Expert Opinion

1. Introduction: oral chemotherapy and rationale for novel formulations
2. Oral chemotherapeutic formulations
3. Intelligent hydrogels: pH-dependent drug loading and delivery
4. Micelles: ease of formulation and drug stabilisation
5. *In vitro* and *in vivo* studies
6. Conclusions
7. Expert opinion

Ashley Publications
www.ashley-pub.com

Intelligent hydrogels for the oral delivery of chemotherapeutics

Lev Bromberg
Massachusetts Institute of Technology, Department of Chemical Engineering, Cambridge, MA 02139, USA

A novel approach toward improvements of oral chemotherapeutic formulations has evolved, which combines solubilisation (molecular dispersion) of the hydrophobic anticancer drugs in micelles attached to large macromolecules or microparticles. The large size of the macromolecules or microgels prevents the gel components from being transported into the systemic circulation. The discussed gels comprise copolymers of poly(acrylic acid) (PAA) and Pluronic® surfactants, linked via C–C bonds. The Pluronic-PAA copolymers are non-irritating when administered orally. The micelles formed in the Pluronic-PAA solutions and in crosslinked microgels can be loaded with chemotherapeutic drugs and then released in contact with the intestine. The microgels are collapsed at the acidic pH of the stomach and expand, thus releasing the loaded drugs at the pH of the lower gastrointestinal tract. Yet the microgels are mucoadhesive and enable longer retention time and prolonged release in the colon. Ease of preparation and formulation of the drugs with the Pluronic-PAA polymers and gels may enable the wider use of oral chemotherapy, resulting in a better patient compliance and improved quality of life of the patients.

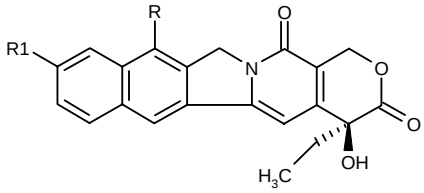
Keywords: chemotherapeutic drugs, micelles, microgels, oral administration, poly(acrylic acid), Pluronic® polyethers, site-specific delivery

Expert Opin. Drug Deliv. (2005) 2(6):1003-1013

1. Introduction: oral chemotherapy and rationale for novel formulations

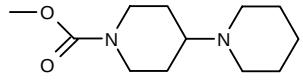
Chemotherapy for cancer refers to the use of chemotherapeutical agents directed at killing or controlling cancerous cells. Chemotherapy involves risks due to drug toxicity, and the more effective drugs tend to be more toxic. Structures of some common chemotherapeutic drugs are presented in Figure 1.

Most conventional regimes of chemotherapy involve drug administration by injection or infusion, resulting in significant concentrations of the toxic drugs in the systemic circulation immediately after administration and below the desired threshold concentration towards the end of the dosing interval. In contrast, oral chemotherapy can provide a prolonged and continuous exposure of the cancer cells to a relatively lower and, thus, safer concentration of the anticancer drugs, hence improving the chances to stop the growth of the tumour blood vessels, enabling an improved efficacy and fewer side effects than the current intermittent chemotherapy could do. Beyond the potential for improved efficacy and lower toxicity, oral chemotherapy is cost effective, flexible in dosing schedule, convenient and thus preferred by the patients, resulting in a better patient compliance and improved quality of life. This is especially important for the patients with advanced or relapsed cancer and the elderly. The availability of an oral preparation would allow for the development of new treatment regimens that can be delivered, with some advantage, in the outpatient setting. Advances in oral chemotherapy can thus promote 'chemotherapy at home', which would be a new concept of cancer treatment [1-5].

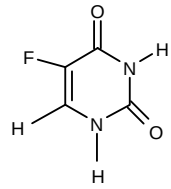


Camptothecins (lactone form)

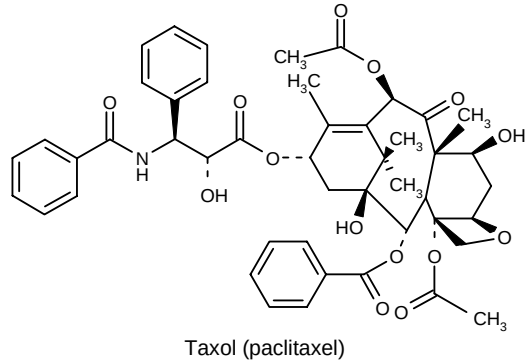
20(*S*)-Camptothecin: R = H; R1 = H
Toptoecan: R = -NMe_2 HCl; R1 = -OH
Irinotecan (CPT-11): R = -CH_3;
R1 =



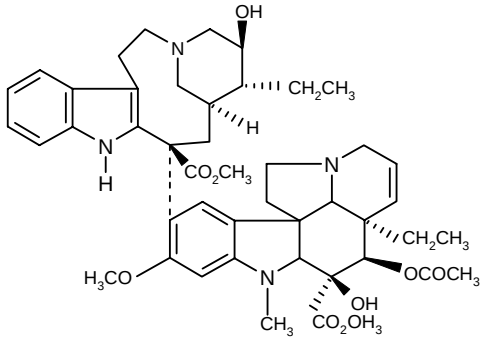
HCl



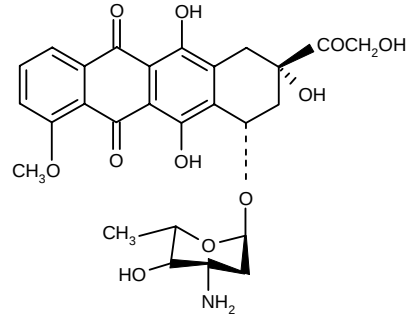
5-Fluorouracil



Taxol (paclitaxel)



Vinblastine



Doxorubicin

Figure 1. Chemical structures of some common chemotherapeutic drugs.

Clinical studies already indicate advantages of oral chemotherapies with drugs exhibiting improved bioavailability such as topotecan and irinotecan, which are semisynthetic derivatives of camptothecin (CPT), a modified monoterpene indole alkaloid produced by *Camptotheca acuminata* and some other species belonging to unrelated orders of angiosperms. Irinotecan and topotecan are used throughout the world for the treatment of various cancers, and over a dozen more CPT analogues are currently at various stages of clinical development. The camptothecins act as specific inhibitors of topoisomerase I, a critical enzyme involved in DNA replication, transcription and chromosomal structure [6,7]. The worldwide market size of irinotecan/topotecan is well over US$1 billion in 2005. At present, topotecan is indicated for the treatment of relapsed small cell lung cancer and ovarian cancer, and has been investigated as a potential treatment for haematological malignancies [8]. Oral topotecan demonstrated better response rates and longer median survival of patients with relapsed small cell lung cancer, compared with patients treated intravenously [9,10]. The oral

dosing was generally better tolerated and more convenient, with lesser occurrence of severe neutropenia (an abnormal decrease in the number of neutrophils in the blood).

However, oral administration of the majority of anticancer drugs other than topotecan, especially those that are very hydrophobic but with excellent anticancer effects, such as paclitaxel (Taxol®), is hampered by the very low availability through the gastrointestinal tract (GI). In addition, the bioavailability can also vary widely between patient populations when administered orally. This is risky from the standpoint of an inappropriate dose due to unpredictable uptake. Oral bioavailability of paclitaxel that had not been specifically formulated was reported to be < 1% [1]. Paclitaxel is eliminated by the cytochrome P450-dependent metabolism processes and by the efflux from the cells by the plasma membrane transporter P-glycoprotein (P-gp) in the intestine, liver, kidney and so on. In order to enhance the bioavailability of paclitaxel, formulations employing organic solvents have been developed. A dosage form presently available for the intravenous administration of paclitaxel uses an adjuvant consisting of polyoxyethylene glycerol triricinoleate (polyoxyethylated castor oil, or Cremophor EL) and dehydrated ethanol. Although Cremophor EL solubilises and stabilises paclitaxel, it also causes serious side effects, including hypersensitivity reactions, nephrotoxicity, neurotoxicity and cardiotoxicity, and its use is associated with anaphylactoid hypersensitivity reactions, hyperlipidaemia, abnormal lipoprotein patterns, erythrocyte aggregation and peripheral neuropathy [11]. When administered orally as a cosolvent with paclitaxel, Cremophor EL limits the absorption of the paclitaxel in cancer patients [12].

Numerous trials involving the oral administration of other chemotherapeutic agents have not indicated significant improvements in drug efficacy. For example, oral delivery of 5-fluorouracil (5-FU), a chemotherapeutic agent widely used in the treatment of solid malignancies [13], has not shown improvements in overall survival rate in patients with colorectal cancer [14]. The oral bioavailability of 5-FU, the catabolism of which is mediated by dihydropyrimidine dehydrogenase (DPD), an enzyme that is especially active in metastatic tumours, is generally low but can be improved by 5-FU prodrugs and analogues such as DPD-inhibiting fluoropyrimidines, eniluracil, as well as coadministration with paclitaxel [15,16]. Nevertheless, there exists much room for improvement of the existing 5-FU oral formulations. Analogously, vinorelbine (a semisynthetic derivative of Vinca alkaloid), approved in the intravenous form for the treatment of metastatic non-small cell lung cancer in elderly patients, shows only minimal activity when administered orally [17]. Specific formulations using vinorelbine can improve its activity and tolerability [18].

2. Oral chemotherapeutic formulations

As is evident from the introduction, it is imperative that novel and effective means of delivering poorly bioavailable drugs via the oral route be found. By encapsulating anticancer drugs into nanoparticles, liposomes, or micelles, an improved adhesion to and absorption through the intestinal cells can be achieved, along with the possibility for the drug to escape from recognition by P-gp [1,19,20]. Notable recent reports in the area of formulations specifically designed for oral chemotherapeutics include work by Peppas and colleagues [5,21,22], which describe hydrogel nanospheres composed of methacrylic acid and poly(ethylene glycol) (PEG), and loaded with a chemotherapeutic agent bleomycin. The interpolymer complex between polymethacrylic acid and PEG is stabilised by hydrogen bonding at an acidic pH characteristic of the stomach, but a higher pH disrupts the hydrogen bonding, thus, enhancing the hydrogel swelling. The swollen nanospheres were shown to release bleomycin in response to a pH increase similar to that seen when passing from the stomach into the upper small intestine [21]. The nanogel particles enhanced the permeability of a cell epithelial model with the potential of improvement of drug transport into the bloodstream. However, the nanosize poses degradability and toxicity limitations with respect to the chemical nature of the materials to be used together with the drug, as these materials will find their way to the systemic circulation.

A novel approach toward improvements of the oral chemotherapeutic formulations has recently emerged, which combines the solubilisation (molecular dispersion) of the hydrophobic anticancer drugs in micelles with a relatively large size of the macromolecules or particles used in the drug formulation, which prevents such larger carriers from being transported into the systemic circulation. Such a novel, yet promising, system for oral chemotherapy, which the author calls intelligent hydrogels, is the subject of the present review.

3. Intelligent hydrogels: pH-dependent drug loading and delivery

Intelligent hydrogels are crosslinked (either through covalent bonds or via physical aggregation or entanglement) polymeric networks that respond to an external stimulus in a controlled, reproducible and reversible manner by changing polymer conformation and/or volume [23]. Macromolecules that possess ionisable groups exist in their expanded state on dissolving in water or another good ionising solvent due to the repulsion between similar charges on the chains. However, should the solvent prevent ionisation, the macromolecular chains assume their compact, folded state. Consequently, transitions from the nonionised state, stabilised by hydrogen bonding, to the ionised state lead to the hydrogel swelling and collapsing, prompting dramatic changes in its volume, sometimes 1000-fold, including volume transitions in fluids of the human body. Such transitions are often caused by changes in pH and are highly relevant for oral drug delivery due to the dramatic differences in pH typical for various parts of the GI tract. The pH of the GI tract gradually increases from the stomach (pH 1.5 – 3) to terminal ileum (pH 7 – 8) and then decreases in the colon to 5.5 – 7.0 because of the acidification

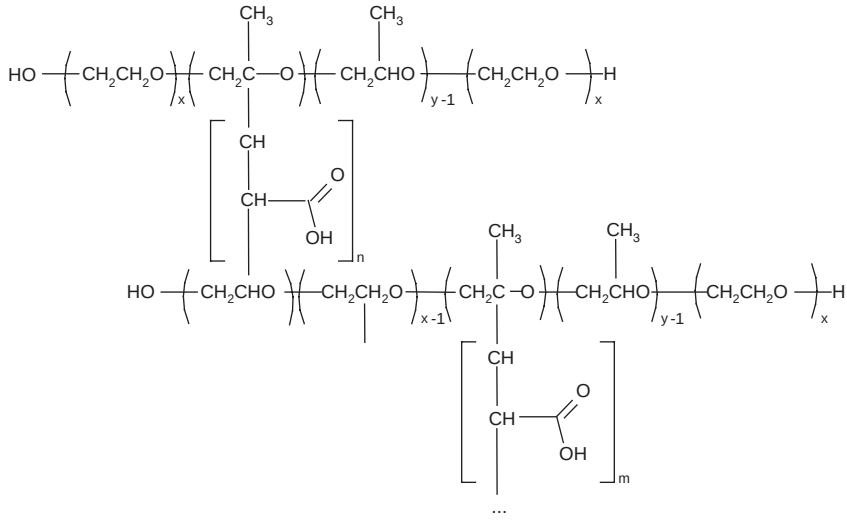


Figure 2. Structure of the Pluronic-PAA copolymers [30].
PAA: Poly(acrylic acid).

of the colonic contents caused by the products of bacterial fermentation [24]. A pH-independent, conventional dosage form dissolves in the stomach or intestinal fluid, and the rate with which the drug absorbs from these parts of the GI tract depends on the properties of the drug. However, the hostile acidic environment of the stomach and high concentrations of proteolytic and metabolytic enzymes in the stomach and proximal regions of the small intestine challenge the effective oral administration of proteinaceous as well as some chemotherapeutic drugs [23]. Thus, the major premise of the dosage forms based on intelligent hydrogels is to protect the drug from the acidic and proteolytic environment and/or prevent its undesirable systemic delivery from the upper GI tract, and facilitate its targeted absorption in the lower parts of the GI tract [23-26]. The design of a hydrogel for a colonic drug delivery system can be based on a site-specific trigger, that is, pH difference between the small and large intestine or site-specific presence of microbial enzymes in the large intestine [23]. Targeted delivery of drugs to the colon is valuable in the treatment of colonic cancer, whereby high local concentration can be achieved while minimising side effects. Notably, however, because of the cytotoxicity of the chemotherapeutic agents, one needs to be concerned with the potentially detrimental effects of such agents on the GI tract mucosa. The potential toxicity of the drugs at their concentration levels afforded by the new dosage forms to the GI tract tissues needs to be addressed for oral administration to succeed. It is generally believed that long-time exposure of the cancer cells to the drug at modest concentrations would have much better effects than a pulsed supply of the drug at a high concentration. A major determinant for the final efficacy of chemotherapy is the area under the curve (AUC) of the time course of the effective drug concentration in the blood [27]. Hence, a sustained release of a drug from its carrier at a desired rate over a sufficiently long duration can lead to effective chemotherapy that can last for days, weeks or even months.

Recently developed hydrogels, based on graft-comb poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide)-*g*-poly(acrylic acid) copolymers (PEO-PPO-PEO-PAA, or Pluronic-PAA), possess many physical and pharmacological features that make dosage forms based on such hydrogels and chemotherapeutic drugs well adapted for the treatment of cancers involving oral administration. The Pluronic-PAA copolymers, where the PAA and polyether are bonded via pharmaceutically acceptable C–C bonds, without foreign chemical moieties (Figure 2), combine ionisable and hydrophobic groups that change the copolymer conformation in aqueous solutions in response to both pH and temperature [28,29].

When chemically crosslinked, the Pluronic-PAA copolymers result in networks that on swelling result in microgels, that is, spherical particles ranging in diameter from tens to hundreds of microns, with the size depending on the polyether involved in the synthesis [31-34]. The microgels can contain either permanent or degradable crosslinks containing disulfide (S–S) or azo (-N=N-) bonds [34]. The latter crosslinks enable microgel degradation in the colon, which is enriched with the azoreductases. Importantly, the microgels feature dangling chains of Pluronic inside each gel particle, which are capable of arranging into micelle-like aggregates at temperatures of the human body (Figure 3).

The micellar 'intra-gel' aggregates solubilise hydrophobic drugs such as paclitaxel (Figure 4), whereas the presence of carboxyls allows for the loading of positively charged drugs [31,32]. A swollen microparticle, within which numerous micelles are formed, would not allow for its intravenous administration. However, the Pluronic-PAA microgel particles can be doubly loaded with both paclitaxel and doxorubicin,

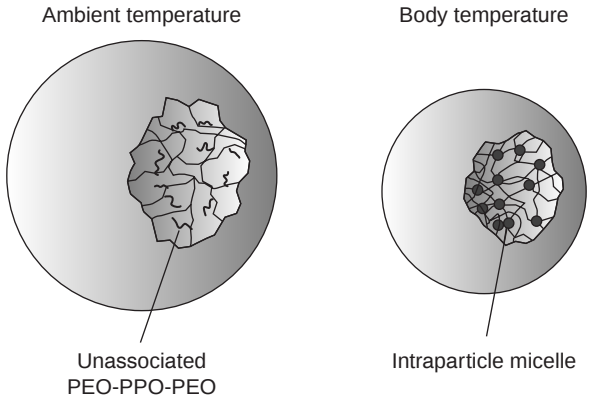


Figure 3. Volume phase transitions of Pluronic-PAA microgels via aggregation of Pluronic dangling chains within gel microparticles. Reproduced with permission from BROMBERG L, TEMCHENKO M, HATTON TA: Dually responsive microgels from polyether-modified poly(acrylic acid): swelling and drug loading. *Langmuir* (2002) **18**(12):4944-4952 [31]. Copyright (2002) American Chemical Society.
PAA: Poly(acrylic acid); PEO: Poly(ethylene oxide); PPO: Poly(propylene oxide).

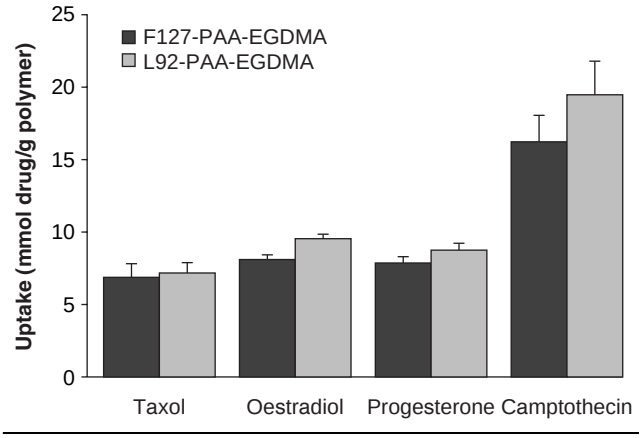


Figure 4. Equilibrium uptake of hydrophobic drugs by Pluronic-PAA microgels at 37°C and pH 7. The microgels are composed of either Pluronic F127 or L92 and PAA (1:1 Pluronic:PAA weight ratio), and are crosslinked by ethylene glycol dimethacrylate. Reproduced with permission from BROMBERG L, TEMCHENKO M, HATTON TA: Dually responsive microgels from polyether-modified poly(acrylic acid): swelling and drug loading. *Langmuir* (2002) **18**(12):4944-4952 [31]. Copyright (2002) American Chemical Society.
EGDMA: Ethylene glycol dimethacrylate; PAA: Poly(acrylic acid).

and can thus prove to be very potent anticancer drug delivery vehicles in oral administration.

General trends that are important for drug loading of the Pluronic-PAA microgels via the ion-exchange mechanism were studied using the potent, weakly basic chemotherapeutic drug doxorubicin [31,32] (Figure 5). As the degree of carboxyl-group ionisation increased with pH, the ion-exchange capacity of the microgels increased, reaching about half of the maximum capacity found by titration, indicating that the loading of doxorubicin could be limited only by the available free volume of the network. Notably, the pH-dependencies of the equilibrium swelling and doxorubicin loading coincided, proving the ion-exchange mechanism of doxorubicin loading into the microgels. The ion-exchange capacity of the Pluronic-PAA microgels has also been shown to result in very high loadings of other weakly basic drugs, such as mitomycin C and mitoxantrone [31].

4. Micelles: ease of formulation and drug stabilisation

The presence of hydrophobic PPO groups makes associations due to hydrophobic effect (i.e., limited solubility of a solute in water) to be a prominent feature of the Pluronic-PAA aqueous solutions. Such associations lead to the formation of micelles and larger micelle-like aggregates, which are useful in drug delivery. Micelles formed from Pluronic-PAA copolymers at body temperature have been shown to enhance the solubility of hydrophobic drugs, such as steroid hormones and camptothecins in aqueous solutions [31,35]. The enhancement of the solubility of compounds by micelles is due to the hydrophobic core of the micelle providing a suitable microenvironment for the hydrophobic solute [29,36]. The solubilising capacity of the Pluronic-PAA micelles depends on the hydrophobicity of a drug [37]. Solubilisation into a hydrophobic and essentially water-free core of the Pluronic-PAA aggregates, composed of polypropylene segments, which is surrounded by the highly swollen corona of the hydrophilic poly(ethylene oxide) and polyacrylic chains (Figure 6), enhances the stability of drugs against hydrolytic and proteolytic factors.

Due to the numerous carboxylic groups in the corona, negatively charged at intestinal pH, the presence of the Pluronic-PAA copolymers in the protein solutions does not induce any significant changes in the tertiary structure of the negatively charged insulin, haemoglobin and albumin, but very pronounced changes are observed in the positively charged trypsin, analogous to the ones observed following autodegradation [39]. The changes in the trypsin structure occur due to the extraction of Ca^{2+} ions, which play an important role in maintaining the thermodynamic stability of the enzyme. Extraction of calcium ions from trypsin by the PAA leads to the total loss of its enzymatic activity. In addition, the formation of mixed Pluronic-PAA-protein micelles with proteins embedded inside the PPO-rich cores adds to the protein stability in solutions. The presence of Pluronic-PAA hinders the insulin degradation by α-chymotrypsin [39]. Thus, using a Pluronic-PAA copolymer in a dosage form could protect a proteinaceous drug from the tryptic degradation in oral administration. The formulation route via simple mixing of aqueous micellar solutions of the Pluronic-PAA and the drug of interest, resulting in drug stabilisation, certainly adds to the formulator's arsenal.

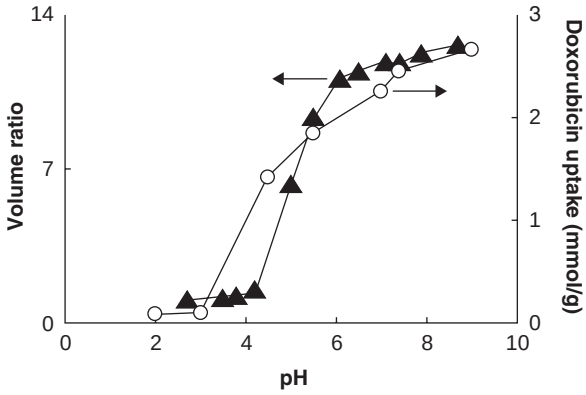


Figure 5. Equilibrium swelling of Pluronic-PAA microgel particles in water (filled points) and equilibrium uptake of doxorubicin by microgels (open points) as functions of pH at 37°C. The microgels are composed of Pluronic F127 and PAA (1:1 weight ratio), and are crosslinked by ethylene glycol dimethacrylate. Reproduced with permission from BROMBERG L, TEMCHENKO M, HATTON TA: Dually responsive microgels from polyether-modified poly(acrylic acid): swelling and drug loading. *Langmuir* (2002) **18**(12):4944-4952 [31]. Copyright (2002) American Chemical Society.
PAA: Poly(acrylic acid).

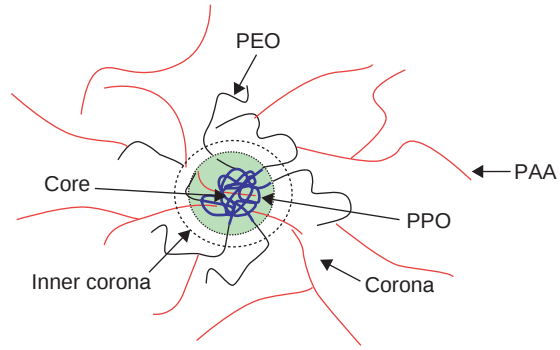


Figure 6. Structure of Pluronic-PAA micelle, comprising of hydrophobic core (diameter ~ 6 nm) of PPO chains surrounded by protective corona (diameter ~ 20 nm) composed of PEO and PAA segments [29,38].
PAA: Poly(acrylic acid); PEO: Poly(ethylene oxide); PPO: Poly(propylene oxide).

Of significance for the chemotherapeutic applications, Pluronic-PAA micelles favourably solubilise and encapsulate CPT and related drugs [35]. By inhibiting DNA topoisomerase I, CPT and its analogues inhibit the growth of a wide range of tumours. However, the high chemical reactivity of the α-hydroxycarbonyl group in the lactone ring, which is required for cytotoxic activity, induces a rapid conversion of the lactone form of CPT into the biologically inactive carboxylate form under physiological conditions. Lactone is converted to carboxylate in a pH-dependent equilibrium (Figure 7) [40].

Importantly from the formulations standpoint, the active lactone form of CPT exhibits poor aqueous solubility. Moreover, the carboxylate form of CPT binds with human serum albumin (HSA) with extraordinary efficiency and, thus, the presence of HSA in blood or serum promotes lactone hydrolysis (Figure 6) and shifts the equilibrium towards the pharmacologically ineffective carboxylate form. Hence, the stability of the lactone ring of CPT is a main concern in the development of an adequate pharmaceutical carrier for this drug. Recently, it has been demonstrated that the solubilisation into the Pluronic-PAA polymer micelles provided an effective barrier against drug decomposition [35]. The copolymers with more hydrophobic L92 copolymer seemed to be especially effective in CPT protection in human serum, with the drug half-life prolonged by ~10-fold. Analogous results were obtained with the CPT analogue CPT-11 (Figure 8). CPT-11 (irinotecan; Figure 1), is a water-soluble CPT analogue that has exhibited remarkable antitumour activity in clinical trials against a variety of human tumours and is currently approved for the treatment of colorectal cancer.

5. *In vitro* and *in vivo* studies

In vivo and *in vitro* studies of Pluronic-PAA copolymers and crosslinked gels have so far focused on various aspects of the safety and efficacy of the use of these copolymers in topical and oral administration [41]. The studies demonstrated that:

- the gelled material enables prolonged contact with the mucous tissue due to enhanced bioadhesion
- the release of a drug by diffusion from Pluronic-PAA micelles enhances the bioavailability of the drug
- due to their large size, Pluronic-PAA copolymers and microgels do not penetrate into the systemic circulation,

and these results are summarised below.

Since both components of Pluronic-PAA copolymers, the Pluronic surfactants and PAA, have an approved regulatory status [42,43], it can be expected that their graft copolymers would be safe. Indeed, the animal toxicological study demonstrated the absence of toxicity of the orally administered copolymers in a rat model [41].

A recent study revealed the effects of novel, permanently crosslinked microgels (diameter in the swollen state 50 – 200 µm) of Pluronic-PAA as possible permeation enhancers for doxorubicin transport through monolayers of cells derived from human colorectal carcinoma (Caco-2) as a GI model. Pluronic segments in the microgels were chosen so that they represented most hydrophobic (Pluronic L61 and L92, with average compositions of $EO_3PO_{30}EO_3$ and $EO_8PO_{52}EO_8$, respectively) and relatively hydrophilic (Pluronic F127, with an average composition of $EO_{99}PO_{67}EO_{99}$) extremes of this class of block copolymers [44]. Without additives such as microgels or Pluronic copolymers, the doxorubicin exhibited highly polarised transport, with the active efflux exceeding the passive

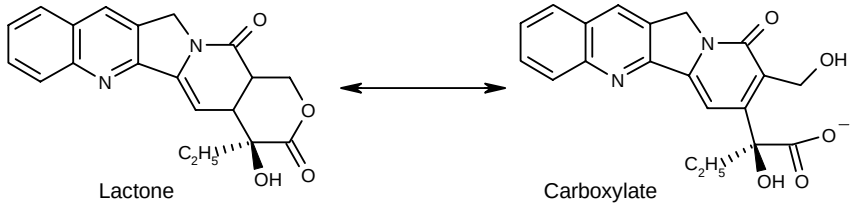


Figure 7. Equilibrium between lactone (pharmaceutically active) and carboxylate (inactive) forms of camptothecin.

influx into the cells. However, microgels and Pluronics (especially Pluronic L92), as well as their combinations, lowered the active efflux of doxorubicin from Caco-2 cells by as much as 2.4- to 3.2-fold. Pluronic L61 is known to be a potent doxorubicin efflux suppressor at concentrations up to critical micellar concentration, above which the effects of Pluronics generally plateau and then decay [45-47]. The Pluronic-PAA microgels were shown to inhibit the doxorobucin efflux from the cells and enhanced the passive influx, thus enhancing the overall cell absorption of doxorubicin in tumour cells. The lower efflux occurs via inhibition of the transmembrane protein P-gp, an energy-dependent drug efflux pump that is overexpressed in tumour cell lines. The enhancement effect was more pronounced than with a known penetration enhancer, Pluronic L61, and was comparable to Pluronic L92. Microgels exhibited synergism of the doxorubicin transport enhancement with verapamil, a known calcium channel blocker and a P-gp inhibitor. In line with the benign nature of Pluronic-PAA copolymers, the microgels exhibited very minor effects on the transepithelial electrical resistance of the cell monolayers. Any deleterious effects were fully reversible, indicating viability of the cells after incubation with microgels. Cytotoxicity studies confirmed that the transport-enhancing properties of the microgels were not due to the damage of the Caco-2 cell monolayers [44]. Examination by means of transient rheological properties, tensile tests and atomic force microscopy revealed significant bioadhesion of the Pluronic-PAA gelled solutions and crosslinked microgels to rat intestinal tissue [30] and mucous substrates over a range of pH values [48]. In many instances, the Pluronic-PAA copolymers exhibited the fracture strength and work of mucoadhesion, significantly exceeding those of the comparable Carbopol® (crosslinked PAA) polymers, which are an established industry standard for bioadhesive polymers [30].

Tensiometric force measurements indicated that hydrophobic interactions, as well as hydrogen bonding and electrostatic interactions, were significant in the mucoadhesion of Pluronic-PAA copolymers. Experiments with a range of Pluronic-PAA copolymers with varying hydrophobic PPO contents in the Pluronic segments showed that hydrophobic interactions play a role in the adhesion of Pluronic-PAA chains to mucin. The length of the PEO segments in Pluronic affected the work of adhesion. The longest Pluronic copolymers bonded to PAA, resulting in copolymeric Pluronic-PAA gels with strong mucoadhesive properties. It would appear that the presence of the PEO chains in the Pluronic-PAA hydrogels lowers the interfacial free energy and may facilitate spreading, and the intimate contact between the mucus and gel surfaces, promoting interpenetration and, thus, the higher mucoadhesive bond strength.

In a study on human volunteers, the gelled Pluronic-PAA solution formed a protective layer over the oesophageal mucosa when administered orally, and efficiently adhered to the mucosa of the human oesophagus [41]. As such a gelled layer provides a platform for localised drug delivery, it may be used in the prevention and treatment of gastro-oesophageal reflux disease and other oesophageal disorders. The delivery of antacids would be of therapeutic value in the neutralisation of the acid reflux. In addition, the oesophageal damage induced by gastric reflux can be prevented by the incorporation of corticosteroids to treat localised oesophageal ulceration and the delivery of cholestyramine to absorb refluxed bile acids [23]. It may be possible to manipulate the tone of the lower oesophageal sphincter via the local effect of loaded drugs as the Pluronic-PAA copolymer concentrates in the mid to lower regions of the oesophagus.

The implications of the Pluronic-PAA microgels on drug release in oral administration have been assessed using a rat model [49]. Due to their proven mucoadhesive properties, the microgels present a potential for combining a sustained release system, which allows controlling kinetics of the drug absorption via optimisation of the drug residence time at the absorption site with an absorption enhancer (surface-active Pluronic segments) that increases the drug absorption rate. This would provide an efficient formulation capable of enhancing the oral bioavailability of drugs, intestinal absorption of which is limited by a certain number of receptors expressed on the surface intestinal barrier. Megestrol acetate (MA) was chosen for a study as an example of such a drug, which is known to have a low and poorly controllable bioavailability due to P-gp-mediated efflux. MA is a synthetic analogue of progesterone, and is widely used for the palliative treatment of advanced breast and endometrial carcinomas [49]. Although the dosing of MA can be up to 800 mg/day, the oral bioavailability of this drug is low and limited by its negligible aqueous solubility and the P-gp-mediated efflux. In the

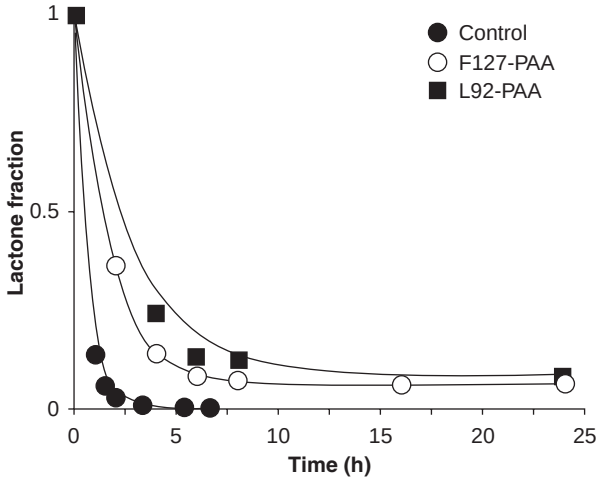


Figure 8. Effect of F127-PAA and L92-PAA micelles on the stability in human serum (pH 7.4, 37°C) of the lactone form of CPT-11. Control experiments were carried out in the absence of the copolymers.
CPT: Camptothecin; PAA: Poly(acrylic acid).

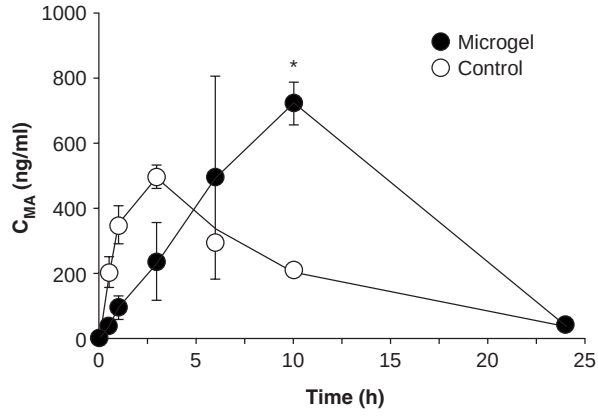


Figure 9. Kinetics of the C_{MA} in plasma following oral administration of the control (suspension of the drug in a 0.5 wt% aqueous solution of methylcellulose) and microgel formulations, in rat model. Dose 10 mg/kg by gavage. Formulation comprised 1 wt% aqueous suspension of the MA-loaded microgels. Reproduced from ALAKHOV V, PIETRZYNSKI G, PATEL K, KABANOV A, BROMBERG L, HATTON TA: Pluronic block copolymers and Pluronic poly(acrylic acid) microgels in oral delivery of megestrol acetate. *J. Pharm. Pharmacol.* (2004) **56**(10):1233-1241 [49], with permission from the authors.
C_{MA}: Concentration of megestrol acetate; MA: Megestrol acetate.
*$p < 0.05$, control versus microgel formulation.

study [49], tablet dosage forms were tested *in vitro*, whereas the MA release from the equilibrium-swollen microgels as well as the radioactively labelled microgel passage through the GI tract were evaluated in rats. The *in vitro* experiments revealed that the drug was essentially retained by either Carbopol or the Pluronic-PAA microgel at pH 1.8 and released slowly at pH 6.8, the conditions within the intestine. Importantly, the microgel provided a more robust retention of the drug at acidic pH, relative to Carbopol 974, as reflected by the three-fold lower initial rate of release. This notion correlated well with the hydrophobic nature of the microgels containing ~ 36% of the water-insoluble poly(propylene oxide) per dry weight. The microgels required higher electrostatic repulsive energy for swelling and tablet disintegration, as compared with Carbopol with its $-\log_{10}$ dissociation constant for an acid of ~ 5. The microgels are more tightly crosslinked by the hydrophobic associations than Carbopol and, hence, exhibit better drug retention at acidic pH.

The Pluronic-PAA microgel formulations containing MA, orally administered by gavage in rats, showed improved pharmacokinetics of the released drug. That is, the mean peak plasma concentration (C_{max}), AUC and the time to achieve C_{max} were all significantly larger than with the control formulations without the microgels (Figure 9). The mean C_{max} of the MA in plasma determined for the rats dosed with microgel formulation and for the control are 723 ± 66 ng/ml and 496 ± 36 ng/ml, respectively ($p = 0.04$), and the AUC values are 9261 ± 1451 ng·h/ml and 4953 ± 402 ng·h/ml, respectively ($p = 0.06$). The time to achieve C_{max} was 10 h for the group treated with the microgel formulation and only 3 h for the control group. The prolonged time to reach C_{max} for the microgel-formulated MA indicated that the microgel carrier did increase the drug residence time at the absorption site. Indeed, the study of the labelled microgel passage through the GI tract proved the significant microgel retention, characteristic of very high molecular weight polymers such as PAA. No significant fractions of the labelled microgels were found in any liver, kidney or blood samples, which proved the absence of any systemic absorption. Hence, the microgels that possess enhanced retention in the GI tract would not present a safety concern when administered orally [49].

6. Conclusions

Modification of PAA, a known pharmaceutical excipient, with benign, nontoxic surfactants, such as triblock copolymers of PEO and PPO (Pluronic) via covalent C–C bonds results in a family of polymers (Pluronic-PAA) with a host of useful properties. The Pluronic-PAA copolymers are known to form micellar aggregates in aqueous solutions and biological fluids. Such micelles are capable of solubilising and stabilising hydrophobic drugs and proteins against hydrolysis and proteolysis. Furthermore, the presence of carboxyl groups as well as dangling polyether chains affords mucoadhesive properties to the Pluronic-PAA copolymers comparable to or exceeding those of the mucoadhesive Carbopol copolymers. In addition, the aqueous solutions of the Pluronic-PAA copolymers yield viscoelastic gels at body temperature, yielding an *in situ* gelling drug delivery vehicle that can be administered as a drink and can coat

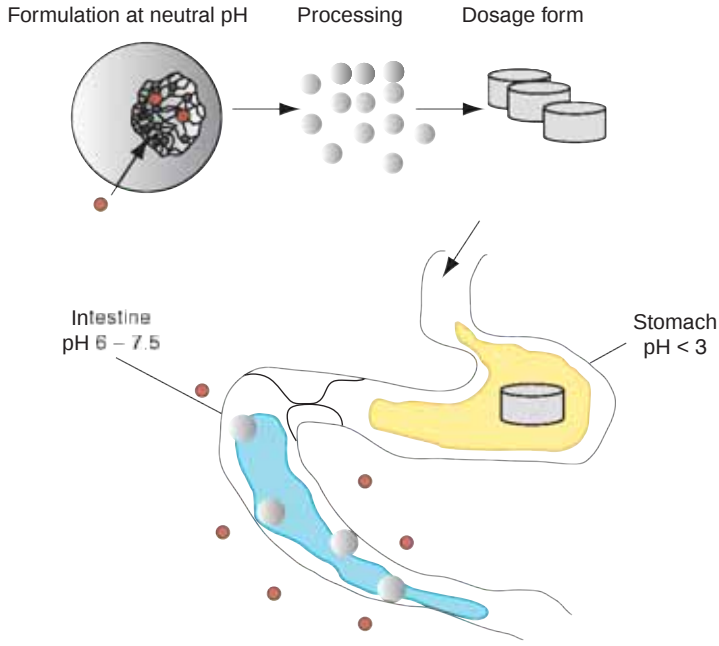


Figure 10. Oral drug delivery with Pluronic-PAA microgels. The microgels are loaded by diffusion and ion exchange in aqueous solutions. They are then lyophilised and the resulting powders are processed into a desired solid dosage form, which remains collapsed and protects the drug in the upper GI tract. The dosage form disintegrates into gel particles at pH 6 – 7.5, which then adhere to the mucosa and provide sustained release of the drug by diffusion through intestinal tissues into the bloodstream. Reproduced from BROMBERG L: Intelligent polyelectrolytes and gels in oral drug delivery. *Curr. Pharm. Biotechnol.* (2003) **4**(5):339-349 [23], with permission from Bentham Science Publishers Ltd.
GI: Gastrointestinal; PAA: Poly(acrylic acid).

the oesophagus and upper GI tract with a water-soluble gel. When crosslinked, the Pluronic-PAA copolymers can be fabricated into spherical microgels capable of being loaded with chemotherapeutic drugs such as hydrophobic camptothecins, steroid hormones and taxol, as well as basic compounds such as doxorubicin, mitomycin C, mitoxantrone and others. Such loaded microgels are collapsed and hold the loaded drugs at an acidic pH characteristic of the upper GI tract. They are also expanded and swollen at neutral pH in the intestine, providing a ready release of the loaded drugs in the lower GI tract. Microgels protect the lactone form of CPT from hydrolysis because of its incorporation into the micelles. The drug release from the microgels enhances its bioavailablity and pharmacokinetic parameters *in vivo*, whereas the microgels pass through the GI tract without absorbing into the systemic circulation due to the large size of the microgels and nonbiodegradable nature of the Pluronic-PAA. Such properties present an opportunity for furthering of the oral chemotherapy concept with this class of polymers.

7. Expert opinion

The useful properties of the Pluronic-PAA copolymers and gels make them a useful excipient for the oral delivery of chemotherapeutics. In this regard, the Pluronic-PAA copolymers are comparable to the thiolated polymers (thiomers), emerging as a promising new tool in oral delivery [50]. Thiomers, such as thiolated chitosan, combine biocompatibility, mucoadhesion and enzymatic inhibition capabilities. Both thiomers and Pluronic-PAA copolymers are mucoadhesive to a larger degree than conventional PAA-based polymers such as Carbopols. Pluronic-PAA has been shown to be a permeation enhancer for doxorubicin, albeit the enhancement is due to the inhibition of the P-gp-mediated efflux of the drug effect that is most likely different from that of the thiomers. However, unlike thiomers, the Pluronic-PAA copolymers possess well-developed surface activity and are capable of forming micelles, which help to molecularly disperse and protect anticancer drugs from hydrolysis. In addition, the Pluronic-PAA solutions and crosslinked microgels can be loaded by the drugs via a straightforward procedure in aqueous solutions, and then readily processed into a powderous form and further into tablets, while still preserving the activity of the loaded drugs (Figure 9). Such tablets, which are the most common orally administered dosage forms, seem to be a rather broad platform to use in the 'chemotherapy at home' concept of cancer treatment (Figure 10).

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. FENG SS, CHIEN S: Chemotherapeutic engineering application and further development of chemical engineering principles for chemotherapy of cancer and other diseases. *Chem. Eng. Sci.* (2003) 58:4087-4114.
   - • A good overview of engineering approaches to chemotherapeutic systems.
2. AJANI J A, TAKIUCHI H: Recent developments in oral chemotherapy options for gastric carcinoma. *Drugs* (1999) 58:85-90.
3. DEMARIO MD, RATAIN MJ: Oral chemotherapy rationale and future directions. *J. Clin. Oncol.* (1999) 16(7):2557-2567.
4. BOTTOMLEY A: The cancer patient and quality of life. *Oncologist* (2002) 7:120-125.
5. BLANCHETTE J, KAVIMANDAN N, PEPPAS NA: Principles of transmucosal delivery of therapeutic agents. *Biomed. Pharmacother.* (2004) 58(3):142-151.
6. LORENCE A, NESSLER CL: Camptothecin, over four decades of surprising findings. *Phytochemistry* (2004) 65(20):2735-2749.
7. MURPHY BA: Topoisomerases in the treatment of metastatic or recurrent squamous carcinoma of the head and neck. *Expert Opin. Pharmacother.* (2005) 6(1):85-92.
8. BERAN M, O'BRIEN S, THOMAS DA *et al.*: Phase I Study of oral topotecan in hematological malignancies. *Clin. Cancer Res.* (2003) 9(11):4084-4091.
9. SCHELLENS JH, CREEMERS GJ, BEIJNEN JH *et al.*: Bioavailability and pharmacokinetics of oral topotecan: a new topoisomerase I inhibitor. *Br. J. Cancer* (1996) 73(10):1268-1271.
10. VON PAWEL J, GATZEMEIER U, PUJOL JL *et al.*: Phase II comparator study of oral versus intravenous topotecan in patients with chemosensitive small-cell lung cancer *J. Clin. Oncol.* (2001) 19:1743-1749.
11. GELDERBLOM H, VERWEIJ J, NOOTER K, SPARREBOOM A: Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation. *Eur. J. Cancer* (2001) 37(13):1590-8159.
12. MALINGRÉ MM, SCHELLENS JH, VAN TELLINGEN O *et al.*: The co-solvent Cremophor EL limits absorption of orally administered paclitaxel in cancer patients. *Br. J. Cancer* (2001) 85(10):1472-1477.
13. DIAZ R, SEGURA A, APARICIO J, CALDERERO V, GUERRERO A, PELLIN L: Lethal toxicity after 5-fluorouracil chemotherapy and its possible relationship to dihydropyrimidine dehydrogenase deficiency: a case report and review of the literature. *J. Chemother.* (2004) 16(6):599-603.
14. SCHILSKY RL, LEVIN J, WEST WH *et al.*: Randomized, open-label, Phase III study of a 28-day oral regimen of eniluracil plus fluorouracil versus intravenous fluorouracil plus leucovorin as first-line therapy in patients with metastatic/ advanced colorectal cancer. *J. Clin. Oncol.* (2002) 20(6):1519-1526.
15. BAKER SD: Pharmacology of fluorinated pyrimidines: eniluracil. *Invest. New Drugs* (2000) 18(4):373-381.
16. NUKATSUKA M, FUJIOKA A, NAKAGAWA F *et al.*: Antimetastatic and anticancer activity of S-1, a new oral dihydropyrimidine-dehydrogenase-inhibiting fluoropyrimidine, alone and in combination with paclitaxel in an orthotopically implanted human breast cancer model. *Int. J. Oncol.* (2004) 25(6):1531-1536.
17. KANARD A, JATOI A, CASTILLO R *et al.*: Oral vinorelbine for the treatment of metastatic non-small cell lung cancer in elderly patients: a Phase II trial of efficacy and toxicity. *Lung Cancer* (2004) 43(3):345-353.
18. GRIDELLI C, MANEGOLD C, MALI P *et al.*: Oral vinorelbine given as monotherapy to advanced, elderly NSCLC patients: a multicentre Phase II trial. *Eur. J. Cancer* (2004) 40(16):2424-2431.
19. ROGERS JA, ANDERSON KE: The potential of liposomes in oral drug delivery. *Crit. Rev. Ther. Drug Carrier Syst.* (1998) 15(5):421-480.
20. YIN WIN K, FENG SS: Effects of particle size and surface coating on cellular uptake of polymeric nanoparticles for oral delivery of anticancer drugs. *Biomaterials* (2005) 26(15):2713-2722.
21. BLANCHETTE J, PEPPAS NA: Cellular evaluation of oral chemotherapy carriers. *J. Biomed. Mater. Res. Part A* (2005) 72A(4):381-388.
   - • One of the first reports on the delivery of chemotherapeutics using responsive copolymers.
22. BLANCHETTE J, PEPPAS NA: Oral chemotherapeutic delivery: design and cellular response. *Ann. Biomed. Eng.* (2005) 33(2):142-149.
23. BROMBERG L: Intelligent polyelectrolytes and gels in oral drug delivery. *Curr. Pharm. Biotechnol.* (2003) 4(5):339-349.
   - • An overview of intelligent hydrogels for oral drug delivery.
24. HAEBERLIN B, FRIEND DR: In: *Oral Colon-Specific Drug Delivery.* DR Friend (Ed.), CRC Press, Boca Raton, FL, USA (1992):1-44.
25. CHOURASIA MK, JAIN SK: Design and development of multiparticulate system for targeted drug delivery to colon. *Drug Deliv.* (2004) 11(3):201-207.
26. PEPPAS NA, WOOD KM, BLANCHETTE JO: Hydrogels for oral delivery of therapeutic proteins. *Expert Opin. Biol. Ther.* (2004) 4(6):881-887.
27. GABIZON A, SHMEEDA H, BARENHOLZ Y: Pharmacokinetics of pegylated liposomal Doxorubicin: review of animal and human studies. *Clin. Pharmacokinet.* (2003) 42(5):419-436.
28. BROMBERG L: Hydrophobically modified polyelectrolytes and polyelectrolyte block-copolymers. In: *Handbook of Surfaces and Interfaces of Materials (Volume 4): Solid Thin Films and Layers.* HS Nalwa (Ed.), Academic Press, San Diego, CA, USA (2001):369-404.
29. BROMBERG L: Hydrophobically modified polyelectrolytes and polyelectrolyte block-copolymers for biomedical applications. (Chapter 51). In: *Handbook of Polyelectrolytes and Their Applications.* SK Tripathy, J Kumar, HS Nalwa (Eds), American Scientific Publishers, Los Angeles, CA, USA (2002):23-46.
30. BROMBERG L, TEMCHENKO M, ALAKHOV V, HATTON TA: Bioadhesive properties and rheology of polyether-modified poly(acrylic acid) hydrogels. *Int. J. Pharm.* (2004) 282(1-2):45-60.
   - • An in-depth description of the mechanism of bioadhesion by Pluronic-PAA hydrogels.
31. BROMBERG L, TEMCHENKO M, HATTON TA: Dually responsive microgels from polyether-modified poly(acrylic acid): swelling and drug loading. *Langmuir* (2002) 18(12):4944-4952.

•• The first description of loading chemotherapeutic drugs into intelligent Pluronic-PAA microgels.

32. BROMBERG L, TEMCHENKO M, HATTON TA: Smart microgel studies. Polyelectrolyte and drug-absorbing properties of microgels from polyether-modified poly(acrylic acid). *Langmuir* (2003) 19(21):8675-8684.

33. BROMBERG L, TEMCHENKO M, MOESER GD, HATTON TA: Thermodynamics of temperature-sensitive polyether-modified poly(acrylic acid) microgels. *Langmuir* (2004) 20(14):5683-5692.

34. BROMBERG L, TEMCHENKO M, ALAKHOV V, HATTON TA: Kinetics of swelling of polyether-modified poly(acrylic acid) microgels with permanent and degradable cross-links. *Langmuir* (2005) 21(4):1590-1598.

35. BARREIRO-IGLESIAS R, BROMBERG L, TEMCHENKO M, HATTON TA, CONCHEIRO A, ALVAREZ-LORENZO C: Solubilization and stabilization of camptothecin in micellar solutions of pluronic-g-poly(acrylic acid) copolymers. *J. Control. Release* (2004) 97(3):537-549.

36. BROMBERG LE, BARR DP: Aggregation phenomena in aqueous solutions of hydrophobically modified polyelectrolytes. A probe solubilization study. *Macromolecules* (1999) 32(11):3649-3657.

37. BROMBERG L, TEMCHENKO M: Loading of hydrophobic compounds into micellar solutions of hydrophobically modified polyelectrolytes. *Langmuir* (1999) 15(25):8627-8632.

38. HUIBERS PD, BROMBERG LE, ROBINSON BH, HATTON TA: Reversible gelation in semidilute aqueous solutions of associative polymers: a small-angle neutron scattering study. *Macromolecules* (1999) 32(15):4889-4894.

39. BROMBERG L: Interactions among proteins and hydrophobically modified polyelectrolytes. *J. Pharm. Pharmacol.* (2001) 53(4):541-547.

40. FASSBERG J, STELLA VJ: A kinetic and mechanistic study of the hydrolysis of camptothecin and some analogues. *J. Pharm. Sci.* (1992) 81:676-684.

41. BROMBERG LE, RON ES: Protein and peptide release from temperature-responsive gels and thermogelling polymer matrices. *Adv. Drug Deliv. Rev.* (1998) 31(3):197-221.

42. *BASF Performance Chemicals. FDA and EPA status.* BASF Corporation, North Mount Olive, NJ, USA (1993):234.

43. Final Assessment Report of the Safety of Carbomers 934, -934P, -940, -941 and -962. *J. Am. Coll. Toxicol.* (1982) 1:109-141.

44. BROMBERG L, ALAKHOV V: Effects of polyether-modified poly(acrylic acid) microgels on doxorubicin transport in human intestinal epithelial Caco-2 cell layers. *J. Control. Release* (2003) 88(1):11-22.

• The first study of cellular chemotherapeutic drug transport enhancement using microgels of Pluronic-PAA.

45. BATRAKOVA EV, LI S, MILLER D W, KABANOV AV: Pluronic P85 increases permeability of a broad Spectrum of drugs in polarized BBMEC and Caco-2 cell monolayers. *Pharm. Res.* (1999) 16(9):1366-1372.

46. BATRAKOVA EV, LI S, VINOGRADOV SV *et al.*: Mechanism of pluronic effect on P-glycoprotein efflux system in blood-brain barrier: contributions of energy depletion and membrane fluidization. *J. Pharmacol. Exp. Ther.* (2001) 299(2):483-493.

47. ALAKHOV V, KLINSKI E, LI S *et al.*: Block copolymer-based formulation of doxorubicin. From cell screen to clinical trials. *Colloids Surf. B: Biointerfaces* (1999) 16:113-134.

48. CLEARY J, BROMBERG L, MAGNER E: Adhesion of polyether-modified poly(acrylic acid) to mucin. *Langmuir* (2004) 20(22):9755-9762.

49. ALAKHOV V, PIETRZYNSKI G, PATEL K, KABANOV A, BROMBERG L, HATTON TA: Pluronic block copolymers and Pluronic poly(acrylic acid) microgels in oral delivery of megestrol acetate. *J. Pharm. Pharmacol.* (2004) 56(10):1233-1241.

• The first *in vivo* study of the oral dosage forms using intelligent Pluronic-PAA microgels.

50. BERKNOP-SCHNÜRCH A, HOFFER MH, KEFEDJIISKI K: Thiomers for oral delivery of hydrophilic macromolecular drugs. *Expert Opin. Drug Deliv.* (2004) 1(1):87-98.

• An insightful review of the thiolated polymers for oral drug delivery.

Affiliation

Lev Bromberg
Massachusetts Institute of Technology,
Department of Chemical Engineering,
Cambridge, MA 02139, USA
E-mail: cpbrolev@mit.edu