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# Different PVA-Hydroxypropyl Guar Gum Irradiated Nanosilica Composite Membranes for Model Drug Delivery Device

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***Abstract***

*High strength and elastic biodegradable membranes are of great demand in modern technology. Similar membranes have been developed by irradiating different weight poly (vinyl alcohol) (PVA) – hydroxypropyl guar gum (HPG) blends and followed by combining with ex situ nanosilica. Polarized light microscopic (PLM) study indicates that electron beam irradiation produced crosslinks and developed crystallinity in PVA-HPG matrix. Atomic force microscopic analysis shows that 1 wt.% nanosilica produced finer dispersion in both high and low molecular weight PVA-HPG matrix resulting nearly 4.5 times higher mechanical strength and controlled swelling-deswelling property e.g., low molecular weight PVA with 1wt% nanosilica content show swelling ratio 3.5. Greater nanosilica and PVA-HPG interaction was observed in low molecular PVA-HPG composite membranes than high molecular weight PVA-HPG composite membranes which finally showed better efficacy towards drug retention and elution under physiological condition.*

***Keywords:*** *Polymer, Irradiation, Membrane, Nanosilica and drug delivery.*

## 1. INRODUCTION

Synthetic polymers are highly effective in our daily life due to their excellent combination of physical and mechanical properties. They are widely explored as film wraps, plastic bags, electric insulation, toys, fabrics, pipes, paints, etc [1]. Again synthetic polymer hydrogels received much attention in biotechnology for formulating various biomedical grafts, implants and transdermal patches [2-4]. But recent environmental concern has diverted the interest towards biodegradable polymers for similar applications [5, 6]. In addition biodegradable polymers have comparatively lower cohesive strength than the synthetic polymers [7]. Thus, it has been realized the use of synthetic polymers. Under such circumstances, blending of natural and synthetic polymers is the most viable option to overcome the deleterious environmental impact [8, 9]. Using blending several compositions involving PVA and other synthetic polymers has already been explored [10, 11].

PVA is very much versatile synthetic polymer having great combination of mechanical strength, flexibility, biocompatibility, air permeability and water absorption properties [12-14]. It is commercially available in several molecular weights and hydrolysis grades [15]. The polymer has already established its potency in formulating contact lens, articular cartilage, artificial muscle and vascular cell culturing hydrogel [16-18]. But all grades of PVA are not biodegradable and also very few literatures compared their different properties in different conditions [19]. We have found huge contrast in physical and mechanical properties in PVA-HPG blends where high molecular weight grade PVA ($PVA_H$, Mn 1,15,000) and its oligomeric grade ($PVA_L$, Mn 14,000) are used. The present article features some unique behaviors of these

two biodegradable PVAs with HPG in a blend composition under low dose (5kGy) electron beam for model transdermal drug delivery application. HPG is a familiar thickener as well as stabilizer used in several food items [20]. Here the chemical crosslinking occurs through free radical generation by high energy electron beam and their subsequent combination with each other. For better property control in polymer, low dose irradiation was used because of its excessive chain degradation prevention and also crosslinking in polymers promotion.

There are many studies which discussed the effect of different nanomaterials into polymer matrix [21,22]. Generally, the nanoparticles enhance the control over the physico-mechanicals properties of the matrix subject to their size, shape, and concentration. One example is addition of anisotropic carbon nanotube and clay in PVA increased mechanical, thermal, and electrical properties [20]. Similarly isotropic nano titanium dioxide ($TiO_2$) has improved thermal and mechanical properties of PVA and became suitable for direct methanol fuel cell application [23] and polyaniline-polystyrene-ZnO nano-composite improved anti-corrosive per-formance of iron surface [24]. Recently PVA encapsulated silver nanoparticles have been synthesized for different application like water purification, drug delivery system etc [25]. The present article compares effect of ex situ nanosilica on dry- and wet-stage physical, mechanical and model transdermal Diltiazem release kinetics under physiological condition between various PVA-HPG/nanosilica membranes. Diltiazem is a calcium channel blocker antianginal drug and oftenly used to treat angina pectoris by reducing oxygen demand of the heart. For an adult the dose is 180 mg/day. Overdose creates several problems and can be neutralizing by extracorporeal membrane oxygenation [26,27]. Isotropic nanosilica has silanol groups (Si-O-H) in surface that produce strong hydrogen bonded interaction with PVA-HPG. In addition, the aqueous sol is nontoxic, cheap, and solubilizes both PVA-HPG and Diltiazem molecules. To the best of our knowledge, not many studies have been carried out with ex situ nanosilica-PVA-HPG composite membranes using different PVAs.

## 2. EXPERIMENTAL

### 2.1. Materials

PVA of widely different number average molecular weights, $1.15x10^5$ and $1.4x10^4$, designated as $PVA_H$ and $PVA_L$, with Polydispersity Index 1.42 were purchased from Loba Chemie, Mumbai, India. HPG was a gift sample received from Hindustan Gum. Haryana, India. Aqueous nanosilica sol with 25% silica content and stabilized at pH 9 was generously supplied by BEE Chem, Kanpur, India. Sodium hydroxide, sodium lauryl sulphate and buffer solution of pH 9.0, all of standard grades, were obtained from indigenous sources. Diltiazem hydrochloride, molecular weight 450.98, was a gift sample received from Ranbaxy Int. Haryana, India

### 2.2. Membrane Preparation

At first HPG and PVA were mixed in 1:10 weight proportion. Then standard 10% (w/v) PVA solution premixed with HPG was prepared by dissolving PVA-HPG mixture in hot distilled water under vigorous stirring. Then the formulated aqueous gel was placed into polyethylene bags with thickness of 5 mm and was irradiated at 5 kGy dose under high energy electron beam. The parameters of the accelerator were: electron energy 1.45 MeV; electron beam current 4mA; scanner width 90 cm and conveyor speed 3.6m $min^{-1}$. Then nanosilica sols premixed with sodium lauryl sulphate were added with post irradiated gel in different proportion at pH 9 under stirring and then sonicated for 1 hour. Finally the gels were cast on plane Teflon sheets for spontaneous drying at room temperature. The average thickness of the membranes was maintained at 0.25

cm during casting. Hybrid membranes that showed excellent physico-mechanical properties from each series were further prepared with diltiazem hydrochloride. In those cases, known weight of diltiazem (1 mg) was added to the gel and sonicated further for another 30 min. Detail of sample composition has been reported in Table 1.

***Table1.*** *Sample composition.*

| Sample designation | PVA (w/v) | HPG (w/v) | Nanosilica(%) ( w.r.t., PVA) |
|---|---|---|---|
| $PVA_H$ | 10 | 0 | 0 |
| $PVA_H$/HPG | 10 | 1 | 0 |
| $PVA_H$/HPG/0.5 | 10 | 1 | 0.5 |
| $PVA_H$/HPG/1 | 10 | 1 | 1 |
| $PVA_H$/HPG/2 | 10 | 1 | 2 |
| $PVA_H$/HPG/3 | 10 | 1 | 3 |
| $PVA_L$ | 10 | 0 | 0 |
| $PVA_L$/HPG | 10 | 1 | 0 |
| $PVA_L$/HPG/0.5 | 10 | 1 | 0.5 |
| $PVA_L$/HPG/1 | 10 | 1 | 1 |
| $PVA_L$/HPG/2 | 10 | 1 | 2 |
| $PVA_L$/HPG/3 | 10 | 1 | 3 |

### 2.3. Polarized Light Microscopy (PLM)

Optical microscopic images of the hydrogels were taken in a polarized light microscope, Leitz GMBH, Germany, using a uniform magnification of 100X. Continuous pictures of the PVA-HPG hydrogel membranes during heating were captured by placing them over an electrically heated glass slide (heating rate $10^{o}$c/min).

### 2.4. Atomic Force Microscopy (AFM)

Further morphology study of the composite membranes were carried out in air at 27±2 $^{0}$C utilizing multimode AFM from VEECO Digital Instruments, Santa Barbara, CA. Topographic phase images were recorded in taping mode (TMAFM) with set point ratio of 0.9 using rotated tapping etched silicon probe (RTESP) tip having spring constant of 40 N/m. The cantilever was oscillated at a resonance frequency of 280 KHz.

### 2.5. Mechanical Properties study

Tensile stress-strain properties of the dry and fully swollen hydrogels were studied in a Lloyd UTM, USA. All the experiments were carried out at room temperature ($27\pm2^{0}$ C) with these hydrogel membranes cut as per dimension of ASTM Die C and were pulled at a rate of 10 mm/min. An average of five test results has been reported for analysis.

### 2.6. Swelling and De-swelling Kinetics Study

Swelling of hydrogel membranes was done after putting membranes of uniform dimension (5x2x0.25 $cm^3$) in distilled water at room temperature ($27\pm2^{0}$ C). After stipulated time interval, the samples were taken out of the water, gently wiped in tissue paper to soak surface water and then weighed in an electronic balance (MK-20E, readability 0.1 mg, Adair Dutt, India). The swelling ratio was calculated by dividing swelled weight (S) by dry weight ($S_0$) of the hydrogel. The experiment was carried out till the samples attained equilibrium. Care was taken to avoid partial sample loss due to dissolution.

De-swelling experiment was done by periodically recording the decreasing weight of the fully swollen gel films in ambient air ($27^{0}$ C, RH: 85) till constant value.

### 2.7. Drug Encapsulation Efficiency (DEE) and Transdermal Diltiazem Release Analysis

DEE was analyzed by immersing the best membranes from each series into saturated diltiazem solution and allowed the drug to diffuse inside the membranes

(sorption). Reduced drug concentration in the solution was monitored through UV spectroscopic measurement at 236 nm (Perkin Elmer Lambda 25 1.27) and comparing that with a standard calibration curve. A plot was generated with % drug absorbed against time interval to demonstrate DEE for each hybrid membrane.

Transdermal release of diltiazemwas analyzed in Franz diffusion cell. Detailed Description of the experiments has been reported in the earlier publication [26].

## 3. RESULTS AND DISCUSSION

### 3.1. Morphological Investigation Through PLM and AFM

Figure 1a-b shows PLM phase image of representative $PVA_H$ and $PVA_L$ hydrogels taken in the post swelled state where crystalline domains appear opaque as the light gets obstructed. Volume concentration of hard crystalline domains increases after irradiation in both PHA-HPG blend matrixes. This is due to shrinkage of amorphous water bound PVA microaggregates and finally part of them associated with the crystalline domain. Opacity is clearly much higher in $PVA_L$/HPG/1 (Figure 1d) as compared to $PVA_H$/HPG/1 (Figure 1c). This may be better mixing ability of $PVA_L$-HPG due to strong cohesive force of attraction or close viscosity between them. With increasing temperature, opacity decreases which indicate the separation of water from the crystalline phase. AFM phase images of 1% nanosilica containing both PVA-HPG membranes were compared in Figure 2(a-b). Bright, near spherical features was due to harder silica domain and dark portions were soft PVA-HPG matrix and the grey portions denote interfacial regions. Better nanosilica dispersion was observed in $PVA_L$-HPG matrix due to excellent $PVA_L$-HPG/nanosilica adhesion which increases crystallinity [28] and the best interaction was observed i.e. finer dispersion (with average diameter 22 nm) in $PVA_L$-HPG/1 composition.

### 3.2. Mechanical Property Analysis

Figure 3 compares mechanical properties of various PVA-HPG/silica hybrid membranes at different silica concentrations in dry and swelled states. Tensile strength of dry $PVA_H$-HPG hybrid membranes increases up to 2 wt.%

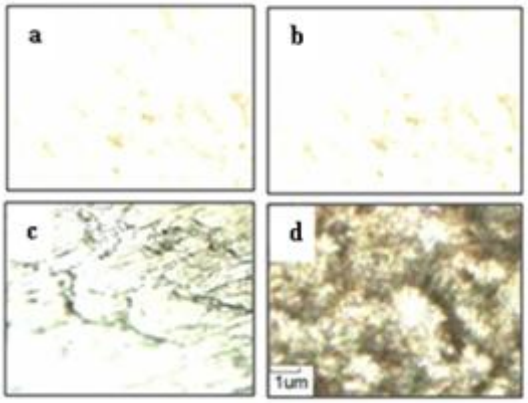


***Figure 1.*** *PLM images of (a) $PVA_H$, (b) $PVA_L$, (c) $PVA_H$-HPG and (d) $PVA_L$-HPG samples.*

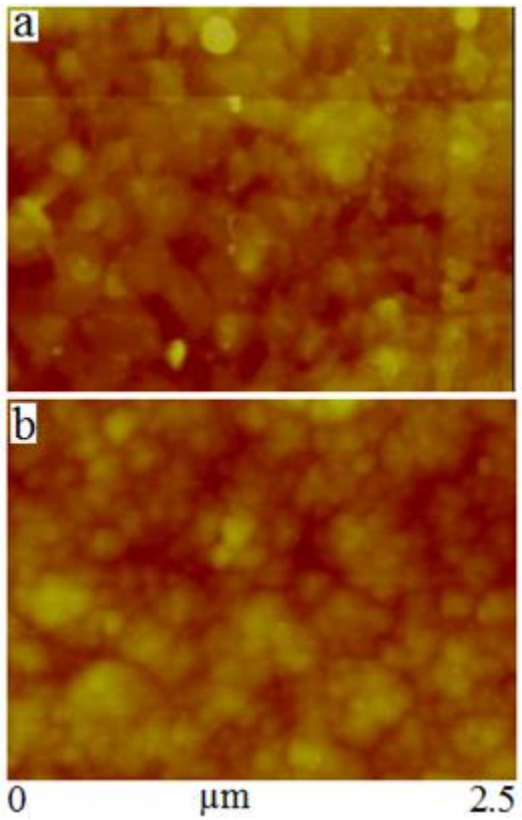


***Figure 2.*** *AFM images of (a) $PVA_H$/HPG/1 and (b) $PVA_L$/HPG/1 samples*

nanosilica content while it is up to 1 wt.% in case of $PVA_L$ and thereafter decreases to

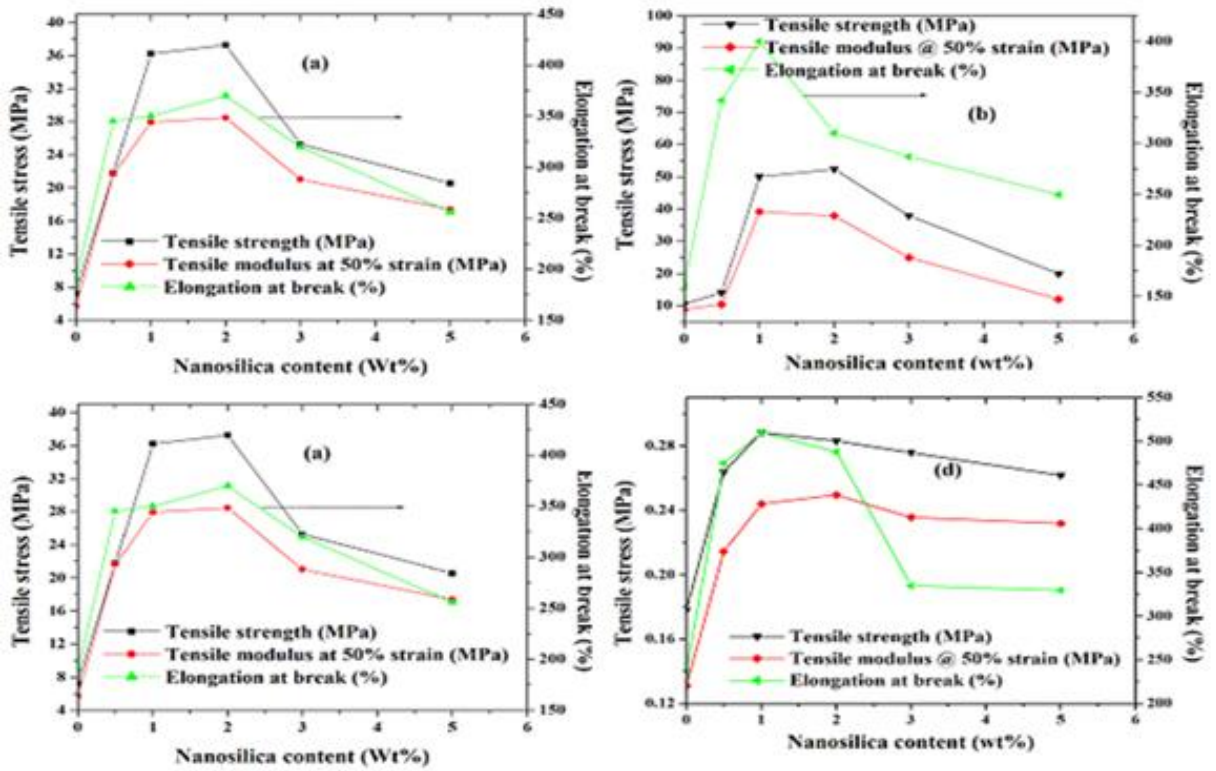


***Figure 2.*** *Mechanical property of (a) $PVA_H$-HPG and (b) $PVA_L$-HPG hybrid membranes in dry state and (c) $PVA_H$-HPG and (d) $PVA_L$-HPG hybrid membranes in swelled state.*

lower value. Similarly tensile modulus is of maximum value with $PVA_H$/HPG/2 and $PVA_L$/HPG/1 dry membranes. Interestingly, $PVA_L$-HPG membranes exhibit more tensile strength and modulus than $PVA_H$-HPG membranes due to uniform nanosilica distribution and consequent rise in crystallinity. Drop in tensile strength and moduli demonstrate deleterious effects of large silica aggregates which decrease PVA-silica interaction beyond 1 and 2 wt%. The closely adhered nanosilica particles at low concentration assisted for dissipating the impressed mechanical stress on the membranes which, at higher silica concentration, has failed since the bigger silica aggregates act as stress concentrators. Similar trend has been observed for the values of elongation at break. In swelled state both tensile strength and moduli decreased from dry state due to plasticization effect and elongation at break rises to a greater extent in the swelled state since accumulated stress released quickly in presence of excess water.

### 3.3. Swelling De-swelling Analysis

Swelling kinetics of high and low molecular weight PVA-HPG/silica hybrid membranes were continued till equilibrium was reached and results are plotted in Table 2. Pure $PVA_H$-HPG swelled at a

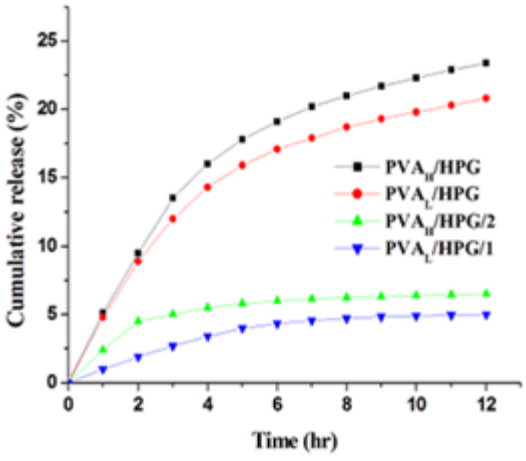


***Figure 4.*** *DEE of $PVA_L$-HPG/1 and $PVA_H$-HPG/2 hybrid membranes.*

faster rate as compared to pure $PVA_L$-HPG and finally equilibrates within much shorter time interval. $PVA_L$-HPG swells slowly than $PVA_H$ due to higher amount of hydroxyl group present in $PVA_H$ attracting water molecules faster than it [19]. The results indicate that overall swelling behaviour of hybrid membranes have been

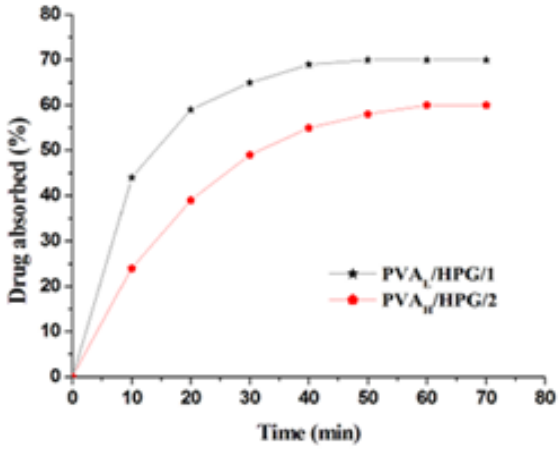


***Figure 5.*** *Cumulative release (%) of diltiazem from $PVA_H$-HPG, $PVA_L$-HPG, $PVA_H$-HPG/2 and $PVA_L$-HPG/1 hybrid membranes.*

affected in presence of ex-situ nanosilica particles. In $PVA_L$-HPG series it is interestingly observed that net swelling ratios of $PVA_L$/HPG/1 are close to $PVA_L$/HPG. Improved swelling behaviour of $PVA_L$/HPG/1 is due to uniform nanoscale dispersion of silica particles which befitted in the available free volume of $PVA_L$/HPG matrix. Conversely, the swelling ratio decreases for membranes at higher silica concentration (2-3 wt.%) in both series. At relatively higher silica concentrations, the particles aggregate into larger domains. These hydrophobic domains bulge out of the surface and restrict diffusion of water molecules inside the membranes. Deswelling kinetics of hybrid membranes show that membranes absorbing higher amount of water also release it at faster rate due to high internal pressure gradient with the environment.

### 3.4. DEE Analysis

Fig. 4 compares DEE between most physico-mechanically balanced PVA-HPG membranes for model diltiazem encapsulation and release analysis. Entrapment of diltiazem within PVA-HPG/silica hybrid was a function of drug-PVA-HPG/silica interaction through supramolecular interaction. The encapsulation by $PVA_L$/HPG/1 was clearly much higher than $PVA_H$/HPG/2, perhaps due to favourable retention vs. elution equilibrium induced by the former. The data shows, within first 10 min, 44% of the drug was absorbed by $PVA_L$/HPG/1 whereas only 24% by $PVA_H$/HPG/2 and finally the saturation achieved within 45 min in $PVA_L$/HPG/1 while in 60 min in $PVA_H$/HPG/2. $PVA_L$/HPG/1 showed better phase mixing between $PVA_L$-HPG which probably excelled drug-polymer interaction. In $PVA_H$/HPG/2, the diltiazem molecules were mostly distributed among PVA and HPG, which, because of their different phase viscosity, could not produce strong drug retention alike $PVA_L$/HPG/1.

### 3.5. Diltiazem Release Kinetics Study

Fig. 5 shows cumulative release (%) of diltiazem from $PVA_H$/HPG/2 and $PVA_L$/HPG/1 membranes fitted in a Franz diffusion cell. Data on $PVA_H$/HPG and $PVA_L$/HPG were also included to understand the variation. The release was monitored for 12 hrs and the time-dependent release data were fitted into the most prevalent power law model stated in equation 1 [29].

$$M_t/M_\alpha = k\, t^n \qquad (1),$$

where Mt/Mα denotes fractional release of diltiazem at time ‘t’. ‘k’ and ‘n’ are constants related to diffusion coefficient and specific drug transport mechanism. Here $n \leq 0.5$ indicates Fickian release behaviour which is diffusion control and depends solely on the swelling behaviour of the polymer matrix. Again $n \geq 0.5 \leq 1$ indicate anomalous release or non-Fickian release mechanism which is very difficult to control because it depends on both

swelling behaviour as well as polymer chain movement [30]. For $PHA_H$-HPG and $PVA_L$-HPG the values of n were 0.79 and 0.84, which lies in the non-Fickian region. However, $n \geq 1$, observed for both $PVA_H$/HPG/2 (1.05) and $PVA_L$/HPG/1 (1.15), fully stands for relaxation controlled release having better control than the others. The probable reason is strong post-swelled mechanical properties in both $PVA_H$/HPG/2 and $PVA_L$/HPG/1. Since the release is fully relaxation based it mainly depends on segmental flexibility of the polymers in the swelled state, which evidently was less in $PVA_H$/HPG/2 and $PVA_L$/HPG/1 due to higher modulus and strength. As $PVA_L$/HPG/1 shows best property control in every case and so finally release only 5% diltiazem in sustain way.

## 4. CONCLUSION

High viscosity of HPG increases better crystallinity in $PVA_L$ than $PVA_H$ due to greater cohesive interaction between them. Electron beam irradiation produces crosslinking in both PVA-HPG matrix and show higher mechanical strength e.g., for $PVA_L$/HPG/1 the increment of mechanical strength is 450%. Low concentration of nanosilica in both cases increases the physic-mechanical properties because of finer dispersion into the matrix and the best result was obtain for $PVA_L$/HPG/1 which shows excellent control release of drug due to its superior property enhancement in all cases [31].


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***Table2.*** *Swelling-deswelling ratio.*

| Sample | Swelling ratio | | | | | | | Deswelling ratio | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 30 sec | 1 min | 2 min | 4 min | 8 min | 16 min | 60 min | 15 min | 30 min | 45 min | 60 min | 90 min | 120 min | 150 min |
| $PVA_H$-HPG | 3.11 | 5.22 | 6.21 | 6.43 | 6.51 | 6.61 | 6.72 | 6.05 | 5.26 | 4.72 | 4.35 | 3.74 | 3.12 | 2.81 |
| $PVA_H$-HPG/0.5 | 1.35 | 1.51 | 2.12 | 3.11 | 3.91 | 4.31 | 4.43 | 4.04 | 3.81 | 3.65 | 3.45 | 3.25 | 3.05 | 2.90 |
| $PVA_H$-HPG/1 | 1.28 | 1.41 | 1.91 | 2.82 | 3.52 | 3.73 | 3.83 | 3.69 | 3.55 | 3.45 | 3.35 | 3.18 | 3.14 | 2.92 |
| $PVA_H$-HPG/2 | 1.26 | 1.35 | 1.82 | 2.58 | 3.32 | 3.43 | 3.61 | 3.50 | 3.44 | 3.31 | 3.25 | 3.22 | 3.11 | 2.93 |
| $PVA_H$-HPG/3 | 1.25 | 1.32 | 1.62 | 2.35 | 2.82 | 3.13 | 3.31 | 3.11 | 3.01 | 2.98 | 2.97 | 2.96 | 2.95 | 2.94 |
| $PVA_L$-HPG | 2.13 | 3.24 | 4.17 | 4.98 | 5.71 | 6.21 | 6.42 | 5.89 | 5.23 | 4.75 | 4.33 | 3.85 | 3.25 | 2.82 |
| $PVA_L$-HPG/0.5 | 1.44 | 1.95 | 2.93 | 3.26 | 3.75 | 3.92 | 4.26 | 5.75 | 5.12 | 4.65 | 4.38 | 3.88 | 3.28 | 2.83 |
| $PVA_L$-HPG/1 | 1.25 | 1.38 | 1.72 | 2.43 | 2.91 | 3.12 | 3.55 | 3.82 | 3.61 | 3.45 | 3.38 | 3.15 | 3.01 | 2.84 |
| $PVA_L$-HPG/2 | 1.23 | 1.25 | 1.62 | 2.25 | 2.61 | 2.92 | 3.21 | 3.43 | 3.33 | 3.25 | 3.15 | 3.08 | 2.99 | 2.84 |
| $PVA_L$-HPG/3 | 1.22 | 1.12 | 1.43 | 1.95 | 2.31 | 2.61 | 2.92 | 2.90 | 2.89 | 2.88 | 2.87 | 2.86 | 2.85 | 2.84 |

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