse criteria for the fabrication of effective transdermal delivery systems. Previous study by Vasile (2020) has mentioned that the polymers used for TDDS could be classified as natural polymers includes cellulose derivatives, gelatin, waxes, natural rubber and chitosan, while synthetic polymers such as poly-vinyl alcohol (PVA), poly-vinyl chloride (PVC), poly-ethylene (PE), poly-propylene (PP), poly-acrylate (PLA), polyamide (PA), polyurethane (PU), poly-vinyl pyrrolidone (PVP), poly-methyl methacrylate (PMMA) etc. However, natural polymers also have some limitations including weak mechanical properties, poor processability, rapid degradation rate and potential immunogenic properties (He et al., 2014).

Hydrogels are defined as materials that are three-dimensional (3D), cross-linked hydrophilic polymer which capable of imbibing a large amount of water or biological fluids and thereby swell (Hoffman, 2012; Monica, 2018). Hydrogels are synthesized using cross-linking networks and can be categorized into three types: physically cross-linked (self-assembled hydrogel), chemically cross-linked, and irradiation cross-linked (Sharma and Tiwari, 2020). PVA is consist of secondary alcohol group connected to a linear carbon chain which is synthesized through hydrolysis of polyvinyl acetate via free radical polymerization of vinyl acetate. (Hassan and Peppas, 2000). PVA is a hydrogel-forming polymer with great interest because possess many desirable characteristics such as neutral, chemical resistance, drug compatibility, non-toxic, non-carcinogenic, bio-adhesive, water-soluble, biodegradability, also exhibit good swelling and physicochemical and mechanical (rubbery and elastic nature) properties, therefore closely simulates natural tissue and can be readily accepted into the body (Hernández et al., 2021; Yang et al., 2004). The previous study also proved that PVA hydrogels prepared at high polymer concentration or under the conditions enhancing mechanical properties would display good viscoelastic properties (Nkhwa et al., 2014; Muppalaneni and Omidian, 2013). Therefore, PVA is extensively used in industrial, biomedical and pharmaceutical applications (Vasanthan et al., 2015; Abitbol et al., 2011 and Keishiro et al., 2014).

To prevent potential toxicity, and the amount of residual cross linker left in the final polymer due to the use of chemical crosslinker, hydrogel produced by the cryogelation (freezing and thawing) process, commonly called a cryogel is used. According to Wankei et al. (2014), the freezing-thawing technique can produce stable physically cross-linked cryogel which resulted from crystalline formations via the interaction of intra and intermolecular hydrogen bonds. It also exhibits higher mechanical strength than the one that obtained using Ultra-Violet (UV) radiation as the cross-linking agent, as mentioned by Gibas and Janik, (2010).

On the other hand, Opanasopit et al. (2012) claimed that electrospinning is the most cost-effective method with simple tooling that uses electrostatic forces to produce electrospun membrane nanofibers with unique characteristics including ultrafine structure, a large surface-area-to-volume ratio, and a high porosity with a small pore

size ranging from submicron to nanometer sizes. Recently, electrospinning techniques gain interest in transdermal drug delivery because of the characteristics mentioned. This supported by Rives et al. (2017) in their studies emphasized that one of the apparent advantages of the electrospinning process compared to conventional film-casting techniques is the highly porous structure of electrospun nanofiber membrane, which exhibits a much higher surface area that allow drug molecules to diffuse from the matrix more effectively.

According to a prior study by Craciun et al. (2019), for a matrix to be employed as a drug delivery system in the medical area, it must exhibit specific features such as biocompatibility, biodegradability, and the ability to form strong forces with the drug in order to prolong its release, regardless of their physicochemical and pharmacological form (Mircioiu et al., 2019). A previous study by Dash et al. (2010) stated that the use of in vitro data on drug dissolution to anticipate *in vivo* bio-performance could be considered rational formulation development for controlled release formulations. The release profile is critical in determining the efficacy of a dose formulation, especially when the controlled release rate of the drug is the main focus. Not only are experimental methods time-consuming, but they are also expensive.

The application of mathematical modelling proved to be very effective in the research of the drug release mechanism. It facilitates in the design of the delivery system over a specified time period, predictions of drug release rate, and determines when the next dosage should be given (Permanadewi et al., 2019). Additionally, mathematic modelling eliminates the need for extensive experimental research. By comparing release data to mathematical models, the physical process of drug release can be determined. This study can predict the effects of design parameters such as shape, size, and composition on the overall level of drug release and accurately predict the drug release profile, thereby improving the drug's overall therapeutic effectiveness and safety (Shaikh et al., 2015). It is also a fundamental tool for designing pharmaceutical formulations, evaluating drug release processes in vitro and in vivo, and determining the optimal design strategy (Peppas and Narasimhan, 2014). Multiple models have been developed to characterize the rate of drug release from various drug delivery systems. Some of important models are, Zero order kinetic model, First order

kinetic model, Higuchi model, Korsemeyer-peppas model (Bhasarkar and Bal, 2019; (Muthappa et al., 2020; Mohamed and Damodharan, 2020). The precise combination of experiment results and models that enable the acquisition of the underlying physics will provide insight into the mechanism of release.

Currently, this research goal is to prepare the drug compatible and cost-effective dual layer PVA patch by using a combination of electrospinning method and cryogelation of PVA via casting and freeze-thaw techniques with an enhancement of its physicochemical and mechanical properties and assess the pharmacokinetic of *in-vitro* DS released by using Franz-diffusion test and to recognize the best fitted mathematical kinetic models (Zero-order, First-order, Higuchi model and Korsmeyer-Peppas model) for potential transdermal DS delivery.

1.2 Problem Statements

To generate a therapeutic impact, conventional oral drug administration generally requires high doses or repeated administration, which can reduce overall efficacy and patient compliance, resulting in missed doses of drugs with a shorter half-life, significant side effects, and even toxicity (Li and Mooney, 2016; Liechty et al., 2010). The previous study by Florence and Jani (1994) proved that oral administration, the most common approach for delivering pharmaceuticals, is frequently limited by poor targeting and short circulation times (<12 hours). Also, research by Priyanka et al. (2018) claimed that the oral form drug undergoes substantial hepatic first-pass metabolism and only about 50% of the administered dose reaches the systemic circulation, besides liver damage is an unfortunate side effect of many soluble tablet drugs. The injection mode of delivery can be used to deliver any size of the drug molecule and is versatile in this regard but suffers from the obvious disadvantage of being invasive and painful. Furthermore, for Rheumatoid Arthritis, patients are advised to take the DS for prolong period, but the side effects such as systemic toxicity, gastrointestinal tract (GIT) irritation, nausea, vomiting, gastric erosion, headache are the main drawbacks of DS.

In general, the hydrogel delivery systems need to preserve the drug bioactivity, and through packaging, transport and storage, both the drug and hydrogel must be chemically and physically stable. As reported by Kenawy et al. (2010), traditional methods for crosslinking, particularly the chemical crosslinking method which uses crosslinking agents, have a side effect on the drugs loaded and on the final applications from the residual crosslinking agent in the hydrogel formed. The majority of chemical crosslinkers utilized in hydrogels have some level of toxicity and biocompatibility, limiting their biological applications (Chaturvedi et al., 2015; Rodríguez-Rodríguez et al., 2020; Omidian and Park, 2010). Thus, hydrogels that are biocompatible, biodegradable, non-toxic, and have a high mechanical strength are highly sought for a wide variety of biomedical applications.

PVA is known as a non-toxic polymeric material that possesses the capability of swelling and retains a certain high amount of water within its structure. Because of its linear polymer in nature, it has to be cross-linked into hydrogel either chemically or physically for the application of the transdermal drug delivery. Considerable interest has arisen from the preparation PVA cryogel as a drug carrier using the freezing-thawing techniques (cryogelation) which had been applied to avoid chemical crosslinking of PVA with the ensuing toxicity and leaching problems (Jensen et al., 2016 and Jaya et al., 2014). A study by Muppalaneni and Omidian (2013) proved that the high-water content of PVA hydrogels results in relatively rapid release of drugs in a short period from the gel matrix, particularly with hydrophilic drugs.

Previous investigations by Vitaliy and Khutoryanskiy (2015), have reported that those created by physical crosslinking are able to swell and load various drugs, but that most of them degrade rapidly over time. This is supported by Taepaiboon et al. (2006) claimed that, as the PVA matrix expanded in shape, molecules drugs were solvated and practically leached out from the matrix rapidly which somehow cause toxic to the body. Prior research has also concentrated on combining two polymers in order to increase the stability of their physical and mechanical properties. According to Figueroa-Pizano et al. (2020), the combination of chitosan and PVA cryogel after 6 freeze-thaw cycles rapidly absorbed large amounts of water during swelling assays; they retained up to 10x their weight after 5 hours and up to 15x their weight after 20

hours. On the other hand, those developed by chemical cross-linking have greater durability but a degradation rate that is often insufficient for in vivo applications (Peppas et al., 2000).

A study by Rives et al. (2017) emphasized that one of the apparent advantages of the electrospinning process compared to conventional film-casting techniques is the highly porous structure of electrospun nanofiber membrane, which exhibits a greater surface area that might allow drug molecules to diffuse from the matrix to the skin more efficiently. However, although electrospun PVA nanofiber has such excellent properties, it has been reported in the literature that the use of electrospun PVA nanofiber membranes in various applications has often been avoided due to their poor mechanical properties and possess relatively low dimensional stability, which limits their use in some applications (Rianjanu et al., 2018). According to a previous study conducted by Hindi et al. (2021), PVA nanomedical self-disappearing patches containing DS were completely dissolved after 3 hours. This occurs as a result of the PVA's great hydrophilicity. Several methods such as reinforcing nanofibers with other cellulose nanocrystals (Peresin et al., 2014), syntactic foam (Colloca et al., 2013), well-aligned cellulose (Cai et al., 2016). However, these methods have been complex and costly.

To author knowledge, the combination of electrospinning and cryogelation techniques for TDDS not yet been scrutinized. Thus, in this research, the combination of cryogel and electrospinning of PVA via casting and freeze-thaw techniques as a dual layer patch will reduce the swelling capacity due to the physical interaction of hydrogen bonds between the cryogel and nanofiber, thereby overcome the burst effect of the initial DS release and improving the physicochemical and mechanical stability of the dual layer PVA patch. For this experimental work, the challenge is to optimize the formulation of the dual layer PVA patch, in terms of physicochemical and mechanical properties and pharmacokinetics of DS released of the dual layer PVA patch.

1.3 Research Objectives

The objectives of this research are:

a) To prepare the unmedicated and diclofenac sodium (DS) medicated-dual layer PVA patch using combined methods of electrospinning and cryogelation of the PVA via casting and freeze-thaw techniques.
b) To characterize the morphological structures, physicochemical and mechanical properties of the prepared unmedicated and DS-medicated dual layer PVA patches.
c) To investigate and assess the effect of electrospun nanofiber thicknesses, freeze-thaw cycles and DS loading percentages on the properties of the unmedicated and DS-medicated-dual layer PVA patches.
d) To evaluate the *in-vitro* DS release of the DS medicated-dual layer PVA patch and pharmacokinetic release using four different mathematical kinetic models.

1.4 Scope of Study

In this study:

a) Preparation of a dual layer PVA patch using a combination of electrospun PVA nanofiber and PVA cryogel via casting and freeze-thaw techniques, at three different DS loading percentages of 1.0, 1.5, and 2.0 percent w/v of PVA solution, with three and five freeze-thaw cycles, and two different nanofiber thicknesses (2ml and 3ml of PVA running volume).

b) Following that, the dual layer PVA patch is characterized using several physicochemical and mechanical instruments, including scanning electron microscopy (SEM) for microscopic analysis, X-ray diffraction (XRD) for crystalline phase analysis, Fourier Transform Infrared spectroscopy (FTIR) to analyze the drug-polymer compatibility and stability, water contact angle (WCA) and swelling in aqueous medium for hydrophilicity observations, and

the Universal Testing Machine (UTM) to identify the ultimate tensile strength, the Young's modulus and percentage of elongation. Thereafter, the amount of in vitro DS released from the prepared patch was determined using a Franz-diffusion cell, and 1.5 ml of DS was taken from the receptor chamber at periodic intervals and then measured using a UV-visible spectrophotometer to determine the cumulative percentages of drug release (% CDR) for each formulation

c) Ultimately, the pharmacokinetic profiles of the DS medicated dual layer PVA patch were predicted using four distinct mathematical models (zero-order, first-order, Higuchi, and Korsmeyer-Peppas).

1.5 Significance of Study

Through this research, the preparation of the biocompatibility and cost-effective dual layer PVA patches using a combination of both electrospinning process and cryogelation process (freeze-thaw cycles) that enhances the physicochemical and mechanical properties to facilitate the drug release from the dual layer PVA patch. Moreover, this DS medicated-dual layer PVA patch improves the efficacy of DS release and provides advantages over conventional oral forms by optimizing pharmacokinetic properties for transdermal DS delivery.

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LIST OF PUBLICATIONS

Journal with Impact Factor

1. **Sa'adon, S**., Ansari, M.N.M., Razak, S.I.A.; Anand, J.S., Nayan, N.H.M., Ismail, A.E., Khan, M.U.A. and Haider, A. (2021) 'Preparation and Physicochemical Characterization of a Diclofenac Sodium-Dual Layer Polyvinyl Alcohol Patch', *Polymers*, 13, 2459. https://doi.org/10.3390/polym13152459 **(Indexed by ISI-WOS, Q1: IF 4.329)**
2. **Sa'adon, S**., Ansari, M.N.M., Razak, S.I.A., Yusof, A.H.M., Faudzi, A.A.M., Sagadevan, S., Nayan, N.H.M., Anand, J.S. and Amin, K.A.M. (2021) 'Electrospun Nanofiber and Cryogel of Polyvinyl Alcohol Transdermal Patch Containing Diclofenac Sodium: Preparation, Characterization and In Vitro Release Studies', *Pharmaceutics,* 13, 1900. https://doi.org/10.3390/pharmaceutics13111900 **(Indexed by ISI-WOS, Q1: IF 6.321)**

Indexed Journal:

1. **Sa'adon, S.**, Razak, S.I.A, Ismail, A.E. and Fakhruddin, K. (2019) 'Drug-Loaded Poly-Vinyl Alcohol Electrospun Nanofibers for Transdermal Drug Delivery: Review on Factors Affecting the Drug Release', *Procedia Computer Science*, 158, pp. 436-442. doi: 10.1016/j.procs.2019.09.073. **(Indexed by SCOPUS)**

2. **Sa'adon, S.**, Razak, S.I.A, Ismail, A.E. and Fakhruddin, K. (2019) 'Fabrication of Dual Layer Polyvinyl Alcohol Transdermal Patch: Effect of Freezing-Thawing Cycles on Morphological and Swelling Ability', *Procedia Computer Science*, 158, pp. 51–57. doi:10.1016/j.procs.2019.09.027. **(Indexed by SCOPUS)**

Indexed Conference Proceedings:

1. **Sa'adon, S.**, Razak, S.I.A, Ismail, A.E., Nayan, N. M. H., and Fakhruddin, K. (2019). Influence of Diclofenac Sodium Loading on Physicochemical and Mechanical Properties of Dual Layer Polyvinyl Alcohol Transdermal Patch. Journal of Physics: Conference Series, Volume 1372, International Conference on Biomedical Engineering 26-27 August 2019, Penang Island, Malaysia. 1372, 012049. doi:10.1088/1742-6596/1372/1/012049. **(Best Paper Award) (Indexed by SCOPUS)**

2. **Sa'adon, S.**, Razak, S.I.A., Fatirah, F. and Nayan, N. M. H. (2018). Review on cellulose nanocrystals (CNCs) as reinforced agent on electrospun nanofibers: mechanical and thermal properties, The International Fundamentum Sciences Symposium 2018 proceedings. IOP Conf. Series: Materials Science and Engineering, 440, 012011. doi:10.1088/1757-899X/440/1/012011. **(Indexed by SCOPUS)**