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Synthesis and Characterization of Microporous Cryogel Matrices with Anti-inflammatory Effect

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ABSTRACT
The aims of this paper are the synthesis, the physicochemical characterization and in vitro analysis of microporous cryogels matrices. Polyvinyl-alcohol (PVA) is a non-toxic linear polymer, highly soluble in water, resistant to organic solvents and frequently used in medical applications. ketoprofen is a non-steroidal anti-inflammatory drug used in various topical and oral pharmaceutical forms. Cryogelation is a technology that makes interconnected pore structure in moderately frozen condition after four freeze/thaw cycles. The morphology of the cryogels, the interaction between the PVA macromolecular chains and ketoprofen has been studied by Scanning Electronic Microscopy. The gels swelling in physiologic medium have been monitored in order to establish the hydrophilic properties. The mechanical properties of the cryogels have been investigated by dynamic mechanical measurements and the concentration of ketoprofen released by spectrophotometry. The new microporous cryogel matrices shows good physical, morphological and drug release properties.
Keywords – Cryogel, ketoprofen, matrices, polyvinyl-alcohol

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I. INTRODUCTION

PVA is relatively safe when administered orally because is poorly absorbed from gastrointestinal tract, and easily eliminated from the body. Hydrogels are three dimensional cross linked hydrophilic polymers with the ability to absorb water or aqueous solutions into their structure [1, 2]. Depending on the degree of chemical or physical cross linking, the amount of absorbed water varies as such they can be classified as low, medium, and high swelling hydrogels.

PVA hydrogels, due to their susceptibility to hydrogen bonding and excessive crystallization, generally offer very low swelling capacity, making them however very desirable for specific biomedical and pharmaceutical applications. Due to their simple structure and unique properties such as adhesiveness, strength, film forming, biocompatibility, swelling, safety, and non-carcinogenicity. The aqueous solutions of PVA polymer at high molecular weight 50,000-130,000 Daltons, high concentration 10-20 % and high degree of hydrolysis up to 98% can be cryogelled under freezing-thawing conditions. The hydroxyl groups of the adjacent polymer chains will interact to form intra and intermolecular hydrogen bonds resulting in formation of crystallites [3, 4]. Parameters affecting the cryogenic treatment are freezing and thawing temperatures and the number of cycles [5]. Since PVA solution in water is converted from liquid to a solid state during cryogelation, the composition of the polymer during such transition would determine the elastic, viscous and viscoelastic properties of these cryogels. Similar to other hydrogel systems, PVA cryogels prepared at high polymer concentration or under the conditions enhancing mechanical properties would display good viscoelastic properties. In general, since the PVA polymer and water are the only components of the hydrogel system, the cryogel property can be modulated to achieve desirable viscoelastic properties.

Gadea et al studied the degree of crosslinking, swelling kinetics and viscoelastic properties of cryogels and they found that the degree of cross linking and viscoelastic properties increased with increasing of freeze-thaw cycles number [2]. The swelling kinetics of cryogels changed linearly with square root of time so cryogels also displayed greater swelling in water at higher temperature [2, 3].

Omidian et al. studied the use of PVA cryogelation to enhancing mechanical properties of super porous hydrogels for gastric retention drug delivery applications. They achieved cross-linking by the simultaneous polymerization of various hydrophilic monomers in the presence of PVA solution, followed by several cycles of freezing and thawing [1]. Properties such as high water content, elastic nature in the swollen state, biocompatibility,

and swelling make the PVA hydrogels a potential candidate as tissue replacement material. The PVA hydrogels have been studied as soft contact lens material, artificial heart linings, artificial cartilages, catheters, skin, and pancreas membranes [4, 5]. PVA hydrogels were also studied for bio prosthetic heart valves [4], reconstruction of vocal cords, artificial kidney membranes for dialysis, and intervertebral disc nuclei.

Because of their biocompatibility, drug compatibility, water solubility, film forming, good mechanical and swelling properties, the PVA hydrogels have been studied as drug delivery systems in oral, transdermal, buccal, intramuscular, rectal routes of administration. Degree of crystallinity plays a major role in controlling diffusion of the drug from Hydrogels.

In general, PVA hydrogels can be designed either as matrix or reservoir drug delivery platforms. To control the drug release from PVA Hydrogels methods like altering gelling properties, solubility, adding copolymers have also been utilized [6].

The aim of this paper is the synthesis and characterization of cryogel matrices in order to establish the morphological structure, the compression behavior and the drug release properties.

II. SYNTHESIS OF CRYOGELS MATRICES

Polyvinyl alcohol (PVA) is a synthetic hydrophilic linear polymer that generally exists as a copolymer of vinyl alcohol and vinyl acetate and was first synthesized by Hermann and Haehnel in 1924 via saponification of poly (vinyl ester) in sodium hydroxide solution. Because vinyl alcohol is unstable and rapidly tautomerizes into acetaldehyde, the polyvinyl alcohol is commercially produced by hydrolysis of Poly (Vinyl Acetate) following a two-step process: free radical polymerization of vinyl acetate to Poly (Vinyl Acetate) followed by its hydrolysis. Therefore, the structural properties of these polymers depend on the degree of polymerization and the degree of hydrolysis. Because PVA has reactive functional groups on its structure, undergoes chemical changes such as esterification and etherification, as well as physical changes such as crystallization and ion-polymer complexation. Both chemically and physically-modified PVA structures have found applications in biomedical and pharmaceutical area [1].

Properties of PVA polymer are associated with the method of preparation, molecular weight, degree of polymerization and degree of hydrolysis. Properties like viscosity, resistance to solvents, adhesive strength, tensile strength, and film-forming are enhanced with increase in molecular weight and degree of hydrolysis. PVA polymers has no color and odor, melt at around 180-228°C and display glass transition at 75-85°C to became rubber.

The synthesis of PVA Hydrogel was achieved by solubilization fo 10 g of polyvinyl alcohol in 100 ml distilled water. Sample about 100 g were prepared by heating two thirds of the total amount of freshly prepared distilled water to 80 °C and then adding the 10 g of polymer thoroughly mixed for dispersion. After complete dissolution of polyvinyl alcohol, 1 g of ketoprofen is gradually added under mild stirring. The gels were triturated for 1 h to a uniform consistency and left overnight to equilibrate. The mixture is left for 12 hours in a refrigerator at 4 degrees Celsius in order to increase the viscosity. Polymer mixture is inserted in the freezer for 24 hours, removed and keeps in the fridge for another 12 hours for drying surface. Freezing-refreezing process is repeated 4 times after the component is left at room temperature for acclimatization and complete drying of the coating. This procedure is required to be held to obtain a super porous polymer.

I. METHODS OF CHARACTERIZATION

Pore distribution and drug particles, in the inner structure of cryogel was accomplished by SEM microscopy.

The porosity and the micro architecture of the prepared scaffolds were assessed by visual image analyzer program IMAQ Vision and scanning electron microscopy (SEM) (SEM, Quanta 3d). Cryogel fragments were cut from its mass and examined microscopically. Morphology of the PVA cryogels was examined by scanning electron microscopy (SEM, quanta 3d). Before analyzing by SEM, the cryogel samples were pre-treated with increasing concentrations of alcohol (ethanol: 70%) for 15 minutes. Dehydrated cryogel sections were then vacuum dried overnight and scanned by SEM operated at high vacuum at 20 kV. The pore size was determined by the IMAQ Vision image software.

Compressive strength was measured by mechanical testing device type. The compression analyses of swollen cryogels were performed using uniaxial compression test by the mechanical tester (CETR Umt-2 with LabVIEW software and load cell). The analysis was done using samples with dimension 0.5 cm height and 8 mm diameter by placing the samples between the two arms of load frame. The samples were then compressed up to 80% of the total length with a speed of 1 mm/min.

The release of the drug was constructed in PBS at pH 7.4 and drug concentration was followed using UV-spectrophotometer.

III. RESULTS AND DISCUSSION

PVA cryogels are opaque, sponge like and elastic. These cryogels can be easily compressed by hand to remove water accumulated inside the pores.

The morphology of the prepared cryogels is presented in SEM image.

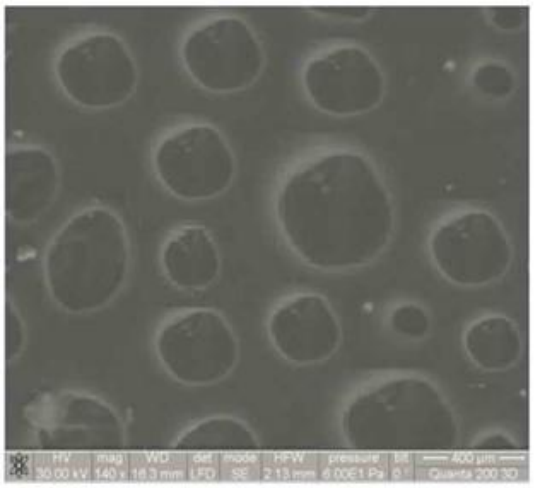

Fig.1. Morphology of PVA cryogels matrices

It could be noticed that all the prepared cryogels have wide range of pores including macro, and micro as it is also confirmed by SEM microphotograph. Cryogel of PVA shows a structure with big pores and smooth pore.

The addition of the drug to the hydrogel leads to the formation of a cryogel with slightly smaller pores interposed with the glass particles of the drug. It is also noted that the incorporation of ketoprofen affects the porosity percentage as it is increased in PVA cryogel and decrease in PVA/ketoprofen composite cryogel. This confirms that the added crystalline drug affecting the average pore diameter and the array of the internal microstructure.

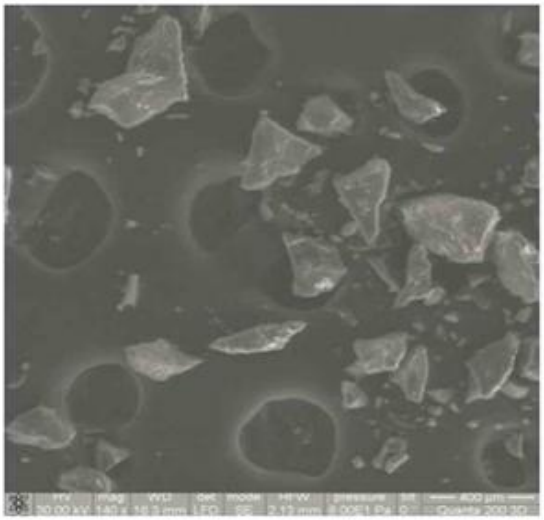

Fig.2. Morphology of PVA cryogels matrices drug loaded

The prepared cryogels showed a microporous structure with porosity percentage by 85% and a pore size of 139 μm for PVA cryogels and porosity percentage by 88% and a pore size of 145 μm for PVA cyogels matrices loaded with ketoprofen.

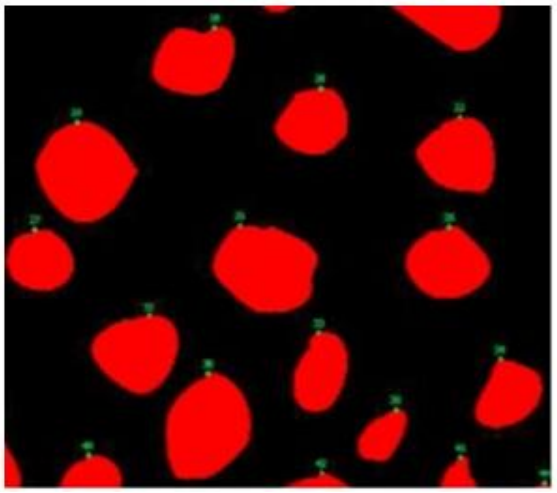

Fig.3. Simulation of pore distribution

Mechanical properties of cryogels were analyzed by its microstructure network. Both PVA and PVA / drug cryogels can bear compression strain of 80% without permanent deformation or mechanical destruction.

The mechanical strength of cryogels is a very important parameter in drug storage and transportation. Young's moduli of cryogels were found to be 6.1 ± 0.46 kPa and 4.6 ± 0.44 kPa.

Such low value of Young's modulus demonstrates the elastic nature of the cryogels and thereby supports the inclusion of ketoprofen. This result also shows the soft nature of the cryogel.

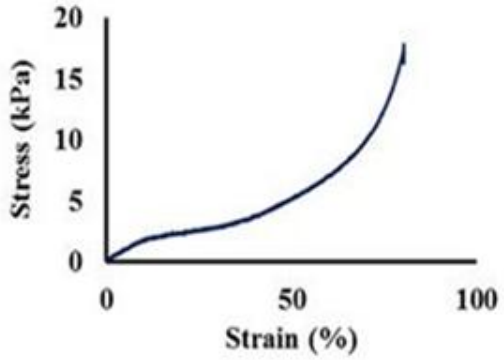

Fig.4. Stress versus strain curve of PVA cryogel in compression tests

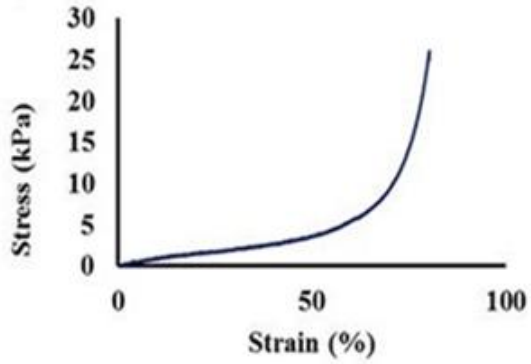

Fig.5. Stress versus strain curve of PVA/ketoprofen cryogel

The soft and elastic nature of the synthesized cryogel provides it with appropriate physical property for drug release.

The release behavior of ketoprofen from cryogel matrices seemed to be in a sustained release profile according to Korsmeyer–Peppas model. This mechanism is based on hydrolysis as the polymer is hydrated, swell and then the drug diffuses through the swollen matrix system to the exterior, which ultimately slows down the kinetic release.

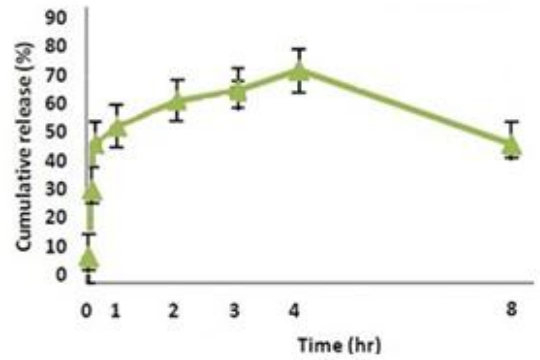

Fig.6. Cumulative release rate of the Ketoprofen from PVA cryogel matrices

In the first four hours the ketoprofen concentration increase slowly in the same time with polymer hydration and after that the concentration decrease during next four hours but remain in optimal level to ensure the therapeutic effect.

IV. CONCLUSION

PVA cryogels can offer unique drug release rate, pore matrices structures and strength properties, which can be vitally beneficial in general health applications, and in particular pharmaceutical use.

cryogels are observed, especially after addition of ketoprofen.

The low value of Young's modulus demonstrates the elastic nature of the obtained cryogels.

Drug delivery is gradually and prolonged, the basic mechanism of release is diffusion through the hydrated matrices.

REFERENCES

[1]. H. Omidian, K. Park, Hydrogels, Fundamentals and Applications of Controlled Release Drug Delivery. 2011.

[2]. J.L. Gadea, L.C. Cesteros, I. Katime, Chemical–physical behavior of hydrogels of poly(vinyl alcohol) and poly(ethylene glycol), European Polymer Journal, 49, 2013, 3582-3589.

[3]. M. Himi, S.D. Maurya, Preparation and evaluation of stomach specific IPN hydrogels for oral drug delivery, Journal of Drug Delivery & Therapeutics, 3(2), 2013, 131-140.

[4]. W.K. Wan, G. Campbell, Z.F. Zhang, A.J. Hui, D.R. Boughner, Optimizing the tensile properties of polyvinyl alcohol hydrogel for the construction of a bioprosthetic heart valve stent, J Biomed Mater Res. 63, 2002, 854-861.

[5]. S. Kaity, J. Isaac, A. Ghosh, Interpenetrating polymer network of locust bean gum-poly (vinyl alcohol) for controlled release drug delivery, Carbohydr Polym. 94, 2013, 456-467.

[6]. N. T.K. Bhoyar, A. Alexander, Recent advances in novel drug delivery through Gel, Journal of Sciences and Allied Health Sciences, 2, 2012, 21-39.

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