DEVELOPMENT OF POLYMERIC NANOCOMPOSITE HYDROGEL USING POLY (VINYL ALCOHOL) REINFORCED WITH ORGANICALLY-MODIFIED LAYERED DOUBLE HYDROXIDES FOR DRUG DELIVERY SYSTEMS

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by

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LIST OF ABBREVIATIONS AND SYMBOLS

°C	Degree Celsius
APS	Ammonium Persulfate
ASTM	American Society for Testing and Materials
BuOH	Butanol
cm	centimetre
cm^3	centimetre cubic
DLS	Dynamic Light Scattering
DMSO	Dimethyl sulfoxide
DS	Degree of swelling
DSC	Differential Scanning Calorimetry
EtOH	Ethanol
FTIR	Fourier Transform Infra-Red
H	hour
Ise	Sodium isethionate
KPS	potassium persulfate
L	Litre
M	Molar
mg	Milligram
ml	Millilitre
mm	Millimetre
mmol	Millimolar
mPa	Megapascal
MRSA	Methicillin-resistant *Staphylococcus aureus*

N_2	Nitrogen
NaOH	Sodium Hydroxide
NCH	Nanocomposite Hydrogel
nm	Nanometre
PBS	Phosphate Buffer Solution
pH	Power of Hydrogen
PVA	Poly (Vinyl alcohol)
PVA-NCH	Polyvinyl Alcohol Nanocomposite Hydrogel
rpm	rotation per minute
SA	Salicylic Acid
SDS	Sodium Dodecyl Sulfate
SEM	Scanning Electron Microscopy
TEM	Transmission Electron Microscopy
TGA	Thermogravimetric Analysis
v/w	volume per weight
v/v	volume per volume
wt./wt.%	weight per weight percentage
XRD	X-ray Diffraction
YM	Young's Modulus
σ	Stress
E	Strain
Tan δ	index of Material Viscoelasticity

PENGHASILAN HIDROGEL KOMPOSIT NANO MENGGUNAKAN POLIVINIL ALKOHOL (PVA) DENGAN PENAMBAHBAIKAN OLEH SEBATIAN TERSISIP HIDROKSIDA BERLAPIS GANDA (LDH) YANG DIUBAHSUAI SECARA ORGANIK SEBAGAI SISTEM PENYAMPAIAN UBAT

ABSTRAK

Bahan termaju daripada polimer polivinil alkohol (PVA) yang berpotensi untuk digunakan sebagai bahan untuk sistem penyampaian ubat telah dihasilkan dengan penambahbaikan oleh sebatian tersisip hidroksida berlapis ganda (LDH) menggunakan dua jenis surfaktan organik iaitu sodium dodesilsulfat (SDS) dan sodium isethionat (Ise) melalui kaedah sintesis pemendakan serentak. Untuk SDS-LDH, pH optimum sintesis ialah pH 9 dan kepekatan SDS yang digunakan hanyalah 3 kali ganda jumlah garam aluminium nitrat. Manakala untuk sintesis Ise-LDH, pH 10 digunakan dalam sintesis pengubahsuaian pada kepekatan surfaktan yang sama. Sebatian tersisip hidroksida berlapis ganda ini kemudiannya dimasukkan ke dalam campuran polimer polivinil alkohol (PVA). Untuk penghasilan hidrogel komposit nano (PVA-NCH), proses pembelahan dilakukan untuk menambahbaik interaksi antara kepingan nano sebatian tersisip hidroksida berlapis ganda dengan rantaian polimer PVA. Dua jenis hidrogel komposit nano (PVA-NCH) berjaya dihasilkan: satu bahan menggunakan SDS-LDH (PVA-NCH 1) dan satu lagi menggunakan Ise-LDH (PVA-NCH 2). Pengoptimuman sebatian tersisip hidroksida berlapis ganda menunjukkan 0.1% (w/w %) didapati berkesan dalam menambahbaik sifat-sifat bahan hidrogel komposit nano. Untuk kedua-dua penghasilan PVA-NCH, sampel dengan 0.1% (w/w %) sebatian tersisip hidroksida berlapis ganda dipilih sebagai bahan untuk diuji dalam pelepasan molekul ubat asid salisilik (SA). Peratusan pengembangan hidrogel masing-masing direkodkan pada nilai 110 ± 24 % and 245 ± 35 % untuk PVA-NCH 1 dan PVA-NCH 2. Nilai-nilai ini adalah yang paling

tinggi jika dibandingkan dengan sampel lain yang berkepekatan berbeza. Ujian tegangan menunjukkan PVA-0.1% SDS-LDH mempunyai nilai modulus Young yang paling tinggi iaitu 0.78 ± 0.2 MPa manakala untuk PVA-NCH 2, PVA-0.1% Ise-LDH juga menunjukkan nilai yang baik iaitu 287 ± 63 MPa. Untuk PVA-0.1% Ise-LDH, data ini sangat memberangsangkan kerana bernilai sepuluh kali ganda berbanding nilai modulus untuk sampel kawalan yang direkodkan pada 29 ± 2.8 MPa. Data menunjukkan bahawa pada kepekatan yang rendah, penambahan sebatian tersisip hidroksida berlapis ganda berupaya menambahbaik sifat kekuatan bahan hidrogel komposit nano tanpa menurunkan sifat pengembangannya. Kemudiannya, penambahan asid salisilik (SA) telah dilakukan untuk PVA-NCH melalui dua cara: pemuatan akhir untuk PVA-NCH 1 dan pemuatan serentak untuk PVA-NCH 2. Untuk kajian kinetik pelepasan molekul ubat SA, kedua-dua sistem selari dengan model pelepasan kinetik pseudo kedua dengan tambahan data: untuk PVA-NCH 1, data pelepasan SA juga adalah selari dengan model pelepasan molekul ubat Susunan Pertama (R^2=0.9904), manakala untuk pelepasan PVA-NCH 2, data menunjukkan bahawa pelepasan SA juga adalah sejajar dengan model pelepasan molekul ubat oleh Higuchi (R^2=0.9979). Melalui kajian ini, PVA-NCH yang digabungkan dengan SA berpotensi untuk digunakan sebagai bahan tampalan berubat untuk rawatan luka.

DEVELOPMENT OF POLYMERIC NANOCOMPOSITE HYDROGEL USING POLY (VINYL ALCOHOL) REINFORCED WITH ORGANICALLY MODIFIED LAYERED DOUBLE HYDROXIDES FOR DRUG DELIVERY SYSTEMS

ABSTRACT

A new advanced polymeric material with a potential for drug delivery systems was developed using the versatile poly (vinyl alcohol), PVA, enhanced with layered double hydroxides (LDH) organically modified with sodium dodecyl sulfate (SDS) and sodium isethionate (Ise) *via* co-precipitation method. For SDS-LDH, the optimum condition was pH 9 and the concentration of SDS used was only 3 times the ratio of aluminum nitrate salt. Whereas for Ise-LDH, pH 10 was proven to be able to reduce the amount of Ise needed for the intercalation into LDH. The chosen intercalated compounds were then further incorporated into PVA matrix for the development of nanocomposite hydrogel (PVA-NCH). Delamination is employed to improve the interaction between the single nanosheets of the modified LDH with the polymer chains of PVA. Two types of PVA nanocomposites were produced: one with SDS-LDH (PVA-NCH 1) and another with Ise-LDH (PVA-NCH 2). The optimization for the incorporation of modified LDH was carried out and it was observed that 0.1% (w/w %) of modified LDH was sufficient in improving the properties of the nanocomposite hydrogel. For both cases of PVA-NCH, ones with 0.1% amount of modified LDH were selected as the working materials for the further application with salicylic acid (SA). Swelling percentages were recorded at 110 ± 24 % and 245 ± 35 % for PVA-NCH 1 and PVA-NCH 2, respectively. These values are the highest as compared to their counterparts. Tensile test showed that for PVA-0.1% SDS-LDH, the value of Young Modulus was highest, recorded at 0.78 ± 0.2 MPa. PVA-0.1% Ise-LDH also shows the highest strength value, recorded at 287 ± 63 MPa, which is remarkably a high value: a tenfold value compared to its control *i.e.,* 29 ± 2.8 MPa. This result shows the

excellent improvement to mechanical property of a material due to a small amount of modified filler, without costing the swelling properties. Next, the incorporation of SA was done *via* two methods: post loading for PVA-NCH 1 and *in-situ* loading for PVA-NCH 2. For both systems, the drug release follows and pseudo-second order with an additional pattern followed: for PVA-NCH 1, release data indicated that it follows first order model. For PVA-NCH 2, it also follows Higuchi model. In this research, PVA-NCH incorporated with SA has good potential to be applied as medicated patches for wound dressing treatment.

CHAPTER 1

INTRODUCTION

1.1 Background Research

Dispersion of LDH has been studied in polymers but delamination is hardly achieved. In this thesis, delamination is the main objective to improve the interaction between LDH and the polymer chosen to apply as possible drug release matrix, producing a new nanocomposite material. The study explores the ability of the nanocomposite hydrogel as a matrix for drug delivery. Throughout the thesis, this material will be termed as hydrogel nanocomposite (NCH) and is aimed to be used as transdermal patches with the unique composition and fabrication method.

Generally, transdermal patches for wound dressing are constructed to be multi-layered and single-dose pharmaceutical preparations (Suksaeree *et al.*, 2021). A commonly available solid adhesive transdermal patch in the market comprises several components: backing layer, liner, reservoir or polymeric matrix with the incorporated active substance, and a rate controlling membrane (Hadžiabdić *et al.*, 2021). Different polymers are usually selected to make those components to allow the modifications over the mechanical and adhesive properties of the transdermal patch. These patches are made to be able to release specific active substances through various mechanisms. In this thesis, selection of PVA as the main polymer matrix is carried out. It is estimated that PVA, a versatile polymer, can act as a single layer transdermal patch for an efficient delivery drug of choice.

Most articles on the development of nanocomposite 3D matrices only emphasized on the mechanical and thermal properties of the material developed. The study into utilization of this advanced product as a prospect wound dressing material

is not thoroughly discussed and investigated. The research is aimed to provide the sufficient data regarding both physicochemical and kinetic study on the developed material of nanocomposite hydrogel. The study is also carried out to discuss the factors affecting the kinetic of the drug from the developed material.

1.2 Scope of Research and Problem Statements

The development of PVA composite hydrogels using freeze-thawing method required several cycles and this makes the fabrication process tedious. Therefore, there is a need to find ways to reduce the cycle of freeze-thawing by incorporating synthesized nanoparticles. It is hypothesized that the incorporation of modified nanoparticles can reduce the freeze-thawing cycles into 3 times only with superior mechanical properties of the nanocomposite hydrogels while maintaining the good swelling properties.

The synthesis of nanoparticles is going to be done using several types of surfactants as the organic modifiers. The modified LDHs will be subjected to delamination in suitable solvents. It is known that DMSO is the alternative to the common solvent for delamination of nanoparticles. We hypothesized that the utilization of DMSO is sufficient to render modified LDHs into single sheets during delamination attempts as to increase the interaction of LDHs and PVA chains. Water is another solvent of choice to delaminate the modified LDHs. It is hypothesized that the modified LDHs can be delaminated at a certain degree in water solvent.

PVA composite hydrogels are mechanically weak hence limiting its application in biomedicine. The incorporation of modified nanoparticles is expected to increase its mechanical properties of the fabricated PVA nanocomposite hydrogels. It is hypothesized that the incorporation of low concentration of nanoparticles will greatly enhance the strength of the nanocomposite material produced.

The nanoparticles are to be incorporated into PVA matrix using different variables (types of delaminating solvents, nanoparticle concentrations and method of addition). The properties of the produced nanocomposite hydrogels are then described *via* several testing for characterizations. The mechanically enhanced nanocomposite material will be further incorporated with selected drug molecules and the release kinetics of the drug will be examined and analysed. Drugs are incorporated using different methods with different drug concentrations.

The importance of this research is to extend the applicability of PVA nanocomposites which – based on literature – has limited application in biomedicine especially as a drug delivery system. This is due to its weak mechanical properties and its inability to carry drug molecules of higher molecular weight. Based on the literature, it can be observed that the utilization of LDH is limited to either nanofiller (polymer) or intercalants (drug release). No study focuses on the usage of LDH or its modified components as a nanofiller and intercalants at the same time.

Therefore, this research is carried out in the attempt to observe the effects of modified LDH in polymer which acts as a nanofiller for the polymer reinforcement, while at the same time acts as a drug intercalant for drug release. This synergistic effect is expected to be observed at the end of the research as justified by the data obtained. This research serves as a basis for the prospect of PVA nanocomposite as the drug delivery system for a wide array of drugs. In literature, not many past researchers delved into understanding the mechanisms of drug delivery using PVA as matrix with modified LDH as its reinforcing component. Hopefully this research will shed some light on the ability of PVA hydrogel and its capacity to be applied as a slow drug release system.

1.3 Objectives of Research

The objectives of the research are:

1. To identify the effect of adding layered double hydroxides (LDH) into polymer/combination of polymers for the development of nanocomposite materials.
2. To investigate the effects of LDH intercalation with chosen organic molecules for the formulation of nanocomposite materials.
3. To examine the delamination mechanism of LDH and intercalated LDHs in various solvents for different polymeric systems. DMSO poses several hazards upon application due to reported toxicity to human cornea upon dermal contact (Galvao *et al.*, 2014) but in this study, this solvent served as the better alternative to formamide and is removed the end of the process presumably through evaporative casting).
4. To improve the interaction of the delaminated LDH with polymer/combination of polymers.
5. To analyse and critically discuss the release kinetics of the selected drug in the nanocomposite materials of different polymers *via* transdermal drug delivery system for controlled release of salicylic acid as the selected drug.

1.4 Expected Outcomes

1. To create a fast and easy method to intercalate surfactants into LDH for delamination in suitable solvents. The choice of the solvents to be used must be green and non-toxic. The method chosen must be able to produce synthesized products at high yield.
2. To delaminate the organically modified surfactant using fast method in suitable solvents for increased interaction with polymers. The method is expected to produce delaminated LDHs using simple yet effective procedures.
3. To achieve fabricated LDH nanocomposite materials from suitable selection of polymer/polymer combination with enhanced properties for the development of materials for biomedicine applications. Usage of PVA as a polymer matrix is carried out due to its versatile nature and diverse utilizations in the field of biomedicine.
4. To obtain improved drug release efficiency of the formulated nanocomposite materials for drug delivery applications. The drug release kinetics of the selected drug type is expected to show the best properties due to the interaction of the selected polymer with the modified nanofiller LDHs.
5. To investigate synergistic advantages provided by the complex network of PVA molecules and LDHs nanosheets when organically modified LDHs are employed as crosslinking agents in PVA matrix.

CHAPTER 2

LITERATURE REVIEW

2.1 Nanocomposite

Nanocomposite is a class of hybrid materials with a promising future. Polymer nanocomposites are a class of hybrid materials composed of an organic polymer matrix with dispersed inorganic fillers that have at least one dimension in the nanometre range (Benaddi *et al.*, 2016). This class of material is made up of polymer mixed with inorganic clays or oxides at the nanoscale level (Wahid *et al.*, 2018). It combines several separate components with the aim to achieve the best attributes of each component for better performance or application.

Nanocomposites are generally categorized into three classes *i.e.,* ceramic-matrix, metal-matrix, and polymer-matrix (Chen *et al.*, 2015; Uozumi *et al.*, 2008). The latter class of organic/inorganic nanocomposites *i.e.,* polymer-matrix nanocomposites has become an area of interest among scientists and material researchers/engineers. Research on enhancement of materials using the nanoparticles as the reinforcing agents keeps on increasing over past decades. One example of the production of nanocomposites involves the *in-situ* polymerization of the organic monomer with the presence of an inorganic counterpart in a simultaneous reaction (Okpala, 2013).

To produce organic-inorganic polymer hybrid materials, there are several fabrication routes including blending processes, sol-gel methods, emulsion polymerization, photopolymerization, intercalation, microwave-assisted, electrochemical synthesis, synthetic routes (surface grafting), and self-assembly (Krasia-Christoforou, 2015). These organic-inorganic polymer hybrids have many

applications in various fields including biomedicine, sensing, environmental remediation, energy, construction, automotive and coating technologies, catalysis, and optoelectronics (Krasia-Christoforou, 2015).

Inorganic layered materials possess well-defined, ordered interlamellar space which can be incorporated with foreign species (Pisson *et al.*, 2003). This property rendered them applicable hosts or matrices for polymers, producing remarkable hybrid of nanocomposite materials (Okpala, 2013). Nanocomposite materials with layered inorganic compounds fall under two categories *i.e.* intercalated and exfoliated (Okpala, 2013). Exfoliated nanocomposites are more interesting due to their reported superior mechanical properties (Chen *et al.*, 2004; Haraguchi *et al.*, 2003; Wang *et al.*, 2005).

Development of nanocomposite involves various scientific disciplines (including material science, biology, chemistry, and physics) in order to produce new materials with superior properties for instance in the fabrication of biomedical products and high-performance materials (Okpala, 2013). Among the prominent application of nanocomposites is as a biomaterial in the emerging field of tissue engineering which aims to boost and restore the biological functions of damaged tissues in the form of 3D scaffolds (Wahid *et al.*, 2018). Table 2.1 shows the combination of different polymer matrices with nanofillers for the fabrication of nanocomposite for various applications in biomedicine.

Table 2.1 Applications of polymer matrix with different nanofillers.

Polymer matrix	**Nanofillers**	**Application of nanocomposites material**
Polyacrylamide (PAM)	Layered double hydroxides (LDH)	Hydrogels for biomedical and industrial application (Hu & Chen, 2014)
Poly (N-isopropylacrylamide) (PNIPAM)	Laponite	Soft material for cell culture and tissue engineering (Haraguchi, 2012)
Poly (N-isopropylacrylamide) (PNIPAM)	Gold nanoparticles	Photo-controlled drug carrier for biomedical applications (Qin *et al.*, 2017)
Gellan gum	Titanium dioxide (TiO_2)	Hydrogel film for wound dressing application (Ismail *et al.*, 2019)
Poly(N-isopropylacrylamide) /polyethylene oxide	Silver nanoparticles	Prospect material in biomedicine (drug-delivery matrices) (Abd El-Mohdy, 2013)
Alginic and hyaluronic acids gel	Iron oxide, silver, and hydroxyapatite	Potential material for an injectable therapeutic scaffold (bone and tissue regeneration) (Ivashchenko *et al.*, 2020)

There are various systems for nanocomposites *e.g.,* multidimensional (1D, 2D, 3D) and amorphous materials which are made of several different components which display various characteristics, with dimension less than 100 nm (Okpala, 2013). In the development of nanocomposite materials, inorganic nanoparticles like carbon nanotubes and clays exhibited a crucial role as fillers in the polymeric matrix. The incorporation of these materials serves to enhance the properties of the nanomaterials to function more effectively for the intended applications.

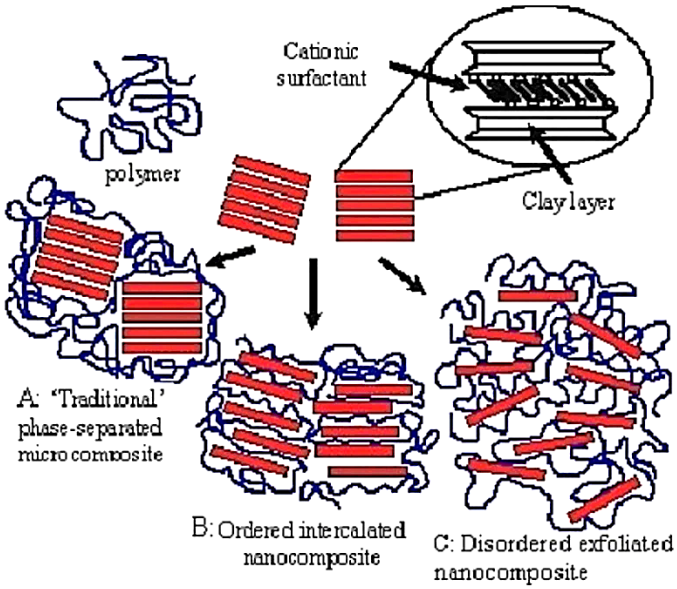

Figure 2.1 Types of nanocomposites using layered 2D nanoparticles: (a) phase-separated micro-composite; (b) ordered intercalated nanocomposites; and (c) disordered exfoliated nanocomposites.

The final type of the fabricated nanocomposite depends on the pre-treatment of the incorporated nanoparticles. Figure 2.1 shows the classification of 2D clay-polymer–nanocomposite based on the different pre-treatment methods of the nanoparticles during their incorporation. When using 2D clay nanoparticles like LDH in the production of nanomaterials, three types of nanocomposites will be produced *i.e.,* phase-separated micro-composite, ordered intercalated nanocomposites, and disordered exfoliated nanocomposites (Akbari *et al.*, 2010).

Phase-separated micro-composites are the conventional types of nanocomposites using layered 2D nanoparticles. The term micro-composites refer to a type of nanomaterials in which nanofillers are agglomerated inside the polymer matrix and hence causing the materials to have separate phases of matrices and nanofillers. Micro-composites are usually characterized by the microsized filler particles *e.g.* epoxy microcomposites are epoxy-based materials containing

microsized silica particles (Krivda *et al.*, 2012). The second type of nanocomposites incorporated with 2D nanoparticles is termed ordered intercalated nanocomposites. Ordered intercalated nanocomposite involves the intercalation of small molecules of monomer into the interlayer gallery during the polymerization process (Haraguchi *et al.*, 2002).

The third type of nanocomposites incorporated with 2D nanoparticles is termed disordered exfoliated nanocomposite. This type of nanocomposite is obtained when the layered or stacked clay is rendered into single nanosheets. These single nanosheets eventually interact with the chain of polymers (Wang & O'Hare, 2012). This is usually achieved by the pre-treatment of the clay materials *via* exfoliation process prior to the production of polymer nanomaterials. The material fabricated *via* exfoliation of clay during the polymerization of monomers was proven to have superior mechanical and thermal properties (Haraguchi *et al.*, 2002). This material - termed nanocomposite hydrogel (NCH) - has prospects for wound dressing material and drug delivery systems. NCH is the field of interest governing this whole thesis.

2.1.1 Nanocomposite hydrogel (NCH)

Nanocomposite hydrogels are polymeric networks that have a unique ability to hold a large amount of water (Sharma *et al.*, 2018). The fabrication of sophisticated hydrogel system incorporated with nanoparticle was inspired by the complicated tissue-specific physiology and the dynamic stimuli of biological processes concerning medical applications (Lavrador *et al.*, 2021). Hydrogels have been widely used in biomedicine because that these materials have a three-dimensional network having high water content and biocompatibility (Ayoubi-Joshaghani *et al.*, 2020). These are key properties that enable fabricated materials to function effectively in the field of biomedicine.

Despite the well-established advantages and practicality of traditional hydrogels, the major drawback of these materials is that they can have low mechanical strength which then limited their functions in certain applications. Hence, nanocomposite hydrogels are fabricated. These new advanced materials are demonstrated to have a high mechanical properties with other additional properties (*e.g.,* electrical conductivity, antibacterial, and antioxidation), rendering them versatile and relevant (Zhao *et al.*, 2020). Nowadays, researchers are doing intensive studies on the mechanism of hydrogel production with the incorporation of nanoparticles using various platforms attempting to produce advanced nanocomposite hybrid materials to eventually grow their range of biomedical applications.

There are several methods adopted and modified for the synthesis of nanocomposite hydrogels. Linear water-soluble chains in both natural and synthetic polymers can be crosslinked to form nanocomposite hydrogels in numerous techniques *e.g.,* linking of polymer chains, ionizing radiations, electrostatics, and crystalline formation (Sharma *et al.*, 2018). Among the main methods to synthesize nanocomposite hydrogel are free radical chain polymerization (Haraguchi *et al.*, 2005), crosslinking (Mao *et al.*, 2020), grafting (Holloway *et al.*, 2013), copolymerization (Puskas *et al.*, 2008), bulk polymerization (Ahmed, 2015), irradiation polymerization (Abd Alla *et al.*, 2012), suspension polymerization (Gupta *et al.*, 2014), microwave-assisted method (Nadagouda & Varma, 2007), and freezing–thawing process (Yang *et al.*, 2008). At one point during those processes, nanoparticles are incorporated for the improvement of the fabricated materials.

Nanocomposite hydrogels are usually produced by modifying nanoparticle-hydrogel physicochemical interactions and choosing different classes of nanomaterials for hydrogel fabrication. This eventually expands the range of desirable properties of NCH to the extent of surpassing the quality of those fabricated *via*

conventional routes. Recently, many studies focused on modulating the stimuli-responsive nanocomposite hydrogels for their application in advanced systems specifically targeted for different biomedical applications (Bardajee *et al.*, 2020; Mamidi & Delgadillo, 2021). To achieve this, a wide array of polymers and nanoparticles are combined for which their physicochemical interactions are studied. In this thesis, attention is given in the utilization of nano clays to produce nanocomposite hydrogels.

2.1.2 Applications of NCH

The main factor contributing to the usefulness of NCH is its unique properties. Among the striking properties of NCH are their swelling/deswelling capability, improved mechanical strength, stimulus sensitivity, and tensile properties. NCH has many benefits especially as the advanced materials in environmental and biomedical applications (Sharma *et al.*, 2018). For environmental applications, NCH is found as adsorbing materials, photocatalysts, ion exchangers, and soil-conditioning agents. Table 2.2 below lists several fabricated nanocomposite hydrogels with different methods of synthesis and their environmental applications.

Table 2.2 Environmental applications of nanocomposite hydrogels fabricated *via* different methods of synthesis.

Name of nanocomposite hydrogels	**Methods of synthesis**	**Applications**
Fe_3O_4/poly (acrylic acid–acrylamide–butyl methacrylate)	Coprecipitation reaction (Li *et al.*, 2011)	Adsorbents for removal and separation of cationic dyes
Poly-(N-isopropylacrylamide)/ clay	Photopolymerization (Ferse *et al.*, 2008)	Tactile communication, microvalves
Lithium magnesium silicate hydrate/poly(N-isopropylacrylamide)	*In-situ* free radical polymerization (Zhang *et al.*, 2014)	Removal of crystal violet from aqueous solution

N-vinyl 2-pyrrolidone/itaconic acid/organo-clay	Free radical polymerization (Çöle *et al.*, 2013)	Removal of basic dye
Polyacrylamide/methyl cellulose/calcic montmorillonite	Free radical polymerization (Bortolin *et al.*, 2013)	Slow release of fertilizers
Acrylamide/kappa-carrageenan/ sodium montmorillonite	Solution copolymerization (Mahdavinia *et al.*, 2014)	Adsorption of methylene blue cationic dye
Poly(N-[3-(dimethylamino) propyl] methacrylamide-coacrylamide)/ montmorillonite	*In-situ* intercalative polymerization (Nie *et al.*, 2014)	Gardening or soil conditioning
Graphene oxide/polypyrrole	One-step co-electrode position (Zhu *et al.*, 2012)	High-performance electrochemical supercapacitor

Other than their eminent roles as advanced materials for environmental purposes, nanocomposite hydrogels are also commonly used in biomedicine due to their biocompatibility and biodegradability (Kumari *et al.*, 2020; Mathew *et al.*, 2019). This results from their ability to a absorb large amount of water which is caused by the formation of cross-linked hydrophilic polymers with acidic, basic or neutral monomers (Sharma *et al.*, 2018). There are numerous forms of nanocomposite hydrogels with different biomedical applications. Among the main applications of nanocomposite hydrogels are in drug delivery systems, tissue engineering, wound dressing, and antibacterial activity. Table 2.3 shows various nanocomposite hydrogels synthesized with different methods for applications in biomedicine.

Table 2.3 Various fabricated nanocomposite hydrogels synthesized with different methods for biomedical applications.

Name of nanocomposite hydrogels	**Methods of synthesis**	**Applications**
Bacterial cellulose/graphene oxide/	One-step *in-situ* biosynthesis	Tissue engineering scaffolds (Si *et al.*, 2014)
Chitosan/silver	*In-situ* crosslinking	Drug delivery and antibacterial (Yadollahi *et al.*, 2015)
Poly (N-isopropyl acrylamide)/laponite	Crosslinking	Controlled drug delivery (Wang *et al.*, 2012)
Poly (N-isopropyl acrylamide)/alginate /laponite	*In-situ* polymerization	Tissue engineering (Wang *et al.*, 2011)
Silver/poly (Acrylamide-coacrylic acid)	grafting	Antibacterial activity (Thomas *et al.*, 2007)
Poly (ethylene glycol) methyl ether ethacrylate/ dimethacrylate/ iron oxide	Free radical polymerization	Hyperthermia cancer therapy (Meenach *et al.*, 2010)
N-maleyl chitosan/ poly(acrylamide)/ montmorillonite	Free radical polymerization	Enzymatic degradation (Yu *et al.*, 2011)
Vinyledmontmorillonite/maltodextrin-codimethylacrylamide	Radical crosslinking	Pharmaceutical formulations (Guilherme *et al.*, 2010)
Ag/poly (N, N-dimethylacrylamide)/ poly (vinyl alcohol)	Free radical polymerization	Antibacterial and drug release (Luo *et al.*, 2009)
2-acrylamido-2-methylpropanesulfonic acid/acrylic acid/ laponite	*In-situ* copolymerization	Contact lens Ophthalmic implant (Chen *et al.*, 2013)
Poly (acrylic acid)/laponite	Free radical polymerization	Wound dressing and tissue engineering (Shen *et al.*, 2014)
Carboxymethyl cellulose/poly (acrylic acid)/montmorillonite	Radical graft polymerization	*In vitro* release of vitamin B12 (Boruah *et al.*, 2014)

From the table, it is observed that the commonly employed method to fabricate the nanocomposite hydrogels *in-situ* polymerization. This results from the fact that the method is fast, easy, and effective. Many types of nanocomposite hydrogels can be fabricated comprising either natural or synthetic polymers. In some cases,

researchers seek to improve the properties of the final nanocomposite hydrogels by combining both synthetic and natural polymers. Polymer blends can greatly improve the physicochemical properties of the final products. Nevertheless, the utilization of several types of polymers can cause many issues, especially in terms of controlling and optimizing the many variables involved in the production of nanocomposite hydrogels. The difference between these two types of polymers is further discussed in the next subtopic.

2.1.3 Biopolymer versus Synthetic NCH

From the literature, there was an increasing trend in the selection of natural biopolymers such as cellulose, carboxymethyl cellulose, chitosan, carboxymethyl chitosan, alginate, starch, and gelatine for the formulation of bio-nanocomposite hydrogels (Gholamali & Yadollahi, 2021). Conventionally, production of nanocomposite hydrogels included the usage of synthetic polymers *e.g.,* polyurethane, n-isopropyl acrylamide (NIPA), poly (vinyl alcohol), and poly (ethylene glycol). There are numerous reports on various properties of these nanocomposite hydrogels (which are based on different types of polymers as precursors) especially regarding their applications in drug delivery systems and wound treatment.

Interestingly, the materials produced are sometimes in combination of several polymers in one formulation hence giving rise to different unique properties. The new materials which are obtained by new network formation of polymer combination are then further enhanced by the incorporation of nanoparticles. The interactions between polymeric molecules and nanoparticles are then explored comprehensively *via* a series of testing and characterizations.

Figure 2.2 shows the comparison of network formation between a biopolymer hybrid (chitosan and starch) incorporated with halloysite (Sabbagh *et al.*, 2017) and a

synthetic poly(N-isopropyl acrylamide), PNIPA incorporated with laponite (Haraguchi *et al.*, 2002). The incorporation of halloysite into chitosan/starch hybrid produces a porous structure which is a vital property for molecular diffusion hence allowing more space for loading of drugs and dyes (Peng *et al.*, 2015). Additionally, the incorporation of halloysites into the hydrogel's network improved the thermal stability of the material. However, this porosity is not observed in the synthetic blend of PNIPA/laponite nanocomposite hydrogel.

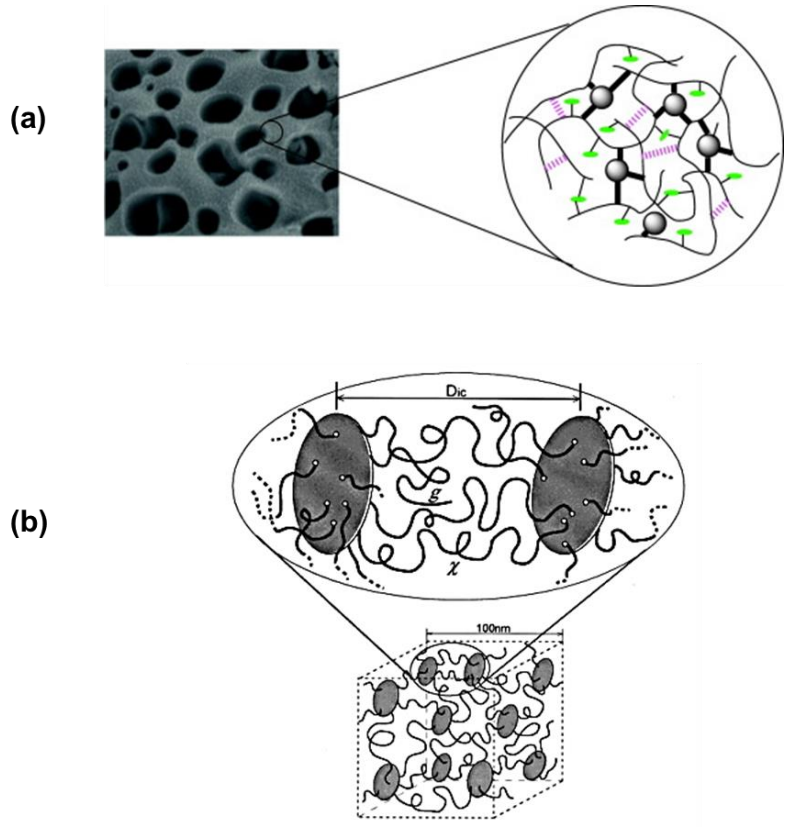

Figure 2.2 Different nanocomposite hydrogel networks arising from utilization of different polymers incorporated with nano clays: (a) biopolymers and (b) synthetic polymer (PNIPA).

Despite the absence of evidential data regarding the porosity of the fabricated nanocomposite hydrogel, the formation of PNIPA/laponite network produced a biomaterial with remarkable mechanical toughness and tensile strengths apart from the evidently improved swelling/deswelling properties. These are among the key requirements for the material to be able to be used effectively in biomedicine. This resulted in the formation of the unique nanocomposite hydrogel network of laponite and PNIPA with high potential for the application in biomedicine. It was also observed that there are significant effects of different laponite contents on various physical properties of nanocomposite hydrogel which eventually gave rise to the formation of unique network of organic PNIPA/inorganic nano clay.

Unlike the network formation of halloysite and chitosan/starch hybrid which majorly involved surface binding *i.e.,* facile formation of imine bonds between halloysite and chitosan/starch hydrogel networks (Sabbagh *et al.*, 2017), laponite acts as a multifunctional crosslinker replacing an organic crosslinker (bis-acrylamide) for PNIPAM nanocomposite hydrogel. This phenomenon could be due to the difference in the size of the polymer matrix (*e.g.,* chitosan and starch both have bigger molecular sizes as compared to n-isopropyl acrylamide which is a type of monomer).

Interestingly, there are also studies reported on formation of nanocomposite hydrogels using synthetic polymers in combination with biopolymers *via* graft copolymerization to produce nanocomposite hydrogel in biomedicine. An example of such unique polymer combination is the formation of nanocomposite hydrogel using carboxymethyl cellulose grafted with polyacrylamide with montmorillonite clay as the nanofillers (Mahdavinia *et al.*, 2017). The new material is magnetic and pH-responsive, making it suitable for colon targeted drug delivery.

Since they combined the properties of different polymers with a nanoparticle in a hydrogel system, bio-nanocomposite hydrogel has drawn a lot of attention as one of the most promising nanoparticulate drug delivery technologies in recent years. It can be observed that substantial advancements were achieved in the field of drug delivery, particularly with the quick development of nanomedicine and the expanding knowledge of infectious and malignant diseases. Due to their extensive properties which included several domains (*e.g.* material science, chemistry, and biological sciences), hydrogels and inorganic/organic nanoparticles are two distinct groups of materials that have attracted a lot of attention recently (Gholamali & Yadollahi, 2021).

Researchers are keen to study the fabrication and the interactions of the elements in hydrogel nanocomposites which have big prospects in the field of biomedicine. There are many types of NCH materials produced using biopolymers and their combination. Table 2.4 shows the utilization of biopolymers incorporated with nano clays for the fabrication of nanocomposite hydrogels, which found their usefulness as drug delivery systems and wound dressing.

Table 2.4 Biopolymer NCH using nano clay and its properties for various applications in biomedicine.

Biopolymer matrix	**Nano clays**	**Properties of organic/inorganic hybrid hydrogels**
Cellulose	Laponite (Boyer *et al.*, 2018)	Injectable reinforced interpenetrating network hydrogel with increased mechanical properties
Carboxymethyl Cellulose (CMC)	Sepiolite (Palem *et al.*, 2021)	Higher tensile strength than the pristine polymer hydrogel Improved thermal properties (glass- and melting-transition) Prolonged release of 5-fluorouracil at pH 7.4 for 32 h Improved biocompatibility of the hydrogels

Chitosan	Halloysite nanotubes (Huang *et al.*, 2017)	Significant increase of mechanical properties and anti-deformation ability of the composite hydrogel Decreased pore size and swelling Low cytotoxicity (biocompatible) Good drug entrapment efficiency of doxorubicin (DOX)
Carboxymethyl Chitosan	Synthetic Hectorite "Laponite XLG" (Ma *et al.*, 2007)	pH and thermo-responsive semi-interpenetrating hydrogels with poly (N-isopropylacrylamide) Improved tensile properties (the elongation of hydrogels reached more than 800%)
Carrageenan	Montmorillonite (Mahdavinia *et al.*, 2010)	Increased water absorbency High mechanical strength
Alginate	Zeolite (da Silva Fernandes *et al.*, 2018)	Improved swelling and thermal characteristics of nanocomposite hydrogel aimed for controlled release formulation
Starch	Sodium Montmorillonite (Al *et al.*, 2008)	Improved water absorbency of nanocomposite hydrogel
Gellan Gum	Montmorillonite (Lee *et al.*, 2019)	Significant enhancement of thermal stability and tensile strength
Gelatin	Bentonite (Sakr *et al.*, 2020)	Enhanced mechanical properties Different pore size with varied concentrations of bentonite Excellent biocompatibility
Pectin	Bentonite (Abou El Fadl & Ibrahim, 2020)	Improved antimicrobial activity
Zein	Illite clay (Ullah *et al.*, 2022)	Enhanced wettability Improved tensile strength

	Biocompatible (aimed for tissue engineering)

As compared to biopolymers, synthetic polymers are also gaining the attention of researchers as the starting material to develop nanocomposite hydrogels. Synthetic nanocomposite hydrogels are a type of soft material that can be produced *via* free radical polymerization of water-soluble monomers in the presence of nano clay in an aqueous solution (Liu *et al.*, 2012). Table 2.5 shows some of the past studies regarding the production of nanocomposite hydrogel using synthetic polymers and the improvement of their properties for the application in biomedicine.

Table 2.5 Fabrication of nanocomposite hydrogel using synthetic polymer with improved properties.

Synthetic polymer matrix	**Nano clay**	**Properties of organic/inorganic hybrid hydrogels**
Polyacrylamide (PAAM)	Halloysite nanotubes	Improvements in mechanical properties due to intercalation of PAAM chains by halloysites (Liu *et al.*, 2012)
Poly (N-isopropylacrylamide) (PNIPAM)	Laponite	High swelling ratio, stimulus sensitivity, super optical transparency, ultrahigh tensile extensibility (Chen *et al.*, 2020; Haraguchi *et al.*, 2002)
Poly (ethylene glycol)	Montmorillonite and siloxane	Good swelling property enabling sustained release of diclofenac for constant treatment for arthritis, gout, migraine, and pain after surgical procedures (Jesus *et al.*, 2018)
Poly (ethylene oxide)	Laponite RD	Improved material elasticity (Morariu *et al.*, 2014)
Polyurethane	Layered silicate	Excellent mechanical strength without compromising optical transparency (Murugesan & Scheibel, 2020)

Poly (N-acryloyl glycinamide)	Silicates	Superior mechanical performances and swelling stability of the hydrogels and scaffolds for bone regeneration (Zhai *et al.*, 2017)
Poly (vinyl alcohol), PVA	Halloysite nanotubes	High thermal and mechanical properties (Azmi *et al.*, 2017; Chen *et al.*, 2021; Kouser *et al.*, 2020)
	Layered double hydroxide (LDH)	High swelling, improved thermal and mechanical properties (Sebri *et al.*, 2020)

However, most study on the development of nanocomposite only emphasized on the mechanical and/or thermal properties of the material. Extensive studies are yet to be carried out to test the developed materials for application as drug carriers. For drug-releasing nanocomposite materials, there are many fashions through which the drug molecules are administered into the bodily system. In terms of mathematical modelling, there are three methods to explain the kinetics of drug release from a drug delivery system *i.e.,* statistics, model-dependent, and model-independent.

Statistically, mathematical modelling is carried out using multivariate (MANOVA) or exploratory data analysis. For model-dependent drug delivery, several models used to describe the kinetic of drug release *i.e.,* zero order, first order, pseudo-second order, Higuchi, Korsmeyer-Peppas, and Hixson Crowell. Mathematical modelling can also be carried out *via* model independent method *i.e.,* difference factor (fi) and similarity factor (f2). The selection of the drug kinetic models is based on drug types and the final form of the drug carriers. However, for most systems, the drug delivery is described by their kinetic models.

2.2 Poly (Vinyl) Alcohol (PVA)

Polyvinyl alcohol (abbreviated as PVA) is a synthetic polymer that originated from polyvinyl acetate through a partial or full hydroxylation process (Baker *et al.*, 2012). The degree of the hydroxylation process affects many properties of the finalized PVA products: physical, chemical, and mechanical properties (Tubbs, 1966). The produced PVA material is rendered extremely soluble in water but impervious to most organic solvents. Figure 2.3 shows the production of PVA from hydrolysis of polyvinyl acetate to remove the acetate groups (Baker *et al.*, 2012).

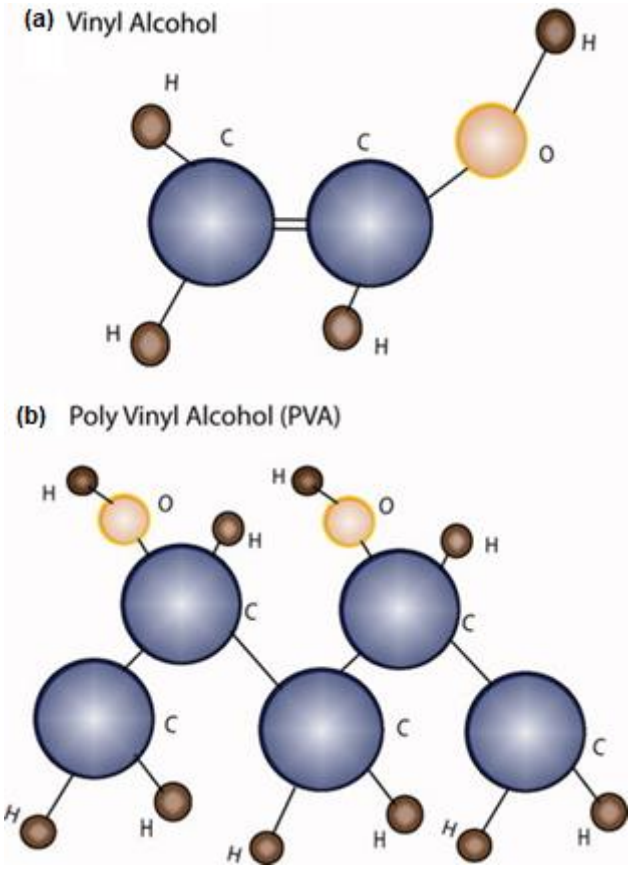

Figure 2.3 Hydrolysis of acetate in vinyl alcohol (a) produces PVA (b).

Because of its water solubility, PVA requires crosslinking before the development of hydrogels for its various applications. Crosslinking, which includes physical and chemical, will provide structural stability for the swelling of PVA hydrogel in the biological fluids (Andrade, 1989). The degree of PVA crosslinking influences the amount of fluid uptake, which eventually affects the chemical, physical, diffusional properties, and biological properties of the polymer (Baker *et al.*, 2012). This ability of the PVA hydrogels to imbibe large amounts of water is the key property to their diverse applications. For example, in the field of medicine, PVA is commonly available in the forms of soft contact lenses, eye drops, embolization particles, tissue adhesion barriers, and as artificial cartilage (Baker *et al.*, 2012).

2.2.1 PVA in Biomedicine

PVA is a polymeric substance used as the starting material for designing nanostructured devices due to its water solubility, biocompatibility, and excellent physical properties (Paradossi *et al.*, 2003). PVA has been widely used in biomedical and pharmaceutical fields due to its gelation ability (Georgieva *et al.*, 2012). This is the quintessential property of a material to be used in biomedicine, especially those involving tissue engineering and wound dressing.

Among the important applications of PVA is in the development of materials such as films, capsules, matrices for tissue engineering, scaffold, gauze, wound dressings, and electro-spun fibre. An example of the application of PVA electro-spun fibre is in the production of PVA nano-fibrous mats loaded with silver nanoparticles for wound healing applications (Nguyen *et al.*, 2011). The fabricated PVA nano mats were proven to have significantly inhibited the bacterial growth of *S. aureus* (gram-positive) and *E. coli* (gram-negative) apart from displaying high mechanical

stability (>45 MPa). Usually, PVA-derived materials found its applications mainly in drug delivery and hydrogel for wound treatment.

2.2.1 (a) Drug Delivery

Among the prominent applications of PVA in biomedicine is as drug delivery systems. However, due to its weak mechanical properties, PVA is often combined with other polymers for the formulation of final products. Many formulations take the benefit of PVA by incorporating this polymer with other synthetic and/or biopolymers. The final products are usually mechanically superior and thermally enhanced with the ability to deliver drugs accordingly (based on their respective applications). Table 2.6 shows the PVA formulations which are used as drug delivery systems.

Table 2.6 Applications of PVA in various formulations.

PVA Formulation	**Application**
PVA/Carboxymethyl cellulose	Drug delivery, food packaging, and agriculture (Arefian *et al.*, 2020)
PVA-co-poly(methacrylic acid)	A potential graft-polymeric carrier for oral delivery of 5-fluorouracil (Minhas *et al.*, 2013)
PVA/poly(ethylene glycol)	Delivery of cytotoxic drugs to myoblasts (Jensen *et al.*, 2016)
PVA coated iron oxide nanoparticles	Targeted drug delivery of doxorubicin (Kayal & Ramanujan, 2010)
Silk nanospheres and microspheres from silk/PVA blend films	Drug delivery system for tetramethylrhodamine conjugated bovine serum albumin, tetramethylrhodamine conjugated dextran, and rhodamine B (Wang *et al.*, 2010)
PVA/chitosan coated with magnetite nanoparticles	Drug delivery system for bovine serum albumin (BSA) (Shagholani *et al.*, 2015)
3D printed multi-compartmental PVA capsules	Drug delivery of powdered dronedarone hydrochloride and ascorbic acid (Matijašić *et al.*, 2019)
PVA/chitosan composite nanofibers	Matrix for transdermal drug delivery of ampicillin sodium (Cui *et al.*, 2018)