Published in final edited form as:

Ind Eng Chem Res. 2011 November 16; 50(22): 12556–12561. doi:10.1021/ie201593h.

Amphiphilic Interpenetrating Networks for the Delivery of Hydrophobic, Low Molecular Weight Therapeutic Agents

Cody A. Schoener¹, Heather N. Hutson², Grace K. Fletcher², and Nicholas A. Peppas^{*,1,2,3}

¹Department of Chemical Engineering, The University of Texas at Austin, Austin, TX 78712, USA

²Department of Biomedical Engineering, The University of Texas at Austin, Austin, TX 78712, USA

³College of Pharmacy, The University of Texas at Austin, Austin, TX 78712, USA

Abstract

To investigate the delivery of hydrophobic therapeutic agents, a novel class of interpenetrating networks (IPNs) were synthesized and composed of two networks: methacrylic acid grafted with poly(ethylene glycol) tethers, P(MAA-g-EG), and poly(n-butyl acrylate) (PBA). The hydrophilic P(MAA-g-EG) networks are pH-responsive hydrogels capable of triggered release of an encapsulated therapeutic agent, such as a low molecular weight drug or a protein, when it passes from the stomach (low pH) to upper small intestine (neutral pH). PBA is a hydrophobic homopolymer that can affect the IPN swelling behavior, the therapeutic agent loading efficiencies in IPNs, and solute release profiles from IPNs. In dynamic swelling conditions, IPNs had greater swelling ratios than P(MAA-g-EG), but in equilibrium swelling conditions the IPN swelling ratio decreased with increasing PBA content. Loading efficiencies of the model therapeutic agent fluorescein ranged from 21 – 44%. Release studies from neat P(MAA-g-EG) and the ensuing IPNs indicated that the transition from low pH (2.0) to neutral pH (7.0) triggered fluorescein release. Maximum fluorescein release depended on the structure and hydrophilicity of the carriers used in these studies.

Keywords

hydrogels; interpenetrating polymeric networks; fluorescein; controlled release; drug delivery

1. Introduction

Novel synthetic techniques have led to significant improvements of materials which can be used in biomedical and clinical applications. Of particular interest to us are biomaterials based on pH-responsive hydrogels. Hydrogels are three-dimensional networks that are insoluble in aqueous environments due to physical and/or chemical crosslinks, but still imbibe large amounts of water or biological fluids.¹ These networks can be synthesized using biocompatible polymers and can be tailored to exhibit desirable physicochemical properties depending on their swollen and collapsed states. These properties change drastically at an appropriate pH shift and can be used to achieve local and targeted drug, peptide, or protein delivery.

For these reasons, pH-responsive hydrogels exhibit promising results as polymer carriers for oral delivery of a variety of proteins and peptides which are traditionally administered

*To whom correspondence should be addressed. Phone: 512-471-6644, Fax: 512-471-8227, peppas@che.utexas.edu.

parenterally or through subcutaneous injections. The expansion of hydrogel research and the evolving nature of pH-responsive hydrogels parallel the large growth of protein and peptide drugs synthesized or utilized by pharmaceutical companies. The translation of these polymer systems for their use and interaction with hydrophobic, low molecular weight therapeutic agents is limited and needs to be optimized or modified for greater success. Clearly, a polymer system balanced with hydrophilic-hydrophobic properties may prove advantageous for the delivery of hydrophobic, low molecular weight therapeutic agents.

Chemotherapeutics are an example of hydrophobic, low molecular weight agents which are heavily used in the treatment against cancer. They include alkylating agents such as cisplatin, antimetabolites such as purines, taxanes such as paclitaxel, and anthracyclines such as doxorubicin. Chemotherapeutics are currently administered intravenously for systemic delivery and requires long profusion times for each treatment. The development of oral chemotherapeutics would eliminate the need for intravenous delivery and potentially improve patient comfort.² A small number of chemotherapeutic agents have been orally delivered and shown promising results such as lower toxicity and clinical efficacy that is equal to or sometime improved when compared to intravenous treatment.^{3–9} Capecitabine (Xeloda®, Roche Ltd, Basel, Switzerland) is an example of an oral chemotherapeutic approved by the FDA for metastatic and colorectal cancers.^{7,10}

The advantages of oral chemotherapeutics include patient preference, equivalent efficacy to intravenous regimens, favorable safety profiles, and cost-effectiveness.¹¹ Patient preferences include reduction of hospital or clinical visits, convenience, elimination of surgically implanted cannulas, and greater control over the dosage and environment of administered chemotherapeutic agent.¹²

Despite the advantages, there are still obstacles that must be overcome for oral administration of chemotherapeutics. These obstacles include the delivery of the agent to the targeted tumor which can either be transported across the epithelium of the gastrointestinal (GI) tract into the bloodstream (breast or liver cancer) or remain in the GI tract for local delivery (colorectal cancer). Potential harm to the stomach and GI tract due to the toxicity of the agent as well as the toxic agent being exposed to the low pH and degradative enzymes of the stomach must be overcome as well. While pH-responsive hydrogels may possess the necessary characteristics for protecting the chemotherapeutic agent and the GI tract from each other, they must be modified with hydrophobic polymer segments for preferential loading of hydrophobic agents.

In this work, we combined the desirable characteristics of pH-sensitive, hydrophilic networks with the hydrophobic thermodynamic behavior of certain homopolymers by synthesizing advanced interpenetrating networks (IPN) that can be used to develop amphiphilic polymer structures for bioapplications.^{13–16} In IPNs, two homopolymers or copolymers are physically entangled within one another, but are not chemically bound; this allows the combinatorial expression of properties from each individual polymer network. In our studies, we synthesized and characterized sequential IPNs composed of a pH-responsive, hydrophilic polymer, P(MAA-g-EG), prepared from methacrylic acid (MAA) grafted with poly(ethylene glycol) tethers, and hydrophobic poly(n-butyl acrylate) (PBA).

Previous work in our laboratory has concentrated on the optimal design of P(MAA-g-EG) hydrogels.^{17–21} These hydrogels contain carboxyl groups on the MAA moiety which will form a hydrogen bond with the etheric oxygen of the PEG chain forming a tight, collapsed network in low pH. In neutral pH, the carboxyl groups become deprotonated causing an expanded network due to ionic repulsion. Thus, this pH shift from the stomach (low pH) to the upper small intestine (neutral pH) can be used as a physiological trigger for releasing

entrapped drug. These hydrogels have been used to orally deliver insulin,^{22–24} calcitonin,^{25–27} and bleomycin.^{28,29}

The synthetic technique used in this work allows incorporation of varying amounts of PBA into the P(MAA-g-EG) hydrogel resulting in IPNs with a distribution of physical properties. PBA's effect on the loading and release of fluorescein, a model hydrophobic agent, is elucidated. The transition from the stomach to the upper small intestine may be used as a trigger for release and is tested.

2. Materials and Methods

2.1 Materials

Methacrylic acid (MAA), n-butyl acrylate (BA), tetraethylene glycol dimethacrylate (TEGDMA), 1-hydroxycyclohexyl phenyl ketone (Irgacure[®] 184), 3,3-dimethylglutaric acid (DMGA), Nile Red, dimethyl sulfoxide (DMSO), and ethanol were purchased from Sigma-Aldrich (St. Louis, MO). 10× phosphate buffer solution (PBS) and sodium chloride were purchased from Fisher Scientific (Fair Lawn, NJ). Poly(ethylene glycol) monomethyl ether monomethacrylate (PEGMMA; 1000 g/mol) was from Polysciences Inc. (Warrington, PA). All chemicals were used as received except for MAA which was vacuum distilled at 54 °C and 25 mm Hg prior to use to remove the inhibitor hydroquinone. Double distilled water was used in all studies.

2.2 Synthesis of P(MAA-g-EG) Hydrogels

Monomers MAA and PEGMMA were added in a 1:1 molar ratio while the crosslinking agent TEGDMA and the initiator Irgacure[®] 184 were added in the amount of 0.75 mol% and 0.5 wt.% of total monomer respectively. A 50:50 (w/w) solution of ethanol in water was added in a 50:50 (w/w) ratio of total monomer to solvent. The solution was mixed, purged with N₂, placed between glass slides, and exposed to UV light (Dymax 2000-EC Light Curing System, Torrington, CT) at an intensity of 16 mW/cm² for 30 min. The resulting polymer film was washed several days with water and either punched into discs or crushed into particles (75 – 500 μm) for future use. Both particles and discs were dried in vacuum at 30 °C for 1 wk.

2.3 Synthesis of IPNs of P(MAA-g-EG) and PBA

In a previous publication we described briefly a new technique for IPN production.³⁰ A solution composed of BA, TEGDMA, and Irgacure[®] 184 was prepared using the same molar ratios as above but without PEGMMA. The solvent composed of ethanol and water was adjusted to 80:20, 75:25, or 70:30 (w/w). This procedure was used for the production of IPNs with increasing PBA content: 80/20 IPN, 75/25 IPN, 70/30 IPN. A dried P(MAA-g-EG) disc was placed in a solution of 80:20 (w/w) ethanol to water, BA, TEGDMA, and Irgacure[®] 184 and shaken for 24 h. Then the disc was purged with N₂ and exposed to UV light (Dymax BlueWave 200 UV Curing Spot Lamp, Torrington, CT) at an intensity of 16 mW/cm² for 45 min. The amphiphilic IPN was washed in 30% (w/w) ethanol in water for several days and either punched into discs or crushed into particles (75 – 500 μm) for future use. In this way the 80/20 IPN and remaining IPNs were synthesized. Both particles and discs were dried in vacuum at 30 °C for 1 wk.

2.4 Characterization of PBA networks in IPNs

Hydrophobic staining, contact angle measurements, and sequential equilibrium weight swelling experiments in two different swelling agents were used to characterize the PBA content in the IPNs. The following protocol was adapted³¹ to stain polymer discs: a 20 mg/mL stock solution of Nile Red, a hydrophobic dye, was prepared by dissolving in methanol.

IPN and P(MAA-g-EG) discs were soaked in a working solution composed of 75 μL of the stock solution and 120 mL 1 $\times$ PBS for 24 h and then washed multiple days with water.

Surface analysis was carried out by measuring contact angles on a goniometer (Rame-Hart Goniometer Model No. 100) using DROPImage software. Using water, 5 μL sessile drops were placed on polymer discs previously swollen in water for 24 h and the angle formed between the drop and surface was determined. The sequential equilibrium weight swelling ratio (g swollen / g polymer) in water, q_w , and in isopropanol, q_i , was performed and the ensuing ratio of q_w divided by q_i was correlated to the hydrophobicity of the polymer systems.³²

2.5 Swelling Behavior of P(MAA-g-EG) and IPNs

Dynamic and equilibrium swelling studies were used to study the pH-responsive behavior of P(MAA-g-EG) and IPNs. Dynamic swelling behavior was determined by swelling P(MAA-g-EG) or IPN samples in 0.1 M DMGA buffers ranging from pH 3.2 to 7.6 which maintained ionic strength using sodium chloride. Polymer discs were placed in the 37 $^{\circ}\text{C}$ DMGA buffers starting with pH 3.2 for 12 min, weighed, and placed in the next higher pH buffer until a pH of 7.6 was reached.

Equilibrium swelling was completed utilizing the same buffer series as above except discs remained in one pH level for 24 h. The swollen discs were weighed and the equilibrium weight swelling ratio determined.

2.6 Loading Fluorescein in P(MAA-g-EG) and IPNs

Fluorescein served as a hydrophobic agent as well as a chemotherapeutic analogue due to its similar hydrophobicity, molecular weight, and chemical structure to several chemotherapeutics.^{33,34} Fluorescein was loaded by equilibrium partitioning in the following manner: a fluorescein stock solution was made with 2 wt.% DMSO in 1 $\times$ PBS (pH 7.4) to a final concentration of 0.145 mg/mL. A 5 mg/mL concentration of P(MAA-g-EG) or IPN crushed particles to fluorescein stock solution was allowed to stir for 24 h. Then the particles were collapsed by adding 1 N HCl to entrap fluorescein within the network, filtered, and rinsed with water and 0.1 N HCl to remove any surface absorbed fluorescein. A fluorescent plate reader (Biotek Synergy-HT, Winooski, VT), operating at a 485 nm excitation and 590 nm emission wavelengths, determined the concentration levels and calculated the loading efficiency as follows:

$$\text{Loading Efficiency} = \frac{C_o - C_f}{C_o} * 100 \quad (1)$$

where C_o is the initial fluorescein concentration and C_f is the final fluorescein concentration remaining in the solution.

2.7 Fluorescein Release Studies

Release experiments were performed on a dissolution apparatus (Distek Dissolution System 2100B, North Brunswick, NJ) operating at 100 rpm and 37 $^{\circ}\text{C}$. For fluorescein release in neutral pH, a concentration of 0.33 mg/mL of fluorescein loaded microparticles to 1 $\times$ PBS (pH 7.4) was used. Over the duration of 6 h, samples were taken and replaced with a solution of 1 $\times$ PBS (37 $^{\circ}\text{C}$, pH 7.4) to maintain sink conditions. Fluorescein release in low pH was conducted in the same manner as neutral pH except 1 $\times$ PBS was adjusted to a pH of 2.0 using 1N HCl.

To mimic the physiological conditions and residence time in the stomach and small intestine³⁵ fluorescein was released using a two-step pH change from low pH (2.0) to high pH (7.0). Fluorescein loaded microparticles were first placed in 1× PBS at pH 2.0. After 90 min, 5N NaOH was added to increase the pH to 7.0 where release continued for 6 h. Samples were obtained as above. The mass of fluorescein released was determined by the fluorescent plate reader and reported as follows:

$$\text{Mass Released} = M_t / M_{\infty} * 100 \quad (2)$$

where M_t is mass released at given time and M_{∞} is total mass released.

3. Results and Discussion

Amphiphilic interpenetrating networks were developed through sequential free radical UV-initiated polymerization of two sets of monomers. The hydrophilic P(MAA-g-EG) network was formed first, followed by polymerization of the hydrophobic PBA network within the P(MAA-g-EG) network. The ensuing IPNs were characterized using contact angles and sequential swelling experiments to determine the presence of the PBA network while swelling, loading, and release studies evaluated their performance as potential oral delivery devices for hydrophobic agents. Contact angle measurements and loading efficiency results have been adjusted due to increased number of samples since the publication of preliminary data.³⁰

3.1 Characterization of PBA Networks in IPNs

The existence of the PBA network was confirmed by soaking P(MAA-g-EG) and IPNs in Nile Red for 24 h. P(MAA-g-EG) samples remained clear and translucent while IPN samples were stained hazy pink indicating the presence of the PBA network in the IPNs (Figure 1). Contact angles measured 52° for P(MAA-g-EG) and progressively increased from 64° to 105° for the IPNs as a function of increasing PBA content (Table 1). The equilibrium weight swelling ratio in water, q_w , divided by the equilibrium weight swelling ratio in isopropanol, q_i , was 1.34 for P(MAA-g-EG) and progressively decreased for the IPNs as a function of increasing PBA content (Table 1). These results led to the conclusion that our synthetic technique allowed us to control the amount of hydrophobic content in the IPN on the surface and in the bulk.

3.2 Swelling Behavior of P(MAA-g-EG) and IPNs

Swelling experiments illustrated the behavior of the polymer drug carrier systems in simulated physiological fluids, specifically the effect of introducing a PBA network into the P(MAA-g-EG) hydrogel samples. For dynamic and equilibrium swelling experiments, minimal swelling occurred in gastric conditions (low pH) due to the anionic nature of the P(MAA-g-EG) network. Because the P(MAA-g-EG) network contains a carboxyl group with a pKa value of 4.8–4.9, swelling is minimized until these values are surpassed.^{36,37}

For all dynamic swelling experiments, the swelling ratios of the IPNs were greater than P(MAA-g-EG) (Figure 2). We believe the presence of the second PBA network reduced the formation of hydrogen bonds between the MAA and PEG resulting in a more open structure in which water could more freely penetrate and deprotonate the carboxyl groups contained in the IPNs versus the P(MAA-g-EG). Equilibrium weight swelling ratios were previously determined, but not discussed in depth.³⁰ These experiments demonstrated as the amount of PBA content increased, the equilibrium swelling ratios diminished. The increasing presence of the PBA network influences the number of physical macromolecular entanglements between both networks, alters free volume for polymer chain movement, and reduces or

shields ionic repulsion between deprotonated carboxyl groups, all which reduce equilibrium weight swelling ratios. Alternative modifications to the original P(MAA-g-EG) hydrogel have been completed previously in our lab and also shown variation in swelling behavior.^{38,39}

3.3 Fluorescein Loading in P(MAA-g-EG) and IPNs

The polymer carrier's structure and ratio of hydrophilic to hydrophobic components caused different loading efficiencies (Table 1). P(MAA-g-EG) had a loading efficiency of $37 \pm 2\%$ and the 75/25 IPN had the highest at $44 \pm 2\%$. We conclude that the absence of the hydrophobic network resulted in reduced loading levels in the P(MAA-g-EG) as compared to the 75/25 IPN. However, the high equilibrium weight swelling ratio of P(MAA-g-EG) allowed it to still maintain high loading levels. On the other hand, the 80/20 IPN's small amount of hydrophobic content and the 70/30 IPN's reduced swelling levels may have contributed to lower loading levels. Weight percent loading ranged from 0.9 – 1.3% and is defined as the mg of fluorescein per mg of polymer.

3.4 Fluorescein Release

In vitro release studies were completed at a constant and two-step pH change to investigate their potential behavior *in vivo*. In neutral pH, maximum release occurred after 2 h with over 90% of fluorescein released for both IPNs and P(MAA-g-EG) (Figure 3). It will be noted that the neutral pH release profiles of only the IPNs were first published and that inclusion of the P(MAA-g-EG) release profile in this publication provides a complete graphical representation.³⁰ Because the pH of the release media is greater than the pKa value of MAA, the polymer carriers can swell and develop pores between networks large enough for fluorescein molecules to diffuse out and into the surrounding solution.

For the two step pH release, IPNs released a maximum of 13% of the total amount released whereas P(MAA-g-EG) released nearly 21% before the pH increase (Figure 4). The PBA network binds or restrains fluorescein from releasing from the surface or bulk of the IPN due to hydrophobic interactions while P(MAA-g-EG)'s lack of hydrophobicity causes a larger burst effect in low pH conditions. Release profiles of P(MAA-g-EG) and 75/25 IPN in low pH reconfirmed this burst effect observation (Figure 5).

An immediate increase in the amount of fluorescein released was observed for all polymers after the pH change from 2.0 to 7.0. Maximum drug release was achieved at 2 and 4 h for IPNs and P(MAA-g-EG), respectively (Figure 5). P(MAA-g-EG)'s slower swelling response to pH shift (Figure 2) explains the slower release rate as compared to IPNs. Final fluorescein concentrations ranged from 2.37 – 4.7 $\mu\text{g/mL}$.

4. Conclusions

Our technique for synthesizing sequential interpenetrating networks allows us to combine hydrophilic, pH-sensitive P(MAA-g-EG) and hydrophobic PBA. Controlling the amount of PBA in the IPNs, a host of polymer carriers with different swelling properties, loading efficiencies, and release profiles were illustrated.

Our studies showed in dynamic swelling conditions IPNs had greater swelling ratios than P(MAA-g-EG), but in equilibrium swelling conditions the IPN swelling ratio decreased with increasing PBA content. PBA can influence IPN physical properties in several ways: 1) disrupts hydrogen bonding between MAA and PEG, creating a more open structure for water to diffuse in deprotonating carboxyl groups and 2) creates entanglements, shields ionic repulsion between deprotonated carboxyl groups, and reduces free volume for polymer

chain movement which decreases the equilibrium weight swelling ratio. Loading efficiencies of fluorescein ranged from 21 – 44% with the 75/25 IPN achieving the highest.

Release studies show IPNs release less fluorescein than P(MAA-g-EG) at low pH. The improved ability to reduce hydrophobic agent release in low pH can be critical in bioapplications. For example, premature release of a chemotherapeutic agent could result in toxicity to the stomach. Furthermore, protecting the chemotherapeutic agent during transit through the stomach increases the amount capable of releasing in the small intestine as well as its mechanism for destroying tumors. When pH shifted from low to neutral, release rate was increased and resulted in fluorescein concentration levels between 2.37 – 4.7 $\mu\text{g/mL}$. For these IPNs to be successful, they must deliver chemotherapeutic agents at minimal concentrations to reduce tumors and these values vary based on the drug used. For example, 5-fluoruracil requires 0.2 $\mu\text{g/mL}$ and doxorubicin requires 5 $\mu\text{g/mL}$.^{40,41} Therefore, an accurate understanding of the loading efficiency and release profiles are important so that the administration of a chemotherapeutic agent is appropriate to destroy tumors while minimizing side effects to surrounding healthy tissue.

As our focus is primarily on the local treatment of colon cancer, this IPN system could be adapted to try to deliver chemotherapeutics to the bloodstream via more permeable tight junctions located in the upper small intestine. This could be achieved by modifying the polymer system with lectins for increased binding to the glycosylated surfaces present on the mucosal layer of the small intestine. Previous work has shown that the modification of the P(MAA-g-EG) network with wheat germ agglutinin does increase mucoadhesiveness.³⁸

The pH-responsiveness of P(MAA-g-EG) combined with PBA's hydrophobicity has allowed for the preferential loading and release of a hydrophobic agent and enabled the pH shift from the stomach to the small intestine to be used as a physiological trigger. It is possible these IPNs may serve as viable oral carriers for chemotherapeutic agents which may improve patient care and comfort and reduce healthcare costs.

Acknowledgments

This research was supported by a grant for the NIH/NCI Center for Oncophysics (CTO PSOC U54-CA-143837). C.A.S. acknowledges the National Science Foundation for a Graduate Research Fellowship.

Literature Cited

1. Peppas NA, Bures P, Leobandung W, Ichikawa H. Hydrogels in pharmaceutical formulations. *Eur. J. Pharm. Biopharm.* 2000; 50:27–46. [PubMed: 10840191]
2. Blanchette J, Kavimandan N, Peppas NA. Principles of transmucosal delivery of therapeutic agents. *Biomed. Pharmacother.* 2004; 58:142–151. [PubMed: 15082336]
3. Mao JH, Balmain A. Genomic approaches to identification of tumour-susceptibility genes using mouse models. *Curr. Opin. Genet. Dev.* 2003; 13:14–19. [PubMed: 12573430]
4. Ohmori K, Sasaki K, Asada S, Tanaka N, Umeda M. An assay method for the prediction of tumor promoting potential of chemicals by the use of Bhas 42 cells. *Mutat. Res., Genet. Toxicol. Environ. Mutagen.* 2004; 557:191–202.
5. Schrenk D, Schmitz HJ, Bohnenberger S, Wagner B, Worner W. Tumor promoters as inhibitors of apoptosis in rat hepatocytes. *Toxicol. Lett.* 2004; 149:43–50. [PubMed: 15093247]
6. Wolfe D. Enhancement of carcinogen-induced malignant cell transformation by prostaglandin F-2 alpha. *Toxicology.* 2003; 188:139–147. [PubMed: 12767686]
7. Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, Bugat R, Findlay M, Frings S, Jahn M, McKendrick J, Osterwalder B, Perez-Manga G, Rosso R, Rougier P, Schmiegel WH, Seitz JF, Thompson P, Vieitez JM, Weitzel C, Harper P. Xeloda Colorectal Canc Study, G. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic

- colorectal cancer: Results of a large phase III study. *J. Clin. Oncol.* 2001; 19:4097–4106. [PubMed: 11689577]
8. Boeck S, Wilkowski R, Bruns CJ, Issels RD, Schulz C, Moosmann N, Laessig D, Haas M, Golf A, Heinemann V. Oral capecitabine in gemcitabine-pretreated patients with advanced pancreatic cancer. *Oncology.* 2007; 73:221–227. [PubMed: 18424886]
 9. Beach DF, Somer R. Novel Approach to Gorlin Syndrome: A Patient Treated With Oral Capecitabine. *J. Clin. Oncol.* 2011; 29:E397–E401. [PubMed: 21357787]
 10. Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, Shimma N, Umeda I, Ishitsuka H. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. *Eur. J. Cancer.* 1998; 34:1274–1281. [PubMed: 9849491]
 11. Irshad S, Maisey N. Considerations when choosing oral chemotherapy: identifying and responding to patient need. *Eur. J. Cancer Care.* 2010; 19:5–11.
 12. Liu G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. *J. Clin. Oncol.* 1997; 15:110–115. [PubMed: 8996131]
 13. Zhang J, Peppas NA. Synthesis and characterization of pH- and temperature-sensitive poly(methacrylic acid)/poly(N-isopropylacrylamide) interpenetrating polymeric networks. *Macromolecules.* 2000; 33:102–107.
 14. Liu YY, Shao YH, Lu J. Preparation, properties and controlled release behaviors of pH-induced thermosensitive amphiphilic gels. *Biomaterials.* 2006; 27:4016–4024. [PubMed: 16563494]
 15. Shin YC, Han DK, Kim YH, Kim SC. Antithrombogenicity of hydrophilic polyurethane-hydrophobic polystyrene IPNs. 2. In-vitro and ex-vivo studies. *J. Biomater. Sci., Polym. Ed.* 1994; 6:281–295. [PubMed: 7986781]
 16. Mohan N, Nair PD. Polyvinyl alcohol-poly(caprolactone) semi IPN scaffold with implication for cartilage tissue engineering. *J. Biomed. Mater. Res., Part B.* 2008; 84B:584–594.
 17. Lowman AM, Peppas NA. Molecular analysis of interpolymer complexation in graft copolymer networks. *Polymer.* 2000; 41:73–80.
 18. Lopez JE, Peppas NA. Effect of poly(ethylene glycol) molecular weight and microparticle size on oral insulin delivery from P(MAA-g-EG) microparticles. *Drug Dev. Ind. Pharm.* 2004; 30:497–504. [PubMed: 15244085]
 19. Kim B, Peppas NA. Analysis of molecular interactions in poly(methacrylic acid-g-ethylene glycol) hydrogels. *Polymer.* 2003; 44:3701–3707.
 20. Madsen F, Peppas NA. Complexation graft copolymer networks: swelling properties, calcium binding and proteolytic enzyme inhibition. *Biomaterials.* 1999; 20:1701–1708. [PubMed: 10503971]
 21. Thomas JB, Tingsanchali JH, Rosales AM, Creecy CM, McGinity JW, Peppas NA. Dynamics of poly(ethylene glycol)-tethered, pH responsive networks. *Polymer.* 2007; 48:5042–5048. [PubMed: 18690288]
 22. Lowman AM, Morishita M, Kajita M, Nagai T, Peppas NA. Oral delivery of insulin using pH-responsive complexation gels. *J. Pharm. Sci.* 1999; 88:933–937. [PubMed: 10479357]
 23. Nakamura K, Murray RJ, Joseph JI, Peppas NA, Morishita M, Lowman AM. Oral insulin delivery using P(MAA-g-EG) hydrogels: effects of network morphology on insulin delivery characteristics. *J. Controlled Release.* 2004; 95:589–599.
 24. Kavimandan NJ, Losi E, Peppas NA. Novel delivery system based on complexation hydrogels as delivery vehicles for insulin-transferrin conjugates. *Biomaterials.* 2006; 27:3846–3854. [PubMed: 16529810]
 25. Carr DA, Gomez-Burgaz M, Boudes MC, Peppas NA. Complexation Hydrogels for the Oral Delivery of Growth Hormone and Salmon Calcitonin. *Ind. Eng. Chem. Res.* 2010; 49:11991–11995. [PubMed: 21344059]
 26. Torres-Lugo M, Peppas NA. Molecular design and in vitro studies of novel pH-sensitive hydrogels for the oral delivery of calcitonin. *Macromolecules.* 1999; 32:6646–6651.
 27. Morishita M, Kamei N, Chiba H, Kavimandan NJ, Peppas NA, Takayama K. Complexation hydrogels for intestinal delivery of interferon beta and calcitonin. *J. Controlled Release.* 2009; 134:98–102.

28. Blanchette J, Peppas NA. Oral chemotherapeutic delivery: Design and cellular response. *Ann. Biomed. Eng.* 2005; 33:142–149. [PubMed: 15771268]
29. Blanchette J, Park K, Peppas NA. Use of complexation hydrogels for oral administration of chemotherapeutic agents. *Trans. Soc. Biomater.* 2003; 89:1606–1613.
30. Liechty WB, Caldorera-Moore M, Phillips MA, Schoener C, Peppas NA. Advanced molecular design of biopolymers for transmucosal and intracellular delivery of chemotherapeutic agents and biological therapeutics. *J. Controlled Release.* 2011 In Press.
31. Hou Y, Schoener CA, Regan KR, Munoz-Pinto D, Hahn MS, Grunlan MA. Photo-cross-linked PDMSstar-PEG hydrogels: synthesis, characterization, and potential application for tissue engineering scaffolds. *Biomacromolecules.* 2010; 11:648–656. [PubMed: 20146518]
32. Munoz-Pinto, D. Ph.D. Dissertation. College Station, TX: Texas A & M University; 2011. Hybrid polyethylene glycol hydrogels for tissue engineering applications.
33. Zhang J, Qian ZY, Gu YQ. In vivo anti-tumor efficacy of docetaxel-loaded thermally responsive nanohydrogel. *Nanotechnology.* 2009; 20:1–8.
34. Patel RB, Carlson AN, Solorio L, Exner AA. Characterization of formulation parameters affecting low molecular weight drug release from in situ forming drug delivery systems. *J. Biomed. Mater. Res., Part A.* 2010; 94A:476–484.
35. Reddy SM, Sinha VR, Reddy DS. Novel oral colon-specific drug delivery systems for pharmacotherapy of peptide and nonpeptide drugs. *Drugs Today.* 1999; 35:537–580. [PubMed: 12973398]
36. Blanchette J, Peppas NA. Cellular evaluation of oral chemotherapy carriers. *J. Biomed. Mater. Res., Part A.* 2005; 72A:381–388.
37. Peppas NA, Wood KM, Blanchette JO. Hydrogels for oral delivery of therapeutic proteins. *Expert Opin. Biol. Ther.* 2004; 4:881–887. [PubMed: 15174970]
38. Wood KM, Stone GM, Peppas NA. Wheat germ agglutinin functionalized complexation hydrogels for oral insulin delivery. *Biomacromolecules.* 2008; 9:1293–1298. [PubMed: 18330990]
39. Phillips MR, Peppas NA. Hydrogels modified with carbohydrates for oral protein delivery. *Trans. Ann. Biomater. Meet.* 2009; 33:267.
40. Krishnaiah YSR, Satyanarayana V, Kumar BD, Karthikeyan RS, Bhaskar P. In vivo pharmacokinetics in human volunteers: oral administered guar gum-based colon-targeted 5-fluorouracil tablets. *Eur. J. Pharm. Sci.* 2003; 19:355–362. [PubMed: 12907286]
41. Liu R, Li D, He B, Xu X, Sheng M, Lai Y, Wang G, Gu Z. Anti-tumor drug delivery of pH-sensitive poly(ethylene glycol)-poly(L-histidine)-poly(L-lactide) nanoparticles. *J. Controlled Release.* 2011; 152:49–56.

Figure 1.

From left to right, Nile Red staining of P(MAA-g-EG), 80/20 IPN, 75/25 IPN, 70/30 IPN.

Figure 2.
pH-Dependent dynamic weight swelling ratio profile of P(MAA-g-EG) (◆), 80/20 IPN (□), 75/25 IPN (▲), 70/30 IPN (○). Standard deviations for the P(MAA-g-EG) and 70/30 IPN are too small to be seen and curves generated are for $n = 3$ studies.

Figure 3.

Fluorescein release in neutral pH of P(MAA-g-EG) (◆), 80/20 IPN (◻)

(◻)

(▲), 75/25 IPN (◻)

(▲)

(○), 70/30 IPN (○) crushed particles (75 – 500 μm). Fluorescein release is expressed as M_t/M_∞ . Standard deviations for all polymer formulations too small to be seen and curves generated are for $n = 3$ studies.

Figure 4.

Fluorescein release in two step pH change from 2.0 to 7.0 of P(MAA-g-EG) (◆), 80/20 IPN (◻), 75/25 IPN (▲), 70/30 IPN (○) crushed particles (75 – 500 μm). Fluorescein release is expressed as M_t/M_∞ . Standard deviations for all polymer formulations too small to be seen and curves generated are for $n = 3$ studies.

Figure 5. Fluorescein release of P(MAA-g-EG) in pH 2.0 (◇) and pH 7.4 (◆) as well as 75/25 IPN in pH 2.0 (△) and pH 7.4 (▲). Standard deviations for all polymer formulations too small to be seen and curves generated are for $n = 3$ studies.

Table 1

Loading efficiency, weight percent loading, and hydrophobic properties for all polymer carriers.

Formulation	Loading Efficiency (%)	Wt loading (%)	Surface Contact Angle (°)	Hydrophobic Swelling Ratio
P(MAA-g-EG)	37 ± 2	1.1	52 ± 2	1.37 ± 0.05
80/20 IPN	30 ± 2	0.9	64 ± 1	0.96 ± 0.04
75/25 IPN	44 ± 2	1.3	73 ± 3	0.87 ± 0.05
70/30 IPN	21 ± 6	1.0	105 ± 1	0.80 ± 0.13