

# Magnetic Hydrogel Based Shoe Insoles for Diabetics

Rahul Patwa<sup>1a)</sup>, Nabanita Saha<sup>1b)</sup> and Petr Sáva<sup>1c)</sup>

<sup>1</sup>Centre of Polymer Systems, University Institute, Tomas Bata University in Zlín, Třída Tomáše Bati 5678, 760 01 Zlín, Czech Republic

<sup>a)</sup> patwa@utb.cz, <sup>b)</sup> Corresponding author:nabanita@utb.cz, <sup>c)</sup>saha@utb.cz

**Abstract.** According to WHO's Global report on diabetes 420 million adults are affected by diabetes worldwide. Foot infections are the most prevailing health complications in diabetics which arise due to neuropathy and peripheral vascular disease. The former concerns with nerve damage whereas the latter causes fatty depositions in blood vessels which reduce the blood flow causing pain, infection and slow healing wounds. One alternative therapy which is gaining popularity is the application of magnetic field to improve blood circulation by use of magnetic insoles. However, hydrogel based magnetic insoles have been scarcely reported. An efficient strategy is employed for the preparation of flexible magnetic hybrid hydrogels consisting of mixture of cobalt ferrite (CoFe<sub>2</sub>O<sub>4</sub>) and iron-oxide (Fe<sub>3</sub>O<sub>4</sub>) magnetic nanoparticles (MNPs) dispersed in PVP/CMC cross-linked hydrogels. Here the MNP ratio has been varied in the ratio of 1:0, 1:1, 1:2, 2:1 and 0:1, respectively. The method involves the formation of cross-linking between the two polymer chains under high pressure and temperature. The hybrid hydrogels were chemically and morphologically characterized using SEM, FTIR, VSM, swellability and mechanical testing. The morphological analysis showed the porous structure while using the VSM magnetic properties of the samples were evaluated. The rheological properties of the hydrogels were also investigated with the aim to verify their behaviour under an applied mechanical stress. The presence of MNPs, the hydrogel is capable of responding to an external magnetic field. Preliminary data show the possibility of use of the material for magnetic insoles for diabetics.

## INTRODUCTION

Magnetic materials have been majorly used for various biomedical applications and devices such as magnetic resonance imaging (MRI), ferrofluids, hyperthermia, etc.<sup>1</sup> Magnetic hydrogels have found new applications in biomedical engineering including tissue engineering, enzyme immobilization, drug delivery and release, soft actuators and cancer therapy, etc. Recently magnetic hydrogels containing micron or nano-sized MNPs such as  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>, Fe<sub>3</sub>O<sub>4</sub>, CoFe<sub>2</sub>O<sub>4</sub> have been reported which enhance their controllability.<sup>2</sup> Hydrogels are polymeric materials with high amount of cross-linking between adjacent polymer chains which give rise to three-dimensional structures which are hydrophilic in nature and non-soluble in water. Initially hydrogels were mainly used for treatment of open wounds as it was established that wet environment can enhance the wound healing process.<sup>3</sup> However, now hydrogel are readily used as soft materials for various bio-medical fields such as scaffolds for tissue engineering, super absorbents, drug delivery, contact lenses, control implants, substitutes for tendons, ligaments, cartilage and even bones, wound or burn dressing material and other medical device fabrication mainly due to the fact that most properties of hydrogels are comparable to the native extracellular matrix.<sup>4</sup>

Poly (N-vinyl pyrrolidone) (PVP) is a hydrophilic synthetic polymer with good biocompatibility discovered in 1939. It is mainly used in pharmaceuticals and personal care products (PPCPs) or food industries.<sup>5</sup> PVP however is known to be fragile and has a less swelling capacity. To obtain improved properties PVP is often blended with other polymers such as polysaccharides. These days many polysaccharides are gaining popularity such as alginate, chitin/chitosan, cellulose/carboxymethyl cellulose (CMC), etc. mainly due to low-cost, abundance, non-toxicity and biodegradability

Cellulose, is the most abundant polymer which is a long chained polysaccharide joined by a B-1,4-glucosidic linkage. The carboxymethyl cellulose (CMC) is a hydrophilic, water soluble ether derivative in which H atoms in hydroxyl groups are replaced by carboxymethyl substituent, -CH<sub>2</sub>COOH. It has been used for a variety of applications

due to its low-cost, abundance, biocompatibility, good-water absorption behavior, etc.<sup>6</sup> Its properties can be improved by blending with other polymers such as gelatin, starch, PVP and glycerol etc.

Diabetes causes neuropathy and peripheral vascular disease which leads to nerve damage and fatty depositions in blood vessels, respectively.<sup>7</sup> The combined effect of two results in reduced blood flow, infection and slow healing wounds especially in the foot where in aggravated cases it might result in foot or leg amputation.<sup>8</sup> An alternative therapy is the use of magnetic insoles to improve blood circulation.<sup>9</sup>

In this work, we discuss the method of preparation of PVP/CMC based magnetic hydrogel its characterization (physical appearance, physicochemical structure, water uptake capacity, magnetic and rheological properties). A series of PVP/CMC blend hydrogels were prepared with different Co/Fe ratios to achieve effective content of composition. It is known that the viscoelastic properties of hydrogels correlate strongly with their microstructures, composition and the concentration of dispersed materials.

## MATERIALS & METHODS

Poly (vinyl pyrrolidone) K-30 PVP, polyethylene glycol 3000 (PEG) and agar was purchased from Fluka, Switzerland; Carboxymethylcellulose (Na-CMC) was supplied from Sinopharm Chem. Reagent Co. Ltd. China. Glycerine was obtained from Lachema Ltd. Czech Republic. Cobalt iron oxide (CoFeO<sub>7</sub>), Iron (II) chloride tetrahydrate 98% (FeCl<sub>2</sub>·4H<sub>2</sub>O), Iron (III) chloride hexahydrate 98% (FeCl<sub>3</sub>·6H<sub>2</sub>O) and ammonium hydroxide soln. (NH<sub>4</sub>OH) was purchased from Sigma Aldrich, Czech Republic.

### Preparation of PVP/CMC Blend Hydrogels

Iron-oxide nanoparticles are prepared by using standard Massart method.<sup>10</sup> Hydrogels were prepared by moist heat treatment method.<sup>11, 12</sup> Solutions of PVP (1wt%) and CMC (1wt%) were prepared separately by dissolving PVP and CMC in deionized water (40mL each) at 80 °C for about 2 h under continuous stirring. Then the two solutions were mixed to prepare homogeneous mixture into which agar (1wt%), PEG (3wt%), glycerol (3% w/v) were added to the homogeneous mixture. Finally, MNPs (1wt%) are added which are previously sonicated in 20mL of DI water. Then the mixtures were autoclaved for 20 minutes. After completion of the process, the hot polymer solution was cast in petriplates and allowed to cool at 37 °C in hot air oven. Finally, dried round flexible films were obtained and termed as PVP/CMC hydrogels. Some samples were also lyophilized.

### Swelling Behavior

The lyophilized hydrogels without unbound water content were cut into small pieces (2×2 cm<sup>2</sup>), weighed and immersed in physiological saline solution (0.9% NaCl, 37 °C) for a total time period of 330 mins. After every 30-minute time intervals the water on the swollen hydrogels was wiped off with wet tissue papers and the weight of the specimens was noted. The Swelling degree and water retention percentage was calculated as per Eq. (2)<sup>13</sup>:

$$(\text{Swelling degree}) \% = [(W_1 - W_2) / W_2] \times 100 \quad (1)$$

$$(\text{De-swelling degree}) \% = [(W_3 - W_4) / W_4] \times 100 \quad (2)$$

where, W<sub>1</sub>, W<sub>2</sub> are weights of swollen, dry and W<sub>3</sub>, W<sub>4</sub> are weights of swollen and deswollen hydrogel, respectively.

### Fourier transform infrared spectroscopy (FT-IR).

Pure PVP, pure CMC, and PVP/CMC gels after were analysed by FT-IR. The ATR-FTIR spectra were recorded using a NICOLET 320 FTIR over the range 4000-600 cm<sup>-1</sup> at room temperature. A uniform resolution of 2 cm<sup>-1</sup> was maintained in all cases.

### X-ray diffraction

X-ray diffraction patterns of powdered samples of MNPs were obtained using Bruker D8-Discover X-ray diffractometer with Cu K $\alpha$  radiation of wavelength 1.54056 Å.

## Vibrating Sample magnetometer

Room temperature magnetic measurements were performed with a Lakeshore Model 7404 vibrating sample magnetometer (VSM).

## Rheological properties

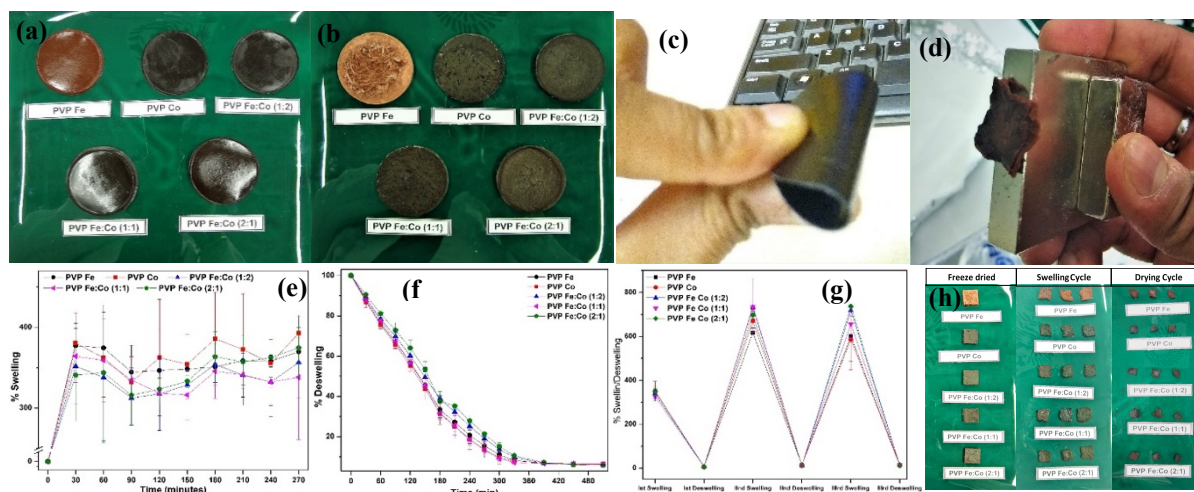
To evaluate the dynamic viscoelastic properties of swelled PVP-CMC hydrogels, a parallel plate Rheometer (Anton Paar, USA) testing machine with a software package was used. A 25 mm diameter parallel plate with a gap of 2-3 mm was used, and frequency sweep (0.1-100 rad/s) measurements at 25 °C were carried out at 1% strain to maintain the measurements within the linear viscoelastic region.

## Scanning electron microscope (SEM)

PVP/CMC blend hydrogels were lyophilized to get spumous samples. SEM image was made by scanning electron microscope. The SEM observation was carried out using Phenom world PRO instrument operating at high-vacuum/secondary electron imaging mode at an accelerating voltage of 5-15 kV. The images were taken at a magnification of 100x to 10 kx magnification factor.

## RESULTS AND DISCUSSION

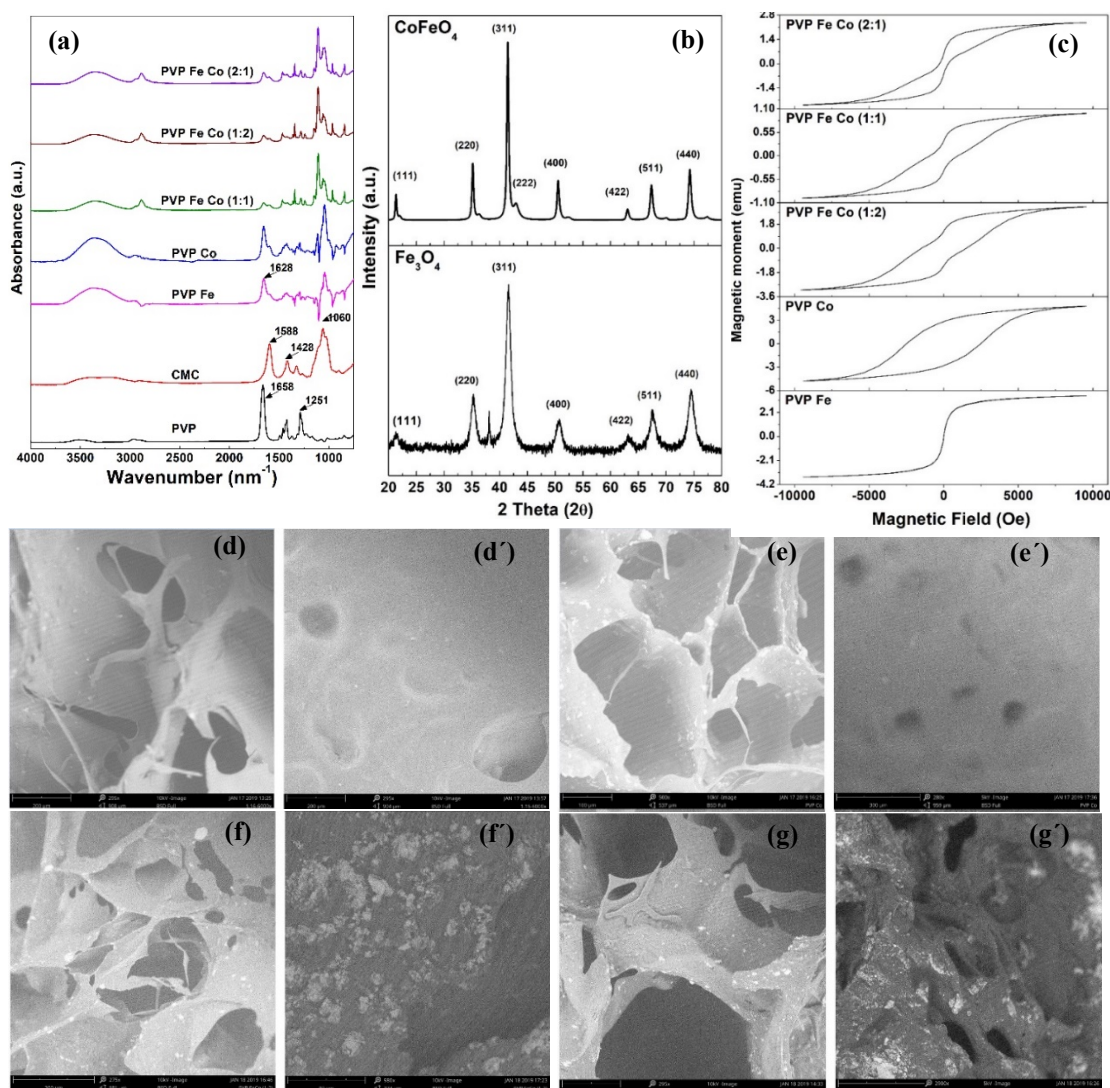
The PVP/CMC blend hydrogels were successfully prepared using different ratios of MNPs. The hydrogels were prepared by simple air-drying (Fig. 1a) and freeze-drying (Fig. 1b). All the samples were highly flexible (Fig. 1c) and showed attraction towards magnet (Fig. 1d) indicating that the prepared hydrogels were magnetic in behavior. The swelling and de-swelling behaviour of the hydrogels is shown in Fig (1e and 1f). The maximum amount of water retention can be seen in the initial 30 minutes and reaches to more or less equilibrium state. It can be seen clearly in Fig 1e that hydrogels prepared using pure composition of MNPs such as PVP Co and PVP Fe have better swelling characteristics. As compared to swelling, the deswelling takes a longer time (~360 min) to take place due to the presence of hydrophilic groups (-CHO, -COO and -OH). Finally, it can be concluded that the water retention and water absorption characteristics of all the hydrogels is highly comparable. In Fig (1g and 1h), it can be seen that all the hydrogels do not undergo disintegration upon extended usage this was checked by subjecting the hydrogels to successive swelling-de-swelling cycles.



**FIGURE 1.** Pictorial representation of (a) air-dried, (b) freeze-dried, (c) flexible behavior of and (d) magnetic behavior of hydrogels, (e) Swelling degree, (f) Deswelling degree, (g) swelling-deswelling cycles and (h) pictorial comparison of original, swelled and dried hydrogels.

FTIR spectra of pure PVP, CMC and fresh hydrogels of PVP-CMC are shown in Fig. (2a). PVP spectra contains the characteristic peaks at 1281 and 1658  $\text{cm}^{-1}$  which are assigned to C-N and C=O stretching vibrations, respectively.

The CMC shows absorption bands at 1588, 1428 and 1060  $\text{cm}^{-1}$  which represents the carbonyl band, C=C stretching and  $\beta$ -1,4-glycosidic band, respectively. It is noteworthy to mention that PVP peak at 1658  $\text{cm}^{-1}$  and CMC peak at 1588  $\text{cm}^{-1}$  gets condensed and appear as one single peak around 1628  $\text{cm}^{-1}$  indicating towards cross-linking or grafting between CMC and PVP chains in PVP/CMC blends. X-ray diffraction patterns shown in Fig (2b) of the synthesized iron-oxide and purchased cobalt ferrite matched closely with the diffraction patterns of  $\text{Fe}_3\text{O}_4$  and  $\text{CoFe}_2\text{O}_4$ , respectively.<sup>14, 15</sup> Magnetic properties measured by VSM revealed that cobalt ferrite MNPs have better coercivity as compared to iron-oxide MNPs as shown in Fig (2c). As a result, the PVP Co showed superior magnetic properties. For the mixed MNPs formulations, PVP Fe Co (1:2) showed highest magnetic properties. The SEM images of all lyophilized PVP/CMC based hydrogels are shown in Fig 2(d-g'). The surface and cross-sectional images clearly show the presence of porous structures in all the hydrogels which arise from the polymer chain entanglements or physical interactions. The presence of pores allow these hydrogels to absorb/retain water inspite of the fact that these hydrogels are prepared using water soluble polymers. It can be observed from the SEM micrographs that the PVP Fe Co (1:2) has the most dense network and numerous small pores.

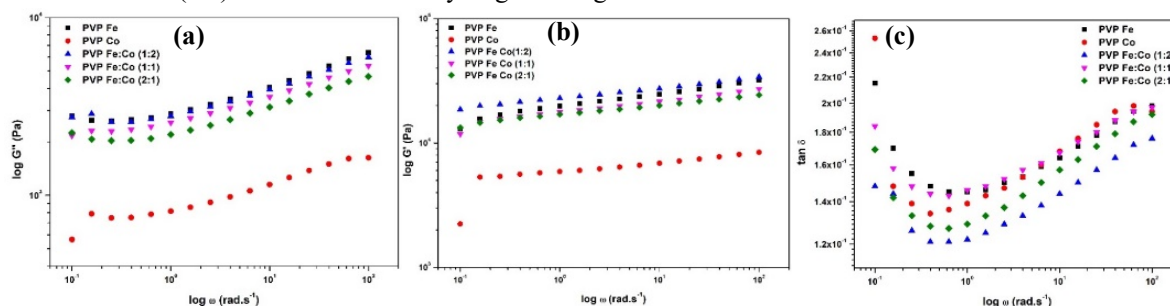


**FIGURE 2.** (a) FTIR spectra of prepared hydrogels; (b) x-ray diffraction patterns of MNPs; (c) VSM magnetic measurements of prepared hydrogels; (d-g') SEM micrographs of cross-sectional and the flat surfaces of (d, d') PVP Fe, (e, e') PVP Co, (f, f') PVP Fe Co (1:2), (g, g') PVP Fe Co (1:1) hydrogel.

Fig 3 depicts the storage modulus (elasticity) and loss modulus (viscous behaviour) with respect to frequency. It can be observed that the storage modulus values are higher than the loss modulus values throughout the frequency



range which is typical for gels hence at low strain (~1%) they show rubbery behaviour. PVP Co shows lowest values of  $G'$  and  $G''$  whereas PVP Fe shows higher  $G'$  and  $G''$  values which indicate that  $Fe_3O_4$  NPs act as lubricant and also it can be said that they induce better crosslinking as compared to  $CoFeO_4$  NPs. Furthermore, it can be concluded that PVP Fe Co (1:2) is the most elastic hydrogel among all others.



**FIGURE 3.** Effect of angular frequency ( $\omega$ ) at 1% strain on (a) loss modulus ( $G''$ , non-filled symbol), (b) storage modulus ( $G'$ , filled symbol), (c) damping factor ( $\tan \delta$ ) for PVP Fe, PVP Co, PVP Fe CO (1:2), PVP Fe CO (1:1), PVP Fe CO (2:1).

## CONCLUSIONS

The main objective of this research work was to develop a hydrogel film as an alternative approach as diabetic shoe insoles. The materials used are all non-toxic and biodegradable. It was found that PVP/CMC hydrogel films containing MNPs could be a promising candidate as a shoe insole material for diabetic care. All the hydrogels are flexible in nature and shows good modulus which is required for durability. Moreover, it was found that PVP Fe Co (1:2) hydrogel has the superior properties as compared with other prepared hydrogels in terms of swellability, magnetic, morphological and rheological properties. This hydrogel composition can be efficiently used as shoe insert by diabetics for increasing blood circulation. In addition, being a hydrogel the material can readily absorb moisture hence reduce bacterial growth thus preventing foul odor.

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