

Smart Microgel Studies.

Interaction of Polyether-Modified Poly(Acrylic Acid) Microgels with Anticancer Drugs

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Abstract—Studies of submillimeter gels composed of covalently cross-linked poly(acrylic acid)-g-poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) (Pluronic-PAA) networks are reviewed in light of potential applications of the microgels as drug carriers in oral delivery. The microgels are capable of volumetric transitions in response to environmental stimuli such as pH and temperature. It is shown that the type of Pluronic used in the microgel synthesis changes the structure of the resulting microgels, with the more hydrophobic Pluronic imparting porosity. Microgels based on Pluronic L92 (L92-PAA-EGDMA) possess higher ion-exchange capacity than microgels based on Pluronic F127 (F127-PAA-EGDMA), albeit the former are more hydrophobic. Analogously, more hydrophobic but heterogeneous L92-PAA-EGDMA exhibit superior capacity for equilibrium loading of hydrophobic drugs such as taxol, camptothecin and steroid hormones, as well as higher capacity for weakly basic drugs such as doxorubicin, mitomycin C, and mitoxantrone.

Index Terms—Anticancer drugs, hydrophobic solutes, oral drug delivery, smart microgels

I. INTRODUCTION

The delivery of drugs currently used in cancer treatment is performed mostly through intravenous drug infusions or topically [1]. Due to unfavorable pharmacodynamics, the infusions need to be performed frequently, exacerbating the potential for side effects. Oral treatment with anticancer drugs can be preferred as this delivery route is convenient to patients, reduces administration costs and facilitates the use of more chronic treatment regimens. Thus far, low oral bioavailability has usually limited the development of cancer treatment by the oral route. We have developed novel temperature- and pH-sensitive gel microparticles as feasible vehicles for oral delivery of anticancer drugs. The microgels consist of covalently cross-linked copolymers of poly(acrylic acid) (PAA) and poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) PEO-PPO-PEO copolymers (trademark Pluronic®). The Pluronic-PAA copolymers are

obtained via a unique one-step template polymerization of acrylic acid in the presence of Pluronic, with a chain transfer to the Pluronic [2-5]. The synthesis results in graft-comb structures of high molecular weight (above 10^5 g/mol) and is optimized to yield extremely low concentration of toxic admixtures, acceptable for medicinal use [2]. The copolymers typically consist of about 50 wt% of PAA chains grafted to the polyether backbone of the Pluronic copolymer via C-C bonding [2-5]. Introduction of divinyl cross-linkers such as ethylene glycol dimethacrylate (EGDMA) into the synthetic route developed for the Pluronic-PAA enables preparation of submillimeter gel microparticles capable of volume phase transitions in aqueous solutions [6]. Since these transitions can be controlled by changing the quality of aqueous solvent, the microgels are termed smart, or intelligent. When swollen, the size of microgels (tens of microns) will prohibit their passage through gastrointestinal walls. Yet, because of the strong mucoadhesive properties of the Pluronic-PAA [7-10], the microgels can adhere longer onto the mucosal tissues, thus providing potential for sustained release of the loaded drugs by diffusion. The Pluronic-PAA have been shown to form micelle-like aggregates in aqueous solutions, capable of solubilization of hydrophobic compounds [11-15]. These considerations motivate the ongoing effort by our group to elucidate the drug-microgel interactions. All the drugs chosen for our studies (Fig.1) are currently in clinical use in various anticancer therapies. Yet, these drugs exhibit vastly different physical and chemical properties (Table 1), depending on the presence of ionizable groups. Compounds such as mitomycin C, doxorubicin, and mitoxantrone are weakly basic and are applied in pharmaceutical formulations as hydrochloride salts, whereas taxol, camptothecin, and steroid hormones estradiol and progesterone are neutral and mostly water-insoluble. As described below, we discovered that because of the unique polyelectrolyte and aggregate-forming structure of the microgels, they are capable of holding large amounts of both ionic and hydrophobic drugs.

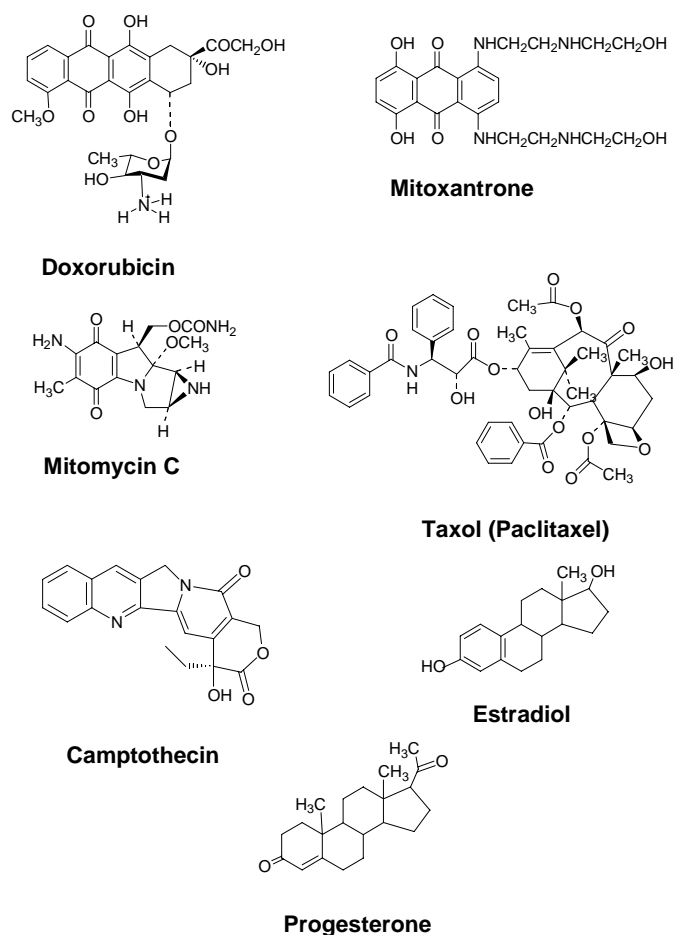


Fig.1. Structures of anticancer drugs under study

II. EXPERIMENTAL

A. Materials

Nonionic polymers Pluronic F127 NF and L92 were obtained from BASF Corp. and used without further treatment. Acrylic acid (99%, vinyl monomer), ethylene glycol dimethacrylate (98%, divinyl cross-linker), dodecane (99+%, solvent), and 4,4'-azobis(4-cyanovaleric acid) (75+%, azo initiator) were purchased from Aldrich Chemical Co. and used as received. Lauroyl peroxide (97%, redox initiator) was obtained from Fluka Chemie AG (Switzerland). Poly(vinylpyrrolidinone-co-1-hexadecene) (Ganex V-216) (dispersion stabilizer) was obtained from International Specialty Products (Wayne, NJ). Doxorubicin hydrochloride and taxol (paclitaxel), both of 99% purity, were obtained from Hande Tech USA (Houston, TX), a subsidiary of Yunnan Hande Technological Development Co.(Kunming, P.R.China). Mitomycin C, camptothecin, mitoxantrone dihydrochloride, β -estradiol and progesterone were obtained from Sigma-Aldrich Co. and used as received. All other chemicals, gases and organic solvents of the highest purity available were obtained from commercial sources.

TABLE I
PROPERTIES OF DRUGS USED IN THE STUDY

Drug	Molecular mass	LogP	Solubility parameter (MPa ^{1/2})
Taxol	853.3	4 ^b	28.7 ^e
Camptothecin	348.4	0.87 ^c	29.2 ^e
Progesterone	314.5	3.77 ^d	17.6 ^f
β -Estradiol	272.4	3.86 ^d	21.1 ^f
^a Mitomycin C	334.1	-0.4 ^g	30.5 ^e
^a Mitoxantrone	444.2	0.24 ^c	27.3 ^e
^a Doxorubicin	543.5	1.85 ^g	27.3 ^e

^a Data for free bases, and not hydrochloride salts.

^b Niethammer, A., Gaedicke, G., Lode, H.N., Wrasidlo, W. *Bioconjugate Chem.*, 2001, 12, 414-420

^c Calculated using ClogP Program (BioByte Corp.)

^d Data from Johnson, M.E., Blankshtein, D., Langer, R. *J.Pharm.Sci.* **1995**, 84, 1144; Kamlet, M.J., Doherty, R.M., Carr, P.W., Mackay, D., Abraham, M.H., Taft, R. *Environ. Sci.Technol.* **1988**, 22, 503.

^e Calculated using Molecular Modeling Pro. (version 2.14, WindowChem Software, Inc.)

^f Hildebrand parameter data are taken from Michaels, A. S., Wong, P.S.L., Pratner, R., Gale, R.M., *AIChe J.*, **1975**, 21, 1073

^g Hansch, C., Leo, A. *Exploring QSAR*, Vols.1-2, American Chemical Society, Washington, DC, 1995

B. Microgel synthesis

Synthesis was carried out on a laboratory scale in an adiabatic mode. Acrylic acid (40 mL) was partially neutralized by addition of 5 M NaOH aqueous solution (0.5 mL). Pluronic (24 g) was dissolved in the resulting solution under nitrogen and a desired amount of ethylene glycol dimethacrylate (EGDMA) was added. The molar ratio of the EGDMA to acrylic acid set in the reaction mixture designates the degree of cross-linking of the microgels [XL, mol% = 100*(number of mols of EGDMA/the number of mols of acrylic acid)]. Lauroyl peroxide (100 mg) and 4,4'-azobis(4-cyanovaleric acid) (100 mg) were dissolved in 2 mL of acrylic acid and added to the solution of Pluronic in acrylic acid. The resulting solution was deaerated by nitrogen bubbling for 0.5 h and added to a 3-necked 0.5-mL flask containing 1 wt% solution of Ganex V-216 in dodecane (200 mL). The flask was vigorously stirred by a mechanical stirrer and deaerated by constant nitrogen purge from the bottom. Then the flask was heated to 70 °C using an oil bath and kept at that temperature under stirring and nitrogen purge. After about 1 h, formation of white particles was observed on the flask walls. The reaction was continued at 70 °C for another 3 h. Then the reactor was disassembled, and the contents of the reactor were filtered using Whatman filter paper (retention size 10 μ m). The microgel particles were extensively washed by hexane and dried under vacuum. Dry and swollen/lyophilized particles were observed using a scanning electron microscope (SEM).

C. Solute loading

Water-soluble solutes

The maximum loading level of doxorubicin, mitoxantrone, and mitomycin C into microgels was measured using a Millipore Ultrafree-MC Centrifugal Filter Device (Millipore, Co.). A microgel was suspended in Tris buffer (5 mM, pH 7.0) and 50 mL of the suspension (2 mg gel/mL buffer) were equilibrated with 3.0 mM stock solution of a drug (450 μ L) for 16 h while shaking. Shaking was performed using a KS10 orbital shaker (BEA-Enprotech Corp., Hyde Park, MA) in an environmental chamber at 37 °C. After equilibration, the microgel particles were filtered off by centrifugation (10000xg, 0.5 h) and supernatant was assayed for drug concentration. A Shimadzu Model 1600 PC spectrophotometer with a temperature-controlled quartz cuvette (path length 1 cm) was used for electronic absorption measurements. The extinction coefficients of doxorubicin ($\lambda=482$ nm) and mitoxantrone ($\lambda=614$ nm) were determined at pH 7.0 to be 12200 and 22100 $M^{-1} cm^{-1}$, respectively. The concentration of mitomycin C was assayed by HPLC using a Capcell Pak MF Ph-1 (100 x 4.6 mm I.D., particle size 5 μ m) column (Phenomenex, Torrance, CA). The HPLC was a Hewlett-Packard 1090 system with an autosampler and a variable wavelength UV detector controlled by the HPLC Chemstation software (Hewlett-Packard). Deionized water was used as the mobile phase (flow rate, 1 mL/min, injection volume, 25 μ L), and detection was carried out at 365 nm. The typical retention time of mitomycin C was 4.88 min. The drug uptake was expressed as:

$$U (\text{mmol drug/g gel}) = [(A_c - A_r) / A_c] V C_s / M_{\text{gel}}$$

where A_c and A_r are the absorbance or HPLC readings in the appropriately diluted stock solution and in the system equilibrated with microgel, respectively, $V=0.5$ ml is the total volume of the system, $C_s=3$ μ mol/mL is the concentration of the stock solution, and $M_{\text{gel}}=0.1$ mg is the microgel mass. The U values were measured in triplicate for each solute and for each gel, respectively.

Hydrophobic solutes

The loading of the hydrophobic solutes such as taxol, camptothecin, and estradiol into microgels was measured by equilibrating solute adsorbed onto steel beads with the 1 wt% suspension of microgels (pH 7.0). Stainless steel beads (1-3 mm diameter) were soaked in 10 mM solution of the solute in either acetonitrile (taxol), dimethylsulfoxide (camptothecin), or absolute ethanol (estradiol, progesterone), following by stripping off the solvent under vacuum. The beads were used in order to enhance the area of contact between the microgel suspension and taxol. The beads were separated into several fractions. One fraction was added to a polypropylene vial containing the microgel suspension (0.5 mL) and the vial was gently shaken in a horizontal position in an environmental chamber at 20 or 37 °C. Then the beads were recovered from the suspension by using a magnet. The beads were dried under vacuum and placed into an appropriate solvent (0.5 mL),

where the solute was extracted after shaking overnight. The solvent fraction was assayed for the solute concentration using HPLC. The control fraction of loaded beads was subjected to the extraction without equilibration with the microgel suspension. The solute concentrations were measured in triplicate using the HPLC system described above. The chromatography assay for taxol comprised the use of a Capcell Pak C18 UG 120 (150 x 4.6 mm I.D., particle size 3 μ m) column (Phenomenex), acetonitrile-0.1% phosphoric acid in DI water (55:45 v/v, 1.3 mL/min) as a mobile phase, and UV detection at 227 nm. The typical retention time of the taxol peak was 3.46 min. For camptothecin assay, a solution of the drug in DMSO (50 μ L) was injected onto the aforementioned C18 column and eluted at 1 mL/min flow rate and 40 °C using 0.1 M ammonium acetate (pH 5.6) and acetonitrile as mobile phase. A linear gradient of 45% to 85% acetonitrile was applied, and the UV/vis detection was carried out at 254 and 370 nm. The retention time of the camptothecin peaks was 7.5-8.5 min. The peak area was integrated and used to calculate camptothecin concentration using standard calibration curves. The HPLC assay of estradiol and progesterone solutions in ethanol was performed as described previously [15].

III. RESULTS AND DISCUSSION

SEM microgel characterization

Significant differences were observed in the shape and structure of as-prepared L92-PAA-EGDMA and F127-PAA-EGDMA particles (Fig.2). The majority of the F127-PAA-EGDMA particles were spherical and contained no observable pores. The size distribution was somewhat broad, ranging from about 5 to 100 μ m. Particle sizing performed in hexane yielded effective median diameter of 13 μ m and polydispersity of 1.4 for this type of particles.

The surface of the spherical F127-PAA-EGDMA particles contained a tree-like pattern with submicron depth. The formation of characteristic patterns in the droplets caused by competition between phase separation and chemical reaction has been observed [16]. In our case, such patterns can be due to rapid polymerization of acrylic acid, followed by phase separation. Note that while acrylic acid monomer is miscible with hydrocarbon where polymerization takes place, the resulting PAA and Pluronic-PAA are not. The phase-separated microdroplets that still contain monomer on their interface are bridged by further polymerization and cross-linking reactions. The droplet interface becomes diffuse over time and the droplets eventually fuse together. It is believed that the differences in the reaction kinetics and phase separation speed imparted by the presence of varying fractions of PPO in different Pluronics resulted in profound differences in the structure of the F127-PAA-EGDMA and L92-PAA-EGDMA particles (compare structures in Figs.2). Unlike larger and smooth F127-PAA-EGDMA particles, their more hydrophobic L92-PAA-EGDMA counterparts consisted of a sponge-like, interconnected and fused network of submicron spherical particles. The resulting "sponge agglomerates" were rough but

spherical and were on average smaller than F127-PAA-EGDMA particles (particle sizing in hexane yielded effective median diameter of 4 μm and polydispersity of 1.5 for L92-PAA-EGDMA). The observed differences in the structure can be traced to the more than 2-fold higher content of PPO in the latter systems.

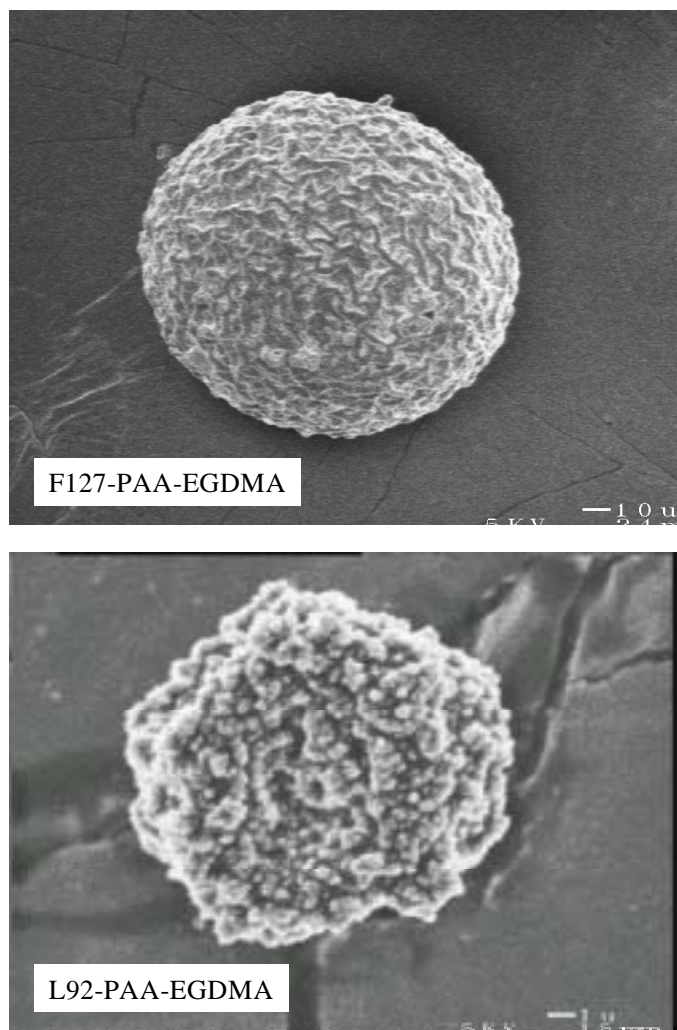


Fig.2. SEM photographs of the F127-PAA-EGDMA and L92-PAA-EGDMA “as made” particles.

We have observed previously [3] that the higher content of PPO in the template polymerization of acrylic acid on Pluronic results in dramatic increase of branching and cross-linking in Pluronic-PAA at the same degree of conversion of acrylic acid. This is because of much higher propensity of PPO (compared to PEO) for the hydrogen abstraction reactions [3]. Certainly, this as well as higher tendency of more PPO-rich Pluronics to phase separate in organic solvents, can translate into the formation of stable microdroplets that get connected at the later stages of polymerization (L92-PAA-EGDMA) as compared to formation of Pluronic-PAA copolymers in relatively large droplets, which become phase separated as a whole at later stages of the polymerization (F127-PAA-EGDMA).

Upon equilibrium swelling in water, the F127-PAA-EGDMA microgels expanded but maintained their spherical shape (Fig.3). The surface pattern developed into 1-2 μm deep “craters” that were not interconnected. We have previously reported that the bulk of the F127-PAA-EGDMA microgels SEM-imaged using freeze-fracturing technique appears to be homogeneous, devoid of any discernible pore structure [6]. In the L92-PAA-EGDMA, the gaps between interconnected micro- or nanospheres (resulting from polymerized microdroplets) widened upon swelling, yielding a well-developed porous structure with the pores on the order of 100 nm wide (Fig.3). The submicron spheres themselves did not expand significantly in water, presumably because of the high PPO content making them hydrophobic.

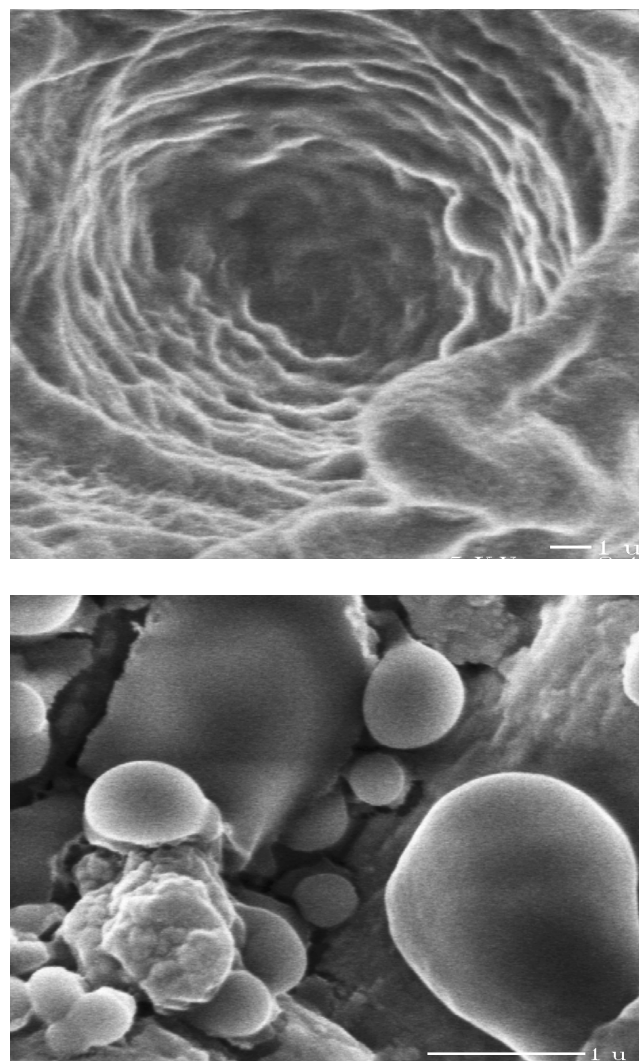


Fig.3. SEM photographs of the surface of the F127-PAA-EGDMA (upper photo) and L92-PAA-EGDMA (lower photo) microgels equilibrium-swollen at pH 7.0 and lyophilized.

Equilibrium drug uptake

The equilibrium loading of weakly basic, ionized drugs into microgels at 37 $^{\circ}\text{C}$ is shown in Fig.4. As is seen, the uptake by porous but more hydrophobic L92-PAA-EGDMA microgels

was consistently higher than for more hydrophilic F127-PAA-EGDMA microgels. This corresponded to the differences in the total ion-exchange capacity of the microgels measured by potentiometric titration to be 6.1 and 7.2 meq/g dry gel for F127-PAA-EGDMA and L92-PAA-EGDMA, respectively. The ratio of the drug loading into these two types of microgels was 0.84-0.91 of the ratio of their respective total ion-exchange capacities. Hence, the loading of the small basic drugs into the microgels is determined by the ion-exchange equilibria.

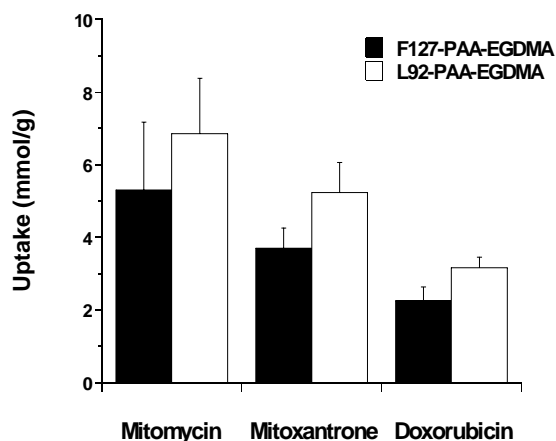


Fig.4. Equilibrium uptake of weakly basic anticancer drugs into microgels at 37 °C and pH 7.0.

General trends important for drug loading via the ion-exchange mechanism were studied using the potent chemotherapeutic drug doxorubicin (Fig.5). As the degree of carboxyl group ionization increases with pH, the ion-exchange capacity of the microgels increases, reaching about half of the maximum capacity found by titration, indicating that the loading of doxorubicin can be limited by the available free volume of the network. Notably, the pH-dependencies of the equilibrium swelling [6] and doxorubicin loading (Fig.5) coincide, demonstrating that the uptake is limited by the collapsed microgels. Clearly, such pH-sensitivity to the uptake and release of the drug provides advantage for the drug delivery, as the microgels can be loaded when swollen and unloaded by pH cycling, which is especially important for targeted oral delivery, where acidic pH is observed in the stomach and neutral pH in the intestine. The uptake of the hydrophobic drugs by our microgels is depicted in Fig.6, which shows that the more hydrophobic L92-PAA-EGDMA possesses a higher capacity for these drugs. Generally, the uptake is on the order of $\mu\text{mol/g}$ gel, which is about 1000-fold lower than in the case of the bases, which are loaded via ion-exchange equilibria. Taxol and other hydrophobic drugs are solubilized by the hydrophobic PPO domains in the microgels. The latter notion is supported by the fact that the equilibrium solubility of taxol in water is many times less than the equilibrium solubility in 1 wt% microgel suspension [6]. The

same holds for the other hydrophobic drugs under study. The solubilizing capacity of the microgels for taxol and steroid hormones is at least equal to that of.

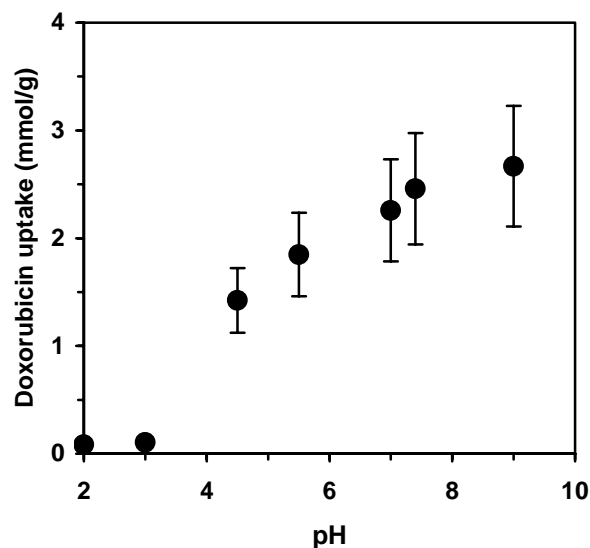


Fig.5. Equilibrium uptake of doxorubicin by F127-PAA-EGDMA microgels as a function of pH at 37 °C.

Pluronic-PAA micelles [15]. The characteristic increase in the drug loading capacity at higher temperatures (compare results at 20 and 37 °C in Fig.6) above critical aggregation temperatures provides additional evidence to the suggested mechanism of hydrophobic drug solubilization into micelle-like aggregates within the microgels via entropic interactions. The formation of the aggregates within microgel particles due to the aggregation of dangling chains of Pluronic has been demonstrated in our previous work [6]. The micelles in Pluronic-PAA solutions typically have solubilizing capacity similar to that in the Pluronic aqueous solutions [15]. A more hydrophobic L92-PAA-EGDMA showed a higher uptake for all the hydrophobic drugs studied than its more hydrophilic counterpart (Fig.6), which is consistent with the aforementioned solubilization mechanism. The least hydrophobic of the four drugs, camptothecin, showed higher uptake by the microgels (see $\text{Log}P$ data in Table 1 and Fig.6). This can be explained by the fact that the loading of the amphiphilic solute can occur both via the solubilization into hydrophobic PPO cores of the aggregates and entrapment into more hydrophilic core-swollen gel interface [12]. The ability of the microgels to effectively load and hold hydrophobic drugs, combined with high loading of basic drugs and mucoadhesive properties provides unusual possibilities for anticancer therapies by oral delivery.

IV. CONCLUSIONS

The study dealt with microgels that consist of loosely cross-linked poly(acrylic acid) onto which Pluronic F127 (formula $\text{EO}_{99}\text{PO}_{67}\text{EO}_{99}$) or L92 (formula $\text{EO}_8\text{PO}_{52}\text{EO}_8$) segments are

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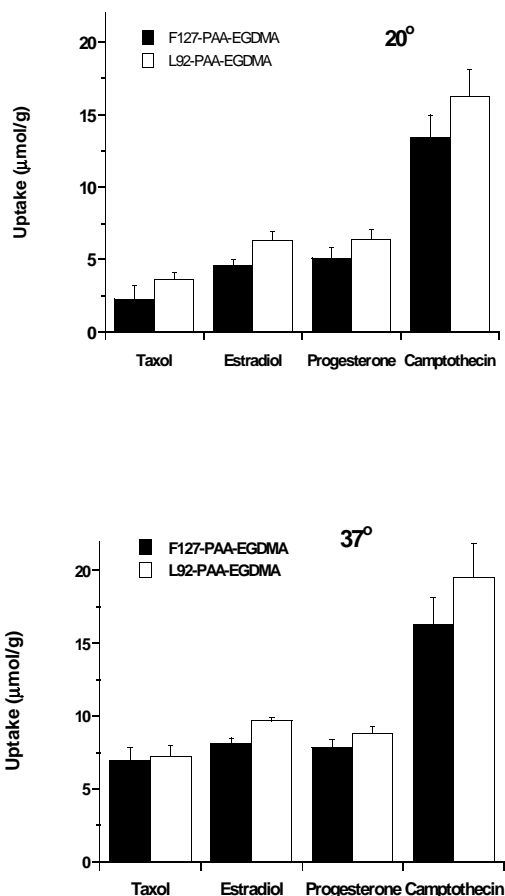


Fig.6. Equilibrium uptake of hydrophobic drugs by microgels at pH 7.0 at 20 and 37 °C.

grafted. The microgels based on more hydrophobic Pluronic L92 exhibited highly porous structure, while the F127-PAA-EGDMA microgels were generally larger and showed smooth, homogeneous structure and lower ion-exchange capacity. The differences in the microgel structure account for the differences in the capacity of the microgels to absorb drugs, either weakly basic or hydrophobic. Further collaboration between MIT and Singapore will concentrate on mechanistic aspects of the drug-microgel interactions and possibly explore protein-microgel interactions. It has been shown that Pluronic-PAA copolymers can stabilize proteins in aqueous solutions because of micellization and polyelectrolyte properties [17]. The novel microgels should add to the arsenal of the pharmaceutical technology because of capacity to change behavior in response to the environmental stimulæ, ability to hold both hydrophobic and ionic drugs and benign, non-irritating nature.

V. ACKNOWLEDGMENT

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Lev Bromberg received his M.Sc. in Chemical Engineering ('82) and Ph.D. in Macromolecular Chemistry ('88) from Moscow State University and conducted postdoctoral studies at the Weizmann Institute of Science and Massachusetts Institute of Technology. He served as a senior and principal scientist at Gel Sciences, Inc., Abbott Laboratories, Periodontix, Inc., and Cabot Corporation. He authored over 170 publications and patents and currently is a research scientist at MIT. His major field of study is intelligent polymers and gels for biomedical and hi-tech applications.

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