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Synthesis of magnetically active interpenetrating polymer network for drug release

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ABSTRACT

Interpenetrating polymer networks (IPN) were formed involving hydrophobic polybutyl acrylate (PBA) and hydrophilic poly hydroxyethyl acrylate (PHEA). PBA prepolymer was first formed in presence of ferric oxide nanoparticles (<30nm) under continuous stirring through free radical polymerization. 2-Hydroxyethylacrylate monomer premixed with crosslinker and initiator was added to it and the reaction was allowed to continue till the gel was formed. The ferric oxide particles were synthesized using thermal arc plasma technique. The particles were characterized by XRD, TEM. The magnetization was determined by VSM. Magnetic response of the IPN was assured after embedment of the iron oxide particles. The signature of particle embedment in IPN gel bulk was confirmed by FTIR and SEM micrographs. Swelling study in three different pH solutions of 4, 6, 9 showed maximum swelling in alkaline pH (9). In vitro biocompatibility was tested on plant cell as well as on bacteria, E-coli. Variation in crosslink density of the IPN in presence of the iron oxide particles was tested and observed to be affecting the drug loading and/or releasing capability of the network. The drug loading and release test of the IPNs with and without iron oxide nanoparticles has been studied for multivitamins, salicylic acid and acetaminophen drugs.

Keywords: *Interpenetrating Polymer network; Iron oxide; Nano particles; Cytotoxicity; Drug loading; Drug release*

INTRODUCTION

Interpenetrating polymer network (IPN) is defined as a special class of polymer alloys, in which at least one component is synthesized and/or crosslinked in the presence of the other component. Therefore, a permanent interlock is formed without any covalent bonding across the networks. Moreover, an IPN, comprising of at least one hydrophilic component, will be suitable as a carrier of drug delivery system, for periodic administration as required in the chronic infection via oral or systemic routes.

Various studies have established that the local application of antibiotics provides high concentration of drug at the site of infection with a low systemic toxicity [1,2]. Various local drug delivery systems with antibiotics have been attempted; however the most widely studied material has been an antibiotic-acrylic composite. In most cases, hydrophilic acrylics, e.g. poly acrylic acid, polyacrylamide, poly(2-hydroxyethyl acrylate), poly (hydroxylethyl methacrylate) etc. are used for biocompatibility and/or biodegradability [3-5]. During IPN synthesis, in-situ polymerisation and crosslinking of one component in presence of the other leads to mixing of the components at segmental level giving rise to a permanent interlocking of morphology. Furthermore, depending upon the nature of weight ratio of hydrophilic and hydrophobic components taken in the system a range of properties can be achieved in terms of porosity, biocompatibility, toughness, % drug loading and release, swelling characteristics and crosslinking density etc. which in turn makes the products applicability in a wide range. G.G Ferrer et al. showed formation of nanodomains (30-100nm) in hydrophilic-hydrophobic IPN based on poly (2-hydroxyethyl acrylate) and poly (ethyl acrylate) and suggested their suitability for cell adhesion on that basis [6].

These properties of the IPN can further be altered by embedment of nanoparticles in the IPN matrix. Moreover, target specific delivery by magnetically induced drug carriers (polymers) using an externally applied magnetic field is by far a common technique. Especially super paramagnetic particles are widely used for such deliveries and when required even under much smaller magnetic field ~ 2-8 Koe [7-9,1- 3]. On account of this, iron oxide embedded polymers can be used as contrast media in magnetic resonance imaging [8,2]. Widder et al. first reported the use of magnetic albumin microspheres [10,4]. Literature reveals that in presence of magnetic field, the magnetic carriers demonstrated 16 fold increase in the maximum drug loading, 6 fold increase in drug release and 6 fold increase in the drug targeting efficiency to rat tail target segments [11,5]. Moreover, iron also acts as electron acceptor for bacteria that can couple organic matter oxidation to Fe (III) reduction in the absence of oxygen [12]. Iron-reducing bacteria are thus able to gain energy from the reduction of soluble or solid iron species [12,6]. Also it is well established that Iron acts both as nutrient and as electron acceptor, on the growth and cultivability of bacteria like Escherichia coli which is a good source of penicillin amidase [13].In view of this, the present report is an effort to synthesize magnetically active IPN hydrogel nano composites. Moreover, the magnetic activity as induced here by embedment of ferric oxide nanoparticles, during in-situ polymerization, is expected to be utilized in binding suitable enzyme like penicillin amidase from *E-coli*. and targeted delivery as and when required.

The main aim of the present study is to see the biocompatibility of an IPN based on hydrophilic along with hydrophobic acrylics and to find out its efficiency as drug carrier for targeted delivery. Semi-II IPN was made of Poly (2-hydroxyethyl acrylate) (PHEA), as the crosslinked hydrophilic component and poly butyl acrylate as the linear hydrophobic part interlocked with each other. Elastomeric PBA was used to give the IPN enough toughness in combination to the hydrophilic nature of PHEA required for the biocompatibility and drug dissolution.

EXPERIMENTAL

Butyl acrylate (BA) from CDH (Delhi,India) was purified by washing first with 2% aqueous potassium hydroxide solution, then by thorough and repeated washings with distilled water (to make alkali free, as tested by litmus paper) and dried over anhydrous calcium chloride and finally vacuum distilled. 2-hydroxy ethyl acrylate (HEA) from Aldrich Chemical Company (Germany) was used without further purification. Benzoyl peroxide (Bz_2O_2) from Loba Chemie Pvt Ltd. (Mumbai,India) was purified by repeated crystallisation from chloroform. Ethylene glycol dimethacrylate (EGDMA) (Aldrich Chemical Company,Germany), without any modification was used as the crosslinker and comonomer.

The powders of iron oxide were prepared by DC thermal arc-plasma method using iron block of commercial grade. The details of the experimental set-up of DC thermal arc plasma method are given in earlier report [12,6].

Synthesis

- **Synthesis of iron(III) oxide nanoparticles**

The arc plasma was initiated between an iron anode and cathode in air ambient in a multi-port stainless steel chamber. The cathode was made up of tungsten and the anode was a block of iron, which was to be evaporated. A DC source with 70 V (200 A) was used for exciting the plasma. The powders were prepared at 100 A in an air ambient. The powder scraped from the walls and covering flange of the deposition chamber was collected.

- **Synthesis of iron(III) oxide embedded semi -II IPN**

Poly butyl acrylate polymer was first formed, under constant stirring and inert atmosphere, in presence of 2% Bz_2O_2 initiator at 80ºC, along with the nanoparticles of iron (III) oxide pre-mixed with it. Fe_3O_4 nanoparticle embedded PBA mass was swelled in a mixture of 2-hydroxyethyl acrylate monomer, the initiator and 2% EGDMA crosslinker for 24 hours at room temperature and then allowed to heat again at 80ºC till the white crosslinked gel was formed. Uniform mixing of iron oxide particles with the PBA polymer was assured from magnetic response of the NP-IPN sample taken randomly from the mass. IPNs were prepared by taking the two acrylates in 50:50 blend ratio (w/w). The samples, designated as "NP-IPN" were purified by distillation from ethanol for 24 hours [6] to remove the unreacted monomers and finally vacuum dried for 24 hours at 50ºC. These dried samples were used for characterization. For comparison of properties, IPNs without iron (III) oxide particles, designated as "IPN-gel", were also prepared and purified in the same way.

THEORY/CALCULATION

Characterization of iron (III) oxide nano-particle

The phase analysis of the powder was carried out by X-ray diffractometer (Philips, PW-1710, Cu-Ka radiation, Ni filter) in the range 2θ=10–900.Transmission Electron Microscopy (TEM Model JEOL, JEM-1200 EX Electron microscope) was used for the morphological (estimate the particle size, shape, nature of agglomerates) studies of the powder.

Characterisation of IPNs

Polymer films of both the types of IPNs were characterised by FTIR spectroscopy (SHIMADZU IR prestige-21, Japan) in ATR mode within the wavelength range 400-4000 cm^{-1}. Crosslink density of the IPNs, with or without the iron (III) oxide particles were determined by using Flory-Rehner equation 1, 2 [14,12] as follows:

$$\gamma = \frac{[V_p + \chi V_p^{\,2} + \ln(1-Vp)]}{[d_r V_s (V_p^{\,1/3} - V_p/2)]} \qquad (1)$$

Where, Vp =volume fraction of polymer in the swollen mass, Vs = molar volume of solvent, ds = density of solvent, dr = density of polymer

$$\chi = \beta + \left(\frac{V_s}{RT}\right) \times (\delta_s - \delta_p)^2 \qquad (2)$$

Polymer-solvent interaction parameter according to Bristow and Watson[14,15, 13], where β =lattice constant (0.34); R, universal gas constant (cal/K/mol); T, absolute temperature (K), δp and δs are solubility parameter of IPN and solvent respectively.

γ =crosslink density of the polymer sample=Mc-1

M_c^{-1}= molecular weight of polymer chain in between two successive crosslinks. The parameter Vp was found out by using equation 3,

$$V_p = 1/1+Q \qquad (3)$$

$$Q = \frac{m - m_0}{m} \times \frac{d_r}{d_s} \qquad (3)$$

m0, m are mass of dry and swollen polymer in gm respectively. IPN samples were dipped in a series of solvents having solubility parameter in the range (18-22 MPa1/2) up to equilibrium swelling in each. The % swelling (Q) was then calculated and with the help of equation 2 degree of crosslinking was determined [15, 12].

The crosslinked networked structure of the prepared IPNs was assessed by swelling behaviour

of the circular samples of 1 cm diameter, as prepared by pressing the gel like mass in between two glass slides under vacuum drying. The dried and pre-weighed samples were immersed in water for 24 h at 37ºC during which period the polymer attained equilibrium swelling. Then the films were carefully taken out at 1h interval, wiped with a filter paper for the removal of free water on the surface, and then weighed. The degree of swelling was calculated using the following equation:

$$SR(\%) = \left[\frac{(w_t - w_d)}{w_d} \right] \times 100 \qquad (4)$$

Where wd and wt are the weights of dry and wet samples at time t respectively. All measurements were triplicated for each sample.

For characterisation of the response to different pH environments, the circular samples of IPNs, as mentioned in swelling experiment, were allowed to reach equilibrium swelling in three different pH solution namely 4 , 6 and 9 at 37ºC. The pH values were selected to allow comparison of swelling behaviour in human G.I. conditions. Equilibrium swelling studies were conducted gravimetrically using the equation 4.

Phase morphology of the IPNs was examined by Scanning Electron Microscope from JEOL Tokyo, Japan, (JSM-6390LV) with magnification of x14000.

Cytotoxicity Study

- **Allium Cepa (Onion root cell)**

In vitro toxicity test for plant cells was performed using Allium Cepa (onion roots). The old roots and loose scales on onion bulbs, purchased from the local market, were carefully removed. The onion bulbs were placed on the swollen polymer gel, taken in a glass petridish. Onion bulbs seated on beaker filled with clean water served as control. Roots were allowed to elongate to 1-2 cm before fixing them in 1:3 (v/v) acetic acid/ ethanol between the hours of 9:00 am and 12:00 noon for 24 hours (3 hrs/day for 8 days).The fixed roots were hydrolysed in 1N HCl for five minutes and rinsed with water. Slides were prepared using the squashing and staining techniques described by Adegbite and Olorode [16]. The slides were observed under the light microscope and data on total cells, total dividing cells and cells carrying chromosomal aberrations were taken from 100 microscope fields on at least 20 slides prepared for each of the different treatments and the control.

- **Bactericidal effect**

In vitro toxicity test of the nanoparticles of Fe_3O_4 was carried out using E-coli (NCIM 2809) bacteria. Proper cleaning of the equipments was made including Gel and Gel embedded with Fe_3O_4 nanoparticles which were washed out with distilled water and autoclaved at 121.5°C, 15 psi for 30 minutes. E-coli bacteria were grown in 50 ml of nutrient broth at 37°C for 48 hours maintaining a pH of 7-7.2 with Gel and Gel embedded with Fe_3O_4 nanoparticles. The samples were all kept in a shaker incubator to set the whole of the bacterial suspension under uniform contact to the nanoparticles during growth. The optical density (absorbance at 600 nm) was then taken using UV-VIS Spectrophotometer at one-hour intervals each for determining the cell counts to study the bacterial growth curve. A growth curve of mother culture had also been obtained in similar manner for comparison. The optical density at 600nm has been calibrated to be equivalent to 10^7cells/ml in our case through serial dilution viable count method. Number of cells per ml against time was then plotted for obtaining the bacterial growth curve.

Drug Loading in the Hydrogel

The drug loading was carried out by swelling the known amount of IPN samples in drug solution at 37 degree Celsius. After immersing the samples in the drug solution for 24 hours, it was taken out, dried and reweighed. The increase in dry weight of the hydrogel was taken as the amount of drug loaded. A 2mg/ml solution of multivitamin (A-Z), acetaminophen (ARK AP) and salicylic acid were used for loading of drug in IPN sample.

In-vitro drug release study

In vitro release of entrapped drug (multivitamin, paracetamol and salicylic acid) was carried out by placing the drug loaded IPN in simulated intestinal fluid (SIF<pH: 9) at 37^0C maintained in an incubator with reciprocating motion (100 rpm) [17]. At periodic intervals, the

release medium was assayed using UV-VIS spectrophotometer, Perkin Elmer, USA. The amount of release at different intervals was determined spectrophotometrically at 468 nm for multivitamin, at 242 nm acetaminophen and at 296 nm for salicylic acid [16,17]. After each observation, gels were put in fresh solution. The amount of drug release was calculated by comparing the absorbance with the standard curve prepared for pure drug in the appropriate concentration region [18,19].

RESULTS AND DISCUSSION

Properties of iron (III) oxide nano-particle

Figure 1 gives the X-ray diffraction (XRD) pattern for the synthesized powder. The XRD pattern shows the formation of iron oxide powder. From JCPDS data, it is clear that all XRD peaks of cubic spinel magnetite (Fe_3O_4) and cubic spinel maghemite (g-Fe_2O_3) phases are similar with small difference in their corresponding d values and lattice constants [20,21]. In the present case, the d values calculated for the XRD patterns are observed to be closer to corresponding values for Fe_3O_4 phase than that of the gamma phase of iron oxide [20]. Further, the lattice parameter calculated for the sample is found to be a^0=8.396 Ao, which is very close to the reported value of 8.3967 Ao for Fe_3O_4 phase [20,21]. The average crystallite size; D was calculated from the Scherrer equation: $D=k\lambda/(\beta\cos\theta)^{-1}$, where, k=0.9, λ=wavelength of X-rays and β=FWHM of (400) reflection. The average crystallite size thus obtained from this equation is found to be ~35 nm.

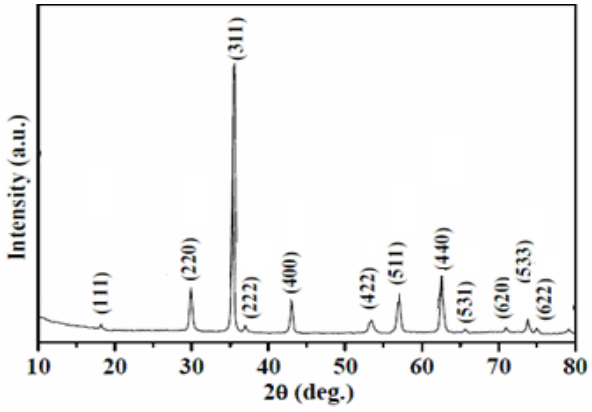

Fig.1. XRD of Fe_3O_4 nanoparticles

The transmission electron micrograph (Figure 2) of the sample shows that almost spherical particles of Fe_3O_4 are formed. The particle size distribution has been shown in the inset of the TEM image. The maximum particles were found to be of ~20 nm. The hysteresis loops of powder samples were recorded at room temperature. Figure 3 exhibits the hysteresis loops for the synthesized powder.

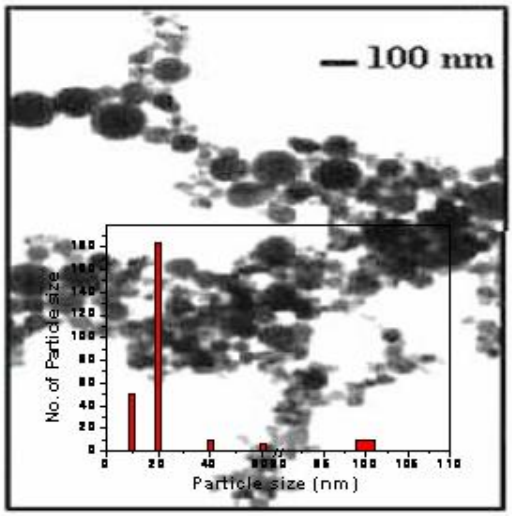

Fig.2. Transmission electron micrographs of Fe_3O_4 nanoparticles

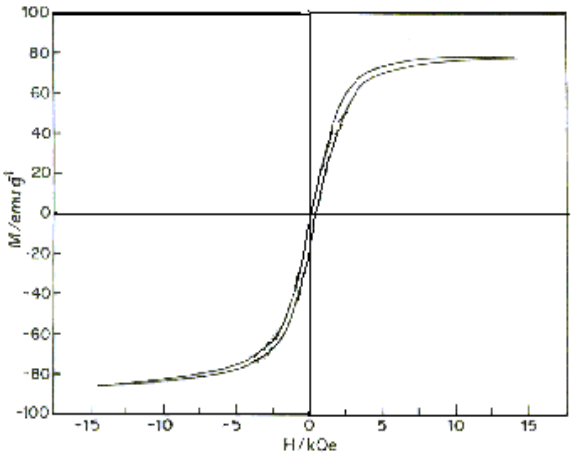

Fig.3. Hysteresis loop for Fe_3O_4 particles

Well-defined hysteresis loop is observed for the sample. The coercivity values are found to be 0.25 ke. The saturation magnetization value of the sample was found to be 88 emu/g. The saturation magnetization at room temperature for sample S3, i.e. 88 emu/g is found to be comparable to the value of 92 emu/g reported for the bulk

magnetic particles of Fe_3O_4 [22, 23]. The reduction in saturation magnetization of Fe_3O_4 particles could be attributed to the presence of non-magnetic layer on the surface of the particles, charge distribution, super-paramagnetic relaxation and spin effect because of ultrafine nature of particles [22,23].

Properties of IPNs

FTIR spectra of IPN-gel and NP-IPN (Figure 4) show characteristic transmittance peaks mentioned in the Table 1. Transmittance, corresponding to both the constituent acrylate polymers, is observed here. The transmittance peak intensities have not been altered due to the embedment of nanoparticles. This indicates the absence of direct chemical bonding of the nanoparticles with the acrylate components. It could be inferred that acrylate polymerization in presence of the nanoparticles, might has taken place without any alteration in reaction mechanism. However, the embedment of Iron (III) oxide particles in the gel is clear from the above results (peak in the range 440-650cm-1).

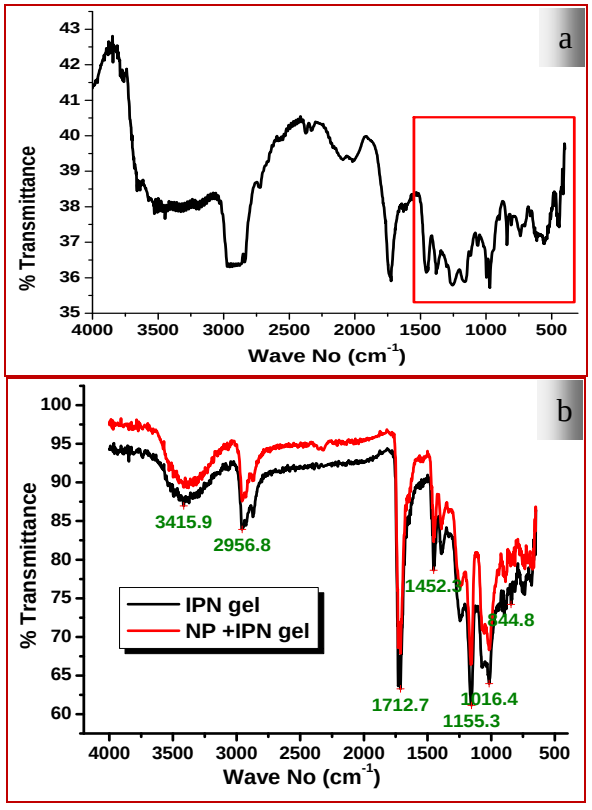

Fig.4. (a). FTIR spectra of NP-IPN showing absorption in the range 500-1500cm-1 (b) FTIR spectra of IPN- gel and NP –IPN

Table 1. Transmittance peaks of IPN gel and NP-IPN from FTIR

Wave Numbers (cm^{-1})	Bond Assigned (IPN-gel)	Bond Assigned (NP-IPN)
3415.9	O-H stretching	O-H stretching
2956 .8	C-H stretching	C-H stretching
1712 .7	C=O stretching	C=O stretching
1155 .3	C-O Stretching	C-O Stretching
445.56	---	FeO
557 .43	---	FeO
613 .46	---	FeO

Figure 5 shows swelling characteristics of IPN-gel with respect to that of the NP-IPN. Hydrogels swollen in deionised water depends on the crosslink density. Greater the crosslink density lower is the penetration of water molecules in the network as is observed here. Decrease (approx.16.9%) in crosslink density is found (Figure 5) due to the embedment of nanoparticles in NP-IPN compared to that of IPN-gel. Free radical polymerization and crosslinking of acrylics depend upon the ease of formation and mobility of the long chain radical through an increasingly viscous medium. Presence of foreign particles, e.g. Iron (III) oxide, particularly when these are agglomerated as found in SEM pictures, in the medium may have restricted the mobility of the chain radicals thereby reducing the probability of the curing reaction.

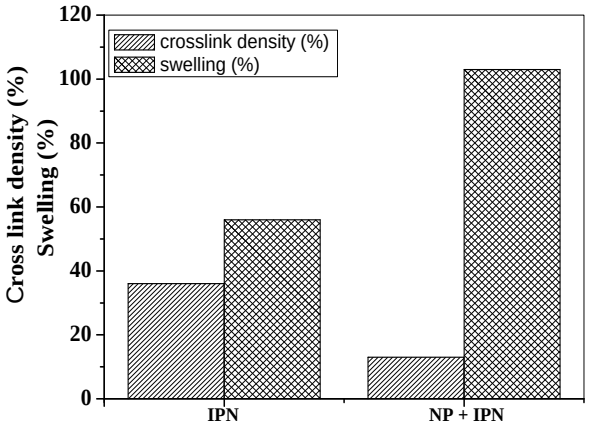

Fig.5. Swelling and crosslink density of the IPN-gel and NP-IPN

Equilibrium swelling of the IPN-gel and NP-IPN has been found to be more significant in alkaline pH than in acidic pH. In Figure 6, NP-IPN has shown almost three times increased swelling compared to that of the IPN-gel. This may be due to preferred degree of ionisation of the NP-IPN through the Iron (III) oxide particles in the alkaline medium as shown in inset of Figure 6.

Interlocked network is quite visible as arrays in the IPN-gel in Scanning Electron Micrographs, Figure 7, whereas the crosslinking is rarely found in the NP-IPNs. Fe_3O_4 particles of size, ~ 20 nm from TEM have almost uniformly been embedded into the interlaced network of IPN although agglomeration of the particles could not be completely avoided in the highly viscous matrix. Decrease in crosslink density in the NP-IPN compared to that in IPN-gels is due to the greater restricted mobility of the growing acrylate polymer chains in presence of the nanoparticles in the medium. However, embedment of nanoparticles in the IPN may give the required mechanical reinforcement of the hydro gel.

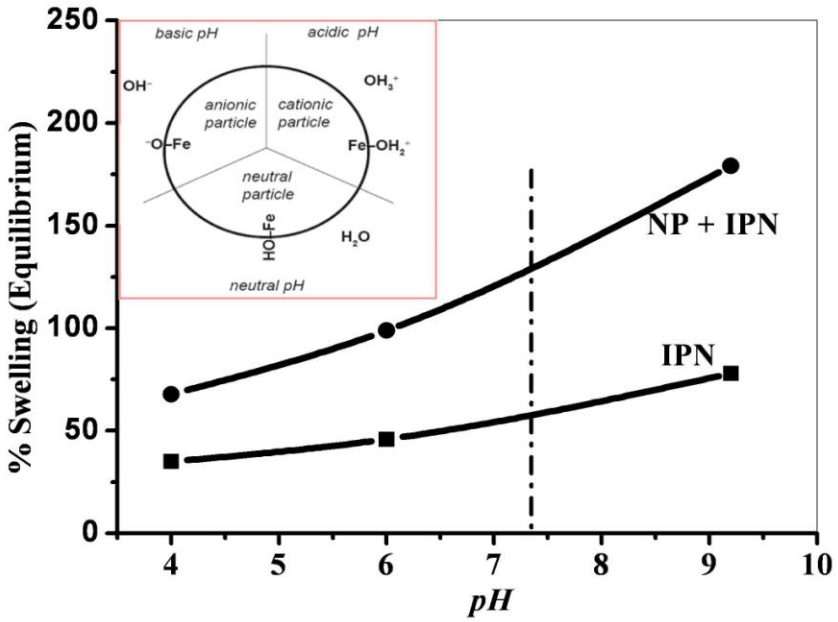

Fig.6. Swelling of IPN-gel and NP-IPN in different pH solutions

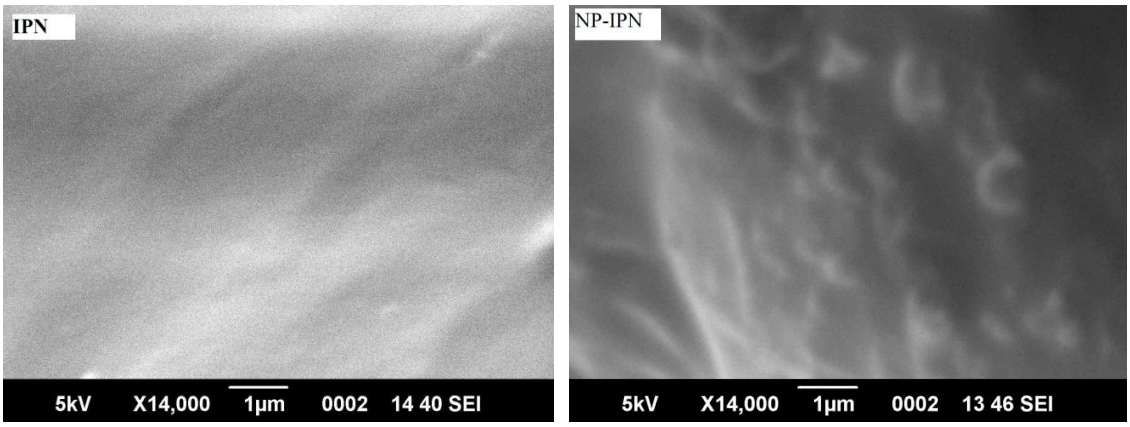

Fig.7. Scanning Electron Micrograph of IPN gel and NP-IPN

Mitotic cell division carried out with Allium Cepa in presence of IPN-gel and NP-IPN are shown in Figure 8.The different phases of cell division have occurred without chromosomal aberration indicating biocompatibility of the polymer systems in plants. Mitotic Index (M.I.) for the cells was calculated from the ratio of cell divided to that of cell undivided. However, cell count data as revealed in Table 2 shows marginal deviation in 'Mitotic Index' (M.I.) for the polymer sample (both IPN-gel and NP-IPN) in comparison to that of the control which may be attributed to the higher viscosity of the swollen IPNs.

Figure 9 shows all the four growth phases, the lag phase, the log phase or exponential phase, the stationary phase and the death phase of a standard bacterial growth phase for control, E-coli with IPN and E-coli with NP-IPN. The comparison of the curve for the bacterial culture with IPN-gel and NP-IPN shows no difference. This confirms the non toxicity of the hydrogel with and without nano-particles. The figure also shows that the iron rich NP-IPN allows multiplication of cells even at the death phase. On the other hand, the realisation of death phase occurs faster for IPN-gel as well as the mother culture. This is due to the iron nano particles present in the NP-IPN. The presence of iron, helped both as a nutrient and as an electron acceptor, thereby increasing bacterial cultivability leading to the delayed death.

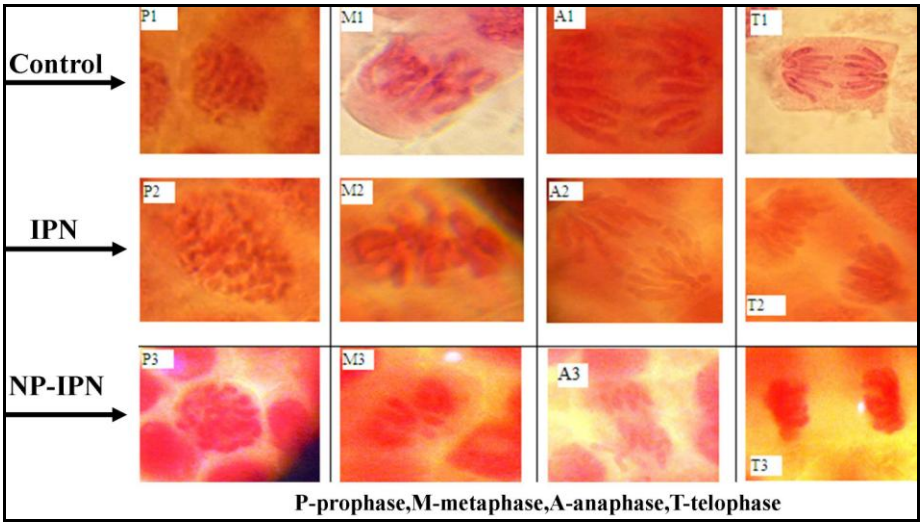

Fig.8. Mitotic phases observed in Alium Cepa cell growth

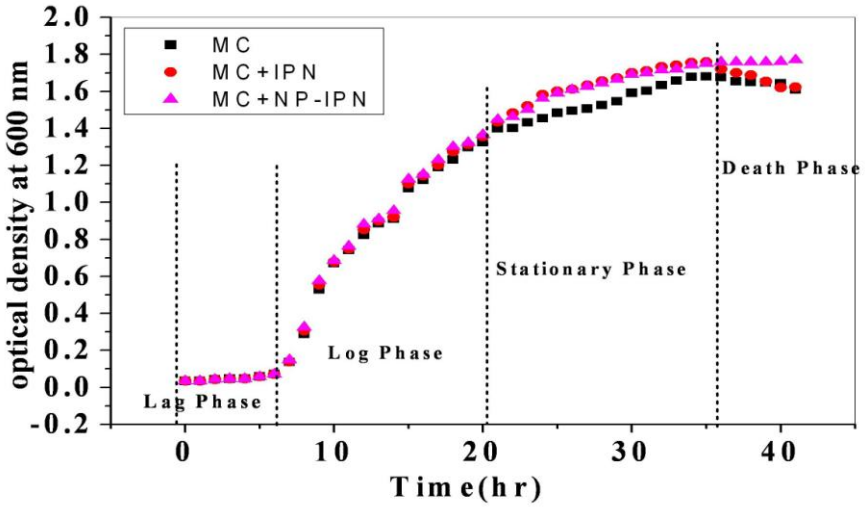

Fig.9. Cell growth curve of *E.Coli* (MC), *E.Coli* in presence of IPN gel (MC+IPN) and *E.Coli* in presence of NP-IPN(, MC+NP-IPN)

Table 2. Cell count data for the Allium Cepa in contact of different polymers

Tests	Control	IPN-gel	NP-IPN
Cell counted	105	228	195
Cell divided	17	24	19
Cell undivided	88	204	176
M.I.	0.184	0.11	0.103

Study of drug loading and release

Drug loading data as observed in Figure 10 shows enhancement of loading in NP-IPN compared to that in IPN-gel. This is due to the lower degree of crosslinking in the former. Percentage loading varies according to the nature of drug e.g. multivitamin shows highest degree of loading in NP-IPN compared to acetaminophen and salicylic acid. This is due to the presence of iron component in the drug which enhances its attraction towards the magnetic NP-IPN. Loading of drugs depends upon the matrix nature as well as the solubility of drugs in the medium [18]. According to Roy et al. the solubility of acetaminophen (37 mg/ml) is greater than that of salicylic acid (3.1 mg/ml) and multivitamin which contains mostly fat soluble components in water at 37˚C. Moreover, Jenquin et al has reported that acrylic polymers interact with salicylic acid in a manner similar to ion exchange resins [24]. The preferable loading of salicylic acid on IPN gel over the other drugs in the present study could thus be inferred.

Figure 11 shows the UV-VIS spectra corresponding to the drug released for NP-IPN and IPN. The absorbance spectra have been calibrated and the percentage drug release has been quantified from the absorbance plot. Drug release study for the IPNs with the different drugs loaded in them reveals (Figure 12) that the extent of drug release is enhanced abruptly with time up to 5 hours followed by steady release in next 10 hours. Moreover, release from NP-IPN became almost of sustained type in the later stage (after 15 hrs) remarkably compared to that from the IPN-gel irrespective of the nature of drugs. At initial stage, % drug release from the NP-IPNs was found to be higher (10-90% within 3 hours) in comparison to that from the IPN-gel (6-75%) for various drugs. This may be due to the loose network formed in the NP-IPNs on account of the presence of nanoparticles which makes the system efficient in carrying drug and releasing it.

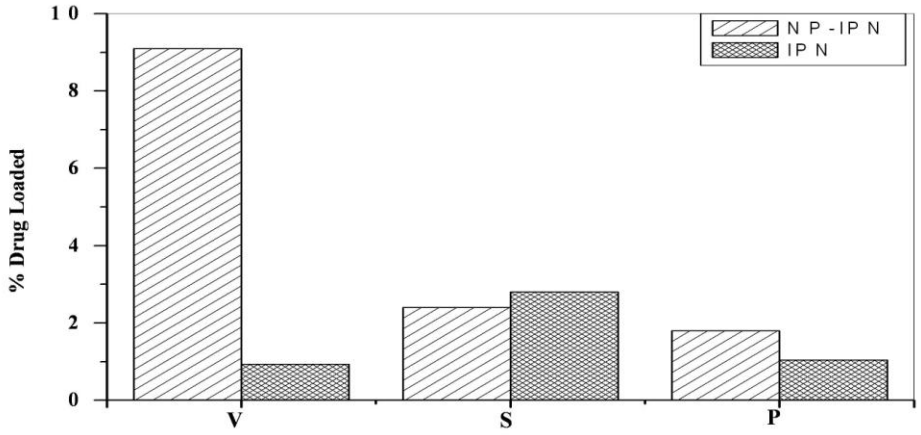

Fig.10. Drug loaded in IPN and NP-IPN with multivitamin (V), salicylic acid (S) and acetaminophen (P)

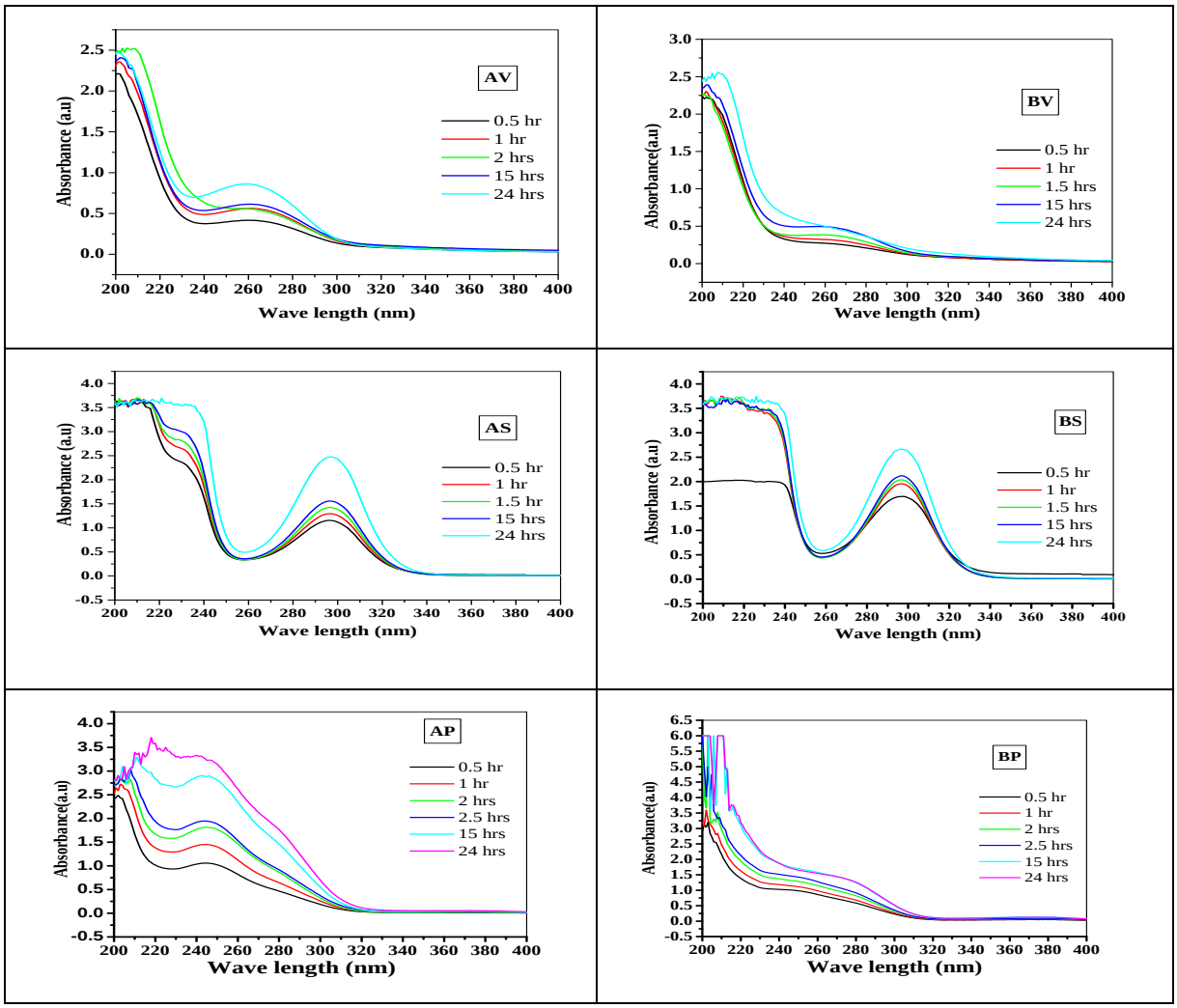

Fig.11. UV-VIS spectra of medium containing drug released from the polymer systems with time, AV-IPN gel-vitamin, BV-NP-IPN vitamin, AS-IPN gel-salicylic acid,BS-NP-IPN salicylic acid, AP-IPN gel acetaminophen, BP-NP-IPN acetaminophen

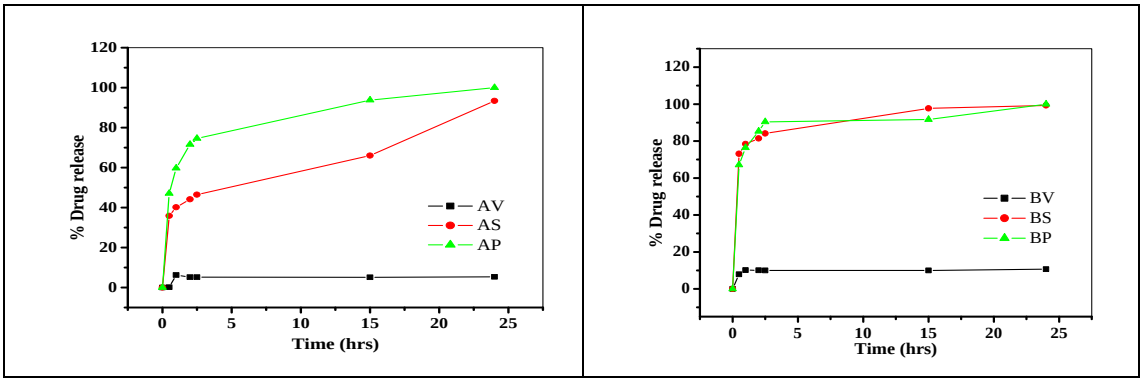

Fig.12. Drug release of loaded IPNs (A:IPN gel, B:NP-IPN) with multivitamin (V), salicylic acid (S), acetaminophen (P) and in alkaline medium (pH-9.2) with time

CONCLUSION

The following conclusions are drawn on the basis of results obtained:

I. Super paramagnetic Fe_3O_4 nanoparticles of size <30 nm showing saturation magnetization 88emu/g at room temperature were synthesized and physically embedded in the bulk of acrylic IPNs.
II. NP-IPNs showed lower degree of crosslinking but enhancement in swelling compared to IPN-gel due to the restricted mobility of growing polymer chains and unavailability of them for curing reaction, in the iron oxide embedded polymer matrix.
III. In-vitro biocompatibility test of the IPNs was successfully observed with both plant and animal cells. The presence of iron in NP-IPN, helped both as a nutrient and as an electron acceptor for *E.Coli* cells, leading to a bacterial cultivability and delayed death compared to that in IPN-gel.
IV. NP-IPNs showed higher percentage of drug loading compared to that of IPN-gels which may be due to the lower degree of crosslinking.

However, % drug release data gives clear indication about the possibility of the NP-IPNs use as controlled release delivery system.

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