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. 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, interstitial 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\(^6-8\). 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\(^10\).

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\(^19, 16\). 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 electroproportion can be reduced to minimize tissue damage by combining electric current.
with low intensity ultra sound using the technique called sonophoresis\textsuperscript{24}.

\textbf{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

\textit{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\textsuperscript{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.

\textit{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\textsuperscript{27, 28}. Prior instillation of DMSO has also been reported to enhance the absorption of chemotherapeutic drug including paclitaxel and pirarubicin\textsuperscript{29, 30}. Intravesical instillation of saponin before administration of anticaner drug (4'-Otetrahydropranylodoxorubicin, 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\textsuperscript{31, 32}.

\textit{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\textsuperscript{33}.

\textit{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\textsuperscript{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\textsuperscript{36}.

\textbf{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\textsuperscript{33}. 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\textsuperscript{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.

\textbf{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\textsuperscript{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\textsuperscript{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°C⁴¹. Sustained delivery of misoprostol afforded by thermosensitive hydrogel was able to protect the rat bladder against cyclophosphamide induced cystitis⁴². 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 bioadhesion⁴³. 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 acyclovir⁴⁷. Post-operative chemotherapy in mice was successful with bioadhesive carriers based on polymers such as alginate, chitosan and fibrinogen loaded with anticancer drugs⁴⁶. Bioadhesive microspheres poly(methylidene malonate-2:1.2) were able to release paclitaxel at the urothelium/urine interface of the mouse bladder for two days⁴³ and a gelatin based delivery system could release drugs for 12 days in the rabbit bladder⁴⁶. Another well known polymer is polyethylene glycol which improves bioadhesion by non-specific interpenetration of its polymer chains with mucus⁴⁷. Polymers such as chitosan and polycarbofil are ideal for a hydrophilic drug because they were able to retain good adhesion to isolated porcine urinary bladder after being fully hydrated⁴⁸, 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 urothelium⁵⁰, ⁵¹. Micelles formed by polyamide detergents such as Big CHAP (N,N-bis-(3-D-Gluconamidopropyl) cholate) can remove lipids from the apical membranes of cells lining the bladder and make the urothelium more permeable for drug or gene transfer⁵². By intravenous route, liposomes show improvement in aqueous solubility of hydrophobic drugs such as taxol and amphotericinB⁵³. 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 rats⁴². 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 organs⁵⁸. Use of multilamellar liposomes as a delivery vehicle improved the antiproliferative capacity of IFN-α in a resistant bladder cancer cell line⁵⁴. Recent studies on non viral gene therapy of skin wounds confirmed the wound healing properties of liposomes⁵⁵, 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 liposomes⁵⁷. 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 emulsion⁵⁸. 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 route⁵⁹. 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.

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. 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 of viral mediated expression of NGF gene in rat urothelium led to bladder hyperactivity. 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 IFNa2b 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. 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. 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 with adenovirus. Instillation of 22% ethanol in rodent bladder before administration of adenovirus was able to improve gene transfer because of disruption in the GAG layer. An even greater increase in gene transfer and expression was achieved by prior instillation of gene transfer-enhancing agent Syn3. However, a recent study showed that co-administration of Syn3 with adenovirus is also successful and intact Syn3 can be used as a vehicle for the adenovirus. 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. 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.

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. 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. 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. 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 cytostectins, 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. In a recent study, a different vector based on cationic liposome, N-[1-(2,3-dioleoyxyloxy)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 bladder74. 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 model75. 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 [14C] 5-FU TA or [14C] 5-FU solution was delivered intravesically in this manner to C3H/He female mice76.

After drug administration, retention of 14C 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/mm², compared with 260 nmol h/mm² 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 afferents77. 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 fiber-evoked 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 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. 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 currents80 that selectively excite and subsequently desensitize C-fibers. Capsaicin desensitization is defined as long-lasting, reversible suppression of sensory neuron activity81. The transient increase in intracellular concentration of calcium ions also leads to activation of intracellular enzymes, peptide transmitter release, and neuronal degeneration82, 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.

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

<table>
<thead>
<tr>
<th>Advanced Delivery Options</th>
<th>Unique Advantage/Disadvantages</th>
<th>Drug/Therapeutic Entity</th>
</tr>
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<tbody>
<tr>
<td>Iontophoresis &amp; electroporation</td>
<td>Suited for Low Mol.wt. Drug</td>
<td>Mitomycin C</td>
</tr>
<tr>
<td>DMSO &amp; saponins</td>
<td>Cytotoxic and Poor Patient Acceptance</td>
<td>Paclitaxel</td>
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<tr>
<td>Liposomes</td>
<td>Tissue Friendly Gene vector</td>
<td>Capsaicin, siRNA, IFNα, IL-2</td>
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<td>Adhesive microspheres</td>
<td>Increased residence time</td>
<td>Paclitaxel, Mitomycin C, 5FU, Oxybutynin</td>
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<td>Thermeosensitive hydrogel</td>
<td>Higher Drug Loading capacity</td>
<td>Capsaicin &amp; Misoprostol</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Higher transduction efficiency</td>
<td>p53 gene,</td>
</tr>
</tbody>
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Fig. 1: Diagrammatic representation of the bladder urothelium

Fig. 2: Reflex connections in the spinal cord
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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.


