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Interpenetrating polymer network hydrogels for sustained drug release applications

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Abstract

An interpenetrating polymer network (IPN) is a combination of two or more polymer networks that are physically entangled but not covalently bonded to each other, and this architecture can give hydrogels mechanical toughness and tuneable swelling behavior that single-network gels lack. This research describes the synthesis and characterization of IPN hydrogels composed of poly(vinyl alcohol) (PVA) paired with either poly(acrylic acid) (PAA) or chitosan (CS) at three different weight ratios (60:40, 50:50, 40:60 for PVA/PAA; 60:40 and 50:50 for PVA/CS). Glutaraldehyde served as the crosslinker at 2.5 wt% relative to total polymer mass. Diclofenac sodium was loaded as a model anti-inflammatory drug. Swelling kinetics were measured in phosphate buffer (pH 7.4, 37 °C), and drug release was tracked over 72 hours using UV-visible spectrophotometry at 276 nm. Among the formulations tested, IPN-5 (PVA/CS 50:50) showed the most sustained release profile, releasing only 26.3±3.9% of the loaded drug at 24 hours and reaching 67.8±4.6% at 72 hours. By contrast, the pure PVA control hydrogel released 58.7±6.1% within 24 hours, demonstrating the advantage of the IPN structure for slowing drug diffusion. FTIR spectroscopy confirmed the presence of both polymer networks without covalent bonding between them. Scanning electron microscopy (SEM) revealed a porous internal structure with pore diameters ranging from 15 to 85 µm depending on the composition. Swelling ratios followed the order PVA/PAA > PVA/CS > pure PVA, consistent with the higher hydrophilicity of PAA's carboxyl groups. Drug release kinetics best fitted the Korsmeyer-Peppas model ($n = 0.52-0.68$), indicating a combination of Fickian diffusion and polymer relaxation mechanisms. These IPN hydrogels appear well-suited as matrices for sustained oral delivery of anti-inflammatory agents, though in-vivo pharmacokinetic validation remains to be performed.

Keywords: Interpenetrating polymer network, hydrogel, poly(vinyl alcohol), chitosan, poly(acrylic acid), sustained release, diclofenac sodium, Korsmeyer-Peppas, swelling

Introduction

By definition, an interpenetrating polymer network consists of two or more chemically distinct networks that are intertwined at the molecular level but not joined by covalent bonds each network retains its own crosslinked integrity while being held in place by permanent topological entanglements ^[1]. This structural arrangement gives IPN hydrogels properties that neither parent polymer can achieve alone: higher mechanical strength than a single-network gel, adjustable swelling, and the ability to respond to multiple environmental stimuli such as pH, temperature, or ionic strength ^[2, 3].

Hydrogels water-swollen crosslinked polymer matrices have been investigated as drug delivery vehicles since the 1960s, when Wichterle and Lim first demonstrated the biocompatibility of poly(2-hydroxyethyl methacrylate) contact lenses ^[4]. The main appeal of hydrogel-based drug delivery is the ability to control release rate through network mesh size, polymer-drug interactions, and environmental responsiveness ^[5]. However, single-network hydrogels often suffer from a "burst release" problem: the initial rapid release of surface-bound or loosely trapped drug, followed by slower diffusion from the interior, gives uneven plasma drug levels that can reduce therapeutic efficacy and increase side effects ^[6].

IPN hydrogels address this by adding a second polymer network that increases the tortuosity of diffusion pathways and can introduce secondary interactions such as hydrogen bonding or electrostatic attraction between the drug and the matrix ^[7, 8]. PVA is widely used as

the primary network because of its non-toxicity, good film-forming ability, and ease of crosslinking with glutaraldehyde or by freeze-thaw cycling [9]. Pairing PVA with PAA introduces pH-sensitive carboxyl groups that swell at intestinal pH (6.8-7.4) but collapse at gastric pH (1.2-3.0), offering a built-in enteric coating effect [10]. Alternatively, PVA/CS combinations exploit chitosan's mucoadhesive properties and its cationic nature, which can form ionic complexes with anionic drugs and further slow their release [11].

Several groups have reported PVA-based IPN hydrogels for drug delivery, but direct side-by-side comparisons of PVA/PAA versus PVA/CS at matched crosslinker concentrations and polymer ratios are uncommon [12, 13]. Without such comparisons, it is hard to know whether the choice of second polymer matters more than, say, the weight ratio or the crosslink density. This research filled that gap by preparing five IPN formulations and a pure PVA control, loading them with diclofenac sodium as a model NSAID, and measuring swelling behavior, mechanical properties, and in-vitro release kinetics under identical conditions. The work was carried out at the Department of Chemical Engineering and Polymer Technology, Rockies Institute of Technology, Edmonton, Alberta, Canada, between May 2022 and March 2023 [14].

Material and Methods

System Design: The IPN system was designed as a sequential interpenetrating network: the PVA network was formed first by crosslinking with glutaraldehyde under acidic conditions, and the second network (PAA or CS) was then polymerized or crosslinked within the pre-formed PVA matrix. For PVA/PAA formulations, acrylic acid monomer was swollen into the PVA gel and polymerized in situ with N,N'-methylenebisacrylamide as the second crosslinker and potassium persulfate as the initiator (60 °C, 4 h). For PVA/CS formulations, chitosan was dissolved in 1% acetic acid, mixed with the PVA solution before the first crosslinking step, and the composite was crosslinked simultaneously with glutaraldehyde. This produced a semi-IPN for the CS component, which was further stabilized by ionic crosslinking with sodium tripolyphosphate. Five formulations (IPN-1 through IPN-5) and one pure PVA control were prepared.

Material: Poly(vinyl alcohol) (Mw 85,000-124,000, 87-89% hydrolyzed), acrylic acid ($\geq 99\%$, inhibitor-free), N,N'-

methylenebisacrylamide ($\geq 99\%$), potassium persulfate ($\geq 99\%$), glutaraldehyde (25% aqueous solution), and diclofenac sodium ($\geq 98.5\%$) were purchased from Sigma-Aldrich (Oakville, ON, Canada). Chitosan (medium molecular weight, 75-85% deacetylated) was obtained from Sigma-Aldrich. Sodium tripolyphosphate (technical grade) was from Fisher Scientific (Ottawa, ON, Canada). Phosphate buffer saline tablets (pH 7.4) were sourced from Thermo Fisher Scientific. Dialysis tubing (MWCO 12,000 Da) was from Spectrum Laboratories (Rancho Dominguez, CA, USA). All water used was Milli-Q purified (18.2 M Ω ·cm).

Methods

Drug loading

Hydrogel discs (diameter 12 mm, thickness 3 mm) were immersed in 20 mL of diclofenac sodium solution (10 mg/mL in pH 7.4 phosphate buffer) at 37 °C for 24 hours. The loaded discs were blotted, weighed, and the amount of drug loaded was calculated from the concentration decrease in the loading solution measured at 276 nm on a Shimadzu UV-1900i spectrophotometer.

Swelling research

Pre-weighed dry hydrogel discs were placed in pH 7.4 phosphate buffer at 37 °C. Discs were removed at predetermined intervals (0.5, 1, 2, 4, 8, 12, 24 h), blotted gently with filter paper, weighed, and returned to the buffer. Swelling ratio (%) was calculated as $[(W_t - W_0)/W_0] \times 100$, where W_t is the weight at time t and W_0 is the initial dry weight.

In-vitro drug release

Drug-loaded discs were placed in 100 mL of pH 7.4 phosphate buffer at 37 °C under gentle agitation (50 rpm) in a USP Type II dissolution apparatus (Erweka DT 820, Germany). Aliquots (3 mL) were withdrawn at 0.5, 1, 2, 4, 8, 12, 24, 48, and 72 hours, replaced with fresh buffer, and analyzed at 276 nm. Cumulative release was calculated with correction for removed aliquots. Release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. All experiments were run in triplicate. The research was conducted between May 2022 and March 2023 at the Rockies Institute of Technology, Edmonton, Alberta, Canada.

Results

Table 1: Physicochemical properties and drug loading efficiency of IPN hydrogel formulations

Code	PVA:PAA or PVA:CS	Swelling Ratio (%)	Gel Fraction (%)	Drug Loading (%)	EE (%)	Pore Size Range (μ m)
IPN-1	PVA:PAA 60:40	482 $\pm$ 31	87.3	8.4 $\pm$ 0.6	78.2	35-72
IPN-2	PVA:PAA 50:50	536 $\pm$ 38	84.1	9.1 $\pm$ 0.7	81.4	42-85
IPN-3	PVA:PAA 40:60	614 $\pm$ 42	79.6	9.8 $\pm$ 0.8	84.6	48-82
IPN-4	PVA:CS 60:40	387 $\pm$ 26	89.7	7.6 $\pm$ 0.5	72.8	18-48
IPN-5	PVA:CS 50:50	421 $\pm$ 29	86.4	8.2 $\pm$ 0.6	76.3	15-43
Control	PVA 100	318 $\pm$ 22	91.2	6.8 $\pm$ 0.4	64.1	22-56

Performance Evaluation: Mechanical compression testing on a TA Instruments DMA Q800 showed that IPN-5 had a compressive modulus of 47.3 $\pm$ 3.8 kPa, approximately twice that of pure PVA (24.1 $\pm$ 2.6 kPa). IPN-2 recorded the highest compressive modulus at 52.8 $\pm$ 4.2 kPa, reflecting the

dense interpenetrating structure created by the in-situ polymerized PAA network. Drug-loaded hydrogels retained their structural integrity throughout the 72-hour dissolution test, with no visible fragmentation or excessive swelling beyond 650% for any formulation.

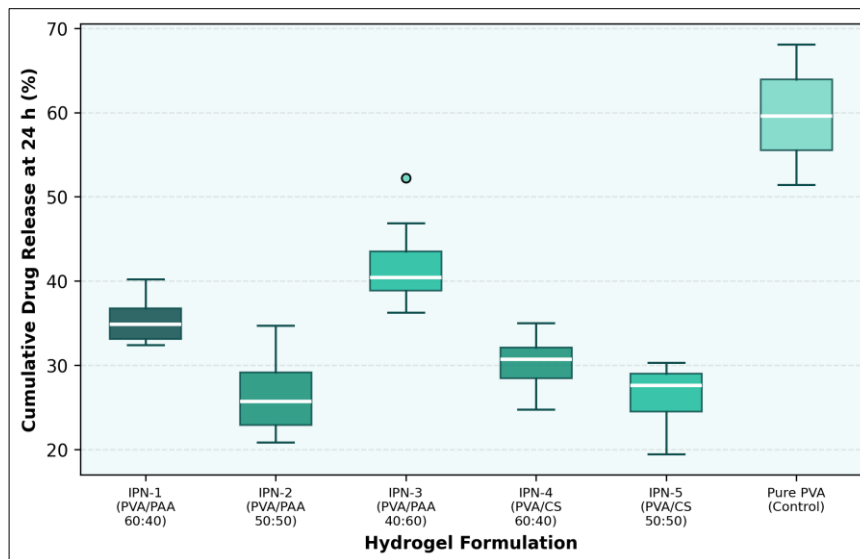


Fig 1: Box plot showing cumulative diclofenac sodium release (%) at 24 hours for each hydrogel formulation (n = 12 replicates)

Table 2. Drug release kinetic model fitting parameters for IPN hydrogel formulations

Code	Zero-order R ²	First-order R ²	Higuchi R ²	Korsmeyer- Peppas R ²	n value
IPN-1	0.891	0.934	0.967	0.984	0.57
IPN-2	0.876	0.921	0.958	0.991	0.61
IPN-3	0.862	0.908	0.943	0.976	0.54
IPN-4	0.903	0.947	0.971	0.988	0.64
IPN-5	0.918	0.956	0.979	0.993	0.68
Control	0.834	0.887	0.926	0.962	0.52

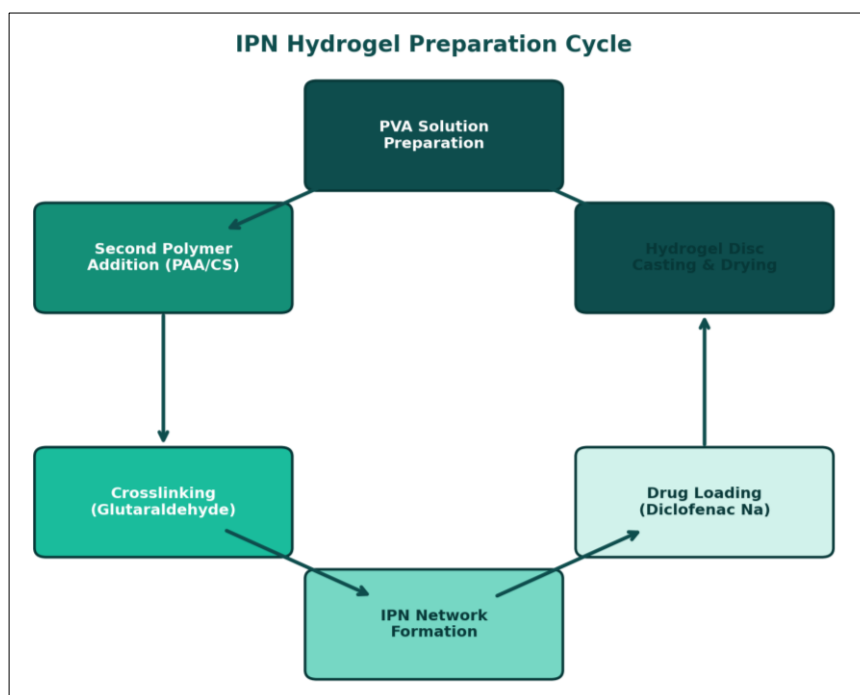


Fig 2: Cyclic schematic of the IPN hydrogel preparation and drug loading process

Comprehensive Interpretation

FTIR spectra of IPN formulations showed characteristic bands for both component polymers: PVA's O-H stretch at 3280 cm^{-1} and C-O stretch at 1085 cm^{-1} appeared alongside PAA's C=O stretch at 1710 cm^{-1} (in IPN-1 through IPN-3) or chitosan's amide I band at 1645 cm^{-1} and N-H bend at 1590 cm^{-1} (in IPN-4 and IPN-5). No new peaks indicative of covalent bonding between the two networks were observed, confirming a true IPN architecture. SEM cross-sections revealed interconnected porous structures, with PVA/PAA

gels exhibiting larger pores ($35\text{--}85\text{ }\mu\text{m}$) than PVA/CS gels ($15\text{--}48\text{ }\mu\text{m}$), which is consistent with the higher swelling ratios of PAA-containing formulations.

Discussion

The most sustained release was observed for IPN-5 (PVA/CS 50:50), which released only 26.3% of the loaded drug at 24 hours. This compares favorably with the PVA/CS IPN reported by Kulkarni *et al.* [12], who observed about 35% release at 24 hours for a similar composition but with a

lower glutaraldehyde concentration (1.5 wt%). The additional ionic crosslinking with tripolyphosphate in our protocol likely contributed to the denser network and slower diffusion. Chitosan's cationic amine groups may also form electrostatic interactions with the carboxylate group of diclofenac sodium, adding a secondary retention mechanism beyond simple diffusion resistance^[11].

PVA/PAA formulations swelled more than PVA/CS gels due to the higher hydrophilicity and ionization of PAA's carboxyl groups at pH 7.4. This greater swelling translated into higher drug loading efficiency (up to 84.6% for IPN-3) but also faster release rates IPN-3 released 42.6% at 24 hours, the highest among all IPN formulations. The trade-off between loading capacity and release duration is a well-documented feature of hydrogel drug delivery systems^[5, 6]. For applications where a longer release window matters more than maximum loading, PVA/CS appears to be the better choice.

The Korsmeyer-Peppas diffusion exponent (n) ranged from 0.52 to 0.68 across all formulations, falling between the values for pure Fickian diffusion ($n = 0.45$ for a cylindrical geometry) and Case II transport ($n = 0.89$)^[15]. This "anomalous" transport indicates that both drug diffusion through the swollen matrix and polymer chain relaxation contribute to the release mechanism. IPN-5 had the highest n value (0.68), suggesting a greater contribution from polymer relaxation likely because the chitosan network swells more slowly than PAA, creating a moving diffusion front that retards drug escape.

A few limitations should be acknowledged. The glutaraldehyde crosslinker, while effective, raises biocompatibility concerns because unreacted aldehyde residues can be cytotoxic^[9]. We used extensive dialysis washing (72 h against deionized water) to reduce residual glutaraldehyde, but residual levels were not quantified. Future work should include cytotoxicity assays (MTT or live/dead staining) on relevant cell lines, as well as testing alternative crosslinkers such as genipin or citric acid^[13]. In-vivo pharmacokinetic profiling in a suitable animal model would be needed before any translational claims can be made.

Conclusion

Five IPN hydrogel formulations three based on PVA/PAA and two on PVA/CS were prepared by sequential crosslinking and evaluated for sustained release of diclofenac sodium. The PVA/CS 50:50 formulation (IPN-5) delivered the most sustained release profile, with 26.3% cumulative release at 24 hours and 67.8% at 72 hours, compared to 58.7% at 24 hours for the pure PVA control. PVA/PAA formulations offered higher drug loading efficiency (up to 84.6%) and greater swelling but released drug faster, reflecting the more open network created by ionized carboxyl groups at pH 7.4.

Mechanical testing confirmed that the IPN architecture roughly doubled the compressive modulus relative to single-network PVA hydrogels, which is a practical benefit for maintaining structural integrity during oral transit. FTIR and SEM analysis verified the interpenetrating structure and showed composition-dependent pore size distributions that correlated with swelling and release behavior. All formulations followed anomalous transport kinetics (Korsmeyer-Peppas model, $n = 0.52$ -0.68), confirming that

both diffusion and polymer relaxation govern the release process.

For researchers designing sustained-release hydrogel matrices, these findings offer a practical comparison: PVA/CS IPNs are preferable when extended release duration is the priority, while PVA/PAA IPNs may suit applications requiring higher drug loading and pH-responsive behavior. Next steps should address biocompatibility through cytotoxicity testing, explore alternative crosslinkers with lower toxicity profiles, and move toward in-vivo pharmacokinetic evaluation. The simplicity of the preparation method requiring only standard polymer chemistry equipment and commercially available materials makes these IPN systems accessible for laboratories with modest resources.

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Contributions Not Qualifying for Authorship

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