Journal of Pharmacy and Alternative Medicine
ISSN 2222-5668 (Paper) ISSN 2222-4807 (Online)
Vol. 2, No. 1, 2013

Review Article

Chitosan/Poly (vinyl alcohol) Based Hydrogels for Biomedical Applications: A Review

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Received Date: 17 January 2013 Accepted Date: 24 February 2013

Abstract

The present review aims to give a closer look of hydrogels based on chitosan and poly (vinyl alcohol) and to discuss their potential biomedical applications in drug delivery system. Various investigations based on chitosan/poly (vinyl alcohol) carried out recently by researchers have been reported in this review. Moreover different chemical and physical crosslinking methods used for hydrogels formulations have been summarized and discussed in this overview. Different characterization tools including Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), X-ray diffraction (XRD), thermo gravimetric analysis (TGA), differential scanning calorimetry (DSC) and rheological analysis used by researchers have also been reported in this review.

Keywords: Hydrogels, Chitosan, Poly (vinyl alcohol), Physical crosslinking, Chemical crosslinking

1. Introduction

Since a large number of active compounds that claims as therapeutics have been discovered, but a very few candidates have shown medical characteristics. A number of factors could be attributed to the poor activity of these compounds such as low bioavailability, the rate and extent at which drug reaches the target site and the response of the receptors at the target tissue to the drug. Various techniques have been implied to prepare biocompatible and biodegradable formulations using natural polymers that are degradable through enzymatic reactions, or using synthetic polymers that contain hydrolysable groups (Bhattarai et al., 2010).

In the last few years, a huge study has been carried out on biomaterials based on polysaccharides. Polysaccharides such as chitosan, starch, dextran and gallan are the biological polymers obtained from various animal and vegetal sources. These biopolymers have received various advantages in the recent years, as researchers continue to investigate and modify these biomaterials for demanding needs of biomedical applications in the drug delivery. It was also found that when they are joined to synthetic polymers such as poly (vinyl alcohol) (PVA) or poly (acrylic acid) (PAA), they increase the mechanical properties of the resulting materials (Cascone et al., 2001).

Chitosan is a linear polysaccharide of β-[1- 4]-linked 2-acetamido- 2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose. Commercially it is obtained by alkaline deacetylation of chitin, a structural component in the exoskeleton of crustaceans and insects. It is abundant in nature and considered as second abundant biopolymer after cellulose (Berger et al., 2004). Table 1 indicates some principal sources of chitin.

Chitosan is playing an ideal role and attaining a great interest for controlled drug delivery. Due to its biocompatible and biodegradable properties, it has various pharmaceutical and biomedical applications such as implantation or injection, topical ocular application. Moreover it is metabolized inside the body by some human enzymes i.e. lysozyme and so considered as biodegradable. Chitosan also has bacteriostatic effects and so enhance wound healing (Costa-Junior et al., 2009).Fig 1 shows structure of cellulose, chitin and chitosan.

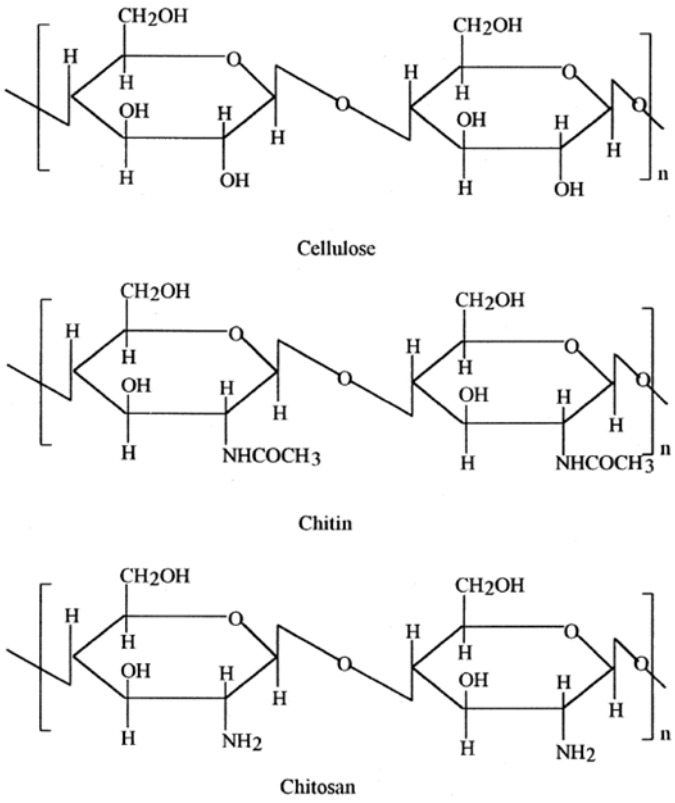

Figure: 1 Structure of Cellulose, Chitin and Chitosan

Table 1: Principal sources of Chitin

Organisms		Chitin contents %
Insects	True fly	51.2
	Sulphur butterfly	66.3
Fungi	Aspergillus niger	40.0
	Mucorrouxii	42.8
Crustacea	Shrimp	67.7
	Crab	70.6
	Lobster	67.6

Poly (vinyl alcohol) (PVA) is a semi-crystalline synthetic polymer which has been studied intensively because of its various desirable properties such as high hydrophilicity, good film forming, process ability, biocompatibility, gel forming and physical properties, good film forming and good chemical resistance. These properties of poly (vinyl alcohol) made its wide use in the production of paper, paints, glues, clothes, pharmaceutical products, ceramics and building materials (Hernandez et al., 2004). Table 2 shows physical properties of polyvinyl alcohol (PVA).

Chitosan combined with other polymers offered the researchers a new window for changing the desire of interest. Figure 2 indicates the structure of poly (vinyl alcohol) (PVA).

Table 2: Physical Characteristics of Poly (vinyl alcohol) (PVA)

S.NO.	Property	Result
1	Appearance	Cream colored granular powder
2	Odour	Odourless
3	Taste	Tasteless
4	Solubility in water	Soluble
5	Solubility in Alcohol	Slightly Soluble
6	Solubility in organic solvents	Insoluble
7	Melting Point	180 to 190 ℃
8	Molecular weight	Between 26,300 and 30,000
9	Degree of hydrolysis	86.5 to 89%.

Hydrogels are crosslinked macromolecular networks swollen in water or biological fluids and have the ability to retain substantial amount of solvent in its structure without undergoing to dissolve (Guanghua et al., 2008). The water absorbing ability of hydrogels is provided by certain hydrophilic functional groups (such as -OH, -COOH, - CONH2, -SO3H) in the polymer chains (Chandra et al., 2013). Due to the presence of these certain functional groups in the polymer chains, hydrogels are considered to be sensitive to the conditions of the surrounding environment such as temperature, pH or ionic strength of the swelling solutions or even to the presence of a magnetic field or ultraviolet light, due to which they are referred to as "intelligent materials" or "smart materials" (Sadeghi et al., 2011). Hydrogels have many applications in the biomedical field which includes contact lenses, wound dressing, catheters, coating for sutures, artificial corneas and electrode sensors (Pal et al., 2007). Hydrogels can be classified into several classes based on the nature of network such as covalently crosslinked networks, entangled networks and networks formed by secondary interactions (Berger et al., 2004).The present review is made to focus on the current applications of Chitosan/Poly (vinyl alcohol) based hydrogels and to discuss the future prospects of biopolymers combined with synthetic materials for the pharmaceutical and medical applications in the drug delivery (Kumar et al., 2000).

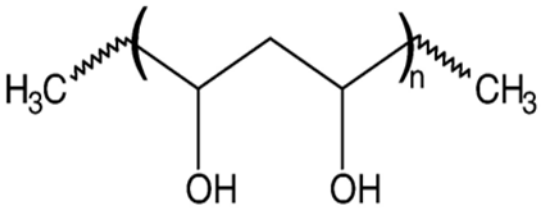

Figure 2: Structure of Poly (vinyl alcohol) (PVA)

2. Hydrogel Crosslinked Network

Different methods of crosslinking have been used in hydrogel formulations. Generally physical and chemical methods have been applied commonly. In chemically crosslinked hydrogels, crosslinking can be produced by covalent bonds between different polymer chains. While in physically crosslinked hydrogels, physical interactions exist between different polymer chains which prevent them from dissolution [Hennink et al., 2002]. These two methods are discussed below in detail.

2.1 Chemically crosslinked hydrogels

Chemically crosslinked networks are also called permanent or chemical hydrogels (Chandra et al., 2013). Chemical crosslinking is a suitable method to generate permanent hydrogel networks by implying covalent bonding between different polymer chains. Chemically crosslinked networks can be produced by chemical reactions between different available functional groups and crosslinkers that can generate number of linkages among the available groups including Schiff base formation and amine carboxylic acid bonding (Hoare et al., 2008; Berger et al., 2004). More particularly these networks can be produced by using low molecular weight crosslinkers, photosensitive agents or enzymes catalyzed reactions and polymer-polymer interactions between activated functional groups. Genipin, the new crosslinking agent is a naturally derived chemical obtained from the gardenia that has been proved to be one biocompatible cross-linking agent (Jin et al., 2004). Genipin has been shown to bind biological tissues (Sung et al., 2001) and biopolymers, such as gelatin and chitosan leading to covalent coupling. It works as an effective cross-linking agent for polymers containing amino groups and is much less cytotoxic than glutaraldehyde (Sung et al., 1999).

In photo crosslinking, polymer mixtures that can form hydrogels can be developed by using photosensitive functional groups. The polymer can form crosslinking with these reactive groups upon irradiation with UV light (Ono et al., 2000). In polymer-polymer crosslinking method, pre-functionalized polymer chains with reactive functional groups are required in order to eliminate the use crosslinker molecule during gelation. In this type of crosslinking, covalent linkages can be formed that mainly depend upon the desired speed of crosslinking and selection of targeted reactive functional groups (Tan et al., 2009).

2.2 Physically crosslinked hydrogels

The interest towards physically crosslinked gels has been increased in recent years due to the elimination of crosslinking agent in these hydrogels (Kumar et al., 2000). Physically crosslinked hydrogels mainly demands two conditions: (1) inter-chain interactions in the molecular network must be strong enough to form semi-permanent junction points (2) The network must allow the penetration of maximum water molecule inside the polymer network (Berger et al., 2004). Several methods have been reported for the preparation of physically crosslinked hydrogels but mainly includes; crosslinking by ionic interactions, crosslinking by crystallization and crosslinking by stereo complex formation (Kumar et al., 2000).

Crosslinking by ionic interactions occur only between oppositely charged groups of polymers or monomers which formulate the hydrogel network. Chitosan which contains cationic amino groups forms ionic complexation of mixed charge system with small anionic molecules such as phosphates, citrates, sulphates (Shu et al., 2002) and also with the metal anions such as Mo(VI),Pt (II), Pd (II) (Dambies et al., 2001). Chitosan make linkage with the anions and other small molecule through protonated amino groups, while in case of metal ions, it forms coordinate-covalent bonds rather than electrostatic repulsion with polymer (Brack et al., 1997).

Crosslinking by crystallization leads to gel formation gradually, when stored at room temperature. However hydrogels formed by means of crystallization may be of low mechanical strength. Polyvinyl alcohol which is water soluble polymer forms gels by crystallization method when its aqueous solution is stored at room temperature. This gel formation is mainly attributed due to formation of PVA crystallites which act as physical crosslinking sites in the network (Yokoyama et al., 1986).

In recent years hydrogels based on stereo complex formation were reported for drug delivery system. It has been investigated that stereo complex formation occurs in blends of triblock copolymers of PLLA–PEG–PLLA and PDLA–PEG–PDLA (Lim et al., 2000).

3. Chitosan/Poly (vinyl alcohol) based hydrogels

Hydrogels based on chitosan and polyvinyl alcohol has various pharmaceutical and biomedical applications in drug delivery system. Huge efforts and large studies have been made to prepare the Chitosan/Poly (vinyl) alcohol hydrogels and their potential for controlled drug delivery has been extensively studied by research workers. The literature related to Chitosan/Poly (vinyl alcohol) based hydrogels is reviewed as under;

3.1 Preparation and characterization of Chitosan/Poly (vinyl alcohol) based hydrogels

Vrana et al., 2008 synthesized PVA/Chitosan hydrogels crosslinked with KOH/Na_2SO_4coagulation bath by freeze/thaw cycle's technique. Authors evaluated the effect of number of freeze/thaw cycles on cell behaviour. Authors modified hydrogels surface using collagen type I adsorption and seeded with bovine aortic vascular smooth muscle and endothelial cells. Authors found that marked increase in hydrophilicity, surface morphology and protein adsorption may occur by increasing the number of freeze/thaw cycles (Vrana et al., 2008).

Mathews et al., 2008 prepared poly (vinyl alcohol)/chitosan hydrogels by freeze/thaw cycles method and investigated the effect of type of chitosan (water soluble or insoluble) and freeze/thaw cycles on the mechanical and morphological properties of the hydrogels. Authors characterized these hydrogels by scanning electron microscope (SEM), uniaxial testing, and a biaxial tubular vessel inflation experiment (Mathews et al., 2008).

Pei et al., 2008 synthesized chitosan/polyvinyl alcohol/alginate composite film by the casting/solvent evaporation method for wound healing. Authors loaded ornidazole (OD) as model drug in hydrogels and studied its potential capacity for use in wound healing. Authors studied the in vitro antibacterial effects of the loaded drug and characterize the gels by FTIR and scanning electron microscope (SEM) (Pei et al., 2008).

Tang et al., 2009 prepared thermo sensitive chitosan/polyvinyl alcohol hydrogels by two synthetic routes i.e. insitue and exsitue routes. The prepared thermosensitive hydrogels contain hydroxyapatite for protein delivery. Authors subjected these gels to characterization by Fourier-transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), scanning electron microscopy (SEM), and rheological analysis (Tang et al., 2009).

Bahrami et al., 2003 synthesized Poly (vinyl alcohol)/chitosan blended films by casting technique using glutaraldehyde as crosslinking agent. Authors characterized the mechanical and physical properties of blended films including water uptake, surface tension, contact angle and tensile properties in the dry and wet states (Bahrami et al., 2003).

Abdeen in 2011 prepared blend semi-synthetic hydrogel film composed of polyvinyl alcohol and chitosan using glutaraldehyde as crosslinking agent by solvent-casting technique. Authors characterized these hydrogels by FTIR spectroscopy for their intermolecular interactions between chitosan and polyvinyl alcohol molecules (Abdeen., 2011).

Kim et al., 2003 synthesized interpenetrating polymer network (IPN) hydrogels consisting of poly (vinyl alcohol)/chitosan by UV irradiation method. Authors investigated the change in swelling of poly (vinyl alcohol)/chitosan (IPN) hydrogels in response to external environment such as temperature and pH (Kim et al., 2003).

Guanghua et al., 2008 prepared physically crosslinked composite hydrogels consisting of poly (vinyl alcohol)/chitosan (CS) by cyclic freezing/thawing techniques. Authors characterized these hydrogels by infrared spectra (IR), scanning electron microscope (SEM) and differential scanning calorimetry (DSC) (Guanghua et al., 2008).

Gunasekaran et al., 2006 synthesized pH-Sensitive Chitosan–Poly (vinyl alcohol) Hydrogels in different molar ratios using glutaraldehyde as crosslinking agent. Authors in this study investigated the effect of pH of medium and salt concentrations on the swelling properties of these hydrogels (Gunasekaran et al., 2006).

Khurma et al., 2006 prepared semi-interpenetrating polymeric networks consisting of chitosan and poly

(vinyl alcohol) of different ratios of constituent's crosslinked by genipin, a naturally occurring crosslinking agent having no toxicity. Authors subjected these hydrogels to characterization by differential scanning calorimetry (DSC) (Khurma et al., 2006).

Cascone et al., 1999 prepared poly (vinyl alcohol) based hydrogels by freezing-thawing technique using varying quantities of dextran and chitosan. Authors characterized these hydrogels by scanning electron microscope (SEM), differential scanning calorimetry (DSC) and dynamic-mechanical analysis (Cascone et al., 1999).

Sung et al., 2010 synthesized cross-linked hydrogel films consisting of polyvinyl alcohol and chitosan by freeze and thawing method. Authors evaluated in vivo wound healing effect, histopathology, release, in vitro protein adsorption and gel properties. Authors loaded the gel with minocycline and observed its healing effect by subjecting it to wound healing test (Sung et al., 2010)

Yang et al., 2008 prepared hydrogels consisting of poly (vinyl alcohol) (PVA) and water soluble chitosan (ws-chitosan) for wound dressing by combined γ-Irradiation and freeze-thawing technique. Authors compared the properties of these gels prepared by combined technique to those prepared by freeze-thawing and irradiation alone. Authors characterized these gels by scanning electron microscope (SEM) (Yang et al., 2008).

Mincheva et al., 2007 developed bicomponent nanofibers composed of N-carboxyethylchitosan and poly (vinyl alcohol) by electro spinning technique using mixed aqueous solutions of the polymers. Authors studied the surface morphology of nanofibers by subjecting these to scanning electron microscope (SEM) (Mincheva et al., 2007).

Rao et al., 2006 prepared novel pH-sensitive interpenetrating polymeric network (IPN) microgels consisting of chitosan, acrylamide-grafted-poly(vinyl alcohol) and hydrolyzed acrylamide grafted-poly (vinyl alcohol) using glutaraldehyde as crosslinking agent. Authors loaded cefadroxil as model drug and used these microgels for the controlled release of drug. Authors characterized these microgels by Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM) and differential scanning calorimetry (DSC) (Rao et al., 2006).

Yang et al., 2004 used chitosan and poly(vinyl alcohol) in various ratio to prepare blended membranes using glutaraldehyde as crosslinking agent. Authors conducted permeability studies of creatinine, 5-FU and vitamin B12, through these blended membranes. Authors characterized these membranes by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), dynamic mechanical analysis (DMA)and thermogravimetric analysis (TGA)(Yang et al., 2004).

Masci et al., 2003 prepared poly (vinyl alcohol) (PVA) physical hydrogels using different derivatives of lactosilated chitosan of varying molecular weight by repeated freeze-thawing cycles technique of aqueous solutions of polymers. Authors characterized these hydrogels by thermogravimetric analysis (TGA), scanning electron microscopy (SEM) and differential scanning calorimetry (DSC) (Masci et al., 2003).

Kim et al., 2003 synthesized interpenetrating polymer networks (IPN) hydrogels consisting of Poly (vinyl alcohol) (PVA)/chitosan by UV irradiation method. Authors measured swelling behaviour of these IPNs hydrogles at various temperature and humidity levels (Kim et al., 2003).

Yang et al., 2007 prepared Chitosan/Poly (vinyl alcohol) blending Hydrogel and used it for surface coating of segmented polyurethane to reduce catheter related complications. Authors used Fourier transform infrared spectroscopy (FTIR) to confirm surface modifications at every step (Yang et al., 2007).

Costa-Junior et al., 2009 prepared blended films composed of chitosan and poly (vinyl alcohol) chemically crosslinked with glutaraldehyde in this work for use in skin tissue repairing. Authors used Fourier Transform Infrared spectroscopy (FTIR) and scanning electron microscopy (SEM/EDX) analysis to study microstructure and morphology of the hydrogel films (Costa-Junior et al., 2009).

Costa-Junior et al., 2009 prepared glutaraldehyde crosslinked novel polymer blends of chitosan/poly (vinyl alcohol) for variety of biomedical applications. Authors characterized these blended films through X-ray diffraction, Fourier transform infrared spectroscopy and scanning electron microscopy analysis to study

crystallinity, structure and morphology of the blended hydrogels (Costa-Junior et al., 2009).

Wang et al., 2004 synthesized pH sensitive semi-interpenetrating polymeric network consisting of chitosan and poly (vinyl alcohol) using glutaraldehyde as crosslinking agent. Authors subjected these gels to Fourier transform infrared spectroscopy (FTIR) for structure confirmation (Wang et al., 2004).

3.2 Applications

Chitosan is versatile biopolymer that is inexpensive and contains some important physiological properties such as biodegradable, biocompatible, non-toxic, non-allergenic and mucoadhesive properties for mammals. These properties of chitosan make it suitable to be used in various fields including biomedicine, agriculture, cosmetics, environmental protection, food, fibre industries and wastewater management (Kumar et al., 2004).

3.2.1 Pharmaceutical and medical applications

Over the last three decades, chitosan and its derivatives have been reported for huge range of biomedical applications in pharmaceutical formulations and drug delivery system.

3.2.1.1 Wound healing

There are many clinical cases suggested that chitosan based materials accelerates wound healing. It was investigated that chitosan granules could induce faster regeneration of normal skin due to increased vascularization in open wounds. Chitosan is believed to have role in tissue growth and differentiation in tissues in wound healing. Table 3 indicates some commercially available haemostatic dressings based on chitosan (Shigemasa et al., 1996).

Table 3: Some commercial hemostatic dressings based on chitosan

Commercial Name	Company	Materials and functions
HemCon®	HemCon	Freeze-dried chitosan acetate salt, for emergency use to stop bleeding
Chitoflex®	HemCon	antibacterial, biocompatible wound dressing prepared to be placed into a wound area to control moderate to severe bleeding
Chitoseal®	Abbott	Based on chitosan, backed with cellulose coating used for wounds bleeding
Clo-Sur®	Scion	Based on chitosan, a pressure pad applied topically to accelerate wound healing
TraumaStat®	Ore-Medix	Freeze-dried chitosan containing highly porous silica
Syvek-Patch®	Marine Polymer Technologies	Composed of fully acetylated, high molecular-weight chitin in a crystalline, three dimensional beta structure array, and separated from the centric diatom Thalassiosirafluviatilis. It is believed to be 7 times quick in achieving haemostasis than fibrin glue.
BST-CarGel®	Biosyntech company	chitosan-glycerophosphate hydrogels, a biodegradable gel used for cartilage repair

3.2.1.2 Subcutaneous delivery

Chitosan based materials have been widely used in the field of subcutaneous delivery and implantable devices due to its lack of immunogenicity and inflammation. As chitosan hydrogels are biodegradable in nature so these systems require no surgical removal after implantation and successfully release therapeutic payload inside the body (Khor et al., 2003).

3.2.1.3 Anticancer properties

In traditional drug delivery systems such as microcapsule, gel system or microspheres, drugs are usually loaded by passive absorption, which keeps the drug loading capacity in limits. Chitosan hydrogels based delivery systems have shown an ideal area of interest for delivery of local chemotherapeutic agents. Chitosan matrices have been successfully loaded with radioisotopes and used for controlled exposure. Chitosan based hydrogels have been used for breast cancer, brain tumour, localized solid tumours, primary and secondary osteosarcoma, osteolysis and lung metastasis (Azab et al., 2007; Lesniak et al., 2004; Ruel-Gariepy et al., 2004).

3.2.1.4 Delivery of growth factor

Chitosan based hydrogels have been extensively used in the controlled delivery of growth factors or glycosaminogylcan (GAG) molecules in the treatment of bone, cartilage and nerve tissues. Table 4 shows some of the examples of drugs loaded in chitosan hydrogels and their role in delivery of growth factor (Mattioli-Belmonte et al., 1999; Suh et al., 2000; Muzzarelli et al., 1997; Park et al., 2005).

Table 4: Drug loaded in chitosan hydrogels and their applications in delivery of growth factors

Drug loaded in Chitosan hydrogels	Applications
Chitosan hydrogels coupled with BMP-7	To improve lesion repair
Chondroitin sulfate loaded in chitosan hydrogels	Cartilage formation
Platelet derived growth factor loaded in chitosan gels	To improve osteoinduction
Chitosan–alginate hydrogels loaded with BMP-2 and mesenchymal stem cells	To induce subcutaneous bone formation

3.2.1.5 Drug delivery in gut

Due to pH sensitivity and mucoadhesive properties, chitosan based hydrogels offers significant targeting drug release depending on the swelling of hydrogels in desired pH of medium. Chitosan based hydrogels have been successfully implied for the delivery of therapeutic moieties to stomach because of their significant swelling in acidic conditions (Patel et al., 1996).Some chitosan based hydrogels have been synthesized that release the loaded drug in intestine after passing through the acidic conditions of stomach (George et al., 2006).

3.2.1.6 Ophthalmic applications

Chitosan based formulations have wide applications in ophthalmic drug delivery systems due to their higher retentions time as compared to conventional systems (e.g eye drops)(Felt et al., 1999). Chitosan

based hydrogels have high bioadhesive and penetration improving characteristics, due to which they are successfully used as drug delivery system in ophthalmic field (Thanou et al., 2001).

3.2.2 Applications in Cosmetics

Chitosan based hydrogels have been believed to have applications in transdermal drug delivery systems because of their high water contents which provides a durable emollient effect on patient's skin (Prausnitz et al., 2004).Chitosan is investigated to act as film forming agent and hydrating agents in hydrogels. The film-forming ability of chitosan helps in imparting a pleasant and emollient feeling of smoothness to the skin and in protecting it from adverse environmental conditions. Chitosan based hydrogels have been used for the delivery of berberine alkaloid to skin (Tsai et al., 1999).

4. Conclusion

The current review claims that researchers have made huge efforts to study chitosan/Poly (vinyl alcohol) based formulations because of safe toxicological profile of chitosan. Due to this unique property of this biopolymer, it has potential application in pharmaceutical and biomedical fields. For formulations of hydrogels drug delivery system both type of crosslinking methods including physical and chemical crosslinking have been used by researchers. For characterization, these hydrogels are subjected to different characterization techniques. It is concluded from wide efforts and huge work of large number of research groups in the fields of hydrogels drug delivery development and characterization that chitosan/Poly (vinyl alcohol) hydrogels have high applications in various pharmaceutical and biomedical fields and can be applied an ideal drug delivery in biomedical fields in future.

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