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Local Drug Delivery to Bladder Using Technology Innovations

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Pharmacologic management of diseases typically affecting the bladder frequently require drug administration by way of a catheter into the bladder. Drug delivery by this route, referred to as intravesical delivery, allows drug delivery at the desired site with reduced systemic side effects compared with oral delivery systems [1]. These characteristics ensure maximal therapeutic benefit to occur at the desired site and provide genuine benefits for patients who have morbid adverse effects from oral administration. Bladder cancer, cystitis, and neurogenic bladder are the common conditions managed by this form of drug administration.

Intravesical delivery of bacillus Calmette-Guérin (BCG) is considered first-line treatment for superficial bladder cancer, and in most patients, the complete response rate from BCG is slightly higher for carcinoma in situ than for papillary tumors [2]. The intravesical route is not the predominant route for other ailments of the bladder, but nearly half of overactive bladder patients cannot tolerate oral administration of anticholinergic agents because of troublesome side effects such as excessive dry mouth, constipation, or blurred vision [3]. The systemic side effects of the most widely used anticholinergic (oxybutynin) are believed to be caused by the high plasma level of its active metabolite, *N*-desethyl-oxybutynin [4]. Delivery of oxybutynin directly into the bladder in such patients can bring about a local anticholinergic effect, with improved drug tolerability and patient compliance [5].

Most of the newer macromolecular drugs have poor bioavailability when administered orally and often fail to induce a clinical response. Drug delivery by the intravesical route can overcome intrinsic shortcomings of oral therapy such as first-pass metabolism or other drug- or formulation-specific vagaries in absorption, metabolism, and renal excretion. For example, the oral route requires thrice-daily administration for 6 months of the cytoprotective drug misoprostol to achieve therapeutic benefit in interstitial cystitis (IC) patients [6]. Low amounts of drug excreted in the urine following oral administration are probably responsible for the prolonged regimen required for therapeutic benefit. The pharmacokinetics of drugs instilled into the bladder have recently been reviewed [7]. The need for a higher concentration of drug inside the bladder can be solved by instillation, and an improvement in efficacy from local delivery can be made by applying the technologic innovations covered in this article.

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History of intravesical drug delivery

The drastic reduction in the incidence of systemic side effects by the intravesical route has allowed the use of very toxic agents. The first human application of drug delivery using a urethral catheter can be traced back to more than a century when Herring [8] tried instilling silver nitrate for the treatment of superficial bladder cancer. Nearly 60 years later in 1967, dimethyl sulfoxide (DMSO) was instilled for treating refractory cases of IC [9,10]. DMSO was approved by the US Food and Drug Administration in 1978 as a 50% solution with primary indication for treating IC [11]. Another member from the list of toxic agents instilled into the bladder is BCG, indicated in the treatment of refractory bladder cancer [12]. Treatment with BCG delays tumor progression and significantly decreases the need for subsequent cystectomy, with improved overall survival rates [13]. BCG triggers a variety of local immune responses including induction of proliferator-activated receptor γ (PPARγ) that appear to correlate with antitumor activity [14]. A member of the nuclear receptor superfamily of ligand-activated transcription factors, PPARγ is expressed in normal urothelium and is known to be involved in cell growth, differentiation, and inflammatory processes [15]. The immunomodulatory activity of BCG also prompted its evaluation for immunotherapy of IC, and BCG produced a favorable outcome in refractory IC patients [16,17]. The ability of prostaglandins to cause smooth muscle contraction was exploited for treating detrusor underactivity or underactive bladder using intravesical therapy of prostaglandin E_2 [18].

Barriers to urothelium and intravesical therapy

Drugs instilled into the bladder have to cross a watertight barrier between blood and urine formed by the bladder lining to elicit any effect. The cell layer lining the interior of the bladder is called urothelium or transistional cell epithelium and forms a barrier that is equally effective in blocking the entry of urine contents and instilled drugs [19,20]. Examination of umbrella cells lying at the luminal surface of urothelium using electron microscopy showed that hexagonally packed uroplakins cover most of the apical side of umbrella cells [21]. The six subunits of each particle are joined together to form a complete hexagonal ring, with lipids contained in its central cavity. The low permeability–barrier urothelium is believed to crop up from the peculiar protein array and the tight junctions between umbrella cells [22,23]. The absorption of drug is further restricted by the glycosaminoglycan (GAG) layer on the surface of umbrella cells [24].

In hypothetical terms, the barrier of urothelium may prove to be tougher than the blood-brain barrier because the former is made up of generally stronger epithelial cells and the latter by generally weaker endothelial cells. Weekly drug instillation into the bladder demonstrated that drug concentration in bladder tissue is linearly dependent on the concentration of drug in urine. The linear relationship suggests that passive diffusion is the only mode of membrane transport available for the intravesical route of drug administration [25]. Because concentration gradient is the sole driving force available for drug absorption, it is logical to expect an increase in drug transport with improvement in the concentration gradient. Complete bladder emptying just before dose administration and restricted fluid intake can be used to mitigate the influence of the kidney on intravesical therapy [26]. This method reduces the immediate dilution of drug concentration by residual urine in the bladder and diminishes the steady dilution by constant urine production during the time period for which instillation is still in the bladder. Increased concentration in urine can improve the efficacy of a drug acting in the bladder without significant enhancement in toxicity [26]. Using such techniques, enhanced penetration of mitomycin C across bladder urothelium in a recent phase III trial nearly doubled the recurrence-free rate in patients who had superficial bladder cancer [27].

Intravesical treatment of interstitial cystitis

Little is known about the pathogenesis of IC, which leaves most treatments including intravesical treatments of IC to be symptomatic. The most consistent finding in IC patients, however, involves dysfunction of the superficial layer of extracellular matrix (GAG layer) and localization of a high number of activated mast cells in the bladder [28,29]. A superficial layer of GAG is covalently attached to the membrane proteins of umbrella cells residing in the topmost layer of urothelium cells of the bladder [22]. Hyaluronic acid is an important component in the urothelium, and sodium hyaluronate has been instilled in IC patients for possible replenishment of bladder GAG in the treatment of IC [30]. Hyaluronic acid inhibits leukocyte migration, aggregation,

and adherence of immune complexes to polymorphonuclear cells. Another GAG analog effective in approximately 50% of IC patients following its instillation is heparin [31]. A recent study showed that intravesically administered fluorescent-labeled chondroitin sulfate in mouse bladder coated the damaged bladder surface, explaining its clinical efficacy [32].

Intravesical treatment of particularly severe chronic IC requires addressing the significant upregulation of afferents in the bladder [33]. C-fiber afferents are considered to be responsible for the aberrant micturition reflex in IC. These C-fiber afferents are believed to be silent under normal conditions but are activated after bladder irritation and spinal cord injury [34]. A viable treatment approach that is gaining ground is the downregulation of sensory nerves by treating them with neurotoxin such as capsaicin or resiniferatoxin [33]. Administration of vanilloids by the intravesical route restricts the potent action of vanilloids to the afferent fibers in the bladder wall, thereby avoiding possible systemic neurotoxicity [35]. The hydrophobic nature of these neurotoxins, however, necessitates the use of ethanol as a cosolvent and saline as the vehicle for instillation into the bladder. Ethanol is well known to induce inflammation in different tissues [36]. Recent studies have demonstrated the superiority of nonalcoholic solvents for vanilloids over alcohol solvents [37,38]. Liposomes have also been used to try to overcome the aqueous insolubility of vanilloids.

Instillation of liposomes

The approach of intravesical drug delivery is amenable to the modulation of release and absorption characteristics of the instilled drugs through its coupling to carrier particles such as microspheres, nanoparticles, liposomes, and so forth. Liposomes were first studied in England in 1961 by Bangham [39] and have since become a versatile tool of study in biology, biochemistry, and medicine. Liposomes are artificial spherical vesicles consisting of an aqueous core enclosed in one or more phospholipid layers. They have been used as intravesical drug carriers after being loaded with a great variety of molecules such as small drug molecules, proteins, nucleotides, and even plasmids [40–43]. The flexibility of their compositions makes liposomes a versatile drug delivery vehicle. The use of multilamellar liposomes proved favorable in cell culture studies, and the antiproliferative capacity of interferon-α in a resistant bladder cancer cell line was improved by using liposomes as a delivery vehicle [44]. Instillation of liposome-encapsulated radiolabeled interferon-α or radiolabeled liposomes into mouse bladder was able to achieve localized therapy with negligible penetration to other organs [45]. Previously, liposomes have proven to improve the aqueous solubility of hydrophobic drugs such as taxol and amphotericin [46]. A recent study reported from the authors' laboratory used liposomes as a vehicle for capsaicin and evaluated their potential as a vehicle for intravesical delivery in rats [38]. Efficacy of a new delivery system for capsaicin was evaluated by measuring micturition reflex in normal rats under urethane anesthesia (Fig. 1).

Awake micturition in such rats with an intact neuraxis is dependent on a spinobulbospinal reflex activated by A delta–fiber bladder afferents, and facilitatory action of capsaicin-sensitive nerves on micturition threshold is more evident in anesthetized rats than awake rats because capsaicin-resistant bladder afferents are more sensitive to the depressant action of urethane than the capsaicin-sensitive afferents [47]. The cystometrogram (CMG) tracings shown in Fig. 2 illustrate that liposomes were able to deliver capsaicin with efficacy similar to ethanolic saline. Tissue histology and morphology studies, however, revealed that toxicity to the bladder was drastically reduced [38]. As reported previously, liposomes can form a film on cell surfaces and have been tested as possible therapeutic agents to promote wound healing [48]. Such reports prompted the evaluation of liposomes devoid of any drug in a rat model of bladder hyperactivity. Liposomes alone were able to partially reverse the high bladder frequency induced by protamine sulfate/potassium chloride (Fig. 3) [49]. These observations suggest that liposomes might enhance the barrier properties of a dysfunctional urothelium and increase resistance to irritant penetration. Liposomes are prepared from the phospholipids that are the major component of cell membranes. Presumably, instillation of liposomes adds to the permeability barrier of urothelium by their adherence to the injured surface (Fig. 4).

Overcoming barriers to intravescial therapy

Inadequate intravesical drug delivery often happens due to the poor penetration of drug through the urothelium. In addition to concentration gradient, factors that can influence transvesical (across urothelium) transport are the molecular weight of the drug and the pH of

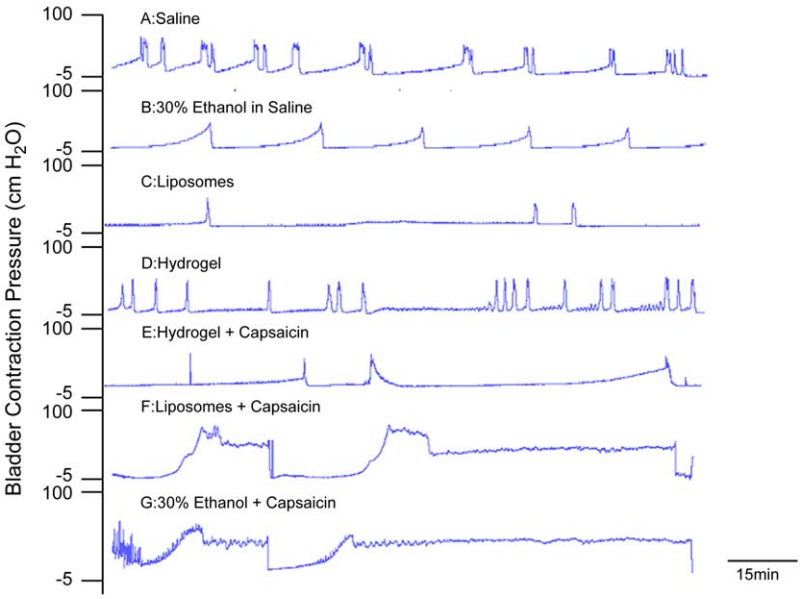

Fig. 1. Representative tracings of CMG after instillation of normal saline showing periodic micturition events under urethane anesthesia. Tracing B and tracing C represent 30% ethanol-treated rats and liposome-treated rats, respectively, in absence of capsaicin, revealing the dissimilar effects of ethanol and liposomes on bladder afferents by decrease in bladder contraction frequency. Tracing D and tracing E are hydrogel-treated rats in the absence of and in the presence of capsaicin, respectively, revealing a decrease in bladder contraction frequency in the presence of capsaicin. Tracing F and tracing G are from rats treated with liposomes and 30% ethanol, respectively, in presence of capsaicin, showing complete blockade of micturition reflex in both cases. A raised plateau of bladder contraction pressure reflects urinary retention.

the instilled solution [50]. Unsuccessful drug delivery using conventional formulations and a resistant drug target are the two main reasons attributed for the undesirable outcomes from intravesical drug delivery. Therapy by the intravesical route can be improved by helping drugs to cross the permeability barrier of urothelium by physical alteration (iontophoresis and electroporation) and by chemical alteration (DMSO, saponin).

Physical approaches

There is a plethora of reports on enhancing transdermal drug transport with the use of electromotive drug administration (EMDA) or iontophoresis [51,52]. In animal studies, very low voltages of electric current have been used for EMDA, which is a technique that drives drugs (mitomycin C, oxybutynin, and bethanechol) and dyes deep into the muscular layers of the

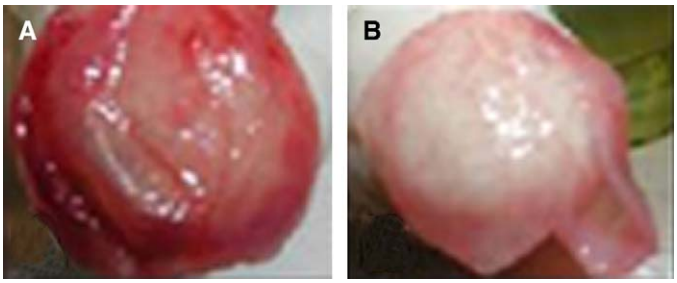

Fig. 2. Bladder morphology pictures after instillation of capsaicin in saline with 30% ethanol (*A*) and in liposomes (*B*). Redness in panel *A* indicates inflammation. Note the absence of redness in panel *B*.

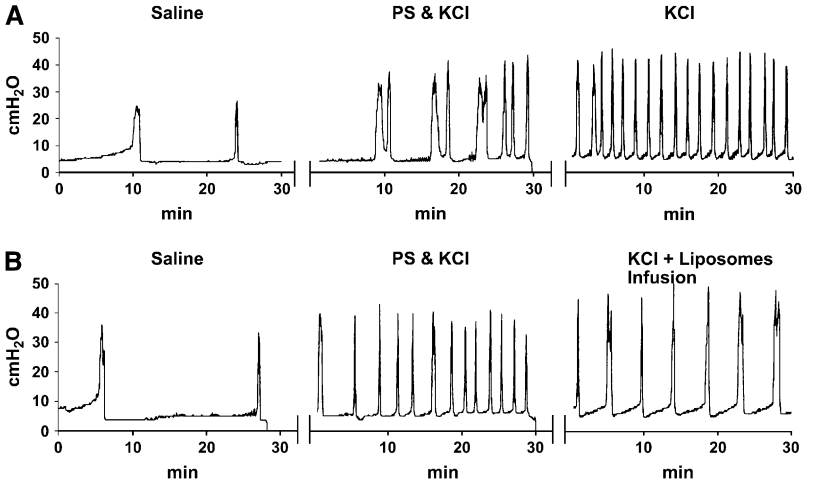

Fig. 3. Effect of liposomes in a bladder injury model induced by protamine sulfate (PS) and irritated by potassium chloride (KCl). (*A*) Liposomes were coadministered with KCl as shown by the CMG tracing in the bottom panel to reduce the bladder contraction frequency. (*B*) Bottom panel shows the CMG of the untreated rat bladder, indicating bladder hyperactivity.

bladder wall. Anesthesia suitable for transurethral resection of bladder tumors, bladder neck incision, and hydrodistension of the bladder has been accomplished clinically after EMDA of local anesthetics by applying an electric current in the range of 20 mA for a few minutes [53,54]. A recent clinical trial combined BCG treatment with increased bladder uptake of mitomycin C through EMDA to improve the response rate in 212 patients who had stage pT1 bladder cancer [55]. In addition to EMDA, the permeability of mitomycin across urothelium was increased by BCG-induced inflammation in the bladder [55]. In most patients, EMDA causes only minor local irritation with no systemic side effects, but a recent case report of transient ischemic attack was reported from Germany following EMDA in elderly men suffering from cystitis [56]. The investigators suspected epinephrine to be cause of ischemic attack after intravesical EMDA. Electroporation is another approach that uses an electrical field to increase tissue permeability. It differs from iontophoresis in that it uses comparatively higher voltage for improving intravesical delivery of drugs in the treatment of bladder carcinoma [57]. In a recent study, the efficacy of intravesically administered mitomycin C on small superficial tumors was enhanced by using local microwave-induced hyperthermia [58].

Chemical approaches

It has been reported that absorption of chemotherapeutic drugs including paclitaxel and pirarubicin can be enhanced by DMSO instillation [59,60]. Sasaki and colleagues [61] reported that intravesical instillation of saponin before administration of the anticancer drug 4′-O-tetrahydropyranyldoxorubicin (THP) can cause

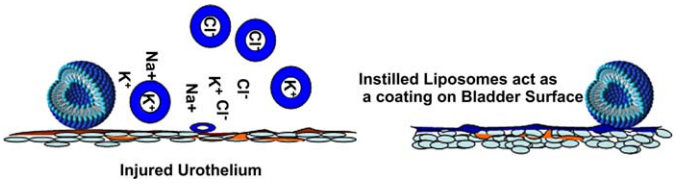

Fig. 4. Illustration of the underlying protective effects of liposomes on the bladder surface injured by protamine and irritated by potassium chloride (*left*). Instilled liposomes form a protective coating on the injured bladder surface (*right*).

vacuolization and swelling of superficial cells. The concentration of THP in bladder tissue was significantly higher than that of untreated animals, but in plasma, no difference was revealed [61,62].

Currently, treatment of severe overactive bladder requires cystoscopic-guided injections of botulinum toxin type A at 20 to 30 different sites of detrusor in the bladder. Botulinum toxin type A provides its long-lasting effect by blocking the release of acetylcholine from nerve endings to impair involuntary detrusor contractions [63]. Instillation of this high molecular weight protein toxin requires improvement in permeability for its absorption. The absorption of this dangerous toxin has to be localized because any systemic absorption can prove fatal; this must be taken into consideration in the development of any future delivery techniques. Pretreatment of urothelium with protamine sulfate to improve the permeability for botulinum toxin type A has been attempted in rats [64,65]. The cationic nature of protamine sulfate allows a charge interaction with the anionically charged GAG layer, leading to a slight increase in permeability of the urothelium [66].

Recently, certain peptides called "cell penetrating peptides" or "protein transduction domains" have been shown to possess the ability to translocate large macromolecular drugs across the blood-brain barrier and membranes of other cells [67]. These peptides, however, lack the ability to be cell selective and are therefore a poor choice for systemic drug targeting [68]. The authors examined the effect of using the short-length TransActivator of Transcription (TAT) peptide derived from HIV for intravesical administration of large macromolecular drugs such as peptide nucleic acid (PNA). Antisense agents that inhibit genes at the mRNA level are attractive tools for genomewide studies and drug target validation, and PNAs have been used for their antisense effect in various studies because they form stable duplexes with the target mRNA and arrest translation of proteins [69]. PNA has superior binding properties and higher stability in biologic media such as urine over a wide pH range compared with traditional oligonucleotides and ribozymes [70]. The eleven–amino acid TAT peptide was coupled to 18mer antisense PNA by Fmoc chemistry, and similar chemistry was used to tag a fluorescent rhodamine probe. Translocation across rat urothelium was visualized by confocal microscopy of the red fluorescence of rhodamine in bladder sections [71].

Sustained drug delivery

Conventional formulations are maintained in the bladder for only short periods—typically less than 2 hours—and often, patients do not completely respond or the response is highly variable among patients. The drug exposure at the urothelium rarely lasts beyond the first voiding of urine after instillation of conventional formulations. Sustained intravesical delivery of drugs can ensure continuous presence of drug in the bladder without the need for intermittent catheterization, and drug concentration in the bladder can be constant without any peaks and valleys. It is also plausible to expect an increase in efficacy with the increased duration of direct contact between the drug and the abnormal urothelium [45]. Attempts to overcome this inherent drawback of intravesical instillation have been reported from various laboratories.

A simple and sensible approach for sustained intravesical delivery is prolonged infusion into the bladder. This technique has often been applied for achieving slow and sustained release of drugs inside the bladder. Prolonged instillation of resiniferatoxin was recently demonstrated as a feasible procedure for treating neurogenic bladder [72]. Resiniferatoxin was infused through a sovrapubic 5F monopigtail catheter for 10 days at the flow rate of 25 μL/h with the help of an infusion pump. Patients were evaluated 30 days after the end of the infusion and after 3 months. A 30% decrease in frequency and a threefold reduction of nocturia with significant reduction of symptoms of pelvic pain for at least 6 months after the end of the infusion were observed. Similar approaches have previously been applied for local therapy of prostaglandins in the treatment of cyclophosphamide-induced cystitis in patients [73]. Cystitis is a major complication from the high-dose cyclophosphamide regimen used against allogeneic or autologous bone marrow transplantation. A 100-mL irrigation of 5 μg/mL of prostaglandin E_2 into the bladder for 3 hours completely freed a 4-year-old patient from all symptoms within 24 hours [74]. Intravescial infusion of carboprost had a success rate of over 60% in patients who had hemorrhagic cystitis after marrow transplantation [75]. Response was achieved by infusing carboprost at 2 μg/mL for an hour four times a day with a fivefold dose escalation every 24 hours.

Forming a drug depot inside the bladder appears to be an attractive option versus prolonged infusion. Aqueous solutions of poly (ethylene glycol-b-[DL-lactic acid-co-glycolic acid]-

b-ethylene glycol) (PEG-PLGA-PEG) triblock copolymers form a free-flowing solution at room temperature and become a viscous gel at body temperature (37°C) [76]. Its formulation does not require organic solvents, and products from its bioerosion of the biocompatible polymer are nontoxic polyethylene glycol, glycolic acid, and lactic acid [77]. Such a thermosensitive hydrogel formed by PEG-PLGA-PEG has been used for in situ gel formation for a depot of hydrophobic and hydrophilic drugs following subcutaneous administration in rats [78]. The triblock copolymer was used for sustaining the residence time of hydrophobic drugs in rat bladder after its instillation at room temperature. The kinetics of drug excretion was studied by fluorescence measurement of urine after instilling fluorescein isothiocyanate–loaded hydrogel. The increased urine concentration over a period of time implies increased penetration into the bladder tissue [25]. The therapeutic benefit of sustained delivery afforded by the thermosensitive hydrogel was demonstrated by delivering misoprostol, an anti-inflammatory drug. It was able to protect the bladder against cyclophosphamide-induced cystitis [79].

Bioadhesion

The presence of a mucin–glycocalyx domain in urotheliun can be used for prolonging the residence time of drugs by exploiting the approach of bioadhesion [80]. Bioadhesion or mucoadhesion defines the interaction between a biologic surface such as bladder mucosa (urothelium) and the polymer. The term *mucoadhesion* is used specifically when adhesion involves mucous coating and an adhesive polymeric device, whereas epithelial cell–specific bioadhesion is termed *cytoadhesion*. Adhesion with mucin and mucoadhesive polymers is usually based on molecular attractive and repulsive forces; in contrast, adhesion to cell surfaces involves highly specific receptor-mediated interactions.

The process is said to occur through the following steps:

1. Initial physical interaction or mutual wetting between the polymer and the surface.
2. Interpenetration of the polymer and the components of the GAG layer on the urothelium.
3. Electrostatic interactions, hydrogen-bond formation, and van der Waals forces between the polymer and biologic surface.

Mucoadhesive materials are generally hydrophilic polymers that swell significantly in contact with water and eventually undergo complete dissolution. Also called wet adhesives, these hydrophilic polymers adhere to the mucosal surface after wetting and can be categorized into the following classes: anionic polymers such as sodium carboxymethyl cellulose and sodium alginate, cationic polymers such as chitosan and dextrans, nonionic polymers such as polyvinylpyrollidone, and cellulose derivatives such as hydroxypropylmethyl cellulose. The bioadhesive strength of a polymer increases with its molecular weight because the extent of interpenetration and molecular entanglement seems to be determined by the length of the polymer chain. Polyethylene glycol can be used as an adhesion promoter between polymer and GAG by diffusion of the polyethylene glycol chains into the polymeric networks of GAG and the polymer [81].

The coupling of bioadhesion characteristics to the carrier particles such as microspheres can lend additional advantages to these delivery systems, such as efficient absorption and enhanced bioavailability of the drugs due to increased surface area for a given volume of drug and a much more intimate contact with the mucus layer. For example, chitosan microspheres were able to increase the ocular residence time and decrease the frequent administration of acyclovir by way of ophthalmic route [82]. Similar expectations have motivated the use of bioadhesives for improving intravesical drug delivery [83]. The application of bioadhesives in intravesical drug delivery should be able to fulfill three main criteria: readily adhere after instillation to the urothelium; be unobtrusive to the micturition function; and be retained in place for at least several hours. Chitosan and polycarbophil retain good adhesion after full hydration, and their ability to increase adhesion of a hydrophilic drug to urothelium was evaluated using isolated porcine urinary bladder [84]. Drug distribution in to the bladder wall was determined by sectioning the frozen bladder and extracting the drug from tissue slices for analysis [84].

The first generation of mucoadhesive polymers lacked specificity, such as the suspensions of algin salts that simply swelled and formed an adherent viscous layer on contact with the mucosa. In contrast to classic mucoadhesion, which relies on nonspecific interpenetration of polymer chains and mucus, the anchoring of plant lectins, bacterial adhesions, and antibodies on the surface of the microspheres can increase the therapeutic

benefit. Any ligand with a high binding affinity for mucin can be covalently linked to the microspheres and expected to influence the binding of microspheres to the mucus surface. The lectin–sugar interaction may represent a step forward toward drug delivery across mucosal surfaces. Lectins are proteins of nonimmune origin that bind to carbohydrates specifically and noncovalently [85]. The epithelial lining of most visceral organs is covered with a mucous layer, and lectins attached to a drug delivery system can interact with the highly glycosylated proteins making up the mucin molecules of the mucus. In addition to lectin-mediated drug delivery systems, the carbohydrate specificity of mucus is used by microorganisms to adhere to the gut or to bladder mucosa. Bacteria use lectin–sugar interactions to adhere to the sterile surface of the bladder and cause urinary tract infection, but in the gut, the same bacterial species constitutes the normal microflora.

Postoperative chemotherapy in mice was successful with bioadhesive carriers based on polymers such as algin, chitosan, and fibrinogen [86]. Mitomycin C–loaded alginate and chitosan bioadhsive carriers were evaluated in the murine bladder cancer model [86]. Intravesical administration of poly (methylidene malonate-2.1.2) bioadhesive microspheres achieved controlled release of the paclitaxel at the urothelium/urine interface of mouse bladder [83]. Spherical 5-μm thick microspheres adhered to the mouse urothelium for up to 2 days and mice that had bladder cancer survived for a significantly longer time following instillation of bioadhesive microspheres loaded with 5% w/w paclitaxel compared with similar doses of the conventional paclitaxel formulation.

Daily micturition events (12–15 events) could not flush out the microspheres from mouse bladder [87]. In another study employing a similar approach, a fibrinogen-based bioadhesive loaded with 5-fluorouracil was used for preventing tumor recurrence in the resected tumor beds of mouse bladder [88]. Storage-Phosphor autoradiography was used to quantify drug retention in the bladder after administration, which showed more than a twofold increase for the bioadhesive drug over drug solution alone.

Temporal and spatial monitoring of instilled microparticles is possible with MRI [89]. Polymeric microparticles were encapsulated with MRI contrast agent gadolinium diethylenetriamine pentaacetic acid for measuring T1 relaxation rate of particles until 5 days after instillation. Retention of doxorubin in dog bladder was increased by instilling microparticles called magnetic targeted carriers and composed of metallic iron and doxorubicin adsorbed onto activated carbon. An externally applied magnetic field was used to achieve extended retention of magnetic targeted carriers following instillation [90]. Another gelatin-based delivery system released drugs for 12 days in the rabbit bladder [91].

Intravesical delivery of oxybutynin has proved suitable for patients who have overactive bladder suffering from side effects of the metabolite *N*-desethyl-oxybutynin following oral administration [5]. The local delivery of oxybutynin into bladder by employing the approach of mucoadhesion achieved partial clinical success in a case study involving six patients [4,92]. The mucoadhesive solution of oxybutynin was prepared by adding hydroxypropylcellulose to the oxybutynin chloride solution (5% w/w) that was instilled twice daily at a dose of 0.5 mg/mL using the catheter used for bladder emptying [92]. CMG was performed on patients before starting the treatment and at 1 week and 3 years after the first instillation of oxybutynin. A significant increase in bladder capacity was observed in four of the six patients. This intravesical oxybutynin therapy is thought to depend on three mechanisms that prevent or improve urge incontinence: the direct effect on bladder muscle, the topical anesthetic effect, and the indirect effect of absorbed oxybutynin and its metabolites [4].

Future perspectives

Recent years have seen an increased interest in nanotechnology, a new technique that involves the creation and manipulation of materials at nanoscale levels to create products that exhibit novel properties. For example, rapid-release, paclitaxel-loaded, gelatin nanoparticles with a particle size ranging from 600 to 1000 nm were recently designed for intravesical bladder cancer therapy [93]. The paclitaxel nanoparticles showed significant activity against human bladder cancer cells and resulted in higher tissue concentrations compared with existing vehicles. Drug exposure in the bladder can be successfully increased using the approach of bioadesion. Before bioadhesion caught the fancy of drug-delivery scientists, this powerful approach had been exploited by *Escherichia coli* for adhesion to the bladder mucosa. Urinary tract infections are

initiated by adhesion of uropathogenic *E coli* to uroplakin receptors in the uroepithelium by way of the FimH adhesin located at the tips of type 1 pili. Perhaps we can learn from *E coli* and design a drug-delivery system that uses bacterial adhesion factors to increase adhesion to epithelial surfaces.

Summary

Intravesical drug delivery is a highly promising alternative when disease has become refractory to treatment with drugs administered from other routes. The recent advances covered in this article have been successful in overcoming the drawbacks of this route in preclinical studies (Fig. 5). The therapeutic benefit from newer therapeutic entities such as botulinum toxin, cannabinoids, and vanilloids against overactive bladder and IC can be augmented by using newer delivery systems. The new approach of liposomes holds tremendous promise as a therapy and a drug delivery platform for drugs administered intravesically. The authors look forward to the day when liposomes can be tested in clinical trials to help patients who have painful bladder syndrome and to improve bladder drug delivery.

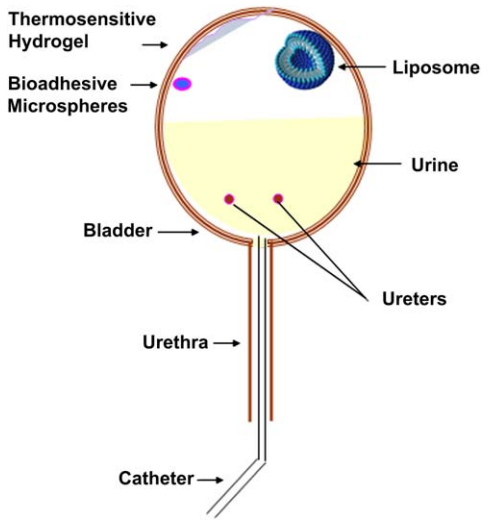

Fig. 5. Illustration of the newer drug-delivery system instilled into the bladder, based on innovative technology. Liposomes and microspheres with bioadhesive coating allow them to adhere to the bladder surface. The thermosensitive hydrogel forms a viscous semisolid gel inside the bladder after being instilled as a fluid.

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