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A Systematic Literature Review of Hemicellulose-Based Hydrogels for Drug Delivery System- A Review

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Abstract

Development of hemicellulose-based hydrogels have gained many interests from researchers in recent years because of their excellent biocompatibility, biodegradability, economically, and non-toxic. Hemicellulose-based hydrogels possessed exclusive properties such as tuneable swelling behaviour and stimuli-responsiveness which have advantages in the preparation of potential hydrogels for drug delivery applications. This study was conducted by a systematic review process guided by PRISMA protocol, involving 20 related studies retrieved from Science Direct and PubMed, and data extraction and analysis were done by thoroughly review all the included articles. Three main themes were raised and discussed mainly focusing on the hydrogel synthesis, properties and drug delivery applications. The findings of this study had shown that hemicellulose-based hydrogels have great performance, functionality, and proven to be a promising drug carrier for controlled and sustained-release drug delivery.

Keywords: Hemicellulose; Hydrogel; Drug delivery

Introduction

In a recent study, hydrogels have been defined as two- or multi- component system that is made up of three-dimensional (3D) networks which are formed by crosslinking the polymer networks. It was found that hydrogel possessed a unique property where they have the ability to absorb and retain a large amount of water in the interstitial spaces between the networks, but unable to dissolve in the surrounding medium (1-3). Hydrogels that contain interactive functional groups along their main polymer chains are commonly known as stimuli-responsive hydrogels. The stimuli-responsive hydrogels are hydrogels which are sensitive to specific environment stimulus changes and exhibit responses by changing their shape and size, changes in its optical, wettability, electric signal and mechanical properties (4,5).

Polymers are resourceful materials composed of repeating structural units forming a macromolecule. There are three main classes of polymers based on their origin which are natural polymers, semisynthetic polymers (or also known as hybrid polymers), and synthetic polymers. Natural polymers are obtained from the natural sources or origins such as plants, animals, and microorganisms. Natural polymers are economically, readily available, potentially biocompatible, and biodegradable in comparison to synthetic and semisynthetic polymers due to their origin (6).

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Polysaccharides are one of the biopolymer classes use in the development of hydrogel preparations due to their useful biocompatibility, biostability and biodegradability as natural polymers (7) which make them harmless and suitable for several biomedical applications such as cell or drug delivery, gene delivery, cell culture, regenerative medicine and tissue engineering.

Hemicellulose is the second most abundant natural polysaccharides after cellulose, that is extensively exists as the component of plant cell walls, and constitute about 20 to 30 percent of the total weight of lignocellulosic biomass. However, unlike cellulose which comprised of 7,000 to 15,000 sugar units per polymer, hemicellulose has shorter chains of 500 to 3,000 sugar units (8).Development of hemicellulose-based hydrogels have gained many interests from researchers in recent years not only because they are from renewable biopolymer resources and cost-effective, but also because hemicellulose-based hydrogels have significant physicochemical properties, including biocompatibility, biodegradability, non-toxic and anti-cancer effect. These exclusive properties of hemicellulose have advantages in the preparation of potential hydrogels for drug delivery applications.

Methodology

Prisma

The reviewers decided to adopt a publication standard called PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement that was first published in 2009. PRISMA is a reporting guideline which aimed to address the poor reporting of systematic reviews by guiding the reviewers to write an accurate, complete, and transparent reports (9). This standard suggests the inclusion of several key points as stated in the PRISMA checklist such as title, abstract, methods, results, discussion and funding sections, with details of content that should be included in each section such as search strategy process, review process, and document selection process. The suitability of PRISMA to be use in this systematic review is because of these benefits: (1) it clearly defines the research questions; (2) it able to identify the inclusion and exclusion criteria, and (3) it attempts to assess and examine the largest amount of available and relevant scientific literature within a specific time period (10).

Resources

Two leading academic research databases were used for this review, which are Science Direct and PubMed. Both databases are considered the leading trusted resources for citations. Both databases published peer-reviewed articles and can be accessed for free. Science Direct is Elsevier's platform which serves as a gateway to millions of academic articles. These two databases are chosen because of their prominence, which is important to ensure the quality of the articles reviewed in this study.

Systematic review process

Identification

Identification is the first phase in the systematic review process of this study, performed in March 30th, 2021. The process involved identification of keywords for information searching purposes. Researchers were using several relevant information sources such as the dictionaries, encyclopaedias, thesaurus and keywords suggested by Science Direct and PubMed for keywords synonyms, possible related terms, and other variations to the term 'drug delivery' were used. Therefore, in this process, the following search items were used for the documents search (see Table 1).

Screening (Inclusion and Exclusion Criteria)

Screening is a phase where the reviewers will determine the criteria of articles are to be included or excluded with the

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Table 1: Keywords and search items for documents retrieval

Databases	Keywords and search items used for systematic searching	
Science Direct, PubMed	(Hemicellulose hydrogel)	AND (Drug delivery OR drug release OR drug carrier OR deliver drug OR release drug)

Table 2: The inclusion and exclusion criteria

Criteria	Inclusion	Exclusion
Document type	Journals (research articles)	Journals (review articles), books, book chapters, conference proceedings
Timeline	Between 2010 to 2021	< 2010
Language	English	Non-English

assistance of the specific databases. In the screening process, inclusion and exclusion criteria were decided to search for suitable articles to be included on the systematic review process. Before the screening process was carried out, duplicate documents were first removed from the retrieved articles. The inclusion and exclusion criteria are as shown in (Table 2).

Eligibility

The third phase is the eligibility phase, which is a manual process of including or excluding the full-text articles according to the reviewers' specific criteria. The articles retrieved were thoroughly reviewed in this process, where any articles that did not meet the criteria were excluded from the study. The articles were screened manually for literature focusing on hemicellulose-based hydrogels for drug delivery application and criteria from the earlier screening processes (inclusion and exclusion criteria). Any papers which do not involve the study on drug delivery application of hemicellulose-based hydrogels were excluded. Additionally, articles that inaccessible were also excluded from the eligibility process.

Assessment of quality

For the assessment of quality of the included papers, this process was done to evaluate the quality of papers to be reviewed and to prevent the risk of bias in reporting. In this review, quality assessment was done by adopting the method suggested by (11), where the remaining included articles obtained in the last process of systematic review were presented, evaluated and ranked by the experts of the topic into three different quality categories namely as high, moderate, and low. In order to maintain good quality reporting, only articles that are ranked in high and moderate categories are to be reviewed. To evaluate the article's rank of quality, experts should focus on the methodology and the finding outcomes of each individual article. Next, authors must come to a mutual agreement that the rank of quality for article must be at least at a moderate level in order to be included in the review. Any disagreement arises should be thoroughly discussed in a professional manner among the authors before deciding on the inclusion or exclusion of the remaining articles for the review.

Data Extraction and Analysis

The remaining articles left from the eligibility process included in this study were evaluated, reviewed, and analysed. Before reviewing the included articles, a spreadsheet form was created to gather the general data compiles the authors, title, journal, publication year, and summary of findings. Data of each article was extracted by reading through the abstracts first, and then the full-text which include an in-depth reading of the whole article to identify and extract the available data.

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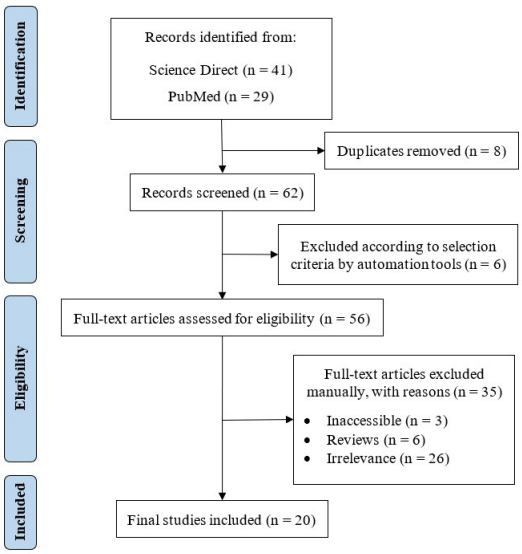

Figure 1: Flow diagram following the PRISMA guidelines, showing the identification, screening, eligibility, and final studies included. 20 papers were included (search performed on March 30th, 2021)

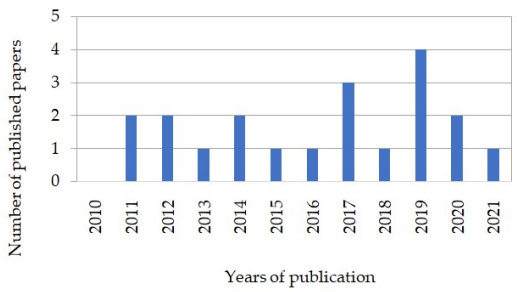

Figure 2: Distribution of published papers per year

A thematic analysis of available data was performed for this study to discuss all the data extracted into different themes and sub-themes. In this process, the extracted data were transformed by authors into useful data and guided by the identification of the concepts, ideas and themes which connect and relate all the available data from the included articles. The final themes discussed are: (1) hydrogels synthesis; (2) hydrogels properties, and (3) drug delivery applications. The themes and sub-themes were developed together with the co-authors by corresponding author. Discussion and re-evaluation of the themes and sub-themes were conducted on ongoing basis. Any disagreements or inconsistencies were resolved in a proper and professional manner. No meta-analysis was done in this review because of the heterogeneity of studies.

Results and Discussion

Findings

Based on the advanced systematic search on the two databases, a total of 70 studies were obtained, where 41 studies were found in Science Direct and 29 studies were found in PubMed using the identified keywords search string. A total of eight studies traced as duplicate articles were excluded first before the screening process, which resulted to 62 studies left. Six studies were excluded automatically by the databases after the inclusion and exclusion criteria filters were applied. Out of 56 studies left, a total of 35 studies were manually excluded from the eligibility process for various reasons, where three studies were inaccessible, six studies were review articles, and 26 studies were irrelevant to this study. Thus, only 20 studies were included for this study (see Figure 1).

Number of Papers Collected by Selection of Keywords

Several keywords were generated in order to refine the systematic searching when collecting the studies with regard to the research question. Table 3 shows the number of papers collected by selection of keywords from each database. Important to note that eight out of the 29 papers identified from PubMed were similar papers retrieved from Science Direct, and were excluded as duplicate papers.

Number of publication by year

The publication year of articles reviewed as described in the inclusion

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criteria were ranging from year 2010 to 2021. Figure 2 shows the distribution of published papers per years. There were no paper prior to 2011, and only one paper published in the first-half of this year period that is related the topic of this study. As shown in Figure 2, the year 2019 have the most published papers regarding hemicellulose-based hydrogels for drug delivery system.

Quality assessment

All the remaining 20 included articles were ranked to be of good quality by the experts of the topic, with 12 of them ranked as high quality, and eight of them ranked as moderate quality. The 20 included articles were thoroughly evaluated and ranked by the experts by focusing on the methodology and the finding outcomes that are related to the topic of this review. As per agreement with the authors, only articles of high and moderate quality were allowed to be included in the review. Since, all the articles were ranked moderate and above, thus all the remaining 20 included articles were eligible for the review.

Journal analysis

In this section, a classification of journals has been made to analyse what type of publications correlates with our topics. Four main categories and other two subcategories from SCImago Journal & Country Rank (SJR) were used to group the journals. The main categories include: (1) material, journals of materials chemistry/material related topics; (2) chemistry, journals focused on the organic chemistry/biochemistry topics; (3) pharmaceuticals, journals focus on the pharmaceutics/biopharmaceutics topics, and (4) multidisciplinary, journals that allow for multiples topics. In addition, the four combined subcategories include: (1) chemistry/material, and (2) material/pharmaceuticals.

Figure 3 shows the distribution of all 11 journals with the number of papers published from each respective journal

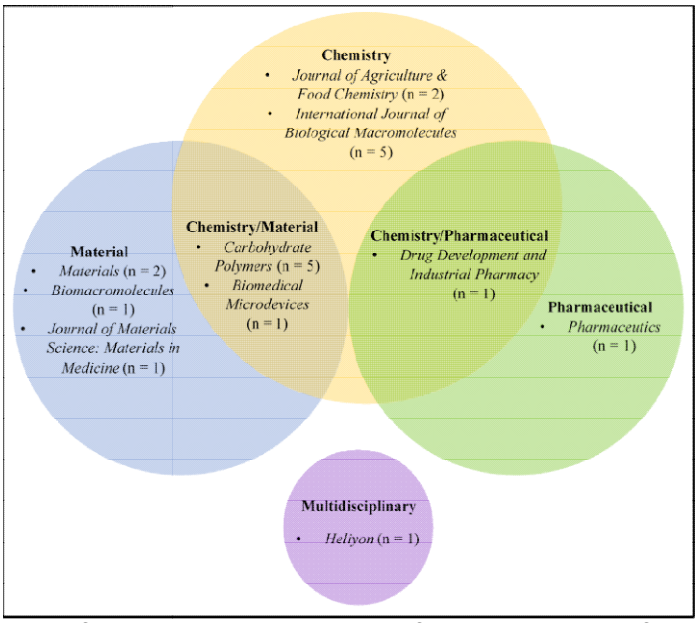

Figure 3: Distribution of journals with the number of papers published from each respective journal category

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category. Journals under Chemistry category contains the highest number of papers retrieved where five out of 20 papers included were from the “International Journal of Biological Macromolecules”. This is because the journal focused on the studies of molecular structure and properties of natural macromolecules, and this include macromolecular carbohydrates which is closely related to our topics. The second highest number of papers retrieved were from the chemistry/material subcategory where “Carbohydrate Polymers” published five out 20 papers included. This is expected to be as this journal covers the study and exploitation of polysaccharides on their potential applications in several areas, where one of them is on drug delivery application. Thus, papers retrieved from this journal correlates best to our topics. The remaining categories and sub-category contain fewer papers, where only one or at most 2 papers were published from them.

Hydrogel synthesis

Materials

Hemicellulose is one of the potential choices of biopolymer material for the preparation of natural hydrogels. This is mainly due to its great advantages which include biocompatibility, biodegradability, economical and most importantly is non-toxic that had been described throughout many studies. Hemicellulose extract in most studies was reported to be extracted from various different plant sources such as bagasse, bamboo, beech wood, hardwood pulp, maize bran, oat spelt, psyllium husk, quince, tamarind seed powder, and wheat straw. Among the many types of hemicelluloses, xylan-type hemicelluloses are the most commonly used as mentioned in 14 out of 20 studies as shown in Table 4, this is probably because xylan is the major hemicellulosic component of plants, and constitute about 20-35% of the biomass, thus making xylan the most abundantly found component from agriculture, forestry, pulp, and paper industries.

Several monomers have been studied in preparation of hemicellulose derivatives-based hydrogels. As shown in Table 4, these monomers include acrylic acid (AA), acrylamide (AM), maleic anhydride (MA), and others. Among all those monomers, acrylic acid is the most used monomer in hydrogel preparation appearing in a total of 7 studies. AA is considered as an important monomer which is widely studied and used for the development of functional hydrogels because it was proven to be effective in forming hydrogel in many studies. Moreover, incorporation of synthetic monomer like AA into the hemicellulose-based hydrogels had shown great improvement in the hydrogel properties, in terms of their water adsorption, swelling capacity, and stimuli responsiveness. Thus, these improvements allow for the hemicellulose-based hydrogels to enhance their uses in drug delivery applications.

Methods of preparation

The preparation of hemicellulose-based hydrogels involved the crosslinking procedure of hemicellulose polymers, with or without presence of other polymers and monomers. In this review, all 20 studies had use different chemical crosslinking approaches in forming the hemicellulose-based hydrogels, where free radical copolymerization was the most commonly used chemical crosslinking method as mentioned in 10 out of 20 studies. Followed with, solution polymerization with 4 studies, and enzymatic reaction with 3 studies. As for the other remaining 3 studies, each had approached with different crosslinking method such as suspension polymerization, reactive extrusion process, and one-pot reaction. Table 5 shows the summary of the crosslinking methods of the hemicellulose-based hydrogels analysed from all the included studies.

Crosslinking by free radical copolymerization

In this review, the most extensively studied crosslinking method for hemicellulose-based hydrogels preparation

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is free radical copolymerization which appeared in 10 studies. This free radical copolymerization method is gaining much interest in preparing hydrogels for bioapplications, including for drug delivery applications, mainly because of its efficiency in the rapid formation of the hydrogel, even if it were done under mild conditions. This method usually involves the grafting of monomer onto the backbone of activated polymer chains, which results to branching and crosslinking between the polymers and monomers, thus forming the hydrogels. Generally, the polymer chains can be activated by the action of various chemical initiators and high-energy irradiations (12), and as to date many initiation systems were introduced for free radical copolymerization method. For instance, there were 3 studies performed by Gao et al., Kong et al., and Yang et al. using photoinitiator such as 2,2-Dimethoxy-2-phenylacetophenone (DMPA) to generate the free radicals when exposed under UV irradiations. DMPA is considered as a highly efficient and most extensively used photoinitiator for UV polymerization, due to their stability. While in another study by Sun et al., they performed the redox initiation system where they successfully grafted the monomer, acrylic acid (AA) onto the backbone of arabinoxylan-type hemicellulose, by using potassium persulfate and anhydrous sodium sulphite as the redox initiator. The polymerization in this study was activated via the redox polymerization by the reduction-oxidation reaction occurred between the oxidizing agent (potassium persulfate) and reducing agent (anhydrous sodium sulphite). Similar crosslinking method using redox initiation system was performed in another 2 studies by Chen et al. and Peng et al.. Meanwhile, there were also other initiator systems mentioned in this review, where 2 studies performed KPS initiator system using potassium persulfate (KPS) as the free radical initiator which activated at temperature of 70 °C, and 1 study each performed free radical polymerization by using azobisisobutyronitrile (AIBN) initiator and ammonium persulfate (APS) initiator, respectively, to generate the radicals for the free radical polymerization.

Hydrogel properties

Porous structure

The morphological characterization of hydrogels is one of the important parameters in hydrogel preparation. This is because morphological structure of hydrogels is differed from changes in the hydrogel's composition to the preparation method, or by any interactions occurred within the polymer matrix (13). As mentioned, slight changes in hydrogel properties, including the structure of hydrogel matrix may influenced the applications of hydrogels. In this review, the morphological characterization of hemicellulose-based hydrogels was analysed by using the scanning electron microscope (SEM) as mentioned in most studies. Among them, 3 studies had presented the freeze-dried hemicellulose-based hydrogels possessed a macroporous structure and the other 4 studies had described the freeze-dried hemicellulose-based hydrogels possessed honeycomb-like porous structure. Meanwhile, 2 studies by Chen et al. and Sun et al., mentioned the resulting freeze-dried hemicellulose-based hydrogels presented with both macroporous and honeycomb-like structure. In overall findings, among all the studies mentioned above, the porous structure of hydrogel matrix can be increased with increasing of crosslinking density, as more open and looser pore network structures were formed. However, with continuous increasing of crosslinking density, it may also lead to uneven crosslinking density which resulted to formation of uneven network structure or cracklike structure. Moreover, the importance of knowing the porous structure of hydrogels was mentioned by this author, where macroporous structure of hydrogels resulted to increase amount of water absorption capacity into the hydrogel matrix, where it is generally known that the

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increasing water absorption capacity is closely related to the increasing swelling capacity of hydrogels, thus may impact the applications of the resulting hemicellulose-based hydrogels for drug delivery system.

Swelling capacity

Swelling ratio (SR) is another important characterization parameter in every hydrogel preparation as it represents the capacity of water being absorbed within the hydrogel matrix and is a function of water retention for the hydrogels. The importance of studying the SR of hydrogels is because it demonstrated the swelling capacity of the resulting hydrogels, and it is considered as the most important property which influenced the applications of hydrogels for drug delivery system. In overall findings of all the studies reviewed, most authors described the SR of hemicellulose-based hydrogels were shown to be influenced with the changes to their network structure, where an increase in SR can be seen in a more expanded or less dense network structure of the hydrogels. Whereas, in a less expanded or denser network will resulted to decrease in the SR. Moreover, the authors also reported that these changes in the hydrogel network structure were mainly due to the effect of changes in hydrogel composition, where 5 studies mentioned the effect of monomer contents and 6 studies mentioned the effect of crosslinker contents had resulted to differed network structure formed during the preparation of hydrogels. There is also 1 study performed by Chang et al. where they introduced pore-forming agents to directly alter the network structure of the hydrogels in order to develop their most desired hydrogels. The summary of these changes and their effects on the hydrogels performed in the studies mentioned above are shown in Table 6. Conclusively, the importance of discovering all the possibilities that could change the structure of hydrogels for this review may be useful in order to guide the future researchers in developing the most-suited and functional hydrogels for drug delivery system.

Effect of monomer

The use of monomer in newer hemicellulose-based hydrogels preparation is significant as it able to improve the properties of pure natural hydrogels, include enhancing their swelling capacity. The effect of monomer content of swelling capacity was reported in 2 studies to have an inverse relationship, where increasing in monomer contents will resulted to a denser network and smaller pore size, thus less water absorption into the hydrogels. Hence, resulted to decrease in SR of hydrogels. However, a contradict result was found in 2 studies, where increasing in monomer contents was resulted to hydrogels had a better water absorbency due increase in monomer molecules to copolymerized with hemicellulose, then formed a better hydrogels network structure and promoted hydrophilicity of the resulting hydrogels. Thus, increase the SR of hydrogels. The reason of these two contradictory results was likely because of there is an optimum value of monomer to hemicellulose weight ratio which serve as the cut-off level whether further increasing of the monomer contents would either improve the SR or reduce the SR. It was found that when the monomer contents were increased to the optimum value, the SR of hydrogels increased. However, when the monomer contents were increased beyond the optimum value, the SR of hydrogels decreased as demonstrated in 1 study by Sun et al.

Effect of crosslinker

Crosslinkers have a significant presence in the hydrogels because they are able to prevent dissolution of the hydrophilic polymer chains in an aqueous environment. The effect of crosslinkers content on swelling capacity was shown to have an inverse relationship where increasing the weight ratios of crosslinkers to hemicellulose, will resulted to the decrease in swelling capacity. This is because increasing the crosslinkers concentration during the preparation of hydrogel, will further increased the degree of crosslinking, and more crosslinking points in

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the hydrogel network structure were produced. This causes the pores became denser, and their diameters became smaller, thus less free spaces among the networks can retain water, which consequently lead to decrease in swelling capacity as demonstrated in 6 studies. The effect of crosslinkers on swelling capacity is important because it was later found that moderate crosslinking density is the principal for drug release and degradation of hydrogels.

Effect of Pore-forming Agents

Apart from altering monomer and crosslinker contents, addition of pore-forming agents into the hydrogel preparation may also change the network structure of hydrogels by modifying the pore size. A study by Chang et al. had shown that different pore-forming agents had different influence on the swelling behaviour of CMX-based hydrogels, where the six different agents were: polyvinylpyrrolidone (PVP) K30, polyethylene glycol (PEG) 2000, carbamide, NaCl, $CaCO^{-3}$, and $NaHCO_3$. Based on results, hydrogels without any pore-forming agents did not reach swelling behaviour within 24 h. In contrast, hydrogels with $CaCO^{-3}$, and $NaHCO_3$ which had the largest pore size, reached swelling equilibrium after 6 h. Meanwhile, hydrogels with PEG 2000 had smaller pore size in comparison to hydrogels without any pore-forming agents, and could not reach the swelling equilibrium after 24 h. Thus, the swelling behaviour of hydrogels is related to the size of their network structure pore. Hydrogels with macroporous structure are more favourable to the diffusion of water molecules into the hydrogels network. Therefore, these macroporous hydrogels had better and faster swelling capability (20).

Stimuli-responsive

In this part, we have reviewed most studies of hemicellulose-based hydrogels on their stimuli-responsive behaviour, and overall findings had demonstrated hemicellulose-based hydrogels have an excellent stimuli responsiveness towards many external stimuli. Among them, 3 studies described the hemicellulose-based hydrogels to show response with changes in temperature of the surrounding medium 10 studies showed response with changes in pH of the surrounding medium and 4 studies showed response towards changes in ionic strength of the surrounding medium (14), while 1 study each described the hemicellulose-based hydrogels showed response when light radiation and magnetic-field (28) were applied to the surrounding medium. The summary of these stimuli response of hemicellulose-based hydrogels and their effects on the hydrogels performed in the studies mentioned above are shown in Table 7.

Temperature-sensitive

The hemicellulose-based hydrogels have an obvious temperature sensitivity as it was found that the SR of hemicellulose-based hydrogels was affected by changes in temperature. The SR of the hydrogels was shown to have an inverse relationship with the temperature level. Thus, increasing the temperature will resulted to decrease in SR of hydrogels. This is because when the external temperature is above the lower critical solution temperature (LCST), the network of hydrogels will shrink and became less expanded, causing the hydrogels to force out the absorbed water, and thus reducing the SR. Generally, LCST is regarded as the temperature point at which the SR of hydrogels declines sharply, and it can be manipulated by changing the ratios of polymer and/or monomer concentrations. Therefore, it permits the hemicellulose-based hydrogels to be a potential material for biomedical applications, and this include application in drug delivery system.

Ph-sensitive

Hemicellulose-based hydrogels were studied to have a pH-sensitive swelling behaviour as when the hydrogels were placed in different pH medias, they exhibit different swelling capacity. In general, the SR of hydrogels declines in an acidic pH. This is

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because the carboxyl ($-COO^-$) groups are protonated and converted into carboxylic (-COOH) groups, which led to decrease in the electrostatic repulsion forces among the $-COO^-$ groups, and increase the hydrogen bonding among the -COOH groups. This causes the network of polymer to collapse, thus reducing the SR. Meanwhile, at alkaline pH, -COOH groups are ionized and converted into $-COO^-$ groups, which increased the electrostatic repulsion forces among the $-COO^-$ groups. This resulted to the network of polymer became expanded, thus increasing the SR. The changes in SR of hydrogels at different pH values are mainly depends on the ionized pendant groups (i.e., carboxylic group), fixed charges on the network of polymer, and the electrostatic repulsive forcers. Therefore, this pH-sensitive swelling behaviour of hemicellulose-based hydrogels may make it useful material for controlled and sustained drug delivery.

Ionic strength-sensitive

Hemicellulose-based hydrogels were determined to be sensitive towards changes in ionic strength because their swelling capacity was found to be strongly depends on the ion concentrations added into the swelling medium. In a study done by Ashraf et al. it was found that SR of hydrogels decreased as the concentration of cations such as Na^+ or Ca^{2+} increased. This is because by increasing these cations concentration will resulted to decrease in the ratio of ions inside the hydrogel to the surrounding medium, and this is mainly due to the ionic interactions that took place between the cations and $-COO^-$ groups. These interactions led to the decrease in osmotic pressure between the hydrogel and water, causing the network of polymer became shrink, and forced out water from the hydrogel. Thus, reducing the SR of hydrogel. Similar findings were also demonstrated in a study by Peng et al. Moreover, when the concentration of electrolytes increased, it resulted to screening of anionic groups ($-COO^-$) of polymer network by the cations. This caused the electrostatic repulsion forces to reduce, and induced the hydrogel to shrink. Since, ions composition did influence the network structure of hydrogels, this finding may be useful in designing a more potential hydrogels preparation for drug delivery system.

Light and magneticfield-sensitive

In overall findings, temperature, pH and ionic strength are the most commonly studied stimuli for the development of stimuli-responsive hydrogels in this review. In the other hand, stimuli such as light radiation and magnetic field can also control the changes in swelling capacity of hemicellulose-based hydrogels. However, as to date, there is a very limited number of studies available on light and magnetic-sensitive hemicellulose-based hydrogels for drug delivery applications. In this review, 2 different studies had each demonstrated the response behaviour of hemicellulose-based hydrogels with the application of light radiation and magnetic-field with their significant effects on polymer matrix of the resulting hydrogels.

A study by Cao et al. on xylan-type hemicellulose hydrogels copolymerized with azobenzene was demonstrated to exhibit a light responsive behaviour. It was found that the stable trans-conformation of the azobenzene get converted into cis-conformation when the resulting hydrogels were exposed to the UV irradiation. However, this cis-conformation of azobenzene would get converted back to its trans-conformation when it was exposed to visible light or deposited in the dark. This signal changes in azobenzene conformation confirmed the trans-cis photoisomerization of azobenzene in the hydrogels, and the trans-cis photoisomerization of azobenzene resulted to the shifting of hydrophilic/ hydrophobic material of the resulting hydrogels. It was further explained that the shifting of hydrophilic/hydrophobic balance in the hydrogels is the one responsible for the drug release behaviour of the hydrogels. Therefore, light responsive hydrogels may

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have the potential for drug delivery application.

Meanwhile, a study by Zhao et al. on the development of hemicellulose-based hydrogels formed with magnetic iron oxide (Fe_3O_4) nanoparticles had shown to exhibit a magnetic responsive behaviour when exposed to the magnetic field. The study demonstrated that the Fe_3O_4 nanoparticles content formed in the hydrogels is responsible for the swelling capacity of the resulting hydrogels, in which the SR of hydrogels decreased as the Fe_3O_4 nanoparticles content increased. This is because the capability to adsorb water reduced with increasing Fe_3O_4 nanoparticles formed in the hydrogels in comparison to pure hemicellulose hydrogels, which resulted to decrease in the SR. In brief, these magnetic nanoparticles proved to be able to control the swelling capacity of the hemicellulose hydrogels, thus have potential in drug delivery application.

Drug delivery application

Aforementioned, hemicellulose-based hydrogels have an excellent tuneable swelling capacity which can be easily modified and controlled. Therefore, many recent studies were published to study the impact of this property on drug delivery applications. In this review, we have identified 15 studies that had performed drug release studies for their hemicellulose-based hydrogels to demonstrate the drug release behaviour from the resulting hydrogels prepared, and their potential applications for drug delivery system. Conclusively, different model drugs had been used in all the mentioned studies, and different potential applications were also identified in those studies. The summary of various model drugs released from the hemicellulose-based hydrogels and their applications for drug delivery system are shown in Table 8.

Controlled-release drug delivery

In this review, the drug release studies of hemicellulose-based hydrogels had shown a direct relation with the swelling ratio (SR) of hydrogels. Generally, the drug release of model drug increased as the SR of hydrogels increased. As mentioned earlier in this review, the SR of hydrogels can be controlled by changes in pH, polymer and monomer weight ratio. In other studies, application of UV radiation, magnetic field and addition of suitable pore-forming agents to the hydrogels may also influenced the SR of hydrogels. Hence, the ability of controlling the SR of hydrogels elucidate the effectiveness on controlling the drug release of model drug from the hydrogels, and serve their use in controlled-release drug delivery applications as demonstrated in 11 studies shown in Table 8, and among them had specifically showed their potential use for protein delivery (1 study), insulin delivery (1 study) and intestinal-specific drug delivery (4 studies).

Protein delivery

Protein delivery is one of many applications of hemicellulose-based hydrogels for drug delivery system. The unique properties of hydrogels making them a desirable approach in delivering protein, and this include their capability of protein adsorption and release behaviours which are useful as carrier for protein delivery. In this review, it was found that a study by Zhao et al. on the development of in situ formation of magnetic Fe_3O_4 nanoparticles during the crosslinking of hemicellulose showed that the magnetic-responsive hydrogels had a higher adsorption BSA capacity (146.5 mg/g) compare to pure hemicellulose-based hydrogels (100.2 mg/g). It was found that the Fe_3O_4 nanoparticles is the one responsible for enhancing the BSA adsorption capacity as the NH_2 groups of BSA can bind to the orbitals of Fe atom. Moreover, the BSA-loaded magnetic-responsive hemicellulose-based hydrogels had shown an effective BSA release in PBS of pH 7.2 to 7.4, with overall BSA release of 74% in 5 days. Therefore, the properties of the hydrogels with tuneable swelling capacity as well as their controllable protein adsorption and release profile had

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proven their potential application in controlled-release protein delivery

Insulin delivery

Developing novel oral insulin delivery by encapsulation of insulin in polysaccharides hydrogels in form of microspheres as an alternative for delivering insulin through oral administration has been studied by several researchers in recent years. This is because microencapsulation of insulin offers many benefits such as protection against degradation in upper gastrointestinal (GI) tract, and colon-specific drug delivery. In this review, it was shown that a study by Martínez-López et al. on the development of insulin-loaded microspheres synthesized by enzymatically crosslinking of arabinoxylan (AX) had shown that the AX microspheres were able to reduce the insulin loss in the upper GI tract during the in vitro control insulin release studies, and able to retain high percentage of insulin of approximate 75% of insulin in the hydrogel matrix. Hence, proven their effectiveness to deliver insulin via oral administration that is also colon-specific. Moreover, in vivo studies on murine to support the prior finding, were reported to have significant hypoglycaemic effects with improved insulin bioavailability, thus, promotes the effectiveness of this enzymatically crosslinked AX microspheres as an oral insulin delivery.

Intestinal-specific drug delivery

Hemicellulose-based hydrogels were proved to be a promising drug carries for the intestinal-specific oral drug delivery as they exhibited great drug release studies in response to pH changes. It was shown that drug release of model drug increased as the pH increased, thus it is ideal to be use to target the drug release specifically in the intestine. In this review, acetylsalicylic acid (ASA) had been extensively studied as a model drug for intestinal-specific drug delivery as reported in 3 out of 4 studies. This mainly due to the fact that ASA release required to be controlled differently in the gastric and intestinal fluids to overcome its major side effect, that is irritation to the stomach. Overall, in those 3 studies, the drug release behaviour of ASA from various preparations of hemicellulose-based hydrogels had shown similar findings, where the cumulative release rate of ASA was significantly higher in the intestinal fluid (pH 7.4) with 85-91% as compare to its cumulative release rate in gastric fluid (pH 1.5) with 24-26%. The mechanism of this high cumulative release rate of ASA from the hemicellulose-based hydrogels in intestinal fluid was probably due to the electrostatic expulsion forces resulting from the ionization of -COOH groups present in alkaline pH. This later caused the expansion of the hydrogel network, and led to a faster release rate of ASA from the hydrogels.

Sustained-release drug delivery

Hemicellulose-based hydrogels have appeal to be suitable drug carriers for sustained-release of encapsulated drugs in the human digestive system as reported in 4 studies. In this review, it was found that a study by Chimphango et al., on the HRP-sustained release from the enzymatically-crosslinked xylan-based hydrogels had shown that the in situ encapsulated HRP, both during and after the formation of xylan-based hydrogels was released in its active form over a period of 180 min, which indicates the resulting xylan-based hydrogels have the potential use for sustained-release drug delivery. Moreover, this study also demonstrated the release rate of HRP was influenced by in situ encapsulation methods of HRP either by after or before the formation of xylan-based hydrogels, in which the in situ encapsulated HRP before the formation of xylan-based hydrogels showed a continuous decline of HRP release rate over time as compare to the stable release rate of encapsulated HRP after the formation of xylan-based hydrogels. This condition explained that the in situ encapsulated HRP after the formation of xylan-based hydrogels had less

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restriction on the release rate of HRP from the hydrogel matrix as compare to the HRP encapsulated before the formation of xylan-based hydrogels. Thus, this finding of the stable release rate of HRP indicates that the in situ encapsulated HRP after the hydrogel formation is significant for an efficient sustained-release drug delivery, and demonstrated that the choice of encapsulation method does matter in modifying the sustained release of model drug from the resulting xylan-based hydrogels.

Conclusion

This study has successfully provided a systematic literature review of hemicellulose-based hydrogels for drug delivery system, with extensive findings on their synthesis, properties and applications for drug delivery. Conclusively, the findings of this study had shown that hemicellulose-based hydrogels have great performance and functionality, and proven to be a promising drug carrier for controlled and sustained drug release, mainly due to their great tuneable and controllable drug release behaviour which can be easily modified. Moreover, the findings of this study have covered many different hemicellulose-based hydrogel preparations available from many recent studies, which most of them presented with many great improvements to their properties which further enhance their applications for drug delivery system. Therefore, this study provides massive evidence of the development of hemicellulose-based hydrogels as a potential drug carrier for drug delivery system and may contribute to the existing scientific knowledge of biopolymers for drug delivery system, and thus promote more interest on researchers to develop a natural-based drug carrier of economical and green renewable resources, and discover a new approach on controlled and sustained drug delivery system to address the current issues or limitations with conventional drug dosage form.

Limitations

This study may have provided extensive findings, however it is still limited by the fact that there were not many studies done specifically on the drug release studies of the hemicellulose-based hydrogels with model drugs, because many studies are more focus on the development of hemicellulose-based hydrogels, and the discussion is limited to the theory of their potential use in drug delivery system. This may hinder the possibility to discover other drug delivery application that would be useful and broaden the knowledge and findings of this study. Apart from that, this study has concluded that most studies on the development of hemicellulose-based hydrogels for drug delivery system were limited to chemical crosslinking method, while there is another crosslinking method available, namely physical crosslinking method.

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Conflicts of interest

The authors declare no conflict of interest.

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