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Review Article

INTRAVESICAL DRUG DELIVERY SYSTEM FOR BLADDER: AN OVERVIEW

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ABSTRACT

The current aspect of any novel drug delivery system is to deliver a drug to specific site for better pharmacological effect as well as better control over the disease condition. The site specificity which demands more attention is brain, spinal and other localised sites like, bladder. The targeted drug delivery to cancerous cell of different organs of the body has reached to its molecular level. The attempt has been made in this review to give an insight into the treatment of genitourinary condition. These conditions require very large dose of medication due to poor absorption and loss of drug due to metabolism. The local effect of drug can be achieved using intravesicular drug delivery system. The physiology of the biological barriers, i.e. urothelium of bladder poses major challenge in the development of intravesicular drug delivery system. This review is prepared with an intension to address all these issue in detail and approaches to overcome barrier for drug delivery to bladder. The role of nanotechnology leads to minimal invasive procedure for bladder, prostate and other surrounding organs for more precise drug delivery has also been discussed in detail.

Keywords: Bioadhesion, Gene therapy, Nanoparticles, Sustained release, Viral vectors.

INTRODUCTION

Traditionally, many genitourinary conditions have been treated with medications administered orally, which requires larger doses, with the concomitant side effects. Systemically therapy for the bladder diseases often fails because only a small fraction of administered drugs reaches the desired site due to poor absorption or due to losses from metabolism. Intravesical drug delivery system (IDD) can prevent losses from first pass metabolism and allows the therapeutic effect of a drug to be localized at the desirable site with minimal systemic side effects.[1] However, IDD has to overcome few challenges and most prominent among them is the low residence time of a drug in the bladder that requires frequent instillation of drug. Conventional vehicles used for the intravesical delivery fail to provide a sustained exposure of drug inside the bladder, which rarely lasts beyond the first voiding of urine after instillation. An important obstacle in the success of IDD arises from the low permeability of transitional epithelium of the bladder also known as urothelium. However, this tough barrier against IDD is somewhat compromised in the disease condition and even then passive diffusion is the only mode of membrane transport possible across urothelium. IDD used in treatment of overactive bladder, intestitial cystitis, bladder cancer, detrusor hyperreflexia etc. The kidney, bladder, and prostate are easily accessible for minimally invasive interventions. Nanoparticles, microparticles, or small-scale implants can simply be deployed and retrieved using percutaneous or endoscopic systems in outpatient settings with minimal patient discomfort and maximal therapeutic benefit.

FACTORS AFFECTING DRUG PERMEABILITY IN BLADDER

Bladder Permeability Barrier

The water tight barrier between blood and urine formed by urothelium represents the toughest barrier to drug delivery known to man. The bladder permeability barrier (BPB) for IDD appears complementary to the Blood Brain Barrier BBB for drug delivery into brain. But, BPB is tougher than the BBB because BPB is

made up of epithelial cells while BBB is by a unique phenotype of endothelial cells lining the blood vessels of the brain. The main site of BPB is located at the superficial cells in transitional epithelium of bladder called umbrella cells named because of their characteristic shape.[2,3] Nearly 90% of the apical surface of umbrella cells is covered by rigid plaques that are composed of four major uroplakins, UPIa (27 kDa), UPIb (28 kDa), UPII (15 kDa), and UPIII (47 kDa).[4] The crystalline lattice structure of uroplakin interacts with specialized lipids of the apical membrane of umbrella cells to aid in the BPB. The permeability of urothelium is further augmented by the mucin layer composed of glycosaminoglycans (GAG) present on the surface of umbrella cells. The hydrophilic nature of the GAG layer forms a thin sheet of stationary aqueous layer on umbrella cells. The GAG layer acts as a major permeability barrier by physically blocking the instilled drug molecules from reaching the underlying tight junctions and cell membranes. Moreover, the apical membrane of umbrella cells (AUM) beneath the GAG layer further reinforces the BPB by its exceptionally low permeability[5-8]. The impermeability of urothelium is frequently exploited for instilling potentially toxic agents into the bladder for achieving localized pharmacological effect.

Bladder Urothelium: Permeability and Drug Diffusion

The main function of the urinary bladder is to store urine while maintaining the composition of urine similar to that produced by the kidneys. The urothelium allows the urinary bladder to minimise alterations in the composition of the urine. Movement across the urothelial cells occurs via two parallel pathways: the ‘‘transcellular pathway’’ (through the cells) and the ‘‘paracellular pathway’’ (through the tight junctions and lateral intercellular spaces)[9]. Tight junctions and cell membranes should be impermeable to urine or blood components, as well as to any drug contained in both compartments. Modifications of either cellular or tight junction permeability alter the efficacy of the barrier properties of the urothelium.

The apical membrane of the bladder urothelium contributes 80% of the resistance to water flow of the epithelium as well as >95% of the resistance to fluxes of urea, ammonia, and protons. If there is appreciable permeation of these substances through the tight junctions, then the apical membrane provides an even higher proportion of the resistance across the epithelium[10].

The “Blood–Urine Barrier”

An essential requirement for normal bladder function is that urine components should not jeopardise the barrier properties of the bladder[11]. Changes within the physiologic range for urine pH or calcium or urea concentrations do not alter the barrier function of the urothelium, as determined from measurements of the transepithelial resistance. Consequently, acid pH, low Ca++, or high urea increases the ion permeability of the urothelium[12]. In experimental studies, urine seems to be able to influence the volume–pressure response of the bladder; bladder capacity can be reduced by administering intravesical solutions of isotonic KCl, hypertonic NaCl, and pH 5. It can be increased by administration of hypotonic NaCl, isotonic mannitol, and pH 8. Furthermore, extracellular K+ and hyperosmolality directly depolarise smooth muscle cells and generate increased activity of the detrusor, whereas hypo-osmolality produces opposite changes[13].

STRATEGIES FOR IMPROVED INTRAVESICAL THERAPY

1) Improving the Permeability

Therapy by intravesical route can be further improved by helping drugs cross the permeability barrier of urothelium by physical (such as iontophoresis) and chemical (such as DMSO) enhancement methods.

a) Physical Approaches to improve permeability

The use of electromotive drug administration (EMDA) or iontophoresis for the enhancement of transdermal drug delivery has a long tradition in medicine[14, 15]. It is an active and potentially effective method for transporting drugs (such as mitomycin C, oxybutynin, and bethanechol) through the urothelium into deeper layers of the bladder[16]. Response rate in high risk superficial bladder cancer was improved with increased bladder uptake of mitomycin C following intravesical electromotive administration[17, 18]. In addition, several clinical reports demonstrate that intravesical EMDA of local anesthetics results in sufficient anesthesia for transurethral resection of bladder tumors, bladder neck incision and hydrodistension of the bladder[19, 16, 20 21]. A different approach of local microwave induced hyperthermia was used to enhance the efficacy of mitomycin C on small superficial tumor with minimal local side effect after intravesical administration[22]. It has been used for improving intravesical delivery of drugs in bladder carcinoma treatment[23]. Voltage used in electroporation can be reduced to minimize tissue damage by combining electric current

with low intensity ultra sound using the technique called sonophoresis[24].

b) Chemical agents and natural polymers as a permeability enhancers

Many chemical agents and natural polymers can be helpful in IDD to improve the permeability, absorption and diffusion of drugs for the treatment of different bladder diseases. Some of them discussed below

i) Chitosan

Chitosan is a polysaccharide composed of glucosamine and N-acetylglucosamine. It is regarded as a biocompatible, biodegradable, and nontoxic polymer. Chitosan can induce desquamation of pig urothelium, which removes all diffusion barriers: glycosaminoglycans, membrane plaques, and tight junctions of umbrella cells. Topical application of chitosan and cyclodextrins is thought to disrupt intercellular tight junctions and increase paracellular transport[25, 26]. Recently developed quaternized chitosan derivatives such as triethyl chitosan and N-diethyl methyl chitosan might prove an efficient tool for improving paracellular transport of hydrophilic drugs in the bladder.

ii) Dimethyl sulfoxide

DMSO also has the unique capability to penetrate living tissues without causing significant damage. It has been used to enhance bladder absorption of chemotherapeutic agents such as cisplatin, pirarubicin and doxorubicin[27, 28]. Prior instillation of DMSO has also been reported to enhance the absorption of chemotherapeutic drug including paclitaxel and pirarubicin[29, 30]. Intravesical instillation of saponin before administration of anticancer drug (4′-Otetrahydropyranyldoxorubicin, THP) can cause vacuolization and swelling of superficial cells, and the concentration of THP in bladder tissue was significantly higher than that of untreated animals, but no difference was revealed in plasma concentration[31, 32].

iii) Antibiotics

Nystatin and gramicidin eliminate the apical membrane as a resistive element for water diffusion. Nystatin is incorporated into the lipid bilayers of sterol-containing biologic membranes and creates aqueous pores. This effect rapidly increases with the addition of the detergent Triton X-100[33].

iv) Protamine sulphate

An ideal model of urothelial injury would involve selective damage to the surface of urothelial or umbrella cells. On the basis of its potential to damage the surface glycosaminoglycan layer of urothelial cells, protamine sulphate (PS) has been instilled into bladders in vivo and the effects on bladder function have been evaluated[34, 35]. It was demonstrated that exposure to PS in vivo causes a clear-cut disruption of the bladder permeability barrier, which starts within 1 h of exposure and recovers during 2–5 days[36].

b) Pharmacological agents used to increase urothelial permeability

Several pharmacologic agents, which increase bladder urothelial permeability, can be used for clinical purposes. A number of nonphysiologic factors cause alterations of the urothelial barrier function. Bacterial products, such as amphotericin B, nystatin, polymyxin B as well as positively charged proteins released from eosinophils and found in sperm (histones and protamine), increase the ion permeability of the urothelium by interacting with the apical membrane. Acetate, propionate, butyrate, or succinate at pH 4.4, but not at pH 5.0, also alters the transepithelial permeability of rabbit urothelium[13]. The increase in transepithelial permeability due to volatile fatty acids is rapid (minutes) and is due, in part, to an increase in the permeability of the apical membrane to sodium and chloride[37].

The incomplete and variable response often seen with the use of conventional formulations for intravesical therapy due to resistant to the drug target or unsuccessful drug delivery to the diseased bladder tissue.

II) Increasing Residence Time in the Bladder

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 would be constant without any peaks and valleys. It is also plausible to expect an increase in efficacy with increased duration of direct contact between the drug and the abnormal urothelium[38]. 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 such as RTX and prostaglandins inside the bladder[39, 40]. Forming a drug depot inside the bladder appears to be an attractive option over prolonged infusion. Aqueous solutions of poly (ethylene glycol-b-[DL-lactic acid-co-glycolic acid]-bethyleneglycol) (PEG-PLGA-PEG) triblock copolymers form a free-flowing solution at room

temperature and become a viscous gel at body temperature of 37°C[41]. Sustained delivery of misoprostol afforded by thermosensitive hydrogel was able to protect the rat bladder against cyclophosphamide induced cystitis[42]. It would be interesting to discover the effect of loading wound healing agents such as growth factors into hydrogels instilled into damaged bladder and assess the speed of wound healing in urothelium.

A) Bioadhesion

Bioadhesion or mucoadhesion defines the interaction between a biological surface such as bladder mucosa (urothelium) and the polymer. The presence of a mucinglycocalyx domain in the bladder mucosa tempts its utilization for prolonging the residence time of drugs through bioadhesion[43]. Application of bioadhesion for IDD should be able to fulfill three main criteria; quick adhesion to the urothelium after instillation, should not bottleneck voiding of urine and should be retained in place for at least several hours. The efficiency of drug absorption is increased after coupling bioadhesion characteristics to microspheres, liposomes or nanoparticles because of improved intimate contact with the mucus layer. Microspheres based on chitosan are strongly mucoadhesive and their ocular instillation was able to increase the ocular residence time and decrease the frequency of administration for acyclovir[47].

Post-operative chemotherapy in mice was successful with bioadhesive carriers based on polymers such as alginate, chitosan and fibrinogen loaded with anticancer drugs[45]. Bioadhesive microspheres poly(methylidene malonate-2.1.2) were able to release paclitaxel at the urothelium/urine interface of the mouse bladder for two days[43] and a gelatin based delivery system could release drugs for 12 days in the rabbit bladder[46]. Another well known polymer is polyethylene glycol which improves bioadhesion by non-specific interpenetration of its polymer chains with mucus[47]. Polymers such as chitosan and polycarbophil are ideal for a hydrophilic drug because they were able to retain good adhesion to isolated porcine urinary bladder after being fully hydrated[48, 49].

NOVEL APPROACHES FOR INTRAVESICAL TREATMENTS

1) Liposomes & Nanotechnology

Liposomes are better suited than micelles for use as carriers of water insoluble drugs administered into the bladder, because instillation of micelles can have deleterious effects on urothelium[50, 51]. Micelles formed by polyamide detergents such as Big CHAP (N,N-*bis*-(3-D-Gluconamidopropyl) cholamide) can remove lipids from the apical membranes of cells lining the bladder and make the urothelium more permeable for drug or gene transfer[52]. By intravenous route, liposomes show improvement in aqueous solubility of hydrophobic drugs such as taxol and amphotericin[53]. In the recent study, liposomes were used as a vehicle for capsaicin and evaluated their potential as a vehicle and to reduce toxicity for intravesical delivery in rats[42]. A similar approach can prove useful in instillation of other vanilloids such as RTX and water insoluble drugs.

Instillation of liposome encapsulated radiolabeled IFN-α or radiolabeled liposomes into mouse bladder were able to achieve localized therapy with negligible penetration to other organs[38]. Use of multilamellar liposomes as a delivery vehicle improved the antiproliferative capacity of IFN-α in a resistant bladder cancer cell line[54].

Recent studies on non viral gene therapy of skin wounds confirmed the wound healing properties of liposomes[55, 56] Based on reports, instillation of liposomes may be able to palliate IC symptoms in a rat model of bladder injury, because of the wound healing properties of liposomes[57, 5]. These observations suggest that liposomes might enhance the barrier properties of a dysfunctional urothelium and increase its resistance against irritant penetration.

Nanoparticles with a well-defined particle size and shape can have immense potential for intravesical delivery as they can enhance the ability of drugs to cross the urothelium. Moreover, higher surface to volume ratio of nanoparticles can also be responsible for increase in transvesical absorption of encapsulated drugs. The rapid release paclitaxel nanoparticles showed significant activity against human bladder cancer cell and resulted in higher tissue concentrations compared with paclitaxel formulated in the commercial cremophor emulsion[58].

Nanotechnology holds tremendous promise for the future of intravesical delivery of drugs and genes into the bladder.

2) Gene Therapy of Bladder Cancer

Intravesical administration of recombinant interferon (IFN) demonstrated only limited efficacy against superficial bladder cancer because of the inherent drawback of the intravesical route[59]. Instillation of protein was only able to offer short term treatment of IFN because of the excretion of the instilled IFN with only a fraction of administered dose remaining after voiding. It was reasonable therefore to

expect that delivery of IFN-α gene into the urothelium might improve this therapeutic modality and potentially provide a continuous secretion of IFN into the tumor microenvironment. Indeed, successful transgene expression into urothelium was able to sustain the production and secretion of the mature 165 amino acid human IFN-α2b protein inside the bladder[60].

Overexpression of NGF mRNA in bladder is considered responsible for symptoms of IC and as expected, viral mediated expression of NGF gene in rat urothelium led to bladder hyperactivity[61]. A short single-stranded oligo fragment can hybridize to its complementary mRNA target sequence and modify RNA processing either through steric blockade or by activating RNase H.

A recent study evaluated the potential of small interfering RNAs (siRNAs) in blocking mRNA for the enzyme Polo-like kinase-1 (PLK-1) involved in proliferation after intravesical administration[63]. PLK controls mitotic entry of proliferating cells and regulate many aspects of mitosis required for cytokinesis. Future studies for modulating gene expression may also employ the decoy approach for evaluating the potential of synthetic DNA fragments in competition against transcription factors. However, the latent potential of rational gene based drug design remains unrealized for intravesical delivery largely due to lack of an adequate drug delivery system. A search is ongoing for suitable vectors for plasmid and oligos that can be used for intravesical delivery.

3) Viral Vectors

The luciferase gene expression was driven by the cytomegalovirus immediate early promoter in the expression cassette in place of the E1 region of the adenovirus vector. Besides, adenoviral mediated delivery of the IFNα2b gene allowed detection of multiple-fold higher interferon concentration in bladder tissue and urine than those observed with instillation of the recombinant IFN protein itself[60]. The gene transfer efficiency using viral vectors is known to be influenced by various physical parameters such as intravesical volume, instillation pressure and chemical treatment of urothelium prior to instillation[63]. Instillation of higher volumes of viral vector was able to restrict significantly higher gene expression only to the bladder, but instillation at higher pressures resulted in higher transgene expression in other systemic organs.

Gene transfer efficiency using attenuated vaccinia virus or canarypox virus is better than withadenovirus[64, 65]. Instillation of 22% ethanol in rodent bladder before administration of adenovirus was able to improve gene transfer because of disruption in the GAG layer[66]. An even greater increase in gene transfer and expression was achieved by prior instillation of gene transfer-enhancing agent Syn3[60, 67]. However, a recent study showed that co-administration of Syn3 with adenovirus is also successful and infact Syn3 can be used as a vehicle for the adenovirus[60, 68]. Previously, a similar strategy of co-administering adenovirus with a transduction-enhancing non-ionic polyamide detergent Big CHAP was used to improve the expression of p53 gene in a phase I study[52]. Although, the use of Syn3 appears to be non-toxic to the bladder tissue, but the use of other transduction enhancing agents have been shown to produce adverse effects on the urothelium[50, 51, 68].

Single instillation of adenovirus containing IFN-α at doses of 1010-1011 particles/ml along with Syn3 was highly effective in reducing the size of human bladder tumors implanted orthotopically in nude mice[69]. The dose-limiting toxicity of adenovirus vector containing p53 gene was evaluated in a phase I study on patients of locally advanced bladder cancer ineligible for cystectomy[70]. However, the clinical toxicity of viral vectors observed following systemic administration will drive the search of nonviral vectors with higher efficiency of gene transfection. Development of efficient nonviral vectors will also serve the needs of intravesical delivery.

4) Nonviral Vectors

The potential of toxicity from inadvertent systemic absorption of viral vectors from the bladder has whetted interest in non-viral vectors. Cationic liposomes have facilitated the delivery of DNA into mammalian cells through endocytosis of the complex followed by its escape into the cytosol from an endocytotic compartment[71, 72]. It is possible that the entry of DNA/lipid complex into the urothelium cells is possibly mediated by endocytosis, which may be further tested using endocytosis inhibitors. Compared to BCG therapy, IL-2 gene therapy using cytofectins, Dimyristoyl Rosenthal Inhibitor Ether (DMRIE) and dioleoylphosphatidylethanolamine (DOPE) proved better in improving survival rate of mice bearing orthotopic bladder cancer and inducing long-lasting tumor-specific immunologic memory[73]. In a recent study, a different vector based on cationic liposome, N-[1-(2,3-dioleoyloxyl)propyl]-N,N,N-trimethyl ammoniummethyl sulfate and methyl-beta-cyclodextrin-solubilized cholesterol to transfer

plasmid containing IFN-α and GM-CSF into tumors implanted into mouse bladder[74]. The *in vivo* effectiveness of siRNA delivered using liposomes composed of lipid analogue 2-*O*-(2-DEAE)-carbamoyl-1,3-*O*-dioleoylglycerol and egg phosphatidylcholine was demonstrated in a murine orthotopic bladder cancer model[75]. Therapy based on siRNA is relatively new and its comparative efficacy with respect to gene therapy in inhibiting bladder cancer needs to be determined in mouse models to make definitive conclusions about its effectiveness. Nonviral vectors has not been evaluated for gene transfer in the clinic and a comparative preclinical study on viral and non viral vectors for gene therapy of bladder cancer will be needed to justify their claim.

ALTERNATIVE BLADDER DRUG DELIVERY

Intravesical administration of traditional drugs has been tried as an alternative to conventional oral administration for the unstable bladder. This route of installation offers the possibility of obtaining a high concentration of drug at the target organ while avoiding systemic side effects. In the properly motivated patient, or patients who cannot tolerate oral anticholinergic agents, intravesical installation should be considered as a nonsurgical option. Agents studied thus far include emepronium bromide, intravesical lidocaine, oxybutynin, and verapamil.

1) The Bladder Pump

Intravesical therapy of anticholinergic drugs is effective, but this method of delivery is just too cumbersome for most patients, as it requires repeated manipulation of the lower urinary tract. However, if constant therapeutic levels of oxybutynin in the bladder without repeated instrumentation could be achieved, this would provide an extremely effective regimen to treat OAB. The key to this intravesical regimen is a long-lasting intravesical pump to deliver the desired drug dose. This technology, called UROS, was developed by Situs Corporation (San Diego, CA). The concept involves a reservoir that can be easily inserted into the bladder and filled with the desired drug. The reservoir size must be balanced so that it is not too small to be voided out yet not too large to cause bladder irritation or obstruction. The reservoir will be able to constantly release a precise drug quantity into the bladder. When the reservoir is empty, for example after 30 days, a flexible cystoscopy can be used to retrieve the empty reservoir and a new reservoir can be inserted. Drugs to treat bladder spasms, pain, and even bladder cancer may all be delivered by this technology in the future.

Initial experience with the bladder pump was presented at the 95th Annual American Urological Association Meeting in Atlanta in 2000. Findings presented at the AUA meeting focused on two clinical studies involving a total of 16 women. In the first (randomized and blinded) study, 13 healthy females received saline via the UROS infusor for three days. Results showed they tolerated the device well and voided normally. In the second trial, three women suffering from overactive bladder were treated with oxybutynin solution using the infusor for 24 hours. The results of the latter trial revealed that two patients experienced a greater than 100% increase in bladder capacity and all three had acceptable tolerance levels and no side effects.

2) Sustained Bladder Drug Release

An intravesical, fibrinogen-based, sustained-retention drug delivery system was developed, termed therapeutic adhesive (TA), for application to resected tumor beds to reduce local tumor recurrences. They evaluated the feasibility, safety, and retention of the TA, formulated with 5-fluorouracil (5-FU TA), after intravesical application in a mouse model. Radiolabeled [^{14}C] 5-FU TA or [^{14}C] 5-FU solution was delivered intravesically in this manner to C3H/He female mice[76].

After drug administration, retention of ^{14}C in the bladder was quantified by storage-phosphor autoradiography. A 2.6-fold increase in retention was observed with 5-FU TA when compared with 5-FU solution. The AUC (2 min-5 h) for 5-FU TA was 685 nmol h/mm^2, compared with 260 nmol h/mm^3 for 5-FU solution. No signs of toxicity in the bladder tissue or treatment-associated adverse effects were observed in the mice.

Moreover, we can easily imagine that sustained intravesical drug release for several hours or a few days would be ideal therapy for urinary tract infections.

3) Intravesical Peppers

This was demonstrated with electrophysiological recording and also by the administration of capsaicin, a neurotoxin that is known to disrupt the function of C-fiber afferents[77]. In normal cats, capsaicin injected systemically in large doses (20–45 mg/kg, s.c.) did not block reflex contractions of the bladder or the A-delta fiberevoked bladder reflex but in chronic-spinal-injured cats, capsaicin (20–30 mg/kg, s.c.) completely blocked rhythmic bladder contractions induced by bladder

distension and the C-fiber-evoked long latency reflex firing recorded from bladder postganglionic nerves. Thus there seems to be a considerable reorganization of reflex connections in the spinal cord of the cat following the interruption of descending pathways from the brain (Figure 2).

The vanilloids, capsaicin and resiniferatoxin activate nociceptive sensory nerve fibers through an ion channel[78] and known as vanilloid receptor subtype 1 (VR1). This receptor is a nonselective cation channel and is activated by increases in temperature to within the noxious range and by protons, suggesting that it functions as a transducer of painful thermal stimuli and acidity in vivo. When activated, the channel opens, allowing an influx of calcium and sodium ions that depolarizes the nociceptive afferent terminals, initiating a nerve impulse that travels through the dorsal root ganglion into the central nervous system[79]. Previously called the capsaicin receptor, VR1 has been localized in the spinal cord, dorsal root ganglia, and visceral organs, including the bladder, urethra, and colon. Activation of VR1 results in spikelike currents[80] that selectively excite and subsequently desensitize C-fibers. Capsaicin desensitization is defined as long-lasting, reversible suppression of sensory neuron activity[81]. The transient increase in intracellular concentration of calcium ions also leads to activation of intracellular enzymes, peptide transmitter release, and neuronal degeneration[82, 83].

4) Magnetic targeting

Magnetic targeting uses a magnet placed externally on the skin covering a predetermined site in the bladder (typically where tumors reside) to localize drug-containing magnetic particles in tumors, thereby providing continuous exposure to high drug concentrations in tumors. In swine bladders, administration of magnetic doxorubicin-loaded microparticles (10 to 80 mg drug in 300–800 mg magnetic particles) followed by 30-min of external magnetic targeting yielded localization of microparticles in superficial and deep tissue layers of the magnetic-targeted sites (primarily in superficial submucosa) that were retained for at least 44 days.

Summary and Future directions for IDD

In summary, Table 1 shows the current methods of IDD and the practice of IDD using various physical and chemical agents.

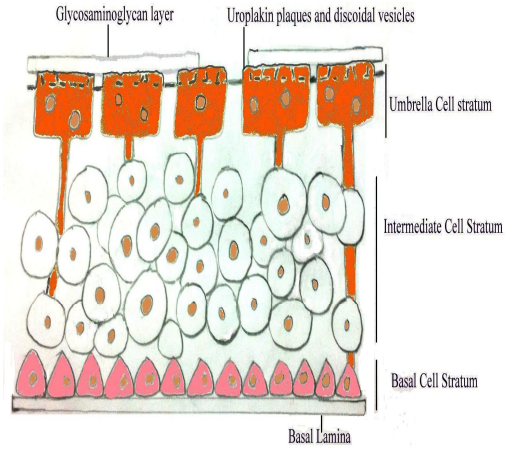

Fig. 1: Diagrammatic representation of the bladder urothelium

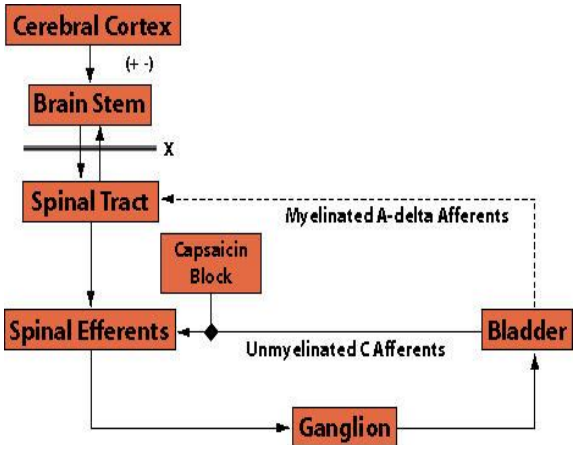

Fig. 2: Reflex connections in the spinal cord

Table 1: Use of delivery options in IDD for different drugs or therapeutic entities

Advanced Delivery Options	Unique Advantage/Disadvantages	Drug/Therapeutic Entity
Iontophoresis & electroporation	Suited for Low Mol.wt. Drug	Mitomycin C
DMSO & saponins	Cytotoxic and Poor Patient Acceptance	Paclitaxel
Liposomes	Tissue Friendly Gene vector	Capsaicin, siRNA, IFNα, IL-2
Bioadhesive microspheres	Increased residence time	Paclitaxel, Mitomycin C, 5FU, Oxybutynin
Thermosensitive hydrogel	Higher Drug Loading capacity	Capsaicin & Misoprostol
Adenovirus	Higher transduction efficiency	p53 gene,

REFERENCES

1. Buyse G, Waldeck K, Verpoorten C, Bjork H, Casaer P, Andersson KE. Intravesical application of a stable oxybutynin solution improves therapeutic compliance and acceptance in children with neurogenic bladder dysfunction. J Urol. 1998;160:892–96.
2. Negrete HO, Lavelle JP, Berg J, Lewis SA, Zeidel ML. Permeability properties of the intact mammalian bladder epithelium. Am J Physiol. 1996;271:886–94.
3. Min G, Stolz M, Zhou G, Liang F, Sebbel P, Stoffler D, Glockshuber R, Sun TT, Aebi U, Kong XP. Localization of uroplakin Ia, the urothelial receptor for bacterial adhesin FimH, on the six inner domains of the 16 nm urothelial plaque particle. J Mol Biol. 2002;317:697–06.
4. Born M, Pahner I, Ahnert-Hilger G, Jons T. The maintenance of the permeability barrier of bladder facet cells requires a continuous fusion of discoid vesicles with the apical plasma membrane. Eur J Cell Biol. 2003;82:343–50.
5. Parsons CL. A model for the function of glycosaminoglycans in the urinary tract. World J Urol. 1994;12:38–42.
6. Lande M, Donovan J, Zeidel M. The relationship between membrane fluidity and permeabilities to water, solutes, ammonia, and protons. J. Gen. Physiol. 1995;106:67–84.
7. Staehelin LA, Chlapowski FJ, Bonneville MA. Lumenal plasma membrane of the urinary bladder. I. Three-dimensional reconstruction from freeze-etch images. J. Cell Biol. 1972;53:73–91.
8. Romih R, Jezernik K. Reorganisation of the urothelial luminal plasma membrane in the cyclophosphamide treated rats. Pflugers Arch. 1996;431:R241–42.
9. Lewis SA, Berg JR, Kleine TJ. Modulation of epithelial permeability by extracellular macromolecules. Physiol Rev. 1995;75:561–89.
10. Hohlbrugger G, Lentsch P. Intravesical ions, osmolality and pH influence the volume pressure response in the normal rat bladder and this is more pronounced after DMSO. Eur Urol. 1985;11:127–30.
11. Parsons CL, Lilly JD, Stein P. Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). J Urol. 1991;145:732–5.
12. Lewis SA, Diamond JM. Na+ transport by rabbit urinary bladder, a tight epithelium. J Membr Biol. 1976;28:1–40.
13. Ping H, Meyers S, Liang F, Deng F, Kachar B, Zeidel ML, Sun T. Role of membrane proteins in permeability barrier function: uroplakin ablation elevates urothelial permeability. Am J Physiol Renal Physiol. 2002;283:200–7.
14. Schuetz YB, Naik A, Guy RH, Kalia YN. Emerging strategies for the transdermal delivery of peptide and protein drugs. Expert Opin Drug Deliv. 2005;2:533–48.
15. Dyson C. Influence of Iontophoresis on the Permeability of the Excised Cornea. Arch Ophthal. 1949;42:416–21.
16. Rosamilia A, Dwyer PL, Gibson J. Electromotive drug administration of lidocaine and dexamethasone followed by cystodistention in women with interstitial cystitis. Int Urogynecol J Pelvic Floor Dysfunct. 1997;8:142–45.
17. Di Stasi SM, Giannantoni A, Stephen RL, Capelli G, Navarra P, Massoud R, Vespasiani G. Intravesical electromotive mitomycin C versus passive transport mitomycin C for high risk superficial bladder cancer: a prospective randomized study. J Urol. 2003;170:777–82.
18. Riedl CR, Stephen RL, Daha LK, Knoll M, Plas E, Pfluger H. Electromotive administration of intravesical bethanechol and the clinical impact on acontractile detrusor management: introduction of a new test. J Urol. 2000;164:2108–11.
19. Jewett MA, Valiquette L, Sampson HA, Katz J, Fradet Y, Redelmeier DA. Electromotive drug administration of lidocaine as an alternative anesthesia for transurethral surgery. J Urol. 1999;161:482–85.
20. Fontanella UA, Rossi CA, Stephen RL. Bladder and urethral anaesthesia with electromotive drug administration (EMDA): a technique for invasive endoscopic procedures. Br J Urol. 1997;79:414–20.
21. Gurpinar T, Truong LD, Wong HY, Griffith DP. Electromotive drug administration to the urinary bladder: an animal model and preliminary results. J Urol. 1996;156:1496–1501.
22. Colombo R, Brausi M, Da Pozzo L, Salonia A, Montorsi F, Scattoni V, Roscigno M, Rigatti P. Thermo-chemotherapy and electromotive drug

administration of mitomycin C in superficial bladder cancer eradication. a pilot study on marker lesion. Eur Urol. 2001;39:95–100.
23. Lee CF, Chang SY, Hsieh DS, Yu DS. Treatment of bladder carcinomas using recombinant BCG DNA vaccines and electroporative gene immunotherapy. Cancer Gene Ther. 2004;11:194–07.
24. Ogawa R, Kagiya G, Feril LB Jr. Nakaya N, Nozaki T, Fuse H, Kondo T. Ultrasound mediated intravesical transfection enhanced by treatment with lidocaine or heat. J Urol. 2004;172:1469–73.
25. Smith JM, Dornish M, Wood EJ. Involvement of protein kinase C in chitosan glutamate-mediated tight junction disruption. Biomaterials. 2005;26:3269–76.
26. Yang T, Hussain A, Paulson J, Abbruscato TJ, Ahsan F. Effect of Cyclodextrins on Nasal Delivery of Low Molecular Weight Heparins: in vivo and in vitro Studies. Pharm Res. 2004;21:1127–36.
27. Melchior D, Packer CS, Johnson TC, Kaefer M. Dimethyl sulfoxide: does it change the functional properties of the bladder wall? J Urol. 2003;170:253–8.
28. See WA, Xia Q. Regional chemotherapy for bladder neoplasms using continuous intravesical infusion of doxorubicin: impact of concomitant administration of dimethyl sulfoxide on drug absorption and antitumor activity. J Natl Cancer Inst. 1992;84:510–5.
29. Chen D, Song D, Wientjes MG, Au JL. Effect of dimethyl sulfoxide on bladder tissue penetration of intravesicalpaclitaxel.Clin Cancer Res. 2003;9:363–69.
30. Hashimoto H, Tokunaka S, Sasaki M, Nishihara M, Yachiku S. Dimethylsulfoxide enhances the absorption of chemotherapeutic drug instilled into the bladder. Urol Res. 1992;20:233–36.
31. Sasaki M, Hashimoto H, Yachiku S. Studies on enhancement of drug absorption through the bladder mucosa Nippon Hinyokika Gakkai Zasshi. 1994;85:1353–62.
32. Hashimoto H, Yachiku S, Watabe Y, Niibori D, Yamauchi K, Osanai H, Ohashi K, Wakabayashi A, Fujisawa M. Postoperative intravesical installation of tetrahydropyranyl-adriamycin (THP) and cytosine arabinoside (CA) for superficial bladder cancer: clinical results of prophylactic effects on recurrence. Gan To Kagaku Ryoho. 1994; 21:833–38.
33. Holz R, Finkelstein A. The water and nonelectrolyte permeability induced in thin lipid membranes by the polyene antibiotics nystatin and amphotericin B. J Gen Physiol, 1970;56:124–45.
34. Chuang YC, Yoshimura N, Huang CC, Chaing PH, Chancellor MB. Intravesical botulinum toxin A administration produces analgesia against acetic acid induced bladder pain responses in rats. J Urol. 2004;172:1529–32.
35. Vemulakonda VM, Somogyi GT, Kiss S, Salas NA, Boone TB, Smith CP. Inhibitory effects of intravesically applied botulinum toxin a in chronic bladder inflammation. J Urol. 2005; 173:621–4.
36. Lavelle J, Meyers S, Ramage R, Bastacky S, Doty D, Apodaca G, Zeidel ML.. Bladder permeability barrier: recovery from selective injury of surface epithelial cells. Am J Physiol Renal Physiol. 2002;283(2):F242–53.
37. Mann FC, Magoun JAH. Absorption from the urinary bladder. Am J Med Sci. 1923;166:96–106.
38. Frangos DN, Killion JJ, Fan D, Fishbeck R, von Eschenbach AC, Fidler IJ. The development of liposomes containing interferon alpha for the intravesical therapy of human superficial bladder cancer. J Urol. 1990;143:1252–56.
39. Lazzeri M, Spinelli M, Beneforti P, Malaguti S, Giardiello G, Turini D. Intravesical infusion of resiniferatoxin by a temporary in situ drug delivery system to treat interstitial cystitis: a pilot study. Eur Urol. 2004; 45:98–102.
40. Miller LJ, Chandler SW, Ippoliti CM. Treatment of cyclophosphamide-induced hemorrhagic cystitis with prostaglandins. Ann Pharmacother. 1994;28:590–94.
41. Jeong B, Bae YH, Kim SW. In situ gelation of PEG-PLGA-PEG triblock copolymer aqueous solutions and degradation thereof. J Biomed Mater Res. 2000;50:171–77.
42. Tyagi P, Li Z, Chancellor M, De Groat WC, Yoshimura N, Huang L. Sustained intravesical drug delivery using thermosensitive hydrogel. Pharm Res. 2004;21:832–37.
43. Le Visage C, Rioux-Leclercq N, Haller M, Breton P, Malavaud B, Leong K. Efficacy

of paclitaxel released from bio-adhesive polymer microspheres on model superficial bladder cancer. J Urol. 2004;171:1324–29.
44. Genta I, Conti B, Perugini P, Pavanetto F, Spadaro A, Puglisi G. Bioadhesive microspheres for ophthalmic administration of acyclovir. Journal of Pharmacy and Pharmacology. 1997;49:737–42.
45. Ozturk E, Eroglu M, Ozdemir N, Denkbas EB. Bioadhesive drug carriers for postoperative chemotherapy in bladder cancer. Adv Exp Med Biol. 2004;553:231–42.
46. Ye Z, Chen J, Zhang X, Li J, Zhou S, Yang W, Zhang Y. Novel gelatin-adriamycin sustained drug release system for intravesical therapy of bladder cancer. J Tongji Med Univ. 2001;21:145–48.
47. Lele BS, Hoffman AS. Mucoadhesive drug carriers based on complexes of poly(acrylic acid) and PEGylated drugs having hydrolysable PEG-anhydride-drug linkages. Journal of Controlled Release. 2000;69:237–48.
48. Lehr CM. Bioadhesion technologies for the delivery of peptide and protein drugs to the gastrointestinal tract. Crit Rev Ther Drug Carrier Syst. 1994;11:119–160.
49. Lehr CM, Bouwstra JA, Bodde HE, Junginger HE. A surface energy analysis of mucoadhesion: contact angle measurements on polycarbophil and pig intestinal mucosa in physiologically relevant fluids. Pharm Res. 1992;9:70–75.
50. Connor RJ, Engler H, Machemer T, Philopena JM, Horn MT, Sutjipto S, Maneval DC, Youngster S, Chan T-M, Bausch J, McAuliffe JP, Hindsgaul O, Nagabhushan TL. Identification of polyamides that enhance adenovirus-mediated gene expression in the urothelium. Gene Therapy. 2001;8:41–48.
51. Ratliff TL. Identification of pretreatment agents to enhance adenovirus infection of bladder epithelium. J Urol. 2005;173:2198–99.
52. Kuball J, Wen SF, Leissner J, Atkins D, Meinhardt P, Quijano E, Engler H, Hutchins B, Maneval DC, Grace MJ, Fritz MA, Storkel S, Thuroff JW, Huber C, Schuler M. Successful adenovirus-mediated wild-type p53 gene transfer in patients with bladder cancer by intravesical vector instillation. Journal of Clinical Oncology. 2002;20:957–65.
53. Ng AW, Wasan KM, Lopez-Berestein G. Liposomal polyene antibiotics. Methods Enzymol. 2005;391:304–13.
54. Killion JJ, Fan D, Bucana CD, Frangos DN, Price JE, Fidler IJ. Augmentation of antiproliferative activity of interferon alfa against human bladder tumor cell lines by encapsulation of interferon alfa within liposomes. J Natl Cancer Inst. 1989;81:1387–92.
55. Lee JP, Jalili RB, Tredget EE, Demare JR, Ghahary A. Antifibrogenic effects of liposome-encapsulated IFN-alpha2b cream on skin wounds in a fibrotic rabbit ear model. J Interferon Cytokine Res. 2005;25:627–31.
56. Jeschke MG, Sandmann G, Finnerty CC, Herndon DN, Pereira CT, Schubert T, Klein D. The structure and composition of liposomes can affect skin regeneration, morphology and growth factor expression in acute wounds. Gene Ther. 2005;12:1718–24.
57. Parsons CL, Benson G, Childs SJ, Hanno P, Sant GR, Webster G. A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosanpolysulfate. J Urol. 1993;150:845–48.
58. Lu Z, Yeh TK, Tsai M, Au JL, Wientjes MG. Paclitaxel-loaded gelatin nanoparticles for intravesical bladder cancer therapy. Clin Cancer Res. 2004;10:7677–84.
59. Malmstrom PU. A randomized comparative dose-ranging study of interferon-alpha and mitomycin-C as an internal control in primary or recurrent superficial transitional cell carcinoma of the bladder. BJU Int. 2002;89:681–86.
60. Connor RJ, Anderson JM, Machemer T, Maneval DC, Engler H. Sustained intravesical interferon protein exposure is achieved using an adenoviral-mediated gene delivery system: a study in rats evaluating dosing regimens. Urology. 2005;66:224–29.
61. Lamb K, Gebhart GF, Bielefeldt K. Increased nerve growth factor expression triggers bladder overactivity. J Pain. 2004;5:150–56.
62. Tsvetkov LM, Tsekova RT, Xu X, Stern DF. The Plk1 Polo box domain mediates a cell cycle and DNA damage regulated interaction with Chk2. Cell Cycle. 2005;4:609–17.

63. Siemens DR, Austin JC, See WA, Tartaglia J, Ratliff TL. Evaluation of gene transfer efficiency by viral vectors to murine bladder epithelium. J Urol. 2001;165:667–71.
64. Siemens DR, Crist S, Austin JC, Tartaglia J, Ratliff TL. Comparison of viral vectors: gene transfer efficiency and tissue specificity in a bladder cancer model. J Urol. 2003;170:979–84.
65. Fodor I, Timiryasova T, Denes B, Yoshida J, Ruckle H, Lilly M. Vaccinia virus mediated p53 gene therapy for bladder cancer in an orthotopic murine model. J Urol. 2005;173:604–09.
66. Engler H, Anderson SC, Machemer TR, Philopena JM, Connor RJ, Wen S-F, Maneval DC. Ethanol improves adenovirus-mediated gene transfer and expression to the bladder epithelium of rodents. Urology. 1999;53:1049–53.
67. Yamashita M, Rosser CJ, Zhou JH, Zhang XQ, Connor RJ, Engler H, Maneval DC, Karashima T, Czerniak BA, Dinney CP, Benedict WF. Syn3 provides high levels of intravesical adenoviral-mediated gene transfer for gene therapy of genetically altered urothelium and superficial bladder cancer. Cancer Gene Ther. 2002;9:687–91.
68. Benedict WF, Tao Z, Kim CS, Zhang X, Zhou JH, Adam L, McConkey DJ, Papageorgiou A, Munsell M, Philopena J, Engler H, Demers W, Maneval DC, Dinney CP, Connor RJ. Intravesical Ad-IFNalpha causes marked regression of human bladder cancer growing orthotopically in nude mice and overcomes resistance to IFN-alpha protein. Mol Ther. 2004;10:525-32.
69. Tao Z, Connor RJ, Ashoori F, Dinney CP, Munsell M, Philopena JA, Benedict WF. Efficacy of a single intravesical treatment with Ad-IFN/Syn 3 is dependent on dose and urine IFN concentration obtained: implications for clinical investigation. Cancer Gene Ther. 2006;13:125–30.
70. Pagliaro LC, Keyhani A, Williams D, Woods D, Liu B, Perrotte P, Slaton JW, Merritt JA, Grossman HB, Dinney CP. Repeated intravesical instillations of an adenoviral vector in patients with locally advanced bladder cancer: a phase I study of p53 gene therapy. J Clin Oncol. 2003;21:2247–53.
71. Gao X, Huang L. A novel cationic liposome reagent for efficient transfection of mammalian cells. Biochem Biophys Res Commun. 1991;179:280–85.
72. Zabner J, Fasbender AJ, Moninger T, Poellinger KA, Welsh MJ. ellular and molecular barriers to gene transfer by a cationic lipid. J Biol Chem. 1995;270:18997–19007.
73. Horinaga M, Harsch KM, Fukuyama R, Heston W, Larchian W. Intravesical interleukin-12 gene therapy in an orthotopic bladder cancer model. Urology. 2005; 66(2):461-6.
74. Wu Q, Mahendran R, Esuvaranathan K. Clin Cancer Res. 2003;9:4522–28.
75. Nogawa M, Yuasa T, Kimura S, Tanaka M, Kuroda J, Sato K, Yokota A, Segawa H, Toda Y, Kageyama S, Yoshiki T, Okada Y, Maekawa T. . Intravesical administration of small interfering RNA targeting PLK-1 successfully prevents the growth of bladder cancer. J Clin Invest. 2005;115:978–985.
76. Brown DM. Drug retention following intravesical delivery of fluorouracil therapeutic adhesive in C3H mouse bladder. Anticancer Drugs. 1996;7:507–13.
77. de Groat WC, Booth AM, Yoshimura N. Neurophysiology of micturition and its modification in animal models of human disease. In: Maggi CA, editor. Nervous Control of the Urogenital System. Vol. 3. London: Harwood Academic Publishers. 1993;227–89.
78. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D.. The capsaicin receptor: A heat-activated ion channel in the pain pathway. Nature. 1997;389:816–24.
79. Clapham DE. Some like it hot: spicing up ion channels. Nature. 1997;389:783–84.
80. Liu L, Simon SA. Capsaicin-induced currents with distinct desensitization and Ca2+ dependence in rat trigeminal ganglion cells. J Neurophysiol. 1996;75:1503–14.
81. Craft RM, Cohen SM, Porreca F. Long-lasting desensitization of bladder afferents following intravesical resiniferatoxin and capsaicin in the rat. Pain. 1995;61:317–23.
82. Kawatani M, Whitney T, Booth AM, de Groat WC. Excitatory effect of substance P in parasympathetic ganglia of the cat urinary bladder. Am J Physiol. 1989;257:R1450–56.
83. Szallasi A, Blumberg PM. Vanilloid receptors: new insights enhance

potential as therapeutic target. Pain. 1996;68:195–208.