Chapter 8

PVP-BASED HYDROGELS: SYNTHESIS, PROPERTIES AND APPLICATIONS

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ABSTRACT

Hydrogels are three dimensionally crosslinked polymeric network which can retain a huge amount of water but do not dissolve in water. Polyvinylpyrrolidone (PVP) is a synthetic polymer with good biocompatibility and transparency and with the action of different stimuli (radiation, heat, pressure, chemicals, etc.) undergoes crosslinking, and can form hydrogels. Due to their tissue compatibility and tissue like consistency, PVP hydrogels are very promising for different biomedical applications. However, because of inferior swelling capacity and poor mechanical property, the use of pure PVP hydrogels is limited. To overcome this problem, PVP is blended with different polysaccharides or other polymers according to requirement and from the standpoint of applications. This review article mainly focuses on different kinds of PVP based hydrogels; their modes of synthesis, properties and a range of applications of these blend hydrogels.

Keywords: Biomaterial, crosslinking, drug delivery, hydrogel, PVP, radiation, wound dressings.

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INTRODUCTION

Polyvinylpyrrolidone (PVP) is a biocompatible synthetic polymer, and for many years has been applied as a biomaterial or additive to drug compositions, e.g. as a blood plasma expander and as vitreous humor substitute [1]. Under action of different stimuli (radiation, heat, pressure, chemicals etc) PVP undergoes crosslinking and lead to the formation of PVP hydrogel. Hydrogels are extremely hydrated polymer gels with macromolecular three dimensional networks that swell but don't dissolve in water. They are physically or chemically cross-linked polymers and the ability of hydrogels to absorb water arises from hydrophilic functional groups attached to the polymeric backbone, while their resistance to dissolution arises from cross links between network chains [2-10]. PVP hydrogel has excellent transparency and biocompatibility.

Till date many findings in research regarding the synthesis and characterization of PVP hydrogels have been reported. However, it is also reported that because of inferior mechanical properties and low swelling capacity, the application of PVP hydrogel is not widespread [4, 11]. There are many detailed account of occurrence about PVP and polysaccharide (chitosan [1, 12-17], carboxymethyl cellulose [4-7, 11, 18], carrageenan [19-22], agar [4-7, 23-25], sodium alginate [26], etc) blended hydrogels, because when PVP is blended with polysaccharides, the properties of hydrogels improve. The hydrogels are generally synthesized by incorporating crosslinking in the polymer matrix. Crosslinked PVP based hydrogels mainly belong to the category of physical hydrogels, and they are synthesized by using γ-irradiation (most common method to prepare hydrogels) [23, 27-47], electron beam radiation [48-49], UV-photo crosslinking [50-60], freeze-thawing [46, 61], moist heat treatment [4-7], etc. They have diversified ways of application, mainly in biomedical field such as: human lens substitution, artificial cartilage, dermal wound healing, semi occlusive wound dressings, implants, controlled drug release, remineralization of enamel on teeth, and so on [23-25, 62-111]. In biomedical application, PVP based hydrogels possess the following important properties i.e. easy replacement, transparency, flexibility, barrier against bacteria, good adhesion, easy handling, oxygen permeability, control of drug dosage, absorption, and prevention of loss of body fluids, etc. According to the application point of view, the properties and structures of the PVP based hydrogels can be tailored, as there are different examples of semi interpenetrating networks (semi-IPN), grafted structure, electrospun mats,

microspheres, nano-composites etc [24, 112-119]. There are many commercialized hydrogels (prepared with hydrophilic polymers) are available in the market throughout the world with different trade names. VIACELL s.r.o is one of the largest suppliers of hydrogels in Czech Republic. They manufacture hydrogels for normal wounds, burns and cuts as well as hydrogels to cure different ulcers [120]. Nu-Gel wound dressing is a contribution from Johnson and Johnson Consumer Products. They provide an optimal moist healing environment for partial thickness pressure ulcers, vascular ulcers, diabetic ulcers, and first and second degree burns. Nu-Gel cools and soothes as an occlusive-hydrogel dressing [121]. Kikgel Company from Poland supplies hydrogel dressing called Neoheal. This dressing material is a new, unconventional mean, facilitating the treatment and accelerating healing of different kinds of wounds, especially: burn wounds, ulcerations, bedsores, all kinds of skin damages in which humid medium is favorable. Hydrogel dressings Neoheal are an aqueous composition of natural and synthetic polymers such as: polyvinylopyrrolidone, polyethylene glycol and agar, cross linked by a beam of electrons. Due to radiation processing the product is fully sterile [122]. The Bhabha Atomic Research Centre (BARC) has developed a process for large-scale production of hydrogels based on cross-linking of PVA by radiation (national and international patent filed) instead of PVP. All ingredients used in the process are low cost, biocompatible and are locally available or can be readily imported. They have a cooling effect on the burn wound and thus reduce the severity of the pain. It further provides moist environment, soften any slough, provides sterile cover and regulates the oxygen supply to the wound site to enable faster healing. The hydrogel has the property of adhering firmly yet gently to the healthy surface. It does not adhere to wet wound surface. This results in painless dressing. The narcotic tissues in the wound stick to the inner surface of the hydrogel and come out with the dressing. Being transparent, the progress of the wound healing can be observed without removing the dressing. These dressings are available in various sizes [123]. This paper is focused about the review of PVP based blend hydrogels.

PVP BASED BLEND HYDROGELS

PVA-PVP blend hydrogel

To increase the mechanical properties of the hydrogels, PVP hydrogel dressings were normally prepared with agar as a second component. But it had some disadvantages, because the presence of agar may facilitate the penetration of

microorganisms into the hydrogel, especially in highly humid environments in tropical regions. It has been reported that incorporation of polyethylene glycol (PEG) could improve the barrier against bacteria. Razzak et al. reported about PVA and PVP blend hydrogel, where instead of using agar as a second material PVA was used, and they were crosslinked using gamma radiation [73, 75]. Irradiation is a very suitable method for hydrogel synthesis. Radiation process shows many advantages such as easy process control, possibility of joining hydrogel formation and sterilization in one technological step, no requirement of adding any initiators and crosslinkers which may be harmful and difficult to remove [124-125].

PVA/PVP interactions occur through interchain hydrogen bonding between the carbonyl group of PVP and hydroxyl group of PVA (Fig.1) resulting in physical crosslinking of these two polymers [77, 126].

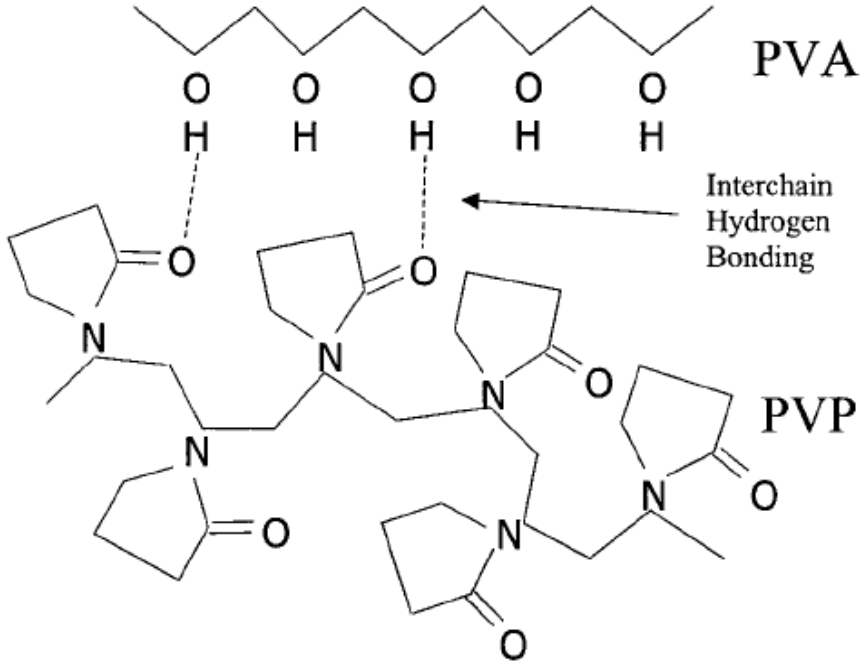

Figure 1. Interchain hydrogen bonding within a PVA/PVP blend occurs between carbonyl groups on PVP and hydroxyl groups on PVA. Reprinted with permission from Ref. [77].Copyright 2003, John Wiley and Sons

PVP-Chitosan Blend Hydrogel

Chitosan is a partially deacetylated product of chitin, containing D-glucosamine, which is a natural polymer present in exoskeleton of crustaceans and cell walls of fungi. Chitosan has been reported to be bioabsorbable, biocompatible and biodegradable with numerous applications in the biomedical, pharmaceutical, agriculture, packaging, and food biotechnology fields. By combining chitosan with the synthetic polymer PVP, a range of blends with a variety of properties and forms has been synthesized. They show blood compatibility [12-17].

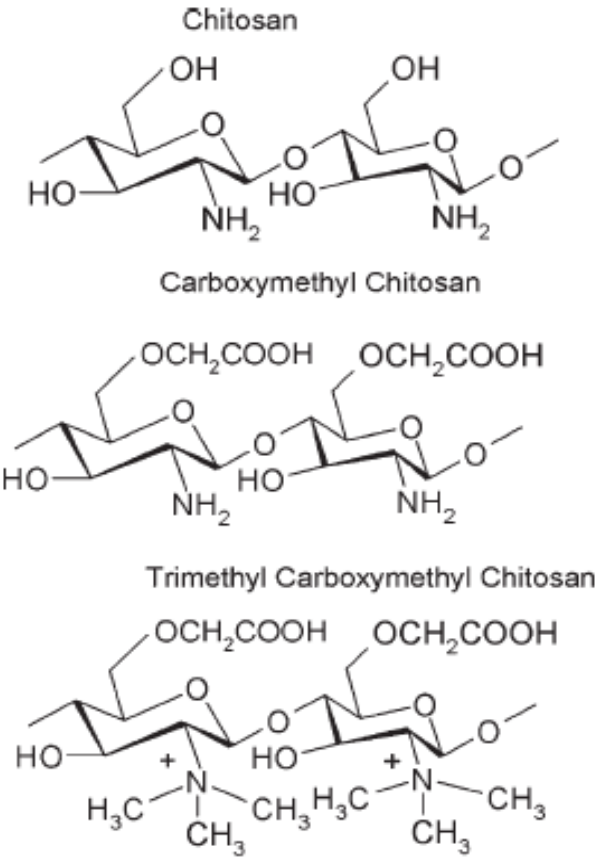

Figure 2. Chemical structures of chitosan, carboxymethyl chitosan and trimethyl carboxymethyl chitosan.. Reprinted with permission from Ref. [17].Copyright 2011, John Wiley and Sons

PVP- Carboxymethyl Cellulose (CMC) Blend Hydrogels

Cellulose is a chain-shaped polymer which contains β-1,4-D-glucosidic linkages without any branches, is the most abundant natural polysaccharide. Carboxymethyl cellulose (CMC) is its ether derivate in which original H atoms of cellulose hydroxyl groups are replaced by carboxymethyl substituent, $–CH_2COOH$. Due to its good water-solubility, biocompatibility, high abundance and low price it has been widely used in many fields [4-7, 11 18].

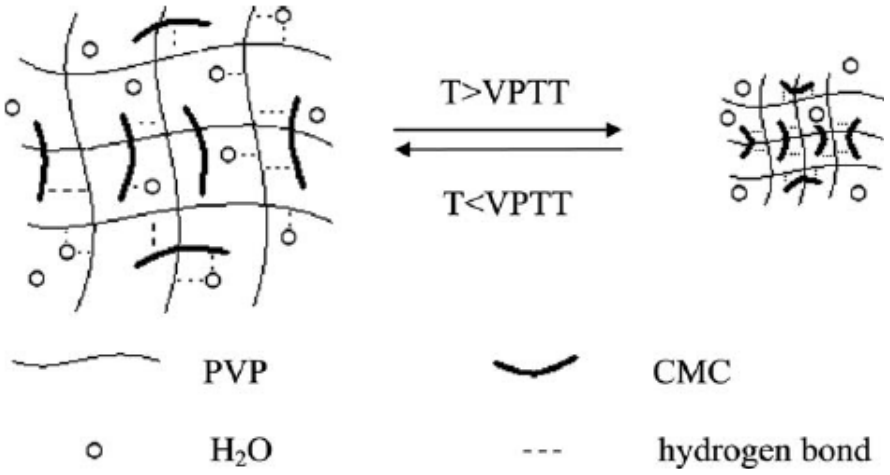

Figure 3. Schematic illustration of PVP/CMC semi-IPN hydrogels structure before and after phase separation. Reprinted with permission from Ref. [18].Copyright 2010, John Wiley and Sons

PVP- Carrageenan Blend Hydrogels

Carrageenan is one of the most abundant polysaccharides, which exists as matrix materials, in numerous species of seaweeds. They are water soluble, sulfated polysaccharides extracted from different species of marine red algae of the class *Rhodophyceae*. Kappa-carrageenan and iota-carrageenan are considered as more important types of carrageenans as they are capable of forming thermoreversible gels. They have the backbone structure consisted of alternating α-1, 4 and β-1, 3-linked galactose residues. Several articles have been published regarding the synthesis of PVP-carrageenan hydrogels by radiation crosslinking [19-22]. Fig.4 shows a proposed mechanism of κ-Carrageenan grafted PVP.

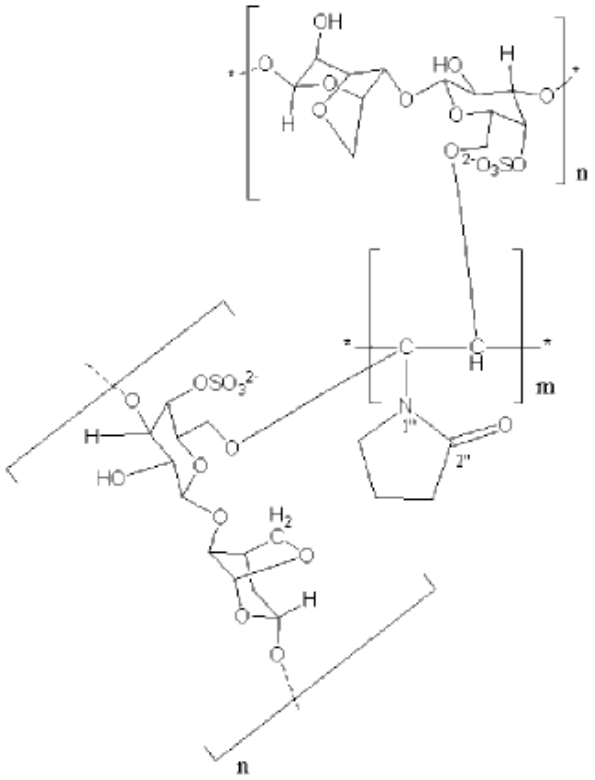

Figure 4. κ-Carrageenan – *graft* – PVP. Reprinted with permission from Ref. [22].Copyright 2006, John Wiley and Sons

Except these very common PVP-polysaccharide blend hydrogels, many different PVP blended hydrogels have been reported such as PVP-agar [4-7, 23-25], PVP-sodium alginate [26, 113], PVP-gelatin [127], PVP-polyethylene oxide (PEO) [128], PVP-I [70-71], PVP-polyacrylic acid (PAA) [72, 112, [129], PVP-2-hydroxyethyl methacrylate (HEMA) [114], and so on.

METHODS OF SYNTHESIS OF PVP-BASED HYDROGELS

Radiation

i. γ- and electron beam radiation: In early 1950s, the pioneers of the radiation chemistry of polymers began some experiments with radiation crosslinking of hydrophilic polymers. The noticeable interest in the application of radiation techniques to obtain hydrogels for biomedical purposes began in the late sixties as a result of the papers and patents invented by Japanese and American scientists, headed by Kaetsu in Japan and Hoffman in USA. Hydrogels can be obtained by radiation technique in several ways, including irradiation of pure polymers, monomers or solution of polymers and/ or monomers in bulk, solution or emulsion. The first method, i.e. irradiation of hydrophilic polymer in dry state has some drawbacks. It may require special sample preparation (like pressing or melting), and some difficulties may be encountered in obtaining homogeneous macroscopic gels. It requires usually much higher doses to obtain a gel as compared to irradiation in solution, and, furthermore, it may be difficult to remove the oxygen fully, a promoter of unwanted side reactions. More frequently the method of monomer irradiation is applied. In this technique, polymerization takes place in the first stage, followed by crosslinking of the formed chains. This way is possibly the most convenient when the chosen monomer is easily available but its polymer is not. Among various methods applied for the production of hydrogels, the radiation technique has many advantages, as a simple, efficient, clean and environment-friendly process. Application of radiation for the formation of hydrogels for biomedical use offers a unique possibility to combine the formation and sterilization of the product in a single technological step. This allows simplifying the technology and reducing production costs. Hydrogels based on PVP to be used as wound burn dressing were invented by Rossiak et al. Radiation production of hydrogel wound dressings started first in Poland at the Technical University of Lodz in 1992. PVP based dressings obtained by e-beam irradiation, were commercialized under the registered trademarks KIK-gel and AQUA-gel [30, 41, 44]. Baccaro and coworkers in 1995, investigated about the mechanical properties of the PVP hydrogels undergoing radiation. It was found that radiation dose increase has no effect on the modulus of elasticity but produces a negative effect on the break-strain and positive initial effect on the peak-load that develops into

a negative effect above a dose value of 30kGy. It refers that peak-load depends strongly on the PVP concentration, the break-strain is inversely dependant on the radiation dose and the modulus of elasticity depends mainly on the PVP concentration [27]. New aspects of the synthesis and characterization of PVP and persulfate containing PVP-hydrogel irradiated by γ-ray has been investigate and discussed by Kaplan Can, et al. in their series of published articles. The gelation doses of persulfate containing polymer solutions were calculated by Charlesby – Pinner equation. It was found that the gelation dose values were shifted to higher values by increasing persulfate concentration in solution [28, 32, 34, 36, 37, 39]. Till now it has been found that using of gamma radiation is the most widespread technique to prepare different PVP-based hydrogels in different ways including synthesis of temperature sensitive hydrogel blends, tissue engineering scaffolds, for the grafting purpose, incorporation of electrical properties in hydrogel blends and so on [29, 31, 33, 35, 38, 40, 42, 43, 45, 47]. Electron beam radiation is also an effective mean of hydrogel crosslinking [48-49]. Dorit Meinhold and coworkers (2003) presented a novel approach to prepare PVP hydrogel coatings on poly (ethylene terephthalate) (PET) surfaces for the surface modification of materials in a wide variety of shapes like foils, fibers, tubes, or films. A schematic diagram is shown in Fig.5 [49].

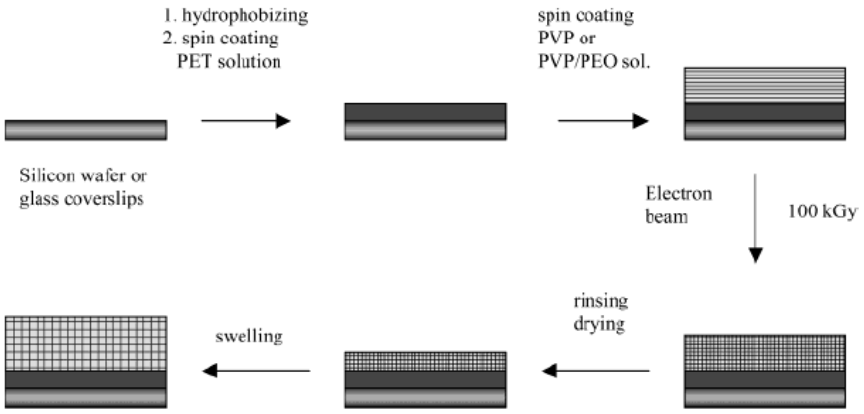

Figure 5. Scheme of the preparation of a PVP Hydrogel Layer on a PET Surface by Electron Beam Cross-Linking. Reprinted with permission from Ref. [49].Copyright 2004, American Chemical Society Publications

ii. Ultraviolet (UV) radiation may be considered as an alternative and effective method for the crosslinking of PVP hydrogels, because typical high energy radiation sources, e.g. γ-radiation, are very expensive and not easily available. Moreover, UV radiation involves very short time for reliable gel formation. This hydrogel preparation procedure appears very promising for the advantage that guest molecules or particles, such as cells or metal nanoparticles, can be easily incorporated in the gel by dissolving or suspending them in the polymer solution to be irradiated. By this simple procedure it is possible to include in the hydrogel formulation other components which could tune the hydrogel functional properties to the specific applications. Catalani and co-workers presented a study related to PVP crosslinking using UV-C radiation (λ=254 nm) from a low pressure arc mercury lamp. The process can be accelerated by the addition of hydrogen peroxide to the polymer aqueous mixture or by Photo-Fenton reaction. The peroxide addition accelerates the crosslinking kinetics through the hydroxyl radical (·OH) generation during its photo-homolysis. Hydroxyl radical reacts with polymer macromolecules giving rise to macroradicals. If macroradicals located on different polymer chains are favorably positioned, they may undergo recombination leading to crosslinking. Photo-Fenton reactions produce hydroxyl radicals through the absorption of the UVA – visible radiation (290 – 400 nm) using simple components like ferric aqueous solution in presence of hydrogen peroxide. UV crosslinked PVP hydrogels showed a strong gel mechanical behavior with viscoelastic moduli values similar to those of biological gels [50-59, 130]. Schemes of hydroxyl radical production are shown in Fig.6.

a) $H_2O_2 + h\nu_{254nm} \rightarrow 2HO\cdot$

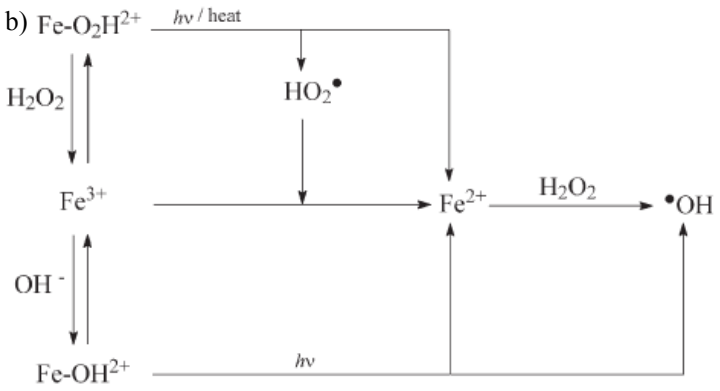

Figure 6. Scheme of production of hydroxyl radical from the (a) photo-homolysis of peroxide, and (b) photo-Fenton reactions Reprinted with permission from Ref. [51].Copyright 2004, Elsevier

Freezing-Thawing or Freezing-Thawing in Combination with Irradiation

Some researchers have reported about another approach for PVP based hydrogel preparation, repeated freezing-thawing or freezing-thawing in combination with γ-irradiation. For the freezing thawing, the polymer solution is kept under very cold condition, called freezing, (can vary from -20ºC to -70 ºC) for a period of time as required depending on the composition of hydrogel mixture and then temperature of the mixture is raised to the room temperature for a duration (thawing). The cycle is repeated several times [46, 61, 74].

Moist Heat Treatment

A novel simple and cost effective method to prepare PVP based hydrogel has been developed in our lab. The technique of hydrogel preparation is designated as "moist heat treatment [4-7]. The hydrogels were developed by applying physical stimulation technique which is an operation friendly technique. The polymer solution was prepared in sealed bottles. Then, the polymer solution was treated in an autoclave sterilizer which provides moist heat condition (107 kPa, 120°C, and 20 minutes), where all the materials were sterilized and the cross-linking phenomena occurred in a single step. Afterwards, the solution was casted into moulds and allowed to cool at room temperature (20-22°C) under an aseptic

environment to achieve the desired hydrogel. During cooling a 3- dimensional network of polymer is developed within the hydrogel and final product of hydrogel is achieved as shown in Fig.7 and 8.

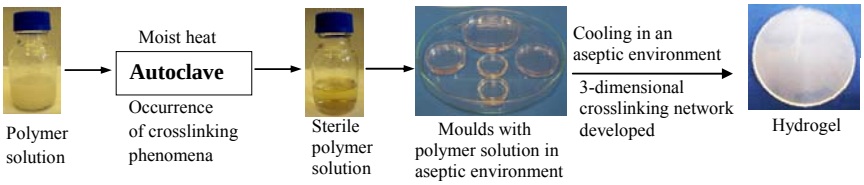

Figure 7. Schematic diagram of hydrogel preparation using moist heat treatment.

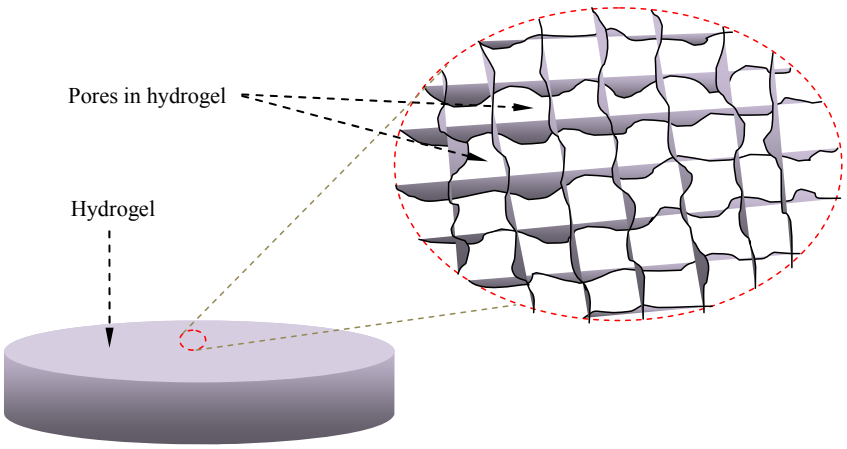

Figure 8. Schematic view of 3dimensionally crosslinked porous structure in hydrogel.

PROPERTIES OF THE PVP-BASED HYDROGELS

PVA-PVP Blend Hydrogels

The mechanisms of radiolysis and network formation (gelation) in mixed solution of PVA and PVP are quite complicated. Investigation of the dynamic rheological behavior of these hydrogels before and after gelation can provide useful information for elucidating these mechanisms, as upon irradiation, the formation of covalent bonds between adjacent polymer chains significantly affects

the viscous and elastic properties of the matrix. Zainuddin et al. in their investigation represented the effect of varying the absorbed dose on the gelation behavior of PVA and PVP solutions. The dynamic rheological behavior of gamma-irradiated 12.8 wt% PVA, 12.8 wt% PVP, and a blend of 8 wt% PVA and 4.8 wt% PVP aqueous solutions have been studied pre- and post-gelation. The viscoelastic behavior observed by rheometry at each dose provides insight not only into the gelation process, but also into the effective network development and the final gel properties. Such a methodology allows us to elaborate the structure-function relationships between gel structure and strength and the radiation dose for these systems [131].

Jonathan and his coworkers showed the feasibility of PVA-PVP blend hydrogel for endoscopic replacement of the nucleus pulposus of a lumbar intervertebral disc. The hydrogels were processed with the use of three freeze/thaw cycles to induce crystallinity. Actually PVA/PVP hydrogels belong to the category of shape memory gels due to their elastic nature, so that they may exhibit predictable, reproducible changes in geometry from the hydrated to dehydrated states. This property of PVA/PVP gel was used in order to develop a procedure to insert the implant into the nuclear cavity endoscopically, implanting the dehydrated material and rehydrating to a desired shape and size *in situ* [76].

Due to their high water content, hydrogels possess excellent biocompatibility and a degree of flexibility similar to natural tissues, which minimizes potential irritation to surrounding membranes and tissues. By controlling the crosslink density, several parameters, such as pore size and elasticity, can be adjusted fitting the requirements of the tissue to be regenerated. Recent strong interest in the development of novel hydrogels and hydrogel composites can be attributed to their unique combination of properties, including biocompatibility, permeability, hydrophilicity, and low coefficient of friction. Zainuddin et al. continued their investigation on PVA/PVP blend hydrogels crosslinked via gamma radiation, and focused on their water diffusion and concentration distribution properties. They mainly extended the studies of Razzak and coworkers. They examined different polymer compositions and doses to identify the optimal condition. Aqueous solution of PVA and PVP containing ~80 wt% water and a mole fraction of PVP of 0.19 irradiated to 25 kGy were found to yield gels that have optimal bioadhesion and good mechanical properties, they were soft and robust and they evoked no significant body tissue response. These hydrogel dressings were capable of absorbing more water than usual and therapeutic drugs could be incorporated into the dressing and, when they are applied the drugs can be released slowly from the dressing into the wound environment [132-133]. In spite of radiation crosslinking, PVA-PVP hydrogels can be crosslinked chemically. As

an example, crosslinked PVA-PVP hydrogels were prepared in aqueous media using $K_2S_2O_8$. In this case it was observed that the gel fraction increases with increasing potassium peroxodisulphate concentration. The swelling rate in water was faster in the beginning and the amount of absorbed water as immersion water uptake of greater than 1400% was obtained. The maximum of swelling was achieved at pH=7 because of the neutrality of the hydrogels and the maximum extent of swelling were followed at 25ºC. However the rate of swelling decreased at higher temperature, thus the swelling behavior of PVA-PVP hydrogels depends on pH and temperature [134]. PVA-PVP hydrogels are ideal candidates for cartilage replacement or as artificial bearing surfaces, because they show better mechanical and network stability when compared with pure PVA hydrogels [78, 79]. Biomaterials developed for the purpose of cartilage replacement should be able to bear the high loads experience in human joints with minimal or no wear and a low coefficient of friction for millions of cycles. Jayanth K. Katta and coworkers have reported the friction/wear test of PVA-PVP hydrogels (prepared using solvent evaporation technique) using a Co-Cr pin articulation (as shown in Fig.9). The experiment was designed to determine the effects of load, lubricant and polymer content on the friction and wear characteristics of PVA-PVP hydrogels [78]. On the other hand Ruyin Ma, et al. reported about the friction properties of the PVA-PVP blend hydrogels (prepared by repeating freezing and thawing method) for the use as an artificial cartilage by using a self made ball-on-disc tribometer [79]. Instead of cartilage replacement PVA-PVP hydrogel can serve for human lens substitution [80].

PVA-PVP hydrogels are found to form a thermodynamically miscible pair and show biodegradability. El-Mohody and Ghanem investigated the biodegradation of PVA-PVP hydrogels by burial method in two types of soils (clay and sandy soils). The pure PVA was the most biodegradable, while the resistance to biodegradation increased with enhanced PVP ratio in the PVA-PVP hydrogel. The highest degradation rate was found to be achieved using clay soil [135].

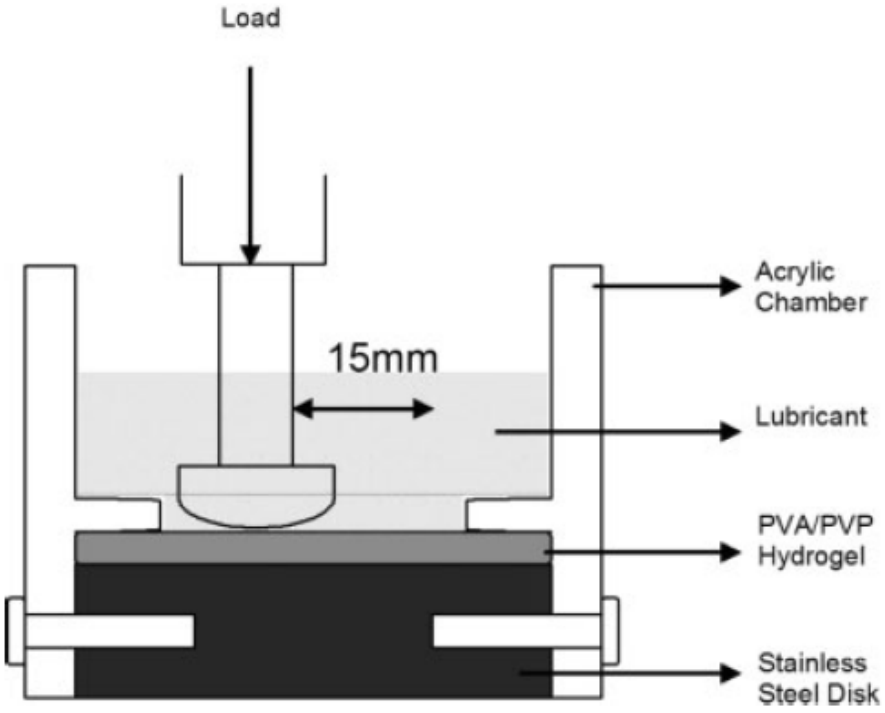

Figure 9. Two-dimensional schematic of a Co–Cr pin articulating against a PVA/PVP hydrogel sample. Reprinted with permission from Ref. [78].Copyright 2007, John Wiley and Sons

PVP-Chitosan Blend Hydrogels

It has already been reported that incorporation of polysaccharides such as chitosan into the PVP/water system obviously increased the gel strength and equilibrium degree of swelling of PVP hydrogel. Comparing with chitosan, carboxymethyl chitosan is an amphoteric polyelectrolyte, which has good hydrophilicity and good miscibility with PVP in aqueous solution. In comparison to PVP hydrogels, these PVP-chitosan blend hydrogels can provide better properties like pH sensitivity, good swelling, good mechanical properties, improved surface property, potential adsorptive capacity for protein, etc. Investigation on PVP-chitosan hydrogels also demonstrated their suitability as a potential candidate for islet immunoisolation, and showed dual properties by

supporting the growth of epithelial cells and selectively inhibiting fibroblast growth [12-17]. Chitosan contains hemostatic properties along with many other biological properties, including bacteriostatic and fungistatic properties that are particularly useful for wound treatment. Nho and Park reported about the hydrogels from a mixture of PVA, PVP and chitosan were made by the combination of freezing-thawing and γ-radiation. Swelling percent was greatly increased as the composition of chitosan in PVA/PVP–chitosan increased. Wounds of 1-cm diameter that formed on the back skin of the rat were covered with hydrogel samples (1.5 x 1.5 x 0.3 cm) and vaseline gauze. At the designated postoperative day, macroscopic observation of wound status was made. The Vaseline gauze dried quickly and stuck to the wound of rat. The PVA/PVP–chitosan hydrogel dressing stopped the bleeding from the wound and had the better curing effect than vaseline gauze [74] (see Fig.10).

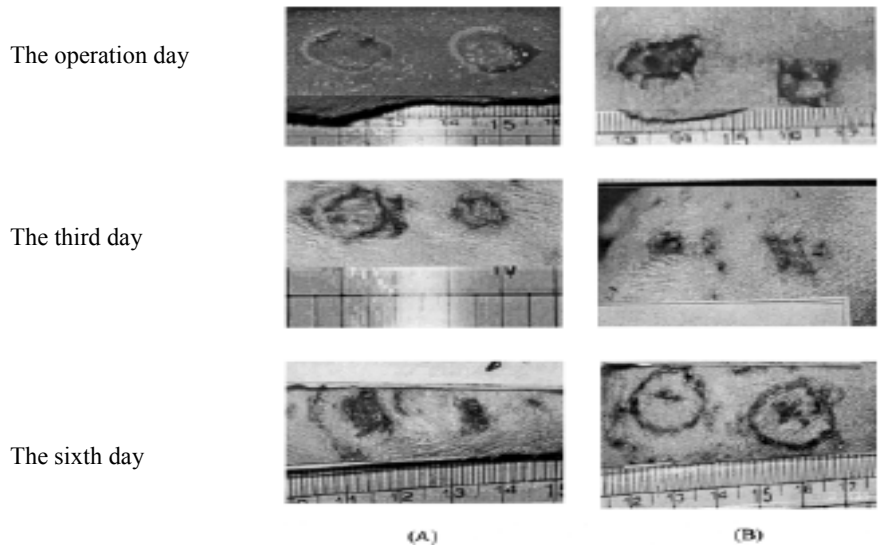

Figure 10**.** Healing process of wound using (A) no dressing (left)/gauze (right), (B) PVA/PVP–chitosan hydrogel (left)/gauze (right). Reprinted with permission from Ref. [74].Copyright 2002, John Wiley and Sons

PVP-CMC Blend Hydrogels

Crosslinked CMC hydrogels possess many excellent properties for utilization of biomaterials, such as high water uptake, biodegradability, and innoxious

quality. However they have very poor mechanical strength, especially in swollen states, which limits their applications. PVP-CMC hydrogel crosslinked by gamma radiation shows better mechanical strength than that of pure CMC hydrogel; better flexibility and swelling behavior than that of pure PVP hydrogel, and similar moisture retention capability to that of a commercial hydrogel wound dressing [11]. Due to the pH sensitive character of CMC, combination of CMC with PVP will produce dual-stimuli vehicles that respond to localized conditions of pH and temperature in the human body [18]. In our lab we have developed PVP-CMC based novel wound dressing hydrogels using a simple technique called "moist heat treatment". This method is very efficient, low cost, does not need extra laboratory set up, and moreover, crosslinking and sterilization of the hydrogels involve a single step like radiation crosslinking, but much safer as the technique does not deal with any kind of radiation [4-7, 11, 18]. Presence of CMC, a polysaccharide, enhanced the swelling property and the viscoelastic properties of the hydrogels, which is very important for a hydrogel wound dressing. The hydrogels must be able to absorb the exudates from the wounds and it must be flexible to be attached to the wound as our body surface is not flat and always in a motion. PVP shows very high miscibility, so it is easier to incorporate drug or antimicrobial agent in the hydrogel. We have incorporated boric acid (BA) as an anti microbial agent in PVP-CMC hydrogel and designated as PVP-CMC-BA. Both PVP-CMC and PVP-CMC-BA show very high water absorption capacity. SEM study reveals that PVP-CMC-BA has denser crosslinking network than PVP-CMC, due to the presence of BA (see Fig.11), which increased the mechanical properties of the hydrgels. FTIR study confirms the interaction of all ingredients used in PVP-CMC and PVP-CMC-BA hydrogels. These hydrogels are highly elastic in nature under no or low strain application, show rubbery consistency with natural tissues. Water vapour transmission test illustrates that these hydrogels are porous and oxygen can pass through them. Agar diffusion test presents that among these two hydrogels only PVP-CMC-BA shows strong antimicrobial property because of the presence of BA (shown in Fig.12) which can protect the wounds from infections and microbial contamination. Positive results achieved from cytotoxicity, skin irritation and sensitization tests prove that both hydrogels are biocompatible; therefore assure the safe use of these hydrogels on human/animal body and can be considered as ideal wound dressings [2-10].

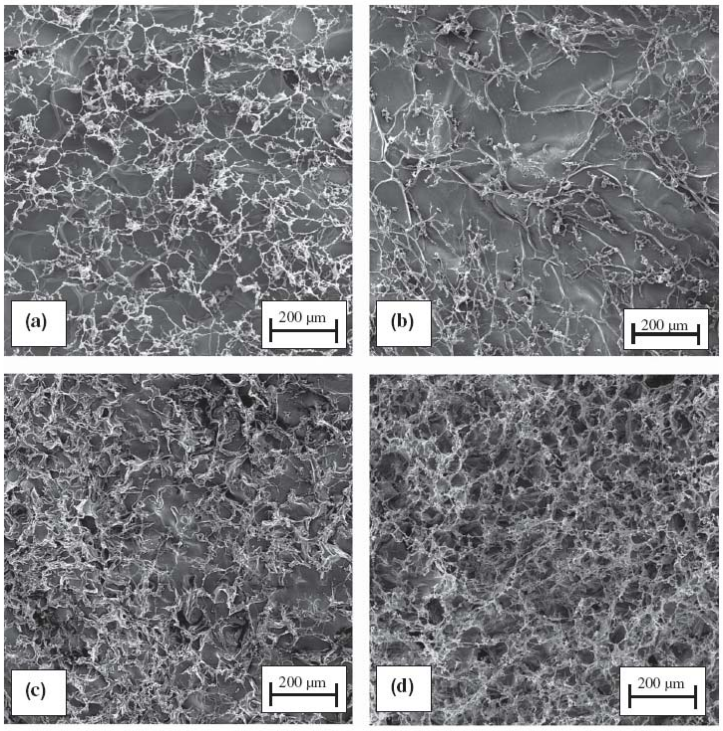

Figure 11. SEM image of freeze dried medicated hydrogels (a) PVP-CMC (surface view), (b) PVP-CMC (cross-sectional view), (c) PVP-CMC-BA (surface view), and (d) PVP-CMC-BA (cross-sectional view).

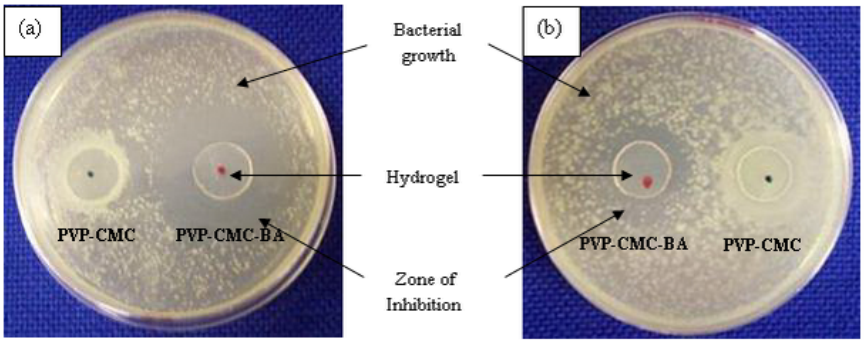

Figure 12. Image of antibacterial effects of PVP-CMC hydrogels without and with 3% boric acid (BA) in presence of skin infection causing common bacteria; (a) *Staphylococcus aureus*, (b) *Escherichia coli*.

PVP- Carrageenan Blend Hydrogels

Several types of carraggeenan are available but the more important types are the kappa-carrageenan (KC) and iota-carrageenan (IC) due to their thermo-reversible gel forming capability. Relleve and coworkers showed that a high degree of swelling was obtained for both IC/PVP and KC/PVP hydrogels in basic solutions owing to both osmotic pressure and electrostatic repulsion between the sulfate groups of carrageenan, while at acidic pH, KC/PVP gels collapse, which results in a low swelling, but surprisingly IC/PVP shows a maximum swelling at pH 4 and collapses below this pH. Due to their excellent swelling properties, i. e., absorption of water by about hundred times its dry weight and stimuli responsive swelling behaviors, these hydrogels may be useful as superabsorbent materials [19]. Gamma irradiation of PVP-KC blends would result in the simultaneous crosslinking of PVP, degradation of KC, and grafting of KC to PVP. A combination of these processes may form a PVP-KC hydrogel with a network structure of (a) a semi-interpenetrating polymer network (SIPN) whereby KC is physically entangled within the crosslinked PVP and (b) a grafted network whereby KC is grafted into the PVP backbone. The overall effect of this network could influence the gel fraction and swelling behavior of the PVP-KC hydrogel. KC acts as a crosslinking inhibitor thereby decreasing the gel fraction of the hydrogels with increasing KC concentrations [20, 21].

APPLICATIONS OF THE PVP-BASED BLEND HYDROGELS

Hydrogel as a biomaterial has been proposed for a wide range of biomedical applications like wound dressings, transdermal drug delivery, oral drug delivery, super absorbents, contact lenses, corneal implants, substitutes for skin, tendons, ligaments, cartilage, and bone [63, 136]. Hydrogels can be successfully used as dressing materials in medical treatment for burns and wounds [4-7, 23]. Due to their hydrophilic properties, hydrogels exhibit low interfacial tensions allowing cells to migrate into the artificial structure which makes them more advantageous over alternative scaffold materials. Hydrogels may also be beneficial as carriers to uniformly disperse living cells or particles serving as drug release system. Gels derived from biologic macromolecules commonly display higher biocompatibility compared to gels made of synthetic polymers because they exert intrinsic bioactivity including certain cellular behaviour.

Wound Healing

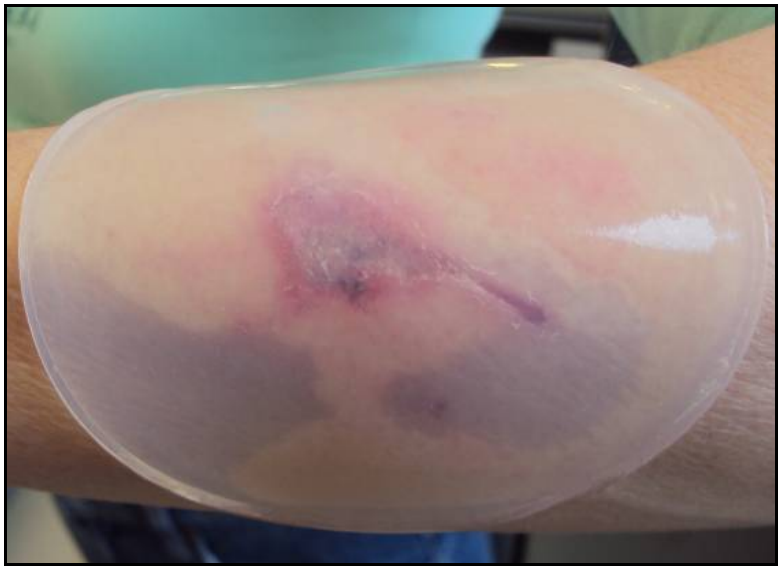

Figure 13. View of PVP-CMC hydrogel prepared by “moist heat treatment”.

Wound healing or wound dressing is one of the major implementations of the hydrogels. There are two kinds of dressings: dry type and wet type. It has been reported that healing with a wet environment is faster than that with a dry environment [62, 66]. Hydrogel dressings in various forms have been used in wound management for over 20 years. Hydrogels for burn wound dressings were first invented by Rosiak et al. in 1989 based on PVP, PEG and agar [23]. Hydrogel wound dressings have many interesting properties like: immediate pain control effect, easy replacement, transparency, barrier against bacteria, good adhesion, easy handling, oxygen permeability, control of drug dosage, absorption and prevention of loss of body fluids, etc [64, 137]. The high moisture content maintains a desirable moist interface which facilitates cell migration and prevents dressing adherence. Hydrogel dressings are available in several forms, based upon a variety of different polymers. Some polymers are cross-linked to impart a degree of structural stability to the final product, which often takes the form of a thin sheet used for application to relatively shallow surface wounds. PVP hydrogel wound dressings are normally prepared in presence of agar as a second component to enhance the mechanical properties of the hydrogels [23, 25, 64, 137]. PVA hydrogel also has excellent transparency, biocompatibility and

smoothness, but one of the major problems in the application of PVA hydrogels is their relatively poor mechanical strength, and the hydrogels become harder with the evaporation of water. The hard gels may damage the wound. This problem is reduced to a significant extent when PVA and PVP are blended together. The properties of the PVP based wound dressings can be monitored according to the composition, mainly upon the different polysaccharides blended with it [62, 69]. PVP-iodine hydrogels are very effective in wound therapy [65, 67]. In our work we have developed the PVP and carboxymethyl cellulose (CMC) based hydrogel by using moist heat treatment, and the hydrogel is designated as PVP-CMC hydrogel. The view of the PVP-CMC hydrogel has been shown on Fig.13.

Drug Delivery

The concept of drug delivery or controlled drug release has emerged from the need for effective management of diseases. These include localized delivery of the drug to a particular part of the body. A variety of drug delivery systems have been developed till now and generally the drug release depends on the pH [100]. Fig.14 shows a model of drug release from swollen hydrogel. Controlled release systems have been developed over a range of pH-domains in the body, such as for the periodontal, oral, gastric and intestinal applications. Because of the soft tissue biocompatibility, hydrogels are of special interest in controlled release applications. It is easier to disperse the drug in the hydrogel matrix, and the high degree of control is achieved by physical and chemical properties of the polymer network. Hydrogels have three dimensionally crosslinked mesh like structure, which provides a matrix for the entrapment of drugs. For example, pH-sensitive chitosan – PVP, semi interpenetrating based controlled released antibiotic delivery system that is well suited for use in a gastric environment [85]. Hydrogels may be impregnated with biologically active agents, such as antibiotics, enzymes, contraceptives, drug antagonists, anticoagulants, and anticancer drugs and may serve as systems for the controlled release of the agents absorbed over a prolonged time period at a specific site of the body. Normally there are two methods for the loading of hydrogels as drug carriers. In one method, the hydrogel monomer is mixed with the drug, an initiator, and a crosslinker and allowed to polymerize, trapping the drug within the matrix. In the second approach, a preformed hydrogel is allowed to swell to equilibrium in a suitable drug solution and then the drug-loaded hydrogel is dried and the device is obtained [86]. Generally, if the crosslinkings are based on physical bonds, such as hydrogen,

ionic, or van der Waal's bonds, the responses of the hydrogels to external stimuli are often reversible [82].

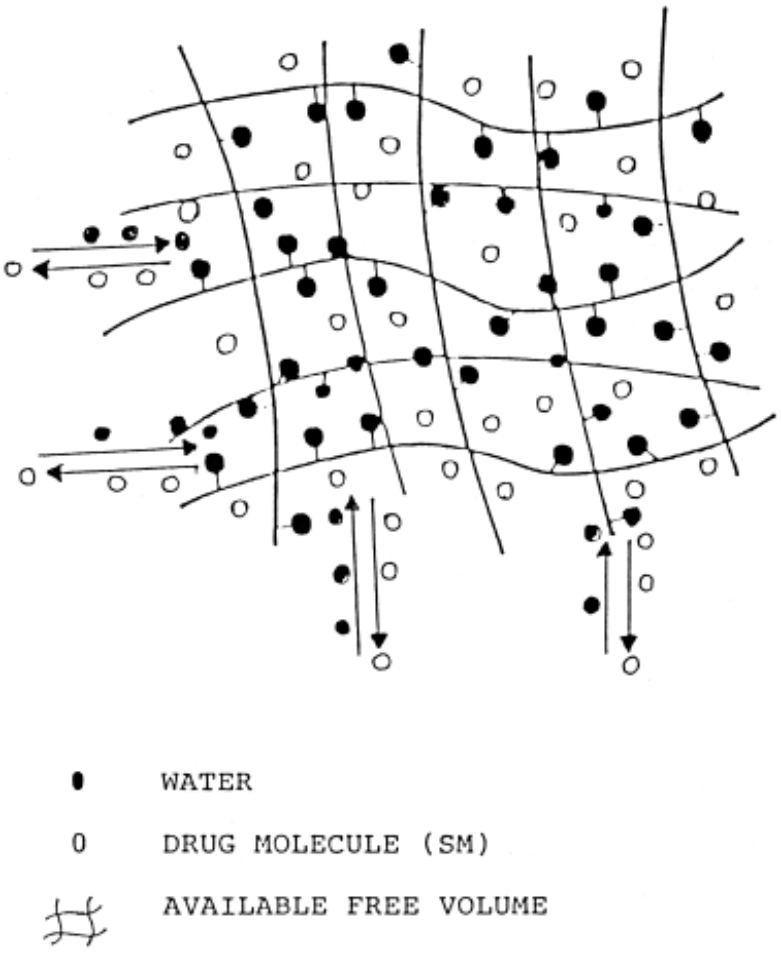

Figure 14. Model depicting release of drug from swollen hydrogel. Reprinted with permission from Ref. [86].Copyright 2001, John Wiley and Sons

Polymeric microsphere, beads, polymeric micelles etc have been shown to be effective in enhancing drug targeting specificity, lowering systematic drug toxicity, improving treatment absorption rates, and providing protection for pharmaceuticals against biochemical degradation [26, 90, 95, 96]. Sodium

alginate beads can be prepared for drug release purpose crosslinked by calcium chloride solution due to the ionotropic bonding between carboxyl groups of sodium alginate and calcium ions according to the well known “egg-box model”. Ionic crosslinking is an effective way for crosslinking of the hydrogels and generally carried out by dispersion of the polymer/drug solution into an aqueous gelation medium. It is a simple and mild process, and the biological activity of drugs can be well retained [26, 90, 95]. Hydrogel nonoparticles are also serving as very promising device for drug delivery. They are of great interest for drug encapsulation and delivery or as embolotherapic agents [81, 87, 98]. Oral delivery of drugs can be significantly improved by using nanoparticles as carriers. S.K. Sahoo and coworkers reported about the preparation of nanoparticles of up to 50 nm diameter which are co-polymers of biocompatible materials made from vinylpyrrolidone and acrylic acid monomers crosslinked with NN'methylene bis acrylamide and which were prepared in reverse micelles for precisely controlling the particle size. FITC-dextran was used as a marker compound which was entrapped in these nanoparticles. These smart hydrogel polymers were very sensitive to pH and temperature effects on the release of the entrapped marker compound [81]. Ferrogels are also in use for drug release purpose. Ferrogels are chemically crosslinked polymer network swollen by a ferrofluid. It’s a new material with magnetic nanocrystals, embedded in a flexible polymer network, that provide high magneto-elasticity. This property makes the material applicable as a drug carrier [88, 89]. Jie Chen, et al. reported about magnetic targeted drug controlled release hydrogel microspheres which were prepared by a radiation technique. Ferric oxide granules of size about 50 nm were used as the core for magnetic field. The PVP ferrogels, i.e. the ferromagnetic nanoparticles in hydrogel microsphere were obtained by irradiating an emulsion of PVP/ferromagnetic granule with cobalt 60 γ – ray [88]. One of the major applications of PVP based hydrogels is transdermal drug delivery [83, 84]. A mathematical simulation was presented by A. L. Iordannskii which describes the in vitro drug delivery kinetics from hydrophilic adhesive water-soluble poly- N-vinylpyrrolidone (PVP)-polyethylene glycol (PEG) matrices of transdermal therapeutic systems (TTS) across skin-imitating hydrophobic Carbosil membranes. Propranolol is employed as the test drug [84]. Ibrahim A. Alsarra et al. represented the study related to different mucoadhesive polymeric hydrogels for nasal delivery of scyclovir. Gels containing PVP were prepared with radiation crosslinking. They also evaluated the gels containing chitosan and carbopol [93, 99]. To determine the drug release capability of the hydrogels many model drugs such as methylene blue, ibuprofenate, salicylic acid, bovine serum albumin, etc are being used to prove their drug release behavior [91, 92, 94, 97].

Implants

The use of hydrogels to replace damaged tissues is a positive approach because of their biocompatibility in contact with human tissues and could be an alternative for an implant. Breast reconstruction with an implant usually implies a sub muscular location to lower the incidence of capsular contracture, and that often necessitates a mastopexy or a reduction mammaplasty of the opposite breast [101, 102, 104, 108]. An ideal prosthesis would be so inert that it could be located subcutaneously without causing any visible contraction. Subcutaneous mastectomy and an immediate reconstruction with a subcutaneously located prosthesis give a good short term cosmetic result with symmetrical breasts. It can also be used in patients with drooping breasts. The development of a new prosthesis is therefore desirable. Silicon gel implants almost invariably cause capsular contraction when placed subcutaneously. Saline-filled implants with a textured rather than a smooth surface have a much lower incidence of such contraction. The Misti1 Gold II (Bioplasty, The Netherlands) breast implants were introduced in 1987. This implant has a textured surface and is prefilled with PVP-hydrogel and has been claimed by the manufacturer to contain a more viscous gel to provide excellent feeling and to be safely removed from the body in the event of traumatic rupture. It has a textured shell that interacts with host tissue to minimize capsular contracture [101]. Novagold breast implants were introduced to the UK in 1996 as a variable alternative to silicone breast implants to overcome the drawbacks of conventional silicone breast implants, like an increased risk of malignancy, autoimmune disease and connective tissue disorders associated with silicone implants. The Novagold used PVP, and guar gum hydrogels as filler, within a textured shell [104].

PVP based hydrogels are also being used as artificial cartilage replacement, because they contain high amount of water which gives good biocompatibility, high elasticity and mechanical strength, and good chemical stability and durability [103, 105, 107]. S.A. Maher and coworkers showed a study to explore the performance of nondegradable hydrogel implants in focal cartilage defects. Their hypothesis was that the structural integrity of a permanent plug and its surrounding tissue would be influenced by the compressive modulus of the material used, and that superior results would be obtained with the implantation of a more compliant material. To test this hypothesis, PVA-PVP hydrogel implants of two different moduli (0.6 MPa vs. 0.2 MPa) were manufactured and implanted into experimentally produced osteochondral defects in a rabbit model that was

followed for up to 6 months. The implants were well tolerated by the animals, and no deaths directly related to the implant were recorded. A view of the implants has been shown in Fig.15 [103].

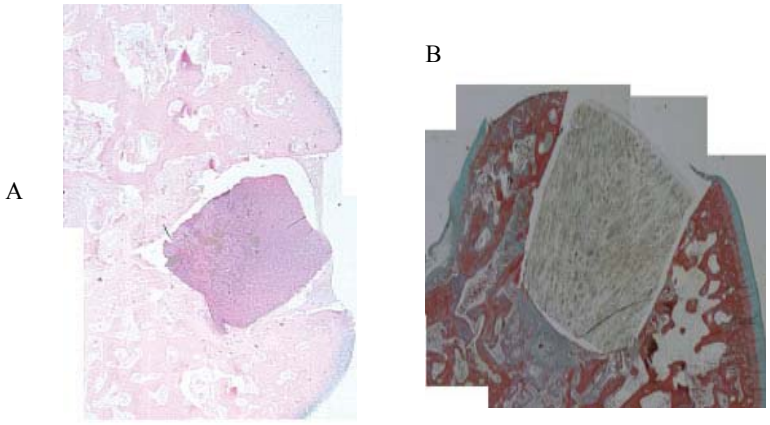

Figure 15. A: Compliant implant at 6 weeks, demonstrating overgrowth of tissue, densification of bone under and around implant, and shrinkage of polymer. B: Stiffer implant at 6 weeks. New bone formation is evident surrounding the plug (Trichrome stain). Reprinted with permission from Ref. [103].Copyright 2007, John Wiley and Sons

Other Applications of PVP-Based Blend Hydrogels

In spite of above mentioned applications PVP-based hydrogels have many other applications, like soft contact lens preparation using PVP and polyhydroxyethyl methacrylate (pHEMA) blend [109], as vitreous substitute [110], PVP coated polyurethane for urological use [111], PVP-acrylic acid (AAc) copolymer hydrogel for the removal of heavy metals from aqueous solution by chelate formation [138, 139], waste water treatment [140], electrically conductive hydrogel (polyaniline (PANI) nanoparticles dispersed in PVP hydrogel) [116], PVP hydrogel supported luminal chemiluminescence for the automatic determination of hydrogen peroxide [141], hydrocarbon degradation [142], superabsorbent nanogel [118], electrospun fiber and mat preparation and their application for remineralization of enamel tooth surfaces [115, 119], food packaging materials [143, 144], water retainers for agriculture [19], and so on.

CONCLUSION

Due to the biocompatibility, transparency, gel forming ability, PVP has become one of the most desirable materials for hydrogel preparation and very demanding in biomedical applications. PVP can be easily blended with other polymers or polysaccharides to tailor the property of the hydrogel with respect to the application point of view. Crosslinking can be introduced in the PVP based hydrogels by means of chemical modifications, γ-radiation, electron beam radiation, UV-radiation, freezing thawing, moist heat treatment, etc. Radiation crosslinking is always preferable than chemically crosslinked products, to avoid side reactions and toxic byproducts. Moist heat treatment for the preparation of PVP based hydrogels is a new concept developed in our laboratory, which is simple and cost effective method for crosslinking, and involves a single step for the formation of crosslinking and sterilization. This method is more advantageous than radiation crosslinking, because no extra laboratory set up is required, comparatively cheaper, and there is no risk of hazard from radiation. With due time the applications of PVP based hydrogels have been increased intensively, the properties are modified, and broadened the field of applications despite of conventional biomedical applications.

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